International Agency for Research on Cancer

World Health Organization

IARC Monographs on the Identification of Carcinogenic Hazards to Humans

Report of the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2025–2029

IARC Monographs on the Identification of Carcinogenic Hazards to Humans

Report of the Advisory Group to Recommend Priorities for *IARC Monographs* during 2025–2029

Lyon, France: 19–22 March 2024

CONTENTS

Acknowledgements

The Secretariat of the *Monographs* programme of the International Agency for Research on Cancer (IARC) wishes to acknowledge the pre-meeting assistance of the following early career and visiting scientists at IARC, who assisted in the preparations for the meeting: Dr Danila Cuomo, Dr John Kaldor, Ms Gabrielle Rigutto, Dr Susana Viegas. IARC gratefully acknowledges the post-meeting contributions of the technical editors: John Cheney, Mark Cleasby, and Alison Lees. The Secretariat gratefully acknowledges outstanding pre- and post-meeting support from Ms Camille Bou, Ms Noëmi Joncour, Ms Niree Kraushaar, Ms Jennifer Nicholson, Ms Solène Quennehen, and Ms Sandrine Ruiz.

Introduction

An IARC Advisory Group to Recommend Priorities for the *IARC Monographs* during 2025–2029 met in Lyon, France, on 19–22 March 2024. IARC periodically convenes such Advisory Groups to ensure that the *Monographs* evaluations reflect the current state of scientific evidence relevant to carcinogenicity.

Before the meeting, IARC solicited nominations of agents via the website of the *IARC Monographs* programme and announcements in the triannual *IARC Monographs* newsletter, and through direct contact with the IARC Governing Council and members of the IARC Scientific Council, WHO headquarters and regional offices, and previous participants in the *Monographs* programme. Nominations were also developed by the Advisory Group and by IARC personnel, including consideration of the recommended priorities remaining from a similar Advisory Group meeting convened in 2019 (IARC, 2019a).

The list of Advisory Group members and all other meeting participants is provided in Annex 1 (see https://monographs.iarc.who.int/wp-content/uploads/2024/01/Short_List_of_Participants_AGP2024.pdf); the preliminary agenda is provided in Annex 2. Dr Amy Berrington de González (United Kingdom) served as Meeting Chair, and Dr Scott Masten (United States of America) served as Meeting Vice Chair. The Subgroup Chairs were Parveen Bhatti (Canada), Renee Turzanski Fortner (Norway), Susan Peters (Kingdom of the Netherlands), Tiina Santonen (Finland), and Marianna G Yakubovskaya (Russian Federation).

Meeting preparation and conduct

Relevant background information was distributed before the meeting and through presentations during the meeting. This included introductory material about the *IARC Monographs* evaluation approach, which was refined in the 2019 Preamble to the *IARC Monographs* (IARC, 2019b).

The Advisory Group considered more than 210 unique candidate agents nominated for consideration. Draft summaries of the evidence supporting each nomination were prepared before the meeting, based on literature search terms developed to identify studies of human exposure (including any evidence of exposure in low- and middle-income countries, LMICs), cancer epidemiology, cancer bioassays in experimental animals, and carcinogen mechanisms (see Annex 3). This evidence was summarized in the drafts, in line with the evaluation approach described in the Preamble to the *IARC Monographs* (IARC, 2019b).

A complementary approach assessed nominations using a chemoinformatics, text mining, and chemical similarity analysis workflow (Guha et al., 2016; Barupal et al., 2021) to help reveal the extent of evidence across data streams, to support decisions on individual agents and groups of chemically related nominations, particularly for the mechanistic evidence stream. In brief, the workflow entailed linking agents to identifiers, performing automated literature searches and queries of relevant online databases supplemented by custom Google searches, and generating hierarchical clustering heat maps. The literature search terms and the heat maps used for this complementary approach are provided in Annex 4.

Information on whether the agent had a high production volume was obtained from the Organisation for Economic Co-operation and Development (OECD) and US Environmental Protection Agency (US EPA). The latest years of availability for these data were 2007 for OECD and 2023 for the US EPA.

At the meeting, the Advisory Group reviewed the writing assignments in subgroups organized by evidence stream (i.e. exposure characterization, cancer in humans, cancer in experimental animals, and mechanisms of carcinogenesis) and by type of agent (e.g. biological agents, complex exposures, occupations, pharmaceuticals, metals, particles and fibres, chemicals), to inform the development of recommendations on priorities. The subgroup sessions developed draft indications, for further discussion and adoption in plenary sessions, of which nominations are of highest priority and readiness for future review, on the basis of (i) evidence of human exposure and (ii) evidence or suspicion of carcinogenicity that could result in a new or revised classification. Agents not meeting these criteria were not recommended for evaluation.

Determining priority

As described in the Preamble to the *IARC Monographs* (IARC, 2019b), priority was assigned for:

(a) A new evaluation of an agent not previously evaluated by the *IARC Monographs* programme.

(b) An agent reviewed previously by the *Monographs* with new evidence of cancer in humans or in experimental animals or of carcinogen mechanisms, to warrant re-evaluation of the classification.

(c) An agent reviewed previously by the *Monographs* and established to be carcinogenic to humans with new evidence of cancer in humans that indicates a possible causal association with new tumour sites. In the interests of efficiency, the review included only human cancer evidence and, if relevant, information on absorption, distribution, metabolism and excretion (ADME) for these new tumour sites.

Priority was assigned on the basis of (i) evidence of human exposure and (ii) the extent and nature of the available evidence for evaluating carcinogenicity (i.e. the availability of relevant evidence on cancer in humans, cancer in experimental animals, and mechanisms of carcinogenesis to support a new or updated evaluation according to the Preamble to the *IARC Monographs*). Any of the three evidence streams could alone support prioritization of agents with no previous evaluation. For previously evaluated agents, the Advisory Group considered the basis of the previous classification as well as the potential impact of the newly available evidence during integration across streams (see Table 4 in the Preamble to the *IARC Monographs*; IARC, 2019b). Agents previously classified as *Group 1 – Carcinogenic to Humans* considered only human cancer evidence for tumour types currently with less than *sufficient* evidence. Agents without evidence of human exposure or evidence for evaluating carcinogenicity were not recommended for further consideration. Agents that were clearly not exogenous were also given no priority for evaluation.

Advice on topics related to prioritization

The IARC/WHO Secretariat invited the Advisory Group to provide advice on several questions related to prioritization of agents for evaluation. The first question was whether agents demonstrating emerging evidence of carcinogenicity should be added to the priorities list. The second question was whether the *IARC Monographs* programme should systematically re-appraise all the Group 1 agents to identify whether there are new cancer sites in humans with *sufficient* or *limited* evidence. The third question related to interpretation of a statement in the Preamble about evidence arising from a single human cancer study.

1. The Advisory Group endorsed the suggestion that agents not currently included on the prioritization list should be added if persuasive evidence emerges before the next Advisory Group meeting regarding evidence for cancer in humans, cancer in experimental animals, or mechanistic evidence.

2. The Advisory Group supported the systematic re-evaluation of the Group 1 agents to identify whether new cancer sites have *sufficient* or *limited* evidence in humans. This is based on the observation that all 10 Group 1 agents that were nominated for review by the 2024 Advisory Group on Priorities were deemed to have such evidence warranting a further *Monographs* review. The Advisory Group suggested that this be conducted (pending available funding) as a parallel process to the existing *Monographs* programme, so that it would not impact the progress of evaluation of new agents or of previously evaluated agents classified in Groups 2A, 2B, or 3.

3. The Preamble notes that "There is no formulaic answer to the question of how many studies of cancer in humans are needed from which to draw inferences about causality, although more than a single study in a single population will almost always be needed." Does the Advisory Group have advice about under what circumstances a study in a single population could be used for causal inference?

The Advisory Group noted examples where a single study could potentially be used for causal inference, including exposures for which there is a large study pooling different populations; exposures that occur only in a restricted geographic location (e.g., erionite or vermiculite, fibres that have shown very high risks for a signature tumour—mesothelioma); exposures for which only single informative highly exposed population is available (e.g., 1,2-dichloropropane in Japanese printing workers); tumour signature data (e.g., for aristolochic acid); or a well-conducted study of cancer as a late effect following a drug trial. Intervention trials might also qualify. The key issue a Working Group must consider in such a circumstance is whether chance, bias, and confounding can be ruled out when there is only a single study. The Advisory Group considered that the number of studies required might differ for an interpretation of *limited* vs. *sufficient* evidence.

Priorities for the *IARC Monographs* during 2025–2029

The types of recommendation made by the Advisory Group encompassed individual agents as well as groups of related agents. In this regard, the Advisory Group recommended to group some individual nominations, to expand the proposed nomination to encompass related agents meriting evaluation in some cases, and, in other instances, to narrow a group of nominated agents. It was further noted that consideration of information from new approach methods in toxicology, such as ToxCast, Tox21, and quantitative structure–activity relationships as well as read-across from structurally similar compounds, could be particularly informative in some cases.

Tabular summaries of the agents recommended for evaluation with *high* and *medium* priority are provided in Tables 1 and 2, respectively. Agents not recommended for evaluation are summarized in Table 3. Elaborations of these recommendations are provided in the sections that follow.

The Advisory Group recognized that agents related to the identified priorities may also warrant evaluation. Furthermore, in line with advice given in the section above, additional agents may merit consideration if new relevant evidence indicating an emerging carcinogenic hazard (e.g. from cancer epidemiology studies, cancer bioassays, and/or studies on key characteristics of carcinogens) becomes available in the next 5 years.

IARC will consider the recommendations of the Advisory Group when selecting agents for future *Monographs* evaluations according to the Preamble to the *IARC Monographs* (IARC, 2019b). The selection will be made consistent with coordination and communication mechanisms agreed between IARC and WHO headquarters and set out in the interim standard operating procedure adopted by the IARC Governing Council (see https://events.iarc.who.int/event/46/attachments/110/483/GC60_13_CoordinationWHO.pdf).

Table 1. Agents recommended for evaluation by the *IARC Monographs* with *high* priority

Agent name	Rationale
Agents not previously evaluated by the *IARC Monographs*	
Sleep disruption; Obesity[§]; Disinfection byproducts in water, including haloacetic acids; Metalworking fluids; Platinum-based chemotherapies as mechanistic class[¶]; Hair straightening products; Dibutyl phthalate; Artificial light at night*; Nitrogen dioxide*; GLP-1 analogues*; Sugar-sweetened beverage consumption*; Fonofos*	Relevant human cancer, animal cancer, and mechanistic evidence
Fusobacterium nucleatum; Human cytomegalovirus; Sedentary behaviour; Anthracyclines as mechanistic class[¶]; Epirubicin; BRAF inhibitors—Dabrafenib, Encorafenib, Vemurafenib; Tetracycline; Tofacitinib and other Janus kinase inhibitors; Ultra-processed food consumption; Perfluorohexanesulfonic acid; Cannabis smoking*; Ultrafine particles*; Assisted reproductive techniques*; Chlorpyrifos*	Relevant human cancer and mechanistic evidence
Electronic nicotine delivery systems; Ozone; Carbadox; Estragole; Alachlor; Cyfluthrin; Cypermethrin; Mancozeb; Neonicotinoid insecticides; Tebuconazole; Vinclozolin; Bisphenol A; Bisphenol S; Bisphenol F; Pentabromodiphenyl ethers; Hexafluoropropylene oxide dimer acid; Diisononyl phthalate; Methanol; 2,3-Butanedione; Carbon disulfide; Glycidamide; Triclosan	Relevant animal cancer and mechanistic evidence
Salmonella typhi; Taconite; Terbufos*	Relevant human cancer evidence
Metyltetraprole; Proquinazid; Chlorinated paraffins; Tris(chloropropyl)phosphate; Butyraldehyde	Relevant animal cancer evidence
Methamphetamine; Congo red; 2,4-Dihydroxybenzophenone; Cumyl hydroperoxide; Parabens; Electronic-waste work*; Polyhexamethyleneguanidine*	Relevant mechanistic evidence
Agents previously evaluated by IARC Monographs[†]	
Coal dust; Textured implants (breast and buttock); Paracetamol/ acetaminophen; Pyrethrins and pyrethroids; Permethrin; Carbaryl; Ethylenedithiocarbamates; Hair colouring products (personal use of)	New human cancer, animal cancer, and mechanistic evidence to warrant re-evaluation of the classification

Table 1. Agents recommended for evaluation by the *IARC Monographs* with *high* priority

Agent name	Rationale
Non-ionising radiation (radiofrequency)*	New human cancer and animal cancer evidence to warrant re-evaluation of the classification
Human papillomavirus β; *Opisthorchis felineus*; Textile manufacturing industry work; Indoor combustion of biomass; Inorganic lead compounds; Daunorubicin; Doxorubicin; Methotrexate; Atrazine; Acetaldehyde; Acrylamide; Merkel cell polyomavirus*; Progestogen-only contraceptives*; Clomiphene citrate*; Chlordecone*	New human cancer and mechanistic evidence to warrant re-evaluation of the classification
Zearalenone; Multiwalled carbon nanotubes; 5-Nitro-*o*-toluidine; *p*-Phenylenediamine; 4-Nitrotoluene; Butyl benzyl phthalate	New animal cancer and mechanistic evidence to warrant re-evaluation of the classification
Hepatitis D virus; Metallic nickel; Very hot beverages and food‡; Carbon tetrachloride*; Tetrachloroethylene*	New human cancer evidence to warrant re-evaluation of the classification
Piperonyl butoxide	New animal cancer evidence to warrant re-evaluation of the classification
Schistosoma japonicum; *S. mansoni*; Patulin; Safrole; Anaesthetics, volatile-isoflurane, sevoflurane, and desflurane; Malathion; 3,3′-Dimethoxybenzidine; 3,3′-Dimethylbenzidine; Isoprene; Bromate compounds; Fluoranthene*	New mechanistic evidence to warrant re-evaluation of the classification
*Helicobacter pylori**; Aflatoxins*; Tobacco smoking and second-hand smoke*; Outdoor air pollution*; Silica dust*; Asbestos*; Hormone replacement therapy*; Radon and its decay products*; Ethylene oxide*; Formaldehyde*	Group 1 carcinogen with evidence for new cancer sites (see Section 3 of Preamble to the *IARC Monographs*; IARC, 2019b)

Evidence of human exposure was identified for all agents. Agents are ordered by readiness for evaluation and then by type (infectious, biotoxins, complex exposures, occupations, particles, fibres, metals, pharmaceuticals, physical agents, nutritional agents, pesticides, dye-related, persistent organic pollutants, solvents, other chemicals)

†See https://monographs.iarc.who.int/list-of-classifications/ for current list of classifications

*Advised to conduct in latter half of 5-year period

§A minority of the Advisory Group considered that obesity is not an exogenous agent and therefore should not be evaluated

¶Advised to evaluate each pharmaceutical individually in the same volume

‡Very hot food has not been previously evaluated

Table 2. Agents recommended for evaluation by the *IARC Monographs* with *medium* priority

Agent name	Previous evaluation status
Toxoplasma gondii; Black cohosh extracts; α-Pinene; Outdoor combustion of biomass; Anatase-type nano-TiO_2; Anti-thymocyte globulin; Neonatal phototherapy; Bifenthrin; Biphenyl; Pendimethalin; Tattoos and permanent make up; Sulfolane	Agents not previously evaluated by the *IARC Monographs*
Fumonisin B1; Pyrrolizidine alkaloids; Selenium and selenium compounds; Xylenes; Ingested nitrate	Agents previously evaluated by the *IARC Monographs*[†]

Evidence of human exposure was identified for all agents. Agents are ordered by type (infectious, biotoxins, complex exposures, particles, metals, physical agents, pharmaceuticals, pesticides, dye-related, persistent organic pollutants, solvents, other chemicals)
[†]See https://monographs.iarc.who.int/list-of-classifications/ for current list of classifications

Table 3. Nominated agents not recommended for evaluation by the *IARC Monographs* during 2025-2029

Agent name	Rationale
Chronic circadian dysfunction; Insomnia; Alefacept; Diabetes; Reduction of sex hormones with human aging; Violation of tissue renewal/regeneration with human aging	No evidence of exposure, or not an exogenous exposure
Dysbiotic microbiota; Poor oral hygiene; Nitrate-reducing bacteria in tobacco; Severe acute respiratory syndrome coronavirus 2; Gene or cell therapy or vectors; Long working hours; Social isolation and loneliness; Cleaning products; Laboratory work and occupation as a chemist; Occupation as a pesticide applicator; Semiconductor industry work; Engineered stone fabrication; Acrylonitrile-butadiene-styrene particles emitted by 3D printers; Micro- and nano-plastics; Aluminium; Phosphorescent paints; Rare earth elements; Gadolinium-based contrast agents; Reversible acetylcholinesterase inhibitors; Glucocorticoids; Intense pulsed light; Dietary salt intake; Indole-3-carbinol; Isoflavones; Sucralose; Artificially sweetened beverage consumption; 2,4-Dichlorophenol; Ametryn; Boscalid; Phosmet; *S*-Ethyl-*N,N*,-dipropylthiocarbamate; Hexythiazox; Cinidon ethyl; Furmecyclox; *o*-Benzyl-*p*-chlorophenol; Ethyl anthranilate; Menthyl anthranilate; Methyl anthranilate; Red dye no. 3 (Erythrosine); Allyl alcohol; *p*-Cresol; 1,2-Cyclohexanedicarboxylic acid, diisononyl ester; 2,4-Dimethylphenol; 2,4,6-Tribromophenol; 2-Hydroxy-4-methoxybenzophenone; Atraric acid; Glutathione; Palmitic acid; Styrene-acrylonitrile (SAN) trimer	Existing evidence does not appear to support a first-time classification
Malaria; Cyclopeptide cyanotoxins; Night shift work; Carbon black, bulk and nanoscale; Dental amalgam; Androstenedione; Oxymetholone; Extremely low-frequency magnetic fields; 1,2-Dibromo-3-chloropropane; Glyphosate; *p*-Dichlorobenzene; 1,1-Dimethylhydrazine; 2,4-Diaminotoluene; *o*-Aminoazotoluene; *p*-Cresidine; Perfluorooctanesulfonic acid; Di(2-ethylhexyl) phthalate; Tris(2-chloroethyl) phosphate; Cumene; Dichloromethane; 1,2-Dihydroxybenzene; 1,4-Dioxane; Catechol; Furan; Nitrilotriacetic acid; Thioacetamide	Existing evidence does not appear to support a change in classification[†]

Agents are ordered by type (infectious, biotoxins, complex exposures, occupations, particles, metals, pharmaceuticals, physical agents, pesticides, dye-related, persistent organic pollutants, solvents, other chemicals)
[†]See https://monographs.iarc.who.int/list-of-classifications/ for current list of classifications

References

Barupal DK, Schubauer-Berigan MK, Korenjak M, Zavadil J, Guyton KZ (2021). Prioritizing cancer hazard assessments for IARC Monographs using an integrated approach of database fusion and text mining. Environ Int. 156:106624. https://doi.org/10.1016/j.envint.2021.106624 PMID:33984576

Guha N, Guyton KZ, Loomis D, Barupal DK (2016). Prioritizing chemicals for risk assessment using chemoinformatics: examples from the IARC Monographs on pesticides. Environ Health Perspect. 124(12):1823–9. https://doi.org/10.1289/EHP186 PMID:27164621

IARC (2019a). IARC Monographs on the identification of carcinogenic hazards to humans. Report of the advisory group to recommend priorities for the *IARC Monographs* during 2020–2024. Lyon, France: International Agency for Research on Cancer. Available from: https://monographs.iarc.who.int/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf, accessed September 2020.

IARC (2019b). Preamble to the *IARC Monographs* (amended January 2019). Lyon, France: International Agency for Research on Cancer. Available from: https://monographs.iarc.who.int/iarc-monographs-preamble-preamble-to-the-iarc-monographs/, accessed September 2020.

Priorities for *IARC Monographs* during 2025 – 2029

001 Dysbiotic microbiota

Current IARC/WHO classification

Dysbiotic microbiota has not been previously evaluated by the *IARC Monographs* programme. Dysbiotic microbiota was given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a).

Exposure characterization

The human body can be colonized by many microorganisms, which are collectively designated the microbiota. These microorganisms include bacteria, archaea, fungi, and viruses. A dysbiotic microbiota is characterized by its capacity to produce a disruption in the microbiota of the gut or other organs or tissues. The prevalence of a dysbiotic microbiota has not been well characterized, since it varies according to the type of host organism in which it is studied. Exposures such as diet, drugs (e.g. antibiotics), food additives, or hygiene may affect the profile of an organism's microbiota; such a modification can have pathogenic implications.

Cancer in humans

The microbiota of the host may increase, decrease, or have no effect on cancer susceptibility. Assigning causal roles in cancer to specific microbes and microbiota profiles, unravelling the interactions between host, microbiota, and environmental factors that are associated with carcinogenesis, and exploiting such knowledge for cancer diagnosis and treatment are areas of intensive research (Hrncir, 2022). However, in reviews of the role of dysbiosis in the development of cancer, numerous microorganisms in the microbiota are usually considered; this highlights the difficulty in ascribing causality to one particular microorganism. An example is a recent review conducted by Cheng et al. (2020), in which the following were examined for their relation to colorectal cancer: *Streptococcus bovis*, enterotoxigenic *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Enterococcus faecalis*, *Escherichia coli*, and *Peptostreptococcus anaerobius* (Cheng et al., 2020). Concerning prostate cancer, case–control studies including a small number of cases ($n \leq 20$) indicated possible associations with *Bacteriodes massiliensis*, *Akkermansia muciniphila*, and species of *Ruminococcaceae* and *Streptococcus* (Fujita et al., 2023). A recent review of studies examined the potential role of dysbiosis in the development of hepatocellular carcinoma (HCC); however, attribution of risk may be difficult, given the presence of many microorganisms (Spanu et al., 2022). Note that *Fusobacterium nucleatum* is reviewed next in the present report (agent 002).

Cancer in experimental animals

Zackular et al. (2013) demonstrated that when gut microbiota from mice with tumours were transplanted into C57BL/6 mice in a germ-free facility, the rate of tumorigenesis in the colon increased significantly. It was shown that manipulation of the intestinal microbiota with antibiotic treatment led to a decrease in the number and size of tumours in colorectal cancer-susceptible mice when antibiotics were administered (Zackular et al., 2013; Schulz et al., 2014).

Mechanistic evidence

Several studies demonstrated that dysbiotic bacteria are involved in mechanisms leading to carcinogenesis. The dysbiotic microbiota releases specific toxins that could directly induce DNA damage

and hinder DNA repair, and modulate tumorigenesis (Nesić et al., 2004; Meira et al., 2008; Wu et al., 2009; Cuevas-Ramos et al., 2010; Arthur et al., 2012). An increase in mutation frequency was shown to activate oncogenes or suppress tumour suppressor genes (Jackson and Loeb, 2001), which could accelerate genomic instability and result in colon cancer (Kawanishi et al., 2006; Mantovani and Pierotti, 2008; Elinav et al., 2013; Grivennikov, 2013; Kostic et al., 2013; Schwabe and Jobin, 2013; Watson et al., 2013; Esteban-Jurado et al., 2014). It has been shown in several studies that dysbiotic microbiota could induce DNA damage, either directly or through increased oxidative stress, chronic inflammation, or an activated signalling pathway (Secher et al., 2010; Olszak et al., 2012; Rubinstein et al., 2013; Chen et al., 2014a; Ray and Kidane, 2016; Sacdalan and Lucero, 2021; Gupta et al., 2022a).

A decrease in lactic acid-producing bacteria and an increase in potentially pathogenic bacteria may increase the risk of chronic inflammation and colitis-associated development of colorectal cancer (Ooi et al., 2013; Assa et al., 2014, 2015).

Biswas et al. (2012) considered that without nucleotide binding oligomerization domain containing 2 (NOD2) protein, a key player in the immune response, the sensing and recognition of bacterial muramyl dipeptide (MDP) are impaired and that these bacteria cannot then be neutralized, so they continue to reproduce in the gut, causing dysbiosis. This dysbiosis alters the host–microbial interactions in the ileal mucosa, leading to an increased inflammatory response and, potentially, cancer development.

Vitamin D and vitamin D receptor play a role in the composition of the gut microbiota and cancer development (Russell et al., 2011; Assa et al., 2014, 2015; Jin et al., 2015). Li et al. (2015a) found that a diet high in fat and sugar resulted in dysbiosis in mice with altered host barrier function.

Several studies have also demonstrated the relation between NOD2 and commensal bacteria in rodents (Petnicki-Ocwieja et al., 2009; Shaw et al., 2011; Couturier-Maillard et al., 2013; Li et al., 2015a). In addition, a single nucleotide polymorphism (SNP) in the ATG16L1 gene was found to be involved in inflammatory responses in both mice and humans. Cadwell et al. (2008) found, in humans and in mice that were homozygous for the Crohn disease risk allele, that there were no morphological abnormalities in the ileum, but abnormalities in Paneth cell granule secretion were displayed. Such mutations caused a defect in an interleukin (IL), IL-10 mediated anti-inflammatory signalling cascade in both IL-10R$^{-/-}$ mice and humans, which resulted in severe intestinal inflammation and increased secretion of proinflammatory cytokines, most notably of tumour necrosis factor alpha (TNFα), from peripheral blood mononuclear cells (PBMCs) (Glocker et al., 2009; Kabi et al., 2012; Gassas et al., 2015).

El Saie et al. (2022) investigated the dysbiotic microbiome metabolites that may lead to bronchopulmonary dysplasia (BPD). Hyperoxia and lipopolysaccharide (LPS) interaction altered the lung microbiome and metabolome, mediating the BPD lung injury sequence. Zackular et al. (2013) demonstrated that gut microbiota extracted from mice with tumours and transplanted into C57BL/6 mice, in a germ-free facility, induced tumorigenesis in the colons of the mice receiving the transplanted microbiota by inducing cell proliferation.

Summary

In humans, the microbiota interacts with the host immune system in multiple ways to influence the development of diseases, including cancer. For instance, the gut microbiota is involved in the initiation, progression, and chemoresistance of several cancers, including colorectal cancer. There is also a possible role of microbiota in the promotion of HCC, mediating increased proliferation. From the perspective of cancer in humans and experimental animals, the agent is too poorly defined to support an evaluation of its carcinogenicity. There is only sparse evidence that a dysbiotic microbiota induces tumorigenesis in experimental animals.

There is some mechanistic evidence that the dysbiotic microbiota exhibits key characteristics (KCs) of carcinogens, including genotoxicity, induction of oxidative stress, and alteration of cell proliferation, along

with evidence of altered immune and inflammatory responses in experimental systems. Although a large body of mechanistic evidence implies that a dysbiotic microbiota is carcinogenic, the definition of the exposure is unclear, and it is unlikely that an evaluation would find epidemiological evidence supporting causality. For an effective evaluation, it would probably be necessary to define exactly which microorganisms should be evaluated. The Advisory Group therefore considered that an *IARC Monographs* evaluation of dysbiotic microbiota is unwarranted at present.

Recommendation: No priority

002 *Fusobacterium nucleatum*

Current IARC/WHO classification

Fusobacterium nucleatum has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

F. nucleatum is a Gram-negative anaerobic commensal bacterium (Brennan and Garrett, 2019). It is found ubiquitously in the oral cavity but is absent or infrequently detected elsewhere in the body under normal conditions (Han, 2015).

Cancer in humans

A large number of relatively recent studies have been conducted to examine the prevalence of *F. nucleatum* in tumour specimens or in the oral cavities of people with cancer, compared with controls. These studies have demonstrated associations with cancer at several organ sites, in particular, the colorectum, oral cavity, and breast. However, one recent nested case–control study (Debertin at al., 2023) found mixed evidence of an association between increased risk of colorectal cancer and an increased serum antibody immunoglobulin G (IgG) response. Another recent nested case–control study (Lo et al., 2021a) did not find an association between *F. nucleatum* and colorectal cancer. It currently remains unclear, however, whether serum antibody IgG response is a valid measure of exposure.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

At least four studies showed that a higher abundance of *F. nucleatum* accelerates tumour growth and metastasis in colon and breast cancer (Kostic et al., 2013; Rubinstein et al., 2013; Bullman et al., 2017; Parhi et al., 2020). In a study by Queen et al. (2021), designed to establish stably colonized mouse models, colonization with *F. nucleatum* induced chronic inflammation (KC6) but did not promote tumorigenesis in germ-free (GF) $Apc^{Min/+}$ mice (Queen et al., 2021).

The mechanisms that have been uncovered using these models include: (i) the promotion of proliferation (which supports KC10); (ii) alteration of the tumour microenvironment to become pro-tumorigenic; (iii) suppression of the immune system in the tumour microenvironment (which supports KC7); and (iv) the induction of inflammation (which supports KC6). Several more papers report the compromise of different barriers by *F. nucleatum*, allowing the bacteria to migrate and establish colonies within tumour sites (Little et al., 2023). However, an in-depth analysis of these studies is required, since the body of evidence includes several different types of knockout mice and diverse experimental designs.

Several published reports support these findings, pointing mostly towards KC6, KC7, and KC10. The presence of intratumour *F. nucleatum* promoted cancer progression through the C-X-C motif chemokine ligand 1 (CXCL1)–C-X-C motif chemokine receptor 2 (CXCR2) axis in a pancreatic cancer model (Hayashi

et al., 2023). It was shown that intratumour *F. nucleatum* suppressed tumour-infiltrating $CD8^+$ T cells by recruiting myeloid-derived suppressor cells (MDSCs), resulting in tumour progression in a pancreatic cancer model in mice – importantly, tumour growth in this model was suppressed by MDSC depletion and the use of cytokine inhibitors (Hayashi et al., 2023). It was also shown that the elimination of *F. nucleatum* using antibiotics in nanogels inhibited tumour growth, resulting in increased animal survival (Xie et al., 2024a). *F. nucleatum* subspecies *polymorphum*, isolated from saliva samples collected from patients with oral carcinoma, was shown to promote oral squamous cell carcinoma (SCC) by activating Yes-activating protein (YAP) in a mouse tongue cancer model (Yamamoto et al., 2023). YAP is a transcriptional coregulator that promotes gene transcription associated with cellular proliferation and apoptosis suppression. Concerning a pro-tumorigenic environment, infection with *F. nucleatum* was shown to alter the microbiota of the colonic mucosa by enriching for pathogens related to the development of colorectal carcinoma (Wu et al., 2022a). Several recent reviews were available: Chiang et al. (2023a), Little et al. (2023), and Pandey et al. (2023). Galeano Niño et al. (2022) reported that spatial and cellular heterogeneity in cancer cells is influenced by the microbiota and its effect on the surrounding environment.

Summary

Fusobacterium nucleatum is a commonly occurring bacterium, primarily found in the oral cavity and the gut. It is strongly linked to the occurrence of periodontal disease, a condition that is more common in people with poor oral hygiene practices. The literature on *F. nucleatum* and cancer is extensive (more than 800 papers) and the epidemiological evidence from case–control studies is consistent with the organism being a possible carcinogen. However, one prospective study did not reveal any association, but it is not clear to what extent serum antibody IgG response to the presence of *F. nucleatum* is a valid measure of exposure. No studies of complete carcinogenesis were available in experimental animals. The mechanistic evidence appears to be convincing, since results observed in different systems point towards consistent mechanisms, with coherent findings, while the examined studies cover a broad and varied range of relevant end-points in mammalian species. The Advisory Group therefore considered an *IARC Monographs* evaluation of *Fusobacterium nucleatum* to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

003 Poor oral hygiene

Current IARC/WHO classification

Poor oral hygiene has not been previously evaluated by the *IARC Monographs* programme. Poor oral hygiene was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of evidence of human cancer obtained from case–control studies.

Exposure characterization

As noted in the 2019 Advisory Group report (IARC, 2019a):

> Oral hygiene concerns keeping one's oral cavity clean, usually by regular brushing of teeth and cleaning between teeth. The lack of oral hygiene promotes commensal bacteria-harbouring plaque and calculus on dentition, and thus this is one among many risk factors for oral health problems, including dental caries, periodontal (gum) disease, tooth loss, and oral leukoplakia. The presence of these problems is often used as a proxy for poor oral hygiene, because they can be

objectively measured and do not rely on self-reports; however, their presence may have other drivers reflecting general poor health.

Regular oral hygiene, including use of toothpaste, is less common in low- and middle-income countries than in high-income countries, and is less common in older adults than in younger adults in general. The percentage of the older population who practice regular oral hygiene ranges from 7.9–41.7% in Africa to 32–84% in south-eastern Asia and 22.2–93% in Europe. Traditional oral self-care using chew sticks or powder is common in low- and middle-income countries.

Cancer in humans

Poor oral hygiene was assigned a *high* priority by the 2019 Priorities Advisory Group (IARC, 2019a). However, consideration needs to be given as to the appropriate agent for evaluation. Researchers in this area have taken one or more of the following approaches to defining exposure.

1. *Behaviours related to hygiene*. As noted in the 2019 Advisory Group report (IARC, 2019a), behaviours such as minimal brushing or non-brushing of teeth have been investigated as possibly associated with specific types of cancer. More studies along these lines have appeared since that report. In the *IARC Monographs* programme, behaviours are generally not evaluated as potential carcinogens, with exceptions being those behaviours related to the use of harmful substances (e.g. tobacco, opium) and various occupations. Evaluation of such behaviours as non-brushing of teeth would therefore represent, to some degree, a departure for the *IARC Monographs* programme.

2. *Health-related conditions*. Several studies, including those that considered the role of behaviours, as summarized in item (1), have been conducted to examine relations between oral or dental health conditions, particularly periodontitis and tooth loss, and the occurrence of specific types of cancer. While such conditions may lie on a pathway that leads to cancer, in the *IARC Monographs* context they would normally be viewed as pathological health states in their own right and therefore not eligible for evaluation as carcinogens.

3. *Infectious pathogens*. As noted in the 2019 Advisory Group report (IARC, 2019a), some infectious pathogens of the head and neck are already classified as *carcinogenic to humans* (Group 1), e.g. human papillomavirus (for oral cancer) and Epstein–Barr virus (EBV, for nasopharyngeal cancer). Other pathogens, particularly bacterial species found in the oral cavity that are understood to contribute causally to periodontitis and related conditions, have become a more recent focus of investigation. This line of investigation builds on expanding interest in the role of perturbations in the microbiome at various body sites as causal factors in a range of health conditions, including cancer. See, for example, the systematic reviews by Su Mun et al. (2021) and Reitano et al. (2021), reporting, respectively, on findings for oral cancer and digestive cancers. Virtually all of the reviewed studies were case–control studies, and a high proportion were recent, with over half of those included in the systematic reviews having been published in the previous 3 years. Some studies have also focused on relations between specific oral bacterial species and cancer, with a particular interest in the role of the periodontitis pathogens *Porphyromonas gingivalis* and *Fusobacterium nucleatum* (agent 002 in the present report).

A large number of studies, mostly case–control studies, have been designed to consider one or more of these types of factor. For example, a systematic review by Bai et al. (2023) focused on cancers of the oral

cavity at multiple sites and found associations with poor or absent dental hygiene behaviours. In several systematic reviews, consistent associations between periodontitis and cancer have been identified, with relative risks in the range 1.5–4, varying by cancer site (e.g. Corbella et al., 2018, and Li et al., 2021a for colorectal cancer). Studies of perturbations in the oral microbiome produced conflicting results, with levels of some bacterial species observed to be more elevated in tumour specimens while other species were found at lower levels, compared with controls. Associations with the presence of *Fusobacterium nucleatum* in tumour tissue, as opposed to the oral cavity, have been summarized in systematic reviews on cancers of the head and neck (Bronzato et al., 2020) and colorectum (Gethings-Behncke et al., 2020).

As noted, the options of defining the exposure as either a behaviour (poor dental hygiene practice) or a disease (periodontitis) are not consistent with the usual approach taken in the *IARC Monographs* programme to define exposures. Therefore, the most likely candidates for evaluation would be one or more of the bacterial species found in the oral cavity, particularly those responsible for inflammatory diseases, such as periodontitis. Issues to be addressed in examining such bacterial species as potential cancer-causing agents include the following. Many species of bacteria are present in the oral cavity microbiome, and there are complex relations between them and, so far, little standardization over testing. In the case–control study designs that predominate in this field, there is a possibility that the occurrence or detection of bacterial species could be influenced by the cancer itself or its treatment, raising the issue of reverse causation. Known risk factors for specific cancers, including diet, alcohol, and tobacco, might also be associated with the oral microbiome; this should be carefully taken into account.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

Specific pathways proposed for the action of oral bacteria in causing cancer are the creation of an inflammatory environment and the suppression of immunological function responsible for surveillance of abnormal cells (reviewed e.g. for *Fusobacterium nucleatum* by Alon-Maimon et al., 2022).

Summary

The most appropriate agents for consideration by the *IARC Monographs* programme are the pathogenic bacterial species recognized as causes of chronic periodontitis and related conditions. *Fusobacterium nucleatum*, which appears to be the best-studied specific agent in this regard, is described elsewhere in the present report (agent 002). The Advisory Group therefore considered that an *IARC Monographs* evaluation of poor oral hygiene is unwarranted at present.

Recommendation: No priority

004 *Helicobacter pylori*

Current IARC/WHO classification

Helicobacter pylori (infection with) was classified by IARC as *carcinogenic to humans* (Group 1), most recently in *IARC Monographs* Volume 100B in 2009 (IARC, 2012a). There is *sufficient* evidence that infection with *H. pylori* causes stomach cancer (including both cardia and non-cardia) and low-grade B-cell mucosa associated lymphoid tissue (MALT) gastric lymphoma in humans.

Exposure characterization

H. pylori is a Gram-negative helical bacterium. It is common throughout the world; in most countries, over one third of the population is infected (Eusebi et al., 2014). However, it is most common in lower-

income countries in Asia and Africa, where it may be found in over 80% of the population. Active pharmaceutical intervention has reduced the exposure prevalence in some high-income countries, but exposure remains widespread.

Cancer in humans

Since the last evaluation, given in *IARC Monographs* Volume 100B, intense interest has been focused on understanding the nature and potency of different strains of *H. pylori* in causing cancer of the stomach and gastric cardia. A recent study estimated that, in Asia, 79% of non-cardia gastric cancers and 62% of cardia gastric cancers are caused by infection with *H. pylori*, with high percentages in Europe and North America as well (Gu et al., 2023). The evidence for a causal role for *H. pylori* in MALT gastric lymphomas also remains strong.

For other cancers, increasing attention has been paid to other digestive tract cancers, including cancers of the oesophagus, pancreas, bile ducts, and colorectum. In a systematic review, Panthangi et al. (2022) identified positive associations between *H. pylori* infection and cancers of the pancreas in 6 of 15 identified studies, including some case–control studies in which exposure was measured after cancer diagnosis. Findings from the reviewed prospective cohort studies or nested case–control studies (in which serum infection was analysed before cancer diagnosis) were mixed. For example, positive associations were seen in a nested case–control study conducted among male smokers in Finland (Stolzenberg-Solomon et al., 2001); however, this finding did not persist in a later analysis of this cohort using a different exposure metric and with a longer period of follow-up (Yu et al., 2013). In a separate meta-analysis, a positive association with pancreatic cancer was observed for cytotoxin-associated gene A (CagA)-negative strains of *H. pylori* (meta-odds ratio, meta-OR, 1.30; 95% confidence interval, CI, 1.02–1.65), but not overall or for CagA-positive strains (Schulte et al., 2015). In a summary review of meta-analyses, Maisonneuve and Lowenfels (2015) concluded that there was "moderate" evidence of a role of *H. pylori* in pancreatic cancer.

Zumkeller et al. (2006) reported a meta-OR of 1.4 (95% CI, 1.1–1.8), based on 11 studies of colorectal cancer, but expressed some concerns about publication bias. By contrast, there is substantial evidence of an inverse association between oesophageal adenocarcinoma, although this has been seen as somewhat paradoxical, given the positive association between *H. pylori* infection and gastroesophageal reflux disease and Barrett oesophagus, which are both strong risk factors for oesophageal adenocarcinoma (Polyzos et al., 2018).

There have also been recent analyses of respiratory cancers in relation to *H. pylori* infection. Two meta-analyses yielded meta-ORs of 3.28 (95% CI, 1.91–5.63) for larynx cancer (Zhou et al., 2016) and 2.29 (95% CI, 1.34–3.91) for lung cancer (Mounika, 2013). For both larynx and lung cancer, prospective studies have been unavailable; thus, the temporality of the association remains unclear.

Mechanistic evidence

Some evidence of *H. pylori* infection in extragastric tissues provides support for some of the mechanisms, such as inflammation and apoptosis, observed for cancers within the gastrointestinal tract; this evidence seems to be growing (Lim et al., 2023a).

Summary

For several cancer types, there appears to be emerging evidence of an association with *H. pylori* infection. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of *Helicobacter pylori* to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

005 *Salmonella typhi*

Current IARC/WHO classification

Salmonella typhi (*S. enterica* serovar Typhi) has not been previously evaluated by the *IARC Monographs* programme. *S. typhi* was given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a).

Exposure characterization

S. typhi is a bacterium that is excreted in faeces and mainly transmitted by faecally contaminated water, sewage, and food items (Monack, 2012). Transmission may also occur in food prepared by a chronic carrier. Humans are the only reservoir of the infection. About 2–5% of infected individuals may develop a chronic carrier state, in which the bacterium persists in the gall bladder (Levine et al., 1982). Annually, there are an estimated 20 million cases of typhoid fever globally (Crump et al., 2004). India and sub-Saharan Africa are considered areas of high endemicity (Gunn et al., 2014).

Cancer in humans

There have been a number of studies, as well as several systematic reviews and meta-analyses (Nagaraja and Eslick, 2014; Koshiol et al., 2016; Duijster et al., 2021) to examine the relation between *S. typhi* infection and gall bladder cancer. Nagaraja and Eslick (2014) reviewed published studies, in which people with and without gall bladder cancer were compared as to the presence of *S. typhi* antibodies or positive culture, as well as a smaller number of cohort studies that included follow-up for people with chronic infection. These studies were generally consistent, demonstrating ORs for either antibody or culture positivity that were well above 1.0, with meta-analytic ORs of 4.28 (95% CI, 1.84–9.96) for chronic carriers and 5.86 (95% CI, 3.84–8.95) on restriction to control participants without gall stones. Limitations noted were small numbers of case participants, a lack of well-matched controls (with or without gallstones), and a lack of homogeneous methods for the detection of *S. typhi*.

Few studies have been conducted to examine the link between *S. typhi* and cancers in other sites, including liver and large bowel. Mellemgaard and Gaarslev (1988) calculated standardized incidence ratios (SIRs) for different cancers and found no increased risk for liver or colon cancer, although the number of cases was small.

Cancer in experimental animals

No studies in experimental animals were available to the Advisory Group.

Mechanistic evidence

Catalano et al. (2023), in an intestinal stem cell murine model, reported that *Salmonella enterica* serovar Typhimurium can alter Wnt/b-catenin signalling by the translocation of antigens through a pathogenicity island (Spi) 2–encoded type III secretion system, thus allows the dissemination of the bacteria in the liver and bloodstream. Increased mRNA expression of Wnt family members (Wnt2, Wnt3, Wnt6, Wnt9a, and Wnt11) and WNT signaling proteins Fzd2, Fzd4, Fzd6, Fzd7, Fzd8, and Fzd9 genes were observed..

The induction of Wnt2 and Wnt11 expression was attributed to *Salmonella* AvrA, a bacterial effector involved in the control of β-catenin ubiquitination and stabilization. The data suggested a role of *S. typhi* in the activation of the Wnt pathway, leading to cholangiocarcinoma. Another study showed that *S. typhi* plays a role in colon cancer transformation by modulating mitogen-activated protein kinase (MAPK)-Akt and Wnt/β-catenin signalling pathways (Mughini-Gras et al., 2018). *S. typhi* has been shown to alter cell signalling pathways and regulate their expression (Scanu et al., 2015). *S. typhi* infection releases specific toxins, called cytolethal distending toxins, which cause DNA damage and cell cycle inhibition, leading to gall bladder cancer (Di Domenico et al., 2017; Sheweita and Alsamghan, 2020; Li et al., 2021b). Jahan et

al. (2022) postulated that *S. typhi* is an intracellular pathogen that evades the innate detection and immune response of the host body, leading to systemic dissemination, and contributing to the damage of epithelium cells.

Summary

S. typhi has been successfully controlled in many countries by sanitary measures. *S. typhi* is a pathogen with a high pathogenic capacity in both humans and animals and is associated with a high rate of cancer in patients with chronic typhoid-induced typhoid fever disease. Gall bladder cancer is commonly associated with *S. typhi*, mainly owing to its ability to form biofilms in cholesterol coagulates in the biliary stream. There is epidemiological evidence of a potentially strong association with gall bladder cancer, although the published studies have limitations. Results derived from studies of cancer in experimental animals are sparse. There is mechanistic evidence indicating that *S. typhi* exhibits certain KCs, such as cell proliferation, DNA damage, inflammation, and modified signalling pathways that lead to cancer. The Advisory Group therefore considered an *IARC Monographs* evaluation of *Salmonella typhi* to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

006 Nitrate-reducing bacteria in tobacco

Current IARC/WHO classification

Nitrate-reducing bacteria in tobacco have not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Nitrate-reducing bacteria, such as those in the *Enterobacteriaceae* family and in the *Corynebacterium* and *Staphylococcus* genera, play a crucial role in tobacco products by converting nitrate to nitrite under anaerobic conditions during fermentation, ageing, or storage of tobacco. These bacteria's dissimilatory nitrate reductases (respiratory nitrate reductases and periplasmic nitrate reductases) are key in generating and exporting nitrite, which reacts with tobacco alkaloids to form tobacco-specific nitrosamines (TSNAs), such as *N*′-nitrosonornicotine (NNN) and 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK), both classified by IARC as *carcinogenic to humans* (Group 1). Tobacco smoking and smokeless tobacco, also classified as *carcinogenic to humans* (Group 1) and used worldwide, lead to exposure to TSNAs (Liu et al., 2023a; Stanfill et al., 2023). However, no specific data on exposure circumstances for this agent were available to the Advisory Group.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

There is no mechanistic evidence that the nitrate-reducing bacteria in tobacco, per se, exhibit any of the KCs. It has been shown that TSNAs are genotoxic and that these TSNAs are formed when bacteria convert nitrate to nitrite in tobacco products (Stanfill et al., 2023). However, these bacteria are not fully characterized.

Summary

Apart from their involvement in the formation of various carcinogenic compounds in tobacco products, there is an absence of evidence that nitrate-producing bacteria in tobacco have a direct carcinogenic effect by themselves or that they exhibit the KCs. The Advisory Group therefore considered that an *IARC Monographs* evaluation of nitrate-reducing bacteria in tobacco is unwarranted at present.

Recommendation: No priority

007 Hepatitis D virus

Current IARC/WHO classification

Hepatitis D virus (HDV) was evaluated by IARC as *not classifiable as to its carcinogenicity to humans* (Group 3) in *IARC Monographs* Volume 59 in 1993 (IARC, 1994a). HDV was given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a).

Exposure characterization

HDV is a bloodborne RNA virus that can only infect those who are already infected with hepatitis B virus (HBV), i.e. positive for hepatitis B surface antigen (HBsAg), so all HDV-positive individuals will also be positive for HBsAg. An estimated 12 million to 72 million people are infected with HDV worldwide (Negro et al., 2023). The global estimated anti-HDV prevalence is 4.5% (95% CI, 3.6–5.7) among HBsAg-positive people. Regional estimates of anti-HDV for HBsAg-positive people range from 3.0% in Europe to 6.0% in Africa (Stockdale et al., 2020). The virus is spread through injecting drugs, needle-stick injuries, haemodialysis, or sexual exposure.

Cancer in humans

As HBV is a known carcinogen, the assumption that coinfection with HDV could increase the likelihood of developing liver cancer in individuals infected with both is plausible. However, data reviewed up to 1993 were not conclusive on this point. Since then, several large cohort studies of HBV-infected individuals have found that those who are coinfected with HDV are at an increased risk of liver cancer. All of the informative cohort studies were published since the previous IARC evaluation, almost all since 2000, whereas most of the negative studies were case–control investigations, many published before the IARC evaluation. Of the cohort studies, a study in France (Mallet et al., 2017), among > 48 000 patients who were chronically infected with HBV, reported a relative risk of 1.53 (95% CI, 1.39–1.68) for liver cancer for those who were coinfected with HDV. A published meta-analysis (Alfaiate et al., 2020) reported a pooled OR for liver cancer of 1.28 (95% CI, 1.05–1.57), although there was considerable heterogeneity between the studies. When stratified by study type, the summary OR was 1.67 (95% CI, 1.28–2.18) for 25 cohort studies and 1.10 (95% CI, 0.82–1.49) for 68 case–control studies. Analyses restricted to 11 prospectively recruited cohort studies found a relative risk of 2.77 (95% CI, 1.79–4.28). Further analyses of studies that had reported findings among individuals negative for infection with hepatitis C virus (HCV) (classified as *carcinogenic to humans* (Group 1) and a cause of liver cancer) found a relative risk of liver cancer in relation to HDV of 1.62 (95% CI, 1.04–2.54). A similar analysis for those negative for HIV, also classified as *carcinogenic to humans* (Group 1), strongly associated with an increased risk of liver cancer, found a relative risk of 1.60 (95% CI, 1.09–3.05). A more recent analysis of specimens stored for 1556 HBV-positive individuals with HIV as part of the pooled Swiss HIV and EuroSIDA cohort studies found a hazard ratio (HR) of 6.3 (95% CI, 2.5–16.0) for HCC for those who were positive for HDV, compared with those who were not (Béguelin et al., 2023).

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

Uncertainty remains as to whether HDV has direct oncogenic effects, since it relies on HBV for infectivity and the machinery needed for replication (Rizzetto et al., 1977). HDV may, instead, enhance the effects of HBV in the development of HCC (Puigvehí et al., 2019). In a study of mice, HBV–HDV coinfection was found to elicit a stronger inflammation response than HBV mono-infection (Giersch et al., 2015). One of the pathways by which HBV induces inflammation is through activation of nuclear factor kappa ß (NF-κB); HDV has also been observed to activate NF-κB signalling (Park et al., 2009a).

HDV may also elicit epigenetic changes that contribute to the occurrence of cancer. In a cell-line study, HDV was shown to induce expression of DNA methyltransferase 3 β, altering DNA methylation patterns that might have affected cell cycle progression (Benegiamo et al., 2013). In a study of liver specimens from patients with hepatitis-associated HCC, dysregulation of the Y3 long non-coding RNA (lncRNA) was observed among those with HDV-related HCC (Zhang et al., 2016a).

Summary

A review of the cohort studies that have been performed since the last evaluation, in 1993, finds that there appears to be substantial evidence for an etiological role of HDV infection. There is a lack of evidence for cancer in experimental animals. Mechanistic evidence remains sparse. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of HDV to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years).

008 Human cytomegalovirus

Current IARC/WHO classification

Human cytomegalovirus (HCMV) has not been previously evaluated by the *IARC Monographs* programme. HCMV was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of mechanistic evidence related to activation of pro-oncogenic pathways.

Exposure characterization

HCMV is a ubiquitous human herpesvirus that is associated with widespread persistent infection (Sinclair and Sissons, 2006). The seroprevalence of HCMV ranges from 40% to 90% (Sinclair and Sissons, 2006; Fowler et al., 2022). Seroprevalence has been found to be higher in women compared with men, older compared with younger age groups, and in LMICs compared with high-income countries (Fowler et al., 2022). Infection occurs via body fluids (e.g. blood, saliva, semen, urine) or through transplacental transfer, blood transfusion, or organ transplantation (de Melo Silva et al., 2021; Fowler et al., 2022). Infected individuals will remain infected for life; however, viral replication can be suppressed by the immune system (Savva et al., 2013).

Inside the body, the virus infects several cell types, particularly lymphocytes. As most tissues will contain blood (including lymphocytes), it is particularly difficult to interpret studies based on the presence of HCMV in tissue samples (Vanarsdall and Johnson, 2012; Griffiths and Reeves, 2021).

Cancer in humans

Associations between cancer and HCMV have been investigated in a variety of studies evaluating cancers of the brain, breast, colorectum, stomach, and other sites. Several reviews, systematic reviews, and

meta-analyses have been published (Bai et al., 2016; Farias et al., 2019; Richardson et al., 2020). In a meta-analysis, Farias et al. (2019) pooled data from 32 studies, with a total of 2190 participants or specimens, and noted a significant association (adjusted OR, 3.0; 95% CI, 1.7–5.3) between HCMV and glioma. In another meta-analysis, Bai et al. (2016) pooled data from 11 studies to examine the prevalence of HCMV in tumour tissues and determine the association between HCMV and colorectal cancer. The tumour tissues showed evidence of a significantly higher rate of virus infection than that for normal tissues from controls (OR, 6.59, 95% CI, 4.48–9.69). Richardson et al. (2020) observed mixed evidence regarding a role for HCMV infection in relation to breast cancer risk.

Cancer in experimental animals

No studies of HCMV in humanized animal models were available to the Advisory Group.

Mechanistic evidence

Studies of human cell lines have demonstrated that HCMV infection exhibits evidence of various KCs, including alteration of cellular proliferation, angiogenesis, metabolic reprogramming, inhibition of apoptosis, and immortalization (Nauclér et al., 2019). These effects appear to be driven by several oncogenes encoded in the HCMV genome. In a study of peripheral blood lymphocytes (PBLs) collected from 20 smokers and 20 non-smokers, infection of PBLs with HCMV was associated with a doubling in the frequency of chromosome aberrations, independent of smoking status (Albrecht et al., 2004). Many human cell-line studies have also found HCMV infection to induce chromosome aberrations (Nauclér et al., 2019), which appear to be driven by expression of HCMV oncogenes (Siew et al., 2009). Additionally, these oncogenes have various immunosuppressive effects that influence both innate and adaptive immune responses. For example, HCMV viral proteins have been observed to suppress natural killer (NK) cell activity (Tomasec et al., 2000) and antigen presentation to T cells (Yang and Bjorkman, 2008).

Summary

The literature was reviewed by the 2019 Advisory Group on Priorities; a review of the evidence that has accumulated since then has revealed convincing evidence for an association between HCMV and glioma and colorectal cancer. There is a lack of evidence regarding cancer in experimental animals. Mechanistic evidence related to the activation of pro-oncogenic pathways remains compelling. The Advisory Group therefore considered an *IARC Monographs* evaluation of human cytomegalovirus to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

009 Human papillomavirus genus beta

Current IARC/WHO classification

Human papillomavirus genus beta (β-HPV) was classified by IARC as *possibly carcinogenic to humans* (Group 2B) in *IARC Monographs* Volume 90 in 2005 (IARC, 2007), with the notable exception that HPV5 and HPV8 were classified as *carcinogenic* to patients with epidermodysplasia verruciformis (EV). Subsequently, in *IARC Monographs* Volume 100B (IARC, 2012a), human papillomavirus genera beta and gamma were re-evaluated as *not classifiable as to its carcinogenicity to humans* (Group 3), with the notable exception that HPV5 and HPV8 were classified as *possibly carcinogenic to humans* (Group 2B) in patients with EV.

β-HPV (cutaneous types) was given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of human cancer and mechanistic evidence.

Considering that many types of HPV have been classified in different groups (IARC, 2012b) and that there is extensive heterogeneity in cancer studies for different types of HPV, it is necessary to specify which types of HPV should be investigated and which stream of studies could change the classification of specific types.

Exposure characterization

β-HPV is one of the five major HPV genera (alpha, beta, gamma, nu, and mu). There are more than 50 types of β-HPV (Tommasino, 2017). They are typically found on the skin and can be considered commensal to humans; asymptomatic infections may persist for several years (Sichero et al., 2019; Al-Soneidar et al., 2023). Transmission of β-HPVs among humans is primarily through skin-to-skin contact (Nunes et al., 2017). Infection is detected by serology and viral DNA detection. Seropositivity for at least one β-HPV in the population is estimated to be up to 70%; prevalence is greater in men. Seroprevalence of cutaneous β HPVs is positively associated with higher ambient ultraviolet (UV) radiation exposure (Antonsson et al., 2003; Kricker et al., 2020).

Cancer in humans

β-HPVs may contribute to the development of non-melanoma skin cancer, especially cutaneous SCC, in individuals with EV, which is a rare genetic disorder characterized by heightened susceptibility to β-HPV infection. Similarly, immunosuppressed recipients of organ transplants have an increased susceptibility to β-HPV infections on the skin and exhibit an elevated risk of cutaneous SCC in later years (Ramezani et al., 2020). Although HPV5 and HPV8 have shown an associated increased risk of cutaneous SCC in healthy individuals (Chahoud et al., 2016), owing to differences in complexities, such as heterogeneities in assays used, as found in a review of case-series studies (Neagu et al., 2023), the role of different types of β-HPV in the progression of cutaneous SCC in the general population and in immunocompetent individuals remains inconclusive.

In a cohort study in Florida, USA, in 1008 individuals who underwent screening tests for skin cancer, the detection of baseline β-HPV significantly predicted the occurrence of cutaneous SCC (HR, 4.32; 95% CI, 1.00–18.66; 149 cases), although HPV DNA was only detected in a small proportion of tumour specimens at the time of diagnosis (Rollison et al., 2021). This study also revealed an association between a larger number of β-HPV types detected in DNA assays and the risk of cutaneous SCC. Furthermore, a nested case–control study, in 385 cases of cutaneous SCC in New South Wales, Australia, found that the presence of β-HPV1 DNA and β-HPV3 DNA significantly increased the risk of cutaneous SCC by 30–40%. This study also demonstrated a positive association between each additional positive β-HPV DNA type and cutaneous SCC (OR, 1.07; 95% CI, 1.02–1.12) (Kricker et al., 2022). Both studies used detailed HPV typing in both normal tissue and skin tumours and both antibody markers in blood specimens and DNA detection in skin and hair samples. However, antibody markers did not indicate a significant association in either study.

A systematic review to explore the association between β-HPVs and cutaneous SCC in immunosuppressed patients found that the prevalence of overall β-HPVs and certain β-HPV types (5, 8, 9, 17, 49, 75, and 76) in immunosuppressed patients with cutaneous SCC was significantly higher than in controls (Ramezani et al., 2020). A similar systematic review showed that the prevalence of HPV infection is higher in immunosuppressed patients with cutaneous SCC than in immunocompetent patients with cutaneous SCC (pooled effect size, 3.01; 95% CI, 2.00–4.52). This review also found a positive association between cutaneous SCC and β-HPV when compared with controls without cancer (pooled effect size, 3.43; 95% CI, 1.97–5.98) (Wang et al., 2014). Another systematic review to assess the association between β-HPV and cutaneous SCC in immunocompetent individuals found, among the 14 studies included for meta-analysis, which involved 3112 cases of cutaneous SCC and 6020 controls, an adjusted pooled OR of 1.42 (95% CI, 1.18–1.72) (Chahoud et al., 2016).

β-HPVs have also been studied for their association with other cancers. A case–control study in New South Wales (Kricker et al., 2022) observed an association between each additional positive β-HPV DNA type and basal cell carcinoma (BCC) (OR, 1.06; 95% CI, 1.03–1.10; 833 cases). However, other studies (Boxman et al., 2000; Escutia et al., 2011; Al-Soneidar et al., 2023) produced inconsistent results. Such inconsistency was also observed in the Florida cohort study (Rollison et al., 2021), involving 132 cases of BCC, in which baseline β-HPV detection and subsequent development of BCC did not show a clear association.

Other epidemiological studies with different biomarkers of β-HPV infections have also been conducted to assess an association with the development of head and neck SCC (Sabol et al., 2016; Agalliu et al., 2018; Karimi et al., 2022). Despite some indications of a positive association between oral β-HPV5 or β-HPV38 and the risk of oropharyngeal, oral cavity, and laryngeal SCCs (Agalliu et al., 2018), general findings were inconclusive.

Cancer in experimental animals

No studies of β-HPV infection and cancer in experimental animal models were available to the Advisory Group.

Mechanistic evidence

HPVs replicate only in humans. Transgenic mouse models are available to study HPV carcinogenesis (Dorfer and Handisurya, 2020), but not cancer etiology in the context of natural viral infections, as described in *IARC Monographs* Volume 100B (IARC, 2012a).

The potential carcinogenicity of β-HPV has been studied in tissue culture and in transgenic mice. The main viral oncoproteins E6 and E7 from β-2 HPV38 and β-HPV49 can immortalize primary human keratinocytes, which are the natural host of the virus (Caldeira et al., 2003; Accardi et al., 2006; Cornet et al., 2012). However, E6 and E7 from other β-HPVs (14, 22, 23, 24, 36) did not induce immortalization in primary human keratinocytes (Cornet et al., 2012). Other studies showed that some β-HPVs (5, 8, 38) deregulate cell cycle, DNA repair, apoptosis, and cell differentiation (Howley and Pfister, 2015; reviewed in Tommasino, 2017). Consequently, the cells may become more susceptible to mutagenic properties of UV-A and UV-B (if exposed to UV radiation) (Viarisio et al., 2017; Bandolin et al., 2020). In normal human epidermal keratinocytes (NHEKs), β-HPV5 E6/E7 oncoproteins significantly enhanced IL-8, monocyte chemoattractant protein-1 (MCP-1), and intercellular adhesion molecule-1 (ICAM-1) expression. In contrast, other β-HPVs, such as HPV38, were able to reduce the induction of the proinflammatory molecules (De Andrea et al., 2007). Interestingly, inducible nitric oxide synthase (iNOS) expression levels and nitric oxide (NO) production were induced at similar levels by all the HPV genotypes tested (De Andrea et al., 2007). In addition, keratinocytes expressing HPV8 estradiol-17β (E2) induced enhanced levels of IL-8 (Venuti et al. 2019). Finally, it has been described that α-HPV types are associated with oxidative stress and chronic inflammation in cancer of the cervix (García-Quiroz et al., 2022).

Transgenic mouse models expressing the oncoproteins E6 and E7 from different β-HPV types (8, 20, 27, 38) in the skin under the control of a keratinocyte-specific promoter were observed to have increased susceptibility to UV-induced carcinogenesis (Michel et al., 2006; Marcuzzi et al., 2009; Viarisio et al., 2011). Transgenic mice expressing β-2 HPV38 E6/E7 genes had a higher incidence of cutaneous SCC than did wildtype mice, which did not develop any type of skin lesion (Viarisio et al., 2018). In addition, other mouse models are available, which involve naturally infecting mice with their corresponding papillomavirus, *Mus musculus* papillomavirus 1 (MmuPV1). MmuPV1 is able to infect immunodeficient as well as immunocompetent laboratory mouse strains (Uberoi and Lambert, 2017). In this experimental model, studies described a connection between UV radiation, MmuPV1, immunosuppression, and the development

of skin lesions (Uberoi et al., 2016; Uberoi and Lambert, 2017). Studies in vitro showed functional similarities between the E6 proteins from β-1 HPV8 and from MmuPV1 (Meyers et al., 2017, 2018).

In skin carcinogenesis, β-HPV probably interferes with the host cell at the beginning of carcinogenesis, enhancing the susceptibility to UV exposure. Indeed, not all neoplastic human keratinocyte carcinomas contain a copy of viral β-HPV (Weissenborn et al., 2005), and β-HPV does not usually integrate into the host cell genome (Viarisio et al., 2017; Bandolin et al., 2020). This proposed mechanism is called hit-and-run. In contrast, the α-HPV-induced carcinogenesis involves expression of the oncoproteins E6 and E7, which is required at each step of carcinogenesis, as well as for the preservation of the neoplastic phenotype (Bandolin et al., 2020).

Summary

Recent informative human studies published since the last meeting of the 2019 Advisory Group on Priorities show a consistent association between β-HPV types and SCC. There was a lack of evidence for cancer in experimental animals.

Some β-HPVs show KCs, including immortalization and alteration of cell proliferation and DNA repair in primary human keratinocytes. Mechanistic data may suggest a potential link between UV radiation, certain β-HPV types, and the development of skin lesions. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of human papillomavirus genus beta to be warranted. Given the complexity of the agent, the Advisory Group suggests a careful focus on specific β HPV species in the next evaluation.

Recommendation: High priority (and ready for evaluation within 2.5 years)

010 Merkel cell polyomavirus

Current IARC/WHO classification

Merkel cell polyomavirus (MCV) was classified by IARC as *probably carcinogenic to humans* (Group 2A) in *IARC Monographs* Volume 104 in 2012 (IARC, 2014a). MCV was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of new epidemiological studies of the association between MCV and Merkel cell carcinoma (MCC) and new mechanistic data (IARC, 2019a).

Exposure characterization

MCV is one of 15 currently known polyomaviruses found in humans (Bopp et al., 2021). The primary infection is asymptomatic and may occur in the first year of life, presumably through direct skin contact or via the respiratory tract. MCV DNA can be detected on healthy skin; prevalence and viral load have been shown to increase with age (Silling et al., 2022). Dermal fibroblasts may be the primary host cell type, and may be naturally and productively infected by MCV (Liu et al., 2016a). MCV has also been shown to infect non-malignant tonsillar tissue (Saláková et al., 2016), non-neoplastic hepatocytes and bile duct epithelium (Klufah et al., 2020), and non-neoplastic B-cells (e.g. reactive hyperplasia and normal lymph node) (Klufah et al., 2021). MCV DNA has also been detected in non-neoplastic tissues of the thyroid gland, adrenal gland, spleen, bone marrow, stomach, gall bladder, pancreas, heart, and aorta (Matsushita et al., 2013).

Cancer in humans

An etiological role of MCV in MCC is supported by case-series and case–control studies, and one cohort study. In case-series studies (21 studies with more than 850 cases of MCC), MCV has been detected in approximately 80% of cases (IARC, 2014a; NTP, 2016c). Case–control studies show ORs ranging from 4.4 (95% CI, 0.99–26.7) to 6.6 (95% CI, 2.3–18.8) for serological markers of MCV infection (Carter et al., 2009; Viscidi et al., 2011) and from 16.9 (95% CI, 7.8–36.7) to 63.2 (95% CI, 24.4–164.0) for serological markers

of viral early gene expression (Paulson et al., 2010). Of note, a prospective study also demonstrated a temporal relation between MCV infection and an increased risk of MCC (OR, 4.4; 95% CI, 1.3–17.4) (Faust et al., 2014).

In terms of evidence of an association between MCV and other cancers, the findings are mixed and based mostly on studies examining the presence of viral DNA in tumours, limiting inference regarding a causal role. In a prospective cohort study, no significant associations were observed between baseline markers of MCV infections and cutaneous SCC or BCC. Fewer than 4.5% of baseline MCV infections were also subsequently detected in keratinocyte cancers (Amorrortu et al., 2021). In a cohort of patients with primary laryngeal SCC, 7% of tumours were MCV positive (Geng et al., 2022). MCV infection may also be associated with a higher risk of glioma (OR, 1.56; 95% CI, 1.10–2.19) (Egan et al., 2021). MCV has been detected in a higher proportion of breast cancer specimens, compared with benign breast disease specimens (14% versus 2%, $P = 0.02$) (Peng et al., 2014). In another breast cancer study, MCV was detected in 3% of breast cancers and none of the non-tumour controls (Reza et al., 2015). MCV has also been detected in oral SCC, with a reported prevalences of 6.6–29%, and in pharyngeal cancer, with a reported prevalence of 50%, but was not detected in a study of head and neck cancers among people who neither smoked tobacco nor drank alcohol (Mulder et al., 2021). Four epithelial ovarian cancers out of 98 (4%) (Robertson et al., 2023) and two cholangiocarcinomas out of 35 (6%) were positive for MCV (Klufah et al., 2020). MCV has also been detected in neoplastic B-cells, e.g. chronic lymphocytic leukaemia cells (Klufah et al., 2021). The MCV genome was detected by polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) in 5 out of 36 (14%) thymomas, while no thymic hyperplasias ($n = 20$) or fetal thymic tissues were PCR positive for MCV (Chteinberg et al., 2019).

Cancer in experimental animals

There is a lack of in vivo models that reproduce natural MCV infection (Spurgeon, 2022).

Mechanistic evidence

The oncogenesis of MCV-associated MCC begins with the integration of MCV DNA into the host genome of human cells (Starrett et al., 2017). MCV affects several molecular pathways in the host cells, resulting in uncontrolled cell proliferation, cell death inhibition, and chronic inflammation (Vescovo et al., 2020). During viral infection, the early gene region is expressed immediately to produce two T antigens (oncoproteins): a small T antigen (sT) and a large T antigen (LT). The LT directly binds to and inhibits the retinoblastoma (RB) tumour suppressor, enhancing an unregulated cell cycle progression (Spurgeon, 2022). The sT induces transformation of rodent fibroblast cells (Rat-1) and tumour formation in p53-null transgenic mice (Shuda et al., 2011, 2015). The interactions between MCV and DNA damage response pathways were reviewed by Studstill et al. (2023). MCV is able to induce the expression of type I and type III interferons during infection of human dermal fibroblasts (Wang et al., 2023a); Mendoza et al. (2020) concluded that MCV infection may induce a rich inflammatory response (Mendoza et al., 2020). MCV T antigens are also able to induce mRNA expression that suppresses genes involved in autophagy induction in MCC cell lines (Kumar et al., 2020) and to promote the glycolytic metabolism that may increase MCC growth (Berrios et al., 2016). The molecular mechanisms of MCV transformation and replication in the host cell are well summarized in the literature (Liu and You, 2020; Ahmed et al., 2021).

Summary

Consistent findings from a case–control study and a recent prospective cohort study of the association between MCV and MCC support a re-evaluation of the classification for MCV. For other cancer types, the epidemiologic evidence is inconsistent and based mainly on studies from tissue samples. There is a lack of evidence in experimental animals. However, mechanistic evidence in epidemiological studies supports the

findings in the human cancer studies. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of Merkel cell polyomavirus to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

011 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Current IARC/WHO classification

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

SARS-CoV-2 is primarily transmitted by respiratory droplets and aerosols (WHO, 2020a). Aerosol transmission can occur in certain settings, such as enclosed spaces with poor ventilation, where infected individuals release particles that can be inhaled by others who are in close proximity or in the same space for an extended period (Jayaweera et al., 2020). Since the virus first appeared in 2019, 774 million cases of coronavirus disease (COVID-19), which is the disease caused by the SARS-CoV-2 virus, have been confirmed (as of March 2024), and exposure to the virus has been found in most individuals of all populations studied (WHO, 2024a). Determinants of severe infection among those infected include older age, male sex, higher body mass index (BMI), and comorbidities (Zhang et al., 2023c).

Cancer in humans

Studies of the relation between SARS-CoV-2 and cancer have usually been focused on an increased risk of SARS-CoV-2 among those with cancer (Lee et al., 2021a). A recent study by Li et al. (2023a) used Mendelian randomization to examine the association between SARS-CoV-2 infection and cancer; most observed ORs were not significant and were approximately 1. Of note, the follow-up time since the epidemic occurred is only a few years. Given the large number of cohorts that have been assembled to examine the long-term effects of infection, additional studies with longer follow-up times are expected and should provide a stronger basis for evaluation of SARS-CoV-2 and cancer in the future.

Cancer in experimental animals

No studies in cancer in experimental mice or rats were found, except one that suggested that spike protein (S1) from recombinant SARS-CoV-2 induces apoptosis and tumour regression in the lungs after chemical induction of tumours using NNK in A/J mice (Sheinin et al., 2022). Hence, the infection followed the cancer and appeared to be helpful in improving outcome. Non-murine experimental animal models (in, e.g. hamsters, cats, ferrets, bats, monkeys) have been and are being sought, owing to the natural resistance of mice to SARS-CoV-2 (Andrade et al., 2021). This resistance is explained by the differences between mouse and human angiotensin converting enzyme 2 (ACE2) that interfere with ACE2–spike complexing (Chu et al., 2022). However, nearly all animal models created thus far were used to investigate infection or immunity parameters, as opposed to cancer or cancer-related parameters. Overall, there are no cancer bioassays to suggest SARS-CoV-2 induces cancer in animals.

Mechanistic evidence

An overwhelming amount of mechanistic evidence pertaining to inflammation and oxidative stress in exposed humans and cell lines exists. However, COVID-19 varies in duration, severity, and immune response character, and while there appear to be three response types (Royal Society of Canada, 2022) that may be relevant to cancer, owing to their inflammatory and oxidative natures, they usually only last weeks (they are not of a chronic nature). In long COVID-19, which lasts 2 months or longer (WHO, 2022a),

inflammation and immunosuppression are frequent and, paradoxically, may both be of relevance to carcinogenicity. It is known that four signalling pathways are common between SARS-CoV-2 infection and cancer: cytokine, interferon (IFN) type I, androgen receptor (AR), and immune checkpoint signalling (Zong et al., 2021). It is also known that the virus plays many other roles: it induces epigenetic alterations, including in circular RNAs; it induces oxidative stress; it induces receptor-mediated effects including the blocking of the tumour suppressor TP53, resulting in the disruption of apoptosis, which alters cell death, as well as inactivating Rb, thereby promoting E2F transcription factors (Policard et al., 2021); it increases proliferation and activates metastasis through vascular endothelial growth factor (VEGF) via IL-6 activation of signal transducer and activator of transcription (STAT) 3, or TNFα/NF-κB; it stimulates epithelial-to-mesenchymal transition; it leads to gut dysbiosis; it suppresses tumour formation through the renin–angiotensin–aldosterone system (see Jahankhani et al., 2023 for a review); it leads to metabolic reprogramming, including altered immunometabolism (Rudiansyah et al., 2022); and it facilitates malignant transformation in triple-negative breast cancer patients via the M protein (Nguyen et al., 2022), or via neutrophil extracellular traps (Francescangeli et al., 2020). However, only a handful of studies have been reported on each of these mechanisms and they, with others, are still under investigation. In addition, interindividual variability in human responses to long COVID-19 is considerable, exacerbating the incoherence in the data – both positive and negative correlations between SARS-CoV-2 infection and cancer have been reported (Li et al., 2022a) – and reducing consistency overall. Moreover, too little time has passed since this virus emerged (late 2019 or early 2020) for clinically observable carcinogenic consequences to have manifested. Importantly, neither severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) nor Middle East respiratory syndrome coronavirus (MERS-CoV) (related viruses for which outbreaks have occurred sufficiently long ago to detect any potential carcinogenicity) have been reported to be associated with cancer, and there is no direct evidence that SARS-CoV-2 acts like known oncogenic viruses (Jahankhani et al., 2023). For a brief and recent review of COVID-19 and cancer, see Costanzo et al. (2023). Overall, the evidence, while broad and evoking 7 of 10 KCs (KC4, KC5, KC6, KC7, KC8, KC9, KC10), remains relatively sparse. Meanwhile, in mouse models, one study showed that lung damage and antibody and cytokine responses were observed in Syrian golden hamsters with COVID-19 (Dhakal et al., 2021), but this study informed more about sex differences than potential cancer mechanisms. Andrade et al. (2021) found that C57BL/6J mice inoculated with mouse hepatitis virus 3 (MHV-3), a surrogate for SARS-CoV-2, developed severe acute lung damage and respiratory distress that preceded systemic inflammation and death, echoing the well-known potential role for inflammatory mechanisms, but its use of MHV-3 complicates any read-across.

Summary

While a few studies of human cancer exist, the literature is sparse, and it is unlikely that a formal classification could be designated at this stage. There is no evidence for cancer in experimental animals. The mechanistic evidence also appears to be inconclusive. Most importantly, too little time has passed since this virus made its way onto the world stage for clinically observable carcinogenic consequences to have manifested. The Advisory Group therefore considered that an *IARC Monographs* evaluation of SARS-CoV-2 is unwarranted at present.

Recommendation: No priority

012 *Toxoplasma gondii* (toxoplasmosis infection)

Current IARC/WHO classification

Toxoplasma gondii (toxoplasmosis infection) has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Toxoplasmosis is a parasitic zoonosis caused by the protozoan *T. gondii*, which can infect humans and other mammals, such as birds, goats, sheep, domestic and feral cats, and other wild mammals. *T. gondii* is facultatively heteroxenous, having many routes of transmission across different host species (Tenter et al., 2000). The primary routes of exposure include ingestion of contaminated food or water, contact with cat faeces, and organ transplantation or blood transfusion. Across the life-cycle of *T. gondii*, it may be transmitted vertically during pregnancy, horizontally through ingestion of oocytes from the environment or trachyzoites or tissue cysts in infected meat or offal, or through contaminated blood products, tissue transplants, or unpasteurized milk (Tenter et al., 2000). The relative importance of the various routes of transmission differs geographically, based on livestock management, culture, and eating habits (Tenter et al., 2000). Nearly one third of humans have been exposed to *T. gondii*, with wide geographical variations globally (Rostami et al., 2020). A systematic review of the global prevalence of toxoplasmosis in pregnant women found an overall global prevalence of latent toxoplasmosis of 33.8%, the highest prevalence rates were in South America (56.2%) and the WHO African Region (48.7%), and the lowest prevalence rate was in the WHO Western Pacific Region (11.8%) (Rostami et al., 2020). The prevalence of *T. gondii* in asymptomatic neonates in Mexico was estimated to be 0.6% (Galvan-Ramirez et al., 2012), while the prevalence for adults in Germany was given as 55% (Wilking et al., 2016).

Cancer in humans

There is controversy over whether *T. gondii* is a cancer inducer or suppressor, whether *T. gondii* can be used in cancer treatment, or whether having cancer puts one at risk of contracting a *T. gondii* infection or *T. gondii* exposure predisposes one to cancer (El Skhawy and Eissa, 2023). A systematic review showed that toxoplasmosis may be associated with an elevated risk of haematological malignancies (Kalantari et al., 2020); specifically, a meta-analysis of six small studies found that *T. gondii* infection might be associated with increased leukaemia risk (Huang et al., 2016). Another study (Hamouda et al., 2024) revealed a significantly higher seroprevalence of *T. gondii* infection in brain tumour cases (62.5%) compared with healthy controls (38%), and a strong association between *T. gondii* seropositivity and brain tumours diagnosed in childhood (OR, 2.7). *T. gondii* exposure was also associated with glioma and meningioma (Abdollahi et al., 2022).

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

T. gondii inoculated in adult male isogenic male Balb/c mice induced DNA damage (measured by the comet assay) in neutrophils but not in the liver and brain (Ribeiro et al., 2004). Also, *T. gondii* induced an inflammatory response in the mouse prostate, resulting in microglandular hyperplasia (Colinot et al., 2017).

TM3 Leydig cell-line co-culture with tachyzoites of *T. gondii* RH strain (Staurengo-Ferrari et al., 2021) produced increased levels of testosterone, as well as of MCP-1 and IFNγ. Also, *T. gondii* tachyzoites induced apoptosis in murine Leydig tumour cell line (MLTC-1) via the endoplasmic reticulum stress pathway (Wang et al., 2023b) and inhibited apoptosis in different cell lines (Dupont et al., 2023).

T. gondii infection specifically altered the levels of different microRNAs (miRNAs) involved in the regulation of processes such as apoptosis, inflammatory response, or the cell cycle, as well as an immune response in the host cell against the infection (de Faria Junior et al., 2021). The miR-17–92 cluster, one of the miRNAs upregulated during infection (Zeiner and Boothroyd, 2010), inhibits host cell apoptosis, a survival strategy of *Toxoplasma* (Lüder and Gross, 2005; Carmen and Sinai, 2007). Primary human astrocytic glioma tissue specimens overexpressed the miR-17–92 cluster, compared with non-neoplastic

brain control tissues. During infection, a decrease in phosphatase and tensin homologue (PTEN) in brain cells by miR-17–92 activated the Akt pathway, which promoted survival and growth in response to extracellular signals, resulting in brain cancer development (Laliberté and Carruthers, 2008). Overexpression of miR-17–92, involved in cell apoptosis and cytokine production, and miR-146a and miR-155, both involved in immune response, were reported in *T. gondii*-infected brain cells (Zeiner and Boothroyd, 2010; Cannella et al., 2014).

Transcriptomic analyses and in vitro cell culture models indicated that the gene signatures and molecular or cellular pathways, including inflammation, immune responses, proliferation, and metastasis, may be altered by *T. gondii*. The results support the concept that a parasite in tissues has the potential to contribute to molecular pathways of cancer or anti-tumour activity (Caner, 2021).

T. gondii infection caused oxidative stress in testis tissue in Wistar rats, with decreased activity of antioxidant enzymes and increased lipid peroxidation (Hoseiny Asl Nazarlu et al., 2020). In another study, (Türkoğlu et al., 2018), increased levels of superoxide dismutase (SOD) and glutathione peroxidase (GPx) were found in the rat liver with no changes in these enzymes in the blood, brain, or kidney after 30 days of inoculation of *T. gondii*.

Summary

There is evidence of significant human exposure to *T. gondii*, and somewhat equivocal evidence of an association with glioma, meningioma, and leukaemia in human cancer studies; hence, a carcinogenicity evaluation is warranted to evaluate this evidence more carefully. There are no data on cancer in experimental animals. There is mechanistic evidence suggesting that *T. gondii* exhibits KCs in experimental systems and perhaps in exposed humans, although most of the studies are small and prone to bias. The Advisory Group therefore considered an *IARC Monographs* evaluation of *Toxoplasma gondii* (toxoplasmosis infection) to be warranted.

Recommendation: Medium priority

013 *Opisthorchis felineus*

Current IARC/WHO classification

Opisthorchis felineus (infection with) was evaluated by IARC as *not classifiable as to its carcinogenicity to humans* (Group 3) in *IARC Monographs* Volume 61 in 1994 (IARC, 1994b). *O. felineus* was given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a).

Exposure characterization

O. felineus (cat liver fluke) is a trematode parasite common in the Russian Federation (with an estimated 1.5 million infected individuals) but has also been detected in many countries of Europe. Humans acquire the parasite by eating raw or undercooked fish. The parasite can infect the liver, pancreas, and gall bladder (Pakharukova and Mordvinov, 2022).

Cancer in humans

O. felineus is closely related to the liver fluke *O. viverrini*, which is endemic in south-eastern Asia and is classified as *carcinogenic to humans* (Group 1). However, there are very few studies of *O. felineus* and cancers of the liver and bile duct (Kovshirina et al., 2019; Fedorova et al., 2023). A case–control study by Fedorova et al. (2023) found that infection with *O. felineus* was associated with an OR for cancer of the bile duct of 3.9 (95% CI, 1.4–10.8). The study by Kovshirina was a report of two cases of bile duct cancer observed in patients infected with *O felineus*.

Cancer in experimental animals

Maksimova et al. (2017) found evidence of cholangiocarcinoma in Syrian golden hamster infected with *O. felineus* with oral administration of dimethyl nitrosamine. For cholangiocarcinoma specifically, it is thought, "The gross morphology and histology of the experimentally induced cholangiocarcinomas are similar to those found in humans, and are considered a suitable model for the study of cholangiocarcinoma". (IARC, 2012a, p. 355). However, the Advisory Group noted that the cholangiosarcomas observed were due to exposure to dimethyl nitrosamine and not *O. felineus* infection. Hence, there are no studies to show carcinogenicity of *O. felineus* in experimental animals.

Mechanistic evidence

At least four studies of cancer in Syrian golden hamsters demonstrate neoplastic characteristics associated with long-term *O. felineus* infection. A study by Semenov et al. (2016) showed hyperplasia and adenomatous transformation in portal tracts and biliary intraepithelial neoplasia in lobar bile ducts, with increased epithelial hyperplasia and invasive growth of cell cords in the bile ducts (Semenov et al., 2016). Gouveia et al. (2017) described portal area enlargement, inflammation, severe periductal fibrosis, and biliary intraepithelial neoplasia in male Syrian golden hamsters (only male hamsters were studied); however, incidence was not reported. Maksimova et al. (2017) found inflammation, bile duct dysplasia, periductal fibrosis, bile duct hyperplasia and proliferation, egg granuloma, and cysts. Pakharukova et al. (2019a) show time-dependent accumulation of oxidative hepatobiliary lesions through the detection of lipid peroxidation by-products 4-hydroxynonenal and malondialdehyde, which correlated with histopathological changes observed in the liver and accumulation of 8-hydroxy-2′-deoxyguanosine, a critical biomarker of oxidative stress and carcinogenesis (Pakharukova et al., 2019a). Gouveia et al. (2017) also identify oxysterol-like metabolites of *O. felineus* – similar to those described for *O. viverrini*. Overall, there appears to be ample evidence for the carcinogenicity of infection with *O. felineus*, because multiple positive results have been found across different studies, and mechanisms resemble *O. viverrini*, although all studies involve one species, the Syrian golden hamster, and differences of cancer induction may exist between hamsters and humans (IARC, 2012a, p. 355).

Numerous studies describing many KCs have been reported since the last review in 2019, including: Gouveia et al. (2017); Pakharukova et al. (2019a, b) (KC1, KC2, KC3, KC5, KC6, KC10); Kokova et al. (2020, 2021) (KC7); and Semenov et al. (2016), Maksimova et al. (2017), and Lvova et al. (2023) (KC6, KC10). Results in different systems are consistent, most often for KC6 and KC10, then KC1, KC2, KC3, and KC5, and, least often, KC7, and studies cover a gamut of relevant end-points. Overall, the mechanistic evidence appears to be strong.

Summary

There is a scarcity of human cancer evidence. While there was a lack of adequate evidence in experimental animals, there appears to be ample mechanistic evidence of KCs. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of *Opisthorchis felineus* (infection with) to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

014 *Schistosoma japonicum*

Current IARC/WHO classification

Schistosoma japonicum (infection with) was classified by IARC as *possibly carcinogenic to humans* (Group 2B) in *IARC Monographs* Volume 61 in 1994 (IARC, 1994b), on the basis of *limited* evidence for cancer in humans and experimental animals.

Exposure characterization

More than 200 million people worldwide contract schistosomiasis, an infection caused by parasitic flatworms (Steinmann et al., 2006). *S. japonicum* is a trematode parasite whose larvae can penetrate human skin. When individuals wade or immerse themselves in infested waters, such as ponds, lakes, or rivers, *S. japonicum* can penetrate the skin and infect the person (Wilson, 1987). This exposure commonly occurs during occupational and recreational activities. Activities such as farming, fishing, swimming, or washing clothes in infested water bodies are the main routes of exposure to *S. japonicum* (Ross et al., 1997). However, socioeconomic status and behavioural factors play a crucial role in contamination as well and the presence of other host reservoirs, such as cattle, buffalo, and pigs, also contributes to human infection (Raso et al., 2009). Snail density can also be a determining factor in human infection and reinfection (Seto et al., 2007). Congenital transmission in humans has not been confirmed (Shi et al., 2001).

Cancer in humans

Since the evaluation by the *IARC Monographs* programme (IARC, 1994b), a few observational studies have been conducted in eastern Asia and south-eastern Asia, where the parasite is endemic (WHO, 2023a). In a study in Japan, an increase in the standardized mortality ratio (SMR) for liver cancer was observed in a region that was formerly endemic for schistosomiasis (Takemura et al., 1998). The study found that the SMRs for liver cancer for men, in the endemic area, were 1.88 in both 1985 and 1990. In this retrospective cohort study, the exposure was measured by assessing the history of residency in the area (Takemura et al., 1998). Qiu et al. (2005) conducted a matched case–control study in rural Sichuan, China, to assess the associations between previous *S. japonicum* infection and liver and colon cancers. The study included 127 cases of liver cancer and 142 cases of colon cancer. One or two controls were selected from patients diagnosed with an illness other than cancer from hospital records and matched by age, sex, hospital, and township for the same year that the cancer case was diagnosed. Study participants were restricted to those without evidence of hepatitis. The exposure, previous *Schistosoma* infection, was determined by examining the medical records or from interviews with the participants or their relatives. There was a significant association between *S. japonicum* infection and both liver cancer (OR, 3.7; 95% CI, 1.0–13) and colon cancer (OR, 3.3; 95% CI, 1.8–6.1). In a related study, Yang et al. (2023) investigated the clinicopathological characteristics of tumours from 1111 patients with gastric, liver, colon, or rectal cancer. That study suggested that schistosomiasis-associated digestive system tumours exhibit distinct clinicopathological features, compared with non-schistosomiasis tumours.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

Eggs of *S. japonicum* trapped in the liver can induce a chronic inflammatory host response, which promotes the formation of egg granuloma and liver fibrosis (Liu et al., 2022a; Licá et al., 2023). In humans infected with *S. japonicum*, there is evidence that miRNAs play an important role in hepatic fibrosis by regulating cellular proliferation, the organization of extracellular matrix proteins, and lipid mobilization, and by limiting the oxidative damage stress (Cabantous et al., 2017). The miRNAs of these parasites may be

involved in carcinogenesis (Leija-Montoya et al., 2022). In experimental systems, concentrations of reactive oxygen species (ROS) are elevated in infected mouse liver tissues, where they enhance M2 macrophage differentiation (Yu et al., 2021a) and induce pyroptotic cell death (Kong et al., 2019). *S. japonicum* infection in mice induced liver inflammation, oxidative stress, proliferation, apoptosis, and metabolic reprogramming (Xu et al., 2019a; Zhao et al., 2021a; Ren et al., 2023). In addition, chronic schistosome infection could lead to systematic or local immune suppression in mouse models (Chen et al., 2012; Lundy and Lukacs, 2013; Lu et al., 2020a; Ren et al., 2023). Extracts of *S. japonicum* showed no mutagenicity in *Salmonella typhimurium* or *Escherichia coli* tests (Ishii et al., 1989).

Using a mouse model of colorectal cancer, Wu et al. (2020a) demonstrated that intraperitoneal injection of *S. japonicum* egg-specific protein (SjE) 16.7 promotes colorectal cancer progression, along with systemic myeloid cell accumulation.

S. japonicum eggs in the colorectum induce chronic colitis in exposed humans. The transition from *S. japonicum* colitis to colorectal cancer has been examined (Ming-Chai et al., 1980; Yang et al., 2023). Ming-Chai et al. (1980) described mucosal changes adjacent to large intestinal carcinoma in colectomy specimens (IARC, 1994b). In exposed humans, Yang et al. (2023) observed, by histopathological analysis, that *S. japonicum* can cause multiorgan and multisystem damage: inflammation, adenoma, and adenocarcinoma were the common lesion types. There is evidence that the diversity and composition of the human gut microbiome change during *S. japonicum* infection (Lin et al., 2022; Zhou et al., 2023a).

Summary

Despite signals of a positive association in studies related to liver and colon cancer, these are mostly case–control or ecological; this limits inference regarding temporality or an association at the individual level. However, studies in infected humans show data for chronic inflammation, alteration of cell proliferation, and multiorgan and multisystem damage, as well as changes in the gut microbiome. There is a lack of evidence for cancer in experimental studies. Experimental studies in vivo show evidence for chronic inflammation, immunosuppression, oxidative stress, alteration of cell proliferation and cell death, and metabolic reprogramming. From the mechanistic point of view, there is evidence supporting a re-evaluation of *S. japonicum*. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of *Schistosoma japonicum* (infection with) to be warranted and suggested that this agent be re-evaluated with other species of *Schistosoma*, for example with *Schistosoma mansoni* (agent 015).

Recommendation: High priority (and ready for evaluation within 2.5 years)

015 *Schistosoma mansoni*

Current IARC/WHO classification

Schistosoma mansoni (infection with) was evaluated by IARC as *not classifiable as to its carcinogenicity to humans* (Group 3) in *IARC Monographs* Volume 61 in 1994 (IARC, 1994b). *S. mansoni* was given a priority rating of *medium* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of new mechanistic evidence.

Exposure characterization

More than 200 million people worldwide contract schistosomiasis, an infection caused by parasitic flatworms (Steinmann et al., 2006). *S. mansoni* is the most common of the schistosomes and is the predominant intestinal schistosome (Baluku et al., 2023). *S. mansoni* is a trematode that lives for years in the mesenteric veins of humans, where it produces hundreds of eggs per day. About one half of the eggs migrate to the intestinal lumen and are passed out of the body. Once in the environment, they infect snails, in which

the adult worms develop. Humans can be infected through the skin if they are exposed to water contaminated with human faeces (IARC, 1994b). Schistosomiasis is endemic in more than 70 countries but is far more prevalent in sub-Saharan countries (Chitsulo et al., 2000).

Cancer in humans

Current evidence suggests that infection with *S. mansoni* eggs has oncogenic potential in the intestines or the liver in humans. Well-designed studies of cancer in humans remain scarce and there has been limited new evidence since the previous evaluation. This evidence includes two studies of liver cancer from Egypt. Hassan et al. (2001) found a higher OR for liver cancer in those with both HCV and *S. mansoni* infections (10.3; 95% CI, 1.3–79.8), compared with those infected with HCV alone (6.5; 95% CI, 1.6–26.6) but no increased OR for those infected with *S. mansoni* alone (0.2; 95% CI, 0.1–6.2). The other study (Sabry et al., 2015) did not present interpretable estimates. Hence, neither of these new studies was informative. There was, in addition, one case–control study of colorectal cancer from Zimbabwe (Katsidzira et al., 2019), which found an OR of 2.4 (95% CI, 1.4–4.2) associated with schistosome infection, although this was assumed to be with either *S. mansoni* or *Schistosoma haematobium*. Hence, the information from that study was inconclusive.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

One study in mice showed synergy between *S. mansoni* and the carcinogen diethylnitrosamine (DEN) in promoting HCC (El-Tonsy et al., 2013). In this study, small cell dysplasia arose earlier, at a higher grade, and after a smaller DEN dose in mice infected with *S. mansoni* than in uninfected mice.

In the years since the last report (IARC, 2019a), three studies have been published. A study by von Bülow et al. (2022) showed that *S. mansoni* eggs reprogramme lipid and carbohydrate metabolism (supporting KC10), resulting in oxidative stress-induced DNA damage (supporting KC1, KC2, KC3, and KC5). In particular, *S. mansoni* eggs induce the activation of ERK, c-Jun, and STAT3 in HepG2 cells stimulated with soluble egg antigens (SEAs), supporting KC10. Härle et al. (2023) showed that c-Jun plays an important role in hepatocyte proliferation and survival (KC10), further explaining their previous finding that *S. mansoni* eggs activate c-Jun via egg-secreted factors such as IL-4 inducing principle from *S. mansoni* eggs (IPSE) (Grevelding, 1995). Moreover, von Bülow et al. (2024) show that *S. mansoni* eggs trigger cellular proliferation (supporting KC10) via oxidative stress (supporting KC5), and importantly, induce proliferation, which may be abolished in human hepatoma cells by treatment with reduced glutathione (GSH). The finding that antigens secreted by *S. mansoni* eggs activate the HCC-associated transcription factors c-Jun and STAT3 in hamster and human hepatocytes (Roderfeld et al., 2020) is supported by von Bülow et al. (2022). A few other animal models also point towards mechanistic evidence in support of these and other KCs. Several reports since 2019 support chronic inflammation (KC6): Ramez et al. (2021), Takaki et al. (2021), von Bülow et al. (2022, 2024), Härle et al. (2023), and MacGregor et al. (2023). Another report supports KC7: Osada et al. (2019). There is also a publication on *S. haematobium*, in which some mechanisms are similar to those in *S. mansoni* (Mbanefo et al., 2020). Overall, there is increasing mechanistic evidence related to the KCs for *S. mansoni*. Detoni et al. (2023) measured oxidative stress in *S. mansoni* – not in the mouse host cells. Lastly, in a study by Amer et al. (2023), all infected mouse groups had smaller measured body weights than corresponding uninfected counterparts, including groups with type 1 diabetes, type 2 diabetes, and obesity; this study also found an association between infection and the induction of chronic inflammation, as have so many others (Amer et al., 2023).

Summary

Evidence of cancer in humans is scarce, as based on few studies of little informativeness. There is some new mechanistic evidence of multiple KCs in experimental systems, but human mechanistic evidence is minimal. Overall, the evidence for cancer in experimental animals appears to be non-existent. However, based on the available mechanistic evidence, and similarities with *Schistosoma japonicum*, there is support for an evaluation. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of *Schistosoma mansoni* (infection with) to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

016 Malaria

Current IARC/WHO classification

Malaria (caused by infection with *Plasmodium falciparum* in holoendemic areas) was classified by IARC as *probably carcinogenic to humans* (Group 2A) in *IARC Monographs* Volume 104 in 2012 (IARC, 2014a), on the basis of *limited* evidence for Burkitt lymphoma in humans, together with *strong* mechanistic evidence that malaria reactivates Epstein–Barr virus, the main cause of Burkitt lymphoma. Malaria was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of new data on animal carcinogenicity, mechanistic studies, and links to other cancer types to support a re-evaluation.

Exposure characterization

Malaria in humans is caused by infection with parasites in the genus *Plasmodium (P. falciparum, P. vivax, P. ovale, P. malarie, and P. knowlesi*) Malarial infection is widespread in some tropical and subtropical regions of the world, particularly in sub-Saharan Africa. The range and severity of infection may be increasing, owing to the effects of climate change (Leal Filho et al., 2023).

Cancer in humans

In *IARC Monographs* Volume 104 (IARC, 2014a), the evidence for human cancer was found to be *limited*, as it was based largely on ecological studies linking Burkitt lymphoma geographically to locations of high malaria prevalence in children. Several case–control studies had serious limitations, particularly in relation to the choice of biological, clinical, and behavioural indicators of past malaria exposure. Since then, there have been further ecological and case–control studies on Burkitt lymphoma in African countries, as well as a systematic review and meta-analysis of its association with malaria. There have also been further investigations of the role of malaria in the etiology of Kaposi sarcoma.

Since *IARC Monographs* Volume 104 (IARC, 2014a), findings from case–control studies of Burkitt lymphoma continue to be mixed. For example, in the largest study of Burkitt lymphoma available, Peprah et al. (2020) found that, across three malaria-endemic countries (Kenya, Uganda, the United Republic of Tanzania), some malaria markers were associated with an increased risk, while others were associated with a lower risk. Redmond et al. (2020) analysed data from the same study combined with data published in other reports for African countries and concluded that, contrary to previous hypotheses, Burkitt lymphoma is more closely related to asymptomatic malaria than to malaria with a high parasite burden and clinical symptoms. A meta-analysis (Kotepui and Kotepui, 2021) found no evidence, overall, for an association between malaria and Burkitt lymphoma, based on all published case–control studies. A new geographical analysis (Broen et al., 2023), also drawing on a three-country dataset of Burkitt lymphoma cases, found a strong geographical correlation between incidence rates and the estimated cumulative number of malaria infections per child. For Kaposi sarcoma, several reports suggest that malaria is related to the prevalence,

transmission, and reactivation of its causative agent, the Kaposi sarcoma-associated herpesvirus (KSHV). However, there does not appear to be a study that has directly investigated the relation between malaria and the occurrence of Kaposi sarcoma.

Exposure assessment continues to be the main barrier to conducting definitive studies of the relation between malaria and both Burkitt lymphoma and Kaposi sarcoma. As both these types of cancer are rare, even in endemic settings, prospective cohorts would need to be infeasibly large, so there has been a reliance on case–control and ecological studies, with their inherent limitations in exposure assessment. A further complexity in these studies is the need to take careful account of the herpesviruses, EBV, the recognized primary cause of Burkitt lymphoma, and KSHV, the recognized primary cause of Kaposi sarcoma, as malaria's role as a carcinogen is considered to operate synergistically with these infections.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

In the previous evaluation, there was *strong* mechanistic evidence, including findings that *Plasmodium falciparum* reactivates latent infection with EBV, a recognized cause of Burkitt lymphoma. There is extensive literature on the pathogenic processes induced by *P. falciparum* infection, including mechanisms that are plausibly related to enhancing the carcinogenic potential of the two herpesviruses through reactivation and other means.

Summary

While there has been a substantial body of new evidence on the role of malaria in the pathogenesis of Burkitt lymphoma and Kaposi sarcoma, and their respective causal herpesviruses, the direct epidemiological evidence for malaria in cancer causation remains mixed. For Burkitt lymphoma, a Working Group would need to rely largely on the ecological studies to consider changing the evaluation of the evidence for human carcinogenicity to *sufficient*. For Kaposi sarcoma, the direct epidemiological evidence for causation by malaria would probably still be viewed as *inadequate*, but mechanistic evidence related to KSHV reactivation may be relevant to Working Group deliberations. Overall, it would make sense to postpone further consideration by the *IARC Monographs* programme until there are stronger human cancer data. Evidence for Burkitt lymphoma is still largely ecological, with mixed findings in case–control studies. There is some evidence for association with KSHV but not Kaposi sarcoma. The Advisory Group therefore considered that an *IARC Monographs* re-evaluation of malaria is unwarranted at present.

Recommendation: No priority

017 Gene or cell therapy or vectors

Current IARC/WHO classification

Gene or cell therapy or vectors have not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Gene therapy is a technique that modifies a person's genes to treat or cure disease. Gene therapies use several mechanisms: (i) replacing a disease-causing gene with a healthy copy of the gene; (ii) inactivating a disease-causing gene that is not functioning properly; or (iii) introducing a new or modified gene into the body to help treat a disease. There are different types of gene therapy product. Plasmids are circular DNA molecules that can be genetically engineered to carry therapeutic genes into human cells. Viral vectors are

viruses that have been modified to remove their ability to cause infectious disease. Because viruses have a natural ability to deliver genetic material into cells, these modified viruses can be used as vectors (vehicles) to carry therapeutic genes into human cells. Bacterial vectors can be produced by modifying bacteria to prevent them from causing infectious disease and then used as vectors (vehicles) to transport therapeutic genes into human tissues. Human gene editing technology can be used to disrupt harmful genes or to repair mutated genes. Patient-derived cellular gene therapy products are obtained by removing and genetically modifying them (often using a viral vector) cells from the patient and are then reintroduced in the patient (US FDA, 2018). The most important vector platforms of the past 20 years are adeno-associated viruses (AAVs), adenoviruses (AdVs), and lentiviruses (LVs) (Minskaia et al., 2023). Successful clinical studies have led to the approval of six AAV-based and three LV-based gene therapies. The AAV-based therapies are alipogene tiparvovec, approved in the EU in 2012 for the treatment of lipoprotein lipase deficiency (European Medicines Agency, 2012); voretigene neparvovec, approved by the US Food and Drug Administration (US FDA) in 2017 for the treatment of retinal dystrophy (US FDA, 2017); onasemnogene abeparvovec, approved in the EU in 2020 for the treatment of babies and young children with spinal muscular atrophy (European Medicines Agency, 2020a); eladocagene exuparvovec, approved in 2022 for the treatment of severe aromatic L-amino acid decarboxylase (AADC) deficiency (European Medicines Agency, 2022a); valoctocogene roxaparvovec, for the treatment of severe haemophilia A in adults; and etranacogene dezaparvovec, for the treatment of haemophilia B in adults (European Medicines Agency, 2022b). The LV-based therapies are atidarsagene autotemcel, for the treatment of infantile metachromatic leukodystrophy (MLD) (European Medicines Agency, 2020b); betibeglogene autotemcel, for the treatment of β-thalassemia; and elivaldogene autotemcel, for the treatment of children with cerebral adrenoleukodystrophy (ALD) (European Medicines Agency, 2021). The US FDA approved five new gene therapies in 2023 (Senior, 2022).

Cancer in humans

Cancer as a side-effect of gene therapy was recognized in early clinical trials (Rothe et al., 2014). Safety monitoring of clinical trials and post-marketing pharmacovigilance studies have reported cases of cancer (particularly acute myeloid leukaemia, AML) after gene therapy (Rafaniello et al., 2020; Kanter et al., 2023). Continued safety monitoring of trials and long-term cohort studies of cancer risks among patients who have received gene therapy should provide relevant data; however, such studies, which could be the basis of an *IARC Monographs* evaluation, have not been identified.

Cancer in experimental animals

No studies of cancer in experimental animals for genetic vectors, cell therapy, or gene therapy were available to the Advisory Group.

Mechanistic evidence

No study was identified regarding mechanistic evidence for genetic vectors, cell therapy, or gene therapy. Insertional mutagenesis, where the vector integrates in human DNA at a site close to a proto-oncogene, is a classic mechanism of viral carcinogenesis in animals. Genomic insertion of a viral vector may reduce expression of proximal tumour suppressor genes or activate proximal proto-oncogenes within the host. In animal models, integration of AAV into the host genome may cause HCC (Sabatino et al., 2022). In humans, retroviral gene therapy targeting severe combined immunodeficiency (SCID) was found to lead to T-cell leukaemia (Kohn et al., 2003). But at that time, only one mouse model was reported to progress towards AML after the insertion of retrovirally transduced bone marrow cells near the cellular proto-oncogene ecotropic viral integration site 1 (Evi1) (Li et al., 2002). It was not, therefore, clear in the study of Kohn et al. (2003) whether insertional mutagenesis or the properties of the cells of patients, their

immunodeficiency, or the transgene they were receiving through therapy was causative of leukaemia. More recently, in two patients who had undergone gene therapy for sickle cell disease and developed myeloid malignancies, stem cell mutations were found in *DNMT3A* and *EZH2* genes associated with accelerated growth (Spencer Chapman et al., 2023). In gene therapies targeting cancer – the majority of gene therapy trials from 1989 through 2015 (Hanna et al., 2017) – patient factors may have induced a predisposition to cancer. Importantly, today's technologies increasingly use directed approaches in what are thought to be safer regions of the genome (Naldini, 2015). Multipotent stromal cells used in cell-based therapies may play a role in the progression of carcinogenesis through spontaneous transformation or may modulate tumour growth and metastasis (Lazennec and Jorgensen, 2008), but more research is required. Overall, the occurrence of cancer in patients receiving cell or gene therapies targeting cancer and non-cancer diseases is diminishing: in 33 clinical holds from 2020 to 2022, only five may be related to cancer-related events: three for CAR-T cells; one for LV; one for AAV; and none for any others (Wills et al., 2023). Moreover, vector design is improving, and regulatory bodies, such as the US FDA (2020) and concerned scientists (Anonymous, 2021) are calling for long-term follow-up for new malignancies, especially for AAVs, herpes viruses, gammaretroviruses, LVs, transposon elements, microbial vectors, and genome editing products (see US FDA, 2020, Table 1). No data from human primary cells or tissues or from experimental systems were available regarding any of the 10 KCs.

Summary

Gene therapies are evolving rapidly, with a growing proportion of the population undergoing gene therapy and therefore becoming exposed. Safety monitoring of clinical trials has found that cancer can be an adverse event of gene therapy with first-generation vectors. Limited evidence available suggests that cancer may be an adverse outcome with second-generation vectors. Continued safety monitoring of trials and long-term cohort studies of cancer risks among patients who have received gene therapy seem warranted. No prospective cohort studies have been identified that could form the basis for a systematic review by the *IARC Monographs* at this time.

Overall, there is a lack of data on cancer in experimental animals. The data regarding mechanistic evidence appear to be minimally informative because the raw data are usually not available and the adequacy of the design, certainly in cancer-targeting therapies, does not allow the untangling of cause and consequence. It appears unlikely that evidence for or against carcinogenicity in humans would be revealed. The Advisory Group therefore considered that an *IARC Monographs* evaluation of gene or cell therapy or vectors is unwarranted at present.

Recommendation: No priority

018 Aflatoxins (CAS No. 1402-68-2)

Current IARC/WHO classification

Aflatoxins have been evaluated repeatedly by the *IARC Monographs* programme and were classified by IARC as *carcinogenic to humans* (Group 1), most recently in *IARC Monographs* Volume 100F in 2009 (IARC, 2012b). There is *sufficient* evidence that aflatoxins cause liver cancer (specifically, HCC) in humans. Aflatoxins were given a priority rating of *medium* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of emerging epidemiological evidence from case–control studies (described in this report) that they may cause cancer of gall bladder in humans. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) conducted a risk assessment of aflatoxins in food most recently in 2016 and calculated a maximum limit (FAO/WHO, 2016).

Exposure characterization

As described in *IARC Monographs* Volume 100F (IARC, 2012b) and the 2019 Advisory Group report (IARC, 2019a), aflatoxins are naturally occurring contaminants of food crops that cause globally widespread health threats and economic burdens. Aflatoxins, as part of a broader group of mycotoxins, are mainly produced by two species of fungi: *Aspergillus flavus* and *Aspergillus parasiticus*. Aflatoxins can flourish in crops grown in moist warm conditions frequently experienced in tropical or subtropical locations, either before or after harvesting (e.g. during transit and storage). Major crops affected include maize, cottonseed, peanuts, tree nuts, coffee, rice, wheat, sorghum, and spices (e.g. Sadef et al., 2023). Efforts continue to reduce exposure to these carcinogenic mycotoxins. For example, JECFA recently established new maximum levels for aflatoxins in grains and cereals, including those typically consumed by children (FAO/WHO, 2022). JECFA estimated that, with the exception of very high estimates of dietary exposure to aflatoxins for some African countries (105–850 ng/kg bw (body weight) per day), all mean dietary aflatoxin exposures were in the range < 0.01–58 ng/kg bw per day with high consumer estimates in the range < 0.01–200 ng/kg bw per day (FAO/WHO, 2018). With increasing global temperatures from climate change, aflatoxin hazards have been extending northward within Europe (Battilani et al., 2016).

Cancer in humans

As noted in the 2019 Advisory Group report (IARC, 2019a), two case–control studies observed an association between aflatoxins and cancer of the gall bladder, one in Chile (Nogueira et al., 2015) and the Shanghai Biliary Tract Cancer study in China (Koshiol et al., 2017). In both of these studies, exposure was measured after the cancer diagnosis, giving rise to concern about reverse causation (i.e. the cancer diagnosis affecting the levels of the aflatoxin analyte through change of diet) and whether the exposure measurement captured the relevant window of susceptibility to cancer induction, leading to concerns about exposure misclassification. Since then, a nested case–control study from the Shanghai Cohort Study in China has observed an association between aflatoxin B_1-lysine albumin adducts measured prospectively (at baseline) and subsequent incidence of gall bladder cancer (Koshiol et al., 2024). The risk of gall bladder cancer was twice as high for those with the adducts at baseline, compared with those without (OR, 2.0; 95% CI, 1.0–3.9), providing the first temporal evidence of exposure preceding the cancer outcome. Furthermore, some evidence was found of an exposure–response trend between quantitative measures of aflatoxin adduct formation and risk of gall bladder cancer ($P = 0.05$), and a higher risk of gall bladder cancer was seen among participants with detectable adduct formation who had gallstones.

Mechanistic evidence

As described in *IARC Monographs* Volume 100F, there is *strong* evidence that aflatoxins operate through a genotoxic mechanism involving metabolic activation to a genotoxic epoxide and subsequent formation of DNA adducts. There is evidence that aflatoxin B_1 becomes concentrated in the biliary tree and causes cellular proliferation, including in exposed humans (Harland and Cardeilhac, 1975; Krishnamachari et al., 1975). Highly clonal mutational signatures of aflatoxin exposure in gall bladder tumours have also been reported (e.g. Nepal et al., 2021; Kang et al., 2022b).

Summary

The epidemiological evidence from the prospective cohort study reinforces the findings from the two previous case–control studies, which, together with the mechanistic evidence, suggests that there may now be *limited* or *sufficient* evidence that aflatoxins cause cancer of the gall bladder in humans. New, potentially informative, studies in areas with high aflatoxin exposure are currently underway. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of aflatoxins to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

019 α-Pinene (CAS No. 7785-26-4)

Current IARC/WHO classification

α-Pinene has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

α-Pinene is a natural compound produced by pine trees and other plants, including *Cannabis* species (Allenspach and Steuer, 2021; ECHA, 2023c). It is extensively used as a fragrance and flavour ingredient. Notably used in the manufacture of turpentine, its annual production and importation in the European Economic Area fall within the range 10 000–100 000 tonnes. Its predominant consumer uses include incorporation in household cleaning products, air care products, cosmetics, and flavoured foods (Waidyanatha et al., 2022; ECHA, 2023c). Exposure to α-pinene primarily occurs through these consumer and lifestyle-related products and in professional settings. Additionally, its presence as a common indoor air pollutant is attributed to its inclusion in long-life materials, such as construction and building materials. Despite α-pinene being a widespread compound, exposure levels in typical indoor environments are generally low, but can be significantly higher in occupational settings, such as the lumber and furniture industry (Hagström et al., 2012; Allenspach and Steuer, 2021; Waidyanatha et al., 2022; ECHA, 2023c).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

No studies on carcinogenicity of α-pinene in chronic experiments on animal were available to the Advisory Group. The Advisory Group was aware of a 2-year bioassay on the carcinogenicity of α-pinene administered by inhalation to F344/N rats and B6C3F$_1$/N mice, in preparation by the National Toxicology Program (NTP).

Mechanistic evidence

α-Pinene induced significant inhibition of gap junctions (half maximal inhibitory concentration, IC_{50}), 12 μM) in a rat Novikoff hepatoma cell line (Mickus et al., 2021) and influenced the ERK/Akt pathway in NK cells, including cytotoxicity (Jo et al., 2021).

α-Pinene induced DNA damage in melanoma cells; this was assessed using phosphorylated H2A histone family member X (γ-H2AX), a biomarker for DNA double-stranded breaks (KC1, KC2, KC3). However, α-pinene did not influence 8-hydroxy-2′-deoxyguanosine (8-OHdG) concentrations and did not induce micronuclei and chromosome aberrations in cultured human blood cells (Türkez and Aydın, 2016). α-Pinene did not induce DNA damage, as assessed by the comet assay in human A549 lung adenocarcinoma cells in a system that allowed exposure to α-pinene in air (Gminski et al., 2010). In addition, α-pinene was not mutagenic at a single concentration of 3 μM in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, with or without metabolic activation from Aroclor 1254-induced rat liver S9 (9000 × *g* supernatant) microsomes, and in strains TA98 and TA100, with or without 3-methylcholanthrene-induced rat liver S9 mix (Florin et al., 1980). Additionally, α-pinene gave negative results in *S. typhimurium* strains TA98 and TA100 when tested at concentrations ranging from 10 to 500 μg/plate with or without S9 mix (Connor et al., 1985) and enantiomers of α-pinene gave negative results in *S. typhimurium* strains TA97a, TA98, TA100, and TA1535 at concentrations ranging from 100–5000 μg/plate with or without S9 mix (Gomes-Carneiro et al., 2005). No increase in micronucleated erythrocytes was seen in male or female mice in the 3-month short-term NTP study (NTP, 2016d). A recent safety assessment concluded that α-pinene is

not genotoxic (Api et al., 2022). α-Pinene is metabolized into α-pinene oxide, which is a genotoxic metabolite (Waidyanatha et al., 2022).

α-Pinene induced mitochondrial dysfunction and ROS accumulation in the murine T-lymphoma cell line EL-4 (Abe et al., 2024) (KC5). However, in cultured human blood cells, α-pinene caused significant increases in total oxidant capacity, while total oxidative stress was influenced only at high concentrations, suggesting that α-pinene acts as an antioxidant (Türkez and Aydın, 2016), while antioxidant effects were previously shown in different cultured cells in vitro (Wang et al., 2008; Karthikeyan et al., 2018).

α-Pinene induces cell cycle arrest in experimental systems in vitro (Xu et al., 2018), reduced tumour cell proliferation, and induced apoptosis in xenograft tumours (Zhao et al., 2018). Moreover, it is followed by wide transcriptome changes associated with the ROS pathway and apoptosis (KC10); in particular, it increased early growth response 1 (*EGR1*) gene expression (KC8) that followed with upregulation of p53, a central mediator of cell cycle arrest and apoptosis (Abe et al., 2024). Several studies demonstrated the pro-apoptotic effect of α-pinene in human cultured cells (Santana et al., 2012; Chen et al., 2014b, 2015; Zhang et al., 2015; Spyridopoulou et al., 2017; Zhao et al., 2018; Hou et al., 2019; Huang et al., 2022a; Abe et al., 2024).

At concentrations ranging from 25 to 35 μM in cell culture medium, α-pinene was clastogenic in V79-C13 Chinese hamster (Catanzaro et al., 2012). Clastogenic activity corresponds to DNA damage assessed by the comet assay, significant increases in micronucleated cells, and induction of chromosomal breakage, as assessed by metaphase analysis (Catanzaro et al., 2012).

Under the conditions of a 3-month inhalation study in male and female rats and mice, α-pinene increased the incidence of transitional epithelium hyperplasia of the urinary bladder, in both sexes (NTP, 2016d).

Summary

No studies of cancer in humans are available. α-Pinene influences oxidative stress regulation without any significant DNA damage in most experimental systems. Moreover, its influence may cause antiproliferative and pro-apoptotic effects in some experimental systems, and it may also have antioxidant effects. There appear to be numerous studies pertinent to mechanistic evidence; however, they appear to have inconsistent findings, especially for KC1, KC2, and KC3. The mechanistic evidence does not support an evaluation of carcinogenicity of α-pinene. A 2-year bioassay on the carcinogenicity of α-pinene administered by inhalation to F344/N rats and B6C3F$_1$/N mice is in preparation by the NTP. The Advisory Group therefore considered an *IARC Monographs* evaluation of α-pinene to be warranted if supported by these bioassay findings.

Recommendation: Medium priority

020 Black cohosh extracts (*Actaea racemosa*) (CAS No. 84776-26-1)

Current IARC/WHO classification

Black cohosh extracts (BCEs, *Actaea racemosa*) have not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

BCEs are derived from the root of *Actaea racemosa* (syn. *Cimicifuga racemosa*), which is a prominent botanical dietary supplement or herbal medicinal product, used particularly in the USA, where it ranked among the top 10 bestselling botanicals. It is traditionally used for various female gynaecological conditions, including premenstrual syndrome (PMS), menopausal symptoms, and labour stimulation (Bernacki et al., 2019; NTP, 2023c).

Actaea racemosa is a North American native woodland herb. Historically, it has been used by indigenous populations in America and later also in Europe to treat gynaecological conditions, and it was introduced to the US medical community in the mid-19th century to treat a range of conditions, including ovarian, uterine, and menstrual disorders, as well as to enhance breast milk production (Anonymous, 2003; EMA, 2018).

Black cohosh preparations are usually obtained by dissolving plant material in a solvent, such as ethanol, to form a liquid extract, which is then dried. These are typically available in solid forms for oral dosage and may also be found in combination with other herbal substances. Specific herbal preparations are authorized in Europe for the relief of menopausal symptoms, and in the United Kingdom (UK) for rheumatic pain relief. BCE include 131 bioactive compounds (Salari et al., 2021) and is generally standardized to the content of triterpene glycosides (Jiang et al., 2006). *European Pharmacopoeia* defines BCE as containing a minimum of 1.0% triterpene glycosides (Council of Europe, 2022). Despite their wide use, there is limited scientific evidence to support the efficacy of black cohosh for many of these applications (EMA, 2018).

Commercial products showed wide variations in triterpene glycoside content (0.36–7.55%, $n = 11$) (Jiang et al., 2006). A key problem in evaluating BCE effects is the limited information on the type, amount, quality, and content of the products used in any study.

Cancer in humans

A cohort study (VITAL, VITamins And Lifestyle) in Washington state, USA, among 35 016 postmenopausal women, aged 50–76 years, with 5–7 years follow-up, found a HR of 1.17 (95% CI, 0.75–1.82) between black cohosh and breast cancer (Brasky et al., 2010). A systematic review of the link between black cohosh and breast cancer included two additional case–control studies, detecting no association between black cohosh and risk of breast cancer (Fritz et al., 2014), whereas the two included case–control studies reported significant inverse associations among postmenopausal women for primary (Rebbeck et al., 2007) and invasive (Obi et al., 2009) breast cancer related to black cohosh exposure, with an adjusted OR of 0.39 (95% CI, 0.22–0.70) for the former and an OR of 0.74 (95% CI, 0.63–0.87) for the latter. An observational retrospective cohort included in the review also showed a protective effect for isopropanolic black cohosh extract and a risk of breast cancer recurrence (adjusted HR, 0.75; 95% CI, 0.63–0.89) (Henneicke-von Zepelin et al., 2007).

Cancer in experimental animals

Two long-term bioassays (gavage) have been conducted in mice (2 years with 12 months interim) and rats (2-year perinatal phase with 2-year post weaning phase) in (NTP, 2023c). There was a marginal increase in the incidence of rare uterine squamous cell papilloma in the mid-dose female rat group that was considered to be equivocal evidence by the NTP, and the incidence of squamous metaplasia of the uterus was significantly increased in the high-dose female group. There was no evidence of carcinogenic activity of perinatal BCE exposure in male rats at all maternal doses tested. There was no evidence of carcinogenic activity of BCE in female mice at all doses tested.

Mechanistic evidence

BCE genotoxicity was shown in an in vitro flow-cytometric micronucleus assay using human B-lymphoblastoid TK6 cells (Smith-Roe et al., 2018). Dose-dependent increases in micronuclei in TK6 cells were observed over a range of 30–500 µg/mL BCE for 4 hours or 10–125 µg/mL for 24 hours in the absence of rat liver S9 mix. Micronuclei induction in TK6 cells by BCE is caused by an aneugenic (whole chromosome loss) versus a clastogenic (chromosome breakage) mode of action. Using a multiflow aneugen molecular mechanism assay, BCE was shown to destabilize microtubules (Bernacki et al., 2019). TK6 cells exposed to 25–250 µg/mL BCE demonstrated DNA damage at 0.5, 1, 2, 4, and 24 hours after exposure using

micronuclei assay (Seo et al., 2021). In addition, the same study revealed DNA damage by comet assay. Tail DNA portion was significantly increased at 0.5, 1, 2, and 4 hours when cells were exposed to 250 µg/mL BCE but was not detected in human hepatoblastoma HepG2 cells. Moreover, phosphorylation of γ-H2AX, as a biomarker for DNA breaks, was observed in TK6 cells after 4 and 24 hours of exposure to BCE (Seo et al., 2021).

Several BCEs of different suppliers were tested for genotoxicity in *S. typhimurium* strains TA100 and TA98 and *Escherichia coli* strain WP2 *uvrA* (pKM101) at doses ranging from 100 to 10 000 µg/plate, with or without 10% induced rat liver S9 mix, and the result was equivocal for only one BCE product in TA98 in the presence of S9 mix and negative in other strains (Smith-Roe et al., 2018). Negative results were observed using the same strains for other BCE products at doses ranging from 187.5 to 6000 µg/plate, with or without activation by rat liver S9 mix (NTP, 2023c).

BCE and actein were shown to induce ROS accumulation in human bladder cancer cell lines BIU-87 and T24 and to induce dose-dependent apoptosis (Ji et al., 2017). Both BCE and actein increased ROS production in human TK6 cells, followed by DNA double-strand breaks; this was revealed by detection of γ-H2AX and resulted in chromosomal damage, as measured by an increased percentage of micronuclei in cells (Le et al., 2022a). At the same time, actein protects against methylglyoxal-induced oxidative damage in murine osteoblastic MC3T3-E1 cells (Suh et al., 2017).

BCE does not appear to cause gene mutations, as assessed in bacterial mutagenicity assays.

BCE increased micronucleated reticulocytes and micronucleated erythrocytes in the peripheral blood of female B6C3F$_1$/N mice at doses ranging from 62.5 to 1000 mg/kg per day via gavage for 13 weeks (Mercado-Feliciano et al., 2012). Significant increases in micronucleated reticulocytes were also observed in the peripheral blood of female Wistar Han rats treated with doses ranging from 15 to 1000 mg/kg per day for 13 weeks via gavage (Mercado-Feliciano et al., 2012). A significant increase in micronuclei frequency was caused in peripheral blood from female B6C3F$_1$/N mice by administration of BCE at 1000 mg/kg per day for 13 weeks by gavage (Cora et al., 2017).

BCE inhibited LNCaP (lymph node carcinoma of the prostate) cell xenograft development in immunodeficient nu/nu mice (Seidlová-Wuttke et al., 2006). BCE significantly potentiated anticancer activity of doxorubicin against MCF-7 xenografts (Płoska et al., 2023).

The estrogenic effects of BCEs are controversial, and the more recent data indicate that there may be an anti-estrogenic activity (Mahady et al., 2002). BCE and actein, one of the main BCE triterpene glycosides, strongly stimulated androgen formation in breast cancer cells in vitro (Poschner et al., 2020).

Summary

Sparse epidemiological data show either null or inverse associations between BCEs and cancer in humans (e.g. for primary breast cancer among postmenopausal women). Equivocal evidence of carcinogenicity in female rats was demonstrated by the high incidence of squamous metaplasia of the uterus in a high-dose group. Moreover, BCEs increased the numbers of pulmonary metastases of mammary tumours in mice. There is substantial evidence that BCEs exhibit KCs in experimental systems. Therefore, the Advisory Group considered an *IARC Monographs* evaluation of BCEs (*Actaea racemosa*) to be warranted.

Recommendation: Medium priority

021 Fumonisin B_1 (CAS No. 116355-83-0)

Current IARC/WHO classification

Fumonisin B_1 (FB_1) was classified by IARC as *possibly carcinogenic to humans* (Group 2B) in *IARC Monographs* Volume 82 in 2002 (IARC, 2002a), on the basis of *sufficient* evidence for cancer in animals and *inadequate* evidence for cancer in humans. JECFA conducted a risk assessment of FB_1 in food most recently in 2016, and the previously established group provisional maximum tolerable daily intake (PMTDI) of 2 µg/kg bw for fumonisin B_1, B_2, and B_3, alone or in combination, was retained (FAO/WHO, 2016).

FB_1 was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a) on the basis of mechanistic evidence.

Exposure characterization

FB_1 is the most prevalent member of a family of toxins, known as fumonisins, produced by several species of *Fusarium* moulds, which commonly colonize different cereals, particularly maize, sorghum, and wheat (Cendoya et al., 2018; Knutsen et al., 2018). Climate change is expected to alter the geographical distribution and growth conditions of these fungi, which in turn might change exposure patterns and increase human exposure to FB_1 (Perrone et al., 2020).

The general population is currently exposed by the oral route, by the ingestion of contaminated foods. FB_1 was found in the urine of exclusively breastfed infants, suggesting that human breast milk can also be an important source of exposure in young children (Njumbe Ediage et al., 2013). Additional exposure routes include inhalation and dermal absorption, which can be particularly relevant in the case of occupational exposure (Viegas et al., 2018; Alvito et al., 2022). Activities implying high exposure to organic dust, such as storage work, loading, handling, or milling contaminated materials (grain, waste, and feed), and other activities, such as caring for animals in animal husbandry settings or waste management tasks, will result in acute exposure to FB_1 by inhalation (Viegas et al., 2018).

In human biomonitoring studies, FB_1 has been detected in urine of the general population from different countries from Europe, South America, and Asia (Afsah-Hejri et al., 2013; Cendoya et al., 2018; Sabbioni et al., 2022).

Cancer in humans

As described in the previous *IARC Monographs* evaluation, epidemiological studies conducted in South Africa and China revealed some evidence of an association between the intake of FB_1 and increased incidence of oesophageal cancer (Marasas et al., 1979, 1981, 1988; Rheeder et al., 1992; IARC, 1993a; Chu and Li, 1994; Yoshizawa et al., 1994; Wang et al., 2000; Sun et al., 2007). Similar studies conducted in Italy did not find an association between the intake of FB_1 and oesophageal cancer incidence (Logrieco et al., 1995; WHO, 2000).

Cancer in experimental animals

The previous *IARC Monographs* evaluation established *sufficient evidence* in experimental animals for the carcinogenicity of FB_1 (IARC, 2002a). Since then, an additional feed study using male p53 heterozygous ($Trp53^{+/-}$) and p53 homozygous ($Trp53^{+/+}$) transgenic mice has been published. Hepatic adenomas and cholangiomas were observed at the highest dose; a low incidence of cholangioma and hepatocellular adenoma was observed in both strains. The similarity in response in both strains supports the notion that the carcinogenicity of FB_1 is due to a non-genotoxic mode of action (Bondy et al., 2012).

Mechanistic evidence

There is little evidence that FB_1 or its metabolites form DNA adducts (IARC, 2002a). FB_1 showed negative results in bacterial mutagenesis assays but induced DNA damage in vitro and in vivo, probably due

to oxidative stress (Chen et al., 2021a). Genotoxicity was described in human leukocytes (Kaminski et al., 2020; Miguel Alfonso et al., 2022). FB_1 induced epigenetic alterations, including DNA methylation and histone modifications in human or non-human mammalian cell lines or in vivo (Zhu et al., 2021a). Oxidative stress was increased by FB_1 in human umbilical vein endothelial cells (Zhao et al., 2020a) and in human or rodent cell lines (Chen et al., 2021a). Oxidative stress caused by FB_1 induced apoptosis and cellular autophagy in experimental systems (Khan et al., 2018; Kim et al., 2018a; Li et al., 2021c). This FB_1-induced immunotoxicity mechanism is mainly involved in oxidative stress. FB_1 usually plays an anti-inflammatory (immunosuppressive) role when stimulatory factors are present and a proinflammatory (immunostimulatory) role when these stimulatory factors are absent (Sun et al., 2022a); this was observed in primary human peripheral blood-derived dendritic cells (Stockmann-Juvala et al., 2008) and in rats (Tryphonas et al., 1997). FB_1 can promote cell proliferation in human oesophageal epithelial cells (Yu et al., 2021c) and in normal human liver cells (Wang et al., 2013).

In addition, FB_1 is a strong inhibitor of ceramide synthase, causing a disruption in sphingolipid metabolism and an accumulation of sphinganine and sphingosine, which seem to induce apoptosis in rodent renal tubule cells and hepatocytes (Voss et al., 2001; Riley and Merrill, 2019). FB_1-induced kidney and liver toxicity in animal models could be linked with the inhibition of ceramide synthase through a series of events: increased mRNA expression of genes modulating apoptosis; increased expression of TNFα; increased expression of genes involved in mitosis or regulating cell cycle progression; oxidative stress and secondary damage to macromolecules; altered lipid biosynthesis; and altered lipid composition in cell membranes (Voss and Riley, 2013). Importantly, inhibition of ceramide synthase was detected in people in Guatemala who consumed corn-based foods with a high content of FB_1 (Riley et al., 2015). Inhabitants of Guatemala also have a high incidence of liver cancer, although this is confounded by the presence of aflatoxin B_1 (Torres et al., 2015). In addition, JECFA concluded that "daily exposure to high levels of FB_1 is likely to result in inhibition of ceramide synthase in humans, similar to what has been described in many animal studies" (FAO/WHO, 2017).

Summary

Since the previous *IARC Monographs* evaluation, only one new human cancer study has become available, and the human cancer evidence remains equivocal. There is already *sufficient* evidence that FB_1 causes tumours in experimental animals. There is substantial new mechanistic evidence relative to several KCs in experimental systems and some evidence in human primary cells. Some studies are available in studies in exposed humans, although there are concerns on potential confounding co-exposure to aflatoxin B_1. On the basis of current mechanistic information, a re-evaluation of the agent could support a change in the classification of the agent. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of fumonisin B_1 to be warranted.

Recommendation: Medium priority

022 Patulin (CAS No. 149-29-1)

Current IARC/WHO classification

Patulin has been previously evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a). JECFA conducted a risk assessment of patulin in food (FAO/WHO, 1995a) and calculated a provisional tolerable weekly intake (PTWI) of 7 µg/kg bw/day.

Exposure characterization

Patulin is a polyketide mycotoxin primarily associated with mouldy fruits, with human exposure mainly occurring through food consumption. It is produced by various species of fungi, including several species of *Penicillium*, *Aspergillus*, and *Byssochlamys*. Patulin has been detected in mouldy fruits and vegetables (e.g. apples, peaches, pears, tomatoes, apricots, bananas, pineapples, grapes, strawberries, melons, paprika, cucumbers, carrots). However, it is not found in unspoiled fruit. Processed fruit and vegetable products can contain patulin. Globally, patulin is one of several mycotoxins whose levels in food are regulated (IARC, 1986; Puel et al., 2010). The European Commission (2006) set maximum levels of 25 µg/kg for solid apple products and 10.0 µg/kg for apple juice or solid apple products intended for infants and young children.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 1987a), there was *inadequate* evidence in experimental animals for the carcinogenicity of patulin. Since that evaluation, some studies have been published.

Patulin is able to initiate carcinogenesis in mouse skin. One single topical application of 400 nmol of patulin in mouse skin followed by twice weekly application of 12-tetradecanoyl-phorbol-myristate-acetate (4 nmol per 0.1 mL of acetone) after a week of initiation was able to induce the formation of SCC after 14 weeks. However, no tumours were observed when patulin was used for 25 weeks, either as a complete carcinogen (80 nmol) or as a tumour promoter (20 nmol and 40 nmol) (Saxena et al., 2011).

The few studies of long-term toxicity on patulin showed an absence of tumours in rats treated orally for 74–104 weeks (Osswald et al., 1978; Becci et al., 1981). These studies were considered in the previous evaluation of patulin by IARC as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1986).

Mechanistic evidence

Patulin has a strong affinity for sulfhydryl (SH) groups; this explains its inhibition of many enzymes (Puel et al., 2010). Patulin adducts formed with cysteine are less toxic than the unmodified compound in acute toxicity, teratogenicity, and mutagenicity studies.

Patulin is hepatotoxic to animals; this toxicity is related to its ability to react with SH groups and to induce oxidative damage (increased ROS levels, decreased GSH levels, increased SOD and catalase activity and increased levels of thiobarbituric acid-reactive substances, TBARS, in the liver) (Puel et al., 2010; Song et al., 2014a; Janik et al., 2020). Patulin induces apoptosis in human colon carcinoma (HCT116) and embryonic kidney cells (HEK293) through a ROS-dependent mechanism involving estrogen receptor (ER) stress and activation of the mitochondrial apoptotic pathway (Boussabbeh et al., 2015).

In vivo studies in mice indicate variable effects of patulin on the immune system. Patulin treatment increased the number of splenic T lymphocytes and depressed serum immunoglobulin concentrations in mice and rabbits (Escoula et al., 1988a), and increased neutrophil numbers and resistance to *Candida albicans* infection (Escoula et al., 1988b). In female $B6C3F_1$ mice treated orally for 28 days, patulin was not able to alter the cell-mediated or humoral response (Llewellyn et al., 1998).

A single topical application of patulin showed enhanced cell proliferation (approximately twofold), along with increased generation of ROS and activation of ERK-, p38-, and c-Jun related MAPKs, in mouse skin. Patulin exposure also showed activation of downstream target proteins, c-fos, c-Jun, and NF-κB transcription factors, along with a significant increase of lipid peroxidation and a decrease in the activities of free sulfhydryls, catalase, SOD, and GSH reductase activities (Saxena et al., 2011).

Patulin was found to reduce the cytokine secretion of IFNγ and IL-4 by human macrophages (Wichmann et al., 2002) and that of IL-4, IL-13, IFNγ, and IL-10 by human PBMCs and human T cells (Luft et al., 2008). This decrease in cytokine secretion was due not to the cytotoxic effects of patulin but to the depletion of intracellular GSH (Luft et al., 2008).

Patulin induced a reduction in the production of IL-2 and IL-5 in thymoma cell line EL-4 treated with patulin (Marin et al., 1996).

Data on genotoxicity were variable; most assays carried out with mammalian cells were positive while assays in bacteria were mainly negative. In addition, some studies indicated that patulin impaired DNA synthesis (Puel et al., 2010).

Patulin treatment induced a significant increase in micronuclei in polychromatic erythrocytes (PCE) and micronuclei in normochromatic erythrocytes (NCE) in male Kunming mouse bone marrow cells (Song et al., 2014a).

Patulin induced chromosomal aberrations in both gaps and breaks and induced a significant increase in chromosomal gaps and breaks in mouse bone marrow cells (Song et al., 2014a).

Patulin induces DNA damage, as measured by the comet assay in the brain, liver, and kidneys in a dose-dependent manner and over a broad dose range (1.0–3.75 mg/kg bw) in male CF-1 mice aged 9 weeks; this is associated with decreased GSH content and increased lipid peroxidation (de Melo et al., 2012).

JECFA (FAO/WHO, 1998a) concluded from the available data that patulin is genotoxic.

Summary

There is an absence of evidence on cancer in humans and cancer in experimental animals. However, there is evidence that patulin exposure exhibits several KCs in experimental systems in vivo and in vitro; this could support a classification regarding the carcinogenicity of patulin. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of patulin to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

023 Pyrrolizidine alkaloids

Current IARC/WHO classification

Hydroxysenkirkine (CAS No. 26782-43-4), isatidine (CAS No. 15503-86-3), jacobine (CAS No. 6870-67-3), retrorsine (CAS No. 480-54-6), seneciphylline (CAS No. 480-81-9), and senkirkine (CAS No. 2318-18-5) have each been previously evaluated by IARC as *not classifiable as to its carcinogenicity to humans* (Group 3). Lasiocarpine (CAS No. 303-34-4) and monocrotaline (CAS No. 315-22-0) have been classified by IARC as *possibly carcinogenic to humans* (Group 2B) in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a) and riddelliine (CAS No. 23246-96-0) has been classified by IARC as *possibly carcinogenic to humans* (Group 2B) in *IARC Monographs* Volume 82 in 2002 (IARC, 2002a). JECFA conducted a health risk assessment for pyrrolizidine alkaloids (FAO/WHO, 2015).

Pyrrolizidine alkaloids (PAs) have never been evaluated as a group. Riddelliine was given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a).

Exposure characterization

PAs are a group of several hundred secondary plant metabolites that are present in plants as a defence against herbivores (BfR, 2020). They mainly occur in some, but not all, plants of the families Asteraceae, Boraginaceae, and Fabaceae (Schrenk et al., 2020a). Human exposure can occur by direct consumption of plants containing PAs or by food contaminated with plants containing PAs, e.g. via weeds.

In food, the highest levels are found in honey, flower pollen, tea, herbal infusions, herbs and spices, flour, spinach, and some food supplements. Intake in food and beverages has been estimated to be in the low ng/kg bw per day in Germany (BfR, 2020) and in Europe overall (EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain) et al., 2017), whereas highest levels among toddlers were estimated to be in the hundreds of ng/kg bw per day. Exposure can also occur through herbal medicines (Schrenk et al., 2020a). In some local populations in Asia, Africa, and the Americas, consumption of particular herbs or the contamination of food has led to higher exposures and thereby poisoning (Culvenor, 1983).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In previous *IARC Monographs* evaluations, *sufficient* evidence for carcinogenicity in experimental animals was identified for lasiocarpine, monocrotaline (IARC, 1987a), and riddelliine (IARC, 2002a). No new studies have been reported for hydroxysenkirkine, isatidine (*limited* evidence), or jacobine since the previous evaluation (IARC, 1987a). Schoental et al. (1954) reported that retrorsine induced hepatomas in male rats and papillary adenomas in female rats. Senkirkine was shown to induce haemangioendothelial sarcomas and liver cell adenomas in male rats (Hirono et al., 1979). No studies of carcinogenicity in animals exposed to seneciphylline were available to the Advisory Group.

Mechanistic evidence

PAs are ester alkaloids that require biotransformation to be excreted from the body. There are three main pathways for metabolism of PAs: hydrolysis of PAs to release necines and necic acids, N-oxidation to form PA *N*-oxides, and oxidation of PAs to produce derivatives of dehydropyrrolizidine alkaloid (DHPA), a pyrrolic ester (Chen et al., 2010). Metabolic activation of PAs plays an essential role in their mutagenicity and in liver tumour initiation (Fu, 2017). The liver is the main target organ of the genotoxicity and carcinogenicity of PAs in animal models (Chen et al., 2010; Ebmeyer et al., 2020). DHPAs can bind covalently with proteins and nucleic acids to generate pyrrole–protein and pyrrole–DNA adducts (Chou and Fu, 2006; Zhu et al., 2017, 2022). Recently, it was shown for the first time that the male rat liver microsomal metabolism of lasiocarpine, retrorsine, monocrotaline, and heliotrine (not only for riddelliine) forms their corresponding pyrrolizidine alkaloid *N*-oxides, producing DNA adducts (DHPA–DNA adducts) in the presence of calf thymus DNA (He et al., 2017). The same research group suggested that a set of DHPA–DNA adducts were biomarkers for PA-induced liver tumour formation (Xia et al., 2013); the PAs tested were retrorsine, lasiocarpine, riddelliine, monocrotaline, riddelliine, senkirkine, heliotrine, and clivorine.

DNA damage of 15 PAs, as measured by micronucleus induction, was observed in HepaRG human liver cells (Allemang et al., 2018). The in vitro genotoxicity of a mixture of structurally different PAs with various potencies was tested in HepaRG human liver cells and an additive effect was shown (Allemang et al., 2022). Importantly, Louisse et al. (2019) observed differences in genotoxic potencies of PAs in HepaRG human liver cells using the γ-H2AX in-cell western assay: the group with the highest potency consisted of open diester PAs and cyclic diester PAs (including riddelliine). PAs induced genotoxicity in metabolically competent TK6 cell lines (Li et al., 2020a).

Recent investigations focused on mutational signatures in liver cancer for the PAs as a group (He et al., 2021); approximately one third of resected human liver samples of 34 patients with HCC contained pyrrole–protein adducts. The same authors identified a PA mutational signature (PAMS), derived from DNA adduction and DNA damage induced by retrorsine exposure in experimental mice and HepaRG cells, which they validated in the genomes of patients with PA-positive liver cancer but not in those of patients with PA-negative liver cancer, confirming the specificity of PAMS for PA-associated liver cancers. Furthermore, the

developed PAMS was checked in public liver cancer genome databases across various regions. Remarkably, the specific PAMS related to PA exposure is more highly prevalent in Asian countries than in Europe and North America (He et al., 2021).

Additionally, further research concerned the changes in gene expression of a group of four structurally different PAs (echimidine, heliotrine, senecione, and senkirkine) in primary human hepatocytes (Luckert et al., 2015). Interestingly, 1304 genes were identified as commonly regulated by all four PAs. These genes are linked to HCC, hepatic steatosis, bile duct cancer, proliferation of liver cancer cells, and dysfunction of glucose metabolism (Luckert et al., 2015).

Summary

No studies on human cancer were available. Previous evaluations (IARC, 1987a) reported *sufficient evidence* in experimental animals for lasiocarpine, monocrotaline, and riddelliine. There is *limited* evidence of carcinogenicity for hydroxysenkirkine and isotidine, and no additional cancer bioassays were identified since the previous evaluation. No cancer bioassays were identified for jacobine or seneciphylline. Senkirkine and retrorsine have been reported to induce tumours in male rats (*limited* evidence). Mechanistic evidence was identified for PAs related to the KCs, including genotoxicity, mostly in experimental systems. One mechanistic study in exposed humans showed mutational signatures of retrorsine (not previously evaluated by IARC) associated with liver cancer. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of pyrrolizidine alkaloids to be warranted and recommended combining evaluations for all PAs in one volume.

Recommendation: Medium priority

024 Safrole (CAS No. 94-9-7)

Current IARC/WHO classification

Safrole was classified by IARC as *possibly carcinogenic to humans* (Group 2B) in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a), on the basis of *sufficient* evidence for cancer in experimental animals.

Exposure characterization

Safrole is the chemical 4-allyl-1,2-methylenedioxy-benzene ($C_{10}H_{10}O_2$), a natural constituent of the sassafras plant oil (up to 93% safrole oil) and camphor tree oil (up to 95% safrole oil). Safrole is also present in extracts and essential oils of numerous plants, e.g. nutmeg, cinnamon, anise, pepper, and sweet basil (European Commission, 2002a; Burdock, 2010; Götz et al., 2023).

In the general population, the main potential routes of exposure to safrole are ingestion and inhalation. Safrole is ingested in edible spices, including sassafras, nutmeg, mace, basil, and their essential oils, and from chewing betel quid. Safrole is also present in cola drinks (Raffo et al., 2013). The average intake (for consumers only) was estimated at 1 mg/person per day from food and spices and 1 mg/person per day from essential oils in 1995, at 0.3 mg/person per day with the 97.5th percentile increasing to 0.5 mg/person per day in 2002, and at 0.1 mg/person per day from nutmeg oil in 2023 (European Commission, 2002a; NTP, 2021a; Davidsen et al., 2023). Safrole was also identified as a minor constituent of bidi cigarettes (mean concentration, 33 µg/cigarette) (Stanfill et al., 2006) and regular tobacco cigarettes (median concentration, 5.2 ng/g of tobacco) (Stanfill and Ashley, 1999). Relatively small amounts of safrole have been released to the environment since 1988, mostly in air emissions (TRI, 2009).

Occupational exposure to safrole may occur by inhalation or dermal contact (HSDB, 2009). Health professionals, such as pharmacists, physicians, and nurses, could be exposed during the formulation, preparation, administration, or clean-up of drugs containing safrole or sassafras. In the US National

Occupational Exposure Survey 1981–1983, the National Institute for Occupational Safety and Health (NIOSH) estimated that 6475 workers (5761 women) were potentially exposed to safrole (NIOSH, 1990b).

Safrole has been banned as a food additive by US FDA since 1960 (CFR, 2024, 21 Code of Federal Regulations §189.180) and in the EU since 2008, and maximum levels have been established for food compounds and non-alcoholic beverages that have been flavoured with flavourings and food ingredients in which safrole occurs naturally (European Parliament, 2008). Safrole itself should not be used as a fragrance ingredient; essential oils containing safrole should not be used at such a level that the total concentration of safrole exceeds 0.01% in consumer products (IFRA, 2009).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 1987a), there was *sufficient* evidence in experimental animals for the carcinogenicity of safrole. Safrole caused liver tumours in two rodent species and by two different routes of exposure. Liver cancer (HCC) in male mice and benign or malignant liver tumours (HCC, adenoma, or cholangiocarcinoma) in rats of both sexes were observed after a dietary administration of safrole (IARC, 1972, 1976b). Liver cancer (HCC) was also observed in mice of both sexes aged between 7 and 28 days treated with safrole by stomach tube, followed by dietary exposure for up to 82 weeks, and in infant male mice treated with safrole by subcutaneous injection (IARC, 1976b). Additional studies have been identified in mice. The incidence of liver tumours (adenoma and carcinoma) was increased in male mice exposed during infancy through their dams' milk and in adult female mice fed a diet containing safrole (Vesselinovitch et al., 1979a, b; Lipsky et al., 1981; Vesselinovitch, 1983).

Mechanistic evidence

Safrole–DNA adducts have been detected in tissues from patients in Taiwan, China, with oesophageal cancer (Lee et al., 2005), oral SCC (Chen et al., 1999), or HCC (Chung et al., 2008). All these patients had a history of habitual areca chewing (areca nut is known to contain a high concentration of safrole). Safrole–DNA adducts were found in peripheral leukocytes from people with a known areca nut chewing history, compared with people without a known areca nut chewing habit (Liu et al., 2004). The genotoxicity of safrole was also tested in vitro in three oesophageal cell lines and four cultures of primary oesophageal keratinocytes from oesophageal mucosa samples of patients with cancer. In two of the oesophageal keratinocyte cultures, adduct formation was increased by treatment with safrole after induction of cytochrome P450 by 3-methylcholanthrene (Lee et al., 2005). Treatment of human buccal mucosa squamous carcinoma (OC2) cells with safrole induced cell proliferation (Huang et al., 2005). In rodents, safrole induced oxidative damage in rat hepatic tissue after a single intraperitoneal injection (Liu et al., 1999) or when treated with gavage (Ding et al., 2015). Safrole induced unscheduled DNA synthesis (UDS) in rat and mouse cultured primary hepatocytes (Burkey et al., 2000). Safrole was mutagenic in mouse lymphoma cells and induced sister-chromatid exchanges (SCE) in Chinese hamster ovary (CHO) cells (NTP, 2024a).

Summary

No studies were identified that evaluated the relation between exposure to safrole and human cancer. There is already *sufficient* evidence that safrole causes cancer in experimental animals. Several studies are available showing evidence of DNA adducts in exposed humans, and of several genotoxicity end-points in human primary cells and in rodents in vivo and in vitro. Safrole induced oxidative DNA damage in rats in vivo, and cell proliferation in human cell line in vitro. The available mechanistic information could support a change in classification. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of safrole to be warranted and recommends evaluating safrole together with estragole (agent 103).

Recommendation: High priority (and ready for evaluation within 2.5 years)

025 Zearalenone

Current IARC/WHO classification

Zearalenone was evaluated by IARC in the context of toxins derived from *Fusarium graminearum*, *Fusarium culmorum*, and *Fusarium crookwellense* as *not classifiable as to its carcinogenicity to humans* (Group 3) in *IARC Monographs* Volume 56 in 1993 (IARC, 1993a). Zearalenone has been evaluated by JECFA (FAO/WHO, 2000), with a PMTDI of 0.5 µg/kg bw per day established.

Exposure characterization

Zearalenone is a β-resorcylic acid macrolide mycotoxin produced primarily by species of *Fusarium*, such as *Fusarium graminearum*. It is a significant contaminant in both food and feed, with human exposure occurring mainly through the consumption of contaminated food products (IARC, 1993a). Zearalenone is commonly found in cereals such as maize, wheat, barley, sorghum, rye, and rice, and can be present in various food products derived from these grains, including baked goods, pasta, breakfast cereals, and bread. It is also detected in beer, corn oil, and in milk when cows consume contaminated feed (IARC, 1993a; Ropejko and Twarużek, 2021).

The occurrence and level of zearalenone contamination can vary depending on climate conditions, with higher levels often found in countries with warm and wet climates. In the context of climate change, the patterns of exposure to this mycotoxin could change, potentially leading to higher frequencies and concentrations of zearalenone in crops (Ropejko and Twarużek, 2021).

While the primary route of human exposure to zearalenone is through food consumption, specific occupational settings may also pose a risk. Workers handling contaminated raw materials or exposed to organic dust in agricultural or milling environments may be at risk of inhalation exposure to zearalenone (IARC, 1993a; Ropejko and Twarużek, 2021).

Cancer in humans

A few epidemiological studies have examined the relation between zearalenone exposure and cancer. Pillay et al. (2002) found no significant difference in plasma levels of zearalenone and its metabolites, α-zearalenol and β-zearalenol, between patients with breast cancer, cervical carcinoma, and healthy people, with mean levels below 0.5 ng/mL. A case–control study (69 cases versus 41 controls) conducted in Tunisia found an association between urinary α-zearalenol, another metabolite of zearalenone, and incident breast cancer (Belhassen et al., 2015).

Cancer in experimental animals

In the previous evaluation (IARC, 1993a), there was *limited* evidence in experimental animals for the carcinogenicity of zearalenone. Zearalenone was tested for carcinogenicity orally (by diet) in one experiment in mice and in one experiment in rats. An increased incidence of hepatocellular adenomas was observed in female mice and of pituitary adenomas in mice of each sex. No increase in the incidence of tumours was observed in rats (NTP, 1982a).

Since the last evaluation, new studies have been identified. Zearalenone inhibited colorectal tumorigenesis in azoxymethane-induced carcinogenesis in mice, reducing total tumour count, colon weight, colonic crypt depth, and colonic collagen fibrosis (Leung et al., 2023). Prepubertal zearalenone exposure suppressed *N*-methyl-*N*-nitrosourea–induced mammary tumorigenesis in female Sprague-Dawley rats (Nikaido et al., 2003). Maternal exposure to zearalenone during pregnancy did not increase carcinogen-induced mammary tumorigenesis in female rat offspring (Hilakivi-Clarke et al., 1999). α-Zearalenol in

combination with perfluorooctanoic acid increased the risk of developing mammary tumours induced by 7,12-dimethylbenz[*a*]anthracene (Su et al., 2022).

Mechanistic evidence

Exposure of human embryonic kidney (HEK293) cells to zearalenone resulted in a concentration-dependent increase in DNA strand breaks, measured using the comet assay (Gao et al., 2013). DNA adducts in female mice and rats treated intraperitoneally or orally with zearalenone were revealed using a ^{32}P-postlabelling method (Pfohl-Leszkowicz et al., 1995). Zearalenone treatment increased DNA methylation levels in mouse ova. Histone methylations were also altered: histone H3 lysine (H3K)4me2, H3K9me3, and H4K20me1, me2, and me3 levels decreased. Zearalenone, as well as α- and β-zearalenol, increased the percentage of chromosomal aberrations in HeLa cells and in mouse bone marrow cells (Ayed et al., 2011). Zearalenone induced different types of chromosome aberration in mice; this was concentration-dependent (2–20 mg/kg bw). These doses corresponded to 0.4–4% of the median lethal dose (LD_{50}) in mice (Ouanes et al., 2005). Zearalenone induced chromosomal aberrations and micronuclei in both Balb/c mice and in vitro cultures of mouse lymphocytes isolated from mouse spleen (Ben Salah-Abbès et al., 2009). Zearalenone was not mutagenic to *Salmonella* strains TA1538, TA98, or TA100 at any concentration (Bartholomew and Ryan, 1980). Zearalenone demonstrated cytotoxicity against HepG2 cells in vitro and arrested the cell cycle in the G_2 phase, although it did not cause DNA damage (Domijan et al., 2023).

In human hepatocytes (HepG2 cells), oxidative damage was one of the main pathways of zearalenone genotoxicity (Hassen, et al., 2007). Zearalenone induced oxidative stress in human cultured prostate cancer cells DU-145 and LNCaP cells followed by DNA damage and G_2/M cell cycle arrest (Kowalska et al., 2020).

In human HCC cells, zearalenone and α-zearalenol significantly increased global levels of DNA methylation and global histone modifications (H3K27me3, H3K9me3, H3K9ac). Expression levels of the chromatin modifying enzymes euchromatic histone lysine methyltransferase (EHMT2), establishment of sister-chromatid cohesion *N*-acetyltransferase 1 (ESCO1), histone acetyltransferase 1 (HAT1), lysine acetyltransferase 2B (KAT2B), protein arginine methyltransferase 6 (PRMT6), and SET domain containing 8 (SETD8) were upregulated. Both compounds also changed expression levels of aryl hydrocarbon receptor (AHR), LXRα, peroxisome proliferator-activated receptor (PPAR) PPARα, PPARg, LAFABP, low density lipoprotein receptor (LDLR), GLUT2, AKT1, and hexokinase 2 (KHK2) genes (Karaman et al., 2020). Zearalenone modulated the invasiveness of prostate cancer PC-3 cells, depending on *ERα* expression (Kowalska et al., 2018).

Zearalenone decreased mouse egg developmental competence by affecting epigenetic modifications (Zhu et al., 2014). Prepubertal zearalenone exposure caused severe endocrine disruption in female Sprague-Dawley rats (Nikaido et al., 2003). In rats exposed to zearalenone, a notable upregulation of protein expression, specifically of STAT2, STAT6, and ISG15, was observed in the colon cells (Ruan et al., 2023). Zearalenone increased the concentrations of plasma insulin, glucose, testosterone, progesterone, and luteinizing hormone (LH) in rats, while the concentration of plasma estradiol was reduced. It also incited expression of TNFα and secreted frizzled-related protein-4 (SFRP4), and led to atresia of follicles. In the rat, exposure to zearalenone intensely influenced plasma hormonal factors and expression of genes related to the polycystic ovary, increasing the risk of its progression (Abbasian et al., 2018). Zearalenone exposure promoted the expression of tumorigenesis genes YAP1, WW domain containing transcription regulator 1 (WWTR1), and cyclin D1 (CCND1) in mouse granulosa cells (Zhang et al., 2018). In an endometriosis model in mice, zearalenone acted as an antagonist in endometriotic tissue in the presence of a sufficient concentration of estrogen but switched to estrogenic activity in the absence of estrogen in the development of endometriosis. Zeranol, a zearalenone metabolite, induced cell proliferation and protein disulfide isomerase expression in the mammary glands of August Copenhagen Irish (ACI) rats (Zhong et al., 2011).

Zearalenone also inhibited ectopic tissue growth by decreasing inflammatory response in an endometriosis model (Yan et al., 2022).

A cohort study found that zearalenone concentrations in the blood of patients with colon cancer were associated with estradiol and progesterone concentrations (Lisieska-Żołnierczyk et al., 2023). Zearalenone and its metabolites exhibited strong estrogenic potency and influenced the production of progesterone, estradiol, testosterone, and cortisol hormones in the human H295R adenocarcinoma cell line (Frizzell et al., 2011).

At low concentrations, zearalenone accelerated the growth of ER-positive MCF-7 and KPL-1 human breast carcinoma cells but did not affect the growth of ER-negative MDA-MB-231 cells. The acceleration of ER-positive cell growth induced by low-dose zeranol (zearalenone metabolite) involved the downregulation of p21 protein, which resulted in cell cycle progression (Yuri et al., 2006).

Zearalenone promoted the progression of MCF-7 cells by a decrease in the G_0/G_1 phase and a significant increase in the S phase. The pro-proliferative activity of zearalenone was due to inhibition of apoptosis through regulation of BAX/BCL2 expression (Yu et al., 2005).

In MCF-7 cells, zearalenone and its metabolites α-zearalenol and β-zearalenol increased the production of CYP1B1-mediated estrogen catechol metabolites, directing the biotransformation of estrogen to 4-hydroxyestradiol, which has been identified previously as a crucial factor in estrogen-induced tumour initiation (Malekinejad et al., 2023). Zearalenone stimulated DNA synthesis, cell proliferation, and anchorage-independent growth in vitro of colon cancer HT29 and SW480 cells. Growth promotion was mediated by the activation of ERK1/2 and YAP1/TAZ signalling (Lo et al., 2021b).

Zearalenone at low concentrations enhanced cell proliferation in colon carcinoma cell line HCT116, increased colony formation, and sped up cell migration after wound healing (Abassi et al., 2016). However, in another study of HTC116 cells, zearalenone inhibited cell proliferation, which was accompanied by an increase in the generation of free radicals, an induction of heat shock protein (Hsp70) expression, and an activation of antioxidant enzymes (catalase and SOD), as well as a loss of mitochondrial membrane potential (El Golli-Bennour et al., 2019).

Summary

While there are only sparse data in humans and experimental animals on the carcinogenicity of zearalenone, the compound exhibits several KCs in experimental systems, including genotoxicity, modulation of receptor-mediated effects, and cell proliferation. This evidence could support a change in the classification of the carcinogenicity of zearalenone. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of zearalenone to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

026 Cyclopeptide cyanotoxins

Current IARC/WHO classification

Microcystin-LR was classified in 2006 by IARC as *possibly carcinogenic to humans* (Group 2B), on the basis of strong mechanistic evidence. Nodularin was evaluated as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 2010c).

Exposure characterization

As noted in the 2019 Advisory Group report (IARC, 2019a):

> Exposure routes of microcystins include drinking contaminated water, bodily contact, inhalation, haemodialysis, and consumption of

contaminated food and blue-green algal dietary supplements. More research has been conducted on microcystins and microcystin-LR in particular than on any other cyanotoxin, and microcystin-LR is the most studied structural variant because of its high occurrence in rivers, lakes, and other reservoirs. The greatest source of exposure to microcystin-LR is water where eutrophication has occurred, and levels may be as high as several milligrams per litre (IARC, 2010c). Of the three routes of exposure to microcystins (dermal, inhalation, and oral), the most important route is thought to be ingestion, via swallowing of contaminated water (drinking-water or through recreational use) and consumption of products such as contaminated blue-green algal supplements (IARC, 2010c).

Cancer in humans

IARC Monographs Volume 94 (IARC, 2010c) included evaluations for two cyclic peptides, microcystin-LR and nodularin, both toxins produced by various cyanobacterial species that proliferate under certain conditions in water bodies. The evaluation concerning human cancer was based on ecological studies, mostly for liver cancer, in which source of drinking-water was taken as a surrogate for exposure to the agents. The determination of *inadequate* evidence for cancer in humans was largely due to the non-specificity of this exposure measurement, despite observed associations being quite strong. Since then, there have been more ecological studies of the same type, and a small number of relevant case–control studies. These ecological studies based on drinking-water source provided mixed results.

A hospital-based case–control study of liver cancer from China (Zheng et al., 2017), in which serum concentrations of microcystin-LR were determined by enzyme-linked immunosorbent assay (ELISA), found a dose–response relation. Comparing the highest and lowest exposure quartiles, the relative risk (RR) was 4, after adjustment for other major liver carcinogens.

Cancer in experimental animals

As noted in the 2019 Advisory Group report (IARC, 2019a), there are sparse data showing little evidence of carcinogenicity of individual microcystins in experimental animals.

Mechanistic evidence

Microcystin-LR and nodularin are considered to be liver toxins in humans, causing inflammation, and possibly fibrosis in the longer term. A wide range of mechanistic studies of these toxins suggest that they exhibit KCs that could cause or promote cancer.

Summary

Apart from the very limited body of literature, a key issue in assessing the human cancer data is the nature of the exposure assessment. As noted previously, studies of cyanobacteria-related toxins and cancer have variously used source of drinking-water, serum detection of microcystin-LR, and in vitro detection of cyanobacterial species. The presence of a variety of liver toxins in these species complicates the interpretation of studies that focus on single toxins, such as microcystin-LR. The diversity of exposure measures complicates the task of synthesizing the evidence in a coherent manner. Adequate adjustment for other major liver cancer risk factors has been undertaken for the case–control studies but not the ecological studies.

Therefore, it is questionable whether the body of evidence from human studies on microcystin-LR accumulated since the last *IARC Monographs* evaluation would enable a re-evaluation of the status of the

evidence. In the absence of cancer evidence in experimental animals, the classification would most probably remain in Group 2B. There has been no advance on human data for other specific toxins related to cyanobacteria. An evaluation of cyanobacteria exposure might be an alternative but would most probably also lead to a finding of *inadequate* evidence in humans, as there appears to be only one small relevant study. The Advisory Group therefore considered that an *IARC Monographs* re-evaluation of cyclopeptide cyanotoxins is unwarranted at present.

Recommendation: No priority

027 Chronic circadian dysfunction

Current IARC/WHO classification

Chronic circadian dysfunction has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

A key consideration for the Advisory Group was whether chronic circadian dysfunction is an external agent that lends itself to prevention (this is the scope of the *IARC Monographs* programme). It is problematic to define exposure to what is essentially a physiological response. Exposures and host characteristics that may lead to circadian disruption include night shift work (NSW); occupations leading to jet lag, e.g. as aircrew; sleep duration and timing; artificial light at night (ALAN); timing of diet and time-restricted eating (including night-time fasting); genetics and host characteristics (e.g. chronotype) – these last two would not be suitable topics for *IARC Monographs* evaluations.

There is an interrelationship between these factors, which might not occur at the same level of a causal chain between exposure and cancer. Some of these exposures (NSW, sleep, ALAN) are reviewed next in the present report (agents 028–030).

Cancer in humans

No studies in humans were available to the Advisory Group for the evaluation of chronic circadian dysfunction. Available studies have evaluated factors that may lead to circadian disruption, e.g. NSW, air crew work, sleep, timing of diet, and ALAN. The submitted nomination for an evaluation of chronic circadian dysfunction focused mostly on suggestions of how to conduct epidemiological studies rather than presenting evidence on how circadian disruption (or chronic circadian dysfunction) could be evaluated within the context of the *IARC Monographs* programme.

Cancer in experimental animals

Several studies in mice and rats have demonstrated that chronic disruption of circadian rhythm by shifting the animals' daily light–dark schedule or exposing the animals to constant light leads to increased spontaneous tumour formation (IARC, 2020; NTP, 2021b). These studies include models of NSW, in which light and dark periods are inverted, and models of chronic jet lag, where the light period is increased or decreased every few days. The 2019 Working Group that evaluated NSW (IARC, 2020) concluded that there was sufficient evidence in experimental animals for the carcinogenicity of alteration in the light–dark schedule.

Mechanistic evidence

The 2019 Working Group that evaluated NSW (IARC, 2020) found ample evidence that it induces circadian disruption and concluded that there is *strong* evidence in experimental systems that alteration in the light–dark schedule is associated with KCs, based on evidence of effects consistent with immunosuppression, chronic inflammation, and cell proliferation. The Working Group noted several

limitations of mechanistic studies in night shift workers, including small sample sizes, a lack of adjustment for potential confounding factors, and issues around the timing of biological specimen collection. These limitations remain an issue for most human mechanistic studies of NSW published since 2019.

Two studies of social jet lag (discrepancy between biological and social time) in humans observed associations with increased inflammation (Bermingham et al., 2022; Girtman et al., 2022). For example, in a study in 931 participants, social jet lag (assessed as ≥ 1.5 hour difference in sleep midpoint on weekdays versus weekend days), was associated with significantly greater fasting levels of glycoprotein acetylation in blood, a marker of systemic inflammation (Bermingham et al., 2022). Mouse models of chronic jet lag have demonstrated evidence for immunosuppression (Aiello et al., 2020; Inokawa et al., 2020). Another study in mice observed suppression of melatonin and glucocorticoid receptors in the liver in association with chronic jet lag (Iwamoto et al., 2014).

Summary

The nomination poses the issue of whether IARC should evaluate circadian disruption itself. Biological pathways or responses have not usually been evaluated by the *IARC Monographs* programme, although there have been some exceptions, including "shift work involving circadian disruption" (IARC, 2010d). Notably, however, the agent was renamed "night shift work" in *IARC Monographs* Volume 124 (IARC, 2020), with measures of circadian disruption described in the mechanistic evidence section. In future, the Advisory Group recommended that the *IARC Monographs* programme evaluate the carcinogenicity of the external factors that generate circadian disruption, e.g. night shift, ALAN, for which there exists evidence in humans and experimental systems. The Advisory Group therefore considered that an *IARC Monographs* evaluation of chronic circadian dysfunction is unwarranted.

Recommendation: No priority

028 Night shift work

Current IARC/WHO classification

Night shift work (NSW) was classified by IARC as *probably carcinogenic to humans* (Group 2A) in *IARC Monographs* Volume 124 in 2019 (IARC, 2020), on the basis of *limited* evidence for cancer in humans (for cancers of the breast, prostate, and colorectum), *sufficient* evidence for cancer in experimental animals, and *strong* mechanistic evidence of immunosuppression, chronic inflammation, and cell proliferation in experimental systems.

Exposure characterization

As described in *IARC Monographs* Volume 124 (IARC, 2020), NSW involves working during the regular sleeping hours of the general population. The disruption of circadian rhythms of body functions as a result of alterations in the environmental light–dark schedule is the most pronounced effect of NSW. NSW is essential for guaranteeing production and activities around the clock. In modern society, the nature of NSW is changing as a result of the diversification of working time patterns. Its prevalence differs between sectors; it is most common in health care, manufacturing, transport, retail, and services. It was estimated (IARC, 2020) that one in five workers worldwide are engaged in NSW, although the definitions, quality, and extent of statistical data vary. Globalization of the labour market has led to increasing use of NSW in LMICs.

Cancer in humans

Several informative cohort, case–cohort, nested case–control, and case–control studies have evaluated NSW. A large number of the available studies were included in the previous IARC evaluation (IARC, 2020);

most of those examined breast cancer, but prostate and colorectal cancer (CRC) were also investigated. The most important development within the body of research in the last decade has been the refinement and expansion of exposure assessment metrics. However, advances in exposure assessment were mostly confined to case–control studies, and the Working Group put more emphasis on evidence from those studies as compared with cohort studies.

Since 2019, there have been several additional publications and meta-analyses. Some evidence was seen of an association between long-term NSW and postmenopausal breast cancer in a cohort of Swedish women, but there were few cases in the long-term exposure group (Gustavsson et al., 2023). There was no association with breast cancer in premenopausal women. A higher risk of breast cancer was observed among women who had ever been exposed to NSW in the Finnish Twin Cohort study (Schernhammer et al., 2023). Overall, there was little evidence that rotating shift work or work at night was associated with a higher risk of breast cancer in the US Sister Study cohort (Sweeney et al., 2020).

An analysis in the UK Biobank cohort found no significant associations between NSW and prostate cancer overall (HR, 1.07; 95% CI, 0.92–1.25) or by rs10830963 polymorphism (GC versus CC, HR, 0.94; 95% CI, 0.86–1.03; and GG versus CC, HR, 0.89; 95% CI, 0.75–1.05) (Yang et al., 2022a). However, these authors found a significant interaction between NSW exposure and rs10830963 polymorphism (melatonin receptor) for the incidence of prostate cancer. A positive association between NSW and rotating shift work and prostate cancer was found in the Japan Collaborative Cohort Study (Arafa et al., 2021), while no associations were observed for breast or CRC. A positive association between NSW (especially rotating shift work) and prostate cancer, with some evidence of chronotype interaction, was seen in the CAPLIFE study in Spain (Lozano-Lorca et al., 2020). Some evidence of circadian genes modulating prostate cancer risk was observed among night shift workers in the EPICAP case–control study in France (Wendeu-Foyet et al., 2020). In that study, there was no overall association between NSW and prostate cancer, although an association was found for aggressive prostate cancer.

For CRC, a positive association was found with long-term NSW among Black women in the USA (Barber et al., 2023). There was no evidence of an association with CRC for men working in night shifts in a pooled study of two German cohorts, although some associations were observed in subgroups (Wichert et al., 2020). Some evidence of an interaction of two insulin receptor substrate genes for NSW in CRC was observed in the Nurses' Health Study, indicating that rotating night shifts might increase the risk of CRC in women with abnormal insulin receptor pathways. Overall, a trend for an increased risk of CRC was observed among those working night shifts for longer than 15 years (Shi et al., 2020).

Cancer in experimental animals

There are no major changes in the evidence on cancer in experimental studies; this evidence has already been evaluated as *sufficient* twice (IARC, 2010d, 2020). The 2019 Working Group evaluating NSW specifically concluded that there is *sufficient* evidence in experimental animals for the carcinogenicity of an alteration in light–dark schedule.

Mechanistic evidence

In the 2019 evaluation (IARC, 2020), the Working Group identified that the mechanistic evidence in experimental systems is consistent and coherent with respect to the KCs on the basis of effects consistent with chronic inflammation, immunosuppression, and cell proliferation. However, the evidence was only suggestive in exposed humans for effects on estrogen levels in female night shift workers. The Working Group noted several limitations of studies in humans, including small sample sizes, lack of adjustment for potential confounding factors, and issues concerning the timing of biological specimen collection. Since 2019, studies evaluating KCs in exposed humans have addressed one or more of these limitations. For example, the HORMONIT study in Spain found lower levels of immune biomarkers, as well as changes in

melatonin and sex-steroid hormone production, in male auto workers working rotating night shifts (Harding et al., 2022a, b). Studies carried out for the Lifelines cohort observed increases in inflammatory biomarkers in men working night shifts (Bizzarri et al., 2022); in addition, DNA methylation pattern effects were observed among women working at night (Wackers et al., 2023). Other large-scale studies are ongoing, with end-points related to the KCs (e.g. within the Exposome Project for Health and Occupational Research, EPHOR; https://www.ephor-project.eu/about-ephor), for which results should become available in the next 2–3 years.

Summary

The carcinogenicity of NSW is a very active area of research, concerning human cancer and mechanistic studies. There have already been two evaluations by the *IARC Monographs* programme, most recently in *IARC Monographs* Volume 124 (IARC, 2020). The Nightingale prospective cohort study (Pijpe et al., 2014) has been designed with high-quality exposure assessment, and results are pending. The Advisory Group suggested that, given the complexity of this agent and the methodological issues, a new evaluation should only be conducted when substantial new evidence becomes available, particularly on mechanistic studies in humans. This emphasis on mechanistic evidence is suggested because that was the area of research with weaker studies during the 2019 evaluation. Although there have been new studies and meta-analyses of epidemiological data for cancer, the evidence concerning cancer in humans has not evolved considerably, compared with that available in 2019. The Advisory Group therefore considered that an *IARC Monographs* re-evaluation of NSW is unwarranted at present.

Recommendation: No priority

029 Artificial light at night

Current IARC/WHO classification

The effect of ALAN has not been previously evaluated by the *IARC Monographs* programme. NSW (which can serve as a proxy for ALAN exposure) has been classified by IARC in 2019 (IARC, 2020) as *probably carcinogenic to humans* (Group 2A). It remains unknown whether exposure to ALAN is carcinogenic in the general population (representing different exposure patterns to ALAN).

Exposure characterization

In contemporary society, artificial lighting has become ubiquitous, extending beyond urban areas to illuminate suburban and rural regions in most parts of the world (Gaston et al., 2015; Falchi et al., 2016; Cox et al., 2022). With the increasing use of light-emitting diode (LED) lamps, screens, and other electronic devices that emit light, individuals are exposed to ALAN for extended periods, altering natural day–night cycles (Cajochen et al., 2011; Kyba et al., 2017, 2023; Sánchez de Miguel et al., 2020; 2022; Falchi and Bará 2023). The principal uses of ALAN are outdoor lighting (e.g. street lights, security lighting, decorative illumination, advertisements), indoor lighting in homes, workplaces, commercial buildings, and public spaces, (e.g. general illumination, task lighting, screens, decorative purposes), transportation lighting (e.g. roadways, airports, railways), and recreational and entertainment lighting (e.g. sports facilities, entertainment venues, outdoor events).

Residential areas near brightly lit public spaces or industrial zones may experience higher levels of ALAN, through both direct and indirect sources (Katabaro et al., 2022; Bará and Falchi, 2023). Methods for exposure assessment in earlier studies included satellite mapping with low resolution and without an evaluation of colour (e.g. evaluation of short wavelengths).

Cancer in humans

A recent search of the literature identified 26 studies on ALAN and cancer (15 cohort, 11 case–control). For most of the studies, outdoor ALAN data came from images from the Defense Meteorological Satellite Program (DMSP), with fewer obtaining data from the Visible Infrared Imaging Radiometer Suite (VIIRS), from both DMSP and VIIRS, the International Space Station, or from self-reported data. In all 10 indoor ALAN studies, the exposure was assessed using questionnaires (relying on poorly worded and highly subjective assessments). There are numerous studies on breast cancer (Davis et al., 2001; O'Leary et al., 2006; Li et al., 2010; Bauer et al., 2013; Hurley et al., 2014; Portnov et al., 2016; James et al., 2017; Keshet-Sitton et al., 2017; White et al., 2017; Garcia-Saenz et al., 2018; Johns et al., 2018; Ritonja et al., 2020; Xiao et al., 2020; Clarke et al., 2021; Xiao et al., 2021a; Sweeney et al., 2022; Prajapati et al., 2023; Song et al., 2023a); overall, they indicate that exposure to higher levels of outdoor ALAN are associated with a higher risk of breast cancer. On excluding studies with low-quality assessment, the association is weakened. The association between indoor ALAN and breast cancer risk is weak, and exposure assessment in those studies is very heterogeneous. A small number of high-quality studies, which, importantly, include blue light, have reported associations of ALAN with cancer of the prostate (OR, 2.05; 95% CI, 1.38–3.03), breast (highest versus lowest tertile, adjusted OR, 1.47; 95% CI, 1.00–2.17) (Garcia-Saenz et al., 2018); and colorectum (OR, 1.6; 95% CI, 1.2–2.2; highest versus lowest tertile of blue light spectrum) (Garcia-Saenz et al., 2020).

Also, several meta-analyses of the association between ALAN and breast cancer have found increased risks of breast cancer among participants with the highest level of visual light exposure compared with those with the lowest levels of exposure (Lai et al., 2021; Urbano et al., 2021; Wu et al., 2021a).

Exposure to ALAN has been associated with several other cancer sites, but for most there are only one or two studies available for distinct cancers: Chowdhury-Paulino et al. (2023) on prostate cancer; Xiao et al. (2021b) on pancreas cancer; Zhong et al. (2023a) on acute lymphoblastic leukaemia (ALL) in Hispanic children; Medgyesi et al. (2023) on endometrial cancer in postmenopausal women; Park et al. (2022) on liver cancer; Zhang et al. (2021a) on thyroid cancer; and Zhong et al. (2020) on non-Hodgkin lymphoma (NHL) among women.

Cancer in experimental animals

The only available evaluation of the evidence for carcinogenicity in experimental animals was made with respect to alteration in the light–dark schedule. There is *sufficient* evidence in experimental animals for the carcinogenicity of alteration in the light–dark schedule. This evaluation, given in *IARC Monographs* Volume 124 (IARC, 2020), was based primarily on lifetime carcinogenicity studies reported by Anisimov et al. (2004) and Kettner et al. (2016).

Kettner et al. (2016) reported a series of independent studies in which male and female mice of three strains (one wildtype and two genetically engineered) were exposed to shifts in the light–dark schedule, in the form of repeated 8-hour advances, until the mice were aged 90 weeks. Compared with control mice of each strain exposed to a regular light–dark schedule of 12 hours in light and 12 hours of darkness, exposure to shifts in the light–dark schedule was observed to significantly increase the incidence of HCC in all three strains. Anisimov et al. (2004) compared tumour incidence and latency in wildtype female mice exposed for life to either a light–dark schedule of 12 hours in light and 12 hours of darkness (control) or continuous light (24 hours in light and 0 hours in darkness). Statistically significant increases in the incidence of lung adenocarcinoma, malignant lymphoma, and total tumours were observed in mice exposed to continuous light. Positive results reported in a few other studies of rodents exposed to shifts in the light–dark schedule or continuous light, and in many studies using carcinogen-induced or transplantable tumour models, support the carcinogenicity of alterations in the light–dark schedule demonstrated in the lifetime carcinogenicity evaluations of Kettner et al. (2016) and Anisimov et al. (2004).

Joechle (1964) reported an increased occurrence of spontaneous mammary tumours in mice housed in constant light. Mhatre et al. (1984) reported that induced mammary tumour incidence was increased in rats exposed to constant light from before birth, compared with those exposed to dark nights. Notably, the administration of melatonin to these rats in a pattern that simulated night-time exogenous release reversed the deleterious effects of constant light. Blask et al. (2005) worked with melatonin-depleted blood from premenopausal women exposed to light at night and found that there was stimulation of the growth of human breast cancer xenografts in nude rats. Schwimmer et al. (2014) demonstrated that dim light during the dark phase also promotes tumour progression in mice with induced mammary adenocarcinoma. Guerrero-Vargas et al. (2017) reported, for an experimental model, that constant lighting conditions may also be favourable for enhanced tumour growth and significantly increase tumour volume and weight, compared with exposure to 12 hours in light and 12 hours of darkness, owing to increased macrophage recruitment and upregulation of genes involved in lipogenesis and glucose uptake. Zubidat et al. (2018) showed that female BALB/c mice previously inoculated with tumour cells and exposed to night schedules with different types of light were able to generate tumours. Yonis et al. (2019) studied the association between light pollution and disruption of daily rhythms; their results indicated cancer progression. Agbaria et al. (2019) reported on a mouse model of breast cancer induced by ALAN and melatonin. Mice exposed to ALAN had significantly reduced 6-sulfatoxymelatonin levels and increased body mass, tumour volume, and lung metastasis, compared with controls. Such effects are decreased by increases in melatonin. Walker et al. (2020) studied light pollution and cancer, setting a basis for light at night (LAN). Walker et al. (2021) reported an association between ALAN and behaviour in tumour-bearing mice. They found that ALAN exacerbated mammary tumour growth in female mice. These authors hypothesized that exposure to ALAN accelerated mammary tumour growth. Adult (> 8 weeks) female C3H mice received a unilateral orthotropic injection of FM3A mouse mammary carcinoma cells (1.0×10^5 cells in 100 µL) into the fourth inguinal mammary gland. Regardless of tumour status, tumour-bearing ALAN-housed mice demonstrated reduced latency to tumour onset (day 5) and increased terminal tumour volume (day 21). It was found that ALAN reduced the latency of tumour onset and increased final tumour volume. This finding supports an association between ALAN and carcinogenesis observed in rodent studies, providing compelling data for a causative effect.

Mechanistic evidence

Emmer et al. (2018) studied the disruption of the light–dark cycle, primarily by exposing animals to LAN, which disturbs biological rhythms and has widespread physiological consequences because of mechanisms such as melatonin suppression, sympathetic stimulation, and altered circadian clock gene expression, which affect metabolism and genomic instability. Stevens and Davis (1996) studied the effect of LAN on laboratory animals and research outcomes. They hypothesized three aspects for such effects: light effects on melatonin, electromagnetic field (EMF) effects on melatonin, and melatonin effects on breast cancer. The strongest of these aspects was considered the effects of light on melatonin. It is clear that the normal nocturnal melatonin rise in humans can be suppressed by light of sufficient intensity. The evidence for an effect of melatonin on breast cancer in experimental animals is strong, but the evidence in humans is scant and difficult to collect. The weakest aspect of the circumstantial case is the EMF effect on melatonin production. IARC (2020) reported several experimental animal designs in which cell proliferation, as a sign of carcinogenicity, was observed. Laboratory studies using animals also reported a positive relation between exposure to LAN and tumour formation and progression. Dauchy et al. (1999) considered that rapid tumour growth, increased tumour incidence, and progression are not limited to exposure to constant light. Marpegan et al. (2009) investigated the effect of diurnal variation in endotoxin-induced mortality in mice and found a correlation with the production of proinflammatory factors. Martynhak et al. (2017) reported altered circadian timing of behaviour with night-time dim light exposure in $Per3^{-/-}$ mice, but not wildtype mice. Guerrero-Vargas et al. (2017) reported, from experiments using an experimental model, that constant

lighting conditions might enhance tumour growth with exposure to 12 hours in light and 12 hours of darkness, owing to increased macrophage recruitment and upregulation of genes involved in lipogenesis or glucose uptake. Zubidat et al. (2018) demonstrated one of the KCs, namely, cell proliferation, in experiments with female BALB/c mice, and showed that chronic exposure to dim LAN disrupted the immune response in old-aged female mice, besides decreasing longevity in aged female mice. Yonis et al. (2019) studied the association between light pollution and disruption in daily rhythms; their results indicated metabolic and hormonal disorders, which affected cell proliferation, metabolism, and epigenetics. They found that ALAN induced DNA hypomethylation in pancreatic tissue, compared with controls, but not in hepatic tissue. Overall, ALAN affected metabolic and hormonal physiology at different levels, indicating flexible crosstalk between melatonin and both epigenetics and metabolic levels. There is a hypothesis regarding breast cancer development and exposure to short wavelength ALAN, as multiple studies suggest that there is a possible link between them.

Agbaria et al. (2019) analysed mouse tumour, lungs, liver, and spleen in a study of the total activity of DNA methyltransferases and levels of global DNA methylation (GDM). Mice exposed to ALAN had significantly reduced 6-sulfatoxymelatonin (6-SMT) levels and increased body mass, tumour volume, and lung metastasis, compared with controls. Such effects were decreased by increases in melatonin. Epigenetic modification was demonstrated in this mouse model through an analysis of the role of DNA methyltransferase, which is suggested to be a mediator for nocturnal melatonin suppression and to play an integral role in circadian regulation, including cell division. It was found that DNA methyltransferase activity and GDM levels showed tissue-specific responses. Thus, changes in cell proliferation and epigenetics were observed. The possibility of early detection and management of breast cancer by monitoring melatonin and GDM levels as early biomarkers of ALAN circadian disruption was suggested. Walker et al. (2021) reported an association between ALAN and an increased risk of developing breast cancer through an effect on cell proliferation. Additionally, tumour-bearing mice housed in dark nights exhibited increased anxiety-like behaviour. Liu et al. (2022b) demonstrated that circadian rhythms disrupted through chronic exposure to dim LAN (dLAN) impaired immune response and survival in aged mice, affecting KCs, such as immunological changes. Aged female mice exposed to dLAN displayed inflammation, as a measure of cell-mediated immune response and decreased lifespan, compared with female mice housed with dark nights. Together, these data indicated that chronic exposure to dLAN affects lifespan in aged female mice and suggested that female mice are more susceptible than males to the detrimental consequences of disrupted circadian rhythms. Richter et al. (2022) indicated that ALAN is a potential precursor of cancer, or at least has high-risk as a carcinogenic agent.

Summary

While ALAN is a component of NSW, which is currently classified by IARC as *probably carcinogenic to humans* (Group 2A), it has not itself been specifically been evaluated by the *IARC Monographs* programme, in either the work environment or the general population. An evaluation of ALAN by the *IARC Monographs* programme is relevant, owing to the extensive and increasing exposure of individuals to ALAN and the emerging evidence concerning the potential effects of ALAN on health. Exposure to ALAN, especially at night, and particularly exposure to blue light, disrupts the body's circadian rhythms. The intrinsically photosensitive retinal ganglion cells (ipRGCs) in the eye are most relevant for circadian rhythm regulation and melatonin production and are most sensitive to short wavelengths (i.e. blue light).

Emerging epidemiological evidence has suggested potential associations between ALAN exposure and an increased risk of certain cancers, particularly breast cancer, in studies conducted in the general population. Methods for exposure assessment of ALAN will be a main issue in any evaluation. Currently, there is *sufficient* evidence in experimental animals for the carcinogenicity of alteration in the light–dark schedule, and these studies were performed with artificial light, as seen for NSW in *IARC Monographs* Volume 124

(IARC, 2020). There is evidence suggesting that ALAN exposure exhibits multiple KCs. The available evidence could support a classification of carcinogenicity of ALAN. Overall, the Advisory Group therefore considered an *IARC Monographs* evaluation of ALAN to be warranted and recommended an evaluation in the latter half of the period, given the many potentially informative studies currently underway.

Recommendation: High priority (and ready for evaluation within 5 years)

030 Insomnia and sleep disruption

Current IARC/WHO classification

Insomnia and sleep disruption have not been previously evaluated by the *IARC Monographs* programme. Sleep was given a priority rating of *medium* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of sparse evidence for human cancer for some factors related to poor sleep quality.

Exposure characterization

The Advisory Group considered that insomnia itself is an unclear target for an evaluation by the *IARC Monographs* programme, because it is a specific type of (or response to) sleep disruption; therefore, it is not further considered here. There is an extensive international body of literature on sleep patterns, on factors associated with sleep duration and, to a lesser extent, on sleep quality (e.g. Brockmann et al., 2017; Park et al., 2023). Studies have compared self-reported sleep patterns with sleep patterns measured using sensors, indicating a degree of exposure misclassification in self-reports. Studies have evaluated sleep duration and sleep quality, and several studies have focused on obstructive sleep apnoea. The prevalence of sleep disorders examined in the general population is high; for example, in the USA, 33% of adults reported short sleep duration (< 7 hours/day) (Pankowska et al., 2023).

Cancer in humans

The relations between sleep, mental health, and chronic disease have gained considerable attention in recent years, and sleep has become identified as a fundamental aspect of human health. In these studies, several sleep attributes have been considered, including sleep duration and quality, as well as specific sleep disorders. Sleep disorders have mostly been associated with neurocognitive, metabolic, and cardiovascular effects, but the association between sleep and cancer has also become a subject of growing interest (Gozal et al., 2016). Numerous studies are available, but results are not entirely consistent. Studies suggest that disrupted sleep patterns may contribute to an increased susceptibility to certain types of cancer, including melanoma and cancers of the breast, prostate, colorectum, and central nervous system (CNS) (Luo et al., 2013; Papantoniou et al., 2021; Turner et al., 2022; Chiang et al., 2023b; Collatuzzo et al., 2023; Papantoniou et al., 2023; Von Behren et al., 2023). One study of the UK Biobank cohort evaluated the combination of sleep and physical activity and observed that participants with poor sleep and low levels of physical activity had the highest mortality risks for total cancer and lung cancer (Huang et al., 2022b). Some studies identified U-shaped associations with sleep duration, e.g. for stomach and CRCs (Papantoniou et al., 2021), similar to the overall pattern observed with all-cause mortality. Perturbations in sleep architecture and continuity have been associated with both initiation and exacerbation or prognosis of cancer.

Rather than using a population approach, most studies on obstructive sleep apnoea were conducted in clinical settings (Nieto et al., 2012; Campos-Rodriguez et al., 2013; Marshall et al., 2014; Theorell-Haglöw et al., 2023). Some studies (Richmond et al., 2019; Huo et al., 2021) used Mendelian randomization approaches. A large study (Richmond et al., 2019), using data from the UK Biobank and the Breast Cancer

Association Consortium (BCAC), observed an adverse effect of increased sleep duration on risk of breast cancer, whereas evidence for insomnia symptoms was inconsistent.

Cancer in experimental animals

One study in mice has shown that sleep fragmentation promoted tumour development in chemically induced colon cancer (Lee et al., 2023a).

Mechanistic evidence

Studies of sleep disruption in animals and in humans have demonstrated associations with several KCs, including DNA damage (Andersen et al., 2009; Cheung et al., 2019) (e.g. oxidative DNA damage), oxidative stress (KC5) (Villafuerte et al., 2015; Shah et al., 2023) (e.g. antioxidant enzyme activity), inflammation (KC6) (Mullington et al., 2010) (e.g. cytokines), immunosuppression (KC7) (Ragnoli et al., 2022) (e.g. increased viral illness), and epigenetic changes (Gaine et al., 2018) (e.g. methylation levels in specific genes). Sleep fragmentation in mice was found to reprogramme the epigenome of haematopoietic stem and progenitor cells, as measured via chromatin accessibility of enhancer elements, increasing cell proliferation and reducing haematopoietic clonal diversity (Kiss et al., 2022; McAlpine et al., 2022).

Summary

Research on sleep and cancer has considerably increased in recent years, with evaluations of sleep duration, sleep quality, and specific pathologies, such as obstructive sleep apnoea. The evidence is not entirely consistent, with, perhaps, more evidence for breast cancer and sleep duration. However, there exists a considerable body of evidence (positive and negative) that refers to an effect of disturbed sleep in the general population, however it is defined, e.g. as short duration of sleep, insomnia, or apnoea. There are still several issues concerning the methods used, since most studies evaluate sleep through self-reports. Although there are well-validated questionnaires and scales to examine sleep, there is a need to examine studies using objective measures, since it has been shown that there is a considerable degree of exposure misclassification when sleep is examined only through questionnaires. In the context of sleep apnoea, it is also important to evaluate studies in the general population in addition to the more common clinical-based studies. The evidence appears strongest for an association between sleep duration (with perhaps a U-shape relation) or sleep quality and breast cancer.

There is evidence from an initiation–promotion study in experimental animals demonstrating increased occurrence of cancer in association with sleep fragmentation, and studies in both animals and humans have linked several KCs to sleep disruption. The evaluation of sleep within the context of other factors that generate circadian disruption could also be considered.

Recommendations

Insomnia: No evaluation

Sleep disruption: High priority (and ready for evaluation within 2.5 years)

031 Long working hours

Current IARC/WHO classification

Long working hours have not been previously evaluated by the *IARC Monographs* programme. A WHO/International Labour Organization (ILO) Joint Estimates analysis of the burden of disease for long working hours has been published (Pega et al., 2021).

Exposure characterization

Long working hours have not been clearly defined in the literature. The International Labour Organization's Hours of Work Convention states a threshold for working hours that certain employed workers should not exceed; the definition includes working hours of 8 hours or more than 12 hours/day or 48 hours/week (ILO, 1919). It has been reported that epidemiologists often use categories of > 40 hours/week for long working hours, with the highest category at > 55 hours/week (Pega et al., 2021) or > 11 hours/day (Hattori et al., 2022). *WHO/ILO Joint estimates of the work-related burden of disease and injury* (WHO, 2024b) indicates that, globally in 2016, 488 million people (8.9% of the global population) were exposed to long working hours (≥ 55 hours/week) (Pega et al., 2021; WHO, 2024b). Between 2000 and 2016, the global prevalence of long working hours increased by 9.3%. Men were more exposed than women, and adults aged between 25 and 50 years were more exposed than older adults. There are marked global regional differences, with the highest exposure prevalence observed in south-eastern Asia (11.7%), and the lowest in Europe (3.5%) (Pega et al., 2021).

Long working hours have been reported to be associated with other cancer risk factors, such as alcohol intake and lack of physical activity (Heikkila et al., 2016).

Cancer in humans

Epidemiological evidence suggests that working long hours has a detrimental effect on health, increasing morbidity and mortality from ischaemic heart disease and stroke (e.g. Pega et al., 2021). The effect of long working hours on cancer risk could be through an association with lifestyle-related exposures, such as sedentary behaviour (see agent 032 in the present report) and lack of physical activity or excessive alcohol intake. Very few studies evaluated long working hours and cancer risk (Nielsen et al., 2008; Heikkila et al., 2016; Hattori et al., 2022). The main positive association identified in the largest study (Heikkila et al., 2016), which was based on the Individual-Participant-Data Meta-analysis of Working Populations (IPD-Work) Consortium, is for breast cancer. While no association was observed for overall cancer incidence, nor for lung, colorectal, or prostate cancer in that study, working 55 hours/week or longer was associated with an increased risk of female breast cancer in age-adjusted analyses (HR, 1.54; 95% CI, 1.09–2.18). This association remained after adjustment for socioeconomic position; night-time work, shift work, and BMI; smoking; or alcohol intake. No adjustment, however, was made for important reproductive factors, e.g. parity. In a cohort study in Japan (Hattori et al., 2022), breast cancer risk tended to be associated with exposure to longer working hours: RR was 1.30 (95% CI, 0.33–5.19) in a group working 9–10 hours/day and 1.74 (95% CI, 0.46–6.64) in a group working ≥ 11 hours/day, compared with a group working 7–8 hours/day.

Cancer in experimental animals

No studies on models of long working hours and cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

Mechanistic data related to long working hours were sparse. A study in 7470 young and middle-aged workers observed that those working for ≥ 52 hours/week had significantly greater circulating levels of high-sensitivity C-reactive protein, a marker of inflammation (Lee et al., 2021b). In another study of 12 487 people, however, no significant overall association between longer working hours (≥ 55 versus < 55 hours/week) and C-reactive protein was observed (Velazquez-Kronen et al., 2023). A study in 604 people observed significantly greater epigenetic age acceleration (as measured by the Hannum and Horvath clocks) in association with working > 40 hours/week (Freni-Sterrantino et al., 2022).

Summary

Only a few studies examined long working hours and cancer risk. In two out of three studies, including a large cohort study based on a consortium, a positive association was found for breast cancer, but the adequacy of the confounding control was questionable in one study. No studies of cancer in animals and few mechanistic studies of long working hours were identified. The mechanistic studies would not support a meaningful evaluation of the carcinogenicity of long working hours. More time is needed to allow more information through research to accumulate. The Advisory Group therefore considered that an *IARC Monographs* evaluation of long working hours is unwarranted at present.

Recommendation: No priority

032 Sedentary behaviour

Current IARC/WHO classification

Sedentary behaviour has not been previously evaluated by the *IARC Monographs* programme. Sedentary behaviour was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of consistent evidence of a positive association with CRC, with mechanistic evidence related to several KCs.

Exposure characterization

There are different definitions of low physical activity and sedentary behaviour. As noted in the 2019 Advisory Group report (IARC, 2019a), in the Global Burden of Disease project, low average weekly physical activity (at work, at home, transport-related, and recreational) is defined as < 8000 total metabolic equivalent minutes per week (Forouzanfar et al., 2016). The prevalence of low average weekly physical activity was estimated to be 46.6% for men and 39.4% for women worldwide, leading to more than 1.6 million all-cause deaths and 35 million disability-adjusted life-years in 2015 (Forouzanfar et al., 2016). A WHO report (WHO, 2022b) provided global estimates to show that 1.4 billion adults (27.5% of the world's adult population) do not meet the recommended level of physical activity. There are wide differences in levels of physical activity between regions, age groups, and sexes. In adults in 2016, levels of inactivity in high-income countries (36.8%) were twice those in low-income countries (16.2%) (Guthold et al., 2018).

Sedentary behaviour is also defined as "any waking behaviour characterized by an energy expenditure ≤ 1.5 [metabolic equivalents] while in a sitting or reclining posture" (Sedentary Behaviour Research Network, 2012). It has been estimated that adults spend approximately 8.2 hours/day sitting down (Baumann et al., 2017) but these estimates differ by region, age, and sex. A major component of sedentary behaviour is sedentary work, which has been increasing globally, particularly in industrialized countries, where technology and automation have led to more desk-bound jobs. With the increase in office-based work, remote work arrangements, and jobs in such sectors as information technology, finance, and administration, many people spend significant portions of their day sitting at desks or in front of computers.

Cancer in humans

In the last available Global Burden of Disease analysis (Forouzanfar et al., 2016), cancer deaths due to physical inactivity were estimated for colorectal and breast cancers, which were presumed to be causally related to physical inactivity based on the available literature. A total of 119 000 (95% CI, 84 000–156 000) deaths due to cancers of the colon and rectum and 48 000 (95% CI, 35 000–61 000) deaths due to cancer of the breast, in 2015, were also estimated to be attributable to low physical activity. There are more than 50 observational epidemiological studies on sedentary behaviour and cancer, and findings have been summarized in systematic reviews and meta-analyses (Schmid and Leitzmann, 2014; Shen et al., 2014; Ma

et al., 2017; Mahmood et al., 2017; Chan et al., 2019; Hermelink et al., 2022; Yuan et al., 2023a). Sedentary behaviour has been shown to increase the risks of colorectal, breast, ovarian, and endometrial cancers.

The most comprehensive review and meta-analysis, which included all previous estimates, evaluating 14 meta-analyses covering 17 different cancer sites from 77 original studies was by Hermelink et al. (2022), who report: "High [sedentary behaviour] levels increase the risk for developing ovarian, endometrial, colon, breast, prostate, and rectal cancers, with RRs of 1.29 (95% confidence interval (CI) = 1.08–1.56), 1.29 (95% CI = 1.16–1.45), 1.25 (95% CI = 1.16–1.33), 1.08 (95% CI = 1.04–1.11), 1.08 (95% CI = 1.00–1.17), and 1.07 (95% CI = 1.01–1.12), respectively". Some of these findings were modified when including studies with more extensive confounding adjustment, for example the association for endometrial cancer became null in the meta-analysis of studies adjusting for BMI. A subsequent meta-analysis on endometrial cancer (Yuan et al., 2023a), reported similar findings, although adjustment for BMI had a smaller effect. In other meta-analyses, sedentary behaviour was found to be associated with a slight to moderate increased risk of cancer (meta-RRs of 1.08 to 1.54), including breast, lung, and CRC (Schmid and Leitzmann, 2014; Shen et al., 2014, Zhou et al., 2015).

Cancer in experimental animals

No studies investigating cancers spontaneously arising in experimental animals after sedentary behaviour were available to the Advisory Group; all of the animal models reported in the last 5 years (2020–2024) were based on cancer induction or inoculation, as described next.

Mechanistic evidence

Between 2020 and 2023, 19 rodent studies investigating the effects of some form of exercise versus sedentary behaviour on benign or malignant tumour induction or inoculation outcome were published. Of these, 16 were conducted in mice, using five different strains, and three were conducted in the rat, using three different strains. Studies in both mice and rats included both sexes and a wide array of tumour or cancer cell types (including mammary, prostate, colon, liver, melanoma, muscle, and pancreas). Also, experiments were designed to investigate the effect of exercise before, after, or before and after cancer induction or inoculation. Among these 19 studies, 15 of 16 mouse studies (94%) and 3 of 3 rat studies (100%) reported worse outcomes for sedentary behaviour groups than for exercise groups. Studies in rodents show that sedentary behaviour has adverse health effects (Arfianti et al., 2020; Garritson et al., 2020; Guarino et al., 2020; Buss et al., 2021; Esteves et al., 2021; Farber et al., 2021; Lamkin et al., 2021; LeGuennec et al., 2021; Yazdani et al., 2021; Gupta et al., 2022b; Malicka et al., 2022; Parry et al., 2022; Sadovska et al., 2022; Wood et al., 2022; Collao et al., 2023; Esteves et al., 2023; Wang et al., 2023c; Nascimento-Gonçalves et al., 2024). One mouse study found no statistically significant difference between groups, but did find a statistically significant difference in the number of polyps and the presence of mucosal ulcerations in the colons of the mice (Neves et al., 2023). Unfortunately, since all of these models are based on tumour or cancer induction or inoculation, the role of sedentary behaviour in carcinogenesis is unclear. Hence, it remains to be seen whether physical activity may be related to cancer prevention; however, it is clear that physical activity may be related to reduced disease-related fatigue or improved survival or physical functioning after cancer induction or inoculation in mice and rats. In these cancer experimental animal studies and other mechanistic evidence studies, there is ample evidence that, in order of frequency, chronic inflammation (KC6), oxidative stress (KC5), epigenetic alteration (KC4), immunosuppression (KC7), and modulation of receptor-mediated effects (KC8) are suboptimal. Overall, there is evidence that sedentary behaviour is associated with these KCs (while not necessarily inducing them), and that physical activity may have reduced them.

In humans, the promotion of apoptosis in cancer cells or of innate immunity against cancer cells, or the expression of myokines, which act systemically and have anti-inflammatory and insulin-sensitizing effects

and increase thermogenesis in adipose tissue, appear to be the main mechanisms in which exercise protects against cancer (Ruiz-Casado et al., 2017). The Advisory Group noted that it is challenging to distinguish sedentary behaviour from physical activity, i.e. exercise, in humans and experimental systems.

Summary

Consistent positive associations in humans have been found between sedentary behaviour (or, alternatively, physical inactivity) and breast and colon cancer or CRC in large studies. The Advisory Group suggests that it is important for the *IARC Monographs* programme to evaluate the cancer hazard associated with sedentary behaviour, even if a separate effort is undertaken in the *IARC Handbooks* programme to evaluate the preventive effect of physical activity, because these behaviours, although related, may demonstrate independent effects. There is no evidence regarding cancer in experimental animals. The mechanistic evidence appears to be strong in exposed humans and experimental systems. The Advisory Group therefore considered an *IARC Monographs* evaluation of sedentary behaviour to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

033 Obesity

Current IARC/WHO classification

Obesity has not been previously evaluated by the *IARC Monographs* programme. However, absence of excess body fatness was evaluated by the *IARC Handbooks* programme in 2016 (IARC, 2018c), much of the available literature on obesity was reviewed, with the conclusion that there is *sufficient* evidence that absence of excess body fatness prevents cancers of the oesophagus, gastric cardia, liver, gall bladder, pancreas, colorectum, kidney, breast, endometrium, and ovary, and multiple myeloma.

Exposure characterization

Obesity is defined as having a BMI (defined as the weight in kilograms divided by the square of the height in metres) of 30 or more. Obesity can be divided into class 1 (BMI, 30.0–34.9), class 2 (BMI, 35.0–39.9), and class 3 (BMI ≥ 40.0) (Lauby-Secretan et al., 2016).

Worldwide, an estimated 880 million adults were obese in 2022, which is 11% of all adults (10% of men and 13% of women) (Phelps et al., 2024). For children, the prevalence of obesity is often combined with that of overweight (BMI, 25–30): it was estimated that 39% of children under the age of 5 years were overweight or obese in 2020 and more than 340 million children and adolescents (aged 5–19 years) were either overweight or obese in 2016 (WHO, 2021a). The global prevalence of obesity nearly tripled between 1975 and 2022. In many LMICs, there has been a rapid increase in the prevalence of obesity and overweight, particularly in urban settings (WHO, 2021a; Phelps et al., 2024).

Cancer in humans

There is substantial scientific evidence indicating a relation between excess body fatness and an increased risk of developing various cancers. As reviewed in the *IARC Handbooks* Volume 16 (IARC, 2018c), increased risks for the highest BMI category, versus normal BMI (18.5–24.9), have been reported for cancers of the oesophagus (adenocarcinoma), gastric cardia, colon and rectum, liver, gall bladder, pancreas, female breast (postmenopausal), corpus uteri, ovary, kidney (renal cell carcinoma), meningioma, and thyroid, and for multiple myeloma. Furthermore, associations are suspected with male breast cancer, fatal prostate cancer, and diffuse large B-cell lymphoma (Lauby-Secretan et al., 2016). Research continues on these and other cancer types that may be associated with obesity.

Cancer in experimental animals

Several studies in rodents demonstrated that obesity increases the incidence of cancers of the mammary gland, colon, liver, pancreas, prostate, and skin, and promotes tumorigenesis (IARC, 2018c).

Mechanistic evidence

The review of mechanistic evidence conducted by the Working Group for *IARC Handbooks* Volume 16 (IARC, 2018c) did not explicitly use the framework of the KCs. The Working Group did conclude that there is *strong* evidence that sex hormone metabolism and inflammation are major mechanisms underlying the link between excess body fatness and certain cancers. They concluded that there is *moderate* evidence for the role of insulin and insulin-like growth factor. Evidence for the involvement of epigenetic alterations, oxidative stress, and DNA repair was considered *weak*. Studies in humans and animal models continue to demonstrate that obesity is associated with chronic inflammation, attributed to the accumulation of Th1 cells, $CD8^+$ T cells, and proinflammatory macrophages in adipose tissue (Harris et al., 2022). This inflammation response leads to oxidative stress, with oxidative DNA damage, decreased antioxidant capacity, and induction of antioxidant enzymes, as observed in both human and animal studies (Setayesh et al., 2018). There is also evidence of immunosuppression in the context of obesity. The immunosurveillance system in adipose tissue seems to become compromised with a decline in regulatory T cells, NKT cells, and eosinophils, and a rise in exhausted memory B cells (Harris et al., 2022).

Summary

The Working Group for *IARC Handbooks* Volume 16 (IARC, 2018c) concluded that there is *sufficient* evidence that the absence of excess body fatness prevents cancer in humans. Despite this evaluation that an absence of excess body fatness is a cancer-preventive factor, the Advisory Group considered it relevant for the *IARC Monographs* programme to consider efficient ways to include obesity or excess body fatness in the list of agents classified as *carcinogenic to humans* (Group 1), given that the evidence for cancer in humans that was reviewed in the *IARC Handbooks* was largely the same as would be considered in an *IARC Monographs* evaluation. There is evidence in experimental animals that obesity induces tumours. Examining mechanistic evidence for obesity (or overweight) using the framework of KCs could also provide valuable scientific insight. For consistency, obesity or overweight could be evaluated with agents that are already classified as *carcinogenic to humans* (Group 1). A substantial minority of the Advisory Group considered that obesity should not be evaluated by the *IARC Monographs* programme, either because its absence is already listed as a cancer-preventive factor in the *Handbooks*, or because they did not consider it to be an exogenous agent. However, the majority of the Advisory Group considered an *IARC Monographs* evaluation of obesity to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

034 Social isolation and loneliness

Current IARC/WHO classification

Social isolation and loneliness have not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Loneliness and social isolation are considered as two separate constructs that may occur independently (i.e. one without the other). People lacking human contact often feel lonely, but social isolation and loneliness are also found not to be significantly correlated. There may be a need to distinguish between social isolation

and loneliness in assessing cancer hazards. It is recognized that measures of social well-being are complex and subjective concepts and go beyond simply describing the situational facts of a person's life (Perissinotto and Covinsky, 2014).

Estimates of the prevalence of loneliness and social isolation in the community differ and may involve some groups more than others, such as low-income adults, young adults, older adults, adults living alone, people with chronic diseases or disabilities, immigrants, or individuals who identify as lesbian, gay, bisexual, transgender, or queer (LGBTQ). Some studies report "marital status (being single)" as a proxy for loneliness, but marital status is a complex variable that involves many different social and behavioural aspects, wider than social isolation and loneliness alone (Yanguas et al., 2018).

Cancer in humans

There are very few studies (perhaps only three) evaluating an association of loneliness or social isolation (or both) with cancer risk. In a longitudinal study in 2570 middle-aged men in Finland, Kraav et al. (2021) described loneliness as being associated with total cancer incidence (and, in a separate publication, mortality) and some specific cancers. Results were attenuated after adjustment for lifestyle and health-related covariates. Fleisch Marcus et al. (2017) reported that, in a cohort of 16 044 US adults with 17–23 years of follow-up, social isolation and higher neighbourhood poverty were independently associated with increased risk of cancer mortality. This increase was more pronounced in women than in men. Associations were attenuated on adjustment for individual socioeconomic status. A follow-up study on breast cancer survival, embedded within the Nurses' Health Study in the USA, evaluated social networks and social support before and after diagnosis. (Kroenke et al., 2006). Socially isolated women had an elevated risk of mortality after a diagnosis of breast cancer, and this was interpreted by the authors as related to a lack of access to care, specifically beneficial caregiving from friends, relatives, and adult children (and not an indication that loneliness is causally related to cancer incidence). Factors associated with cancer survivorship are not within the scope of the *IARC Monographs* programme.

Several mediators may influence any association between social isolation and cancer; these include the influence of social isolation and loneliness on health behaviours. Some studies have found loneliness and social isolation to be associated with poorer health behaviours, including smoking, physical inactivity, and poorer sleep.

Cancer in experimental animals

Only one study measured cancer parameters in spontaneously occurring cancer in isolated rodents versus grouped rodents; the rodents were studied over their entire life-cycle (15 months); social isolation was associated with increases in tumour size, number, distribution, and malignancy (Hermes et al., 2009).

Mechanistic evidence

There is evidence that social isolation alters cell proliferation, cell death, or nutrient supply (KC10), induces chronic inflammation (KC6), increases neovascularization (KC9), induces oxidative stress (KC5), and is immunosuppressive (KC7), in order of frequency (Fleisch Marcus et al., 2017; Kraav et al., 2021). However, complete and precise mechanisms have yet to be described. Moreover, drastic differences in outcome were observed: while 9 of 12 studies showed increased tumour burden, one showed decreased tumour volume and no difference in survival (Farbstein et al., 2021), another showed only transient differences (Madden et al., 2013), and yet another showed drastically reduced survival (Budiu et al., 2017). Hence, the body of evidence is inconclusive. In addition, exposure to social isolation was almost always for only a few weeks at most (i.e. subchronic), except for two studies, in which isolation lasted 5 (Verza et al., 2021) or 15 months (Hermes et al., 2009), i.e. was chronic. Studies using longer exposure to social isolation and less-potent inductions that mirror carcinogenesis in humans more closely are lacking. Currently, the

research literature in humans is rich in observational studies based on self-reports on social isolation and loneliness in subjects already diagnosed with cancer, in subjects with advanced cancer, or in cancer survivors. Major gaps exist from the lack of studies monitoring subjects before the diagnosis of cancer (such as in smokers or subjects with cancer mutations, such as the breast cancer-associated gene BRCA1) and involving repeated observations of the mechanisms and KCs most frequently found in social isolation and loneliness (listed previously), using blood tests to monitor proinflammatory factors, for example, over long periods of time, and comparing these variables for high versus low levels of social isolation and loneliness.

Summary

Overall, there is sparse evidence in humans on the association of social isolation and loneliness with cancer. There are methodological issues regarding the definition of the exposure. The interpretation of the findings on such variables as loneliness and social isolation, which involve numerous interconnected pathways to disease, is complex. Overall, only one study investigated cancer in experimental animals, and the bulk of the data appears to be inadequate. The mechanistic evidence appears to be inadequate. On the one hand, while the findings in experimental animals are suggestive of isolation-stress-induced changes to tumour growth and proinflammatory and neoangiogenic supports, they cover a narrow range of observational perspectives, rarely evaluating naturally or spontaneously occurring cancers, and some incoherence remains across studies. On the other hand, the studies in exposed humans most often involve self-reporting and most are concerned with the situation after cancer has already developed. More time is required to allow better designed and informative studies to take place. The Advisory Group therefore considered that an *IARC Monographs* evaluation of social isolation and loneliness is unwarranted at present.

Recommendation: No priority

035 Tobacco smoking and secondhand tobacco smoke

Current IARC/WHO classification

Tobacco smoking and secondhand tobacco smoke were classified by IARC as *carcinogenic to humans* (Group 1), most recently in *IARC Monographs* Volume 100E in 2009 (IARC, 2012f). There is *sufficient* evidence that each causes lung cancer. There is also *sufficient* evidence that active smoking causes cancers of the oral cavity, pharynx, oesophagus, stomach, colorectum, liver (in smokers and their children), bile duct, pancreas, nasal cavity and paranasal sinuses, larynx, upper aerodigestive tract, uterine cervix, ovary, kidney, renal pelvis and ureter, urinary bladder, and (acute and chronic) myeloid leukaemia. There is *limited* evidence that active smoking causes breast cancer, and that parental smoking causes both childhood acute leukaemia (lymphocytic and myeloid) and all childhood leukaemia combined. There is *limited* evidence that secondhand smoke causes cancers of the pharynx and larynx.

Secondhand smoke was given a priority rating of *medium* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of new epidemiological studies showing a positive association between active smoking, secondhand smoke, or both, and breast cancer, as well as studies showing associations between parental smoking and childhood leukaemia.

Exposure characterization

In the context of the WHO Framework Convention on Tobacco Control, massive efforts have been underway over the past 20 years to reduce the rates of tobacco use globally. Still, WHO estimates that there remain 1.25 billion adult tobacco users across the globe (WHO, 2024c). While, on average, roughly 20% of the global population are tobacco users, this percentage is higher in the South-East Asian Region (26.5%) and European Region (25.3%). The majority of tobacco users (83% globally) smoke tobacco (in any form)

(WHO, 2024c). Rates have been declining among women in most regions, but those among women in the European Region are more than twice the global average and are declining only slowly.

Cancer in humans

Since the most recent *IARC Monographs* evaluation (IARC, 2012f) in 2009, many cohort studies have reported a positive association between smoking (active, secondhand, or both) and breast cancer in different populations, including in women who do not consume alcohol (e.g. Gram et al., 2015, 2022; Gaudet et al., 2017; Kim et al., 2018b; He et al., 2022a; Scala et al., 2023). Positive associations have also been observed for different tumour subtypes (e.g. by menopausal or hormone receptor status). The risk is higher with increasing number of years smoked before first childbirth, and exposure–response relations have been observed between risk of breast cancer and age of starting to smoke or number of cigarettes, years, and pack-years smoked (Jones et al., 2017a; Scala et al., 2023). At least 15 reviews or meta-analyses have concluded that there is an association between smoking (active, secondhand, or both) and a higher risk of breast cancer, although of modest magnitude, e.g. Scala et al. (2023) found a meta-RR of 1.12 (95% CI, 1.08–1.16) for a smoking intensity of 20 cigarettes/day. Causal conclusions are reflected in the incorporation of burden estimates for breast cancer, owing to both tobacco smoking and secondhand smoke exposure, as well as estimates of the attributable fraction from tobacco smoke exposure (e.g. Ou et al., 2022; Tran et al., 2022; Azadnajafabad et al., 2023).

New studies are available on the association between parental tobacco smoking and childhood cancer (including brain tumours and leukaemia) since the previous evaluation in *Monographs* Volume 100E (IARC, 2012f). A meta-analysis of parental risk factors for childhood brain tumours estimated a meta-RR of 1.18 (95% CI, 1.00–1.40) for maternal smoking > 10 cigarettes/day during pregnancy in cohort (but not case–control) studies (Onyije et al., 2022). In a meta-analysis of 17 case–control studies, paternal exposure before conception and during pregnancy was associated with childhood ALL; meta-RRs were 1.15 (95% CI, 1.04–1.27) for paternal exposure before conception and 1.20 (1.12–1.28) for exposure during pregnancy (Cao et al., 2020). Findings were robust to a variety of sensitivity analyses related to confounding, and evidence of a positive trend with increasing exposure was also observed: risk of ALL was approximately doubled at roughly 35 cigarettes/day prenatally. As noted in the 2019 Advisory Group report (IARC, 2019a), pooled and meta-analyses of childhood AML from the Childhood Leukaemia International Consortium reported an increased risk and an exposure–response relation between paternal smoking and childhood AML. More recently, positive associations were observed between paternal smoking before conception, during pregnancy, and after birth and childhood AML (but not ALL) in Costa Rica (Frederiksen et al., 2020).

Mechanistic evidence

Many of the compounds in tobacco smoke, e.g. polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and *N*-nitrosamines, have been found to induce mammary tumours in experimental animals. Several studies have identified an association of epigenetic markers of maternal prenatal smoke exposure with genetic deletions seen in cases of childhood ALL (Xu et al., 2021a).

Summary

The recent literature suggests that evidence has strengthened for a causal association between tobacco smoking and secondhand tobacco smoke and several additional cancer types, including breast cancer and childhood ALL. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of tobacco smoking and secondhand tobacco smoke to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

036 Electronic nicotine delivery systems

Current IARC/WHO classification

Electronic nicotine delivery systems (ENDS), also known as electronic cigarettes or e-cigarettes, have not been previously evaluated by the *IARC Monographs* programme. ENDS were given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of mechanistic evidence related to DNA adduct formation or a reduction in DNA repair activity in exposed humans and experimental systems, including in studies of rodents exposed to vapour from e-cigarettes.

Exposure characterization

Electronic cigarettes are battery-powered devices designed to deliver nicotine without combusting tobacco. Using an e-cigarette is commonly known as vaping. ENDS generate aerosols by heating a liquid (known as an e-liquid) composed of nicotine and flavours in propylene glycol (propane-1,2-diol) or glycerol (propane-1,2,3-triol) (Lechasseur et al., 2022). The variety of devices and e-liquids has increased substantially over the years (CDC, 2019a). ENDS became widely available around 2010, and quickly emerged as the most popular alternative to combustible cigarettes. In the USA, more than 5.6 million adults reported ENDS use in 2018–2019 (Cook et al., 2023). Surveys on ENDS awareness and use among urban adults in five large Chinese cities in 2017–2018 showed that 4.8% of respondents had ever used ENDS, and 0.9% had used ENDS in the previous 30 days (Huang et al., 2020a). In the UK, the percentage of then-current users of ENDS increased from 1.2% of the population in 2012, to 9.1% in 2023 (ASH, 2023).

The 2019 Advisory Group report (IARC, 2019a) noted the large variety of carbonyl compounds produced by heating glycerol and propylene glycol, including formaldehyde (IARC Group 1), acrolein (Group 2A), and acetaldehyde (Group 2B), as well as propanal, glyoxal, and methylglyoxal (Group 3) (Bekki et al., 2014; Pisinger and Døssing, 2014; Pisinger, 2015; Kim et al., 2016). ENDS vapour also contains volatile organic compounds, including benzene (Group 1), styrene (Group 2A), ethylene benzene (Group 2B), and toluene (Group 3) (Pisinger and Døssing, 2014; Pisinger, 2015; Kim et al., 2016). Many other potentially carcinogenic substances have been reported in ENDS, including nanoparticles, heavy metals, and tobacco-specific nitrosamines (Group 1), such as NNN and NNK (Goniewicz et al., 2014; Pisinger and Døssing, 2014; Pisinger, 2015; Kim et al., 2016). In addition, a variety of flavouring compounds (e.g. diacetyl) may be present in electronic cigarette refill fluids.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

Chronic exposure (12 weeks) to e-cigarette smoke (ECS) induced lung adenocarcinoma and bladder urothelial hyperplasia in male FVB/N mice (Tang et al., 2019), implicating ECS as a carcinogen in mice. Although FVB/N mice are known to have increased cancer rates, expected neoplasms are lung alveolar–bronchiolar tumours (Huang et al., 2008), not adenocarcinoma, which arises from a different lung cell type, Hence, this suggests that the lung adenocarcinoma observed by Tang et al. (2019) is relevant to ECS exposure. However, the Advisory Group has noted that the duration of the study (12 weeks) was inadequate, and that the study was performed only in one sex and one species (male mice).

Rats initiated with *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN) and then exposed to nicotine through drinking-water had dose-dependent increases in the incidence of urothelial carcinoma of the urinary bladder (Dodmane et al., 2014).

Mechanistic evidence

Carcinogenicity in A/J mice after full-lifespan (15-month) exposure to aerosols generated from heated tobacco products was less severe than that in mice exposed to cigarette smoke, with reports of numerous statistically significant, dose-dependent increases in nasal and laryngeal epithelial hyperplasia, metaplasia, or "hyperplasia of metaplastic epithelium", compared with a group with exposure only to air ($P < 0.01$, minimum) (Wong et al., 2020). Lung function was reduced, and lung histopathological findings were positive. In addition, urogenital problems, which were described as apparently "related to congenital factors rather than test item exposure", might have been associated with tobacco heating system (THS) use since "in previous studies, this mouse strain did not present with urogenital problems" (Wong et al., 2020, p. 63), and since urothelial hyperplasia was previously observed in at least three other ECS or nicotine studies in rodents (Dodmane et al., 2014; Suzuki et al., 2018; Tang et al., 2019). Nicotine exposure through drinking-water was previously associated with hyperplasia of the urothelium in female Wistar Han rats, and in female C57BL/6 mice, but to a lesser extent (4/10 mice versus 7/10 rats) (Dodmane et al., 2014), Importantly, nicotinic acetylcholine receptor (nAChR) inhibitors prevented proliferation and hyperplasia induced by nicotine (Suzuki et al., 2018), supporting a causal relation.

Lee et al. (2018) showed that long-term exposure (12 weeks) to ECS led to DNA adducts and reduced DNA repair activity in the lungs, heart, and bladder of male FVB/N mice, and to reduced DNA repair proteins in their lungs; in addition, they showed that treatment of human BEAS-2B lung and UROtsa bladder cells with NNK plus nicotine also damages DNA and reduces repair activity in vitro (Lee et al., 2018), making cells more susceptible to the accumulation of mutations. Several lines of evidence point towards: the creation of DNA adducts and reduction of DNA repair (Lee et al., 2018; Tang et al., 2019); increased proliferation and hyperplasia (Dodmane et al., 2014; Suzuki et al., 2018; Tang et al., 2019; Wong et al., 2020); the induction of chronic inflammation and immunosuppression (Wong et al., 2020; Bhat et al., 2023); and the induction of oxidative stress (Flach et al., 2019; Bhat et al., 2023). In addition, there is strong potential for the hundreds of different flavour additives in ENDS to be genotoxic (Hung et al., 2020). Lung damage was recently reported, together with the induction of chronic inflammation (Phillips et al., 2015; Yang et al., 2022b; Zhao et al., 2024). Epithelial-to-mesenchymal transition was observed in vitro (de Lima et al., 2023), as was increased migration (Flach et al., 2019). Many reports exist on the effects of nicotine (the major compound found in ENDS) on metastasis (Momi et al., 2013; Shimizu et al., 2019) and there is at least one report on the effects of e-cigarettes on metastasis (Kyte and Gewirtz, 2018).

Summary

There is no evidence regarding cancer in humans. Overall, there is some evidence for cancer in experimental animals. Ample mechanistic evidence is available, suggesting that ENDS exhibit multiple KCs across the full range of systems, including exposed humans. The Advisory Group therefore considered an *IARC Monographs* evaluation of ENDS to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

037 Cannabis smoking

Current IARC/WHO classification

Cannabis smoking has not been previously evaluated by the *IARC Monographs* programme. Cannabis smoking was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of findings of an association with testicular

cancer (in particular, for non-seminoma testicular cancer) in humans and mechanistic evidence of mutagenicity and of modulation of receptor-mediated effects.

Exposure characterization

The term cannabis describes the dried seeds, stems, flowers, and leaves of the *Cannabis sativa* plant. Inhaling smoke from combusting the plant's flowers, leaves, resin, or oil created thorough distillation or extraction is the most common method of consumption. The psychoactive effects of cannabis plant are attributed to tetrahydrocannabinol (THC) (CDC, 2022a)

After alcohol and tobacco, cannabis is the third most widely used controlled substance worldwide (Peacock et al., 2018). In the USA, cannabis is the most commonly used federally illegal drug; in 2021, about 19% of Americans had smoked cannabis at least once (SAMHSA, 2022). In Canada, 94% of recreational cannabis users in 2017 reported having consumed the drug by smoking it (Government of Canada, 2017).

The chemical composition of cannabis smoke has been addressed in only a few studies. The presence of known carcinogens, such as some PAHs, in cannabis smoke has been reported. PAHs are found in lower concentrations in mainstream cannabis smoke than in tobacco smoke; in sidestream smoke, the concentration of PAHs is higher in cannabis than in tobacco (Moir et al., 2008).

With the potential for additive health effects, the co-use of both cannabis and tobacco is relatively common. For example, in the USA, 21% of young adults in general had co-used tobacco and cannabis in the previous 30 days (Cohn et al., 2019). This co-use of tobacco and cannabis can take several forms: cannabis rolled in a cigar leaf (blunt), cannabis and loose-leaf tobacco combined in a joint (spliff), or sequential smoking of cannabis and then cigarettes (chasing) (Reboussin et al., 2021). There may be occupational and environmental exposure to secondhand cannabis smoke (Wiegand et al., 2020).

Cancer in humans

At the time of the 2019 Advisory Group meeting (IARC, 2019a), most studies of upper aerodigestive tract or lung cancers had mixed results or null findings, with challenges noted about potential confounding by tobacco smoking. As noted in the 2019 Advisory Group report (IARC, 2019a), four epidemiological studies (one prospective cohort and three case–control studies) in Sweden and the USA each reported increased risks of testicular cancer. The Swedish study found a twofold RR among heavy cannabis users, compared with non-users (Callaghan et al., 2017), and a pooled analysis of the three US case–control studies found an association, specifically with non-seminoma testicular cancer.

Since then, more evidence has accrued for various cancer types. In 2019, a review with pooled analysis of 25 studies (19 case–control, 5 cohort, 1 cross-sectional) was published. For case–control studies, an association was not found between any previous use of marijuana and head and neck SCC or oral cancer. Marijuana use for > 10 years was associated (in three case–control studies) with testicular germ cell tumour (OR, 1.36; 95% CI, 1.03–1.81; $P = 0.03$; $I^2 = 0\%$) and non-seminoma testicular germ cell tumour (OR, 1.85; 95% CI, 1.10–3.11; $P = 0.04$; $I^2 = 0\%$) (Ghasemiesfe et al., 2019).

Cohn et al. (2021) reviewed studies on cannabis and cancer risk for epidemiologic studies published between 2014 and November 2020; 40 epidemiological studies on cannabis smoking and the risk of cancer were identified. For lung cancer, there were four case–control studies: in two studies conducted in Tunisia ORs of 8.2 (95% CI, 1.3–15.5) and 2.4 (95% CI, 1.6–3.8) were reported. A population-based study in Los Angeles, USA, found no association between cannabis use and risk of lung cancer for more joint-years of use, whereas a study in New Zealand reported a very modest increase in risk.

For testicular cancer, there were mixed results in three case–control studies and one cohort study. A study conducted in Washington state, USA reported a twofold risk for daily cannabis use compared with no use, and similar levels of risk, whether cannabis was used for < 10 years or ≥10 years. A cohort study among

49 343 men, conducted in Sweden, showed no association, except that an OR of 2.57 (95% CI, 1.02–6.50) was observed for more than 50 times of cannabis use [the study did not specify whether exposure routes other than smoking were considered] (Cohn et al., 2021).

Cancer in experimental animals

As noted in the 2019 Advisory Group report (IARC, 2019a), no studies were identified regarding cancer in experimental animals for exposure to cannabis smoke or combustion products. The Advisory Group noted that evidence from experimental animals is complicated by the fact that cannabis use for any purpose, whether recreational or research, is banned in several countries.

Mechanistic evidence

Eight recent studies relevant to the KCs are available, focused on KC2 and KC3 (is genotoxic; alters DNA repair or causes genomic instability), KC6 (induces chronic inflammation), or KC7 (is immunosuppressive). Three studies declared smoking to be the main route of exposure to cannabis. One study observed an increase in micronucleated cells in buccal mucosa, as well as DNA breakage in peripheral blood cells in marijuana smokers (suggesting KC2 and KC3) (Souza et al., 2020). Another study found increased expression of toll-like receptor 2 (TLR2) in cannabis smokers (suggesting KC6) (Bailey et al., 2019). The third study, an investigation of mixed types of cannabis use, including smoking, found that women who reported cigarette smoking and marijuana use had lower plasma levels of the anti-inflammatory cytokine IL-10 than did women who did not report cigarette smoking or marijuana use (suggesting KC6) (Saadat et al., 2022). These studies were conducted in exposed humans. One study found that cannabis is related to many congenital anomalies and fulfils epidemiological criteria of causality (suggesting KC2 and KC3) (Reece and Hulse, 2022). Ajrawat et al. (2022) reported that humans exposed to cannabis in various forms have statistically significantly higher levels of eotaxin (a chemoattractant of eosinophils) and interleukin subunit IL-12p40 (produced mostly by activated inflammatory cells, including macrophages, neutrophils, microglia, and dendritic cells, after contact with pathogenic or inflammatory agents). Cannabis users were reported to have 30% higher levels of proinflammatory cytokines than non-users (Krsak et al., 2021). Additionally, cannabis is shown to have anti-inflammatory effects, with BMI also playing a role in this mechanism (suggesting KC7) (Schrock et al., 2022). Studies in mouse models on cannabis smoke exposure unveiled numerous KCs, including KC5, KC6, KC7, and possibly KC10. Δ9-THC caused oxidative stress (KC5) and inflammation (KC6) in endothelial cells (Wei et al., 2022). In a mouse model, cannabis smoke modulated immune cell populations and mediators in both male and female BALB/c mice, with increases in airway and lung tissue macrophage populations, including tissue-resident alveolar macrophages, monocyte-derived alveolar macrophages, and interstitial macrophage subpopulations (KC6) (Fantauzzi et al., 2021). Acute inhalation of cannabis smoke modulated the pulmonary immune response in mice, decreasing the percentage of lung alveolar macrophages while increasing that of lung interstitial macrophages, and decreasing percentages of lung dendritic cells, and Ly6C-intermediate and Ly6C-low monocytes, while increasing those of lung neutrophils and $CD8^+$ T cells (KC6, KC7) (Haidar et al., 2023). Marijuana exposure led to severe airway hyperresponsiveness, inflammation, tissue destruction, and emphysema in CD1 mice (Helyes et al., 2017). Apoptosis and autophagy (in addition to oxidative stress) were also observed in human gingival epithelial cells (Tazi et al., 2022). Hence, numerous KCs are highlighted by these studies: KC2, KC3, KC5, KC6, KC7, and KC10.

Summary

There appears to be evidence supporting an association between cannabis smoking and cancer in humans, specifically non-seminoma testicular cancer. There is no evidence regarding cancer in experimental animals. The evidence that cannabis smoking exhibits KCs in exposed humans, in human primary cells, and

in experimental systems appears to be convincing. The Advisory Group therefore considered an *IARC Monographs* evaluation of cannabis smoking to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

038 Disinfection by-products in water, including haloacetic acids

Current IARC/WHO classification

Some haloacetic acids (HAAs) have been previously evaluated by the *IARC Monographs* programme. Bromodichloromethane, bromochloroacetic acid, dibromoacetic acid, trichloroacetic acid, and dichloroacetic acid were previously classified by IARC as *possibly carcinogenic to humans* (Group 2B) on the basis of *sufficient* evidence for cancer in experimental animals, in *IARC Monographs* Volumes 71 in 1998, 101 in 2011, and 106 in 2012 (IARC, 1999d, 2013c, 2014b). Other HAAs, such as bromodichloroacetic acid, chlorodibromoacetic acid, and tribromoacetic acid have not been evaluated. HAAs and other disinfection by-products were given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of evidence of bladder cancer in humans (for mixtures of HAA in disinfected drinking-water), cancer in experimental animals, and mechanistic evidence for several KCs, including electrophilicity, genotoxicity, alteration of DNA repair, and oxidative stress.

Disinfection by-products are considered in the WHO Guidelines for Drinking-Water Quality (WHO, 2024d).

Exposure characterization

HAAs, specifically chlorinated or brominated di- and tri-HAAs, and trihalomethanes (THMs) are predominant by-products of the water disinfection process (WHO, 2004). Chlorine-based disinfection agents (e.g. chlorine, chloramine, chlorine dioxide) react with organic molecules in the source water to produce HAAs and THMs. The HAAs most frequently detected in drinking-water are monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, monobromoacetic acid, bromodichloroacetic acid, and dibromoacetic acid; the THM most commonly found in drinking-water is chloroform. Bromoform, dibromochloromethane, and bromodichloromethane are other THMs (NTP, 2018c).

Some haloacetic acids are listed as high production volume chemicals by the US Environmental Protection Agency (US EPA, 2024a). In the USA and European countries, HAAs and THMs constitute between 50% and 75% of all the halogenated disinfection by-products (Krasner et al., 2016a).

Exposures in western Europe and North America were considerably higher before the introduction in the 1980s or 1990s of regulations limiting concentrations of trihalomethanes in drinking-water. There is a lack of evidence on the concentration of disinfection by-products in drinking-water and of time trends at a global level (Evlampidou et al., 2020; Villanueva et al., 2023). Dermal exposure and inhalation are major routes of exposure for the general population (showering, washing dishes, and swimming pools), and the ingestion of tap water – plain or in instant drinks, or in food prepared using chlorinated drinking-water – is another possible route (NTP, 2018c).

Information regarding occupational exposure is scarce; however, occupational exposure in pool attendants and water treatment plant employees has been documented (Westerlund et al., 2015; NTP, 2018c).

Cancer in humans

As noted in the 2019 Advisory Group report (IARC, 2019a), there is extensive evidence on THMs and bladder cancer, from around 10 cohort and case–control studies. Most studies identified a positive association, and a positive exposure–response relation, for THMs, even at concentrations below the current

regulatory limits of around 80–100 µg/m^3 for THMs (Villanueva et al., 2004; Costet et al., 2011). An increased risk has frequently been found in men but not women. Increased risks have also been found, in most studies, of CRC. Epidemiological evidence on HAAs is limited to three studies conducted in the Iowa Women's Health Study, examining CRC (Jones et al., 2019), cancer of the endometrium (Medgyesi et al., 2022), and kidney cancer (Jones et al., 2017b), with mixed findings. Sparse data indicate a positive association between exposure to HAAs and THMs and rectal cancer. A plausible mechanism of action involving glutathione *S*-transferase theta 1 (GSTT1) has been postulated (DeMarini et al., 1997; Pegram et al., 1997) and was identified in a large bladder cancer case–control study in Spain, (Cantor et al., 2010) but this finding was not observed in a study in New England (Beane-Freeman et al., 2022).

Cancer in experimental animals

As noted in the 2019 IARC Advisory Group report (IARC, 2019a), carcinogenicity associated with exposure to bromodichloroacetic acid has been observed in many studies of experimental animals, demonstrating an increased occurrence of various malignant and non-malignant neoplasms. The 2019 Advisory Group on Priorities also referred to an NTP monograph (NTP, 2018c) that summarized findings from 41 rodent studies. Based on these studies, the NTP classified 6 of the 13 HAAs in chlorinated drinking-water studied as "reasonably anticipated to be a human carcinogen". Of these six HAAs, three have not yet been evaluated by the *IARC Monographs* programme. Bromodichloromethane, bromochloroacetic acid, and dichloroacetic acid were previously classified by IARC as *possibly carcinogenic to humans* (Group 2B), based on *sufficient* evidence for cancer in experimental animals. The occurrence of liver neoplasms in association with di- and tri-HAA exposures and the occurrence of malignant mesotheliomas associated with three bromide-containing HAAs, bromodichloroacetic acid, chlorodibromoacetic acid, and tribromoacetic acid, which have not been previously evaluated by the *IARC Monographs* programme, were reported. Bromodichloroacetic acid administered in drinking-water caused liver tumours in rats and mice. Four of the six HAAs were also found to be associated with an increased occurrence of various malignant and non-malignant neoplasms, including mesothelioma and mammary tumours (NTP, 2018c).

Mechanistic evidence

On the basis of evidence from studies of bacteria, rodents, and human cell lines, the 2019 IARC Advisory Group (IARC, 2019a) concluded that HAAs show many of the KCs, including electrophilicity and the ability to induce genotoxicity, alter DNA repair, cause oxidative stress, alter nuclear receptor signalling, alter the cell cycle, and alter cell proliferation or cell death. A cancer hazard assessment for 13 HAAs that were evaluated for carcinogenesis in rodents (NTP, 2018c), and that included literature searches for mechanistic studies focused on the KCs (Atwood et al., 2019), identified experimental evidence linking HAAs to most of the KCs, with the strongest evidence observed for electrophilicity, genotoxicity, induction of oxidative stress, and alteration of cell energy metabolism, and weaker responses for receptor-mediated effects and epigenetic effects. Trichloromethanes have been shown to cause chronic inflammation and altered immune responses in exposed humans (Villanueva et al., 2021).

Summary

There is extensive evidence for a positive association between disinfection by-products in water and cancer in humans, particularly bladder and CRCs. Studies have most frequently modelled levels of THMs in drinking-water. There are few studies on HAAs, and all evidence comes from a single cohort.

Several bioassay studies of HAAs have demonstrated increased occurrence of cancers, and HAAs have been linked to many of the KCs. Evidence has been demonstrated for the carcinogenicity of dichloroacetic acid, dibromoacetic acid, bromochloroacetic acid, and bromodichloroacetic acid in rodents, and there is strong evidence that chlorodibromoacetic acid and tribromoacetic acid are involved in mechanisms linked

to carcinogenesis. There is evidence of an association between THMs and other major disinfection by-products and bladder cancer and chronic inflammation and immune responses in exposed humans.

A main issue to be addressed is that the epidemiological evidence is available for a mixture (all disinfection by-products or, more frequently, THMs), while there is evidence for cancer in experimental animals and mechanistic data for individual compounds in this group. Therefore, HAAs and THMs and some of the halogenated by-products resulting from drinking-water disinfection may be considered for joint evaluation as disinfection by-products. The Advisory Group therefore considered an *IARC Monographs* evaluation of disinfection by-products in water, including haloacetic acids, to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

039 Metalworking fluids

Current IARC/WHO classification

Metalworking fluids have not been previously evaluated by the *IARC Monographs* programme. Metalworking fluids were given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of evidence of higher rates of bladder cancer and several other cancer types in workers exposed to metalworking fluids in the automotive industry, as well as positive cancer bioassay evidence for certain specific mixtures, and mechanistic evidence of genotoxicity.

Exposure characterization

Metalworking fluids are a complex mixture of oil- or water-based fluids and additives used for lubricating and cooling metals during operations like cutting and grinding. They are often classified as straight fluids (neat or mineral oils), soluble fluids (a mixture of water-based fluids and mineral oils), and synthetic fluids (water-based, no oil). Some water-based metalworking fluids have been shown to be contaminated with mycobacteria (Kreiss and Cox-Ganser, 1997; Wilson et al., 2001) and endotoxins (Dahlman-Höglund et al., 2022). In the course of a range of operations involving metal processing, inhalation and dermal exposures are likely. The use of metalworking fluids in automotive and other industries is widespread, and occupational exposures are still commonplace. Specific agents for which relevant data are available, including animal carcinogenicity bioassays, include those used in the general machining and grinding of automotive aluminium parts and in light to moderate machining and grinding of light steel, stainless steels, hardened steels, and other materials (NTP, 2015). A proprietary oil-based metalworking fluid used for cleaning tools and parts, and during grinding, drilling, cutting milling as a lubricant and coolant, was tested by the US NTP (2016e), as described below.

Cancer in humans

There is an extensive body of observational research into the association between occupational exposure to metalworking fluids and cancer risk, yielding mixed findings. As described in the 2019 Advisory Group report (IARC, 2019a), modest positive associations have been identified for various tumour sites, with compelling evidence derived from numerous investigations within a large pooled cohort of automobile workers in the USA (Eisen et al., 1994, 2001; Bardin et al., 1997; Sullivan et al., 1998; Agalliu et al., 2005; Thompson et al., 2005; Malloy et al., 2007; Friesen et al., 2009, 2011; Costello et al., 2011; Betenia et al., 2012; Shrestha et al., 2016; Garcia et al., 2018b). Given the challenges in assessing exposure, for human data, quantitative metrics in exposure–response evaluation are generally lacking. Nonetheless, several longitudinal studies using exposure surrogates have examined exposure–response relations, finding positive associations for cancers of the female breast, bladder, oesophagus, rectum, prostate, and larynx (Eisen et al.,

2001; Agalliu et al., 2005; Malloy et al., 2007; Colt et al., 2011, 2014; Shrestha et al., 2016; Colin et al., 2018; Garcia et al., 2018b).

Additionally, a study has provided evidence of gene–environment interactions concerning occupational exposures and susceptibility loci for bladder cancer. Specifically, concerning glutathione S-transferase mu 1 (GSTM1), the relevance of rs798766 (TMEM129-TACC3-FGFR3) for specific exposure to straight metalworking fluids was highlighted (Figueroa et al., 2015).

Since the 2019 Advisory Group report (IARC, 2019a), four new studies were identified. Izano et al. (2019) and Costello et al. (2020) reported updated results of the cohort studies conducted in three automobile manufacturing plants in Michigan (46 316 workers). These reports provide evidence for an association between straight metalworking fluid exposure and colon cancer risk. The corresponding RRs were 2.39 (95% CI, 1.12–5.08) for straight metalworking fluids, 1.43 (95% CI, 0.67–3.04) for soluble metalworking fluids, and 1.08 (95% CI, 0.51–2.30) for synthetic metalworking fluids (Izano et al., 2019). Additionally, a heightened risk of skin and female breast cancers was reported for straight fluids. For the first time, an increased risk of mortality due to stomach cancer was identified. In the highest exposure categories, an HR of 2.13 (95% CI, 1.04–4.39) was observed (Costello et al., 2020).

Colbeth et al. (2023) examined the incidence of 14 types of cancer, with a focus on digestive, respiratory, and hormonal cancers, in the United Auto Workers–General Motors cohort of workers exposed to metalworking fluids (39 132 workers). The main results were an increased incidence of stomach and kidney cancer with higher levels of straight metalworking fluid exposure and an increased incidence of rectal and prostate cancer with increased water-based synthetic metalworking fluid exposure. Only NHL and prostate cancer were associated with soluble metalworking fluid. All results for colon and lung cancers were null.

Park (2018a) estimated aggregate excess lifetime risk, using published findings on exposure–response relations for each cancer site. With a constant workplace metalworking fluid exposure of 0.1 mg/m^3 over 45 years working life, the risk of attributable cancer found was 3.7%.

Cancer in experimental animals

In a 2-year inhalation study of rats, a proprietary metalworking fluid, TRIM VX, was found to be carcinogenic for lungs in male and female rats, but the evidence was based on the combined occurrences of bronchioloalveolar adenoma or carcinoma of the lung. There was clear evidence of lung carcinogenicity of TRIM VX in male and female mice in a 2-year inhalation study, based on the increased combined incidence of bronchioloalveolar adenoma or carcinoma (primarily carcinoma) of the lung (NTP, 2016e).

Under the conditions of 2-year inhalation studies in male and female rats, there was equivocal evidence of carcinogenic activity of CIMSTAR 3800, another metalworking fluid, based on the increased incidence of prostate gland adenoma or carcinoma (combined) in male rats. There was equivocal evidence of carcinogenic activity of CIMSTAR 3800 in female rats, based on the incidence of squamous cell papilloma or keratoacanthoma (combined) of the skin and adenocarcinoma or mixed malignant Müllerian tumour (combined) of the uterus. There was no evidence of carcinogenic activity of CIMSTAR 3800 in male mice. There was some evidence of carcinogenic activity of CIMSTAR 3800 in female mice, based on the incidence of follicular cell carcinoma of the thyroid gland and bronchioloalveolar adenoma or carcinoma (combined) of the lung (NTP, 2015).

Mechanistic evidence

TRIM VX showed no evidence of genotoxicity in bacterial mutation tests or in vivo tests for chromosomal damage (micronuclei) (NTP, 2016e). CIMSTAR 3800 was mutagenic in *Escherichia coli* (*E. coli*) strain WP2 *uvrA*/pKM101 in the absence of exogenous metabolic activation (S9); no mutagenic activity was observed in . *typhimurium* strains TA98 and TA100, with or without S9, or in the *E. coli* strain with S9 (NTP, 2015).

Sauvain et al. (2021) reported that aerosolized metalworking fluids induce oxidative stress, especially for exposure in occupational settings (Sauvain et al., 2021). In male and female F344 rats and male and female B6C3F$_1$/N mice exposed to whole-body inhalation of metalworking fluid (concentration, 0–400 mg/m^3) for 16 weeks, hyperplasia and squamous metaplasia were observed in the respiratory epithelium. In addition, significant increases in chronic active inflammation, histiocytic infiltration, and fibrosis were observed (Ryan et al., 2017). Dermatitis, an immune response reaction, is frequently reported in workers exposed to metalworking fluid (Sauvain et al., 2021). Evidence for genotoxicity of metalworking fluids in humans is sparse and equivocal in rodents.

Summary

Metalworking fluids are complex mixtures of lubricating fluids, additives, and contaminants. Epidemiological cohort studies provide evidence for a positive association between metalworking fluid exposure and cancers of the breast, bladder, oesophagus, rectum, prostate, larynx, stomach, and kidney. These data could support an evaluation of metalworking fluids by an *IARC Monographs* Working Group. There is evidence that two specific metalworking fluid mixtures induced carcinogenicity in experimental animals. In addition, some mechanistic evidence is reported in humans and in laboratory animals. The Advisory Group therefore considered an *IARC Monographs* evaluation of metalworking fluids to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

040 Cleaning products

The Advisory Group considered the agent to be too broadly defined to warrant evaluation.

Recommendation: No priority

041 E-waste work

Current IARC/WHO classification

E-waste work has not been previously evaluated by the *IARC Monographs* programme. The Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 concluded that e-waste burn sites should not be evaluated, given the heterogeneous nature of the exposure and the possibility that risk assessment based on the individual components based on existing knowledge may be more feasible (IARC, 2019a).

Exposure characterization

E-waste can be defined as waste from any electrical or electronic equipment, including all components, subassemblies, and consumables.

About 80% of e-waste from high-income countries is illegally exported to LMICs (including Brazil, China, Ghana, India, Nigeria, and Pakistan), where local workers process the e-waste in recycling shops and sites (Parvez et al., 2021). In the EU, for example, only 3.3 million tons [3.0 million tonnes] of 9.5 million tons [8.6 million tonnes] of e-waste was processed within the EU itself (Scheepers et al., 2021).

Exposure to e-waste has been associated with higher levels of exposure to many toxic substances, including lead, cadmium, mercury, manganese, chromium, nickel, PAHs, polybrominated diphenyl ethers, polychlorinated biphenyls (PCBs), dechlorane plus, polychlorinated dibenzo-*p*-dioxins and furans (PCDD/Fs), new flame retardants, bromophenols, perchlorate, thiocyanate, polybrominated biphenyls,

phthalate esters, bisphenols, and organophosphates (Parvez et al., 2021). However, fewer studies have examined long-term exposures among these workers.

E-waste work activities in modern processes can be categorized as: sorting (either by hand or semi-automated), dismantling (often by hand), shredding and pre-processing (on a belt by electrostatic, density, magnetism, colour separation, etc.), metal processing (melting metals for reuse), and polymer processing (to a granulated material for reuse) (Scheepers et al., 2021). More primitive methods for processing e-waste, resulting in high exposure levels for workers, are observed in the informal sector, on scrap yards. Tasks may involve dismantling of electrical and electronic devices using very basic tools, burning cables and other components using insulating foam from dismantled refrigerators or car tyres, and searching through ashes for valuable metals (Fischer et al., 2020).

Cancer in humans

No studies of cancer in e-waste workers were available to the Advisory Group.

Cancer in experimental animals

No data were available to the Advisory Group pertaining to cancer in experimental animals specifically exposed to e-waste, although studies for specific components of e-waste, many of which have been previously evaluated by the *IARC Monographs* programme, are available.

Mechanistic evidence

Mechanistic evidence exists for specific agents classified by IARC as *carcinogenic to humans* (Group 1), e.g. cadmium, and benzo[*a*]pyrene (IARC, 2012b, c), and for other agents that have been previously been evaluated by the *IARC Monographs* programme. In addition, numerous studies have investigated the association between exposure to e-waste, including its constituents, and DNA damage.

A systematic review and meta-analysis conducted by Issah et al. (2021) synthesized evidence on DNA damage among e-waste-exposed populations. The review included studies to assess various biomarkers of DNA damage, such as micronuclei, comet assay parameters, 8-OHdG, telomere length, apoptosis rate, and chromosomal aberrations. The meta-analysis revealed a significant increase in DNA damage, particularly in micronuclei frequency, among individuals exposed to e-waste, emphasizing the association between e-waste exposure and genotoxic effects (Issah et al., 2021).

Berame et al. (2020) investigated the presence of micronuclei in exfoliated buccal epithelium cells among e-waste workers in Payatas, the Philippines. The study found a significant association between the length of e-waste exposure and the number of micronuclei, indicating genotoxic damage induced by prolonged exposure to e-waste materials.

Alabi et al. (2020) assessed blood concentrations of lead, nickel, cadmium, and chromium, as well as DNA damage in exfoliated buccal cells of teenage scavengers at an e-waste dumpsite in Lagos, Nigeria. The study found significantly elevated concentrations of these metals in the blood of scavengers, compared with controls, accompanied by increased frequencies of micronuclei and other nuclear abnormalities in buccal cells.

Franco de Diana et al. (2018) investigated genetic damage in women working as waste pickers in a landfill in Paraguay using the comet assay and micronucleus test. The study revealed a significant increase in DNA damage and nuclear alterations among exposed women, compared with controls, indicating the genotoxic effects of occupational exposure to e-waste contaminants.

Brina et al. (2018) evaluated mutagenic and cytotoxic effects in workers involved in the collection and segregation of urban solid waste in southern Brazil, finding significantly higher frequencies of micronuclei and other nuclear abnormalities in exposed workers than in controls, indicating exposure to mutagenic and cytotoxic agents in the workplace.

A study by Zhang et al. (2016b) investigated the effect of elevated lead levels on NK cells in children from an electronic waste recycling area. It was found that increased lead exposure was associated with adverse effects on NK cells, which play a crucial role in the immune system's defence against infections and tumours. This suggests that lead pollution in such areas may compromise children's immune function.

Guo et al. (2020) examined the effect of exposure to PCBs and halogen flame retardants (HFRs) on thyroid hormone-related proteins and gene expression in children living in a Chinese e-waste recycling area. Significant changes were found in these proteins and gene expression, suggesting that PCBs and HFRs may disrupt thyroid hormone regulation in children.

Summary

No evidence is available regarding cancer in humans occupationally exposed to e-waste, and no evidence is available for cancer in experimental animals. Occupational exposure to e-waste involves the potential for exposure to several agents that have been classified by IARC as *carcinogenic to humans* (Group 1) or *probably* (Group 2A) or *possibly carcinogenic to humans* (Group 2B). There is mechanistic evidence that humans exposed to e-waste or to some of its major constituents exhibit KCs. One issue is whether exposures are sufficiently homogeneous for a meaningful hazard assessment to be performed that would be representative of a large majority of existing e-waste sites. Overall, the Advisory Group considered an *IARC Monographs* evaluation of e-waste work to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

042 Laboratory work and occupation as chemist

Current IARC/WHO classification

Laboratory work and occupation as chemist have not been previously evaluated by the *IARC Monographs* programme. Laboratory work and occupation as chemist were given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a).

Exposure characterization

Individuals engaged in laboratory work or work as a chemist have employment in diverse laboratory settings. Laboratory workers or chemists may have exposure to known or suspected carcinogens, with substantial heterogeneity in the type and extent of exposure, depending on the type of laboratory work conducted and the context-dependent chemical, biological, or physical hazards involved. One study assessed thyroid exposure to radiation during the production of radiopharmaceuticals, concluding that estimated annual exposure in employees remains within acceptable limits (Wrzesien, 2018). Another study measured thyroid burdens of ^{125}I in hospital laboratory workers over two decades, revealing varying contamination levels among different personnel categories and a decreasing trend over time, owing to improved working conditions and radiation protection measures (Jönsson and Mattsson, 1998). Contact with potential carcinogens is included in the ILO's international hazard datasheets on occupation for analytical and physical chemists and laboratory workers (ILO, 2012a, b, c).

Cancer in humans

The identified literature is extensive and includes exposure to a diverse array of laboratory work (e.g. polymer research, chemical manufacture, biomedical sciences), and studies of cancer incidence and cancer mortality are available. Overall, studies on the topic have evaluated varying occupational exposures, which may have differing effects on cancer risk, and thus are challenging to interpret with respect to the composite exposure of laboratory work and occupation as chemist. As an overall limitation, studies generally lacked

information on the exposure–response relations and were prone to healthy worker biases. Few relevant studies have been published since the previous review by the 2019 Advisory Group on Priorities.

A registry-based study of 15 million people in five Nordic countries identified associations between chemical processing work and selected incident cancers, e.g. of the digestive tract, lung, or cervix (Pukkala et al., 2009). A review reported associations between exposures that may be encountered in laboratory work, and laboratory work itself, with leukaemia (Polychronakis et al., 2013). A subsequent national registry-based study in Brazil noted an elevated (crude) mortality rate ratio for leukaemia for individuals in benzene-exposed occupational groups, including chemists and laboratory assistants (Moura-Corrêa, 2023).

Associations by cancer site and even within cohorts are somewhat inconsistent. For example, an elevated risk of haematolymphoid tumours was observed in a first evaluation in a Swedish cohort study of medical laboratory workers (Gustavsson et al., 1999), but no association was observed on further follow-up (Gustavsson et al., 2017). A higher risk of breast cancer was observed in the earlier study, with attenuated associations in the follow-up study (Gustavsson et al., 1999, 2017). Another study, a case–control analysis, suggested that certain occupational exposures, such as to acrylic and nylon fibres, monoaromatic hydrocarbons, and organic solvents, may increase the risk of postmenopausal breast cancer, particularly for exposures occurring before the age of 36 years (Labrèche et al., 2010). Associations between laboratory-related exposures and breast cancer have been observed in case–control studies. A recent case–control study in Canada estimated occupational exposure to organic solvents, observing an association for select organic solvents and postmenopausal breast cancer (Westra et al., 2023). These findings are in agreement with other case–control studies reporting higher breast cancer risk among women who are occupationally exposed to chemicals (Labrèche et al., 2010; Videnros et al., 2020).

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

Mechanistic data are difficult to describe holistically; however, information on specific agents in the laboratory is informative. For example, increased levels of chromosomal aberrations and DNA damage were found in laboratory workers exposed to formaldehyde, which is classified by IARC as *carcinogenic to humans* (Group 1), and other organic solvents (Souza and Devi, 2014; Costa et al., 2015; de Aquino et al., 2016).

Summary

In summary, the potential for exposure to carcinogenic substances is present for laboratory work and occupation as a chemist; however, the question is whether the exposures are sufficiently homogeneous to be evaluated together. Data from epidemiological studies are most consistent for breast cancer, with additional studies on that cancer site added since the 2019 review. Overall, however, only sparse data on cancer in humans have been added since this topic was reviewed by the 2019 Advisory Group on Priorities. Mechanistic data concerning these exposures to various agents classified by IARC in laboratory settings can be challenging to describe fully, but specific information on certain agents is available. However, the variety of workplace settings and agents will make it impossible to come to a conclusion for all laboratory workers. The Advisory Group therefore considered that an *IARC Monographs* evaluation of laboratory work and occupation as chemist is unwarranted at present.

Recommendation: No priority

043 Occupation as a pesticide applicator

Current IARC/WHO classification

Occupation as a pesticide applicator has not been previously evaluated by the *IARC Monographs* programme. This agent was assigned *no priority* for evaluation by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a).

Exposure characterization

Pesticide applicators are responsible for applying pesticides to crops, gardens, houses, and other areas where pests may be present. Applicators may apply a huge range of pesticides, including herbicides, insecticides, fungicides, nematicides, and rodenticides, as well as bactericides, algicides, and virucides. WHO (2020b) states that over 1000 different pesticides are used around the world, and the European Commission (2024.) database lists nearly 1500 active substances, safeners, and synergists.

Pesticide applicators use a wide range of application methods, including spraying, injecting, and laying baits. Spraying may be from aircraft, from tractors or other farm machinery, or using a backpack or hand-held spray. A wide variation in the use of control measures is also seen, with particularly high levels of exposures and low use of controls in countries with lower socioeconomic status.

Cancer in humans

Many studies are available on exposure to individual pesticides and different types of cancer, with a PubMed search for this agent identifying over 3000 articles. A PubMed search for "pesticides" AND "cancer" discloses more than 11 000 papers on this topic. Of these, there are 138 meta-analyses and a further 75 systematic reviews, half of them published in the past 5 years. However, not all of these will be specifically relevant to occupational exposure as a pesticide sprayer. One recent meta-analysis of occupational exposure and NHL concluded that occupational exposures to various hazards, including pesticide occupation, were associated with an increased risk of NHL but did not provide a meta-estimate (Francisco et al., 2023). There are challenges in interpreting the literature on general occupational exposure to pesticides, given the heterogeneous nature of the exposure and the pesticides.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

Mechanistic evidence in exposed humans is available from studies of individual compounds or for mixed exposures.

Gómez-Martín et al. (2015) investigated occupational exposure to pesticides and found an elevation in N^7-methyldeoxyguanosine DNA adducts in individuals exposed to these chemicals, potentially leading to mutations, and genomic instability, contributing to carcinogenesis. The study also highlighted the influence of genetic polymorphisms in such enzymes as paraoxonase-1 (PON1) and glutathione-S-transferase (GST), which play crucial roles in detoxification pathways.

Usman et al. (2022) reviewed the association between GSTM1/GSTT1 null genotypes and cancer risk among pesticide workers. They highlighted an increased susceptibility to adverse health effects, owing to the absence of key xenobiotic metabolizing enzymes, although some individuals with null genotypes do not exhibit susceptibility. Pesticides, exacerbated by null GSTT1/GSTM1 genotypes, induce genotoxicity and cancer through mechanisms involving oxidative stress and miRNA dysregulation. Sherif et al. (2023) conducted a systematic review and meta-analysis to assess the genotoxic effects of agricultural pesticide exposure among workers in Arabic countries. Results indicated a higher level of DNA damage in exposed

individuals, emphasizing the need for further research to elucidate the genotoxic effects of occupational pesticide exposure in the Middle East.

Lucio et al. (2023) conducted a study in Brazil demonstrating genetic instability in farmers using pesticides, as evidenced by a combination of alkaline comet and micronucleus assays. Similarly, Kaur and Kaur (2018) discussed how impaired DNA repair mechanisms, often compromised by pesticide exposure, can lead to the accumulation of DNA damage, increasing the risk of cancer development over time. Dos Santos et al. (2022) assessed genomic instability and telomere length in Brazilian family farmers exposed to pesticides and found evidence of genomic instability using the buccal micronucleus cytome (BMCyt) assay, a technique that detects DNA damage, in pesticide-exposed farmers. Additionally, telomere length, which is associated with cellular ageing and genomic stability, may be affected by pesticide exposure, suggesting a potential biomarker for assessing the effect of pesticides on genomic health.

Benedetti et al. (2018) investigated DNA damage and epigenetic alterations in soybean farmers exposed to a complex mixture of pesticides. They found evidence of both DNA damage and epigenetic changes in exposed individuals, suggesting that pesticide exposure may induce genetic and epigenetic modifications that could contribute to adverse health effects. This study emphasizes the importance of understanding the molecular mechanisms underlying the toxicity of pesticide mixtures. Jiménez-Garza et al. (2023) reviewed DNA methylation modifications in blood cells from workers exposed to toxic agents. Findings suggested global hypomethylation and promoter hypermethylation in exposed groups, highlighting the importance of epigenetic mechanisms in pesticide-induced toxicity.

Pesticide exposure is known to induce oxidative stress, a condition characterized by an imbalance between ROS production and the body's antioxidant defence mechanisms. Ledda et al. (2021) and Hilgert Jacobsen-Pereira et al. (2018) both observed elevated levels of oxidative stress markers and DNA damage in agricultural workers after pesticide exposure. Kisby et al. (2009) also reported similar findings, further emphasizing the role of oxidative stress in pesticide-related carcinogenesis. Barbosa de Sousa et al. (2023) investigated mitochondrial DNA copy number variation in Brazilian farmers occupationally exposed to pesticides. Mitochondrial dysfunction has been implicated in pesticide-induced toxicity, and alterations in mitochondrial DNA copy number may reflect cellular responses to pesticide exposure. Understanding mitochondrial dysfunction in pesticide-exposed populations can provide insights into the mechanisms underlying pesticide toxicity and associated health outcomes.

Chronic inflammation has been implicated as a contributing factor in various cancers, and pesticide exposure can exacerbate inflammatory processes in the body. Zanchi et al. (2024) found a link between redox imbalance, inflammation, and an increased risk of depression in Brazilian pesticide-exposed farmers. Additionally, Ramos et al. (2021) documented multibiomarker responses indicative of inflammation in an agricultural population from central Brazil, further supporting the association between pesticide exposure and chronic inflammation.

Lerro et al. (2018a) reported an association between occupational pesticide exposure and subclinical hypothyroidism. Similarly, Blanco-Muñoz et al. (2016) found alterations in thyroid hormone levels in floriculture workers exposed to organochlorine pesticides, suggesting disruption of the endocrine function. Moreover, Mardhiyah et al. (2021) observed differences in thyroid hormone levels between female farmers and non-farmers in Indonesia, further implicating pesticide exposure in endocrine dysfunction and potentially cancer development.

Andreotti et al. (2015) investigated the effect of pesticide use on leukocyte telomere length, a marker of cellular ageing and immortalization. Their study found a correlation between pesticide exposure and shorter leukocyte telomeres, suggesting a potential mechanism by which pesticides might promote cellular immortalization and contribute to carcinogenesis.

Summary

Pesticide applicators are exposed to a myriad of toxic substances during their work. These pesticide-specific exposures have been linked to an increased risk of cancer through several key mechanisms, as elucidated by recent research. Studies of mechanistic end-points in pesticide applicators have found some evidence of KCs, including DNA damage, genomic instability, oxidative stress, chronic inflammation, receptor-mediated effects, and immortalization. However, given the complex mixture of pesticides and different mechanisms, it will be difficult to give a uniform evaluation on carcinogenic hazard for pesticide applicators in general. The rationale for evaluating pesticide applicators as an occupation is not clear, given that a number of specific pesticides and their active ingredients have already been evaluated or are prioritized for future evaluation by the *IARC Monographs* programme (including many described in the present report). The Advisory Group therefore considered that an *IARC Monographs* evaluation of occupation as a pesticide applicator is unwarranted.

Recommendation: No priority

044 Semiconductor industry work

Current IARC/WHO classification

Semiconductor industry work has not been previously evaluated by the *IARC Monographs* programme. Working in the semiconductor industry was given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a).

Exposure characterization

Individuals working in the semiconductor industry have heterogeneous levels of exposure to a variety of hazardous chemicals, as well as sources of ionizing and non-ionizing radiation. Production processes and involved chemicals may be trade secrets (Choi et al., 2018; Kim et al., 2018c), and exposures change over time, owing to advances in technology (Choi et al., 2018), representing a challenge in exposure characterization. Issues with exposure characterization have been noted in epidemiological studies on semiconductor workers (Park, 2018b).

A cross-sectional study of semiconductor workers in the Republic of Korea identified elevated levels of exposure to some agents, such as solvents, shift work, and heavy metals (Kim et al., 2022a); the influence of non-occupational exposure could not be excluded for some of these agents.

Cancer in humans

Reviews of the epidemiological literature (Kim et al., 2014a, 2022b) and more recently published studies (Rodrigues et al., 2020; Lee et al., 2023b) have reported excess cancer incidence or mortality among workers for various sites including brain and breast, and for haematolymphoid cancers. The human cancer data published since 2019 are sparse. Of the more recently published studies, one nested case–control study in the USA included 120 cases of cancer of the CNS, with somewhat inconsistent results by facility location (Rodrigues et al., 2020), and a retrospective cohort in the Republic of Korea reported significantly higher excess deaths from lymphohaematopoietic cancers and leukaemia only among female operators (Lee et al., 2023b).

On balance, previous studies are generally limited by such issues as inadequate exposure characterization, minimal control for confounding factors, and potential lack of comparability between comparison groups (i.e. healthy worker biases).

Few studies evaluated exposure–response associations (Kim et al., 2014a). A recent case–control study considered cumulative exposure by job group and cancers of the CNS, including the brain (Rodrigues et al.,

2020). Significant trends or associations were noted for select chemicals across tertiles of exposure, including agents already classified as *carcinogenic to humans* (Group 1), as well as others (e.g. molybdenum) classified as *possibly carcinogenic to humans* (Group 2B) or (e.g. 2-butoxyethanol, cyclohexanone, orthodichlorobenzene) evaluated as *not classifiable as to its carcinogenicity to humans* (Group 3).

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

Mechanistic data for semiconductor exposure as a whole are not widely available; however, studies on specific agents used in semiconductor manufacturing may be informative. One study reported evidence of increased frequency of micronuclei in lymphocytes in semiconductor workers in Germany exposed to boron trifluoride and boron trichloride, compared with non-exposed semiconductor workers. In replicate analysis, the difference disappeared after the implementation of protective measures for reducing exposures, described only as "complex mixtures of chemical waste products" (Winker et al., 2008). Studies by Yoon et al. (2020) and Song et al. (2022a) emphasized the presence of such carcinogenic materials as sulfuric acid, chromic acid, ethylene oxide, crystalline silica, potassium dichromate, and formaldehyde in semiconductor manufacturing, as well as occupational exposure to refractory ceramic fibres (RCFs) during maintenance activities.

Epidemiological investigations by Rodrigues et al. (2020) found positive associations between cancers of the CNS, including the brain, and specific operations and chemicals in semiconductor facilities. Despite a decrease in mean exposures to carcinogens over time, workers remain at risk during certain operations, as demonstrated by Rodrigues et al. (2019) and Park et al. (2011).

Mechanistically, the carcinogenicity of semiconductor-related compounds, such as indium phosphide and indium oxide, involve oxidative stress, inflammation, genotoxicity, and interference with DNA repair mechanisms (NTP, 2001; Bomhard, 2018). Additionally, exposure to RCFs can induce chronic inflammation, fibrosis, and oxidative stress, leading to DNA damage and carcinogenesis (Song et al., 2022a).

In a study designed to characterize the genotoxic effects of a complex mixture of perhalogenated hydrocarbons, genotoxic effects were associated with exposure to this mixture, indicating potential DNA damage (Müller et al., 2002). In addition, Bustamante et al. (1997) investigated the effects of semiconductor agents arsenic and indium on rat thymocytes. The researchers found that both arsenic and indium induced apoptosis (programmed cell death) in the thymocytes.

Summary

Epidemiological investigations have highlighted positive associations between certain operations and chemicals in semiconductor facilities and cancers of the CNS, including the brain.

There is some mechanistic evidence that occupational exposure in the semiconductor industry exhibits KCs, including genotoxicity, alteration of DNA repair, oxidative stress, and chronic inflammation. However, an evaluation of carcinogenicity would be extremely challenging, owing to the heterogeneity of exposure and changes in the exposure over time. The Advisory Group therefore considered that an *IARC Monographs* evaluation of semiconductor industry work to be unwarranted.

Recommendation: No priority

045 Textile manufacturing industry work

Current IARC/WHO classification

Textile manufacturing industry work has been previously evaluated by the *IARC Monographs* programme, most recently in *IARC Monographs* Volume 48 in 1989 (IARC, 1990b), and was classified by IARC as *possibly carcinogenic to humans* (Group 2B), on the basis of *limited* evidence for cancers of the nasal cavity and bladder in humans.

Exposure characterization

The global fashion and furnishing industries employ more than 75 million workers worldwide. Most of these industries are located in parts of the world, especially LMICs, where occupational health legislation may be weak or non-existent. Textile manufacturing workers produce textiles of all types, with the exposure consisting of inhalation of cotton dust and other types of dust, including from silk, wool, and a wide array of synthetic fibres. Textile workers are also exposed to a variety of dyes, solvents, mineral oils, and other chemicals (IARC, 1990b; Singh and Chadha, 2015, 2016). Historically, there has also been exposure to asbestos fibres (Deng et al., 2012).

Cancer in humans

Numerous occupational epidemiology studies have been conducted among textile workers in different countries around the world. *IARC Monographs* Volume 48 (IARC, 1990b) outlines dozens of studies among textile workers. A large number of these studies have been summarized in one extensive review (Singh and Chadha, 2016).

In the previous evaluation, the evidence was found to be *limited* for cancers of the nasal cavity and bladder. Although consistent positive associations were seen in several studies, there were concerns about confounding by other causes of these cancers. Few studies of sinonasal cancer among textile workers have been published since *IARC Monographs* Volume 48 (IARC, 1990b). A hospital-based case–control study in France observed a positive association between sinonasal cancer and textile dust exposure among women; it was not possible to separate the effects of wood dust from those of textile dust among men (Luce et al., 1997). Textile workers were found to be at increased risk of nasal cancer in a small, population-based case–control study (Teschke et al., 1997). In a national surveillance system in Italy, some patients with sinonasal cancer were found to have been exposed to textile dusts (Binazzi et al., 2018).

In the most recent IARC evaluation (IARC, 1990b), there were five case–control studies among textile dyers, all of which showed elevated risks of bladder cancer. Since then, a possible association of textile production work with bladder cancer has been investigated in cohort or population-based case–control studies (e.g. Zheng et al., 1992; Serra et al., 2000, 2008; Reulen et al., 2007; Colt et al., 2011). One motivation was the use of dyes derived from aromatic amines. These studies have also observed an increased risk of bladder cancer in various subgroups of textile workers (e.g. weavers and winding, warping, or sizing workers; Serra et al., 2008), although the possibility that risk factors other than dye-related aromatic amines were involved in at least some of these studies could not be excluded. Notably Colt et al. (2011), who controlled well for smoking and other occupational risk factors, observed an OR of 2.0 (95% CI, 1.2–3.3; $P_{\text{duration trend}} = 0.0013$) among male textile and leather machine operators.

Several studies focused on the risk of lung cancer since the previous evaluation. A case–control study in India found a higher risk of lung cancer among male textile workers, controlling for smoking (Notani et al., 1993). In some cohorts, it was identified that workers had been exposed to asbestos fibres, owing to the type of textile produced or the technology used in the industry, or both (Deng et al., 2012; Elliott et al., 2012; Wang et al., 2012). Many studies focused specifically on endotoxin exposure among workers handling cotton fibres (e.g. Astrakianakis et al., 2007; Fang et al., 2013). For example, a study in female textile

workers in Shanghai found an inverse relation between lung cancer risk and cumulative endotoxin exposure that occurred 20 years or more before the onset of risk (Agalliu et al., 2011). This suggests a possible early anti-carcinogenic effect of endotoxin exposure. However, the association between lung cancer and endotoxin exposure accumulated in more recent windows (< 20 years before risk) was weaker and not statistically significant, indicating the importance of temporal aspects in understanding carcinogenic mechanisms in textile manufacturing (Applebaum et al., 2013). In a large case–cohort study conducted among women textile workers in Shanghai, which carefully reconstructed exposures to chemicals and particles, some evidence was seen of a positive association of lung cancer with silica dust and formaldehyde among the small percentage of women exposed to these agents (Checkoway et al., 2011).

Cancer in experimental animals

No studies on exposure through working in the textile-manufacturing industry and cancer in experimental animals were available to the Advisory Group, but carcinogenicity studies are available for some individual exposure types in the textile manufacturing industry.

Mechanistic evidence

Textile workers are frequently exposed to a wide range of agents, including aromatic amines, PAHs, formaldehyde, particulate matter, asbestos, and NSW. Several of these have already been classified by IARC as *probably carcinogenic to humans* (Group 2A) or *carcinogenic to humans* (Group 1). All of them have been shown to exhibit several of the KCs. Mechanistic evidence of the KCs for occupational exposure in a textile factory in exposed humans is not extensive.

In a cross-sectional study, Fanlo et al. (2004) observed a significant increase of urinary mutagenicity in 117 workers in a textile factory, mainly exposed to dyes, compared with matched 117 non-exposed workers. A similar increase of urinary mutagenicity was observed in 70 textile workers exposed mainly to arylamines, compared with control non-exposed workers (Sinués et al., 1992). In a biomonitoring study conducted in Türkiye, Diler and Çelik (2011) observed a significant increase of micronuclei frequency in buccal mucosa cells collected from a group of 50 carpet fabric workers (25 smokers and 25 non-smokers), compared with controls. Similar genotoxicity damage, by means of increased micronuclei frequency, was observed in PBLs collected from workers at a textile painting factory in southern India (Sellappa et al., 2010).

More recently, in a pre- and post-test randomized experimental control trial, Prasetyo et al. (2019) observed significant decreases in immunoglobulin A (IgA) levels and pulmonary function, markers of altered inflammatory response, in a group of 30 young healthy workers from a textile company in Indonesia. Levels of IgA were increased after the use of protective masks.

Summary

Several new human cancer studies since the previous *IARC Monographs* evaluation show an association between exposure from work in the textile manufacturing industry and cancers of the sinonasal cavity, urinary bladder, and lung. No evidence is available for cancer in experimental animals. There is some evidence that occupational exposure in a textile factory might be associated with the KCs, including genotoxicity and chronic inflammation. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of textile manufacturing industry (work in) to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

046 Outdoor air pollution

Current IARC/WHO classification

Outdoor air pollution and particulate matter in outdoor air pollution were previously classified by IARC as *carcinogenic to humans* (Group 1) in *IARC Monographs* Volume 109 in 2013 (IARC, 2015). There is *sufficient* evidence that these two agents cause lung cancer in humans, and *limited* evidence that outdoor air pollution causes bladder cancer. Outdoor air pollution was given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a).

Exposure characterization

Air pollution has been defined as the presence of one or several substances (e.g. NO_2, particulate matter of aerodynamic diameter < 2.5 μm ($PM_{2.5}$), ozone, soot, ultrafine particles, diesel engine exhaust, benzene and other volatile organic compounds) in air at a concentration or duration above natural levels, with the potential to cause an adverse effect (IARC, 2015) As noted in the 2019 Advisory Group report (IARC, 2019a), outdoor air pollution exposure remains widespread globally, with both anthropogenic sources (e.g. industrial, transportation, domestic, agricultural) and human-enhanced natural sources (e.g. increasing wildfires due to climate change). In 2021, WHO published a major revision of its air quality guidelines since the previous evaluation in 2005; the guideline level for $PM_{2.5}$ was reduced from 10 μg/m^3 to 5 μg/m^3 (WHO, 2021b). The new guideline notes that air quality has improved in most high-income countries since the 1990s, but that there has been deterioration in most LMICs.

Cancer in humans

Evidence for cancer sites in addition to the lung has been examined extensively since the previous evaluation of outdoor air pollution (IARC, 2015). In a pooled analysis of six European cohorts, some components of outdoor air pollution (i.e. $PM_{2.5}$, soot, NO_2) showed positive but imprecise associations with cancer of the intracranial CNS (Hvidtfeldt et al., 2023). A separate meta-analysis also estimated positive but imprecise associations between $PM_{2.5}$ and adult brain tumours but found stronger associations for soot and NO_2 (Shen et al., 2023). A meta-analysis of 13 studies (mainly of cohorts) observed an association between $PM_{2.5}$ and cancers of the liver (meta-RR, 1.31; 95% CI, 1.07–1.56) and colorectum (meta-RR, 1.35; 95% CI, 1.08–1.62), with most studies evaluated as having a "probably low" risk of bias (Pritchett et al., 2022).

A meta-analysis found meta-RRs of 1.03 per 10 μg/m^3 change in $PM_{2.5}$ exposure for breast cancer incidence (95% CI, 0.93–1.13) and 1.18 per 10 μg/m^3 change in $PM_{2.5}$ exposure for mortality (95% CI, 0.81–1.73) (Yu et al., 2021b). Two other meta-analyses found stronger associations with breast cancer for NO_2 than for $PM_{2.5}$ (Gabet et al., 2021; Wei et al., 2021a). For cancers of bladder (mortality) and kidney (incidence), a systematic review found that most of the studies identified observed positive associations, although many were imprecise, and differences in study metrics precluded meta-estimation (Zare Sakhvidi et al., 2020). Adequacy of control for confounding was a concern in these studies. A large, well-conducted study observed null associations for bladder cancer incidence and $PM_{2.5}$ (Pedersen et al., 2018).

A meta-analysis was conducted for metrics of outdoor air pollution and childhood leukaemia (Filippini et al., 2019). Only 3 of 29 studies included measures of $PM_{2.5}$, and no meta-estimate was provided. Most of the studies used indirect metrics, such as traffic count, road density, or distance from a major road. The meta-RR for traffic density (highest compared with lowest category) was 1.09 (95% CI, 1.00–1.20). For benzene exposure, which was estimated in seven of the studies, the meta-RR for all childhood leukaemia was 1.27 (95% CI, 1.03–1.56) and was higher for AML (meta-RR, 1.84; 95% CI, 1.31–2.59).

Summary

For several cancer types, including cancers of the breast, liver, and colorectum, there appears to be increasing evidence of an association with outdoor air pollution and particulate matter in outdoor air pollution. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of outdoor air pollution to be warranted. It may be efficient to conduct such an evaluation in conjunction with other metrics of air pollution (e.g. NO_2, soot, ultrafine particulates, combustion of biomass, ozone), some of which are described elsewhere in the present report (agents 047–050).

Recommendation: High priority (and ready for evaluation within 5 years)

047 Indoor and outdoor combustion of biomass

Current IARC/WHO classification

Indoor emissions from household combustion of biomass have been classified as *probably carcinogenic to humans* (Group 2A) in *IARC Monographs* Volume 95 in 2006 (IARC, 2010e), on the basis of *limited* evidence for cancer in humans (specifically, lung cancer) and *sufficient* evidence of carcinogenicity of wood smoke extracts in experimental animals. Outdoor emissions from combustion of biomass have not been previously evaluated by the *IARC Monographs* programme, although outdoor air pollution and particulate matter in outdoor air pollution were classified as *carcinogenic to humans* (Group 1) in *IARC Monographs* Volume 109 in 2013 (IARC, 2015). Combustion of biomass was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of new evidence of lung cancer in humans from indoor sources of biomass combustion.

Exposure characterization

Combustion of biomass includes burning of wood, branches, twigs, and dung (IARC, 2010e). As noted in the 2019 Advisory Group report (IARC, 2019a):

> These fuels are used by about half of the world's population, primarily in low- and middle-income countries, for cooking and heating, often in poorly ventilated spaces (Rehfuess et al., 2006). Products of incomplete combustion contain respirable particles and many volatile and non-volatile organic compounds, including carcinogens such as benzo[*a*]pyrene, formaldehyde, and benzene.

The highest levels of $PM_{2.5}$ have been found in houses with older wood stoves (Fleisch et al., 2020). Women and young children who are most often at home may be the highest exposed to indoor sources of biomass combustion (IARC, 2010e).

Outdoor exposure to biomass combustion is also largely due to wood smoke, which contributes 56–77% of particulate matter (PM) levels during the winter in some areas in Canada (Ward and Lange, 2010). In Asia, smoke haze from vegetation and peatland fires is a serious problem, with the smoke, consisting of a complex mix of chemicals, often resulting in unhealthy air quality for long periods of time (Phung et al., 2022a). Wildfires are another major contributor to outdoor exposure, both for the general population and as occupational exposure of wildland firefighters (IARC, 2023a).

Cancer in humans

The 2019 Advisory Group report (IARC, 2019a) noted:

> A meta-analysis including 14 case–control studies of biomass cooking or heating reported [an OR] for lung cancer risk of 1.17 (95% CI, 1.01–

> 1.37) with biomass for cooking and/or heating overall […] (Bruce et al., 2015). Sensitivity analyses restricted to studies with adequate adjustments for potential confounders and a clean-fuel reference category resulted in ORs of 1.21 (95% CI, 1.05–1.39) for men and 1.95 (95% CI, 1.16–3.27) for women. Exposure–response relationships were observed for men, and higher risk was found for women in low- and middle-income countries than for those in high-income countries.

Since then, various new studies have been published. A recent study in the USA showed an increased risk of lung cancer among women who used a wood-burning fireplace or stove for ≥ 30 days/year (HR, 1.68; 95% CI, 1.27–2.20) compared with women who did not use a wood-burning fireplace or stove (Mehta et al., 2023). This association remained for women who had never smoked. A case–control study also reported an association between indoor wood smoke exposure and lung cancer, for which the risk was higher for more hours of exposure per year (Báez-Saldaña et al., 2021). In *IARC Monographs* Volume 132 (IARC, 2023a), a few studies of cancer in humans included wildland firefighters.

Cancer in experimental animals

Few carcinogenicity study data from experimental animals are available. In a study in China by Liang et al. (1988), in which mice and rats were exposed to natural wood smoke, there was a significant increase in the incidence of lung tumours in rats. Mumford et al. (1990) demonstrated the incidence of skin tumours after 77 weeks in SENCAR mice exposed to extracts from indoor air pollutants from wood combustion. The Advisory Group considered that there are limitations in the aforementioned bioassays to be considered in evaluating the carcinogenicity of biomass combustion.

Mechanistic evidence

One study found high potency of air extracts to induce sustained levels of cellular stress, including oxidative stress, genotoxicity, DNA damage response, and proinflammatory signalling (de Oliveira Galvão et al., 2020). Combustion-derived particles from biomass sources have been found to promote epithelial-to-mesenchymal transition in human lung A549 cells (Marchetti et al., 2021). In the same cell line, inflammatory responses, as measured by the production of IL-6, IL-8, and TNFα, were observed after exposure to particles of wood combustion (Karlsson et al., 2006). Additionally, solid fuel combustion emissions increased the generation of ROS in human ocular cell lines (Karakoçak et al., 2019). Long-term exposure to indoor biomass smoke was shown to cause DNA damage in airway cells and oxidative stress, micronucleus formation, and chromosomal aberrations in PBLs in exposed humans, (Mumford et al., 1993; Musthapa et al., 2004; Mondal et al., 2010; Mukherjee et al., 2013). In CHO cells, a dose–response increase in SCE was observed for exposure to wood smoke (Hytönen et al., 1983; Salomaa et al., 1985). In mouse macrophages (RAW264.7 cells), exposure to wood smoke led to increased levels of lipid peroxidation, activation of inflammatory and immune responses, and DNA damage through the generation of ROS (Leonard et al., 2000).

When biomass materials are burnt, they release a variety of pollutants, including mutagenic and carcinogenic compounds, such as PAHs. Combustion biomass materials may exhibit KCs, including genotoxicity, oxidative stress, and chronic inflammation, particularly in the lungs and possibly in other organs (Alfheim and Ramdahl, 1984; Bell and Kamens, 1990; Mutlu et al., 2016; Champion et al., 2020).

Summary

There appears to be growing evidence of an association between exposure to combustion of biomass indoors and risk of lung cancer in humans, which could support an evaluation of whether there is now *sufficient* evidence for lung cancer in humans. Little evidence is available from animal studies for

combustion of biomass and carcinogenicity. However, there are some reports of genotoxic effects, immunomodulation, and inflammatory response owing to exposure to particles from indoor biomass combustion in exposed humans, and for wood smoke for human cell lines, in bacterial systems, and in rodents.

The emerging new human cancer evidence and mechanistic evidence in exposed humans supports a re-evaluation of this agent, previously classified in IARC Group 2A. For outdoor air combustion, the human cancer evidence is sparse. The mechanistic evidence in experimental systems and mechanistic studies in wildland firefighters may be relevant to this agent. The Advisory Group therefore considered an *IARC Monographs* evaluation of these agents to be warranted. In the interest of efficiency, it may be useful to combine these two agents in an evaluation. These two agents may be considered with outdoor air pollution (agent 046) in a future meeting.

Recommendations

Indoor biomass combustion: High priority (and ready for evaluation within 2.5 years)
Outdoor biomass combustion: Medium priority

048 Ultrafine particles

Current IARC/WHO classification

Ultrafine particles (UFPs) have not been previously evaluated by the *IARC Monographs* programme. However, particulate matter in outdoor air pollution (without specification of size) was classified as *carcinogenic to humans* (Group 1) in *IARC Monographs* Volume 109 in 2013 (IARC, 2015).

Exposure characterization

UFPs are less than 100 nm in diameter and are also denoted $PM_{0.1}$ (Schraufnagel, 2020). UFPs can originate from both natural sources (e.g. volcanoes, wildfires) and anthropogenic sources (e.g. traffic, industrial emissions) (Li et al., 2016a). Exposure to UFPs occurs primarily via general air pollution, as well as in occupational settings.

Since UFPs are an important component of traffic-related air pollution, many people are exposed, but UFPs have a large variation on a fine spatial scale. For example, models in the Netherlands estimated levels from 7691 particles/cm^3 for the 1st percentile to 23 390 particles/cm^3 for the 99th percentile (Bouma et al., 2023). Across the continental USA, estimated levels ranged from 1808 to 20 896 particles/cm^3 (Pond et al., 2022).

In occupational settings, exposure to UFPs mainly occurs after high-temperature and mechanical treatments of materials, owing to unintentional heating of semi-volatile materials, or to combustion processes (Manigrasso et al., 2019). Highest concentrations of $PM_{0.1}$ have been observed in welding facilities, machine shops, basic metal industries, traffic-related occupations, and restaurants, with concentrations of 0.7–4.7×10^6 particles/cm^3, 60–450 times as high as background levels (Viitanen et al., 2017).

Cancer in humans

In a US cohort, UFPs were significantly associated with all-cancer mortality in single-pollutant models, but risk estimates became insignificant after controlling for $PM_{2.5}$ or NO_2 (Pond et al., 2022). In a Dutch national cohort study on long-term exposure to UFPs (Bouma et al., 2023), a significant association was found between annual average UFP exposure and lung cancer mortality, with an HR of 1.038 (95% CI, 1.028–1.048). In two-pollutant models, this association was attenuated but remained significant. Similarly, a study in California (Jones et al., 2023a), USA, evaluating long-term outdoor UFP exposure and lung cancer risk, found a modest association for lung cancer overall. In analyses by histological subtype, an increased

risk of adenocarcinoma was observed among men, but not women. A Canadian study on childhood cancer (Lavigne et al., 2020) found that exposure to UFPs during the first trimester of pregnancy was positively associated with overall cancer incidence diagnosed before the age of 6 years after adjusting for $PM_{2.5}$, NO_2, and for personal- and neighbourhood-level covariates. An HR per 10 000/cm^3 increase of 1.13 (95% CI, 1.03–1.22) was reported.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

UFPs from domestic wood stoves have been shown to be genotoxic, increasing DNA damage in human lung carcinoma A549 cells (Marabini et al., 2017). However, UFPs from an urban area in Malaysia tested negative in the Ames test, both without and with metabolic activation (Siew et al., 2023). UFPs have been associated with inflammatory responses in exposed humans (Ohlwein et al., 2019). In human primary monocytes, exposure to UFPs resulted in increased oxidative stress and a dose-dependent increase in the release of proinflammatory cytokines, such as TNFα, that could also affect the immune response (Bliss et al., 2018). Wei et al. (2016) have shown that UFPs affect both cell proliferation and DNA methylation (epigenetic changes) in human neuronal cell line SH-SY5Y (Wei et al., 2016).

Organic UFPs containing PAHs increased oxidative stress in human BEAS-2B bronchial epithelial cells in an air–liquid interface model (Juarez Facio et al., 2022). Ultrafine dusts induced DNA damage in rat lungs (Rittinghausen et al., 2013). In vitro studies have consistently shown that UFPs induce a pulmonary inflammatory response, and in vivo studies have demonstrated that UFPs lead to proinflammatory and cellular responses related to oxidative stress (Oberdörster et al., 2005). Suggested mechanisms by which UFPs induce lung diseases include the induction of oxidative stress and both innate and adaptive immune responses (Leikauf et al., 2020).

Summary

There appears to be a growing body of evidence for an association between exposure to ultrafine particles and risk of cancer, principally lung cancer. These studies involve several correlated exposures, including to $PM_{2.5}$ and other components of air pollution. There are no data in experimental animals for UFP carcinogenicity. Mechanistic evidence is available for some of the KCs, including cell proliferation, oxidative stress, and inflammation in exposed humans, human primary cells, and experimental systems. The Advisory Group therefore considered an *IARC Monographs* evaluation of ultrafine particulates to be warranted and recommended its evaluation together with other agents related to air pollution (e.g. ozone, nitrogen dioxide, or combustion of biomass).

Recommendation: High priority (and ready for evaluation within 5 years)

049 Nitrogen dioxide (CAS No. 10102-44-0)

Current IARC/WHO classification

Nitrogen dioxide (NO_2) has not been previously evaluated by the *IARC Monographs* programme. NO_2 is a component of diesel and gasoline engine exhausts, and of outdoor air pollution, all of which have been previously evaluated by the *IARC Monographs* programme.

NO_2 was given a priority rating of *medium* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of emerging epidemiological evidence for a causal role in cancers of lung and breast, and of mechanistic evidence.

Exposure characterization

As reported by the 2019 Advisory Group on Priorities (IARC, 2019a), "NO_2 is emitted from fossil fuel combustion, microbial activity, biomass burning, and oxidation of nitrous oxide. Globally, NO_2 concentrations increase in proportion to the population raised to an exponent that varies by region (Lamsal et al., 2013)." NO_2 is one of the major components of air pollution, which are moderately to highly correlated (Stafoggia et al., 2022). NO_2 is often used as a proxy for exposure to traffic-related air pollution (Hamra et al., 2015). Exposure contrasts exist geographically across the globe, as well as, at a smaller scale, within cities. The exposure concentrations vary by the route one takes, or the mode of transport. For example, cyclists and pedestrians are exposed to compositions of outdoor air pollution that differ from those to which car occupants or bus riders are exposed (Tainio et al., 2021).

Cancer in humans

The association between increasing exposure to NO_2 and mortality or morbidity from lung cancer, breast cancer, and other cancer types has been evaluated in a growing number of epidemiological studies, including long-term cohort and case–control studies. A meta-analysis of 16 cohorts found an HR for lung cancer mortality of 1.05 (95% CI, 1.02–1.08) per 10 $\mu g/m^3$ increment in NO_2 (Atkinson et al., 2018). A recent study in seven European cohorts gave an HR of 1.093 (95% CI, 1.053–1.134) for lung cancer mortality per increment of 10 $\mu g/m^3$ NO_2 (Stafoggia et al., 2022).

A review of eight case–control studies and nine cohort studies saw more consistent findings for elevated NO_2 and risk of breast cancer (White et al., 2018), which was also supported by more recent studies (Goldberg et al., 2019; Amadou et al., 2023). A few studies suggested a potentially increasing risk of non-melanoma skin cancer, cancers of the mouth and throat, and brain tumours (Jørgensen et al., 2016; Datzmann et al., 2018).

The correlations between air pollutants make it difficult to identify independent effects. For example, in two-pollutant models in the seven European cohorts, only for $PM_{2.5}$ was a consistent positive association with incidence of lung cancer observed, whereas no association with NO_2 was observed (Brunekreef et al., 2021).

Cancer in experimental animals

In a mid-term inhalation carcinogenicity study (26 weeks) using p53-knockout mice, there was equivocal evidence of lung carcinogenicity in male mice, with an increased trend in the incidence of lung adenoma at the highest concentration (40 ppm) in male mice. No carcinogenicity was observed in female mice (JBRC, 2019a). In another mid-term inhalation carcinogenicity study (26 weeks), using rasH2 mice, there was equivocal evidence of spleen carcinogenicity in male mice, with an increased trend in the incidence of haemangioma and haemangiosarcoma (combined) in the spleen at the highest concentration (40 ppm) in male mice. No carcinogenicity was observed in female mice (JBRC, 2019b).

Mechanistic evidence

Positive findings have been obtained for NO_2 in various in vitro genotoxic assays (Victorin, 1994; Koehler et al., 2011). At urban-relevant concentrations, NO_2 induced micronucleus formation and DNA fragmentation in human nasal epithelium cells from donors (Koehler et al., 2010; Koehler et al., 2013). Inhalation of NO_2 led to chromosome aberrations and mutations in lung cells in rats (Isomura et al., 1984). Additionally, inhalation exposure of rats to NO_2 caused DNA strand breakage and the formation of DNA–protein crosslinks in cells from various internal organs, as well as a noticeable increase in micronucleus frequency in the bone marrow cells of rats (Han et al., 2013).

Summary

There appears to be growing epidemiological evidence of an association between exposure to NO_2 and risk of various cancers in humans, including cancer of the lung and breast. Exposures to other components of air pollution make it difficult to evaluate NO_2 separately. A careful evaluation of the quality (including exposure assessment) and informativeness of the studies would be warranted to determine whether there is *sufficient* or *limited* evidence for the carcinogenicity of NO_2.

There is some evidence in experimental animals for the carcinogenicity of NO_2; however, it is limited to only a single species and a single sex.

There is mechanistic evidence related to the KCs, including genotoxicity for NO_2 in exposed humans and in experimental systems. On the basis of the available information, the Advisory Group recommends the evaluation of carcinogenicity of NO_2 and suggests evaluating it together with other agents related to air pollution (e.g. ozone, ultrafine particles).

Recommendation: High priority (and ready for evaluation within 5 years)

050 Ozone (CAS No. 10028-15-6)

Current IARC/WHO classification

Ozone (O_3) has not been previously evaluated by the *IARC Monographs* programme. Ozone was given a priority rating of *medium* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of bioassay and mechanistic evidence.

Exposure characterization

Ozone is listed by the OECD as a high production volume chemical (OECD, 2007).

Ozone is an important gaseous component of the mixture of air pollutants,; it is formed in a chemical reaction involving solar radiation and ozone precursors (volatile organic compounds, CO, NO_x, CH_4) (The Royal Society, 2008). Ozone is produced naturally, and pre-industrial levels are estimated to have been approximately 30 µg/m^3. Background levels are now about twice that (IARC, 2015). Ozone concentrations can change according to the weather and can peak during heat waves (The Royal Society, 2008; de Hoogh et al., 2018). There is also spatial variability, for example with estimated concentrations ranging from < 75 µg/m^3 in northern Europe to > 110 µg/m^3 in southern Europe (de Hoogh et al., 2018). Ozone exposure as a component of air pollution is also described in *IARC Monographs* Volume 109 (IARC, 2015). In urban areas with photochemical pollution, ozone levels probably reached levels greater than 1000 µg/m^3 in Los Angeles, USA, in the 1970s, but current levels in urban areas are lower, e.g. with summertime peaks of less than or approximately 400 µg/m^3 (IARC, 2015). Ozone generators used as air purifiers for the removal of bioaerosols, which gained interest after the COVID-19 pandemic despite a lack of clarity over their effectiveness, may be an indoor air pollution source of ozone (Kakaei et al., 2023).

Cancer in humans

Available informative studies are cohort studies examining cancer risk associated with components of air pollution. The US EPA Integrated Science Assessment (ISA) (US EPA, 2013a) concluded that there was inadequate evidence for a causal relation between ozone and cancer and that only a limited number of epidemiological studies were available. In 2016, a meta-analysis including several cohort studies (among them the Harvard Six Cities Study, California Teachers Study, American Cancer Society Cancer Prevention Study II, the UK Clinical Practice Research Datalink) showed no increased risk of lung cancer associated with ozone exposure (Atkinson et al., 2016). Among the recently published informative studies not included

in the meta-analysis, a project pooling seven large air pollution cohorts across Europe did not observe an association between ozone and lung cancer (Hvidtfeldt et al., 2021a). Sparse data exist for other cancer types.

Cancer in experimental animals

In a 2-year bioassay conducted using Good Laboratory Practice (GLP), inhalation of ozone caused a marginal increase in the incidence of bronchioloalveolar adenoma or carcinoma (combined) in male and female mice and of bronchioloalveolar carcinoma in female mice. In a GLP lifetime study in the same laboratory, ozone caused an increase in the incidence of bronchioloalveolar carcinoma in male mice and of bronchioloalveolar adenoma in female mice (NTP, 1994b).

Mechanistic evidence

A substantial number of studies relevant to ozone associated with air pollution and KCs are available. The ISA for ozone (US EPA, 2013a) suggested that ozone may contribute to DNA damage. Ozone has been observed to cause degradation of DNA in several different models and bacterial strains. Other experimental studies found increased DNA strand breaks in respiratory cells from guinea-pigs (Ferng et al., 1997) and mice (Bornholdt et al., 2002). Cestonaro et al. (2017) exposed rats to ozone from an air purifier, for 3 hours/day or 24 hours/day for 14 or 28 days, and found a statistically significant increase in DNA damage in the 24-hours exposure group, relative to the other groups. In lung tissue from rats, Zhang et al. (2017) reported a significant increase in 8-oxoguanine after ozone exposure. In addition, several mechanistic studies in human primary cells and exposed humans considered the association between ozone and genotoxicity (Chen et al., 2006a; Giovannelli et al., 2006; Huen et al., 2006; Tovalin et al., 2006; Palli et al., 2009; Holland et al., 2015).

Ozone has been linked to decreased activity of DNA methyltransferases and hypermethylation on the apelin promoter in experimental rats (Miller et al., 2018). Prenatal exposure to ground-level ozone has also been linked to sex-specific differential methylated regions in cord blood samples in the Early Autism Risk Longitudinal Investigation (EARLI) prospective study (Ladd-Acosta et al., 2019). Surface-level ozone induces locus-specific hypomethylation of the genes encoding angiotensin converting enzyme (ACE), endothelin-1 (ET-1), and arginase (ARG) in healthy residents in Shanghai, China (Niu et al., 2018; Xia et al., 2018). A decrease in methylation of Alu, the most abundant repetitive element in the human genome, and an increase in DNA damage associated with ozone were observed in samples of peripheral blood collected from traffic police officers (Munnia et al., 2023). In addition, several studies in experimental animals and in exposed humans are available, associating ozone with induction of chronic inflammation (US EPA, 2013a; Hung et al., 2022; Liu et al., 2022c) and oxidative stress (US EPA, 2013a; Zhang et al., 2019a).

It is important to note that medical ozone, used in ozone therapy, has been shown to improve chronic inflammation (Zeng et al., 2020; Viebahn-Haensler and León Fernández, 2021). Ozone therapy can induce an adaptive antioxidant activity (Clavo et al., 2021), decreasing endogenous oxidative stress. Ozone restrains the proliferation and migration potential and epithelial−mesenchymal transition (EMT) process of liver cancer cells via ROS accumulation and PI3K/AKT/NF-κB suppression (Li et al., 2021d) and acts in several other mechanisms that are considered protective from carcinogenesis (DiMauro et al., 2019).

Summary

Regarding evidence of cancer in humans, the available epidemiological studies do not show a positive association between ozone and lung cancer, and there is a lack of data for other cancer types. There is evidence in experimental animals for the carcinogenicity of ozone. Mechanistic studies in experimental systems and exposed humans show that ozone exhibits KCs. The Advisory Group therefore considered an *IARC Monographs* evaluation of ozone to be warranted.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

051 Silica dust (CAS No. 14808-60-7)

Current IARC/WHO classification

Silica dust (crystalline, in the form of quartz or cristobalite) was previously classified by IARC as *carcinogenic to humans* (Group 1) in *IARC Monographs* Volume 100C in 2009 (IARC, 2012c). There is *sufficient* evidence that crystalline silica dust exposure causes lung cancer. WHO and ILO have published joint estimates of the burden of disease for dusts (WHO, 2024b).

Exposure characterization

Silica dust is listed by the OECD (2007) and the US EPA (2024a) as a high production volume chemical. However, the main exposure hazard in crystalline silica dust is through process-generated exposure in a variety of settings (e.g. mining, stonecutting, concrete and cement drilling and cutting, and fabrication of engineered stone – see agent 052 in the present report). Despite the recognition more than 15 years ago of silica dust as an important cause of lung cancer, there is widespread occupational exposure globally.

Cancer in humans

The literature on crystalline silica in relation to cancer sites other than the lung has been relatively sparse since the previous evaluation in 2009 (IARC, 2012c). A meta-analysis of the association between occupational exposure to crystalline silica and gastric cancer, including studies up to 2014, found a meta-RR of 1.25 (95% CI, 1.18–1.34). Study heterogeneity was partially explained by industry differences, with larger effect sizes observed in the mining and foundry industries (Lee et al., 2016a).

For laryngeal cancer, a meta-analysis of cohort and case–control studies of workers exposed to silica dust found a meta-SMR of 1.13 (95% CI, 0.82–1.45) overall, and a meta-SMR of 1.38 (95% CI, 0.79–1.96) for workers with silicosis (Chen and Tse, 2012). In case–control studies, a meta-OR of 1.39 (95% CI, 1.17–1.67) was seen. More recently, the SYNERGY–International Head and Neck Cancer Epidemiology (INHANCE) study applied a quantitative job-exposure matrix for four established occupational lung carcinogens to five case–control studies within the consortium. Quantitative exposure levels for respirable crystalline silica were assigned to occupational histories of 2256 laryngeal cancer cases and 7857 controls, recruited from 1989 to 2007 (Hall et al., 2020). The risk of laryngeal cancer from occupational silica exposure was estimated by sex, adjusted for many potential confounders (e.g. smoking and co-exposure to occupational carcinogens). Among men, values for linear trend were $P < 0.05$ for cumulative exposure and $P < 0.05$ for exposure duration to respirable crystalline silica; the strongest associations were observed for respirable crystalline silica at ≥ 30 years duration (OR, 1.4; 95% CI, 1.2–1.7).

Summary

New studies of cancer in humans are available to support a potential evaluation of *sufficient* or *limited* evidence for additional cancer sites related to crystalline silica exposure. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of silica dust to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

052 Engineered stone fabrication

Current IARC/WHO classification

The fabrication of engineered stone has not been previously evaluated by the *IARC Monographs* programme. However, silica dust (crystalline, in the form of quartz or cristobalite), which is the main constituent of engineered stone, was classified as *carcinogenic to humans* (Group 1) in *IARC Monographs* Volume 100C in 2009 (IARC, 2012c). The Working Group concluded that silica dust causes lung cancer (see agent 051 in the present report). WHO and ILO have published joint estimates of the burden of disease for dusts (WHO, 2024b).

Exposure characterization

Engineered stone is a composite material made up of silica powder mixed with adhesives to create a solid surface that mimics natural stone. It is also known as artificial stone, agglomerated stone, or manufactured stone, and by various trade names. The main use of engineered stone is in kitchen and bathroom benchtops.

Different engineered stone products vary widely in composition (Kumarasamy et al., 2022). Most contain between 87.9% and 99.6% SiO_2, but this is made up of varying percentages of quartz and cristobalite (León-Jiménez et al., 2020; Kumarasamy et al., 2022). Other materials found in engineered stone products include metals (e.g. Al, Na, Fe, Ca, Ti), volatile organic compounds (e.g. styrene, toluene, *m*-xylene), and other hydrocarbons (e.g. phenanthrene, naphthalene) (León-Jiménez et al., 2020).

Engineered stone was first developed in the 1960s and became increasingly popular in North America, Europe, and Australasia in the 2000s. Most engineered stone is now manufactured in China and India, but no studies of exposure during manufacture of the original product were available to the Advisory Group.

Exposure to process-generated agents occurs when the manufactured product is cut, ground, shaped, and polished to fit the requirements for a kitchen or bathroom. Initially, fabrication is performed in workshops, but often some final shaping and cutting is needed during in-home installation. The dust produced when dry cutting engineered stone is very fine (< 1 µm) and consists of > 80% respirable crystalline silica (Ramkissoon et al., 2023). Engineered stone dust particles seem to be more irregular than natural stone dust particles, with more sharp edges and fractures along the surface (Ramkissoon et al., 2023).

Several studies have investigated levels of worker exposure to respirable quartz during cutting, grinding, and shaping of engineered stone. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a health-based threshold limit value (TLV) air concentration of 0.025 mg/m^3 but most countries have a TLV between 0.05 and 0.1 mg/m^3 (IFA, 2024). Levels of exposure above 0.1 mg/m^3 are common when workers use dry cutting, even for relatively short periods (Phillips et al., 2013). Wet cutting reduces exposure levels considerably, but exposures above 0.05 mg/m^3 are commonly seen, even with wet cutting. For example, in an Australian study of 123 workers who all used wet cutting, the geometric mean (GM) respirable crystalline silica (RCS) was 0.034 mg/m^3 as an 8-hour time weighted average (TWA) (90% credibility interval, 0.030–0.040 mg/m^{3r}), with a 95th percentile of 0.174 mg/m^3, and the highest exposure measured was 0.33 mg/m^3 (Weller et al., 2024). Similarly, a US study of 47 workplaces found an 8-hour TWA of over 0.05 mg/m^3 in 25% of workshops, and observed that in half the workplaces at least one worker had an 8-hour TWA exposure above 0.05 mg/m^3, despite all facilities using wet cutting (Surasi et al., 2022). The lowest exposures occur when the cutting is remote-controlled or automated (Phillips et al., 2013).

In December 2023, the Australian governments decided that manufacturing, supplying, processing, and installing engineered stone would be banned as of 1 July 2024 because of the risk of silicosis (Safe Work Australia, 2023). No other country has yet banned engineered stone.

Cancer in humans

No studies directly relatable to exposure to engineered stone and cancer in humans were available to the Advisory Group.

Cancer in experimental animals

No studies specifically on engineered stone and cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

There is increasing evidence associating occupational exposure to engineered stone with inflammatory markers in human cell lines in vitro (Ramkissoon et al., 2023) and with the development of pulmonary silicosis (García-Núñez et al., 2022; Hoy et al., 2023) and fibrosis (León-Jiménez et al., 2020) in exposed humans. These could be considered end-points relevant for chronic inflammation. Ramkissoon et al. (2023) found that, in addition to silica, aluminium, and cobalt were also associated with the inflammatory response, highlighting the importance of non-silica elements. Patients with silicosis caused by occupational exposure to engineered stone present a rapid progression from simple silicosis to progressive massive fibrosis (García-Núñez et al., 2022). In addition, molecular end-points associated with chronic inflammation and oxidative stress have been identified in experimental systems (Scalia Carneiro et al., 2020; Ramkissoon et al., 2023) and in exposed humans (Blanco-Pérez et al., 2021).

Summary

Fabrication of engineered stone releases high levels of dust, which consists primarily of fine silica particles. There are other components as well, including metals and resins, in lower concentrations. It is well established that silica dust causes cancer in humans and it is currently classified by IARC as *carcinogenic to humans* (Group 1) (see agent 051). There are no studies available regarding cancer in humans from engineered stone fabrication. There is sparse mechanistic evidence that engineered stone induces chronic inflammation in experimental systems and in exposed humans. The Advisory Group considered that this evaluation would be a specific exposure scenario for crystalline silica, which is already classified in Group 1 and therefore considered that an *IARC Monographs* evaluation of engineered stone fabrication is unwarranted.

Recommendation: No priority

053 Carbon black, bulk and nanoscale (CAS No. 1333-86-4)

Current IARC/WHO classification

Carbon black (bulk-scale) was previously classified by IARC as *possibly carcinogenic to humans* (Group 2B) in *IARC Monographs* Volume 93 in 2006 (IARC, 2010f), on the basis of *sufficient* evidence for cancer in experimental animals for both carbon black and its extracts.

Carbon black was given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a).

Exposure characterization

Carbon black, a particulate form of elemental carbon, serves as a key reinforcing filler and is widely used in the rubber industry (e.g. in tyre manufacturing). Distinguished from soot (i.e. black carbon) – an undesired by-product of incomplete combustion in materials containing carbon – exposure scenarios encompass various occupational environments, such as in the production of rubber, paint, ink, plastics, paper,

and ceramics, as well as in printing and coating applications (IARC, 2010f). Inhalation is the primary exposure route for humans.

Carbon black is listed by the OECD (2007) and the US EPA (2024a) as a high production volume chemical.

Cancer in humans

Since the meeting in 2006 for *IARC Monographs* Volume 93 (IARC, 2010f), additional analyses of the three main cohort studies on the carcinogenicity of carbon black in humans were conducted. Following IARC's recommendations on controlling potential biases and confounding, as well as considering dose–response assessment (Ward et al., 2010a; Turner et al., 2023), these reports introduced new metrics and statistical analysis approaches compared with previous studies. These industry-supported reanalyses generally found that carbon black exposure was not associated with lung cancer mortality (Yong et al., 2019). In a UK cohort update, carbon black (or chemicals associated with its production) was associated with lung cancer mortality at two plants, but no such association was found at three other plants studied (Sorahan and Harrington, 2007). A similar method of evaluation in a German cohort, focusing on the first 15 years after employment, did not find a similar decline in the risk of lung cancer after cessation of employment (Morfeld and McCunney, 2007). Other reports for the German cohort, using a multimodel Cox regression approach and Bayesian procedure, also found no association (Morfeld and McCunney 2009, 2010). In the last follow-up study of a US cohort, following IARC recommendations for dose–response assessment, higher cumulative exposure cut points showed an elevated risk of lung cancer mortality without a statistically significant dose–response relation (Dell et al., 2015). Furthermore, in a recent meta-analysis, which combined SMR and Cox proportional hazards results from the US, UK, and German cohort studies, a small and statistically non-significant positive slope estimate was indicated when exposure was measured with no lag. In this study, introducing a 20-year lagging time for exposure showed a slope close to null (Yong et al., 2019).

Cancer in experimental animals

In the previous evaluation (IARC, 2010f), there was *sufficient* evidence in experimental animals of the carcinogenicity of carbon black. Ultrafine carbon black, when administered by intratracheal instillation, caused benign and malignant lung tumours in rats (Kolling et al., 2011). Spleen haemangioma and lung adenoma have been observed in rasH2 mice after subcutaneous administration of ultrafine carbon black (Takanashi et al., 2012).

Mechanistic evidence

Carbon black nanoparticles caused DNA damage in a human A549 alveolar epithelial cell line and in a human THP-1 monocytic cell line (Don Porto Carero et al., 2001). They increased mRNA expression and protein levels of IL-6 and IL-8 in human bronchial epithelial cells in vitro (Boland et al., 1999; Zhang et al., 2023d), and of NOD-like receptor protein 3 (NLRP3) inflammasome in human corneal cells (Long et al., 2020; Xiao et al., 2022). Ultrafine carbon black by inhalation in pregnant mice induced persistent lung inflammation in mothers and DNA strand breaks in the livers of mothers and their offspring (Jackson et al., 2012a). Exposure of pregnant mice to carbon black by intratracheal instillation affected several biological pathways (cellular signalling, inflammation, cell cycle, and lipid metabolism) in female offspring (Bourdon et al., 2012; Jackson et al., 2012b). Induced DNA strand breaks in BAL cells and lung tissue (Kyjovska et al., 2015), as well as perturbations of inflammatory cytokine and chemokine transcripts, supported by concomitant changes in BAL cell counts (Bourdon et al., 2012), were also observed in female mice after intratracheal instillation of Printex 90 carbon black nanoparticles. The expression levels of mRNAs associated with angiogenesis, cell migration, proliferation, chemotaxis, and growth factor production were

altered in the cerebral cortex of offspring after maternal exposure to carbon black nanoparticles (Win-Shwe and Fujimaki, 2011; Onoda et al., 2017).

Summary

Carbon black differs from soot (or black carbon). The evidence from epidemiological studies of cancer in humans is not robust. No evidence that carbon black exhibits KCs in exposed humans or human primary cells has been identified; therefore, a re-evaluation of the agent would be unlikely to lead to a change in the classification from Group 2B. The Advisory Group therefore considered that an *IARC Monographs* re-evaluation of carbon black (bulk and nanoscale) is unwarranted at present.

Recommendation: No priority

054 Coal dust

Current IARC/WHO classification

Coal dust was previously evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in *IARC Monographs* Volume 68 in 1996 (IARC, 1997). WHO and ILO have published joint estimates of the burden of disease for dusts (WHO, 2024b). Coal dust was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of new findings of lung cancer in cohort and case–control studies of coal miners, as well as mechanistic evidence of KCs (e.g. genotoxic and epigenetic effects) in exposed miners.

Exposure characterization

Coal dust is a heterogeneous by-product of coal mining, comprising a mixture of carbon-based main compounds and more than 50 different other elements and their oxides. Across the globe, coal is primarily used as a fuel to generate electric power. Coal is the second largest energy source worldwide, and global consumption appears to be increasing. Coal is listed as a high production volume substance by the US EPA (2024a).

Occupational exposure to coal dust occurs predominantly in coal mining and to a lesser degree via other industrial processes. The general population might be exposed through environmental air pollution (IARC, 2019a). Household coal use for heating and cooking occurs particularly in LMICs and is expected to lead to some coal dust exposure.

Cancer in humans

As noted in the 2019 Advisory Group report (IARC, 2019a), an exposure–response association between exposure to coal dust and lung cancer mortality was reported in a cohort of coal miners in the USA (Graber et al., 2014). A case–control study, pooling data from 20 centres in Europe, Canada, and New Zealand, reported excess lung cancer risk in miners, after adjustment for smoking history and work in other at-risk occupations (Taeger et al., 2015). Similar findings were reported in a cohort of miners with coal workers' pneumoconiosis in Czechia (Tomášková et al., 2017). A meta-analysis on the association between coal mine dust and lung cancer mortality reported a meta-SMR of 1.16 (95% CI, 1.03–1.30), although with considerable heterogeneity (I^2 = 94.8%) (Li et al., 2021e). Another meta-analysis on coal mine workers, however, reported no increased risk for lung cancer, whereas a suggestive positive association was observed for stomach cancer (Alif et al., 2022) A higher SIR was also observed for stomach cancer among male coal workers, compared with non-coal workers (SIR: 1.318 versus 1.267) in a study conducted in the Republic of Korea and published after the meta-analyses mentioned (Kang et al., 2021a). A recent publication on US

coal miners showed increased mortality for lung cancer, compared with the non-mining US population (Almberg et al., 2023).

Cancer in experimental animals

IARC Monographs Volume 68 (IARC, 1997) reports that there is *inadequate* evidence in experimental animals for the carcinogenicity of coal dust. Coal dust was not found to induce lung tumours in inhalation carcinogenicity studies (Martin et al., 1975; Busch et al., 1981; Nikula et al., 1997). Increased lung tumours were reported after repeated intratracheal instillation of coal dust in a lifetime rat carcinogenicity study (Pott and Roller, 2005), although no detailed carcinogenicity data are available from this paper.

Mechanistic evidence

Exposure-related genotoxicity in oral mucosa cells of coal miners was observed (da Silva Júnior et al., 2018). Additional studies on exposed workers revealed exposure-related genotoxic, epigenetic, and cytostatic effects, including an increased frequency of binucleated lymphocytes with micronuclei, nucleoplasmic bridges, and nuclear buds, as well as decreased telomere length and DNA hypermethylation (Rohr et al., 2013; Sinitsky et al., 2016; Miranda-Guevara et al., 2023). Furthermore, oxidative stress and alterations in gene expression associated with DNA damage were detected in lung cells (Calu-1 cells) exposed to coal dust (Li et al., 2022b; Tirado-Ballestas et al., 2022). Inflammation and fibrosis were reported in a mouse model of coal workers' pneumoconiosis after exposure for 1 and 3 months (Wang et al., 2022c). Pinho et al. (2004) reported oxidative stress and inflammation in lung epithelium of male Wistar rats after acute exposure to coal dust (Pinho et al., 2004). Inhalation of coal dust was reported to cause bronchioloalveolar hyperplasia in 7 days or 14 weeks, in rat studies (Kolling et al., 2011; Kania et al., 2014).

Summary

There is human evidence of carcinogenicity of coal dust, particularly for lung cancer and stomach cancer. Evidence of the carcinogenicity of coal dust in experimental animals is sparse. There is ample mechanistic evidence related to the KCs in exposed humans and in experimental systems; this supports the re-evaluation of coal dust. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of coal dust to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

055 Acrylonitrile-butadiene-styrene particles emitted by 3D printers

Current IARC/WHO classification

Acrylonitrile-butadiene-styrene (ABS) copolymers were evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in *IARC Monographs* Volume 19 in 1978 (IARC, 1979c) and *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a).

Exposure characterization

The use of 3D printing technology has expanded from workplace use in industries and small businesses to schools and homes; this is expected to increase the number of workers and consumers who use these devices. However, the number of exposed individuals is not documented. The most commonly used filament materials in fused deposition modelling 3D printers are polylactic acid (PLA) and ABS. ABS is a petrochemical-derived copolymer created by the copolymerization of the monomers acrylonitrile, 1,3-butadiene, and styrene. (Jyoti et al., 2015).

The 3D printing process releases particles, which are mostly ultrafine (diameter, < 100 nm), and volatile organic chemicals from melting thermoplastic filaments (Byrley et al., 2019). Ultrafine particles are released at rates of billions of particles per minute during operation (Stephens et al., 2013; Stefaniak et al., 2017;

Byrley et al., 2021). Across the literature, it is generally concluded that ABS filaments produce higher particle number emission rates than PLA (Azimi et al., 2016; Stefaniak et al., 2017). In addition to particles, 3D printers also emit numerous volatile, semi-volatile, and non-volatile organic compounds during thermal processing, such as aldehydes, ketones, alcohols, aromatics (benzene, toluene, ethylbenzene, xylenes, styrene), and phthalates (Stefaniak et al., 2017; Kim et al., 2022c; Wojnowski et al., 2022).

Cancer in humans

No relevant studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

Acrylonitrile, butadiene, and styrene monomers have each been previously evaluated by the *IARC Monographs* programme; it was established that there was *sufficient* evidence in experimental animals. However, no carcinogenic data for experimental systems for ABS polymer particles emitted by 3D printers were available to the Advisory Group.

Mechanistic evidence

ABS particle emissions induce significant dose-dependent increases in cytotoxicity, oxidative stress, apoptosis, and the production of proinflammatory cytokines and chemokines in human small airway epithelial cells (Farcas et al., 2019; He et al., 2024). The evidence for carcinogen mechanisms is sparse in laboratory animals (Farcas et al., 2019). A significant increase in proinflammatory markers (IL-12p70, IL-13, IL-15, IFNγ, TNFα, IL-17A, VEGF, MCP-1, and MIP-1α) was observed in an in vitro model in primary normal human bronchial epithelial (NHBE) cells, isolated from the epithelium of human bronchi, first passaged in differentiation medium and then exposed to ABS filaments in an air–liquid interface (Farcas et al., 2022). There was no evidence of genotoxicity or of any effect on cell viability.

Summary

No studies were available on human cancer or cancer in experimental animals after exposure to ABS particles emitted by 3D printers. There is minimal available mechanistic evidence of ABS related to the KCs and in regard to ABS polymer behaviour, in comparison with the behaviour of the monomers. Interpretation of some of the mechanistic evidence is complicated; for example, apoptosis could reduce the numbers of problematic cells, such as those exhibiting oxidative stress. The Advisory Group considered that additional mechanistic information would be required for an evaluation of ABS particles emitted by 3D printers to be warranted.

Recommendation: No priority

056 Microplastics and nanoplastics

Current IARC/WHO classification

Micro- and nanoplastics have not been previously evaluated by the *IARC Monographs* programme. A WHO report, identifying research needs and defining the scope of future work needed on microplastics particles, was published to address current uncertainties (WHO, 2022c).

Exposure characterization

Plastics are widely used in daily life; thus, large amounts of plastics waste are released into the environment, either directly or through improper reuse or recycling (Stapleton, 2021). According to the UN Environment Programme, 400 million tonnes of plastics waste are produced every year (UNEP, 2023).

In the environment, primary and secondary micro- and nanoplastics can be found. Primary micro- and nanoplastics are processed plastics particles that are commonly added to personal care products (e.g. cosmetics, detergents, toothpastes, scrub facial cleansers, drug carriers). Secondary micro- and nanoplastics are plastics debris that degrade from large pieces of plastics waste, through UV radiation, physical wear, and biodegradation in the environment (Jiang et al., 2020b).

Micro- and nanoplastics are widely distributed in the environment (food, water, air) and have been found in human faeces, suggesting exposure through the digestive tract (Schwabl et al., 2019; Jiang et al., 2020b). The main routes of exposure are inhalation and ingestion. Indoor air measurements have reported 1600–11 000 microplastics fibres/m^2 per day, depending on indoor environment and lifestyle (Stapleton, 2021; Sangkham et al., 2022).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

Micro- and nanoplastics alter molecular and functional traits associated with the carcinogenic process, such as, in mouse embryonic cells, the ability to grow independently of anchorage, migration, and invasion (Barguilla et al., 2022). Exposure to microplastics and nanoplastics may also induce genotoxicity or mutagenicity in human cells (Domenech et al., 2023). Micro- and nanoplastics seem to induce cellular toxicity through genotoxicity, oxidative stress, membrane damage, and regulation of the immune response in human cells (epithelial, cerebral, or haematopoietic cells) (Schirinzi et al., 2017; Rubio et al., 2020; Banerjee and Shelver, 2021; Llorca and Farré, 2021; Baj et al., 2022). Microplastics regulate immune responses in human cell lines by regulating genes and proteins involved in innate immunity (Chiu et al., 2015; Forte et al., 2016; Choi et al., 2021).

Summary

No evidence is available regarding cancer in humans or in experimental animals from exposure to micro- and nanoplastics. There is some mechanistic evidence that micro- and nanoplastics exhibit KCs in experimental systems, including genotoxicity, oxidative stress, inflammation, and immunosuppression. Despite emerging evidence regarding KCs in experimental systems (including human cells), this field is rapidly evolving; this suggests that an evaluation within the next 5 years may be premature. The Advisory Group therefore considered that an *IARC Monographs* evaluation of microplastics and nanoplastics is unwarranted at present.

Recommendation: No priority

057 Asbestos (CAS No. 132207-32-0)

Current IARC/WHO classification

Asbestos was classified by IARC as *carcinogenic to humans* (Group 1), most recently in *IARC Monographs* Volume 100C in 2009 (IARC, 2012c). There is *sufficient* evidence that exposure to all forms of asbestos causes mesothelioma and cancers of the lung, larynx, and ovary. Evidence for cancers of the pharynx, stomach, and colorectum was found to be *limited*. A WHO report was published to assist WHO Member States in managing health risks of exposure to chrysotile asbestos (WHO, 2014).

Exposure characterization

Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibres of the serpentine and amphibole series (IARC, 2012c). Past exposure conditions for asbestos have been characterized in *IARC Monographs* Volume 100C and previous volumes (IARC, 1973, 1977, 1987a, 2012c). Despite bans on most uses of asbestos in many countries, exposure continues to occur globally, through its continued widespread use in countries that have not implemented a ban (Lin et al., 2019), and because of legacy materials used in building and vehicle construction. Thus, WHO estimates that 125 million people are exposed occupationally to asbestos (WHO, 2018), and residential exposure is expected to continue to occur.

Cancer in humans

Dozens of studies have been published since the 2009 meeting for *IARC Monographs* Volume 100C (IARC, 2012c) on the association of asbestos with cancer types other than mesothelioma, or cancers of the larynx, lung, and ovary, particularly across the digestive tract, and such results are the focus here. A meta-analysis of the association between occupational exposure to asbestos and oesophageal cancer found a meta-SMR of 1.24 (95% CI, 1.13–1.38) among 20 cohort studies (Li et al., 2016b). A meta-analysis of CRC after occupational exposure to asbestos found a meta-SMR of 1.16 (95% CI, 1.05–1.29), which was higher for studies that also showed an elevation in lung cancer risk (meta-SMR, 1.43; 95% CI, 1.30–1.56) (Kwak et al., 2019). Since then, a study of a large cohort of chrysotile asbestos workers in Asbest, Russian Federation, observed inconsistent increases in cancers of the stomach and colorectum across dust and fibre exposure categories for men, with null findings for women (Schüz et al., 2024). A study pooling 51 asbestos-exposed cohorts in Italy found elevated rates of bladder cancer, but not of cancers of the oral cavity or pharynx, or digestive cancers (Ferrante et al., 2024).

There is also emerging evidence for an association between asbestos exposure and intrahepatic cholangiocarcinoma (ICC), sometimes called intrahepatic bile duct cancer. In a population-based case–control study in Italy, an elevated risk of ICC was observed among those who had been exposed occupationally, compared with those who had never been exposed (adjusted OR, 4.8; 95% CI, 1.7–13.3) (Brandi et al., 2013). A nested case–control study in the Nordic Occupational Cancer (NOCCA) cohort reported an increased risk of ICC with cumulative exposure to asbestos (≥ 15.0 fibres/mL per year, compared with those never exposed; OR, 1.7; 95% CI, 1.1–2.6) (Farioli et al., 2018). Among shipbreaking workers in Taiwan, China, an increased risk of intrahepatic bile duct cancer was seen among those with high asbestos exposure (HR, 1.60; 95% CI, 1.08–2.36) (Wu et al., 2015a). A recent case-series study examining patients with ICC, which stratified into small duct (sd-ICC) and large duct (ld-ICC) morphological subtypes, suggested that sd-ICC might be more frequently associated with asbestos exposure than ld-ICC (Vasuri et al., 2023).

Mechanistic evidence

There is evidence that asbestos can reach tissues outside the respiratory tract, as discussed in *IARC Monographs* Volume 100C (IARC, 2012c) and in other works (e.g. Kobayashi et al., 1987; Ehrlich et al., 1991; Brandi and Tavolari, 2020). A recent review of 12 studies that examined asbestos fibres in extrapulmonary tissues confirmed that asbestos fibres have been detected in 10 abdominal organs and tissues: stomach, small intestine, pancreas, spleen, colon, liver, gall bladder, kidney, urinary bladder, and abdominal lymph nodes, although with wide variability in sample sizes and fibre concentrations and counting methods (Caraballo-Arias et al., 2023).

Summary

The evidence for a causal association between asbestos and extrapulmonary organs and tissues, particularly in the digestive tract, appears to have strengthened since the last evaluation. The plausibility of exposure within the digestive tract has concomitantly increased. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of asbestos to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

058 Taconite (CAS No. 12249-26-2)

Current IARC/WHO classification

Taconite has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Taconite is a low-grade iron ore, with a natural iron concentration of approximately 30%. Taconite deposits can contain high concentrations of non-asbestiform amphibole elongate mineral particles (EMPs). Taconite iron ore has been extensively mined in the Mesabi Iron Range in Minnesota and the Marquette Iron Range in Michigan, USA, since the mid-1950s, and is used in steel production and road patching. Taconite mining is an open pit process that involves blasting rock with explosives, crushing the rock into powder, magnetically extracting the iron, and reforming a more concentrated product into high-grade iron ore pellets (Allen et al., 2015). Mining and processing of taconite may result in exposure to non-asbestiform amphibole and non-amphibole EMPs, respirable silica, and cleavage fragments (Hwang et al., 2013; Allen et al., 2015).

Taconite ore-containing wastes have been deposited throughout the environment, including in the Great Lakes (Wilson et al., 2008). There has been associated concern over airborne and drinking-water environmental exposure among the general public, although the primary exposure is inhalation exposure among taconite miners and ore-processing workers.

Cancer in humans

A cohort study of 40 720 Minnesota taconite miners, employed between 1937 and 1983, found 51 incident cases of mesothelioma and 973 cases of lung cancer. SIRs of 2.4 (95% CI, 1.8–3.2) for mesothelioma and 1.1 (95% CI, 1.0–1.3) for lung cancer, compared with state rates, were reported (Allen et al., 2015). A subsequent nested case–control study found positive exposure–response associations for mesothelioma with number of years employed in the taconite industry (RR, 1.03; 95% CI, 1.00–1.06) and cumulative EMP exposure (RR, 1.10; 95% CI, 0.97–1.24) (Lambert et al., 2016).

Cancer in experimental animals

In a lifetime carcinogenicity study of unfiltered city tap water in Duluth, Minnesota, USA, municipal water reservoir sediment suspension, taconite plant tailings, amosite asbestos, and diatomaceous earth in Sprague-Dawley rats, the incidence of malignant tumours was not significantly different from that in control rats (Hilding et al., 1981). No carcinogenicity studies in experimental animals in compliance with GLP or OECD guidelines were available to the Advisory Group.

Mechanistic evidence

Dimethyl taconite, a taconite derivative, was shown to inhibit angiogenesis in cultured human endothelial cells and also to modulate the immune response in cultured human endothelial cells (Vidal et al., 2022). There is a lack of evidence regarding the genotoxicity of taconite or of non-asbestiform EMPs found in taconite iron ore in exposed humans or experimental systems. However, there are reports of inflammation and immune responses in taconite mine workers who were co-exposed to silica and quartz, which are

ingredients of respirable dust in taconite mining (Balmes and Speizer, 2012). In a cross-sectional study of 1188 taconite-exposed miners in north-eastern Minnesota, pleural abnormalities were found in 18% of the miners, with evidence of an exposure–response relation using EMP exposure measures (Perlman et al., 2018). Notable gaps are apparent in the understanding of the specific dimensions, such as length and width, as well as the biopersistence characteristics, of EMPs. These have not yet been thoroughly characterized in terms of their structure–activity relations; they could lead to lung injury (Goodman et al., 2023).

Summary

There is evidence from a single, but large, exposed population of miners of an association of exposure to non-asbestiform amphibole EMPs derived from taconite with risk of mesothelioma and lung cancer. There are sparse data for experimental animals regarding taconite-induced carcinogenesis. Evidence on whether taconite exhibits the KCs in exposed humans or experimental systems is also sparse. However, studies in taconite miners with co-exposures to respirable silica and quartz have found evidence of increased pleural plaques, inflammation, and immune response associated with occupational exposures. Given that mesothelioma and pleural plaques have been found almost exclusively to be associated with exposure to asbestiform fibres, the Advisory Group therefore considered an *IARC Monographs* evaluation of taconite to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

059 Multiwalled carbon nanotubes (CAS No. 308068-56-6) and other carbon nanotubes

Current IARC/WHO classification

Multiwalled carbon nanotubes (MWCNTs) were previously evaluated by the *IARC Monographs* programme in *IARC Monographs* Volume 111 in 2014 (IARC, 2017c). In that evaluation, one specific type of MWCNT (MWCNT-7) was classified as *possibly carcinogenic to humans* (Group 2B), and every other type, as well as single-walled carbon nanotubes (SWCNTs), was evaluated as *not classifiable as to its carcinogenicity to humans* (Group 3). The classification arrived at for MWCNT-7 was based on *sufficient* evidence for cancer in experimental animals.

MWCNTs other than MWCNT-7 were given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), pending the publication of a bioassay underway at the US NTP (IARC, 2019a).

Exposure characterization

Carbon nanotubes are tubes made of carbon with diameters in the nanometre range. They are manufactured in several important forms, including SWCNTs, double-walled carbon nanotubes (DWCNTs), and MWCNTs and are used in several types of product (e.g. electronics, lithium-ion batteries, polymer composites, pharmaceutical or biomedical devices) (NIOSH, 2013) Occupational exposure studies have been conducted in Asia, Europe, and the USA, with the main exposure concerns being inhalation and dermal exposure among workers manufacturing or using carbon nanotubes (CNTs) (Fatkhutdinova et al., 2016b; Kuijpers et al., 2016; Dahm et al., 2018; Guseva Canu et al., 2020a). In a USA-wide study of 12 facilities manufacturing or using MWCNTs, SWCNTs, or carbon nanofibres (CNFs), nearly all workers had inhalation exposure, 70% of workers showed evidence of dermal exposure, and 18% had detectable CNTs or CNFs in induced sputum (Dahm et al., 2018). The extent to which CNTs occur in non-occupational settings is unclear. A case report found evidence of CNTs of various sizes and types in lung biopsy specimens

of several patients who had been exposed to high concentrations of dust at the World Trade Center collapse and also found CNTs in samples of the dust (Wu et al., 2010).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

Since the previous IARC evaluation (IARC, 2017c), new studies have emerged. A 2-year study of intratracheal instillation exposure to MWCNT-7 in F344 rats showed significant increases in lung adenomas, lung carcinomas, and pleural mesotheliomas (Hojo et al., 2022). In a study by Fukushima et al. (2018), MWCNT-7 were administered by different routes (intraperitoneal, intrascrotal, subcutaneous, inhalation, intratracheal instillation) in rats and mice. Inhalation exposure increased lung tumour incidence in rats, whereas intraperitoneal injection in mice and rats induced peritoneal mesothelioma. Intratracheal instillation of MWCNTs induced lung carcinomas and mesothelioma in rats.

In a 2-year whole-body inhalation study in F344 rats, bronchioloalveolar carcinoma, and combined carcinoma and adenoma, were significantly increased in the highest dose group (2 mg/m^3) in male and female rats exposed to MWCNT-7 (Kasai et al., 2016).

Takagi et al. (2012) reported that a single intraperitoneal injection of 300 µg/mouse of µm-MWCNT-7 in p53-heterozygous mice induced granuloma and hyperplasia, even in a low-dose group. In male Wistar rats injected intraperitoneally with a single dose of MWCNT, an increased incidence of mesothelioma was observed (Muller et al., 2009).

Another straight type, MWCNT-N, was administered to male rats by transtracheal intrapulmonary spraying (TIPS) during the initial 2 weeks of an experiment and the rats were observed for up to 109 weeks. MWCNT-N induced malignant mesothelioma and lung carcinoma (Suzui et al., 2016). A tangled-type, MWCNT-B, was found to be carcinogenic to the rat lung when administered into the airway by TIPS (Saleh et al., 2020). DWCNTs administered to the rat lung through the airway by TIPS developed lung tumours (adenoma and adenocarcinoma) and mesothelioma (Saleh et al., 2022).

The Advisory Group is also aware of 2-year inhalation studies, being conducted under GLP, that are underway to determine the effect of another type of MWCNT (1020 long MWCNT), in male and female rats and mice (NTP, 2019a).

Overall, there is persuasive evidence of the induction of lung tumours in male and female rats by MWCNTs other than MWCNT-7, for which an evaluation of *sufficient* evidence from experimental animals has already been established.

Mechanistic evidence

Several studies relevant to KCs have been conducted in workers exposed to CNTs. As summarized in a review article (Kumah et al., 2023), five studies of workers exposed to CNTs examined biomarkers of chronic inflammation (including fibrosis markers) and oxidative stress. Associations of these markers with CNT exposures were observed in most of the studies (e.g. Liao et al., 2014; Fatkhutdinova et al., 2016a; Vlaanderen et al., 2017; Beard et al., 2018). A study involving workers handling CNTs found a decreased immunological response to several microbial immunostimulants administered ex vivo to whole blood, in relation to measured CNT exposure in the workplace (Schubauer-Berigan et al., 2020).

Kumah et al. (2023) summarized the available literature on human primary cells and human cell lines. Most studies identified oxidative stress biomarkers, and several identified evidence of genotoxicity, inflammation, and alteration of cell proliferation or cell death (KC10). DNA strand breaks were observed in studies of human bronchial epithelial cells and human lymphocytes (Ghosh et al., 2011; Lindberg et al., 2013). Studies in immortalized human BEAS-2B bronchial epithelial cells exposed to 30 µg/mL MWCNT-

7 for 24 hours demonstrated a significant increase in cytokines TNFα, IL-1β, IL-6, IL-8, IL-10, and IL-12 (Tsukahara and Haniu 2011). More recently, Fraser et al. (2020) showed induction of the formation of micronuclei, cytotoxicity, oxidative stress, and DNA double-strand breaks in human bronchioepithelial cells exposed to CNTs. Similar findings were observed by another group (Fatkhutdinova et al., 2024) using the comet assay in three human cell lines of respiratory origin (BEAS-2B bronchial epithelial cells, A549 alveolar epithelial cells, MRC5-SV40 fibroblasts).

While some studies in mice and rats exposed to MWCNT-7 showed DNA strand breaks (Jacobsen et al., 2009; Ghosh et al., 2011), others have shown oxidative DNA damage measured by 8-OHdG (Folkmann et al., 2009; Kato et al., 2013; Xu et al., 2014). Inhalation studies in rats showed an increased inflammatory response (Ma-Hock et al., 2009; Pauluhn 2010; Kim et al., 2015a; Kasai et al., 2016). Chronic inflammatory response was observed in male ICR mice with intratracheal installation of MWCNT-7 (Park et al., 2009b). Horibata et al. (2022) observed genotoxic effects in lung cells of mice exposed to whole-body inhalation of MWCNTs. In another in vivo study in mice exposed to MWCNT-7 orally, a genotoxic effect was observed using a single-cell alkaline gel electrophoresis assay (Snegin et al., 2020).

Summary

The evidence for cancer in experimental animals and mechanistic evidence for several KCs, including genotoxicity, inflammation, and immune response in exposed humans, human primary cells, and cell lines, and in experimental animals exposed to MWCNTs, provide support for an *IARC Monographs* evaluation. The Advisory Group is also aware of 2-year inhalation studies, conducted under GLP, of the effect of 1020 long MWCNTs in male and female rats and mice, which are underway (NTP, 2019a).

The Advisory Group considered an *IARC Monographs* re-evaluation of multiwalled carbon nanotubes and other carbon nanotubes to be warranted and recommends evaluating MWCNTs together with DWCNTs and SWCNTs, and to consider grouping together CNTs with similar structural properties.

Recommendation: High priority (and ready for evaluation within 2.5 years)

060 Anatase-type and other types of nano-titanium dioxide

Current IARC/WHO classification

With a few exceptions, nanomaterials have not been previously evaluated by the *IARC Monographs* programme. MWCNTs, which were evaluated in *IARC Monographs* Volume 111 in 2014 (IARC, 2017c), have been nominated separately (see agent 059). Nanoscale cobalt compounds were evaluated in *IARC Monographs* Volume 131 in 2022 (IARC, 2023b). Bulk-scale titanium dioxide (TiO_2) was classified by IARC as *possibly carcinogenic to humans* (Group 2B) in Volume 93 in 2006 (IARC, 2010f), on the basis of *sufficient* evidence of carcinogenicity in experimental animals. This classification is presumed to include at least some nanoscale forms of some types of TiO_2.

Nanoscale TiO_2 and other nanomaterials were given a priority rating of *medium* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of anticipated findings for studies in humans and experimental systems.

Exposure characterization

Nanomaterials can be described as materials containing primary particles with at least one dimension as small as 1–100 nm, according to the definition of the International Organization for Standardization (ISO) (Gebel, 2012). The development of precision technology has led to an increase in the production of nanomaterials. Nanosized TiO_2 particles are some of the most widely manufactured nanoparticles on a global scale and are in the top five nanoparticle types used in consumer products (Rollerova et al., 2015).

Engineered nanomaterials are used in a variety of applications and consumer products, such as medical products, cosmetics, textiles, paints, food packaging, and other personal care products, and exposure of the human body is expected to increase (Mackevica et al., 2016). Ultrafine TiO_2 is widely used in several applications, including white pigment in paint, ceramics, as a food additive, in food packaging material, sunscreens, cosmetic creams, and as a component of surgical implants (Rollerova et al., 2015).

Human exposure to nanomaterials occurs through the respiratory tract and may occur through absorption in the skin, digestive tract, and eyes. However, a few studies have revealed that the TiO_2 nanoparticles could penetrate the skin and translocate to other tissues, and intravenous injection is indicated as another probable route of exposure (Shakeel et al., 2016).

Cancer in humans

In Canada, Europe, and the USA, epidemiological studies have been conducted on the association of exposure to TiO_2 with cancer of the lung, but not specifically on nano-TiO_2. In a French cohort of 833 male workers, the fully adjusted model yielded a HR of 3.7 (95% CI, 0.79–17.95) for TiO_2-exposed workers versus unexposed workers and a HR of 27.3 (95% CI, 4.35–172) for those exposed to > 2.4 mg/m^3 as an annual average concentration (Guseva Canu et al., 2020b). A pooled European cohort of 7341 male workers employed in TiO_2 production in Finland, France, Italy, and the UK showed evidence of healthy worker survivor bias (HWSB) that masked an increase in lung cancer risk: at the age of 70 years, the estimated number of lung cancer deaths expected in the cohort after 35-year exposure was 293 for an exposure of 2.4 mg/m^3, 235 for an exposure of 0.3 mg/m^3, and 211 for an exposure of 0 mg/m^3, after controlling for the HWSB (Guseva Canu et al., 2022).

Importantly, these studies are not explicitly of nanoscale forms of TiO_2. The possibility that nanoparticles of substances may cause cancer in humans has been postulated, but no studies are available (Becker et al., 2011).

Cancer in experimental animals

In a 2-year inhalation carcinogenicity study of rats exposed to anatase-type nano-TiO_2, bronchioloalveolar carcinoma incidence showed a significant increase, including a positive trend in male rats. In female rats, the incidence of bronchioloalveolar carcinoma exceeded the upper bound of the range for historical control data. Therefore, the substance showed evidence of lung carcinogenicity in male and female rats (JBRC, 2020a, b).

In a 26-week inhalation study in rasH2 mice, anatase-type nano-TiO_2 did not exhibit carcinogenic effects (Yamano et al., 2022a). However, 26-week inhalation exposure to p53-knockout mice of anatase-type nano-TiO_2 showed equivocal evidence of carcinogenic activity in the lungs of male mice but no evidence of carcinogenic activity for female mice (JBRC, 2019).

Mechanistic evidence

The effects of fine particles scattered throughout the body or accumulated in the lungs are most apparent through the respiratory tract (Pietroiusti et al., 2018). TiO_2 is a genotoxic substance, and it is suggested that this genotoxicity is mediated by a secondary mechanism, rather than by direct DNA reactivity.

Numerous studies have shown that nano-TiO_2 can cause oxidative stress through the generation of ROS, and hence oxidative DNA damage and genotoxicity, suggesting that nano-TiO_2 is genotoxic in human cell lines and bacteria, and also induces cell proliferation (Bhattacharya et al., 2009; Jomini et al., 2012; Valdiglesias et al., 2013; Botelho et al., 2014; Kirkland et al., 2022; Shi et al., 2022). γ-H2AX, a marker of DNA damage, was increased in pulmonary proliferative lesions of rats exposed to anatase-type nano-TiO_2 by inhalation (Yamano et al., 2022b).

In vivo studies have consistently shown that the inflammatory response to nano-TiO_2 is characterized by the infiltration of neutrophils in mice and rats (Ferin et al., 1992; Renwick et al., 2004; Chen et al., 2006b). This response is accompanied by an increase in particle-laden macrophages (Chen et al., 2006b; Johnston et al., 2009). Inflammation is likely to be mediated by increases in IL-8, and TNFα that have been observed in vivo and in vitro in rodents (Johnston et al., 2009). Moreover, nano-TiO_2 has been shown to induce reactive alveolar epithelial type 2 cell hyperplasia in rat lungs after subchronic inhalation exposure to anatase-type nano-TiO_2 (Yamano et al., 2022a).

Anatase-type nano TiO_2 has been shown to have more toxicity than rutile TiO_2, owing to its physical properties (Dunford et al., 1997).

Summary

The available human cancer studies do not explicitly evaluate nanoscale forms of TiO_2. Therefore, there is no human cancer evidence yet for anatase-type nano-TiO_2 that could be evaluated by the *IARC Monographs* programme. The carcinogenicity study for anatase-type nano-TiO_2 in experimental animals conducted at the Japan Bioassay Research Center (JBRC), performed in accordance with OECD guidelines and GLP, has shown positive evidence that might be considered *sufficient* by a Working Group. It is to be noted that the inhalation concentration for the anatase-type nano-TiO_2 carcinogenicity study in rats was extremely low (8 mg/m^3) compared with that (250 mg/m^3) for the rutile-type-TiO_2 carcinogenicity study in rats (IARC, 2010f).

There is mechanistic evidence that nano-TiO_2 particles exhibit KCs, including genotoxicity, chronic inflammation, and altered cell proliferation in experimental systems. Anatase-type nano TiO_2 has been shown to have greater toxicity than rutile TiO_2, owing to its physical properties. The Advisory Group therefore considered an *IARC Monographs* evaluation of nano-TiO_2 particles to be warranted. No other nanomaterials were considered in the prioritization for this nomination.

Recommendation: Medium priority

061 Inorganic lead compounds (CAS No. 7439-92-1)

Current IARC/WHO classification

Inorganic lead compounds were previously classified by IARC as *probably carcinogenic to humans* (Group 2A) in *IARC Monographs* Volume 87 in 2004 (IARC, 2006b), on the basis of *sufficient* evidence for cancer in experimental animals and *limited* evidence for cancer in humans (specifically, for cancers of the stomach, lung, kidney, and brain). The JECFA last evaluated lead in 2011 and concluded that no PTWI in food could be determined, owing to the lack of a detectable threshold for neurodevelopmental and other effects (FAO/WHO, 2011a).

Inorganic lead compounds were given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of emerging evidence regarding lung cancer, as well as convincing evidence of KCs (including genotoxicity) in exposed humans.

Exposure characterization

Several inorganic lead compounds, including a variety of lead salts, lead oxides, and lead metal, are listed as high production volume chemicals by OECD (2007) and the US EPA (2024a). Ambient inorganic lead exposure in non-occupational environments primarily occurs through the ingestion of lead-containing paint chips and soils and through drinking-water in lead pipes (US EPA, 2024b). The typical blood lead level for adults in the USA is 0.855 µg/dL of blood (CDC, 2019b). In the USA, occupational exposures to lead mainly occur in the mining, construction, manufacturing, and service industries (NIOSH, 2024). In 2021,

the number of US workers with blood lead concentrations ≥ 10 µg/dL was 11.32 workers per 100 000 employed workers (NIOSH, 2024). However, the legacy of environmental lead contamination remains high, with the continued exposure of sensitive populations, including children, to household lead sources, such as lead-based paint and contaminated soils.

Cancer in humans

In the 2019 Advisory Group report (IARC, 2019a), several new studies were noted with positive findings for lung cancer, including a pooled mortality study in Finland, the UK, and the USA (Steenland et al., 2017) and a pooled incidence study in Finland and the UK (Steenland et al., 2019). A new analysis of the Finnish cohort (with slightly extended follow-up) confirmed the strong positive associations seen in the pooled incidence study, and incorporated adjustment for such confounders as smoking and co-exposures to lung carcinogens (Anttila et al., 2022). In an update for the US cohort, positive associations and an associated trend with exposure were strong for lung cancer (Barry and Steenland, 2019). A study of lead smelting workers in France, who were followed up for more than 45 years, found a positive trend in lung cancer mortality with cumulative lead exposure ($P = 0.008$), but the association was reported to be non-significant after controlling for exposure to asbestos and other lung carcinogens (Leroyer et al., 2022). A few population-based studies found null associations; however, a positive trend with prediagnostic blood lead exposure and lung cancer mortality was seen among women in a follow-up study of the National Health and Nutrition Examination Survey (NHANES) II and III cohorts (Rhee et al., 2021).

For other cancer sites, notably the brain, kidney, bladder, and larynx, some positive associations, including exposure–response trends, have been reported with lead exposure (e.g. Rajaraman et al., 2006; van Wijngaarden and Dosemeci, 2006; Chowdhury et al., 2014; Steenland et al., 2017, 2019). A strong positive association was observed for cumulative lead exposure and liver cancer among lead smelter workers (Leroyer et al., 2022), which persisted after adjustment for co-exposures to carcinogens. Coffee intake was found to enhance the association between lead and renal cell carcinoma in a nested case–control study among smokers (Wu et al., 2022b). Recent findings for stomach cancer have been largely null (e.g. Steenland et al., 2019; Leroyer et al., 2022).

Recently, many studies have examined lead concentrations in case–control studies, using blood or urine measurements collected after case diagnosis and (in some instances) treatment (e.g. He et al., 2022b). Such studies are of limited utility in cancer hazard identification, owing to uncertainty in the temporal relation between lead exposure and cancer.

Cancer in experimental animals

The previous evaluation of inorganic lead compounds found s*ufficient* evidence in experimental animals (IARC, 2006b). Key studies from the previous evaluation include positive findings after oral exposure in rats (e.g. Zawirska and Medraś, 1968, 1972; Azar et al., 1973; Waszynski, 1977; Zawirska, 1981; Koller et al., 1985; Nogueira, 1987; Fears et al., 1989) and mice (e.g. Van Esch and Kroes, 1969; Stoner et al., 1976; Poirier et al., 1984). Other studies showed tumour occurrence after subcutaneous injection of inorganic lead compounds in rats (e.g. Tönz, 1957; Baló et al., 1965; Roe et al., 1965; Furst et al., 1976).

The Advisory Group did not identify new findings from experimental animals on inorganic lead compounds and carcinogenesis.

Mechanistic evidence

Wang et al. (2023d) reported DNA methylation and genotoxicity in a cohort of 250 workers exposed to lead in northern China. In a study by Minozzo et al. (2004), increased frequency of micronuclei was observed in workers exposed to lead through recycling automotive batteries, as compared with controls. Increased frequencies of SCEs and micronuclei were reported in occupationally exposed cohorts in Thailand

(Wiwanitkit et al., 2008). In a Polish cohort of battery workers, DNA damage was reported (Palus et al., 2003). Steinmetz-Beck et al. (2005) reported evidence of DNA damage in peripheral lymphocytes of workers exposed to lead using the comet assay. Xie et al. (2005) reported lead chromate induced DNA damage in human lung cells, and this was confirmed by another study, by Holmes et al. (2006), in human bronchial fibroblasts. In human lymphocytes exposed to lead nitrate, a dose-dependent increase in the COMET tail length (indicative of DNA damage) was observed (Woźniak and Blasiak, 2003; Pasha Shaik et al., 2006).

Valverde et al. (2001, 2002) reported single-strand breaks and genotoxicity in mice. Robbiano et al. (1999) reported DNA strand breaks in fish exposed to lead.

Summary

There is growing epidemiological human cancer evidence for inorganic lead and cancer, specifically cancer of the lung, since the last evaluation. There was already a finding of *sufficient* evidence that inorganic lead compounds induce tumours in experimental animals. There appears to be evidence, including in exposed humans, that inorganic lead compounds induce genotoxicity. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of inorganic lead compounds to be warranted.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

062 Metallic nickel (CAS No. 7440-02-0)

Current IARC/WHO classification

Metallic nickel was previously classified by IARC as *possibly carcinogenic to humans* (Group 2B) in *IARC Monographs* Volume 49 in 1990 (IARC, 1990a), based on *sufficient* evidence for cancer in experimental animals. Metallic nickel was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of findings for lung cancer in humans and of mechanistic evidence of KCs, including for genotoxicity, epigenetic alterations, and oxidative stress.

In *IARC Monographs* Volume 100C, nickel compounds were classified as *carcinogenic to humans* (Group 1), based on human and animal evidence (IARC, 2012c). For human evidence, it was stated that "mixtures that include nickel compounds and nickel metal" cause cancers of the lung and of the nasal cavity and paranasal sinuses (IARC, 2012c). For animal evidence, it was concluded that there is *sufficient* evidence for carcinogenicity in animals for metallic nickel. The overall evaluation (Group 1) pertains only to nickel compounds.

Despite the data described above, the conclusions of the Working Group on the carcinogenicity in humans or animals were not carried over into an overall evaluation for metallic nickel. Thus, the overall conclusion in *IARC Monographs* Volume 100C is that nickel compounds are *carcinogenic to humans* (Group 1) (IARC, 2012c), while metallic nickel is classified as *possibly carcinogenic to humans* (Group 2B).

In the US NTP *14th Report on Carcinogens* (RoC) (NTP, 2021f), metallic nickel was "reasonably anticipated to be a human carcinogen", on the basis of *sufficient* evidence of carcinogenicity from studies in experimental animals.

It is somewhat unusual in IARC evaluations of metals to have two separate evaluations, one for the metallic form (the pure element) and one for all compounds combined. Usually, a holistic approach has been adopted, by classifying the metal and the compounds together (see other metals included in *IARC Monographs* Volume 100C: beryllium and cadmium). For cobalt, instead, an approach with a separate evaluation for each form has been taken, with separate evaluations for cobalt metal (without tungsten carbide

or other metal alloys), soluble cobalt(II) salts, cobalt(II) oxide, cobalt(II,III) oxide, cobalt(II) sulfide, and other cobalt(II) compounds (IARC, 2023b).

Exposure characterization

Nickel metal is listed by the OECD (2007) and the US EPA (2024a) as a high production volume chemical. Metallic nickel is widespread in nature and occurs in air, water, and soil (Genchi et al., 2020). Occupational exposure occurs in a variety of settings, including in the industries that produce and use nickel (e.g. alloy and stainless-steel production, electroplating and electrowinning, welding) (IARC, 2012c). Exposure to metallic nickel was reported to be higher in nickel-producing industries than in nickel-consuming industries, with mean inhalable levels in the range of 0.01–6 mg/m^3 in nickel-producing industries and 0.05–0.3 mg/m^3 in nickel-consuming industries (IARC, 2012c). 90% of all nickel is used in the production of stainless steel and other nickel-containing alloy, in which oxidic and metallic nickel are the primary forms of nickel exposure (Sivulka, 2005). For workers, the main exposure route is through inhalation, but ingestion and dermal absorption can also be involved (IARC, 2012c).

Nickel is present in the environment (air, water, soil) in the form of nickel compounds, such as salts, oxides, or different nickel-containing minerals (IARC, 1990a). The general population is exposed to nickel through the ingestion of food and drinking-water, as the primary route of exposure, and through inhalation from ambient air (IARC, 2012c); however, this is unlikely to be metallic nickel (IARC, 1990a; EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain) et al., 2020).

Cancer in humans

In *IARC Monographs* Volume 100C (IARC, 2012c), few studies were identified as presenting separate effect estimates for metallic nickel. In most occupational and environmental studies, exposure to various forms of nickel occurs, and it is difficult to separate the effects of individual forms in epidemiological studies.

One study in workers in a nickel refinery in Clydach, UK, attempted to separate the effects for various forms of nickel (metallic, soluble, oxidic, sulfidic); the best-fitting model showed increased lung cancer risk for metallic nickel and soluble nickel (Easton et al., 1992). However, uncertainty remained over the role of metallic nickel, as the model without metallic nickel did not have a significantly worse fit than the best-fitting model. Sivulka et al. (2014) updated the exposure assessment for this Welsh cohort (1953–2000), providing a job-exposure matrix with percentage of exposure to various form of nickel, including metallic nickel, and indicated the need of an updated analysis of the Welsh cohort using the job-exposure matrix.

A nested case–control study in a Norwegian nickel refinery, conducted by Grimsrud et al. (2002), showed an increased lung cancer risk associated with high metallic nickel exposure (OR, 2.4; 95% CI, 1.1–5.3); however, the association was attenuated (OR, 0.9) after adjustment for water-soluble nickel.

A study by Arena et al. (1998) among US nickel alloy workers showed an elevated but small increase in lung cancer risk associated with metallic nickel exposure, but such exposure was in combination with nickel oxide, which the Working Group for *IARC Monographs* Volume 100C considered to be the primary exposure.

In *IARC Monographs* Volume 100C, only one cohort was identified as exposed to metallic nickel in the absence of other forms of nickel (the Oak Ridge Gaseous Diffusion Plant), but this cohort had a small sample size (814 workers) and used plutonium workers as a comparison group (Cragle et al., 1984). Other studies reviewed by Sivulka (2005) for metallic nickel were not considered to provide evidence for carcinogenicity for metallic nickel because of their small sample size and the mixed exposure scenario (IARC, 2012c). Since *IARC Monographs* Volume 100C, few new analyses in occupational studies are available that evaluate metallic nickel separately. A recent case–control study of multiple myeloma nested within an update of the Oak Ridge Gaseous Diffusion Plant (follow-up 1985–1998, n = 47 941) found no association between nickel metal and multiple myeloma (Yiin et al., 2009); however, no updated analysis on this cohort was published

for lung cancer or nasal cancer. A recent pooled analysis of 14 case–control studies from Europe and Canada (the SYNERGY analysis) found an OR for lung cancer in men associated with nickel exposure of 1.29 (95% CI, 1.15–1.45) but was unable to stratify by type of nickel (Behrens et al., 2023).

An update of the Ontario nickel mining and refinery workers has recently been published, reporting mortality for lung cancer, nasal cancer and other respiratory and non-respiratory cancers (Lightfoot et al., 2017; Seilkop et al., 2017). Results are presented by employment area, duration of employment, and decade of employment, but no results by form of nickel exposure are presented, given the lack of reliable exposure information (Seilkop et al., 2017). The available exposure information indicates that the prevalent exposures in this cohort were to nickel compounds (Seilkop et al., 2017). These results are of limited informativeness for nickel metal evaluation in the absence of a quantitative characterization of the exposure.

Large studies on $PM_{2.5}$ and cancer risk, exploring the effect of a nickel component in $PM_{2.5}$, are likely to be minimally informative, as the nickel component to $PM_{2.5}$ includes nickels compounds (Hvidtfeldt et al., 2021b; So et al., 2023).

Cancer in experimental animals

In the previous evaluation (IARC, 2012c), there was *sufficient* evidence in experimental animals for the carcinogenicity of nickel metal. Metallic nickel caused tumours in two rodent species, at several different tissue sites, and by several different routes of exposure. Metallic nickel increased the incidence of adrenal pheochromocytomas in male rats and adrenal cortex tumours in female rats, when administered by inhalation. Lung tumours were also observed in rats that had been exposed to metallic nickel powder by intratracheal administration (Oller et al., 2008). In addition, metallic nickel caused local tumours in rats when administered by injection (intratracheal, intrapleural, subcutaneous, intramuscular, intraperitoneal) (Hueper, 1952, 1955; Mitchell et al., 1960; Heath and Daniel, 1964; Furst and Schlauder, 1971; Berry et al., 1984; Sunderman, 1984; Judde et al., 1987; Pott et al., 1987, 1990).

Mechanistic evidence

Numerous mechanistic studies relevant to the KCs are available. Observational studies showed positive correlations between DNA damage marker 8-OHdG and (human) 8-oxoguanine DNA glycosylase (hOGG1) levels among workers in a nickel-smelting plant who were routinely exposed to different forms of nickel. The amount of DNA damage increased with increasing employment length and was related to the inhibition of hOGG1 repair capacity (Wu et al., 2015b). In nickel electroplating workers, significantly lower levels of anti-oxidants GSH, catalase were observed in workers with an exposure to high nickel levels compared with those with a lower exposure to nickel; however, only GSH showed an independent association after multivariable adjustment (Tsao et al., 2017). Chromosomal aberrations have been observed in workers occupationally exposed to nickel (Senft et al., 1992). In human cell lines in vitro, nickel metal particle powder induced DNA strand breaks, as well as a significant increase in intracellular ROS production in bronchial epithelial cells (Åkerlund et al., 2018; Di Bucchianico et al., 2018), and inflammation in THP-1 monocytic cells (Åkerlund et al., 2019). Nickel can bind ionically to cellular components, including DNA. The reduction–oxidation activity of the nickel ion may produce ROS that attack DNA, and exposure to nickel ion in vitro or in vivo can result in the production of 8-OHdG in target tissues for cancer caused by nickel (IARC, 1990a, Kasprzak et al., 1990; Lu et al., 2005; Chen and Costa, 2017; NTP, 2021f). Nickel, in various forms, has been shown to induce epigenetic alterations in blood samples. It induces hypermethylation of in the promoter region of tumour suppressor genes such as E-cadherin and p16 in workers with regular exposure to nickel (Yang et al., 2014), and by altering global histone post-translational modifications in PBMCs from workers in a nickel-smelting plant (Ma et al., 2015) and workers of a nickel refinery (Arita et al., 2012a, b), and in other experimental systems, both in vitro and in vivo (Zhang et al., 2013a; Chen et al., 2019a; Jose et al., 2019).

Summary

In the occupational studies available, it has been difficult to disentangle the effect of metallic nickel from that of other nickel compounds, given that exposure in industries rarely occurs solely for metallic nickel. The Norwegian and Welsh refinery cohorts each showed an increased risk of lung cancer for metallic nickel; however, uncertainty remains over the role of co-exposure to other nickel compounds.

The available mechanistic data suggest that nickel exhibits KCs. Increased DNA damage, inhibition of DNA repair, epigenetic alterations, and oxidative stress have been observed in exposed workers and in human cell lines. However, these workers were known to be exposed to different forms of nickel and probably to other metals as well. No studies in human primary cells exposed to metallic nickel have been identified. The uncertainty as to whether the exposure is specific to the metallic form of nickel and not to other nickel compounds in the occupational studies in humans limits the relevance of the resulting mechanistic evidence for a proper evaluation of the agent. Overall, the Advisory Group considered an *IARC Monographs* re-evaluation of metallic nickel to be warranted.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

063 Aluminium (CAS No. 7429-90-5)

Current IARC/WHO classification

Aluminium, as a metal, has not been previously evaluated by the *IARC Monographs* programme. Aluminium production, as a manufacturing process, has been classified as *carcinogenic to humans* (Group 1), with *sufficient* evidence for cancers of the bladder and lung. However, these findings were considered most likely to be due to heavy exposure to PAHs in this industry. Aluminium was given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a). However, the 2019 Advisory Group on Priorities noted that exposure in aluminium production is confounded by exposure to other carcinogenic agents, such as PAHs and smoke. WHO conducted an evaluation for aluminium in 2009 for the preparation of guidelines on drinking-water quality (WHO, 2009a). JECFA carried out a risk assessment in 2011 and specified a PTWI of 2 mg/kg bw (FAO/WHO, 2011b).

Exposure characterization

Aluminium is listed by the OECD (2007) and the US EPA (2024a) as a high production volume chemical. Aluminium is widely distributed in the environment in the form of silicates or hydroxides, in (trivalent) Al^{3+} ions, formed by weathering of rocks. Aluminium compounds are used in water treatment, leather tanning processes, the manufacture of cooking utensils, and in fireworks, explosives, cosmetics, and pharmaceuticals. Occupational exposure to aluminium is associated with mining, smelting, welding, and scrap metal recycling. Human exposure is mainly through inhalation (of the fumes during production) and ingestion from food additives and drinking-water. Dermal absorption through cosmetics is another possible route of exposure.

Cancer in humans

Several epidemiological studies have suggested an association of aluminium compounds in antiperspirants with a risk of benign diseases in the breast (Darbre et al., 2013; Darbre, 2016) and a risk of lung and bladder cancer in smelters (Maltseva et al., 2016). However, the association is not yet clear.

Cancer in experimental animals

No studies of cancer in experimental animals exposed to aluminium were available to the Advisory Group.

Mechanistic evidence

Several studies have shown that aluminium compounds induce oxidative stress and lipid peroxidation (Kaneko et al., 2007; Exley et al., 2010). There is evidence of immunosuppression induced by exposure to aluminium (Yu et al., 2019a). Aluminium is also considered proinflammatory, inducing organ inflammation in rodents (Pineton de Chambrun et al., 2014; Gherardi et al., 2016).

Summary

At present, there does not appear to be convincing evidence from any of the evidence streams to warrant an evaluation of aluminium. It is important to note that all the aforementioned studies and observations were for aluminium compounds, such as $AlCl_3$ or aluminium phosphate, and not metallic aluminium. Although there are studies indicating metallic aluminium exposure, there is little evidence linking this exposure to cancer in humans or experimental animals. The Advisory Group therefore considered that an *IARC Monographs* evaluation of aluminium is unwarranted at present.

Recommendation: No priority

064 Selenium and selenium compounds (CAS No. 7782-49-2)

Current IARC/WHO classification

Selenium and selenium compounds have been previously evaluated by IARC as *not classifiable as to its carcinogenicity to humans* (Group 3) in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a). The International Program on Chemical Safety has published a report on the health effects of selenium and selenium compounds (WHO, 1991).

Selenium and selenium compounds were given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of cancer bioassay evidence.

Exposure characterization

Selenium is a naturally occurring element, with exposures occurring through food, water, and soil. Selenium is thought to have hormetic effects, with nutritional value at low doses (Bjørklund et al., 2022). For adults, the average daily recommended selenium intake is 55 µg (Institute of Medicine, 2000), and an upper limit of 255 µg/day has been established (EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) et al., 2023). Sources of selenium in the diet include meat, eggs, and nuts (Kieliszek, 2019). Occupational exposures to selenium occur in several industries, including glass-making, pharmaceutical production, and semiconductor industries (Göen et al., 2015).

Cancer in humans

Many epidemiological studies have considered populations, including children and adults, with varying selenium levels. The majority of studies for many types of cancer yield conflicting findings, with many of the more recent results showing no effect or a protective effect with increasing selenium levels. As a consequence of these findings, a series of randomized clinical trials were conducted to evaluate the efficacy of chemoprevention by dietary selenium supplementation. However, these trials did not show a detectable reduction in cancer risk, but instead, unexpectedly, indicated an excess of some histotypes of prostate cancer (Klein et al., 2011; Yarmolinsky et al., 2018). Two studies published since the review of Yarmolinsky et al. (2018) did not identify a risk of the development of prostate cancer with higher selenium levels (Van Hemelrijck et al., 2019; Outzen et al., 2021). An updated literature search (2019–2023) was conducted to evaluate epidemiological studies associated with selenium levels and cancer development. Most of the

studies did not show a dose–response relation between serum concentrations of selenium and cancer development. In fact, many of the studies continued to purport a protective effect (i.e. higher serum concentrations of selenium resulted in a smaller risk of cancer development), including some meta-analyses and reviews for breast and liver cancers (Gong et al., 2019; Zhu et al., 2021b). These continued contradictory findings obscure interpretation as to the potential carcinogenicity of different forms of selenium, which would be challenging in an evaluation by the *IARC Monographs* programme.

Cancer in experimental animals

Animal bioassays published before 1987 were evaluated in Supplement 7, with the conclusion that there was *inadequate* evidence of carcinogenicity in experimental animals (IARC, 1987a). A gavage study from the US NTP (1980) was positive but was not reviewed. In that study, selenium sulfide was found to be carcinogenic for F344 rats and female B6C3F_1 mice, inducing HCC in male and female rats and female mice and bronchioloalveolar carcinoma and adenoma (combined) in female mice. Selenium sulfide was not found to be carcinogenic for male mice. Dermal application of selenium sulfide did not result in cancer in mice (NTP, 1980). Several studies focusing mostly on the suspected cancer-protective effects of selenium have been published since then. The results of these studies have been mixed; both suppression and promotion of carcinogenic lesions have been reported (see e.g. studies by Ankerst and Sjögren, 1982; LeBoeuf et al., 1985; Perchellet et al., 1987; Birt et al., 1988, 1989; Woutersen et al., 1999; Chen et al., 2000; Novoselov et al., 2005; Su et al., 2005). No new cancer bioassays supporting carcinogenicity in experimental animals were published since the last nomination, in 2019.

Mechanistic evidence

There are many studies relevant to KCs, including genotoxicity, epigenetic alterations, oxidative stress, and immunological effects (e.g. Cemeli et al., 2006; Letavayová et al., 2006; Santos et al., 2009; Uğuz et al., 2009; Brozmanová et al., 2010; Valdiglesias et al., 2010; Lee and Jeong, 2012; Lv et al., 2021a). However, as with the carcinogenicity data, many of the available studies focus on the suspected cancer-protective mechanisms of selenium intake. Although there is also evidence on the genotoxic effects of excess selenium (Brozmanová et al., 2010; Valdiglesias et al., 2010), the database on the mechanisms of toxicity of excess selenium intake is still less abundant, compared with the number of studies related to the potential beneficial effects of selenium and their mechanisms (Lv et al., 2021a; Tsuji et al., 2021).

Summary

There are continued mixed findings for the relation between selenium exposure and many types of cancer in humans. The human cancer study data would be unlikely to support a determination of at least *limited* evidence. Two long-term animal carcinogenicity studies are available, suggesting the carcinogenicity of selenium. The available mechanistic evidence is inconsistent and does not support the evaluation or a change in the classification of the agent. Overall, the Advisory Group considered an *IARC Monographs* re-evaluation of selenium and selenium compounds to be warranted.

Recommendation: Medium priority

065 Dental amalgam

Current IARC/WHO classification

Dental material was previously reviewed by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in *IARC Monographs* Volume 74 in 1999 (IARC, 1999a).

Exposure characterization

Dental amalgams are commonly used to repair cavities and delay tooth decay around the world. Formulations for dental amalgams vary but they typically comprise approximately 40–50% inorganic mercury and other major metal components (5–70%), including tin, copper, and silver (Berry et al., 1994; IARC, 1999a; Jirau-Colón et al., 2019). Other minor metal components (< 5%) have included indium, zinc, and palladium (Berry et al., 1994). Dental amalgams have been in use for at least 150 years in both adults and children (Richardson et al., 2011; Jirau-Colón et al., 2019; WHO, 2021c; Yin et al., 2021). In the USA, amalgams are more prevalent in older adults, with non-amalgam usage more prevalent in children and adults aged < 40 (Beltrán-Aguilar et al., 2023). Exposure to inorganic mercury has been of the highest concern, owing to continued release from dental amalgams to form mercury vapour that can be inhaled (US FDA, 2021). Although dental amalgams release inorganic mercury vapour, some evidence has suggested that it can be methylated and biotransformed into organic mercury compounds through interaction with oral bacteria (Mueller, 2006; Jirau-Colón et al., 2019; US FDA, 2021). Occupational exposures to inorganic mercury through dental amalgams have also been noted in dental personnel (Nagpal et al., 2017; Tuček et al., 2020).

Cancer in humans

Only a couple of epidemiological studies were identified in humans since the last IARC evaluation of dental amalgams in 1999 (IARC, 1999a). In a retrospective cohort study of members of the New Zealand Defence Force (29 680 with dental records), no associations with cancer and dental amalgams were reported (Bates et al., 2004; Bates, 2006). A study of 490 individuals with dental amalgam fillings evaluated the relation between timing of first amalgam placement and age at cancer onset and concluded that there was a statistically significant earlier age of cancer onset for colon, breast, endometrial, cervical, and testicular cancers, and for a pool of 14 other cancers, for patients who had amalgam fillings earlier in life, compared with those who had fillings later in life (Mueller, 2006), although this may have been due to an age-cohort effect (Mannetje, 2006).

Cancer in experimental animals

No studies of cancer in experimental animals caused by dental amalgam were identified. The earlier IARC evaluation on mercury concluded that the evidence regarding cancer in experimental animals was *inadequate* for metallic mercury, *limited* for mercury chloride, and *sufficient* for methylmercury (IARC, 1993b). No new carcinogenicity studies in experimental animals for metallic or inorganic mercury were available to the Advisory Group.

Mechanistic evidence

There are a few studies suggesting genotoxicity and oxidative stress in humans with dental amalgam fillings or other dental restorative materials (Bloching et al., 2008; Di Pietro et al., 2008; Mary et al., 2018; Trutina Gavran et al., 2023). There are experimental studies performed with mercuric dichloride, showing genotoxic effects for soluble inorganic mercury (Al-Saleh et al., 2012). Methylmercury and inorganic mercury have been shown to cause epigenetic effects (Gadhia et al., 2012; Goodrich et al., 2013). Some studies have compared the ability of amalgam and alternative materials to cause local inflammation (Nadarajah et al., 1996; Chandwani et al., 2014). Mechanistic data dissociating the effects of amalgam from those of mercuric dichloride are not clear.

Summary

Dental amalgams have been widely used around the world for over 150 years. Only a few studies have evaluated the evidence of cancer in humans, and the evidence is minimal. Similarly, animal carcinogenicity

data are lacking for dental amalgam, although components (e.g. metallic mercury, methylmercury) have been previously evaluated by IARC. The mechanistic evidence relevant for carcinogenicity is sparse. Overall, the available data are unlikely to result in a change in the IARC classification. The Advisory Group therefore considered that an *IARC Monographs* re-evaluation of dental amalgam is unwarranted at present.

Recommendation: No priority

066 Phosphorescent paints

Current IARC/WHO classification

Phosphorescent paints [e.g. strontium aluminate plus europium (in paints); zinc sulfide plus copper (in face paints)] have not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Few studies were identified that evaluated exposures to phosphorescent paints and face paints. Huang et al. (2023a) reviewed the properties of mechanoluminescent strontium aluminate materials and discussed the use of powder paints incorporating strontium aluminate and europium since the 1960s, including uses in cathode ray tubes and lamps. Given the mechanoluminescent properties of these mixtures, they are also used in many consumer products, such as glow-in-the-dark sporting equipment (Huang et al., 2023a), often used by children. Several methods of industrial production exist for these materials and involve the formation of powders and gels that could presumably result in occupational exposures, although no direct exposure studies were identified. No consumer-based studies were identified on powders incorporating strontium aluminate and europium either.

Few studies were identified for face paints incorporating zinc sulfide and copper (also often used by children). Face paints containing these compounds are approved by the US FDA, with indications that they should not be used around the eyes and are intended for use on “limited, infrequent occasions” (US FDA, 2000). In addition, these products should not contain more than 10% by weight of zinc sulfide and should be free from other impurities, such as copper, lead, arsenic, mercury, and cadmium.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

Yellowtail damselfish were exposed indirectly to light from a white fluorescent bulb (photoperiod groups: 12 hours of light and 12 hours of darkness or 14 hours of light and 10 hours of darkness) or directly to a long-afterglow phosphorescent pigment for 4 months. In the phosphorescence-exposed group, plasma concentrations of follicle-stimulating hormone (FSH), LH, and estradiol-17β (E2) were significantly higher than those in either photoperiod group. In addition, mRNA and protein expression of gonadotropin hormones [GTHs, including GTHα and LHβ], ER, and vitellogenin of the phosphorescence-exposed group were significantly higher than those in the photoperiod groups (Choi et al., 2015). However, this study did not include proper unexposed controls.

Summary

No data for phosphorescent paints are available for the evaluation of cancer in humans or experimental animals. There is no mechanistic evidence that phosphorescent paints exhibit KCs. The Advisory Group

therefore considered that an *IARC Monographs* evaluation of phosphorescent paints is unwarranted at present.

Recommendation: No priority

067 Rare earth elements

Current IARC/WHO classification

Rare earth elements have not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

The rare earth elements (REEs) are a group of 17 elements that have similar chemical properties: lanthanum (La), cerium (Ce), praseodymium (Pr), neodymium (Nd), promethium (Pm), samarium (Sm), europium (Eu), gadolinium (Gd), terbium (Tb), dysprosium (Dy), holmium (Ho), erbium (Er), thulium (Tm), ytterbium (Yb), lutetium (Lu), scandium (Sc), and yttrium (Y). REEs are critical for many applications related to semiconductors, luminescent molecules, catalysts, batteries, and many others (Salfate and Sánchez, 2022). Of these elements, cerium is the most abundant in the Earth's crust. Cerium carbonate, cerium phosphate, cerium silicate, and cerium (hydr)oxide minerals have been mined and processed for pharmaceutical uses and industrial applications and, in more recent years, for CeO_2 nanoparticles in industrial applications (Dahle and Arai, 2015). In 2022, China accounted for more than two thirds of the total global REE production. Second and third were the USA (14%) and Australia (6%) (Statista, 2024). REEs may also be recovered from e-waste (Ramprasad et al., 2022).

REEs in soils in mining areas can contaminate surrounding ecosystems and groundwater and may enter the human body through several exposure pathways, especially food ingestion (Li et al., 2013a). For example, most of the REEs studied have been determined in wines (Marengo and Aceto, 2003). Gadolinium is used as contrasting agent in medicine (see agent 068); it is then excreted in urine, and has been found in wastewater treatment plants, so may be present in water sources (Salfate and Sánchez, 2022). For example, gadolinium-based contrast agents were traced and found in drinking-water at several water plants in Germany (Birka et al., 2016a, b) up to 159 pmol/L (Birka et al., 2016b). Exposure to REEs may also occur in cigarette smoke; higher levels of REEs have been found in both active and passive smokers (Na et al., 2022).

Cancer in humans

Few observational human studies have been found on REEs and the risk of cancer. A case–control study on oral cancer in China, in which 33 trace elements in blood samples were investigated, found positive associations for lanthanum, praseodymium, europium, and dysprosium levels, whereas negative associations were observed for cerium, samarium, scandium, and yttrium (Wang et al., 2022a). A study on tongue cancer in China showed positive associations for lanthanum, praseodymium, and dysprosium, and inverse associations for cerium and scandium (Wang et al., 2023e).

Cancer in experimental animals

No published studies on cancer in experimental animals after exposure to rare earth metals were available to the Advisory Group. As part of an EU-funded NANoREG project (Regulatory testing of Nanomaterials; RIVM, 2023), a combined chronic and carcinogenicity whole-body inhalation study has been performed with cerium dioxide nanoparticles (not cerium); results on the cancer are not published yet and the test substance may behave differently from pure cerium. The Advisory Group noted that this study is performed on nanoparticles, not on the nominated agent.

Mechanistic evidence

Cerium oxides, mainly in the form of nanoparticles, have been most widely studied among the rare earth metal compounds. Several in vitro genotoxicity studies suggest genotoxicity of cerium oxide nanoparticles in human primary cells (e.g. Könen-Adıgüzel and Ergene, 2018). Also, in vivo genotoxicity data exist, with both positive (Kumari et al., 2014a, b; Nemmar et al., 2017) and negative (Cordelli et al., 2017) findings. Some studies have also included microsized particles and reported differences in the genotoxic response between micro- and nanosized cerium oxide particles (Kumari et al., 2014a). It has been suggested that cerium oxide nanoparticles induce oxidative stress and inflammation both in vitro and in vivo (e.g. Nemmar et al., 2017; Gosens et al., 2014; Hong et al., 2014; Schwotzer et al., 2017, 2018). When compared with cobalt oxide nanoparticles, immunological responses to cerium oxide nanoparticles were less pronounced in human bronchial cells in vitro (Verstraelen et al., 2014).

Although some studies have suggested oxidative damage and genotoxicity of lanthanum, two recent in vivo genotoxic studies reported negative outcomes (Yang et al., 2016a; Han et al., 2021). One study evaluated the ability of lanthanum oxide nanoparticles to induce chronic lung inflammation in mice (Sisler et al., 2016).

Some available studies on either yttrium compounds or yttrium nanoparticles suggest the induction of oxidative stress or genotoxic effects (or both) (Panyala et al., 2019; Xiong et al., 2022).

Data on the genotoxicity of gadolinium compounds is limited. Individual studies suggest DNA methylation changes and genotoxicity caused by gadolinium compounds (gadoversetamide radiocontrast agent) in experimental systems, including human primary cells (Yongxing et al., 2000; Cho et al., 2014; Liu et al., 2021a; Cobanoglu, 2022).

Data for other rare earth metals are limited, although a few individual studies exist on genotoxicity or the induction of oxidative stress by neodymium, dysprosium, praseodymium, or lutetium, or of mixtures of various REEs (e.g. Jha and Singh, 1994, 1995; Pagano et al., 2016; Hanana et al., 2021a, b; Liu et al., 2021a; Siciliano et al., 2021).

Cerium, lanthanum, and yttrium nitrates have been studied for their ability to cause immunosuppression in mice. Long-lasting effects were observed with lanthanum and yttrium after in utero and early postnatal exposure (Wang et al., 2022b; Ge et al., 2023; Yuan et al., 2023b).

Summary

Evidence from studies of cancer in humans and experimental animals is scarce. A few studies suggest that some REEs exhibit KCs. In particular, mechanistic data suggest that cerium oxide nanoparticles exhibit several KCs. Gadolinium-based radiocontrast agents (agent 068) have also been considered separately in the present report. The Advisory Group therefore considered that an *IARC Monographs* evaluation of REEs is unwarranted at present.

Recommendation: No priority

068 Gadolinium-based contrast agents

Current IARC/WHO classification

Gadolinium-based contrast agents (GBCAs) have not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Gadolinium is a rare earth metal widely used for various industrial and medical purposes, particularly in magnetic resonance imaging (MRI) of the brain. GBCAs have been widely used since the late 1980s. Three

MRI contrast agents were approved for clinical use in the USA as of 1994. Six more MRI GBCAs were approved by the US FDA for clinical use from 1995 through 2017: gadopentetate dimeglumine, gadodiamide, gadoteridol, gadoterate meglumine, gadobenate dimeglumine, and gadobutrol (Ibrahim et al., 2023). GBCAs are the most common agents used in MRI and are currently used in about one in three MRI scans (Fraum et al., 2017). Globally, about 30 million procedures are carried out annually (Iyad et al., 2023). Two GBCAs are not approved for contrast-enhanced MRI of the CNS. Gadofosveset trisodium was indicated for the visualization of abdominal or limb vessels in adults but was withdrawn in Europe in 2011 by request of the marketing authorization holder (US FDA, 2008; EMA, 2011). Gadoxetic acid-enhanced MRI is currently the most efficient method for the detection and analysis of focal liver lesions (Ichikawa and Goshima, 2024). Gadoxetate disodium is used exclusively in MRI of the liver (Knipe, 2023).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

GBCAs are administered intravenously and are mostly eliminated via the kidneys. Recently, residual gadolinium has been found within the brain tissues of patients who received multiple doses of GBCAs over their lifetimes. For reasons that remain unclear, gadolinium deposition appears to occur preferentially in certain specific areas of the brain, even in the absence of clinically evident disease and in the setting of an intact blood–brain barrier. Excretion into breast milk of GBCAs and gastrointestinal absorption from ingested breast milk by an infant are expected to be extremely low (ACR, 2023).

A series of studies in human primary cells and experimental systems have reported that GBCAs can induce DNA damage, oxidative stress, and inflammatory responses. For example, gadoversetamide, lanthanum(III), and gadolinium(III) induced an increase in micronucleus formation in human lymphocytes (Yongxing et al., 2000; Cobanoglu, 2022). Lanthanum(III) and gadolinium(III) were observed to induce increase in DNA single-strand breaks and UDS (Yongxing et al., 2000). Similar findings were reported in human lymphocytes by Cho et al. (2014), who also observed increases in apoptotic cell death and ROS production. Oxidative stress, as a sign of neurotoxicity, was observed in rat cortical neurons by Xia et al. (2011) and Feng et al. (2010). Gadolinium-induced cytotoxicity in neurons occurred via oxidative injury and endoplasmic reticulum stress-related signal transduction and it was observed to alter mitochondrial metabolism, thus inducing oxidative stress followed by apoptosis.

Summary

There is no evidence regarding cancer in humans or experimental animals. The mechanistic evidence is sparse. Some evidence suggests that GBCAs might exhibit KCs, including genotoxicity (KC2) and oxidative stress (KC5), in human primary cells and experimental systems. Overall, the Advisory Group considered that an *IARC Monographs* evaluation of GBCAs is unwarranted at present.

Recommendation: No priority

069 Platinum-based chemotherapies as a mechanistic class

Current IARC/WHO classification

Cisplatin has been previously evaluated by IARC as *probably carcinogenic to humans* (Group 2A) in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a). There was *sufficient* evidence in animals and

inadequate evidence in humans (IARC, 1987a). The evaluation had been upgraded to Group 2A based on mechanistic evidence that cisplatin induced DNA damage (IARC, 1987a). Etoposide in combination with cisplatin and bleomycin has been evaluated by IARC as *carcinogenic to humans* (Group 1) (IARC, 2012d). No other platinum-based chemotherapies have been previously evaluated by IARC.

Exposure characterization

Platinum-based chemotherapies are metal-based chemotherapeutic agents used in the treatment of a wide range of cancers, including cancers of the testis, bladder, cervix, ovary, gastrointestinal tract, breast, head and neck, and lung, as well as malignant mesothelioma, sarcoma, and lymphoma (NCI, 2014; Ghosh, 2019; Zhang et al., 2022a). Approved platinum-based chemotherapies include cisplatin (US FDA-approved in 1978, NCI, 2014), carboplatin (approved in 1989), and oxaliplatin (approved in 2002), which are all listed in the WHO Model List of Essential Medicines (WHO, 2023b) and are all administered intravenously. Other cisplatin analogues are currently being tested in clinical trials (Ghosh, 2019). Analysis of the US Surveillance, Epidemiology, and End Results (SEER) Medicare database shows that, among patients treated with initial chemotherapy, the use of platinum-based chemotherapeutic agents increased from 35% (2000–2001) to 59% (2012–2013). In analyses by first primary cancer, the use of platinum compounds for initial chemotherapy for oesophageal cancer increased during the study period, from 63% to 95%. In 2012–2013, platinum compounds were used for most patients receiving initial chemotherapy: small cell lung cancer, 97%; non-small cell lung cancer, 91%; cervical cancer, 96%; uterine cancer, 93%; ovarian cancer, 97%; and fallopian tube cancer, 97% (Morton et al., 2019). Exposure also occurs in occupational settings among workers involved in the production, preparation, or administration of platinum-base chemotherapies or during the clean-up of medical waste (NTP, 2021a). Cisplatin, oxaliplatin, and carboplatin are included in the US NIOSH hazardous drug list (NIOSH, 2016b).

Cancer in humans

Platinum-based chemotherapies have been associated with treatment-related leukaemia. This evidence comes from large cohorts of cancer survivors. In a large cohort of ovarian cancer survivors (n = 28 971) from Europe and North America, an increased risk of leukaemia was found for platinum-based chemotherapies (RR, 4.0; 95% CI, 1.4–11.4), with evidence of a dose–response relation (Travis et al., 1999), and for cisplatin (RR, 3.3; 95% CI, 1.1–9.4) and carboplatin (RR, 6.5; 95% CI, 1.2–36.6), when evaluated separately. These risk estimates were consistent with those reported for a cohort of testicular cancer survivors (n = 18 567) for platinum-based chemotherapy, mostly cisplatin (Travis et al., 2000). Reports from the US SEER database showed an elevated SMR for therapy-related myelodysplastic syndrome (tMDS) or AML associated with receipt of chemotherapy for solid tumours in a period with a high prevalence of use of platinum-based chemotherapies (Morton et al., 2019; Dores et al., 2023).

Evidence is also emerging for an increased risk of subsequent solid malignant neoplasms, particularly gastrointestinal and kidney cancers in survivors of testicular germ cell tumours during the era of platinum-based chemotherapies (Fung et al., 2013; Groot et al., 2018; Hellesnes et al., 2020), including evidence of a dose–response relation for platinum-based chemotherapies (Groot et al., 2018), and in survivors of childhood cancer (Henderson et al., 2012a; Wilson et al., 2013).

Cancer in experimental animals

Since 1987, when *sufficient* evidence for cancer in experimental evidence was identified, a study from the NTP found an increased incidence of benign lung tumour (adenoma) in female mice and an increased incidence of leukaemia in both male and female rats after intraperitoneal administration of cisplatin (NTP, 2021b). Satoh et al. (1993) showed an increased in the incidence of benign lung tumours after intraperitoneal injection of cisplatin in female mice. In a similar study in metallothionein-I/II double-knockout mice (which

lack a metal-binding protein thought to mitigate the toxicity of various metals), a single intraperitoneal injection caused a dose-related increase in HCC (Waalkes et al. 2006). In an initiation–promotion study (Diwan et al., 1993), cisplatin injection late in gestation-initiated tumours in mice. Renal tubular dysplasia and thymic lymphoma were observed in rat offspring: in a transplacental exposure study (Diwan et al., 1995), renal cell adenomas were observed in male offspring, and HCC in both male and female offspring.

Mechanistic evidence

All platinum-based compounds share the same mechanism of action, which involves the binding of platinum to DNA, causing DNA damage (formation of intrastrand and interstrand crosslinks, single-nucleotide damage of guanine), and eventually leading to apoptosis (Ghosh, 2019; Stefanou et al., 2021). Cisplatin has been reported, in a review by Ghosh (2019), to not only cause DNA damage by forming adducts with the purine bases but also to elicit receptor-mediated responses, leading to the activation of cell-apoptotic signalling pathways (Ghosh, 2019).

Platinum from platinum-based chemotherapies remains partially active when circulating in the blood and is detectable even 10 years after treatment (Tothill et al., 1992; Brouwers et al., 2008). Renal clearance is the primary means of excretion (Gerl and Schierl, 2000). Platinum-amine DNA adducts have been observed in patients treated for cancer and also in rodent tissue (Poirier et al., 1992).

Whole-genome sequencing studies have provided direct evidence for the role of platinum-based chemotherapy in the development of clonal haematopoiesis and therapy-related myeloid neoplasms, through the identification of a platinum-based chemotherapy mutational signature in treatment-related myeloid leukaemia (Boot et al., 2018; Bolton et al., 2020; Pich et al., 2021; Diamond et al., 2023). Those studies showed that platinum compound exposure strongly correlates with clonal haematopoiesis in specific DNA damage response genes TP53, PPM1D, CHEK2, similarly to topoisomerase II inhibitors and radiation (Bolton et al., 2020; Pich et al., 2021).

Cisplatin and related platinum-based therapeutics, such as carboplatin and oxaliplatin, have been shown to induce oxidative stress (Saad et al., 2004; Dasari and Tchounwou, 2014) in experimental animals. Jennerwein and Andrews (1995) has shown that cisplatin can modulate calcium signalling by receptor modulation. There is additional evidence of receptor modulation and interference in cell signalling by cisplatin in several other studies (Hayakawa et al., 2000; Winograd-Katz and Levitzki, 2006; Jones et al., 2007), as well as evidence of DNA damage (Basu and Krishnamurthy, 2010) and of cell apoptosis and modulation of gene expression (Shen et al., 2012)

Summary

Most epidemiological studies have evaluated the risk of platinum-based chemotherapies, without further differentiating on the type of drug. Large and well-conducted epidemiological studies consistently showed an increased risk of leukaemia, large in magnitude and with evidence of a dose–response relation for platinum-based chemotherapies, particularly for cisplatin. Emerging evidence shows associations with the risk of kidney and gastrointestinal cancers. These findings add to evidence from whole-genome sequencing studies identifying a specific mutational profile in therapy-related myeloid neoplasm associated with earlier platinum-based chemotherapy treatment.

Reports from the NTP and several other studies on rodent models have shown the carcinogenic potential of several platinum-based drugs. There is evidence, including in exposed humans, that platinum-based drugs exhibit KCs, including genotoxicity, oxidative stress, receptor-mediated effects, and cell proliferation induction. In addition, the same mechanism of action shared by all platinum-based chemotherapies would support a mechanistic class evaluation for drugs pertaining to the pharmaceutical class of platinum-based chemotherapies, given that cisplatin is currently classified as *probably carcinogenic to humans* (Group 2A).

The Advisory Group recommends evaluating, as separate agents, cisplatin, carboplatin, and oxaliplatin, and possibly other drugs pertaining to the pharmaceutical class of platinum-based chemotherapies, in the same *IARC Monographs* volume, as they may belong to a mechanistic class.

Recommendation: High priority (and ready for evaluation within 2.5 years)

070 Anthracyclines as a mechanistic class

Current IARC/WHO classification

Anthracyclines as a mechanistic class have not been previously evaluated by the *IARC Monographs* programme. However, daunomycin (daunorubicin) has been classified by IARC as *possibly carcinogenic to humans* (Group 2B), based on *sufficient* evidence for cancer in experimental animals in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a). Adriamycin (doxorubicin) has been classified by IARC as *probably carcinogenic to humans* (Group 2A), based on *sufficient* evidence for cancer in experimental animals and *inadequate* evidence in humans; the classification had been upgraded to Group 2A on the basis of mechanistic evidence in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a). A priority rating of *high* was given for "some anthracyclines" by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), based on human cancer evidence (IARC, 2019a). Separate nominations were also made for daunorubicin, doxorubicin, and epirubicin (see agents 071 to 073 in the present report).

Exposure characterization

Anthracyclines are antibiotics of the class of topoisomerase II inhibitors used for cancer chemotherapy. Doxorubicin and daunorubicin are included in the WHO Model List of Essential Medicines (WHO, 2023b). Doxorubicin, daunorubicin, epirubicin, and idarubicin are the four most common anthracyclines, with doxorubicin and daunorubicin having been the first used in clinical practice, in the 1970s (McGowan et al., 2017). Anthracyclines are widely used to treat solid and haematological malignancies, including breast cancer (in 32% of patients), leukaemia, lymphoma (57–70%), and childhood cancer (50–60%) (McGowan et al., 2017; Mattioli et al., 2023; Venkatesh and Kasi, 2023). In the past 20 years, in response of the need to reduce radiotherapy side-effects, the use of anthracyclines has increased, especially in children (Wang et al., 2023f).

Anthracyclines are often used together with alkylating agents and with radiotherapy, both known leukaemogenic agents (IARC, 2012d). Workers may be exposed during the manufacture and handling of these agents. All four agents mentioned (doxorubicin, daunorubicin, epirubicin, and idarubicin) are included in the US NIOSH hazardous drug list (IARC, 2012e; NIOSH, 2016b).

Cancer in humans

Available studies have mainly been conducted in cohorts of cancer survivors. Anthracyclines have been associated with tMDS or AML, a rare but highly fatal outcome (Freedman et al., 2017), and also with an increased risk of solid cancer, especially subsequent breast cancer (SBC) (Lee et al., 2023c; Wang et al., 2023f).

For tMDS or AML, a pooled analysis of data from clinical trials of 9679 women with breast cancer in North America reported an HR of 5.16 (95% CI, 1.47–18.19), comparing the use of any anthracyclines against no use (Freedman et al., 2017); however, there was a limited ability to separate the effect of cyclophosphamide, an alkylating agent (classified by IARC as *carcinogenic to humans* (Group 1), with *sufficient* evidence for bladder cancer, in *IARC Monographs* Volume 100A in 2008 (IARC, 2012d)). In the SEER Medicare database, among 56 251 female survivors of breast cancer, an increased risk of

myelodysplastic syndrome (MDS) or AML (HR, 1.86; 95% CI, 1.33–2.61) was found for women treated using the anthracycline/cyclophosphamide regimen (Calip et al., 2015). In a cohort of 153 565 women with early-stage breast cancer within a nationwide health database for the Republic of Korea, the risk of MDS or AML was increased in patients who had ever been treated with anthracyclines compared with those who had not received chemotherapy (HR for MDS, 2.56; 95% CI, 1.60–4.10; HR for AML, 9.53; 95% CI, 4.16–21.86); however, there was a limited ability to disentangle the effect of co-exposure to alkylating agents (Lee et al., 2023c). In a nested case–control study in a cohort of French survivors of breast cancer, the use of anthracyclines (versus none) was associated with an increased risk of MDS or AML (RR, 3.11; 95% CI, 1.96–4.96), after controlling for other chemotherapy treatments, including alkylating agents (Le Deley et al., 2007). The risk was similar when stratified by type of anthracycline (epirubicin, doxorubicin) (Le Deley et al., 2007). Evidence of low leukaemogenicity of cyclophosphamide at the low cumulative doses used in modern chemotherapeutic regimens (Tallman et al., 1995; Crump et al., 2003; Balduzzi and Castiglione-Gertsch, 2005; Le Deley et al., 2007) might also indicate that cyclophosphamide may not be a strong confounder. Additionally, given that anthracycline is a topoisomerase II inhibitor, it is possible to look for specific characteristics of MDS or AML induced by topoisomerase II inhibitors (see the section on mechanistic evidence in this report, and the evaluation of etoposide in *IARC Monographs* Volume 100A in 2008 (IARC, 2012d)).

For breast cancer, a recent pooled analysis of 17 903 5-year survivors of female childhood cancer included in five cohorts (Childhood Cancer Survivor Study, Dutch Childhood Cancer Survivor Study-LATER, Jude Lifetime Cohort Study, French Childhood Cancer Survivors Study, Dutch Hodgkin Late Effects cohort) and one case–control study (Swiss Childhood Cancer Survivors Study) showed a dose–response relation for cumulative doxorubicin dose with SBC risk (Wang et al., 2023f). In models fully adjusted for radiotherapy and cyclophosphamide use, doxorubicin was associated with increased SBC (HR per 100 mg/m^2, 1.24; 95% CI, 1.18–1.31), daunorubicin was weakly associated with increased risk (HR per 100 mg/m^2, 1.10; 95% CI, 0.95–1.29), and use (versus no use) of epirubicin was associated with increased SBC (HR, 3.25; 95% CI, 1.59–6.63). Reports from the single cohorts pooled in Wang et al. (2023f) also showed an association for the use of anthracyclines with SBC (Inskip et al., 2009; Teepen et al., 2017; Veiga et al., 2019), including evidence of a dose–response relation for anthracyclines as a group (Teepen et al., 2017; Veiga et al., 2019).

Anthracycline use has also been studied in relation to subsequent soft tissue sarcoma in some of the largest cohorts of childhood cancer survivors (Henderson et al., 2012b; Teepen et al., 2017) and in a cohort of breast cancer survivors, in which the use of any anthracycline was associated with a 3.6-fold increased risk of angiosarcoma (95% CI, 1.00–13.3) (Veiga et al., 2022).

Cancer in experimental animals

In the previous evaluation (IARC, 1987a), there was *sufficient* evidence in experimental animals for the carcinogenicity of daunomycin (daunorubicin) and adriamycin (doxorubicin), from studies in rats receiving intravenous doses of these agents (e.g. Bertazzoli et al., 1971; Marquardt et al., 1976; Solcia et al., 1978; Bucclarelli, 1981).

Several studies have become available since the previous evaluation in 1987. In a study in female Sprague-Dawley rats (Howell et al., 1989), a single intravenous injection of daunorubicin (10 mg/kg) resulted in the formation of mammary tumours. When injected with morpholino adriamycin, Sprague-Dawley female rats were shown to develop mammary tumours (Westendorf et al., 1987). Chun et al. (2012) showed that intraductal administration of pegulated liposomal doxorubicin (PLD) in Her2/neu mice induced malignant mammary tumours, as observed with daunomycin and adriamycin in rats.

Mechanistic evidence

Certain anthracyclines have been reported to be topoisomerase II inhibitors (Nitiss, 2009; Pommier et al., 2010). Pommier et al. (2010) reviewed the role of doxorubicin and other anthracyclines as inhibitors of topoisomerase, specifically topoisomerase II (alpha and beta isoforms). Similar findings have been reported by several studies, showing that doxorubicin induces DNA damage through topoisomerase II inhibition (Lyu et al., 2007; Deng et al., 2014; Linders et al., 2024). The mechanisms of action of anthracyclines include interaction with topoisomerase II, promoting growth arrest and apoptosis, and intercalation to the DNA between two adjacent pairs, inhibiting DNA and RNA synthesis (Nitiss, 2009; McGowan et al., 2017; McNerney et al., 2017).

Anthracyclines, such as doxorubicin, have been reported to induce chromosomal aberrations in human leukocytes (Vig, 1971), such as SCE in patients treated with the drug, DNA strand breaks, chromosomal aberrations, and SCE in PBLs of patients, and also in occupational exposure to these drugs (Nevstad, 1978; Norppa et al., 1980; Wiencke et al., 1982; Tucker et al., 1990; Tompa et al., 2016). Some anthracyclines (daunorubicin, doxorubicin) have been shown to induce DNA lesions, strand breaks (Westendorf et al., 1987), oxidative stress (Sawyer et al., 1999), DNA adducts, and chromosomal aberrations (Westendorf et al., 1985).

In a recent study by Stefanova et al. (2023), human retinal pigment epithelial (RPE1) cells, when treated with doxorubicin, showed DNA strand breaks, chromatin rearrangement, and topoisomerase II inhibition (Stefanova et al., 2023). Adriamycin has been shown, using the Ames assay, to be strongly mutagenic in *Salmonella typhimurium* strains T98 and TA100 (Bhuyan et al., 1983). In mice treated with doxorubicin, dose-dependent chromatid and chromosome-type aberrations were observed (Larramendy et al., 1980).

Anthracyclines are also capable of inducing ROS in the presence of cytochrome P450 reductase, NADH, and xanthine oxidase. They also form DNA adducts (McGowan et al., 2017) and cause chromatin damage (van der Zanden et al., 2021).

Etoposide, another topoisomerase II inhibitor, has been classified by IARC as *carcinogenic to humans* (Group 1) in *IARC Monographs* Volume 100A in 2008 (IARC, 2012d). AML after exposure to topoisomerase II inhibitors often presents with specific translocations on chromosomes 11 and 21 after a relatively short (2–3 years) latency, irrespective of the type of topoisomerase inhibitor (Stanulla et al., 1997; Mistry et al., 2005; McNerney et al., 2017). This is also noted in the evaluation of etoposide in *IARC Monographs* Volume 100A (IARC, 2012d), in which it is stated that AML induced by topoisomerase II inhibitors presents distinctive characteristics that allow distinctions for AML induced by alkylating agents (IARC, 2012d).

Summary

The available evidence in humans, together with evidence related to absorption, distribution, metabolism, and excretion (ADME) and mechanism of action (especially topoisomerase II inhibition), suggest that different anthracyclines share similar effects. However, studies of cancer in humans often provide a risk estimate for the entire class of anthracyclines, rather than single drugs. Overall, there is a consistent positive association between anthracycline use and a risk of MDS or AML, from studies conducted in diverse geographical settings. Concern over confounding by co-exposure from cyclophosphamide seems to be minimal. The pooled analysis by Wang et al. (2023f) offers clear evidence of a dose–response relation for doxorubicin and breast cancer, and some evidence for daunorubicin, with the ability to rule out confounding by concomitant treatment. There is ample evidence from experimental studies of cancer and mechanistic end-points in animals to show that anthracyclines (doxorubicin, daunorubicin) have carcinogenic potential.

The Advisory Group therefore considered an *IARC Monographs* evaluation of anthracyclines as a mechanistic class to be warranted and recommends evaluating the individual anthracyclines doxorubicin, daunorubicin, epirubicin, and possibly idarubicin, in the same volume.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

071 Daunorubicin (anthracycline) (CAS No. 20830-81-3)

Current IARC/WHO classification

Daunorubicin (an anthracycline) has been previously classified by IARC as *possibly carcinogenic to humans* (Group 2B) in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a), based on *sufficient* evidence in experimental animals. A priority rating of *high* was given for "some anthracyclines" by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), based on human cancer evidence (IARC, 2019a). Anthracyclines as a mechanistic class were nominated separately (see agent 070 in the present report).

Exposure characterization

Daunorubicin is the first identified anthracycline (antibiotics of the class of topoisomerase II inhibitors used for cancer chemotherapy) and among the most common anthracyclines used (McGowan et al., 2017; Mattioli et al., 2023). It was approved by the US FDA in 1979 (NIH, 2024a). The section on anthracyclines as a mechanistic class (agent 070 in the present report) gives further details on the use of anthracyclines. Daunorubicin is approved by the US FDA to treat non-lymphocytic leukaemia in children and adults (Saleem and Kasi, 2023). As part of the cyclophosphamide, daunorubicin, vincristine, and prednisone (CHOP) regimen, it is used to treat T-cell leukaemia (Saleem and Kasi, 2023). Off-label, daunorubicin is used to treat Kaposi sarcoma in patients with advanced HIV (Saleem and Kasi, 2023). Daunorubicin for intravenous administration is included in the WHO Model List of Essential Medicines (WHO, 2023b). Workers may be exposed during the manufacture and handling of daunorubicin. Daunorubicin is included in the US NIOSH hazardous drug list (NIOSH, 2016b).

Cancer in humans

Available studies have been conducted in cohorts of cancer survivors. Most of the studies have evaluated anthracyclines together, without separate analyses for types of anthracycline. These studies are informative for the evaluation of daunorubicin, if they include a sizeable proportion of patients treated with daunorubicin. Because daunorubicin is not used to treat solid cancer, cohorts of survivors of breast cancer or other solid cancers are not informative. For more details of studies of anthracyclines as a pharmaceutical class, see the section on anthracyclines as a mechanistic class (agent 070 in the present report).

In some of these studies, the analysis was stratified by the type of anthracycline. Notably, stratification by treatment type is possible only in very large studies, because power may be an issue. In a large pooled analysis of five cohorts of survivors of childhood cancer (Wang et al., 2023f), about 12% of the patients were exposed to daunorubicin, and the study found an association between daunorubicin and an increased risk of breast cancer; however, the risk was small (HR per 100 mg/m^2, 1.10; 95% CI, 0.95–1.29).

Cancer in experimental animals

In the previous evaluation (IARC, 1987a), there was *sufficient* evidence in experimental animals for the carcinogenicity of daunorubicin, based on studies of intravenous dosing in rats (Bertazzoli et al., 1971; Marquardt et al., 1976; Solcia et al. 1978). Two studies have become available since the previous evaluation. In a study by Howell et al. (1989), in female Sprague-Dawley rats, a single intravenous injection of daunorubicin (10 mg/kg) resulted in the formation of mammary tumours. In another study (Westendorf et

al., 1987), when injected with morpholino adriamycin, Sprague-Dawley female rats were shown to develop mammary tumours.

Mechanistic evidence

Westendorf et al. (1987) showed that morpholino daunomycin is weakly mutagenic in Chinese hamster cells or *S.typhimurium* but showed genotoxic effects, mainly DNA repair, in cultured rat hepatocytes. Another study by the same group (Westendorf et al., 1985) showed the formation of DNA adducts and chromosomal aberrations in rat hepatocytes exposed to daunorubicin and variants of the drug. In a study by Sawyer et al. (1999), daunorubicin was shown to induce apoptosis and oxidative stress in rat ventricular myocytes. Howell et al. (1986) showed that, in Sprague-Dawley rats, treatment with daunorubicin caused DNA lesions in mammary epithelial cells and DNA strand breaks in rat hepatocytes. No specific mechanism or ADME characteristics differed between daunorubicin and other anthracyclines (Mattioli et al., 2023).

Summary

Few studies of cancer in humans are available specifically for daunorubicin, given the more limited use of daunorubicin in comparison with other anthracyclines. There is already *sufficient* evidence for cancer in experimental animals for daunorubicin. Daunomycin shares ADME characteristics and mechanisms of action with other anthracyclines in forming DNA adducts and causing DNA damage and chromosomal aberrations. As noted in the summary for anthracyclines as a mechanistic class (agent 070 in the present report), the Advisory Group considered an *IARC Monographs* evaluation of daunorubicin (anthracycline) to be warranted and recommends re-evaluation of daunorubicin and other anthracyclines (doxorubicin and epirubicin) in the same volume, as they may belong to the same mechanistic class.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

072 Doxorubicin (anthracycline) (CAS No. 23214-92-8)

Current IARC/WHO classification

Doxorubicin (adriamycin) has been previously evaluated by the *IARC Monographs* programme as *probably carcinogenic to humans* (Group 2A) in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a). This classification was based on *sufficient* evidence in experimental animals and *inadequate* evidence in humans. The evaluation had been upgraded to Group 2A based on mechanistic evidence.

A priority rating of *high* was given for "some anthracyclines" by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), based on human cancer evidence (IARC, 2019a). Anthracyclines as a mechanistic class were nominated separately (see agent 070 in the present report).

Exposure characterization

Doxorubicin is among the most common anthracyclines used (McGowan et al., 2017; Mattioli et al., 2023). The section on anthracyclines as a mechanistic class (agent 070 in the present report) gives further details on the use of anthracyclines. Approved by the US FDA in 1974 (PubChem, 2024a), doxorubicin is used in the treatment of several adult and paediatric solid cancers (soft tissue and bone sarcoma, cancers of the breast, ovary, and bladder, and small cell lung cancer) and haematological cancers (ALL, acute myeloblastic leukaemia, Hodgkin lymphoma) (Johnson-Arbor and Dubey, 2023). Doxorubicin for intravenous administration is included in the WHO Model List of Essential Medicines (WHO, 2023b). Workers may be exposed during the manufacture and handling of doxorubicin. Doxorubicin is included in the US NIOSH hazardous drug list (NIOSH, 2016b).

Cancer in humans

Available studies have been conducted in cohorts of cancer survivors. Most of the studies have evaluated anthracyclines together, without separate analyses for types of anthracycline. These studies are informative for the evaluation of doxorubicin, given that doxorubicin is the most common anthracycline used (e.g. Wang et al. (2023f) use the prevalence of doxorubicin in the cohort). For more details of studies of anthracyclines as a pharmaceutical class, see the section on anthracyclines as a mechanistic class (agent 070 in the present report).

Some of these studies have been able to stratify the analysis by the type of anthracycline. Notably, stratification by treatment type is possible only in very large studies. Large nested case–control studies in a cohort of survivors of breast cancer in France showed an elevated risk of MDS or AML for doxorubicin use (RR for ever use, 2.72; 95% CI, 1.39–5.34) (Le Deley et al., 2007). A very large pooled analysis of five cohorts of survivors of childhood cancer showed a clear dose–response relation for doxorubicin and risk of SBC (HR per 100 mg/m^2, 1.24; 95% CI, 1.18–1.31), with adjustments for cyclophosphamide and radiation treatment (Wang et al., 2023f). Positive associations of doxorubicin dose with SBC were also published in some of the cohorts pooled in Wang et al. (2023f): the Childhood Cancer Survivor Study (Inskip et al., 2009; Veiga et al., 2019) and the Dutch Childhood Cancer Survivor Study-LATER (Teepen et al., 2017).

Cancer in experimental animals

In the previous evaluation (IARC, 1987a), there was *sufficient* evidence in experimental animals for the carcinogenicity of doxorubicin, based on studies of intravenous administration in rats (Bertazzoli et al., 1971; Solcia et al., 1978; Bucclarelli, 1981). One study has become available since the previous evaluation in 1987. A study conducted by Chun et al. (2012) showed that 20 µg of intraductal injection of doxorubicin induced mammary tumours in Her2/neu mice.

Mechanistic evidence

Doxorubicin has been reported to induce chromosomal aberrations in human leukocytes (Vig, 1971), for example, SCE in patients treated with the drug (Tucker et al., 1990). There were also reports of DNA strand breaks, chromosomal aberrations, and SCE in PBLs of patients and nurses handling the cytotoxic drugs in other studies (Nevstad, 1978; Norppa et al., 1980; Wiencke et al., 1982; Tompa et al., 2016). Human fibroblasts exposed to doxorubicin at 100 mM showed an increased frequency of DNA strand breaks and DNA crosslinks (Lambert et al., 1983).

Pommier et al. (2010) reviewed the role of doxorubicin (and other anthracyclines) as inhibitors of topoisomerase, specifically topoisomerase II (alpha and beta isoforms). Similar findings have been reported by several studies, which show that doxorubicin induces DNA damage via topoisomerase II inhibition (Lyu et al., 2007; Deng et al., 2014; Linders et al., 2024).

In a recent study by Stefanova et al. (2023), human RPE1 cells, when treated with doxorubicin, have shown DNA strand breaks, chromatin rearrangement, and topoisomerase II inhibition (Stefanova et al., 2023). Doxorubicin has been shown to be strongly mutagenic, using the Ames assay, in *Salmonella typhimurium* strains T98 and TA100 (Bhuyan et al., 1983). In mice treated with doxorubicin, dose-dependent chromatid and chromosome-type aberrations were observed (Larramendy et al., 1980).

Summary

Few epidemiological studies, of those available exploring the association between anthracyclines and cancer, were able to stratify by type of anthracycline treatment. The pooled analysis by Wang et al. (2023f) offers clear evidence of a dose–response relation for doxorubicin and breast cancer, with the ability to rule out confounding by concomitant treatment. Notably, such analyses are difficult to conduct in single cohort studies, so large cohorts are needed to disentangle the effect of each cancer therapeutic agent. The previous

evaluation of doxorubicin has been that there is *sufficient* evidence for cancer in experimental animals (IARC, 1987a). In addition, there is emerging mechanistic evidence in exposed humans, human cells, and experimental systems of genotoxic and mutagenic effects of doxorubicin, which could support a change in classification. As noted in the summary for anthracyclines as a mechanistic class (agent 070 in the present report), the Advisory Group therefore considered an *IARC Monographs* re-evaluation of doxorubicin (anthracycline) to be warranted and recommends evaluation of doxorubicin together with other anthracyclines in the same volume, as they may belong to the same mechanistic class.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

073 Epirubicin (anthracycline) (CAS No. 56420-45-2)

Current IARC/WHO classification

Epirubicin, an anthracycline, has not been previously evaluated by the *IARC Monographs* programme. Adriamycin (doxorubicin), another anthracycline, has been classified by IARC as *probably carcinogenic to humans* (Group 2A) in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a), based on *sufficient* evidence for cancer in experimental animals and *inadequate* evidence in humans; the classification had been upgraded to Group 2A on the basis of mechanistic evidence (IARC, 1987a). A priority rating of *high* was given for "some anthracyclines" by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a). Anthracyclines as a mechanistic class were nominated separately (see agent 070 in the present report).

Exposure characterization

The section on anthracyclines as a mechanistic class (agent 070 in the present report) gives further details on the use of anthracyclines. Approved by the US FDA in 1999 (Chaurasia et al., 2023), epirubicin is administered intravenously and is used to treat cancers of the breast, gastrointestinal and genitourinary tracts, sarcomas, and lymphomas (Mattioli et al., 2023). Workers may be exposed during the manufacture and handling of epirubicin. Epirubicin is also included in the US NIOSH hazardous drug list (NIOSH, 2016b).

Cancer in humans

Available studies have been conducted in cohorts of cancer survivors. Most of the studies have evaluated anthracyclines together, without separate analyses for types of anthracycline. These studies are informative for the evaluation of epirubicin, depending on the prevalence of use of epirubicin in these studies. For more details on studies of anthracyclines as a pharmaceutical class, see the section on anthracyclines as a mechanistic class (agent 070 in the present report).

Some studies have been able to stratify the analysis by the type of anthracycline. Notably, stratification by treatment type is possible only in very large studies. Large French nested case–control studies in a cohort of breast cancer survivors showed an elevated risk of MDS or AML for epirubicin use, similarly to doxorubicin and anthracyclines combined (Le Deley et al., 2007). In 7110 patients with early breast cancer, who were enrolled in a trial for adjuvant therapy with epirubicin, a higher planned epirubicin dose/cycle, a higher planned epirubicin dose intensity, and higher administered cumulative doses of epirubicin and cyclophosphamide were associated with an increased risk of AML or MDS (Praga et al., 2005).

Use (versus no use) of epirubicin was associated with an increased risk of breast cancer (HR, 3.25; 95% CI, 1.59–6.63) in a very large pooled analysis of five cohorts of childhood cancer survivors (Wang et al., 2023f).

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

No specific mechanism or ADME characteristics differ between epirubicin and other anthracyclines (Mattioli et al., 2023). There are reports of circulating epirubicin modifying inflammasomes and causing immunomodulation and cytotoxicity (Eakin et al., 2020). There have not been many studies of epirubicin specifically in animals or humans for carcinogenic mechanistic evidence.

Summary

Few epidemiological studies were able to stratify by type of anthracycline treatment to evaluate epirubicin. There is some evidence of an association of epirubicin with MDS and AML. Despite the absence of a dose–response analysis in Wang et al. (2023f), the magnitude of the risk estimates and adjustment for concomitant chemotherapy or radiotherapy offers compelling evidence of an association between epirubicin and with the risk of SBC. Notably, large cohort sizes are needed to better disentangle the effect of each cancer therapeutic agent.

There are no experimental bioassays to support epirubicin as a carcinogen and there is very sparse information on mechanism of action.

As noted in the summary for anthracyclines as a mechanistic class (agent 070 in the present report), the Advisory Group therefore considered an *IARC Monographs* evaluation of epirubicin (anthracycline) to be warranted and recommends an evaluation of epirubicin and other anthracyclines (doxorubicin and daunorubicin) in the same volume, as they may belong to the same mechanistic class.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

074 Textured implants

Current IARC/WHO classification

Breast implants made of silicone have been evaluated as *not classifiable as to its carcinogenicity to humans* (Group 3) in *IARC Monographs* Volume 74 in 1999 (IARC, 1999a), based on *evidence suggesting lack of carcinogenicity* of breast implants made of silicone in humans for female breast cancer, and *inadequate* evidence in experimental animals regarding the carcinogenicity of breast implants made of silicone. Textured breast implants were given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), based on emerging findings of anaplastic large-cell lymphoma (a rare malignancy) in patients receiving these implants.

Exposure characterization

Breast (mammary) implants are used in breast augmentation, as well as reconstruction after mastectomy (Pittet et al., 2005). These medical devices differ in the compositions of their shells (e.g. silicone or other) and fillers (e.g. gel or saline) and in their textures (e.g. smooth, modified, coated) (Bondurant et al., 2000). Foreign substances have been used to augment or reconstruct the breast for over 100 years, and silicone breast implants were introduced in the early 1960s (Bondurant et al., 2000). The use of textured breast implants peaked in 2016 in the USA (16%) and then declined to 0% in 2021 (Stein et al., 2023); in contrast, textured implants are still widely used in Sweden (84%) (BRIMP, 2020).

Breast augmentation is the most common cosmetic surgical procedure in women, with more than 2.2 million procedures in 2022 (ISAPS, 2022). Their use is widespread around the world, including in middle-income countries, such as Brazil, but there is a lack of high-quality data to formally estimate prevalences and trends (Jalalabadi et al., 2021). In the UK, a newly established Breast and Cosmetic Implant Registry recorded more than 20 000 patients as having at least one breast implant operation between October 2016 and June 2018 (NHS England, 2018). A Dutch registry was established in 2015, with more than 38 000

implants in 18 000 women recorded (Becherer et al., 2019), and data from four national breast implant registries including 207 189 implants are also now available (Becherer et al., 2023).

Cancer in humans

In 1997, a case of a rare malignancy – anaplastic large-cell lymphoma (ALCL) – was reported adjacent to a breast implant in a survivor of breast cancer. In 2016, the WHO Classification of Tumours programme labelled this new variant breast implant associated ALCL (BIA-ALCL), with specific diagnostic criteria (Alaggio et al., 2022). As of 30 June 2023, the US FDA has received 1264 reports of BIA-ALCL, with approximately half coming from the USA and half from outside the USA (US FDA, 2023a). While still very rare, the incidence of BIA-ALCL is reported to be increasing in several countries, including the USA (Kinslow et al., 2022a, b) and Australia and New Zealand (Magnusson et al., 2019).

In a Dutch case–control study of 11 cases of breast ALCL and 35 matched controls with other types of lymphoma the OR for breast implants was 18.2 (95% CI, 2.1–156.8) (de Jong et al., 2008). Wang et al. (2016) subsequently reported an 11-fold increased risk of ALCL in women with breast implants in the prospective California Teachers Study, based on 2 cases, compared with 10 cases in those without implants. In an expanded Dutch registry study in 2018, based on 43 cases of breast ALCL, 32 were found from medical records to have ipsilateral breast implants, resulting in an OR of 421.8 (95% CI, 52.6–3385.2) (de Boer et al., 2018). Of note, almost all cases had arisen in conjunction with a textured implant, as opposed to a smooth type of implant, despite the substantially greater number of smooth implant types in current use. The average interval between implant placement and diagnosis was estimated to be 10 years. The 2019 Advisory Group on Priorities also noted emerging case reports for gluteal (buttock) implants (e.g. Shauly et al., 2019), which may warrant a broadening of this agent to consider cosmetic implants more generally.

Cancer in experimental animals

Early tumour initiation and promotion studies in rodents had reported that implants of various materials can induce carcinogenesis, specifically fibrosarcoma, through foreign-body carcinogenesis (Moizhess and Vasiliev, 1989); however, these studies were limited to body implants. In another study, James et al. (1997) reported that two different forms (gel or elastomer) of silicone implant induce fibrosarcoma in rats. Full carcinogenicity studies in rodents for textured implants since the previous IARC evaluation were not available to the Advisory Group.

Mechanistic evidence

Studies related to some KCs are available. Specifically, chronic inflammation involving enhanced cytokine production (CD30, IL-10, IL-13) has been considered as an important mechanism in exposed humans (see e.g. Bizjak et al., 2015; Kadin et al., 2020; Hu et al., 2023). Alterations in the Janus kinase signal transducer and activator of transcription 3 (JAK-STAT3) pathway associated with cell proliferation (KC10) and mutations in PI3K-Akt/mTOR and loss-of-function mutations in the *TP53* tumour suppressor gene have been suggested to play a role in carcinogenicity related to breast implants (Laurent et al., 2020; DeCoster et al., 2021).

Summary

The new human cancer data support an IARC review, as they could lead to a new classification for textured implants, including for implantation sites other than the breast. A positive initiation–promotion study reviewed by the previous Working Group in 1999 has been considered by the 2019 Advisory Group on Priorities. The new criteria of the *IARC Monographs* Preamble may lead to a new evaluation of the evidence of cancer in experimental animals.

There are also mechanistic data supporting epidemiological evidence and evaluation of silicone breast implants. Inflammation resulting in alterations in cell proliferation is considered the relevant mechanism of cancer caused by silicone breast implants.

The Advisory Group therefore considered an *IARC Monographs* evaluation to be warranted and recommended focusing an evaluation only on the textured type of implant, but expanding the evaluation to sites of implantation beyond the breast (e.g. buttocks); thus, the proposed evaluation would be for textured implants.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

075 BRAF inhibitors – dabrafenib (CAS No. 1195768-06-9)

Current IARC/WHO classification

Dabrafenib has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Dabrafenib is an inhibitor of BRAF (B-Raf proto-oncogene, serine/threonine kinase, or v-raf murine sarcoma viral oncogene homologue B1). It is a protein kinase involved in cell signalling pathways and plays a critical role in transmitting signals within the cell. It is a standard treatment option for patients with metastatic melanoma harbouring a V600 mutation, which occurs in 60% of melanomas (Chen et al., 2019b). Combination with anti-MAPK kinase (MEK) agents (trametinib) has become a standard of care, as this combination is thought to reduce the risk of secondary skin cancer (Dhillon, 2016; Gouda and Subbiah, 2023a). The US FDA approved a combination of dabrafenib and trametinib for melanoma (adult, stage III, with V600 mutation), non-small cell lung cancer, anaplastic thyroid carcinoma, and low-grade paediatric glioma; moreover, this US FDA approval was extended in 2023 to adults and paediatric patients with unresectable or metastatic solid tumours with BRAF V600E mutation as a tissue-agnostic indication (Gouda and Subbiah, 2023a). Workers may be exposed during the manufacture and handling of dabrafenib, but no studies could be identified. Dabrafenib is included in the US NIOSH hazardous drug list (NIOSH, 2016b).

Cancer in humans

The cutaneous toxicity profile of dabrafenib, including the risk of cutaneous SCC, is well known from clinical trial observations. In a recent meta-analysis, the overall prevalence of cutaneous SCC in patients receiving monotherapy of dabrafenib was 16% (95% CI, 11–24%) and that in patients receiving dabrafenib in combination with trametinib was 10% (95% CI, 4–22%) (Peng and Jie-Xin, 2021). A meta-RR including studies comparing combination therapy against monotherapy gave a RR of 0.4 (95% CI, 0.18–0.89), indicating that the combined therapy reduced the risk of cutaneous SCC, compared with monotherapy (Peng and Jie-Xin, 2021).

Genotyping studies of cutaneous SCC or other skin cancers that developed in patients treated with BRAF inhibitors have shown a distinct mutational profile in tumours that developed in patients treated with BRAF inhibitors (Oberholzer et al., 2012; Su et al., 2012; Boussemart et al., 2016). These observations have supported the hypothesis of a molecular mechanism involving a paradoxical activation of MAPK signalling. Indeed, the combination with anti-MEK agents (e.g. trametinib) has become the standard of care; however, it remains unclear whether this combination is truly effective in preventing skin cancer (Larkin et al., 2014; Boussemart et al., 2016; Gouda and Subbiah, 2023a).

Cancer in experimental animals

No cancer bioassays were identified that assessed the induction of cancer after in vivo treatment with dabrafenib. Grigore et al. (2020) developed a transgenic mouse model for melanoma, which allows for the

temporal control of mutant BRAF expression with doxycycline and is able to mimic human BRAF-inhibition induced cancers. This has been used to study the mechanisms of cancers after BRAF inhibition (Grigore et al., 2020).

Mechanistic evidence

Mutations in the BRAF gene, resulting in uncontrolled cell proliferation, are commonly observed in melanomas. Dabrafenib is an inhibitor of BRAF serine-threonine kinase, which can inhibit mutated BRAF kinase-driven cell proliferation. Resistance to dabrafenib (and other BRAF inhibitors) and paradoxical activation of the RAF/MEK/ERK pathway, resulting in oncogenesis, is a phenomenon that has been studied in experimental systems (Kakadia et al., 2018). The available studies are largely focused on elucidating the genetic or epigenetic mechanisms related to BRAF-inhibitor resistance formation and paradoxical oncogenesis (e.g. Grigore et al., 2020) and include both studies in experimental systems (e.g. Grigore et al., 2020; Jandova and Wondrak, 2022) and the mutational profiling of human cancers observed after treatment with BRAF inhibitors (Oberholzer et al., 2012; Su et al., 2012; Boussemart et al., 2016). Dabrafenib is also known to have photosensitizing properties. According to a drug safety evaluation report by the European Medicines Agency (EMA), dabrafenib is not genotoxic (European Medicines Agency, 2024a).

Summary

The evidence of cutaneous SCC induced by dabrafenib in human cancer studies is based on its high prevalence, as reported in clinical trials and on distinct mutational patterns observed in studies of BRAF inhibitors. Given the available information, including mechanistic data supporting findings in humans, the Advisory Group therefore considered an *IARC Monographs* evaluation of dabrafenib to be warranted. The Advisory Group recommends evaluating dabrafenib, encorafenib, and vemurafenib together in the same volume.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

076 BRAF inhibitors – encorafenib (CAS No. 1269440-17-6)

Current IARC/WHO classification

Encorafenib has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Encorafenib is a second-generation BRAF inhibitor, approved for patients with metastatic melanoma harbouring a V600 mutation, which occurs in 60% of melanomas (Chen et al., 2019b; Carr et al., 2020). The US FDA approved a combination of encorafenib and binimetinib for melanoma in 2018 (Shirley, 2018). Combination with anti-MEK agents (e.g. binimetinib) has become a standard of care, because BRAF-inhibitor monotherapy has been linked with oncogenic activity, owing to the MAPK paradoxical activation pathway; therefore, combination with anti-MEK agents is thought to reduce the risk of secondary skin cancer (Gouda and Subbiah, 2023b). Workers may be exposed during the manufacture and handling of encorafenib, but no studies were available to the Advisory Group.

Cancer in humans

Cases of cutaneous SCC were seen in patients treated with encorafenib in clinical trials (Hauschild et al., 2012; Carr et al., 2020), similar to observations for other BRAF inhibitors, such as dabrafenib and vemurafenib (agents 075 and 077 in the present report) (Chen et al., 2019b; Peng and Jie-Xin, 2021). Genotyping studies of cutaneous SCC or other skin cancers that developed in patients treated with BRAF inhibitors have shown a distinct mutational profile in tumours that developed in patients treated with BRAF

inhibitors, supporting a molecular mechanism involving a paradoxical activation of MAPK signalling (Oberholzer et al., 2012; Su et al., 2012; Boussemart et al., 2016), as discussed below. For this reason, the combination with anti-MEK agents has become the standard of care in patients treated with BRAF inhibitors; however, it remains unclear whether this combination is truly effective in preventing skin cancer (Larkin et al., 2014; Boussemart et al., 2016; Gouda and Subbiah, 2023b).

Cancer in experimental animals

No cancer bioassays to assess the induction of cancer after in vivo treatment with encorafenib were available to the Advisory Group. Grigore et al. (2020) developed a transgenic mouse model for melanoma, which allows for the temporal control of mutant BRAF expression with doxycycline and is able to mimic human BRAF-inhibition induced cancers. This has been used to study the mechanisms of cancers after BRAF inhibition (Grigore et al., 2020).

Mechanistic evidence

Mutations in the BRAF gene, resulting in uncontrolled cell proliferation, are commonly observed in melanomas. Encorafenib is an inhibitor of BRAF serine-threonine kinase, which can inhibit mutated BRAF kinase-driven cell proliferation. Resistance to encorafenib (and other BRAF inhibitors) and paradoxical activation of the RAF/MEK/ERK pathway, resulting in oncogenesis, is a phenomenon that has been studied in experimental systems (Kakadia et al., 2018). The available studies are largely focused on elucidating the genetic or epigenetic mechanisms related to BRAF-inhibitor resistance formation and paradoxical oncogenesis and include both studies in experimental systems (e.g. Grigore et al., 2020; Jandova and Wondrak, 2022) and the mutational profiling of human cancers observed after treatment with BRAF inhibitors (Oberholzer et al., 2012; Su et al., 2012; Boussemart et al., 2016). Encorafenib is also known to have photosensitizing properties. According to EMA's drug safety evaluation report, encorafenib is not genotoxic (European Medicines Agency, 2024b).

Summary

The evidence of SCC induced by encorafenib in human cancer studies is based on the high prevalence of cutaneous SCC reported in clinical trials and on the results of mutational profile studies on BRAF inhibitors. Given the available information on human cancer and mechanistic evidence, the Advisory Group therefore considered an *IARC Monographs* evaluation of encorafenib to be warranted. The Advisory Group recommends evaluating dabrafenib, encorafenib, and vemurafenib in the same *Monographs* volume.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

077 BRAF inhibitors – vemurafenib (CAS No. 918504-65-1)

Current IARC/WHO classification

Vemurafenib has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Vemurafenib is a BRAF inhibitor, and a standard treatment option for patients with metastatic melanoma harbouring a V600E mutation, which occurs in 60% of melanomas (Chen et al., 2019b). Patients with melanoma receiving BRAF inhibitors are treated in combination with anti-MEK agents (e.g. cobimetinib) as a standard of care, because BRAF-inhibitor monotherapy has been linked with oncogenic activity, owing to the MAPK paradoxical activation pathway; therefore, combination with anti-MEK agents is thought to reduce risk of secondary skin cancer (Gouda and Subbiah, 2023a). Vemurafenib is currently being considered for treatment for other cancers (e.g. cancers of the breast or prostate or urothelial cancer) (Chen

et al., 2019b). It was approved by the US FDA in 2011 (Kim and Cohen, 2016). Workers may be exposed during the manufacture and handling of vemurafenib, but no studies could be identified. Vemurafenib is included in the US NIOSH hazardous drug list (NIOSH, 2016b).

Cancer in humans

The development of cutaneous SCC is a well-documented secondary effect in clinical trials of vemurafenib (Kim and Cohen, 2016). A recent meta-analysis estimated the overall prevalence across vemurafenib trials for the development of cutaneous SCC to be 18% (95% CI, 12–26%) (Chen et al., 2019b). After drug approval, a multicentre international observational study began to test the efficacy of the drug in clinical practice (44 countries, $n = 3226$); 12% of patients developed cutaneous SCC after beginning treatment with vemurafenib, within a median period of 2.6 months (Kim and Cohen, 2016). Also, three cases of cutaneous T-cell lymphoma were recorded (Kim and Cohen, 2016).

Because of the observed increased risk of cutaneous SCC, which is hypothesized to be due to an MAPK paradoxical activation pathway, combination with anti-MEK agents has become the standard of care; however, it remains unclear whether this combination is truly effective in preventing skin cancer (Larkin et al., 2014; Boussemart et al., 2016; Gouda and Subbiah, 2023a).

Genotyping studies of cutaneous SCC or other skin cancers that developed in patients treated with BRAF inhibitors have shown a distinct mutational profile in tumours that developed in patients treated with BRAF inhibitors, supporting the hypothesis of a molecular mechanism involving a paradoxical activation of MAPK signalling (Oberholzer et al., 2012; Su et al., 2012; Boussemart et al., 2016).

Cancer in experimental animals

No cancer bioassays to assess the induction of cancer after in vivo treatment with vemurafenib were available to the Advisory Group. Grigore et al. (2020) developed a transgenic mouse model for melanoma, which allows for the temporal control of mutant BRAF expression with doxycycline and is able to mimic human BRAF-inhibition induced cancers. This has been used to study the mechanisms of cancers after BRAF inhibition (Grigore et al., 2020).

Mechanistic evidence

Mutations in the BRAF gene, resulting in uncontrolled cell proliferation, are commonly observed in melanomas. Vemurafenib is an inhibitor of BRAF serine-threonine kinase, which can inhibit mutated BRAF kinase-driven cell proliferation. Resistance to vemurafenib (and other BRAF inhibitors) and paradoxical activation of the RAF/MEK/ERK pathway resulting in oncogenesis is a phenomenon that has been studied in experimental systems (Kakadia et al., 2018). The available studies are largely focused on elucidating the genetic or epigenetic mechanisms related to BRAF-inhibitor resistance formation and paradoxical oncogenesis and include both studies in experimental systems (e.g. Grigore et al., 2020; Jandova and Wondrak, 2022) and the mutational profiling of human cancers observed after treatment with BRAF inhibitors (Oberholzer et al., 2012; Su et al., 2012; Boussemart et al., 2016). In a recent study by Jandova and Wondrak (2022), enhancement of tumorigenesis and metastasis after treatment with vemurafenib was seen in BRAFV600E/NRASQ61K-recipient mice injected intracardially with A375 melanoma cells.

Vemurafenib is also known to have photosensitizing properties (Kim and Cohen, 2016). According to the EMA's drug safety evaluation report, vemurafenib is not genotoxic (European Medicines Agency, 2024c).

Summary

The evidence of cutaneous SCC induced by vemurafenib in human cancer studies is based on its high prevalence, as reported in clinical trials and on observations of distinct mutational profiles. Given the available information on cancer in humans and mechanistic evidence, the Advisory Group considered an

IARC Monographs evaluation of vemurafenib to be warranted. The Advisory Group recommends evaluating dabrafenib, encorafenib, and vemurafenib in the same *Monographs* volume.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

078 Tetracycline (CAS No. 60-54-8)

Current IARC/WHO classification

Tetracycline has not previously been evaluated by the *IARC Monographs* programme. Tetracyclines and other photosensitizing drugs, as a group, were given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), based on findings from cancer in human studies and mechanistic evidence of photosensitivity.

Exposure characterization

Tetracycline is one of the most-used of the broader class of tetracycline antibiotics. They are widely used for the treatment of many infectious diseases, off-label to treat *Helicobacter pylori* infections, and as a sclerosing agent for pleurodesis (Shutter and Akhondi, 2023). They are also used in the treatment of acne and skin conditions, resulting in potential longer-term exposure. Tetracycline is listed in the WHO Model List of Essential Medicines (WHO, 2023b). Workers may also be exposed during the manufacture or handling of tetracycline.

Cancer in humans

Typically, epidemiological studies have focused on the class of tetracyclines, rather than tetracycline per se. As noted by the 2019 Advisory Group on Priorities (IARC, 2019a), a large study combining three US cohorts (Nurses' Health Study, Nurses' Health Study 2, Health Professionals Follow-Up Study) showed an association between self-reported use of tetracycline (the drug) and non-melanoma skin cancer (NMSC) in the three cohorts (Li et al., 2018). In another study, an association was found between the class of tetracyclines and NMSC in a nationwide record-linkage study in Denmark (Kaae et al., 2010). Another US-based case–control study provides additional evidence for BCC, especially early-onset BCC, with exposure to the class of tetracyclines (Robinson et al., 2013). No additional studies addressing the risk of skin cancer were found.

Tetracyclines have been evaluated for their association with colon cancer, under the hypothesis that an alteration of the microbiome can induce cancer; however, results were null (Zhang et al., 2019b; Murphy et al., 2023). Some positive results for an association for the class of tetracyclines with breast cancer were reported (Friedman et al., 2006; Simin et al., 2020); however, there is evidence of potential confounding by indication (Velicer et al., 2004), because tetracyclines are used to treat rosacea, which is suspected to indicate a predisposition to an increased risk of breast cancer, owing to alterations in sex hormonal levels and chronic inflammatory status (Long et al., 2019; Velicer et al., 2004). The indication of tetracyclines to treat skin disorders may also challenge the interpretation of findings for NMSC.

Cancer in experimental animals

A feeding study of tetracycline hydrochloride in male and female rats and mice, conducted by the US NTP, was negative (NTP, 1989a).

Mechanistic evidence

Tetracycline is known to induce photosensitivity and increase the vulnerability of the epidermis and dermis to damage induced by UV radiation (Blakely et al., 2019). Tetracycline was found to inhibit mitochondrial function, leading to decreased mitochondrial translation and adenosine triphosphate (ATP)

production via oxidative phosphorylation, increased levels of $NADH^+$ and mitochondrial ROS in $CD4^+$ T cells, and $CD4^+$ T-cell proliferation (Franz et al., 2022). Tetracycline induced oxidative stress, liver injury, mitochondrial cristae and rough endoplasmic reticulum swelling, and early apoptosis in HL-7702 liver cells (Liu et al., 2019). In addition, tetracycline treatment induced significantly higher levels of expression of caspases CASP3 and CASP9 (pro-apoptosis), SOD3 and GPX3 (antioxidant enzymes), and transforming growth factor alpha (TGFA) and IL1B (inflammatory) genes in human retinal MIO-M1 cells (Salimiaghdam et al., 2022). The expression of antioxidant indices and immune-related genes was suppressed in zebrafish exposed to oxytetracycline (5 mg/L) for 48 hours (Yu et al., 2019b). Exposure to tetracycline activated the NF-κB pathway and induced an NF-κB-mediated immune response in fish primary macrophages, showing elevated endogenous ROS generation, antioxidant enzyme activity, and cytokine expression (Qiu et al., 2020). Moreover, a significant reduction in the percentage of T lymphocytes and the key cytotoxic and T helper subpopulations, and elevation of the absolute number of leukocytes (especially lymphocytes, but also granulocytes and monocytes) were found in tetracycline-treated mice (Grabowski et al., 2023). The hepatic gene expression involved in lipid transport (e.g. APOA4 and FABP11) and lipogenic factors (e.g. PPAR) was significantly upregulated in the livers of tetracycline-exposed zebrafish (Keerthisinghe et al., 2020).

Summary

A few large studies have shown an increased risk of NMSC or BCC associated with tetracycline exposure; however, these are mainly based on self-reported information or on exposure to the class of tetracyclines. Positive findings have been reported regarding exposure to the class of tetracyclines and breast cancer; however, concerns exist on confounding by indication. Negative results regarding cancer in experimental animals were reported. There is evidence that tetracycline exhibits KCs in human primary cells or experimental systems, in particular, the induction of oxidative stress and chronic inflammation, immunosuppression, modulation of receptor-mediated effects, and alterations of cell proliferation or cell death.

The human cancer data available are for tetracyclines as a pharmaceutical class, while the mechanistic evidence is for the drug tetracycline. The Advisory Group therefore considered an *IARC Monographs* evaluation of tetracycline to be warranted and recommends the evaluation of tetracycline alone, based on the available evidence.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

079 Carbadox (CAS No. 6804-07-5)

Current IARC/WHO classification

Carbadox has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Carbadox (methyl (2*E*)-2-[(1,4-dioxidoquinoxalin-2-yl)methylene]hydrazinecarboxylate) is used in swine as an antibacterial drug for the prevention of dysentery and enteritis and as an additive for weight gain and improved feed productivity (WHO, 2003; US FDA, 2023b). No acceptable daily intake (ADI) has been established by JECFA (WHO, 2023c). The drug and some of its metabolites have been banned for use in several countries, including the EU (EU, 1998), Australia, and Canada (WHO, 2003; PubChem, 2023; US FDA, 2023b). As of 2023, it was still available for use in the USA (US FDA, 2023b). The physical state of this drug is a crystalline powder; inhalation and ingestion have been described as routes of exposure; presumably this could result in occupational exposure for veterinary and agricultural workers, although no

specific occupational exposure data were identified (INCHEM, 2003). Carbadox has been identified in urine samples obtained for biomonitoring from children in China (Wen et al., 2023) and in surface water samples collected in the USA (Ferrey et al., 2015).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

Long-term regulatory studies were conducted in rodents (INCHEM, 2003; WHO, 2023c). In one study Stebbins and Coleman (1967), a treatment-related increase in total tumours was observed in rats exposed to increasing concentrations of carbadox (0–100 mg/kg bw per day) in the diet for 26 months. Also, carbadox exposure, in feed or intraperitoneally, induced an increased incidence of hepatic tumour in rats exposed for 1 year (Sykora and Vortel, 1986). In addition, in another long-term study in rats, the metabolite desoxycarbadox was reported to induce an increase in the incidence of tumours after 10 months exposure in the diet: the most pronounced change occurred in the liver; tumour incidence was also elevated at other sites, including the skin and mammary glands (King, 1976).

Mechanistic evidence

Positive findings were reported in several genotoxicity studies in experimental systems (INCHEM, 2003; WHO, 2023c). A study on rat liver cells (Kimura et al., 2016) indicated cell proliferation activity, expression of molecules related to the G_2 to M phase and spindle checkpoint, and apoptosis at weeks 2 and 4, and tumour promotion activity at week 6. The carcinogenicity of carbadox is related to mutagenicity (Suarez-Torres et al., 2021), genotoxicity (Liu et al., 2016b), and the induction of aberrant cell cycle regulation and apoptosis in rats (Kimura et al., 2015).

Summary

No data are available on cancer in humans. There is evidence that carbadox and its metabolite induce liver tumours in experimental animals. There is some mechanistic evidence suggesting that carbadox exhibits KCs, including genotoxicity, and alteration of cell proliferation, cell death, or nutrient supply. The Advisory Group therefore considered an *IARC Monographs* evaluation of carbadox to be warranted.

Recommendation: High (and ready for evaluation within < 2.5 years)

080 Paracetamol (acetaminophen) (CAS No. 103-90-2)

Current IARC/WHO classification

Paracetamol (also referred to as acetaminophen) has been previously evaluated by IARC as *not classifiable as to its carcinogenicity to humans* (Group 3) in *IARC Monographs* Volume 73 in 1998 (IARC, 1999b).

Exposure characterization

Paracetamol is listed as a high production volume chemical by OECD (OECD, 2007) and the US EPA (US EPA, 2024a). Paracetamol is one of the most-used analgesics and antipyretics around the world, and many countries have reported increasing sales over recent decades (e.g. Wastesson et al., 2018).

Cancer in humans

There have been many studies of paracetamol and kidney cancer, summarized most recently in a meta-analysis by Karami et al. (2016). Regular use of paracetamol was associated with a 25% increased risk of

kidney cancer in this meta-analysis of nine case–control and four cohort studies (95% CI, 10%–41%). There were increased risks for both cohort and case–control studies. There was a dose–response relation with increasing duration of use for over-the-counter paracetamol in a US kidney cancer case–control study (10 years use versus no use, OR, 2.01; 95% CI, 1.30–3.12), but no clear trend with duration in the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial cohort (although there were few long-term users) (10 years use, RR, 1.14; 95% CI, 0.65–2.01) (Karami et al., 2016). An earlier pooled analysis of case–control studies did not report a clear association, but the number of regular users was smaller at that time (McCredie et al., 1995). A smaller number of studies have evaluated the risk of liver cancer, including several cohort studies that found an increased risk for regular users, e.g. UK Biobank (Tian et al., 2024), the UK's Clinical Practice Research Datalink (Yang et al., 2016b), and a Danish cohort study (Friis et al., 2002).

Cancer in experimental animals

In the previous evaluation (IARC, 1999b), there was *inadequate* evidence in experimental animals for the carcinogenicity of paracetamol. In IF strain mice, exposure to paracetamol in the feed for 18 months significantly increased the incidence of total liver tumours in male and female mice and HCCs in male mice (Flaks and Flaks, 1983). Flaks et al. (1985) studied the induction of bladder and liver tumours by paracetamol in the feed in the rat. Paracetamol induced bladder carcinoma in three rats. A low yield of tumours at various other sites also arose after paracetamol feeding. Paracetamol was not found to be carcinogenic in male or female F344/DuCrj rats when administered in pelleted diets (Hiraga and Fujii, 1985). Hasegawa et al. (1988a) studied the tumour-initiating effect of paracetamol in two-stage liver carcinogenesis of male F344 rats. The potential liver-tumour-initiating activity of paracetamol was investigated in male F344 rats. Paracetamol was administered by intragastric intubation, either as 10 doses over 5 weeks or as a single dose 24 hours after two thirds partial hepatectomy. These initiating treatments were followed by the administration of 0.1% phenobarbital in drinking-water for 12 weeks as the promoting regimen. No tumour-initiating activity was observed in the rat liver. Paracetamol in the diet for 104 weeks in rats and mice significantly increased the incidence of mononuclear cell leukaemia in female rats but did not induce any tumours in mice (NTP, 1993).

Mechanistic evidence

Some published data show that paracetamol causes chromosomal damage in vitro in mammalian cells at high concentrations and indicate that similar effects occur in vivo at high dosages (Bergman et al., 1996). In 2019, the California Office of Environmental Health Hazard Assessment reviewed the carcinogenic hazard potential of paracetamol and concluded that there was no clear evidence that paracetamol causes DNA damage in the absence of toxicity (Kirkland et al., 2021). Experiments conducted by Flaks et al. (1985) showed that paracetamol induces foci of cellular alteration in the livers of high-dose mice of both sexes, and also in low-dose male mice, suggesting cellular proliferation. Hu et al. (2016a) studied non-toxic doses of paracetamol in mice and concluded that paracetamol could cause transient mitochondrial dysfunction that might synergize with other stresses to promote liver damage and steatosis. Xu et al. (2023a) showed that inhibitor of NF-κB kinase subunit epsilon (IKBKE)-deficient mice treated with paracetamol exhibited severe liver injury, worsened mitochondrial integrity, and enhanced GSH depletion, compared with wildtype mice.

Summary

Consistent positive associations between paracetamol (acetaminophen) use and kidney cancer were found in several well-conducted epidemiological studies, with evidence of a dose–response relation. There is also emerging epidemiological evidence for an association with liver cancer in humans. Animal studies of paracetamol showed an increased incidence of liver cancer in male and female mice and of mononuclear cell leukaemia in female rats. These new human cancer and animal studies may support a change in *IARC*

Monographs classification. The Advisory Group therefore considered an *IARC Monographs* evaluation of paracetamol (acetaminophen) to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

081 Anaesthetics (volatile): isoflurane (CAS No. 26675-46-7), sevoflurane (CAS No. 28523-86-6), desflurane (CAS No. 57041-67-5)

Current IARC/WHO classification

Anaesthetics (volatile) have been previously evaluated by IARC as *not classifiable as to its carcinogenicity in humans* (Group 3) in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a).

Exposure characterization

Isoflurane, sevoflurane, and desflurane pertain to the class of halogenated inhaled anaesthetics, used in clinical and veterinary medicine (Pokhrel and Grady, 2021). Isoflurane and sevoflurane are included in the 2023 WHO Model List of Essential Medicines (WHO, 2023b). Exposure occurs in patients and in workers (Mulvenon, 2015). In clinical and veterinary operating theatres, exposure can occur through inhalation at low concentrations (Pokhrel and Grady, 2021). Dermal exposure in occupational settings can also occur (Pokhrel and Grady, 2021).

Cancer in humans

No studies of cancer in humans evaluating risk from exposure to isoflurane, sevoflurane, and desflurane were available to the Advisory Group. Indirect evidence from studies evaluating cancer risk in medical professionals with a higher likelihood of exposure to these anaesthetics may be considered; however, there are inconsistent results across studies. Those studies are also difficult to interpret, given co-exposure in medical professions to other known or probable carcinogens (ionizing radiation, antineoplastic agents, NSW) and probable healthy worker biases (IARC, 1987a; Carpenter et al., 1997; Alexander et al., 2000; Fritschi, 2000).

Cancer in experimental animals

Male and female Swiss/Webster mice aged 8 weeks were exposed to either air ($n = 181$), 0.1% isoflurane ($n = 167$), or 0.4% isoflurane ($n = 165$), for 4 hours/day, 5 days/week, for 78 weeks. Throughout most of the study, the mean body weights of mice exposed to 0.1% isoflurane were lower by 1–5% and the mean body weights of mice exposed to 0.4% isoflurane were lower by 5–8%. There were no statistically significant differences between the groups for the number of mice with a particular tumour at a specific site, the ratio of benign to malignant tumours, or the time to tumour appearance (Baden et al., 1988).

Mechanistic evidence

Anaesthetists exposed to an 8-hour TWA of 0.2 ppm sevoflurane experienced an increase in SCE in their lymphocytes (Wiesner et al., 2008). In human lymphocytes, isoflurane and nitrous oxide produced an increase in the rate of SCE (Hoerauf et al., 1999). The levels of DNA damage in lymphocytes and bone marrow of Sprague-Dawley rats that were exposed to isoflurane were increased (Kayser et al., 2011). In addition, increased levels of γ-H2AX were observed in isoflurane-exposed mice and human neuroglioma cells (Ni et al., 2017).

Isoflurane was found to decrease histone acetylation (H3K14, H4K5, and H4K12 acetylation) in the brains of adult male C57BL/6 mice (Zhong et al., 2014), to disrupt m6A-regulated genes in the brains of male and female neonatal mice (Wu et al., 2023a), and to increase miRNA 21 in human ovarian epithelial carcinoma cell lines SKOV3 and TOV21G (Guo et al., 2017).

Sevoflurane was found to disrupt m6A-regulated genes (Wu et al., 2023a), and to alter the expression of miRNA in the liver of rats (Ishikawa et al., 2012) and in A549 cancer cells (Wang et al., 2018a).

A systematic review concluded that anaesthesia induces oxidative stress in the brains of neonatal patients (Gascoigne et al., 2022). In addition, the peripheral lymphocytes in patients exposed to sevoflurane (2%) had increased DNA damage and decreased GSH content (Lee et al., 2015). In animal studies, protein oxidation levels were significantly increased in the plasma, brains, and lungs of rats exposed to isoflurane (Kayser et al., 2011).

Isoflurane has been shown to increase ROS accumulation in H4 human neuroglioma cells and primary neurons from C57BL/6J mice (Zhang et al., 2010), mouse hippocampus neurons (Zhang et al., 2012a), and isolated rat heart mitochondria (Hirata et al., 2011).

Anaesthesia with 3% sevoflurane for 2 hours daily for 3 days induced neuroinflammation in juvenile but not adult mice (Shen et al., 2013). On postnatal day 7 (P7), littermate mouse (C57BL6/J) pups were exposed to 1.5% isoflurane in 2.5% sevoflurane for 4 hours; levels of IL-1β, IL-6, and TNFα were significantly increased at 0, 4, or 24 hours after exposure to isoflurane (Zhao et al., 2020b). Isoflurane and sevoflurane increased IL-6 and NF-κB levels in mouse microglia, but not mouse primary neurons (Zhang et al., 2013b). Treatment with 2.5% sevoflurane for 1 hour promoted mouse primary microglia polarization in the anti-inflammatory microglia/macrophage phenotype, and increased nuclear factor erythroid 2-related factor 2 (Nrf2) nuclear expression and GSK-3β phosphorylation against oxygen–glucose deprivation (Cai et al., 2021). Isoflurane reduced the levels of IL-1β, IL-6, TNFα, macrophage inflammatory protein 2 (MIP2), iNOS, and nuclear NF-κB in a mouse model of zymosan-induced inflammation (Lee et al., 2015), and also reduced brain ischaemia or reperfusion-induced NF-κB, IL-1β, and IL-6 in the ischaemic penumbral brain tissues (Li et al., 2013b).

Volatile anaesthetics have been shown to suppress innate immunity by impairing or suppressing neutrophil adhesion, monocytes, macrophages, and NK cells, and affecting resident cells in tissues, such as platelets and microglial cells. Volatile anaesthetics also suppressed adaptive immunity by decreasing the proliferation of lymphocytes such as $CD4^+$ and $CD8^+$ T cells, as well as B cells (Stollings et al., 2016). Desflurane decreased the counts of NK cells in the blood of 20 breast cancer surgery patients (Woo et al., 2015). Desflurane anaesthesia for breast cancer surgery induced an adequate immune response (Pirbudak Cocelli et al., 2012). Sevoflurane increased serum estradiol and corticosterone levels in rats (Li et al., 2020b).

Summary

Only sparse and indirect evidence from studies of cancer in humans is available. There is a lack of data on the carcinogenicity of the three anaesthetics in experimental animals. There is evidence that the three agents exhibit multiple KCs. There is available data showing genotoxicity, epigenetic alterations, oxidative stress, and immunosuppression in exposed humans, human primary cells, or experimental systems. Overall, the data available could support an evaluation of isoflurane, sevoflurane, and desflurane. The Advisory Group therefore considered an *IARC Monographs* evaluation of isoflurane, sevoflurane, and desflurane to be warranted.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

082 Methamphetamine (CAS No. 537-46-2)

Current IARC/WHO classification

Methamphetamine has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Methamphetamine is a highly potent amphetamine (INN name, amfetamine)-type stimulant (Courtney and Ray, 2014). It is approved by the US FDA for the treatment of attention deficit hyperactivity disorder (ADHD) and obesity (DEA, 2020). However, its major use is as an illicit recreational drug, with various routes of exposure (smoking, snorting, intravenous injection, peroral). Inhalation exposure may occur through smoking or in contaminated homes used for clandestine manufacture (Wright et al., 2021). Amphetamine-type stimulants are the second most common class of illicit drug used worldwide, and their use may be increasing (Courtney and Ray, 2014). Methamphetamine is probably the most widely consumed synthetic drug in the world (UNODC, 2023). Occupational exposure has been described in workers training dogs in drug detection (Stout et al., 2006).

Cancer in humans

An elevated incidence of HCC was reported in users of methamphetamine in a small study that did not adequately control for known risk factors for HCC (Si et al., 2023). In patients with HIV, amphetamine use has been linked to NHL in a single large prospective study (Chao et al., 2009), but not in other case–control studies in patients with HIV (Armenian et al., 1996; Holly and Lele, 1997).

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

An investigation in 76 long-term users of methamphetamine and 98 unexposed controls demonstrated that total methamphetamine exposure correlated with frequencies of micronucleus and SCE in cultured lymphocytes. Meanwhile, it was also found that levels of micronucleus formation in lymphocytes of methamphetamine consumers were higher than those in non-users and increased with increasing dose (Li et al., 2003). Methamphetamine caused induction of DNA damage and chromosomal aberrations in human-derived liver and buccal cells (Ropek et al., 2019).

Takemura et al. (2022) compared patients with methamphetamine dependence and healthy controls (n = 24 each) using DNA methylation profiles obtained from whole-blood samples and found that patients with methamphetamine dependency showed significant acceleration in phenotypical age and GrimAge (an estimate of biological age that is based on DNA methylation), as well as a trend for significant acceleration in DNA methylation-based telomere length (Takemura et al., 2022). Several studies documented that methamphetamine, administered at short time intervals, increases H4 acetylation (H4K5ac and H4K8ac) in the rat nucleus accumbens and striatum (Renthal et al., 2008; Martin et al., 2012; Cadet et al., 2013; Harkness et al., 2013). In addition, at the striatal level, methamphetamine-induced DNA methylation affected the gene promoters of corticosterone and glucocorticoid receptors (Numachi et al., 2004, 2007).

Methamphetamine was found to induce oxidative stress. *N*-acetylcysteine suppressed methamphetamine-induced activation of RAS/ERK1/2 pathways, leading to the arrest of HCC xenograft formation in nude mice (Si et al., 2023). Potula et al. (2010) presented evidence that methamphetamine exposure resulted in mitochondrial oxidative damage and caused dysfunction of primary human T cells. Methamphetamine treatment of T lymphocytes led to a rise in intracellular calcium levels that enhanced the generation of ROS (Potula et al., 2010). In brain endothelial cells, oxidative stress is involved in methamphetamine-induced injury of the blood–brain barrier (Ramirez et al., 2009).

Davidson et al. (2022) found that the expression of inflammatory markers was higher in the brain in methamphetamine-treated mice than in sham controls. Methamphetamine induced the expression of TNF receptor and proinflammatory cytokines (TNFα, IL-6) in the human dopaminergic neuroblastoma SH-SY5Y cell line, the murine BV2 microglial cell line, and a primary culture of rat embryo mesencephalic neurons

(Park et al., 2017). In addition, in highly aggressively proliferating immortalized (HAPI) cells, a rat microglial cell line, methamphetamine reduced cell viability in a concentration- and time-dependent manner and initiated the expression of IL-1β, IL-6, and TNFα (Tocharus et al., 2010).

Methamphetamine disrupted the immune system function, leading to the suppression of mitogen-stimulated lymphocytes, a reduction in circulating lymphocyte numbers, and alterations in T lymphocyte cytokine secretion as well as B-cell proinflammatory cytokine secretion. Kalayasiri et al. (2023) discovered that patients who used methamphetamine persistently showed a robust immunosuppressive effect for all immunological profiles in samples of peripheral blood, compared with controls (Kalayasiri et al., 2023). Mice exposed to methamphetamine had an altered G1 cell cycle phase and impaired T-cell proliferation. In addition, T-cell subsets exposed to methamphetamine showed significantly decreased expression of cyclin E, CDK2, and transcription factor E2F1, indicating that methamphetamine exposure results in altered T-cell cycle entry and progression (Potula et al., 2018).

A marked reduction of nuclear PPARγ-expressed cells was seen in the striatum 3 days after methamphetamine injections (4 mg/kg × 4, intraperitoneally at 2-hour intervals) in male BALB/c mice (Tsuji et al., 2009). Male Wistar rats who received an increasing regimen of methamphetamine (1–10 mg/kg, intraperitoneally, twice a day for 10 days) showed that methamphetamine-induced memory impairment is concomitant with decreased mRNA levels of thyroid hormone nuclear receptor α1 (TR-α1) (Tamijani et al., 2022). In addition, mice treated once daily with 1 mg/kg methamphetamine subcutaneously for seven consecutive days exhibited significantly extended escape latency in the learning phase of a maze test and reduced the number of target crossings in the memory test phase, as well as decreasing the expression of brain-derived neurotrophic factor (BDNF), N-methyl-d-aspartate (NMDA) receptors, tropomyosin receptor kinase B/tyrosine receptor kinase B (TrkB) receptors, calcium calmodulin-dependent protein kinase II (CaMKII), βIII tubulin, and synaptophysin (Veschsanit et al., 2021). Huang et al. (2022d) found that methamphetamine upregulated α-synuclein expression in neurons extended to astrocytes, thereby eliciting astrocyte activation, disrupting IL-1β, IL-6, TNFα, and glial cell line-derived neurotrophic factor (GDNF) levels by downregulating nuclear receptor-related 1 (NURR1) protein expression, and ultimately damaging the blood–brain barrier.

C57BL/6 male mice (8 weeks) treated with methamphetamine by intraperitoneal injection over a 26-day period showed evidence of hypoxia, including increased levels of hypoxia-inducible factor 1α (HIF1A) and VEGFa, and angiogenesis in the retina (Lee et al., 2021c). Chronic exposure to methamphetamine combined with brain infection by EcoHIV (a chimeric retrovirus construct) resulted in the enhanced proliferation of neural progenitor cells in the subventricular zone in male C57BL/6 mice (Park et al., 2021). Methamphetamine promoted cell viability and cell proliferation and in HUH7 cells (0.1, 1, or 10 nM) and HepG2 cells (1, 10, or 100 nM). In addition, methamphetamine inhibited apoptosis by decreasing the expression of cleaved caspase-3 (Si et al., 2023).

Summary

Regarding human cancer evidence, only sparse data exist, mainly on amphetamines. There are no studies of cancer in experimental animals. There is evidence that methamphetamine exhibits KCs, in particular, for genotoxicity, alterations in epigenetics, oxidative stress, inflammation, immunosuppression, receptor-mediated effects, and alterations of cell proliferation and cell death in exposed humans and human primary cells and experimental systems. Overall, given the available data, the Advisory Group considered an *IARC Monographs* evaluation of methamphetamines to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

083 Reversible AChE inhibitors, such as rivastigmine, donepezil, and galantamine

Current IARC/WHO classification

Reversible acetylcholinesterase (AChE) inhibitors, such as rivastigmine, donepezil, and galantamine, have not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Reversible AChE inhibitors, such as rivastigmine, donepezil, and galantamine, are used to treat Alzheimer and Parkinson diseases (Colović et al., 2013). Data from Spain showed that rivastigmine is the most commonly used treatment for Alzheimer disease (37%) (including in new patients, 46%), followed by donepezil and memantine (Olazarán et al., 2023).

AChE is an enzyme associated with the cholinergic signal system; its classic role is to remove acetylcholine from acetylcholine receptors. Excessive activity of AChE causes different neuronal problems, especially dementia and neuronal cell death (Joe and Ringman, 2019). The US FDA has approved donepezil, rivastigmine, tacrine, and galantamine for the treatment of Alzheimer disease.

Cancer in humans

In a matched cohort study of 116 106 users of AChE inhibitors and 348 318 controls in the Longitudinal Health Insurance Database, in Taiwan, China, the reported HR for lung cancer was 1.198 (95% CI, 0.765–1.774; $P = 0.167$); among patients aged ≥ 65 the HR was 1.498 (95% CI, 1.124–1.798; $P < 0.001$) (Liu et al., 2022d).

Cancer in experimental animals

Song et al. (2003) demonstrated the role of acetylcholine in the growth of lung cancer cell xenografts in nude mice. No specific animal carcinogenicity data on rivastigmine, donepezil, or galantamine were available to the Advisory Group (Colović et al., 2013).

Mechanistic evidence

No relevant mechanistic evidence associated with the KCs was identified.

Summary

Currently, the association between AChE and cancer risk in humans has only been explored in one study, and there are minimal data on cancer in experimental animals and mechanistic evidence. Overall, the evidence does not support an evaluation by IARC. The Advisory Group therefore considered that an *IARC Monographs* evaluation of reversible acetylcholinesterase (AChE) inhibitors, such as rivastigmine, donepezil, and galantamine, is unwarranted at present

Recommendation: No priority

084 Tofacitinib (CAS No. 540737-29-9) and other Janus kinase inhibitors

Current IARC/WHO classification

Tofacitinib and other Janus kinase (JAK) inhibitors have not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Tofacitinib is a targeted synthetic disease-modifying antirheumatic drug that inhibits JAK. It is US FDA-approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and polyarticular juvenile idiopathic arthritis (Padda et al., 2023). The drug is also approved by EMA (Hoisnard et al., 2022). The drug is included in the US NIOSH list of hazardous drugs (NIOSH, 2016b).

Cancer in humans

The US FDA box warning for cancer events for tofacitinib was motivated by the results of the Oral Rheumatoid Arthritis Trial (ORAL) surveillance, an industry-sponsored trial (Ytterberg et al., 2022a). Observation of cancer, including lymphoma, in clinical trials was reported as a rationale for the conduct of the trial. The ORAL surveillance was a randomized, post-authorization, noninferiority trial that aimed to test the hypothesis that the risk of major events (including cancer) would not be at least 1.8× higher with tofacitinib (at doses of 5 mg or 10 mg), compared with TNF inhibitors. During a median follow-up of 4 years, the use of tofacitinib at any dosage was associated with an increased risk of any cancer (excluding NMSC) (HR, 1.48; 95% CI, 1.04–2.09), compared with TNF inhibitors. NMSC was a secondary end-point, and its incidence was found to be higher, compared with TNF inhibitors, in the groups receiving 5 mg (HR, 1.90) and 10 mg (HR, 2.16) doses of tofacitinib. There was no analysis by other cancer types. However, in response to a letter to the journal editor highlighting the importance of publishing results for lymphomas, the incidence rate for lymphoma was reported for each group (0.07 for tofacitinib at 5 mg, 0.11 for tofacitinib at 10 mg, and 0.02 for TNF inhibitors, without specifying the time period, although it may be inferred as over the entire 5.5 years of the trial period) (Ytterberg et al., 2022b).

An increased risk of overall cancer has not been consistently reported in clinical trials of JAK inhibitors; however, there is heterogeneity across trials in terms of comparators, and most of the trials have limited follow-up or sample size (Russell et al., 2023).

An industry-funded analysis of the WHO pharmacovigilance data (VigiBase) showed that adverse event reporting for skin neoplasms and leukaemias were significantly increased for several JAK inhibitors (Hoisnard et al., 2022). Also, an analysis of the US FDA adverse reporting system and another analysis of VigiBase has shown increased reporting of NMSC, melanoma, and MCC for tofacitinib and other JAK inhibitors (Jalles et al., 2022; Liu et al., 2023b). Concern over the interpretation of these findings relates to confounding by indication, as patients with rheumatoid arthritis are known to be at increased risk of lymphomas or melanomas (Smedby et al., 2006; Simon et al., 2015).

Cancer in experimental animals

Tofacitinib was found to increase hibernoma in a dose-dependent manner in female rats at a dose range of 30–100 mg/kg per day (Radi et al., 2013).

Mechanistic evidence

The available evidence suggests that tofacitinib is not genotoxic. It showed negative results in various assays, including the Ames bacterial reverse mutation assay, the in vitro gene mutation assay in CHO/HGPRT assay, the in vivo rat micronucleus assay, and the in vivo rat hepatocyte UDS assay. Joustra et al. (2024) conducted epigenome-wide (DNA methylome) profiling of peripheral blood cells of patients with moderate to severe ulcerative colitis who had been treated with tofacitinib and found a tofacitinib-specific epigenetic signature, suggesting potential epigenetic mechanisms underlying cancer risk.

JAK inhibition disrupted T cell-induced macrophage activation and reduced downstream proinflammatory cytokine and chemokine responses in $CD14^+$ monocytes and $CD4^+$ T cells (Nyirenda et al., 2023). In primary bone marrow-derived macrophages, the selective JAK inhibitor ruxolitinib increased TNF, IL-6, and IL-12 secretion when stimulated with LPS. This effect was primarily attributed to an ability

to block IL-10–mediated feedback inhibition on cytokine transcription in macrophages (Pattison et al., 2012).

Adult cynomolgus monkeys developed lymphomas, including two B-cell lymphomas associated with LCV, probably linked to the immunomodulatory properties of tofacitinib and reduced immune surveillance of virally infected cells (T cells, NK cells). No lymphomas were observed in juvenile monkeys (Collinge et al., 2018).

Tofacitinib treatment in amyotrophic lateral sclerosis NK cells reduced TNFα and IFNγ expression. A similar effect was observed in control NK cells (Figueroa-Romero et al., 2022). In mice, tofacitinib decreased $CD127^+$ pro-B-cells, impaired germinal centre B-cell formation, and reduced germinal centre numbers (Onda et al., 2014). In a mouse model of systemic sclerosis, tofacitinib suppressed adaptive and innate immune responses, reducing splenocytes, total lymphocytes, $CD4^+$ T helper cells (especially Th2 and Th17 subtypes), IL-6-producing B-cells, and dendritic cells in the spleen. It also decreased macrophage infiltration in the skin and lungs (Aung et al., 2021). Tofacitinib exposure might impair NK cell activation and lymphoma cell killing efficacy by reducing degranulation and cytokine secretion capacity (Nocturne et al., 2020). In addition, there is evidence that tofacitinib increases herpes zoster infection in humans (Winthrop et al., 2018; Olivera et al., 2020)

In PBMCs, tofacitinib reduced IFNγ production, proliferation, activation, and CXCR3 expression of varicella zoster virus (VZV) specific $CD4^+$ T cells in a dose-dependent manner (Almanzar et al., 2019). The drug also induced apoptosis in plasmacytoid dendritic cells (PDCs), inhibited IFNα production by toll-like receptor (TLR)-stimulated PDCs, and counteracted the suppressive effects of IFNα on viral replication (Boor et al., 2017). In human PBMCs, tofacitinib decreased lymphocyte activation and proliferation, leading to a relative reduction in NK cells, B-cells, and CD8 T cells, compared with CD4 T cells (Piscianz et al., 2014).

Summary

Regarding human cancer studies, clinical trials or pharmacovigilance studies are available; however, they mainly focus on overall cancer as the outcome. Despite this, reporting of increases in NMSC seems consistent across the available studies. There is a lack of studies assessing the risk of lymphoma, and little information is available in the literature.

There are animal cancer bioassays showing that tofacitinib increases hibernoma in female rats. Mechanistic evidence from animal models showed the development of lymphomas in adult cynomolgus monkeys, and of increased lung cancer metastasis in an experimental lung metastasis mouse model of colon cancer.

There is evidence that tofacitinib exhibits KCs, in particular for epigenetic alterations and immunosuppression, in exposed humans, human primary cells, or experimental systems.

The available data could support an evaluation of tofacitinib and perhaps other JAK inhibitors. The Advisory Group therefore considered an *IARC Monographs* evaluation of tofacitinib and other JAK inhibitors to be warranted.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

085 Alefacept (CAS No. 222535-22-0)

Current IARC/WHO classification

Alefacept has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Alefacept is a genetically engineered immunosuppressant for the treatment of moderate to severe chronic plaque psoriasis. It received US FDA approval in 2003, but the production of intramuscular alefacept has been discontinued, and the drug was not approved in the EU (AdisInsight, 2023). Alefacept is included in the US NIOSH hazardous drug list (NIOSH, 2016b). The manufacturers withdrew this drug from the market in 2011 (LiverTox, 2021; DrugBank Online, 2024a).

Cancer in humans

There are several case reports of lymphoma after the use of drugs in this category, but only one case was reported specifically after the use of alefacept (Dommasch and Gelfand, 2009). There are no formal epidemiological studies, but some cancers were reported as adverse events in clinical trials (Goffe et al., 2005).

Cancer in experimental animals

In a chronic toxicity study, cynomolgus monkeys were given intravenous injections of alefacept weekly for 52 weeks. After 28 weeks, one animal in the high-dose group developed a B-cell lymphoma (Vahle et al., 2010).

Mechanistic evidence

Cynomolgus monkeys developed B-cell hyperplasia of the spleen and lymph nodes after having received alefacept for 28 weeks. There was no evidence of alefacept-related lymphoma or B-cell hyperplasia in any of the remaining treated monkeys 1 year after treatment (Vahle et al., 2010).

The lymphocyte function associated antigen 3 (LFA-3) portion of alefacept binds to the cluster of differentiation 2 (CD2) receptor on the T lymphocytes, thereby blocking the interaction between LFA-3 and CD2. This, in turn, inhibits T cell activation and results in immunosuppression. In addition, the FcγRIII IgG portion of alefacept binds to the FcγRIII IgG receptors on NK cells and macrophages, resulting in T-cell apoptosis (Hodak and David, 2004). Numbers of epidermal T cells ($CD3^+$) and dermal T cells decreased after 2, 6, or 13 weeks of alefacept treatment in 12 patients with psoriasis. At 13 weeks after alefacept treatment in 12 patients with psoriasis, key inflammatories IL-23 and iNOS and chemokines MIG (monokine induced by IFNγ) and IL-8 decreased (Chamian et al., 2005). Treatment with alefacept for 12 weeks in 229 patients with psoriasis reduced counts of effector memory T lymphocytes and peripheral blood effector memory T lymphocytes ($CD45RO^+$) (Ellis and Krueger, 2001). Of 16 patients with psoriasis who received alefacept 7.5 mg once weekly for 12 weeks, the numbers of NK T cells were reduced significantly, while no statistically significant changes occurred in NK cells or $CD4^{(+)}$ $CD25^{(high)}$ cells (Larsen et al., 2007).

Summary

The only human cancer evidence consists of a few case reports of cancers in patients in clinical trials. There are no carcinogenicity data in experimental animals. There is evidence that alefacept exhibits KCs for immunosuppression in exposed humans and human primary cells. While the available mechanistic evidence could support a classification of alefacept by an *IARC Monographs* Working Group, the Advisory Group noted there is no evidence of exposure occurring in humans because the production of this drug has ceased. The Advisory Group therefore considered that an *IARC Monographs* evaluation of alefacept is unwarranted at present.

Recommendation: No priority

086 Anti-thymocyte globulin

Current IARC/WHO classification

Anti-thymocyte globulin (ATG) has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

ATG is an infusion of horse or rabbit-derived antibodies used to remove functional T cells to induce a nonspecific immunosuppression. Standard clinical indications are the treatment of severe aplastic anaemia or prophylaxis of graft-versus-host disease after an allogenic bone marrow transplant (Siddiqui et al., 2019). ATG is also used in induction in solid transplants, with the aim of delaying the use of calcineurin inhibitors (Ruan et al., 2017). This indication was approved for renal transplant by the US FDA in 1998, but ATG is commonly used off-label for heart transplants (Ruan et al., 2017).

Cancer in humans

Several follow-up studies of patients with aplastic anaemia who underwent ATG immunosuppression report an increased incidence of mainly haematological malignancies; however, they do not account for potential subsequent treatment with haematopoietic stem cell transplantation (HSCT), which is recommended after the failure of ATG immunosuppression in those patients (Socié et al., 1993, Frickhofen et al., 2003). A study in 93 patients, which censored patients undergoing HSCT, found an SIR for myeloid malignancies of 46.7 (95% CI, 35.2–103.6) and an SIR for non-myeloid malignancies of 2.4 (95% CI, 1.3–3.8), compared with the general Dutch population (van der Hem et al., 2017). In solid organ transplants, within the large Collaborative Transplant Study database (approximately 200 000 transplants), induction therapy with muromonab-CD3 or ATG was found to increase lymphoma in the first year after transplant (Opelz and Döhler, 2004). In the US Scientific Registry of Transplant Recipients (n = 41 000), an increased risk of post-transplant lymphoproliferative disorder (PTLD) was found to be associated with equine (HR, 1.50; 95% CI, 0.93–2.43) and rabbit (HR, 3.00; 95% CI, 1.53–5.89) ATG (Bustami et al., 2004). In the United Network of Organ Sharing registry, rabbit ATG was not associated with PTLD, whereas equine ATG was (Dharnidharka and Stevens, 2005). ATG was associated with an increased risk of PTLD in a Medicare analysis of solid transplants patients (HR, 1.55; 95% CI, 1.2–1.99) (Caillard et al., 2005). Polyclonal anti-T-cell induction (which includes ATG) has been linked to an increased risk of melanoma but not NHL in the US Transplant Cancer Match Study (Hall et al., 2015). Other studies in patients receiving solid organ transplants have focused on overall malignancies, with more conflicting results (Ruan et al., 2017). Challenges in interpreting the available data include differences across studies in the definition of the outcome (PTLD is a spectrum of different pathologies, including malignant diseases such as lymphomas) and the exposure, with some studies estimating the effect by type of ATG.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

The polyclonal nature of ATG is reflected in its diverse effects on the immune system, including T-cell depletion in blood and peripheral lymphoid tissues through complement-dependent lysis and T-cell activation and apoptosis, modulation of key cell surface molecules that mediate leukocyte–endothelium interactions, induction of apoptosis in B-cell lineages, interference with dendritic cell functional properties, and induction of regulatory T and NKT cells (Mohty, 2007).

ATG has been shown to induce a temporary increase in levels of IL-7 and IL-15 during lymphopenia in 80 children (Kielsen et al., 2021), to increase procalcitonin (PCT) and C-reactive protein concentration in

blood in 26 adult patients, and also to increase serum levels of 1,25-dihydroxyvitamin D3 in 197 patients. ATG has increased 1,25-dihydroxyvitamin D3 in human monocyte-derived dendritic cells (Matos et al., 2022). ATG facilitated erythroid differentiation in leukaemic cells from two patients and K562 cells (Panella and Huang, 1990), and triggered the release of pro-angiogenic factors, such as VEGF, C-X-C, and CC chemokines (Lichtenauer et al., 2012).

ATG decreased the numbers of dendritic cells in five patients (Fang et al., 2005) and induced dose-dependent lymphocytopaenia in the blood and dose-dependent T-cell depletion in the spleen and lymph nodes in cynomolgus monkeys (Préville et al., 2001). ATG strongly induced apoptosis in vitro against naive, human activated B-cells and bone marrow resident plasma cells at clinically relevant concentrations (1–100 ng/mL) (Zand et al., 2005). Furthermore, ATG expanded $CD4^+CD25^+Foxp3^+$ regulatory T cells (Lopez et al., 2006), and induced a dose-dependent down-modulation of cell surface expression of β2-integrin on rabbit lymphocytes, monocytes, and neutrophils (Michallet et al., 2003).

Summary

Regarding studies of cancer in humans, some studies reported a high magnitude of risk for different types of haematological cancer; however, the inconsistencies across studies on the type of outcome and exposure assessed would need to be examined in detail in any future *IARC Monographs* evaluation. No studies of cancer in experimental animals were available. There is some evidence that ATG exhibits KCs, in particular, immunosuppression, in exposed humans, human primary cells, and experimental systems; however, there are concerns related to the quality of the studies. Overall, the Advisory Group considered an *IARC Monographs* re-evaluation of ATG to be warranted.

Recommendation: Medium priority

087 Methotrexate (CAS No. 59-05-2)

Current IARC/WHO classification

Methotrexate has been previously evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a).

Exposure characterization

Methotrexate is an antimetabolite most commonly used in cancer chemotherapy and an immunosuppressant widely used to treat inflammatory conditions, including rheumatoid arthritis, psoriasis (including psoriatic arthritis), and Crohn disease. It has been used since the 1950s and has become a low-cost standard of care in the treatment of rheumatoid arthritis in adults. It is used around the world and is included in the WHO Model List of Essential Medicines (WHO, 2023b), but no reliable data on levels of use were identified by the Advisory Group. Workers may be exposed during the manufacture and handling of methotrexate. Methotrexate is also included in the US NIOSH hazardous drug list (NIOSH, 2016b).

Cancer in humans

A Danish case–control study based on medical records found an increased risk of BCC (the most common malignant neoplasm in humans) (n = 131 477; OR, 1.29; 95% CI, 1.20–1.38), cutaneous SCC (n = 18 661; OR, 1.61; 95% CI, 1.37–1.89), and melanoma (n = 26 068; OR, 1.35; 95% CI, 1.13–1.61) for the use of methotrexate (≥ 2.5 g) ≥ 1 years before diagnosis with some evidence of a dose–response relation for BCC and cutaneous SCC (Polesie et al., 2023).

A randomized trial of low-dose methotrexate (15–20 mg weekly) for the prevention of atherosclerosis in 4786 patients with previous cardiometabolic diseases was stopped after 2.3 years, owing to a lack of efficacy and a variety of adverse events, including an increased risk of non-basal-cell skin cancers (33 versus

12 events; RR, 3.08; $P = 0.002$) (Ridker et al., 2019). However, psoriasis could also be a risk factor for NMSC, which makes confounding by indication difficult to rule out (Trafford et al., 2019).

In a retrospective matched cohort study of patients prescribed methotrexate ($n = 101\,966$) in Sweden and patients prescribed other drugs ($n = 509\,279$), there was a higher cumulative 5-year risk of melanoma (0.48% versus 0.41%; $P < 0.001$) (Polesie et al., 2017). It was noted that this seemed to be restricted to women older than 70 years at the start of treatment. A nested case–control study of melanoma in a cohort of patients with psoriasis in Sweden did not find an association with methotrexate prescriptions (395 cases and 3950 controls; OR, 1.0; 95% CI, 0.8–1.3) (Polesie et al., 2020).

A pooled analysis of meningioma among survivors of childhood cancer who received methotrexate found an increased risk (OR, 3.43; 95% CI, 1.56–7.57) but no dose–response relation (Withrow et al., 2022).

Cancer in experimental animals

In the previous IARC evaluation, the available experimental data on cancers in animals, consisting of oral studies on mice and hamsters and studies of intraperitoneal or intravenous administration in mice and rats, was evaluated as *inadequate*. No new animal cancer bioassays were available to the Advisory Group.

Mechanistic evidence

Several available mechanistic studies suggest that methotrexate may possess several KCs. Its therapeutic effect in the treatment of rheumatoid arthritis and other autoimmune diseases is based on its immunosuppressive properties, mediated by its ability to prevent dihydrofolate reductase (DHFR), which is involved in nucleotide biosynthesis (Zhao et al., 2022). There are also several studies available on methotrexate's ability to cause oxidative stress and genotoxicity in experimental systems, both in vitro and in vivo (e.g. Dadhania et al., 2010; Sekeroğlu and Sekeroğlu, 2012; Hess and Khasawneh, 2015; Said Salem et al., 2017; Rjiba-Touati et al., 2018; Rababa'h et al., 2020; Ezhilarasan 2021; Aghajanshakeri et al., 2023). Although some positive results on genotoxicity have been observed in humans treated with methotrexate, negative studies also exist (Jensen et al., 2021).

Summary

There is consistent evidence of an increased risk of skin cancer, particularly non-melanoma subtypes, associated with the use of methotrexate, from a few well-conducted record-linkage studies in Nordic countries; however, the role of confounding by indication remains a concern. Mechanistic evidence shows that methotrexate exhibits KCs, i.e. genotoxicity, oxidative stress, and immunosuppression. Based on the new human cancer data and mechanistic evidence, the Advisory Group therefore considered an *IARC Monographs* re-evaluation of methotrexate to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

088 Glucocorticoids

Current IARC/WHO classification

Glucocorticoids have not been previously evaluated by the *IARC Monographs* programme. Glucocorticoids were given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of human cancer and mechanistic evidence.

Exposure characterization

Glucocorticoids are synthetic analogues of the natural steroid hormones produced by the adrenal cortex and are widely used in the treatment of various inflammatory and autoimmune disorders and other conditions, including renal insufficiency, acute and chronic inflammatory conditions, and some leukaemias.

Cancer in humans

The report of the 2019 Advisory Group on Priorities (IARC, 2019a) indicated positive evidence and associations between some glucocorticoids and several types of cancer, including SCC and BCC, bladder cancer, and NHL. Notably, however, Purdue (2003) has proposed a reanalysis of the data of Karagas et al. (2001), showing possible confounding or effect modification by atopic conditions hypothesized to be protective for SCC. Purdue suggested that the lack of association with inhaled corticoids reported in Karagas et al. (2001) could be explained by a similar confounding effect of asthma. However, the potential for this bias, which would bias estimates towards the null, was not further explored.

In an analysis of data from a clinical trial in 1051 participants, Baibergenova et al. (2012) reported an elevated risk of BCC among those who used prednisone for more than 30 days (HR, 1.26; 95% CI, 0.9–1.78), but not for SCC (HR, 1.03; 95% CI: 0.66–1.60). An increased risk of cancers of the liver and lung was found to be associated with glucocorticoid use in an analysis of the sample cohort database of the National Health Insurance Service of the Republic of Korea (Oh and Song, 2020).

There is also some evidence regarding other cancer types. An increased risk of specific subtypes of breast cancer (in situ, and stages 3 and 4) with the use of systemic glucocorticoids was reported for the *Étude Épidémiologique auprès de femmes de la Mutuelle Générale de l'Éducation Nationale* (E3N) cohort (Cairat et al., 2021). The same study reported an inverse association for other breast cancer subtypes (ER-negative). No increased risk of CRC with the use of systemic glucocorticoids was reported in one nested case–control study in Denmark (Ostenfeld et al., 2013). Associations between specific glucocorticoid medications and NHL were found in a systematic screening of medication prescription and cancer risk in a primary care database in Scotland (McDowell et al., 2021).

Cancer in experimental animals

As noted in the 2019 Advisory Group report (IARC, 2019a), studies have found equivocal evidence of tumorigenicity of different glucocorticoids.

Mechanistic evidence

The report of the 2019 Advisory Group on Priorities (IARC, 2019a) notes:

> Mechanistic studies have demonstrated anti-apoptotic effects of glucocorticoids including increasing anti-apoptotic proteins Bcl-2 and Bcl-xL, and by inhibiting IFN-gamma-anti-Fas-induced apoptosis (Wen et al., 1997; Bailly-Maitre et al., 2002; Sorrentino et al., 2017). A study in human bladder tumour tissues (Ishiguro et al., 2014) supported the experimental evidence (Zheng et al., 2012) suggesting an inhibitory role of glucocorticoid receptor signals in bladder cancer outgrowth: glucocorticoid receptor expression was downregulated in bladder tumours.

Other studies relating to DNA damage, oxidative stress, receptor-mediated effects, and tumour progression have been published for individual glucocorticoids.

Summary

Across the identified epidemiological studies of human cancer, there appears to be little consistency regarding the cancer sites for which an association is reported. The Advisory Group further considered that a single evaluation of the entire class of glucocorticoids is unwarranted at present. There might be evidence for some of the glucocorticoids, mainly for immunosuppression; however, the evidence remains rather sparse at this time, particularly for individual glucocorticoids, and there is not enough evidence to make a judgement for this entire class of drugs.

Recommendation: No priority

089 Androstenedione (CAS No. 63-05-8)

Current IARC/WHO classification

Androstenedione is an androgenic anabolic steroid. Androgenic anabolic steroids were classified by IARC as *probably carcinogenic to humans* (Group 2A) in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a), based on *sufficient* evidence for cancer in animals and *limited* evidence for cancer in humans. Androstenedione was given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a).

Exposure characterization

Androstenedione is endogenously synthesized by the human adrenal cortex and gonads. Androstenedione is weakly androgenic and can be converted to estrogens and more potent androgens in peripheral tissues. Androstenedione, along with dehydroepiandrosterone, may be the dominant circulating androgen in prepubertal girls (during adrenarche) and postmenopausal women. For more information on the classification of androstenedione as an androgenic anabolic steroid, see Yesalis and Bahrke (2002), US FDA (2022), and DrugBank Online (2024b). 5-Androstenedione is the exogenous drug, whereas 4-androstenedione is endogenous.

Cancer in humans

Little new evidence has accrued on cancer in humans associated with exogenous androstenedione. There is evidence for an association between endogenous androstenedione of some cancer types, particularly ovary cancer (e.g. Chen et al., 2011; Schock et al., 2014; Iqbal et al., 2019); however, it is likely to be subtype-specific, and the evidence is currently mixed. Most studies concerning breast cancer were null (e.g. Sturgeon et al., 2004; Baglietto et al., 2010; Fourkala et al., 2016).

Cancer in experimental animals

The studies supporting the classification of *sufficient* evidence for cancer in experimental animals are described in *IARC Monographs* Supplement 7 (IARC, 1987a). This evidence would be unlikely to result in a new evaluation.

Mechanistic evidence

As noted in the report of the 2019 Advisory Group on Priorities (IARC, 2019a):

> Limited information was identified on the relationship between the key characteristics of carcinogens and androstenedione. As a steroid hormone, androstenedione has both weakly androgenic and estrogenic effects on the respective steroid nuclear receptors. ToxCast data indicate that androstenedione is active in several high-throughput

> assays, mostly nuclear receptor and cell cycle assays, at concentrations considerably below those that were cytotoxic. Furthermore, ToxCast endocrine models indicate active agonist calls for the integrated estrogen receptor and androgen receptor bioactivity models (US EPA, 2019). The genetic toxicity of androstenedione was tested in several strains of *Salmonella* and *E. coli*, and in rat bone marrow and mouse peripheral blood (NTP, 2010).

Summary

Androstenedione administered exogenously is currently classified by IARC as *probably carcinogenic to humans* (Group 2A). There does not currently appear to be evidence available that would lead to a change in classification. Most of the newly available epidemiological evidence is on the endogenous form of androstenedione, and the *IARC Monographs* programme does not evaluate purely endogenous hazards. The Advisory Group therefore considered that an *IARC Monographs* evaluation of androstenedione is unwarranted at present.

Recommendation: No priority

090 Oxymetholone (CAS No. 434-07-1)

Current IARC/WHO classification

Oxymetholone was evaluated together with other anabolic steroids, which were analysed as a class by IARC as *probably carcinogenic to humans* (Group 2A) in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a), on the basis of *limited* evidence for cancers of the liver, bile duct, and prostate in humans. Oxymetholone was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), which had overlooked the previous evaluation of anabolic steroids.

Exposure characterization

As noted in the report of the 2019 Advisory Group on Priorities (IARC, 2019a), oxymetholone is a 17α-alkylated anabolic–androgenic steroid synthesized from testosterone (Pavlatos et al., 2001; NTP, 2021e). Oxymetholone is used for the treatment of several conditions, including hypogonadism, delayed puberty, and hereditary angioneurotic oedema, and to stimulate the production of erythrocytes (NTP, 2021e). Oxymetholone is also used to stimulate weight gain (Hengge et al., 1996). In addition, athletes may use it in an attempt to improve performance (Socas et al., 2005).

Cancer in humans

Very few new human cancer studies were identified for oxymetholone since the previous evaluation.

Cancer in experimental animals

The 2019 Advisory Group on Priorities noted:

> The United States National Toxicology Program bioassay (NTP, 1999a) showed increased incidence of subcutaneous tissue fibroma and fibroma or fibrosarcoma (combined) of the skin, variably increased incidence of benign and benign or malignant pheochromocytoma (combined) of the adrenal gland, and increased incidence of renal tubule adenoma in male F344/N rats. In female F344/N rats, there was increased incidence of hepatocellular

neoplasms. Increased incidence of bronchioloalveolar neoplasms and skin neoplasms in female rats was also seen with administration of oxymetholone (NTP, 1999a). Oxymetholone was not positive in transgenic mouse models (Blanchard et al., 1999; Holden et al., 1999; Stoll et al., 1999). Administration of oxymetholone by stomach tube increased the combined incidence of benign and malignant liver tumours (hepatocellular adenoma and carcinoma) in female rats. Benign lung tumours and benign and malignant skin tumours in female rats also were considered to be related to exposure to oxymetholone (NTP, 1999a).

Mechanistic evidence

Numerous studies are available for the KCs, particularly on receptor-mediated effects. However, it is unclear that these would result in a change of the current classification.

Summary

Given the current evaluation of oxymetholone, as an anabolic steroid, by IARC as *probably carcinogenic to humans* (Group 2A), there does not appear to be enough new human cancer or mechanistic evidence to suggest that a change in classification would be likely. The Advisory Group therefore considered that an *IARC Monographs* evaluation of oxymetholone is unwarranted at present.

Recommendation: No priority

091 Glucagon-like peptide-1 (GLP-1) analogues

Current IARC/WHO classification

Glucagon-like peptide-1 (GLP-1) analogues, also known as GLP-1 receptor agonists, have not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

GLP-1 is an intestinal peptide, synthesized by gut neuroendocrine cells, that stimulates pancreatic β cell proliferation, inhibits glucagon secretion, increases satiety through alterations in the hypothalamic signalling pathways, and delays gastric emptying. The GLP-1 receptor agonists constitute a class of anti-diabetics that act as insulin secretagogues and reduce postprandial glucose levels in patients with type 2 diabetes. Liraglutide, lixisenatide, and exenatide are GLP-1 receptor agonists approved clinically for the treatment of diabetes.

GLP-1 analogues are drugs that are widely used to treat type 2 diabetes, and some have been recently approved to treat obesity. The US FDA approved liraglutide, a GLP-1 receptor agonist in 2010. Semaglutides belong to this class of medications, and three are currently approved by the FDA.

Workers may be exposed during the manufacture and handling of GLP-1 analogues. Liraglutide is included in the US NIOSH hazardous drug list, with a note regarding the box warning for risk of thyroid C-cell tumour (NIOSH, 2016b). However, NIOSH has proposed removing liraglutide from the hazardous drug list in workers, but this has not yet been finalized (US Federal Register, 2024).

Cancer in humans

Based on the animal data, the primary concerns for this class of drugs are cancers of the medullary thyroid and pancreas (Parks and Rosebraugh, 2010). The current human data come mostly from studies of people with type 2 diabetes. In a nested case–control study in France that used a health insurance database

of individuals with diabetes, there were 2562 cases of thyroid cancer and 45 184 control subjects. Use of GLP-1 receptor agonist for 1–3 years was associated with an increased risk of thyroid cancer (HR, 1.58; 95% CI, 1.27–1.95), particularly medullary thyroid cancer (HR, 1.78; 95% CI, 1.04–3.05) (Bezin et al., 2023). In a meta-analysis of 64 randomized trials of these drugs to treat people with type 2 diabetes (n = 48) or obesity (n = 16), the RR for thyroid cancer was calculated as 1.52 (95% CI, 1.01–2.29) (Silverii et al., 2024).

In an analysis using the US FDA adverse event reporting system, a total of 3703 cases of pancreatic cancer were reported in users of GLP-1 receptor agonists (Cao et al., 2023). In a record-linkage study in Israel of people with diabetes covered by a single health insurer, the HR for pancreatic cancer was 0.50 (0.15–1.71) for GLP-1 receptor agonist, compared with basal insulin (Dankner et al., 2024).

Cancer in experimental animals

Byrd et al. (2015) studied the tumorigenic potential of dulaglutide in rats and transgenic mice, concluding that GLP-1 had no carcinogenic effect. In rats, dulaglutide injected subcutaneously induced a significant increase of thyroid C-cell adenoma in male and female rodents. The incidence of thyroid C-cell carcinoma also increased but did not reach statistical significance. In transgenic male and female mice (aged 8–9 weeks) dosed subcutaneously twice weekly with dulaglutide at 0, 0.3, 1, or 3 mg/kg for 26 weeks, the effects of dulaglutide were limited to the thyroid C-cells. No dulaglutide-related C-cell neoplasia was observed at any dose (Byrd et al., 2015).

Animal experiments were designed to study C-cell hyperplasia and tumour formation after long-term dosing with GLP-1 receptor agonists in rodents (Chiu et al., 2012). In rats, the incidence of C-cell tumour formation at 104 weeks increased in a dose-dependent manner and reached statistical significance (Chiu et al., 2012).

Mechanistic evidence

The prime pharmacological property of agonists of the GLP-1 and gastric inhibitory polypeptide receptors is glucose homeostasis through the stimulation of insulin secretion (the incretin effect) (Baggio and Drucker, 2007). Several studies employing rat thyroid C-cell lines and thyroid tissues have demonstrated that activation of the GLP-1 receptor leads to calcitonin secretion. Calcitonin, a hormone secreted by thyroid C-cells, is regarded as an important clinical biomarker for C-cell diseases, such as medullary thyroid carcinoma and hereditary C-cell hyperplasia, because of its high sensitivity and specificity (Chiu et al., 2012).

Results of the micronucleus test in bone marrow, performed as part of a 13-week repeat-dose toxicity study in rats, showed a small but statistically significant increase in the frequency of micronucleated polychromatic erythrocytes at intermediate (1 mg/kg per day) and high (3 mg/kg per day) dose levels. The results of the Ames test, the micronucleus test in mouse L5178Y $tk^{+/-}$ lymphoma cells, and the chromosome aberration test in human lymphocytes showed no indication of genotoxicity (Guérard et al., 2014). In a carcinogenicity study of dulaglutide, diffuse C-cell hyperplasia and adenoma were observed in rats, but not in transgenic mice (Byrd et al., 2015). After 13 weeks of continuous exposure to GLP-1 receptor agonist, liraglutide administration was associated with marked increases in plasma calcitonin concentration and the incidence of C-cell hyperplasia in wildtype mice (Madsen et al., 2012). Liraglutide or exenatide administration in mice for 9–12 weeks was accompanied by C-cell hyperplasia, which was reversed after a 15-week recovery period. In contrast to results in rodents, liraglutide had no effect on plasma calcitonin concentrations, and no C-cell hyperplasia was observed in cynomolgus monkeys after single doses or during 87 weeks of dosing (Bjerre Knudsen et al., 2010).

Liu et al. (2022e) investigated molecular mechanisms of liraglutide in breast cancer cell lines and tissues derived from mice bearing 4T1 cells. Liraglutide accelerated breast cancer progression in vitro and in vivo, through the NOX4/ROS/VEGF pathway.

Summary

There is emerging evidence for an increased risk of thyroid cancer associated with GLP-1 analogues, which is mainly based on studies with a short-term follow-up. GLP-1 analogues induced tumours in experimental animals. There is mechanistic evidence that GLP-1 analogues exhibit KCs in experimental systems. Overall, the available information supports an evaluation of carcinogenicity of the agent. The Advisory Group therefore considered an *IARC Monographs* evaluation of glucagon-like peptide-1 (GLP-1) analogues to be warranted but, given the rapidly evolving evidence for the agent, an evaluation in the latter half of the period is recommended.

Recommendation: High priority (and ready for evaluation within 5 years)

092 Progestogen-only contraceptives

Current IARC/WHO classification

Progestogen-only contraceptives, as a group, were classified by IARC as *possibly carcinogenic to humans* (Group 2B) in *IARC Monographs* Volume 72 in 1998 (IARC, 1999c), based on *sufficient* evidence for cancer in experimental animals, while there was *inadequate* evidence in humans. Medroxyprogesterone acetate, individually, was evaluated as *possibly carcinogenic to humans* (Group 2B), based on *sufficient* evidence in animals and *inadequate* evidence in humans, in *IARC Monographs* Supplement 7 (IARC, 1987a). Combined estrogen-progestogen oral contraceptives were classified by IARC as *carcinogenic to humans* (Group 1) in *IARC Monographs* Volume 100A, in 2008 (IARC, 2012d).

Exposure characterization

Progestogen-only contraceptives are a group of natural and synthetic progestogens used for contraception without estrogens. Different progestogen-only contraceptives are available as oral formulations (e.g. norethindrone, norgestrel, levonorgestrel, desogestrel), injectables (e.g. medroxyprogesterone acetate), subcutaneous implants (e.g. etonogestrel), or progestogen-releasing intrauterine devices (IUDs) (e.g. levonorgestrel). Injectable medroxyprogesterone acetate, injectable norethisterone enanthate, and progesterone-releasing vaginal rings are included in the WHO Model List of Essential Medicines (WHO, 2023b). Injectable progestogen-only contraceptives are the most commonly used injectable contraception types. Globally, 6% of women use injectables, but the percentage is highest in sub-Saharan Africa (43%), with injectables accounting for 50–76% of contraceptive use in LMICs (Jacobstein and Polis, 2014).

Variations exist by countries. In the UK, in 2019–2020, progestogen-only pills constituted 57% of all oral contraceptive prescriptions (Bury et al., 2023). In Denmark, from 1998 to 2010, the use of progestogen-only contraceptives increased from 2.5% to 4.5% (Wilson et al., 2012). In Sweden, progestogen-only pills were prescribed more frequently in women with obesity (44%) than in women of normal weight (25%) (Sundell et al., 2019). Starting in 2024, a progestogen-only contraceptive pill (0.075 mg oral norgestrel) will be the first non-prescription contraceptive available in the USA (Fleurant et al., 2023; US FDA, 2023c); it has been available without prescription in the UK since 2021 (Medicines and Health care products Regulatory Agency, 2021).

In addition to contraception, progestogen-only formulations are used for infertility treatment, menopause, menstrual disorder, the prevention and treatment of miscarriage and preterm labour, and gender transition treatment (female-to-male transition) (Edwards and Can, 2023).

Cancer in humans

Since *IARC Monographs* Volume 72 (IARC, 1999c), new epidemiological data are available, especially concerning the risk of breast cancer associated with progestogen-only contraceptive use. A nested case–control study within the UK Clinical Practice Research Datalink found an increased risk (20–30%) of breast cancer associated with oral, injected, or progestogen-only-releasing IUDs (Fitzpatrick et al., 2023). Similarly, a meta-analysis showed an increased risk (20–30%) for all types of progestogen-only contraceptive preparation (Fitzpatrick et al., 2023). The meta-analysis included several informative cohorts from Norway, Sweden, and Denmark (Kumle et al., 2002; Mørch et al., 2017; Busund et al., 2018), as well as case–control studies (Fitzpatrick et al., 2023).

Increasing amounts of evidence, including from the large Ovarian Cancer Association Consortium, indicate that depot-medroxyprogesterone acetate (in the injectable form) or a progesterone-releasing IUD may reduce ovarian cancer risk (Phung et al., 2021). It remains unclear, however, whether progestogen-only contraceptives exhibit the same protective effect on the risk of endometrial cancer (Iversen et al., 2020).

A nested case–control study within the nationwide cancer registry in Denmark reported an OR of 2.4; (95% CI, 1.1–5.1) for the risk of glioma associated with the long-term use of progestogen-only contraceptives, but other studies reported mixed results on glioma risk after hormonal therapy; however, they were unable to distinguish the type of hormonal contraception (Andersen et al., 2015). An analysis using the national Danish birth registry did not find an increased risk of childhood brain cancer (Hargreave et al., 2022) or childhood leukaemia (Hargreave et al., 2018) for maternal exposure to oral progestogen-only contraceptives. The NTP has conducted a scoping review of health effects in offspring for progestogens during pregnancy; however, few results for cancer risk were included (NTP, 2020a).

Progestogen-only contraceptives have traditionally been prescribed to women with a higher BMI, because combined formulations increase the risk of venous thrombosis; thus, obesity may be a potential confounding factor (Andersen et al., 2015). However, confounding by BMI seems a minimal concern because of adjustment for BMI in informative studies and because such confounding would not explain the inverse association for ovarian cancer, which is also obesity-related.

Cancer in experimental animals

The IARC reported *sufficient* evidence in experimental animals for the carcinogenicity of medroxyprogesterone acetate in *IARC Monographs* Volume 72 in 1998 (IARC, 1999c).

Mechanistic evidence

Progestin is a synthetic progesterone, which acts on nuclear, mitochondrial, and membrane progesterone receptors (PRs) (Fedotcheva, 2021). Since "all progestins are not created equal" (Stanczyk, 2003), because of their chemical structure, they will bind to PRs with different affinities, activating different molecular pathways and differing in metabolism, pharmacokinetics, efficacy, and toxicity (Stanczyk et al., 2013). The progestin dose and route of administration will also contribute to different effects on the female genital tract (Dinh et al., 2015) and other PR-expressing tissues, such as the breast (Druckmann, 2003) or brain (Pletzer et al., 2023). Many progestins bind not only to PRs, but also to glucocorticoid, androgen, and mineralocorticoid receptors, and possibly ERs (Africander et al., 2011). Receptor-mediated effects of medroxyprogesterone acetate (MPA) and levonorgestrel in humans are described in *IARC Monographs* Volume 72 (IARC, 1999c). New studies are currently available, especially in exposed humans and human primary cells or tissue, describing several KCs. The genotoxicity of MPA was described as causing

chromosomal aberrations in cultured human PBLs (Siddique et al., 2006) and in human lymphocytes of patients treated for precocious puberty (Lovell and Coco, 1984). Endometrial oxidative stress increased in seven women receiving long-term progestin-only contraceptives (LPCs) (Hickey et al., 2006); this finding was confirmed in experimental settings where human endometrial stromal cells were treated with LPCs (Guzeloglu-Kayisli et al., 2014). Different studies confirm that LPCs enhance abnormal angiogenesis in human endometrial stromal cells (Krikun et al., 2004; Lockwood et al., 2004) and in the human endometrium (Levy et al., 1997). LPC also causes inflammatory changes in cervicovaginal cytokine concentrations in women (Roxby et al., 2016; Bradley et al., 2022) or in human primary endocervical epithelial cells (Govender et al., 2014). MPA, unlike progesterone, was described as repressing inflammatory genes in human PBMCs in a dose-dependent manner, through the glucocorticoid receptor, at concentrations within the physiologically relevant range (Hapgood et al., 2014).

Eigeliene et al. (2006) showed that MPA increases the proliferative activity and thickness of acinar and ductal epithelium and decreases apoptosis in epithelial cells in cultured human breast explants treated for 7 or 14 days. Eigeliene et al. (2006) also found that the expression of α and β ERs were downregulated in human breast explants treated with MPA for 21 days. The proliferative effects of progestins in breast tissue or breast cells have been confirmed in several studies (Anderson et al., 1989; Mol et al., 1996; Pasqualini et al., 2001; Otto et al., 2007). The action of progestins on the proliferation of mammary epithelium could be explained by a local biosynthesis of growth hormones caused by the stimulatory effect of progestins (Mol et al., 1996) or the activation or downregulation of steroid receptors (an off-target effect) (Jordan et al., 1993; Söderqvist, 1998; Giersig, 2008).

Summary

Several highly informative epidemiological studies consistently indicate that an increased risk of breast cancer and a decreased risk of ovarian cancer are associated with the use of progestogen-only contraceptives. Epidemiological studies on ovarian cancer are in progress. Emerging evidence shows an association for an increased risk of brain tumour with the use of progestogen-only contraceptives. Mechanistic evidence is available for several of the KCs, suggesting genotoxicity, the modulation of receptor-mediated effects, and cell proliferation in exposed humans and human primary cells or tissues. Overall, the Advisory Group considered an *IARC Monographs* re-evaluation of progestogen-only contraceptives to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

093 Menopausal hormone replacement therapy

Current IARC/WHO classification

Menopausal hormone replacement therapy (HRT) was classified by IARC as *carcinogenic to humans* (Group 1) in *IARC Monographs* Volume 100A in 2008 (IARC, 2012d). Two separate evaluations were reported in *IARC Monographs* Volume 100A: (i) for estrogen-only menopausal HRT (*sufficient* evidence in humans for cancers of the endometrium and ovary, *limited* evidence for breast cancer, and *evidence suggesting lack of carcinogenicity* for CRC); and (ii) for combined estrogen-progestogen menopausal HRT (*sufficient* evidence in humans for cancers of the breast and endometrium) and estrogen-progestogen oral contraceptives (*sufficient* evidence in humans for cancers of the breast, cervix, and liver).

There was also *sufficient* evidence in experimental animals for some estrogens or estrogen-progestin combinations used in HRT. Mechanistic evidence highlighted a receptor-mediated effect and a genotoxic mechanism for estrogen-only menopausal HRT and for combined estrogen-progestogen menopausal HRT.

The Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a) recommended re-evaluation with a priority rating of *high*, based on *sufficient* or *limited* epidemiological evidence on estrogen-only menopausal HRT and new cancer sites.

Exposure characterization

Menopausal HRT, commonly simply referred to as HRT, refers to the replacement of hormones lost during the menopausal transition. It is available in different formulations: peroral (pill), transdermal (patch, gel, aerosol), or vaginal (tablet, cream, ring) (Harper-Harrison and Shanahan, 2024). Menopausal HRT exists as estrogen-only menopausal HRT (for women who have had a hysterectomy) and as combined estrogen-progesterone HRT (for women with intact uteri), but the type of estrogen or progestogen mainly used varies by country; for example, conjugate equine estrogen is the major estrogen used in the USA, while in Europe estradiol derivatives are more commonly used (Harper-Harrison and Shanahan, 2024).

Approximately 75% of perimenopausal women are affected by vasomotor and genitourinary menopausal symptoms, for which menopausal HRT has proven to be the most effective treatment (Eubanks, 2023). HRT is also prescribed to reduce the risk of osteoporosis in menopause or after oophorectomy. HRT is mostly used in high-income countries; its use in western Europe and North America peaked in 2000 (at the time of the publication of trial results showing an increased risk of cardiovascular disease), with around 35 million users, and then stabilized at around 12 million users/year (Collaborative Group on Hormonal Factors in Breast Cancer, 2019; Sundell et al., 2023). An increase in use has been documented after 2017 in some countries, after changes in clinical guidelines informed by new results from the Women's Health Initiative (WHI) trial (Sundell et al., 2023). It is estimated that between 12% and 50% of women worldwide use HRT; however, its use is underestimated in countries where HRT is available over the counter without medical supervision, such as in Latin America (Baena et al., 2023).

Cancer in humans

The previous IARC evaluation established that there was *sufficient* evidence of carcinogenicity for breast cancer in humans for combined progesterone-estrogen HRT formulations and *limited* evidence of carcinogenicity for breast cancer in humans for estrogen-only HRT formulations. Major studies published after *IARC Monographs* Volume 100A (IARC, 2012d) are summarized next.

A case–control study nested in a pooled cohort of 58 prospective cohort studies with information on HRT and breast cancer follow-up (n = 108 647) showed an increased risk of breast cancer for estrogen-only and progesterone-estrogen HRT formulations (Collaborative Group on Hormonal Factors in Breast Cancer, 2019). The risk was increased for any type of estrogen or progestogen constituent and any mode of administration (oral, transdermal, vaginal estrogen). The use of vaginal estrogen is generally considered safe and recommended as an option for survivors of breast cancer (Zhang et al., 2021b; Baena et al., 2023); however, there was a borderline statistical association in the 58-study pooled analysis (RR, 1.09; 95% CI, 0.97–1.23), and studies showing increased breast cancer recurrence with vaginal estrogen have been the subject of debate (Cold et al., 2022; Pederson et al., 2023). Other studies conducted in racially and ethnically diverse populations have also reported a consistent positive association of HRT, including estrogen-only formulations, with breast cancer in the USA (Phung et al., 2022b), although the latest follow-up for the WHI trial reported a decreased risk for conjugated equine estrogen alone in women with hysterectomy, compared with a placebo (Chlebowski et al., 2020).

Numerous studies have evaluated HRT and the risk of non-melanoma or melanoma skin cancer; a recent meta-analysis reported an increased risk of melanoma for both estrogen-only (HR, 1.22; 95% CI, 1.16–1.29) and estrogen-progestogen combinations (HR, 1.11; 95% CI, 1.05–1.18) and an increase of NMSC for estrogen-only HRT (HR, 1.21; 95% CI, 1.10–1.33) (Lallas et al., 2023). These observations are consistent with a possible cumulative phototoxic effect of estrogen (Cahoon et al., 2015).

In *IARC Monographs* Volume 100A, there was *sufficient* evidence for ovarian cancer for estrogen-only HRT (IARC, 2012d). Studies published after Volume 100A have also shown an increased risk of ovarian cancer for estrogen-progestogen combinations, including in racially and ethnic diverse population (Petrick et al., 2023); however, with some inconsistencies across studies (Bakken et al., 2004, Yuk and Kim, 2023). In a large prospective ovarian cancer cohort consortium, a positive association was observed for combined estrogen-progesterone HRT (Wentzensen et al., 2016). In the French E3N cohort, risk was elevated only for some types of estrogen-progestogen combination (HR for having ever used estrogen with progesterone or dydrogesterone, 1.25; 95% CI, 1.04–1.57), but not for others (Fournier et al. 2023); therefore, it is possible that the inconsistency in the results is due to different types of progestogen.

In a pooled cohort analysis of about 1 million women, an increased risk of thyroid cancer was associated with having ever used HRT (HR, 1.16; 95% CI, 1.02–1.33), but no analysis was presented by type of HRT (O'Grady et al., 2024). An increased risk was also reported for meningioma and HRT in a meta-analysis (RR for having ever used HRT, 1.14; 95% CI, 0.98–1.33) (Zhang et al., 2021b), which also included the positive findings (ever used HRT versus never used: HR, 1.62; 95% CI, 1.04–2.54) in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (Michaud et al., 2010).

In addition to colon cancer, a consistent reduced risk associated with HRT was reported for lung (Wen et al., 2022), gastric, and oesophageal cancers (Song et al., 2023b, Zhang et al., 2021b), and for pancreatic cancer (Jang et al., 2023).

Summary

Recent studies consistently show an increased risk of skin cancer for both combined estrogen-progestogen and estrogen-only HRT formulations. For breast cancer, consistent with *IARC Monographs* Volume 100A, studies show positive associations between combined progesterone-estrogen HRT formulations and breast cancer. New evidence is expected within the next 2–5 years. For estrogen-only formulations, large observational studies have also reported an increased risk of breast cancer, but the inconsistency with other reports needs to be closely evaluated. Informative studies also show an increased risk of ovary cancer for combined estrogen-progestogen HRT formulations and, although without stratification by HRT formulation, of thyroid cancer and meningioma. Very consistent evidence shows a protective effect of HRT for various digestive organ sites and lung cancer. The Advisory Group therefore considered an *IARC Monographs* evaluation stratified by administration route of menopausal HRT to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

094 Clomiphene citrate (CAS No. 50-41-9)

Current IARC/WHO classification

Clomiphene citrate was evaluated by IARC as *not classifiable as to its carcinogenicity to humans* (Group 3) in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a). Fertility treatment was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of epidemiological evidence for gynaecological cancers and mechanistic evidence for the modulation of receptor-mediated effects and alteration of cell proliferation. It was noted that, for epidemiological evidence, few studies were able to separate the effect of each specific drug.

Exposure characterization

Clomiphene citrate is a selective ER modifier and has been used to stimulate ovulation for fertility treatment since 1960 (Carson and Kallen, 2021). The use of ovary-stimulating drugs has increased in recent

years, especially in high-income countries. Clomiphene citrate has been used preferentially in women with polycystic ovary syndrome (Silva et al., 2009).

Cancer in humans

Clomiphene citrate was evaluated by IARC as *not classifiable as to its carcinogenicity to humans* (Group 3) in *IARC Monographs* Supplement 7 in 1987 (IARC, 1987a), based on *inadequate* evidence regarding cancer in humans and in experimental animals. The 2019 Advisory Group on Priorities highlighted general challenges in interpreting the epidemiological studies on fertility treatment, including the relative rarity of exposure, limited follow-up time, a lack of data on the number of cycles or doses, and potential confounding by subfertility or infertility for cancers of the ovary, endometrium, or breast (IARC, 2019a). The 2019 Advisory Group report also emphasized that no clear evidence of increased risk of endometrium and breast cancer for fertility treatment has emerged from Cochrane reviews or several meta-analyses, and that a possible excess risk of borderline ovarian tumours could be due to the intrinsic characteristics of these tumours or to surveillance bias.

The most recent meta-analysis of epidemiological studies of infertility treatments and cancer risk found an OR for ovarian cancer overall of 1.19 (95% CI, 0.98–1.46), with a stronger association for borderline ovarian tumours (OR, 1.69; 95% CI, 1.27–2.25) (Barcroft et al., 2021). In further subgroup analyses, the incidence of ovarian cancer was shown to be significantly higher in a group treated with clomiphene citrate (OR, 1.40; 95% CI, 1.10–1.77) (Barcroft et al., 2021). Updates of the Ovariumstimulatie en Gynecologische Aandoeningen (OMEGA) cohort in the Netherlands and a cohort in Israel, which have more detailed data on treatments and potential confounders, have not yet been published.

Several cohort studies in Norway, the UK, and the USA have also found exposure to clomiphene citrate to be associated with an increased risk of endometrial cancer (Silva et al., 2009; Brinton et al., 2013; Reigstad et al., 2017), but some uncertainty remains on confounding by indication in women with polycystic ovary syndrome. There is also emerging evidence for an increased risk of other cancer sites, particularly melanoma and thyroid cancer; however, findings are somewhat inconsistent (Brinton et al., 2015).

Cancer in experimental animals

In the previous evaluation (IARC, 1987a), there was *inadequate* evidence in experimental animals for the carcinogenicity of clomiphene citrate. Clomiphene citrate was tested in an experiment in newborn rats, to which it was administered by single subcutaneous injection; reproductive tract abnormalities, including uterine and ovarian tumours, were reported (IARC, 1979a). No new data regarding cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

Clomiphene citrate has a very similar structure and binding affinity to that of tamoxifen (classified by IARC as *carcinogenic to humans*, Group 1), suggesting its role as a possible estrogenic substance in the endometrium (Fang et al., 2001).

No data were available on the genetic and related effects of clomiphene citrate in humans. Clomiphene citrate did not induce chromosomal aberrations or micronuclei in the bone marrow cells of mice treated in vivo. In experimental systems, a micronucleus assay suggested a dose-dependent effect of clomiphene citrate on genomic instability in bone marrow stem cells in vivo (Duran et al., 2006). A review by Yilmaz et al. (2018) showed clomiphene citrate to be genotoxic, cytotoxic, embryotoxic, and teratogenic. In polycystic ovary syndrome, clomiphene citrate may be associated with lower antioxidant levels in women with drug resistance and also has associations with prolactin-producing tumours that generate mild inflammation characteristics (Kettel et al., 1993; Ide et al., 2020; Akre et al., 2022).

Summary

Positive associations between clomiphene citrate and cancers of the ovary or endometrium have been reported in several cohort studies, with uncertainty remaining as to the role of confounding by indication. A positive study of cancer in experimental animals that was reviewed by the previous Working Group in 1987 has been considered by the Advisory Group. The mechanistic evidence and structural similarity to tamoxifen supports a re-evaluation and potential change in the classification. Overall, the Advisory Group considered an *IARC Monographs* re-evaluation of clomiphene citrate to be warranted. This should take place in the latter half of the next 5 years to accommodate expected updates of some informative cohort studies.

Recommendation: High priority (and ready for evaluation within 5 years)

095 Assisted reproductive techniques

Current IARC/WHO classification

Assisted reproductive techniques (ARTs) have not been previously evaluated by the *IARC Monographs* programme. Fertility treatment, a broader term that includes ARTs, was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), based on evidence of cancer in humans and mechanistic evidence. The 2019 Advisory Group on Priorities indicated emerging evidence of childhood cancer in children conceived with the aid of ARTs, noting, however, inconsistency of results, an inability to disentangle findings for specific drugs or techniques, and a lack of control for birth defects or perinatal factors.

Exposure characterization

An ART is any fertility treatment that involves manipulation of the eggs or embryo; in vitro fertilization (IVF) is the most common among these techniques (Jain and Singh, 2023). Therefore, ARTs involve exposing the mother undergoing fertility treatment to different techniques or drugs, as well as, at an embryonic stage, children born after that treatment. There may also be maternal exposure to ovary-stimulating drugs, such as clomiphene citrate, which is described separately in the present report (agent 094), or to exogenous gonadotropins (Jain and Singh, 2023).

In 2021, the Centers for Disease Control and Prevention (CDC) estimated that nearly 240 000 patients underwent ARTs, resulting in 97 000 liveborn infants (CDC, 2021). Approximately 2.3% of infants born in the USA were conceived using ARTs, compared with 1.5% in 2011 (Sunderam et al., 2014). In China, the number of infants born after the use of ARTs was over 300 000 in 2016, 1.7% of live births (Bai et al., 2020). The use of ARTs is increasing around the world, including in LMICs (Chambers et al., 2021).

Cancer in humans

The 2019 Advisory Group on Priorities noted that several studies have reported an increased risk of cancer (particularly haematological malignancies) in children born after the use of ARTs, but few have examined specific drugs or techniques, and results have not been consistent (IARC, 2019a). Since then, more record-linkage studies have been published but still with inconsistent findings. In a recent large cohort study in Israel, the RR for paediatric cancer after an ART was 0.95 (95% CI, 0.76–1.19). The RR was 1.09 (95% CI, 0.79–1.48) for IVF treatments (Gilboa et al., 2019). In an associated meta-analysis of 13 cohort studies, with a total of 750 138 women exposed to ARTs (with 1152 cases of paediatric cancer) and 214 008 000 unexposed controls (with cases of 30 458 paediatric cancer), there was also no increased risk of paediatric cancer (RR, 0.99; 95% CI, 0.85–1.15) (Gilboa et al., 2019). In a large cohort in Taiwan, China, of 2 308 016 parent–child triads and 1880 children with incident childhood cancer, conception using ARTs was associated with an increased risk of childhood cancer (primarily leukaemia and hepatic tumours), compared with

natural conception (HR, 1.58; 95% CI, 1.17–2.12), and compared with subfertility but non-ART conception (HR, 1.42; 95% CI, 1.04–1.95) (Weng et al., 2022).

A nationwide cohort registry study in four countries in Scandinavia also reported an increased risk of childhood cancer specifically for children born from the transfer of frozen and thawed embryos, compared with other techniques (fresh embryo transfer or spontaneous conception) (Sargisian et al., 2022). A cohort study in the USA of 126 125 children born after the use of ARTs found that the use of ARTs was associated with an increased risk of cancer, primarily owing to an increased risk of birth defects (Luke et al., 2022). An increased risk of childhood neoplasms was also reported in a record-linkage study of ART-born children in the UK (Sutcliffe et al., 2023).

An increased risk of ovarian cancer in women undergoing ARTs has been reported in studies comparing ART-treated women with the general population, raising concerns over potential confounding by nulliparity (Spaan et al., 2021). A recent publication from the OMEGA cohort had, indeed, shown an increased risk of ovarian cancer only when women undergoing ART were compared with the general population and not when they were compared with women who were subfertile but not undergoing ART (Spaan et al., 2021).

Cancer in experimental animals

Neonatal female Sprague-Dawley rats were injected on day 1 of life with clomiphene (50 µg/rat). After 100 days, the rats exhibited uterine cystic hyperplasia, uterine metaplasia, and endometrial disorganization, as well as tumours of the uterus. Uterine tumours were observed in only a few animals; however, no animals older than 100 days were included in this study (Clark and McCormack, 1977).

Mechanistic evidence

It has been shown that conception using ARTs is associated with aberrant DNA methylation in imprinted loci and other genes in various tissues (Barberet et al., 2022). In addition, ART-conceived neonates displayed widespread differences in DNA methylation, and overall less methylation across the genome (Håberg et al., 2022). Furthermore, children conceived after the use of ARTs into 67 families not diagnosed with oligoasthenoteratozoospermia had a significantly shorter leukocyte telomere length than those conceived spontaneously (Wang et al., 2022d). ARTs also induced global reduction in DNA methylation in mice (de Waal et al., 2015). Yang et al. (2021a) reported that placentas from intra-cytoplasmic sperm injection (ICSI), but not IVF, showed global H3K4me3 alteration compared with those from natural conception. Further, sex-stratified analysis found that, compared with cord blood mononuclear cells (CBMCs) sampled after natural conceptions in same-sex neonates, CBMCs from boys conceived after ICSI presented more genes with differentially enriched H3K4me3 (n = 198) than those from girls conceived after ICSI (n = 79), girls conceived after IVF (n = 5), and boys conceived after IVF (n = 2). In addition, 11 out of 84 microRNAs in the granulosa cells obtained from follicular ovarian retrieval from seven patients in a group receiving FSH (225 IU recombinant FSH) and six patients in a group receiving FSH and LH (150 IU recombinant FSH and 75 IU recombinant LH) were differentially expressed between the FSH and LH group and the FSH group. Differentially expressed miRNA profiles are related to estrogen signalling, oocyte meiosis, and pluripotent cell regulation (Vigo et al., 2021).

One study showed that 69 patients undergoing conventional IVF had more $CD45^+$ leucocytes, fewer $CD8^+$ T cells, decreased concentrations of IL-8 in follicular fluid, and increased VEGF concentrations in serum, compared with patients undergoing natural cycle IVF (Kollmann et al., 2017). Pregnancies after egg donation (n = 25) showed reduced concentrations of stromal cell-derived factor 1α (SDF1α) in the third trimester, compared with pregnancies after natural conception (n = 25) and IVF (n = 25) (Martínez-Varea et al., 2015).

Clomiphene citrate (agent 094) has been shown to increase serum concentrations of progesterone and blood concentrations of estradiol and progesterone in women who are infertile (Hammond and Talbert, 1982;

Fukuma et al., 1983). Repetitive cycles of hormonal stimulation during IVF procedures induced strong cytoplasmic positivity of ERα and PR in atypical melanocytes of two specimens of melanoma from patients (Dika et al., 2017).

Ovariectomized rats treated with clomiphene (5 mg/kg) for 24 hours showed depletion of cytosol estrogen receptors (Kurl and Morris, 1978). In addition, clomiphene reduced the number of cumulus–oocyte complexes (COCs) and E2 levels in the ovary and serum and induced membrane blebbing in oocytes, Bax protein expression, and DNA fragmentation in ovarian follicular cells and ovulated COCs in immature female rats (Chaube et al., 2005).

Clomiphene citrate induced DNA fragmentation in two breast cancer cell lines: MCF-7 and BT20. (Elloumi-Mseddi et al., 2015).

Summary

Findings regarding associations between ARTs and childhood cancer remain inconsistent, with few studies available that are able to disentangle the contribution from each different technique or drug or that have good control for confounding (from the presence of birth defects, perinatal risk factors, or infertility). The Advisory Group noted a lack of data for cancer in experimental animals for nearly all ARTs.

There is evidence that ARTs exhibit KCs; in particular, there is evidence for epigenetic alterations and immunosuppression in exposed humans and experimental systems. Clomiphene induces receptor-mediated effects and alterations of cell proliferation and cell death in exposed humans, experimental systems, or both. The Advisory Group therefore considered that an *IARC Monographs* evaluation of assisted reproductive techniques is warranted but recommended waiting until more defined protocols are available, to help focus the evaluation of specific ART components beyond clomiphene citrate (agent 094).

Recommendation: High priority (and ready for evaluation within 5 years)

096 Neonatal phototherapy

Current IARC/WHO classification

Neonatal phototherapy has not been previously evaluated by the *IARC Monographs* programme. Neonatal phototherapy was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), based on evidence from studies of cancer in humans and mechanistic evidence.

Exposure characterization

Neonatal phototherapy refers to the use of visible light (green-blue light at wavelengths of 420–550 nm) to treat neonatal jaundice, owing to high serum concentrations of unconjugated bilirubin in the neonate (Wang et al., 2021a). It is the standard treatment of choice for hyperbilirubinemia in neonates and is a preventive and treatment strategy for severe neonatal jaundice (Wang et al., 2021a). The median duration of treatment has been reported to be 50 hours (interquartile range, 27–85 hours) (Mukherjee et al., 2018).

Cancer in humans

The priority recommendation of *high* for neonatal phototherapy by the 2019 Advisory Group on Priorities was based mainly on positive findings for childhood cancers in cohort studies from Canada (Auger et al., 2019) and the USA (Newman et al., 2016; Wickremasinghe et al., 2016). The 2019 Advisory Group on Priorities noted an inconsistency between the cancer sites across studies and the possibility of confounding by indication, which was suggested by attenuation of the risk of leukaemia, non-lymphocytic leukaemia, and liver cancer reported after adjustment for propensity score (which incorporated bilirubin levels, chromosomal disorders, and congenital anomalies, among other covariates) in the Kaiser Permanente

northern California dataset (Newman et al. 2016). An update of this Kaiser Permanente analysis, with an additional 5 years of follow-up, did not confirm the previous finding of an increased risk (Digitale et al., 2021). A recent large cohort study from Israel (Bugaiski-Shaked et al., 2022) reported an increased risk of cancer after phototherapy, but with adjustment to perinatal factors limited to only preterm birth and maternal age. An increased risk for all cancers and benign tumours was also reported in a sensitivity analysis excluding children with malformations. HRs for phototherapy exposure are increased for haematological malignancy and leukaemia; however, only unadjusted models are presented (Bugaiski-Shaked et al., 2022).

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

Several publications are available for studies in exposed humans on the suspected genotoxic effects of neonatal phototherapy (Aycicek et al., 2008; Karadag et al., 2009; Zúñiga-González et al., 2012; Kahveci et al., 2013; Yahia et al., 2015). The role of oxidative stress as a potential mechanism, resulting in DNA damage in neonates – whose antioxidative defence systems are still immature – has also been evaluated in several studies (El-Farrash et al., 2019). Some studies have evaluated the effect of phototherapy on the immune system, including the levels of immune cells and various cytokines, but with variable findings (Sirota et al., 1999; Kurt et al., 2009; Procianoy et al., 2010; Jahanshahifard et al., 2012).

Summary

The epidemiological evidence of an association between neonatal phototherapy and cancer risk is inconsistent across studies. No studies of cancer in experimental animals are available. Some supportive mechanistic evidence is available for the KCs for neonatal phototherapy. Concerns remain on confounding factors to assess the effects of neonatal phototherapy in human cancer and mechanistic studies. The Advisory Group therefore considered an *IARC Monographs* evaluation of neonatal phototherapy is warranted.

Recommendation: Medium priority

097 Intense pulsed light

Current IARC/WHO classification

Intense pulsed light (IPL) has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

IPL therapy involves emitting flashes of polychromatic light with a wavelength range of 400–1400 nm and is used in the treatment of several dermatological diseases and for hair removal (ANSES, 2021; Gade et al. 2023). Specific wavelengths can be targeted for treatment with the application of filters, allowing for certain tissues to be targeted. In the USA, IPL therapies were first approved in 1995 by the US FDA. Currently, the US FDA has approved IPL devices for several dermatological diseases or conditions (telangiectasias, photorejuvenation, facial wrinkles, hyperpigmentation, lentigines, ephelides, melasma, rosacea, acne vulgaris, poikiloderma of Civatte, port wine stains, haemangioma, leg veins, venous malformations, and removal of unwanted hair) and to treat dry eye disease resulting from meibomian gland dysfunction (Gade et al., 2023).

Devices are available for both professional and home use (ANSES, 2021). IPL therapy involves four variables of exposure: wavelength, pulse duration, fluence (amount of energy per unit area), and spot size (diameter of illuminated area). Light is absorbed by the skin, leading to photothermolysis. Treatment is contraindicated in some circumstances, such as having a history of skin cancer or having certain other

medical conditions (e.g. autoimmune disease, photosensitive dermatitis) (ANSES, 2021) Exposures are almost entirely limited to end users, though there might be some occupational exposure for health care personnel operating these devices in professional settings.

Cancer in humans

In their review, the French Agency for Food, Environmental, and Occupational Health & Safety (ANSES, 2021) did not identify any cancers related to IPL treatment that were induced by thermal effects. However, ANSES (2021) indicated that the relatively recent development and use of this treatment have not necessarily allowed a sufficient latency period for the detection of cancer in humans. Dessinioti et al. (2023) reviewed studies looking at changes in nevi after IPL treatment; only three small prospective studies of around 30 subjects were included, while the rest of the studies were case reports. Non-malignant changes in nevi were noted, but no melanoma was identified.

Cancer in experimental animals

Sixteen female DBA/2JRccHsd mice (aged 21 weeks) were used in a mouse model of two-stage skin carcinogenesis to evaluate the effects of IPL on skin carcinogenesis (Faustino-Rocha et al., 2016). Animals were divided into two groups: IPL-exposed and non-IPL-exposed. The skin of the dorsal region of all animals was shaved using a machine clipper every 2 weeks. Both groups received a single topical application of 7,12-dimethylbenz[*a*]anthracene (DMBA) in that region. Four days afterwards, 12-*O*-tetradecanoylphorbol-13-acetate (TPA) was applied topically to all animals, twice per week for 22 weeks. The IPL-exposed animals received two applications of IPL on the dorsal region, at an intensity of 2 $J \cdot cm^{-2}$, on the days of TPA application, over 22 weeks. IPL-exposed animals developed fewer preneoplastic and neoplastic epidermal lesions ($n = 28$; 3.5 lesions/animal) than non-IPL-exposed animals ($n = 46$; 5.8 lesions/animal). Six of the eight IPL-exposed animals developed epidermal neoplastic lesions (incidence, 75%), while all eight non-IPL-exposed animals developed epidermal neoplastic lesions (incidence, 100%). Hence, the IPL-exposed animals developed fewer neoplastic lesions ($n = 20$; 3.3 lesions/animal) than non-IPL-exposed animals ($n = 38$; 4.8 lesions/animal). Although the difference was not statistically significant, there were more microinvasive SCCs in IPL-exposed animals ($P = 0.317$). Grade II and III papillomas were the most frequent papillomas observed in both groups. Only four papillomas developed into invasive SCC after 22 weeks of TPA application.

In 2006, Hedelund et al. (2006) investigated whether IPL treatment had a carcinogenic potential in itself or whether it could influence carcinogenesis induced by UV radiation: hairless mice with light skin ($n = 144$) were used and received three IPL treatments, at 2-week intervals. No tumours appeared in untreated control mice or in mice treated only with IPL. Skin tumours developed in mice exposed to UV radiation independently of IPL treatment.

Mechanistic evidence

The findings of Faustino-Rocha et al. (2016) suggest that IPL application increases oxidative stress in skin samples, and causes an increase in DNA damage in keratinocytes, although no alterations of p53 expression were detected after the exposure (supporting KC1, KC2, KC3, KC5). All animals developed an inflammatory stromal response characterized by a diffuse, scarce-to-moderate mononuclear inflammatory infiltrate in the superficial dermis; the inflammatory response was strongly related to tumour promotion (supporting KC6). Faustino-Rocha et al. (2016) demonstrated that all animals exhibited epidermal hyperplasia (supporting KC10). Malekzadeh Gonabadi et al. (2023) reported an increase in TP53 gene expression in skin after IPL treatment. Sorg et al. (2007) reported that exposure to IPL induced the formation of lipid peroxides and thymine dimers in human skin in vivo (KC1, KC2, KC3). Chan et al. (2007) studied the effects on p16 and proliferating cell nuclear antigen (PCNA) expression of repeated treatment with a

high-energy laser and IPL source in a study on male ICR mice and found that repeated use of a high-energy laser and IPL source did not cause any toxicity or tumours in mice; the effects of increased p16 and PCNA were unclear. A significant increase in TP53 gene expression, measured using computer image analysis of immunostained tissue samples, was observed in skin biopsies after IPL treatment in patients with Fitzpatrick skin types III to IV (El-Domyati et al., 2013). However, the levels were found to be "statistically insignificantly lower […] 3 months after treatment than at the end of treatment", suggesting reversibility.

Summary

Human cancer studies with adequate size and follow-up are not yet available. There are initiation–promotion and co-carcinogenicity studies in experimental animals indicating a positive effect of IPL. There is sparse available mechanistic evidence related to the KCs, including genomic instability, oxidative stress, inflammation, and cell proliferation, in experimental systems and in exposed humans. However, the evidence is limited or inadequate for supporting an evaluation of carcinogenicity for IPL. Overall, the available evidence does not justify an evaluation. The Advisory Group therefore considered that an *IARC Monographs* evaluation of IPL is unwarranted at present.

Recommendation: No priority

098 Extremely low-frequency magnetic fields

Current IARC/WHO classification

Extremely low-frequency magnetic fields (ELF-MF) were classified by IARC as *possibly carcinogenic to humans* (Group 2B), based on *limited* evidence in relation to childhood leukaemia, in *IARC Monographs* Volume 80 in 2001 (IARC, 2002b). No evaluation was recommended for ELF-MF by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), because of a lack of new informative epidemiological findings, no cancer bioassay evidence, and little supporting mechanistic evidence.

Exposure characterization

People are exposed to ELF-MF (1–100, 3–300, or 3–3000 Hz) resulting from the generation, transmission, distribution, and use of electricity, e.g. from electric power lines and infrastructure, household wiring, electric and electronic appliances, electric cars, and industrial devices. Close to certain appliances, the magnetic field values can be of the order of a few hundred microteslas. Underneath power lines, magnetic fields can be about 20 μT. Average residential power-frequency magnetic fields in homes are about 0.07 μT in Europe and 0.11 μT in North America (WHO, 2007). Exposure levels for the general population are typically 0.01–0.2 μT for magnetic fields (IARC, 2002b). In France, the background reference level is 0.1 μT (Deschamps and Deambrogio, 2023); 0.1% of the population are estimated to be living in an area potentially exposed to a magnetic field of > 0.4 μT (Deshayes-Pinçon et al., 2023). TWA occupational exposures of 2–4 μT have been reported for welders, logging workers, sewing machine users, linemen, and train drivers. Exposure to ELF-MF while at school may represent a significant fraction of a child's total exposure (IARC, 2002b). Magnetic field exposures have been reported based on magnetic flux density measurements, distances between a child's home and power lines, and wire codings (Brabant et al., 2022).

Cancer in humans

Since the latest IARC evaluation (IARC, 2002b), several meta-analyses or pooled analyses have been published, showing a positive association between ELF-MF exposure and childhood leukaemia. A recent meta-analysis of case–control studies by Seomun et al. (2021), including both studies included in the previous IARC evaluation (IARC, 2002b) and new studies, reported a summary OR for childhood leukaemia

of 1.26 (95% CI, 1.06–1.49) for an ELF-MF of 0.2 μT, while those exposed to 0.4 μT had an OR of 1.72 (95% CI, 1.25–2.35). Another pooled analysis, including only four recent case–control studies (Pedersen et al., 2015; Salvan et al., 2015; Bunch et al., 2016; Kheifets et al., 2017), reported no association with childhood leukaemia; however, the exposure assessment methods in those studies were weaker (Amoon et al., 2022). The proximity of children's households to high voltage cable lines and occupational exposure by their parents to ELF-MF during certain periods before or during pregnancy were inconsistently associated with childhood leukaemia (Talibov et al., 2019; Park, 2023).

A recent case–control study in Italy reported an excess risk for both overall leukaemia and ALL among children with residential distances < 100 m from power lines (Malagoli et al., 2023), while no overall association between residential proximity to transformer stations and childhood leukaemia was detected (Malavolti et al., 2023). An international study of childhood leukaemia in residences near electrical transformer rooms found weak evidence for an elevated risk (Crespi et al., 2024).

An increased risk of AML was reported in workers with occupational exposure to high levels of ELF-MF (Koeman et al., 2014) and for high levels and a long duration (Huss et al., 2018). In the general adult population, significant associations between cumulative duration of living < 50 m from high voltage lines and all brain tumours (OR, 2.94; 95% CI, 1.28–6.75) and glioma (OR, 4.96; 95% CI, 1.56–15.77) were found (Carles et al., 2020). In a cohort study on adult haematological malignancies and brain tumours in relation to magnetic fields from indoor transformer stations, the HR for glioma was 1.47 (95% CI, 0.84–2.57) (Khan et al., 2021).

Cancer in experimental animals

The previous IARC evaluation concluded that there was *inadequate* evidence in experimental animals for the carcinogenicity of ELF-MF. This conclusion was based on the evaluation of four long-term bioassays, and several multistage carcinogenesis studies to evaluate the effect of ELF-MF alone or in combination with other carcinogens (IARC, 2002b). Among those four studies, three provide no evidence that exposure to ELF-MF causes cancer in any target organ. The fourth found an increased incidence of thyroid C-cell tumours in male rats exposed to ELF-MF at two intermediate flux densities. In addition, several other studies of limited design, or multistage carcinogenesis studies had mixed results (IARC, 2002b).

Since then, one study evaluated the possible carcinogenic effects of exposure to ELF-MF on male and female Sprague-Dawley rats from prenatal life until natural death and concluded that lifespan exposures to continuous and intermittent ELF-MF, alone, did not represent a significant risk factor for neoplastic development (Bua et al., 2018). One study conducted in mice observed that long-term exposure to ELF-MF induced the development of cancer. C57BL/6NJ female mice were exposed in late pregnancy to ELF-MF for 1 week and their offspring were exposed for 15.5 months. In female mice, the incidence of chronic myeloid leukaemia in the exposed group was significantly greater than in the control group (Qi et al., 2015). Other studies investigating the tumour-promoting effect of ELF-MF showed that lifespan exposure to ELF-MF in combination with formaldehyde, or with acute low-dose gamma radiation might enhance the carcinogenic effects in Sprague-Dawley rats (Soffritti et al., 2016a, b). In an initiation–promotion study using DMBA as an initiator in Fischer 344 rats, ELF-MF promote mammary tumorigenesis (Fedrowitz and Löscher, 2008).

Mechanistic evidence

The previous IARC evaluation (IARC, 2002b) concluded that the studies reporting an increased frequency of chromosomal aberrations and micronuclei induced by ELF-MF were inconclusive. Since then, other studies investigating the genotoxicity of ELF-MF in exposed humans are available. Most investigations were on PBLs. In some of the studies, buccal epithelial cells were also investigated. A review of studies on the genotoxicity of ELF-MF in exposed humans indicated inconsistent results (Maes and Verschaeve, 2016).

In addition, occupational exposure to ELF-MF in a power plant increased the frequency of single-strand breaks in DNA in 29 male utility workers but not in control subjects (Zendehdel et al., 2019). Other studies have reported no evidence that exposure to ELF-MF causes genotoxicity in exposed humans or human primary cells (Albert et al., 2009; Lv et al., 2021b).

In addition, several studies, mostly conducted in human cell lines and experimental systems, suggested that ELF-MF exhibits other KCs besides genotoxicity, especially the induction of epigenetic alterations (Giorgi and Del Re, 2021), oxidative stress (Schuermann and Mevissen, 2021), and cell proliferation (Barati et al., 2021).

Summary

There are only a few new scientific papers since the publication of *IARC Monographs* Volume 80, with weak exposure assessment and showing a weaker association. Overall, evidence remains consistent in showing an association between exposure to ELF magnetic fields and childhood leukaemia, based largely on studies evaluated in the previous monograph. New initiation–promotion studies show tumour-promoting activity of ELF-MF. Since the previous evaluation, new mechanistic studies related to the KCs in experimental systems, and new studies evaluating the genotoxicity of ELF-MF in exposed humans, became available. However, the findings across all systems remain inconsistent. Overall, the available information does not support a re-evaluation. The Advisory Group therefore considered that an *IARC Monographs* evaluation of ELF-MF is unwarranted at present.

Recommendation: No priority

099 Radiofrequency electromagnetic fields including wireless mobile radiation

Current IARC/WHO classification

Radiofrequency electromagnetic field (RF-EMF) radiation (including from wireless mobile telephones) has been previously classified by IARC as *possibly carcinogenic to humans* (Group 2B) in *IARC Monographs* Volume 102 in 2011 (IARC, 2013a), based on *limited* evidence in humans for glioma and acoustic neuroma. RF-EMF was given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of new cancer bioassay evidence in two independent studies (described below).

WHO is undertaking a health risk assessment of RF-EMF for a variety of outcomes, including cancer. This will be published as a monograph in the *Environmental Health Criteria* series and is based on several, currently ongoing, systematic reviews commissioned by WHO (Lagorio et al., 2021; Mevissen et al., 2022).

Exposure characterization

In *IARC Monographs* Volume 102, RF-EMF radiation was defined as radiation in the frequency range 30 kHz to 300 GHz (IARC, 2013a). Exposure occurs in the general population and in occupational settings, with sources including mobile phones, wireless network, television, radio, 5G technologies, Bluetooth, microwaves, cooking hobs, industrial heating of materials, radar, anti-theft devices, and MRI (IARC, 2013a). Exposure to mobile phones is ubiquitous, considering that nearly 95% of the population in high-income countries and 49% in low-income countries own a mobile phone (International Telecommunications Union, 2022). Source-exposure matrices for the general population and workers are available (Vila et al., 2016; van Wel et al., 2021).

Cancer in humans

The 2019 Advisory Group report (IARC, 2019a) indicated that results from epidemiological studies published after *IARC Monographs* Volume 102 were mixed (Benson et al., 2013; Hardell et al., 2013; Coureau et al., 2014; IARC, 2019a; Röösli et al., 2019). Since the 2019 Advisory Group report (IARC, 2019a), results from the MOBI-Kids study, an international study of brain cancer and the use of EMF technology by children and adolescents (Castaño-Vinyals et al., 2022), the update of the UK Million Women Study (Schüz et al., 2022), and the European Cohort Study of Mobile Phone Use and Health (COSMOS) (Feychting et al., 2024) were published. No increased risk of neuroepithelial brain tumour was found in the MOBI-Kids study (Castaño-Vinyals et al., 2022). In the Million Women Study update, the increased risk for acoustic neuroma reported previously (10+ years use versus never, RR, 2.46; 95% CI, 1.07–5.64) (Benson et al., 2013) was attenuated (10+ years use versus never, RR, 1.32; 95% CI, 0.89–1.96), and no increased risk was found for other cancer subtypes (glioma, glioblastoma, pituitary, eye tumour); however, the exposure assessment was crude. The previous analysis (Benson et al., 2013) reported $P_{trend} = 0.03$ for acoustic neuroma by duration of use, but such an analysis was not reported in the updated publication (Schüz et al., 2022). COSMOS followed 264 574 participants for a median of 7.12 years (recruitment, 2007–2012, in Denmark, Finland, the Netherlands, Sweden, and the UK). For 100 regression-calibrated cumulative hours of calls (country-specific regression-calibrated estimates based on data collected from operators were applied to the self-reported measurements), HRs were 1.00 (95% CI, 0.98–1.02) for glioma, 1.01 (95% CI, 0.96–1.06) for meningioma, and 1.02 (95% CI, 0.99–1.06) for acoustic neuroma (Feychting et al., 2024).

Mobile phone use was associated with increases in overall cancer and NMSC, urinary cancer (in men only), prostate cancer, and vulva cancer, but not brain cancer, in the UK Biobank cohort (Zhang et al., 2024). There was also a significant trend by length of use for NMSC and prostate cancer (Zhang et al., 2024) Concern exists over exposure misclassification, as mobile phone use was captured only at baseline. These findings are not consistent with those of a Danish nationwide cohort study (Schüz et al., 2006).

In *IARC Monographs* Volume 102 (IARC, 2013a), selection bias and recall bias from case–control studies were noted as being of major concern. Bias analysis available at the time of that evaluation showed that the J-shaped response curve observed in the Interphone study, the largest case–control study on mobile phone use contributing to the evidence published in *IARC Monographs* Volume 102 (IARC, 2013a), could have been explained by selection bias, leading to underrepresentation of unexposed controls (Vrijheid et al., 2009a). A recent bias analysis using Monte Carlo simulations showed that the J-shaped relation observed in the Interphone study was compatible with a scenario of greater systematic (> 10%) and random error in cases compared with controls, in the absence of any effect (Bouaoun et al., 2024). Validation studies within the Interphone study showed that there was little differential exposure misclassification between cases and controls; however, in heavy users, overestimation was greater in cases than in controls (Vrijheid et al., 2009b).

Cancer in experimental animals

The 2019 Advisory Group report (IARC, 2019a) noted the availability of new data from the large US NTP study that show clear evidence of an increased incidence of malignant schwannoma in the heart (and possibly some evidence of malignant glioma in the brain) in male rats exposed to radiofrequency radiation at frequencies used by mobile phones; however, no clear increased risk was seen in female rats. Some equivocal evidence was observed of increased evidence of malignant glioma in the brain, malignant schwannoma in the heart, and pheochromocytoma in the adrenal medulla (NTP, 2018a, b). An increased risk of schwannoma of the heart observed in male rats exposed to the highest dose was found in an experimental study conducted at the Ramazzini Institute (Falcioni et al., 2018). International studies, aimed to verify the NTP studies, are ongoing in Japan and the Republic of Korea and are expected in 2024 (Ahn et

al., 2022). Currently, a systematic review of the effects of RF-EMF on cancer laboratory animals is ongoing as part of a WHO risk assessment project (Mevissen et al., 2022).

Mechanistic evidence

As noted in the 2019 Advisory Group report (IARC, 2019a): "The previous IARC evaluation concluded that there was weak evidence that radiofrequency radiation was genotoxic but that there was no evidence for mutagenicity (IARC, 2013a)." Since then, there have been many new publications on the genotoxicity of RF-EMF radiation, including studies in exposed humans. The formation of micronuclei on buccal mucosal cells was shown in several studies on mobile phone-emitted radiation (Rashmi et al., 2020; Revanth et al., 2020). Other studies found no evidence of micronucleus formation (de Oliveira et al., 2017) or no conclusive evidence for induction of DNA damage or for alterations of the DNA repair capacity in human cells exposed to several frequencies of RF-EMF radiation (Schuermann et al., 2020). In other studies, no effects of RF-EMF exposure on oxidant or antioxidant capacity, apoptosis, or mutations in the TP53 gene were revealed, regardless of the frequency (Khalil et al., 2014; Gulati et al., 2020). The authors of a meta-analysis to investigate whether RF-EMF emitted by mobile phones have genotoxic or cytotoxic effects on the oral epithelium concluded that the evidence for genotoxic effects was weak (Dos Santos et al., 2020). In experimental systems, there is a large body of literature on investigations of the genotoxicity of RF-EMF (Meltz, 2003). A study showed that rat gliomas appear to share some genetic alterations with IDH1 wildtype human gliomas, and rat cardiac schwannomas also harbour mutations in some of the queried cancer genes (Brooks et al., 2024). An independent systematic review of the genotoxicity of RF-EMF in in vitro mammalian models is ongoing (Romeo et al., 2021).

In addition, evidence associated with other KCs is available. For example, chronic exposure to RF-EMF emitted from mobile phones may induce oxidative stress and an inflammatory response in rats (Singh et al., 2020). Currently, a systematic review of the effects of RF-EMF on biomarkers of oxidative stress in vivo and in vitro is ongoing as part of the WHO risk assessment project (Henschenmacher et al., 2022). Several studies have investigated the immunotoxicity of RF-EMF (Yadav et al., 2022). Mobile phone radiofrequency radiation was found to be associated with thyroid gland insufficiency and alterations in serum thyroid hormone levels in exposed humans and in rodents, with a possible disruption in the hypothalamic–pituitary–thyroid axis (Alkayyali et al., 2021).

Summary

Since the last evaluation, there have been several new high-quality studies. Overall, the human cancer evidence is mixed. There is new evidence of carcinogenicity in experimental animals. Since the previous evaluation, there is new mechanistic evidence related to the KCs, especially genotoxicity in experimental systems and in exposed humans. However, several of the genotoxicity studies in exposed humans provided inconsistent results. Thus, the mechanistic available evidence currently available may be inconclusive.

Overall, the new evidence regarding cancer in humans and in experimental animals could support a re-evaluation, although a change in the current classification of the carcinogenicity of RF-EMF is uncertain. The Advisory Group therefore considered an *IARC Monographs* evaluation of RF-EMF to be warranted but suggests an evaluation in the latter half of the next 5 years, to await the results of ongoing cancer bioassays, which may provide additional mechanistic evidence.

Recommendation: High priority (and ready for evaluation within 5 years)

100 Radon-222 and its decay products (CAS No. 14859-67-7)

Current IARC/WHO classification

Radon-222 and its decay products were repeatedly classified by IARC as *carcinogenic to humans* (Group 1), most recently in *IARC Monographs* Volume 100D in 2009 (IARC, 2012e), when there was found to be *sufficient* evidence for cancer in humans for lung cancer and *limited* evidence in humans for leukaemia. WHO has published a handbook on reducing harmful health effects from indoor radon exposure (WHO, 2009b).

Exposure characterization

Radon is a naturally occurring radioactive gas, which decays into other radioactive progeny. Among the different isotopes of radon, radon-222 is the most prevalent in the environment, owing to its longest half-life (3.82 days), compared with other radon isotopes (IARC, 2012e). Thus, radon in the environment is mainly constituted of radon-222. Exposure to radon progeny is widespread from natural background radiation, enhanced natural background radiation (e.g. concentrated indoors in basement areas with poor ventilation), and occupational sources, with high concentrations occurring in some scenarios globally, for example in areas with high soil concentrations, where gases may be trapped indoors in subterranean living areas, in underground mines and tourist caves, and in water treatment facilities (Daniels and Schubauer-Berigan, 2017; Hosoda et al., 2021). The annual per capita dose in the USA from inhalation of radon gas and its progeny typically represents about half of the effective dose received by members of the general population from all natural sources of ionizing radiation. For certain occupations, radon and its progeny also dominate occupational radiation exposure. For example, in the nuclear fuel cycle, radon inhaled after its release from uranium mines makes a substantial contribution to workers' doses (UNSCEAR, 2019).

Cancer in humans

The evidence available on leukaemia risk after radon exposure in *IARC Monographs* Volume 100D (IARC, 2012e) consisted mainly of studies conducted among uranium miners. A combined analysis of 11 underground miner cohorts found no increase in leukaemia risk (Darby et al., 1995), and no association of leukaemia was observed in a separate large cohort of miners in Germany (Kreuzer et al., 2008). However, a significant trend in relation to duration and cumulative exposure among miners in Czechia was noted, but the contribution of external gamma radiation was unclear (Tomásek and Zárská, 2004; Tomášek and Kubik, 2006). It was further noted in *IARC Monographs* Volume 100D that most case–control studies of leukaemia, including childhood leukaemia, had null findings. Notably, the Working Group for *IARC Monographs* Volume 100D considered ecological studies to be less informative than cohort and case–control studies.

Since 2009, new findings related to leukaemia in adults or children have been published, including three meta-analyses. A dose–response meta-analysis examined 9 case–control, 8 ecological, and 15 ecological–cohort studies. In the ecological studies, positive correlations were observed for radon air concentrations and leukaemia among adults ($P = 0.46$; 95% CI, 0.05–0.74) and children ($P = 0.67$; 95% CI, 0.53–0.77). For case–control studies, the dose–response meta-analysis found significantly positive pooled exposure–response estimates for lymphoid leukaemia (meta-OR, 1.0361; 95% CI, 1.0014–1.0720), myeloid leukaemia (meta-RR, 1.2257; 95% CI, 1.0034–1.4972), and childhood leukaemia (meta-OR, 1.0309; 95% CI, 1.0050–1.0575), each measured per 100 Bq/m^3 increase in radon dose (Moon and Yoo, 2021). Another meta-analysis (Ngoc et al., 2022) identified 13 studies (8 case–control, 5 cohort) that examined residential radon exposure in relation to childhood leukaemia; 5 of these studies (Bräuner et al., 2010; Del Risco Kollerud et al., 2014; Pedersen et al., 2014; Demoury et al., 2017; Nikkilä et al., 2020) were published since the previous evaluation. Among the case–control studies, the meta-OR for the highest compared with lowest exposure category was 1.43 (95% CI, 1.19–1.71), with low heterogeneity, and among the cohort studies the meta-RR

was 1.15 (95% CI, 0.92–1.45), with higher heterogeneity. There was little evidence of a dose–response pattern among the ORs for the case–control studies. A third meta-analysis (Lu et al., 2020b) identified another study that had some positive findings for childhood leukaemia (Hauri et al. (2013).

For cancers other than lung cancer and leukaemia, few studies have been published since the previous evaluation. A recent review (Reddy et al., 2022) cites several null cohort studies for skin cancer but indicates several studies with ecological metrics of exposure that suggest a positive association for melanoma.

In the Pooled Uranium Miners Analysis (PUMA), which pools seven cohorts of uranium miners in Canada, Czechia, France, Germany, and the USA, increased SMRs have been observed for some cancers other than lung cancer (e.g. cancers of the stomach, liver and gall bladder, and larynx), but exposure–response associations have not yet been published (Richardson et al., 2021).

Mechanistic evidence

There remains uncertainty about the extent to which radon progeny can irradiate tissues outside the respiratory tract. However, exposure of uranium miners to tissues of the digestive tract is plausible, owing to mucociliary clearance after inhalation exposure.

Summary

Emerging evidence suggests that childhood leukaemia and some forms of leukaemia in adults may be associated with exposure to radon progeny, although most of the evidence arises from studies of residential radon, which may be more susceptible to unmeasured or residual confounding, owing to the low doses involved. Important emerging evidence for cancers other than lung cancer (e.g. cancers of the larynx, brain, kidney, and stomach, leukaemia, and multiple myeloma) is expected in the next few years from the PUMA cohort, which could provide key evidence for an evaluation (Rage et al., 2020). The Advisory Group therefore considered an *IARC Monographs* evaluation of radon-222 and its decay products to be warranted, timed for the latter half of the 5-year period.

Recommendation: High priority (and ready for evaluation within 5 years)

101 Very hot beverages and very hot food

Current IARC/WHO classification

Drinking very hot beverages, at temperatures above 65 °C or above, was classified by IARC as *probably carcinogenic to humans* (Group 2A) in *IARC Monographs* Volume 116 in 2016 (IARC, 2018a), on the basis of *limited* evidence of carcinogenicity in both human (for SCC of the oesophagus) and animals. Very hot foods and beverages were given a priority rating of *high* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), based on findings of an association with oesophageal cancer in humans.

Exposure characterization

Very hot beverages and very hot food are defined as having temperatures > 65 °C when consumed. Tea and coffee stand out as the most widely consumed hot beverages globally (IARC, 2018a). Although there are recommendations for the appropriate temperatures for hot beverages, the preferred consumption temperatures vary across different contexts. In addition, in epidemiological studies, it is crucial to differentiate between brewing temperatures and serving temperatures (Abraham and Diller, 2019). Furthermore, reliance solely on temperature, often determined by self-reported drinking temperature, is unreliable and lacks comprehensiveness as a metric for evaluating human exposure to very hot foods and beverages (Middleton et al., 2019a). These challenges lead epidemiological studies to use more objective metrics and incorporate alternative exposure measures, including sip volume, temperature throughout a

drinking episode, drinking frequency, speed, volume, waiting time before consumption, and the frequency of burning of the mouth or tongue.

Cancer in humans

IARC Monographs Volume 116 noted that there was consistent association between drinking hot beverages and an increased risk of oesophageal SCC; however, this was mainly based on case–control studies, with only one prospective study showing a positive association (IARC, 2018a). Since *IARC Monographs* Volume 116, at least two cohort studies have been published. In the first, a report of the Golestan Cohort Study, a study established from 2004 to 2008,in the Islamic Republic of Iran, 50 045 individuals aged 40–75 years were followed up for a median duration of 10.1 years. This study found that drinking hot black tea increased the risk of oesophageal SCC by more than twofold and that drinking very hot black tea increased the risk of oesophageal SCC by more than eightfold, compared with drinking warm black tea. The study's reference group consisted solely of individuals who drank tea, mostly in large amounts, at lower temperatures. This approach might offer more robust evidence regarding the association between tea-drinking temperature and risk of oesophageal SCC, compared with scenarios where the reference group includes those who did not drink tea or those who consumed tea infrequently. The study employed both objective and self-reported metrics for exposure assessment, enhancing the reliability of its findings. Different measures were found to be significantly associated with the risk of oesophageal SCC (Islami et al., 2020).

In another prospective cohort study, conducted from 2004 to 2008 in China, in over 450 000 participants followed up until 2015 (median follow-up of 9.2 years) and comprising 1731 incidence cases of oesophageal cancer, findings indicated that combining high-temperature tea consumption with either alcohol consumption or smoking was associated with a higher risk of oesophageal cancer, compared with the risk associated with hot tea consumption alone (Yu et al., 2018). The participants' tea consumption was self-reported once at baseline, introducing a potential source of non-differential measurement error. Additionally, the study primarily focused on exploring the interaction between alcohol consumption and smoking with hot tea consumption, and thus might be of little informativeness for the evaluation of hot beverages alone.

At least three recently published population-based case–control studies were conducted in China (Tai et al., 2017; Yang et al., 2018; Lin et al., 2020). All those studies indicated a positive and strong association between the temperature of consumed beverages (beverages and food together in Tai et al., 2017) with risk of oesophageal SCC. In addition to population-based case–control studies in China, two reports of the Esophageal Squamous Cell Carcinoma African Prevention Research (ESCCAPE) study have recently been published, one from Malawi and the United Republic of Tanzania (Masukume et al., 2022), and the other from Kenya (Middleton et al., 2019b). In these reports, it was observed that consumption of very hot beverages (which also included porridge) was strongly associated with oesophageal SCC risk, and the association was consistent in different subgroups and several exposure metrics. Masukume et al. (2022) also showed positive associations for hot porridge consumption as separate metrics. Considering that these studies are the first reports from the geographical area, they are likely to be informative for evaluating the consistency of the association between very hot beverages and food and risk of oesophageal SCC.

Furthermore, two recent meta-analyses, one comprising a total of 23 reports with 5050 cases and 10 609 controls, and the other encompassing a total of 12 case–control studies with 5253 cases and 8273 controls, found that the consumption of hot tea significantly increased the risk of oesophageal SCC (Luo and Ge, 2022; Zhong et al., 2022).

A recent meta-analysis, including only studies published in countries in Africa (11 studies), found a meta-RR for consumption of hot beverages or food and risk of oesophageal SCC of 1.68 (95% CI, 1.13–2.49) (Simba et al., 2023). In that analysis, hot food and beverages were combined as an indicator of potential oesophageal injury resulting from exposure to high temperatures (Simba et al., 2023).

Cancer in experimental animals

No new studies of cancer in experimental animals published since the previous evaluation were available to the Advisory Group.

Mechanistic evidence

New mechanistic evidence associated with the KCs is sparse. Ernst et al. (2021) described the effect of drinking hot beverages on exfoliated cells of the oral mucosa sampled from a group of 73 participants from a region in the northern Islamic Republic of Iran. An increase in the cell division rate of the mucosa, without an increase in the frequency of micronucleus formation, was observed in subjects consuming ≥ 3 cups of hot beverage daily over a period of 21 days (Ernst et al., 2021). One study described in a series of oesophageal SCC models (in vitro and in vivo) the potential of hot water (65 °C) to induce cell proliferation and non-neoplastic lesions to malignant phenotypes through the expression of miR-132-3p, a miRNA known to be highly expressed in various cancer types (Wang et al., 2023g).

Summary

Evidence of an increased risk of oesophageal SCC associated with drinking very hot beverages has strengthened with positive findings from a very informative cohort study and several other case–control studies conducted in geographically diverse populations, some of them including food other than beverages in the exposure metrics. There is no new evidence for cancer in experimental animals, and little mechanistic evidence is available since *IARC Monographs* Volume 116 (IARC, 2019a). Overall, the Advisory Group considered an *IARC Monographs* evaluation of very hot beverages and very hot food to be warranted.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

102 Dietary salt intake

Current IARC/WHO classification

Dietary salt intake has not been previously evaluated by the *IARC Monographs* programme. Chinese-style salted fish was classified by IARC as *carcinogenic to humans* (Group 1) in Volume 100E in 2009 (IARC, 2012f). Pickled vegetables (traditional Asian) were classified by IARC as *possibly carcinogenic to humans* (Group 2B) in Volume 56 in 1992 (IARC, 1993a). The JECFA assessed dietary salt intake in 1985 (FAO/WHO, 1986).

Exposure characterization

As noted in the 2019 Advisory Group report (IARC, 2019a):

> Salt is used in cooking and food preservation. The main dietary sources of salt are processed foods, such as bread, pizza, and other industrially processed foods, and salt-preserved foods, such as processed meats, salted meats or fish, and pickled vegetables. Table salt contributes little to total salt intake. The average adult intake of salt varies by country, from less than 6 g to 18 g per day.

Cancer in humans

As mentioned in the 2019 Advisory Group report (IARC, 2019a), there are studies of human populations showing that salting as a food preparation method is associated with an increased risk of stomach cancer. However, there are issues related to confounding by *Helicobacter pylori* infection. A review of the recent

literature suggests that there are also large challenges in separating dietary salt intake from processed meat consumption, which is classified by IARC as *carcinogenic to humans* (Group 1).

Cancer in experimental animals

As described in the 2019 Advisory Group report (IARC, 2019a), "numerous studies in animals infected with *H. pylori* have shown an increased incidence of gastric cancer with high-salt diets (Fox et al., 1999; Bergin et al., 2003)."

Mechanistic evidence

As noted previously, in mechanistic studies in humans and animals, it is difficult to disentangle the effects of dietary salt intake from those of co-exposures to *H. pylori* or processed meat consumption.

Summary

The Advisory Group noted that it would be very challenging to conduct a cancer hazard assessment of dietary salt intake, and it is unclear that the evidence warrants such an evaluation. The Advisory Group therefore considered that an *IARC Monographs* evaluation of dietary salt intake is unwarranted at present.

Recommendation: No priority

103 Estragole (CAS No. 140-67-0)

Current IARC/WHO classification

Estragole has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

Estragole is listed by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a) as a high production volume chemical.

Estragole is a volatile compound with an anise-like odour that occurs naturally in some plants, such as basil, fennel, anise, and tarragon (Bristol, 2011). Environmental persistence is expected to be low. It is used as a fragrance or flavour additive in foods, beverages, cleaning agents, and cosmetics.

The general population is widely exposed to estragole through the ingestion of food and beverages that contain estragole, either naturally (fennel tea, use of herbs) or as an additive, as well as through such consumer products as detergents and cosmetics (Bristol, 2011; Lopez et al., 2015). Electronic cigarette refill liquid and the smoke of Indian flavoured bidi cigarettes contain estragole; this makes the consumption of these products an additional exposure source (Stanfill et al., 2003; Omaiye et al., 2020). Estimates of total daily exposure range between 10 and 70 µg/kg bw per day (SCF, 2001; Smith et al., 2002). Occupational exposure might occur during the extraction of estragole or in the manufacture of estragole-containing products.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

No full cancer bioassay has been conducted to assess the carcinogenicity of estragole in animals. However, 3-month toxicity studies of estragole administered by gavage to F344/N rats and $B6C3F_1$ mice have shown that estragole induced two cholangiocarcinomas and one hepatocellular adenoma in the rat liver, concurrent with non-neoplastic lesions in rats and mice (Bristol, 2011).

Mechanistic evidence

Estragole is an allyl alkoxybenzene and contains a methoxy group and an allyl group. It is structurally similar to other agents, e.g. methyleugenol, eugenol, and safrole. Of note, methyleugenol was recently classified by IARC as *probably carcinogenic to humans* (Group 2A) (Riboli et al., 2023; IARC, 2024a). Estragole is biotransformed to active metabolites through CYP1A2 or SULT1A1 (Jeurissen et al., 2007; Suzuki et al., 2012a). SULT1A1 also mediates the formation of DNA adducts (Phillips et al., 1984; Alhusainy et al., 2013). It can form DNA adducts in various test systems in vitro, including primary rat hepatocytes, and in vivo (Randerath et al., 1984; Paini et al., 2012; Ding et al., 2015; Yang et al., 2020a). Estragole is not mutagenic in bacteria; however, mutagenicity was reported in a humanized model of *Salmonella* strains engineered with human sulfotransferases (Oda et al., 2012). It was shown to induce UDS, SCE, and DNA damage, by the comet assay, in cells in vitro and to induce gene mutation in transgenic rodents (Martins et al., 2012; Suzuki et al., 2012b). Cell proliferation, in combination with DNA adducts and mutations, was observed in liver tissues of rats exposed to estragole, and inhibition of protein phosphatase 2A (PP2A) seemed to contribute to the estragole effects (Auerbach et al., 2010; Ishii et al., 2017)

Summary

No studies on human cancer after exposure to estragole were available to the Advisory Group. There is evidence that estragole induces tumours in the liver of rats. The Advisory Group noted that these tumours are very rare in animals of the age used in the study and considered them treatment-related. There is mechanistic evidence that estragole exhibits KCs, including electrophilicity and genotoxicity, mainly from experimental systems but also from humanized models. The Advisory Group therefore considered an *IARC Monographs* evaluation of estragole to be warranted and recommends evaluating estragole together with another alkoxybenzene, safrole (agent 024), described in the present report.

Recommendation: High priority (and ready for evaluation within 2.5 years).

104 Indole-3-carbinol (CAS No. 700-06-1)

Current IARC/WHO classification

Indole-3-carbinol (I3C) has not been previously evaluated by the *IARC Monographs* programme. I3C was given a priority rating of *medium* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a), on the basis of positive findings in a bioassay performed by the US NTP.

Exposure characterization

As noted in the 2019 Advisory Group report (IARC, 2019a):

> Exposure to I3C through cruciferous vegetables is highly dependent on dietary patterns (Fujioka et al., 2014; Baenas et al., 2017). I3C is also available in dietary supplements, alone or in combination with a variety of herbs and/or vitamins. Clinical trials of oral administration have been performed for ovarian cancer and breast cancer, showing that co-treatment with I3C improves cancer outcomes (Thomson et al., 2017; Kiselev et al., 2018).

Cancer in humans

The 2019 Advisory Group on Priorities noted that human cancer studies have generally shown evidence of a protective association of I3C with various types of cancer in case–control and cohort studies, as well as clinical trials.

Cancer in experimental animals

In the NTP bioassay (NTP, 2017), I3C was found to increase the incidence of malignant uterine neoplasms (primarily adenocarcinoma), as well as fibroma and fibrosarcoma in the skin of female Harlan Sprague-Dawley rats. In male B6C3F$_1$/N mice, I3C increased the incidence of hepatocellular adenoma, HCC, hepatoblastoma, and their combination (NTP, 2017). Conversely, the cancer chemopreventive properties (and therapeutic properties) of I3C have been highly investigated in recent years, and there are also long-term studies in rodents showing protective effects against cancer. For example, I3C has been found to inhibit tumorigenesis in rodents (Benninghoff and Williams, 2013; Baena Ruiz and Salinas Hernández, 2016; de Moura et al., 2018).

Mechanistic evidence

A review of the literature associated with the KCs indicates more studies showing preventive mechanisms than mechanisms associated with induction of the KCs. For example, mechanistic studies have found that I3C exhibits a broad spectrum of effects relevant to the KCs or cancer prevention, including effects on apoptosis, cell cycle progression, hormonal homeostasis, DNA repair, angiogenesis, and multiple drug resistance (Weng et al., 2008).

Summary

Human cancer studies have generally shown cancer-protective effects of I3C. The heterogeneity of the bioassay and mechanistic evidence would complicate the cancer hazard assessment of I3C. The Advisory Group therefore considered that an *IARC Monographs* evaluation of I3C is unwarranted at present.

Recommendation: No priority

105 Isoflavones

Current IARC/WHO classification

Isoflavones and the broader class of phytoestrogens have not been previously evaluated by the *IARC Monographs* programme. Isoflavones and phytoestrogens were given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a).

Exposure characterization

The main isoflavones are genistein, daidzein, glycitein, formononetin, biochanin A, and puerarin. Humans are exposed to isoflavones and phytoestrogens primarily from the dietary consumption of soybeans and soy products, as well as other legumes. As noted in the 2019 Advisory Group report (IARC, 2019a), exposure is highest in certain countries in Asia (Spagnuolo et al., 2015; Applegate et al., 2018).

Cancer in humans

As described in the 2019 Advisory Group report (IARC, 2019a), most of the available studies of cancer in humans have shown inverse or null associations with genistein and other phytoestrogen exposures.

Cancer in experimental animals

A study conducted by the US NTP in female rats exposed to genistein from conception until the age of 2 years found an excess of tumours of the mammary gland and pituitary gland (NTP, 2007a). In mice, genistein was shown to enhance proliferation and metastasis of patient-derived prostate cancer cells (Nakamura et al., 2011).

Mechanistic evidence

Some clinical trials have shown soy supplementation to increase the breast cell proliferation rate of premenopausal women (McMichael-Phillips et al., 1998) or increase the expression of genes associated with possible adverse effects in premenopausal women (Khan et al., 2012).

However, the cancer chemopreventive properties (and therapeutic properties) of isoflavones have been highly investigated in recent years. The mechanistic evidence in vivo and in vitro further emphasized the chemopreventive potential of genistein (Tuli et al., 2019), in view of which genistein has been upscaled to clinical trials (Khan et al., 2012). A study has shown the promising role of genistein in combination with the FOLFOX (folinic acid, fluorouracil, oxaliplatin) chemotherapy regimen to treat metastatic CRC (Pintova et al., 2019). In addition, epidemiological data also suggest that isoflavone may be associated with a reduction in the risk of breast cancer (Trock et al., 2006; Zhao et al., 2019). Overall, the data, albeit not consistent regarding a potential risk reduction, appear to exclude an adverse effect of exposure to dietary isoflavones, at the intake levels investigated, on the incidence of breast cancer for pre- and postmenopausal women (Hüser et al., 2018).

The Advisory Group also noted that it may be of interest to consider possible estrogenic effects in postmenopausal women and prepubertal boys. A systematic review noted that, in postmenopausal women, urinary excretion of estrone (E1), progesterone, FSH, LH, and sex hormone-binding globulin (SHGB) was not modulated by isoflavone treatment, and suggested that isoflavone intake does not affect estrogen homeostasis (Finkeldey et al., 2021). Additional research would be helpful to investigate any differential response of pre- and postmenopausal women to isoflavones.

Summary

Given the lack of evidence of human cancer and mechanistic findings, the Advisory Group considered it premature to conduct a cancer hazard identification for genistein and other isoflavones and phytoestrogens and therefore considered that an *IARC Monographs* evaluation of isoflavones is unwarranted at present.

Recommendation: No priority

106 Sucralose (CAS No. 56038-13-2)

Current IARC/WHO classification

Sucralose has not been previously evaluated by the *IARC Monographs* programme. Sucralose was given a priority rating of *low* by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (IARC, 2019a).

Exposure characterization

Sucralose is a widely used non-nutritive sweetener found in various foods, including baked goods, beverages, chewing gum, gelatins, and frozen dairy desserts (US FDA, 2023d). It was originally approved for use as a food ingredient in Canada in 1991. In 1998, the US FDA authorized the use of sucralose, initially in a limited number of foods and beverages, and later for use in all categories of foods and beverages. In 2004, the EU approved the use of sucralose in a variety of products. The ADI of sucralose was established

at 5 mg/kg bw in the USA and 15 mg/kg bw in the EU (Soffritti et al., 2016). Sucralose is currently approved for use in more than 80 countries (Brusick et al., 2010). Even for high-intake consumers, average daily intakes are probably less than 3 mg/kg per day (Magnuson et al., 2017).

Cancer in humans

There are no specific studies on sucralose and cancer in humans, but there have been studies of non-nutritive sweeteners and the risk of cancer. In the French NutriNet-Santé cohort, it was estimated that sucralose represented 9.7% of all artificial sweeteners consumed in that population (Debras et al., 2022). While overall consumption of artificial sweeteners, and of aspartame more specifically, was associated with a small, but statistically significant increase in the risk of cancer, the data were not adequate to analyse sucralose separately because of the relatively low proportion of sucralose-containing foods consumed by the population. In this, as well as in other prospective cohort studies, most of the intake of artificial sweeteners was as saccharin or aspartame, rather than sucralose.

Cancer in experimental animals

Two studies, one in mice and one in rats, were negative (Mann et al., 2000a, b). The carcinogenicity of sucralose was evaluated by exposing mice or rats to dietary concentrations at the highest dose, 3.0% of sucralose for up to 104 weeks after parturition. Sucralose did not increase the incidence of any tumour in either mice or rats (Mann et al., 2000a, 2000b).

A recent lifespan study in mice, with sucralose administered in feed beginning prenatally (from 12 days of gestation) through the lifespan, reported a significant dose-related increase in the incidence of haematopoietic neoplasia in male mice, but not in female mice (Soffritti et al., 2016).

Recent review papers have further refuted the carcinogenicity of sucralose (Berry et al., 2016; Chappell et al., 2020). However, a study reported that sucralose promotes the risk of colitis-associated CRC in a mouse model, along with changes in microbiota (Li et al., 2020c).

Mechanistic evidence

Sucralose tested negative in several genotoxicity screening assays, with the exception of an independent comet assay (Sharma et al., 2007; Brusick et al., 2010; Kundu et al., 2020; Schiffman et al., 2023). However, some studies report positive results for genotoxicity; sucralose induced DNA damage in gastrointestinal organs of mice (Sasaki et al., 2002) and caused DNA damage and oxidative stress in the blood cells of *Cyprinus carpio* (Heredia-García et al., 2019). In addition, sucralose promoted ROS accumulation and adipogenesis in human adipose tissue-derived mesenchymal stromal cells (Kundu et al., 2020). Pasqualli et al. (2020a) observed genotoxicity and mutagenicity effects in cultured human lymphocytes, accompanied by cytotoxicity (Pasqualli et al., 2020a).

Several studies report the induction of oxidative stress (KC5) in experimental systems in vitro and in vivo (Heredia-García et al., 2019; Kundu et al., 2020; Schiffman et al., 2023); chronic inflammation (KC6) (Bian et al., 2017; Bessler and Djaldetti, 2019; Li et al., 2020c; Aguayo-Guerrero et al., 2023), alteration of the immune response (KC7) (Rahiman and Pool, 2014; Rosales-Gómez et al., 2018; Pasqualli et al., 2020a; Zani et al., 2023), and KC10 (Dhurandhar et al., 2018; Lizunkova et al., 2019; Shil et al., 2020). Sucralose activates taste receptors and has been shown to affect gut microbiota.

Heavy sucralose ingestion during pregnancy affects neonates' anthropometric, metabolic, and inflammatory features (Aguayo-Guerrero et al., 2023). Sucralose may increase the risk of developing tissue inflammation by disrupting the gut microbiota; this is supported by elevated proinflammatory gene expression in the liver of sucralose-treated mice (Bian et al., 2017). Conversely, sucralose was found to inhibit the induction of proinflammatory and increased anti-inflammatory cytokine release of human PBMCs co-cultured with colon cancer cells (Bessler and Djaldetti, 2019).

Summary

There are no studies investigating sucralose and human cancer risk. From the available studies in experimental animals, only one showed an increased incidence of tumours in male rats. It is noted that the effect of inflammation and immune responses within animal facilities should be carefully evaluated when interpreting the results of haematopoietic neoplasia induction in studies of sucralose carcinogenicity.

There is some evidence that sucralose exhibits the KCs of oxidative stress, and chronic inflammation and cell proliferation, cell death, and nutrient supply. However, several of the studies are of questionable quality. Overall, the Advisory Group does not recommend an *IARC Monographs* evaluation of sucralose.

Recommendation: No priority

107 Sweetened beverage consumption, including sugar-sweetened beverages and artificially sweetened beverages

Current IARC/WHO classification

Sweetened beverage consumption, including sugar-sweetened beverages (SSBs) and artificially sweetened beverages (ASBs) have not been previously specifically evaluated by the *IARC Monographs* programme. Three specific artificial sweeteners (aspartame, cyclamates, and saccharin) have been evaluated by the *IARC Monographs* programme. Aspartame was classified by IARC as *possibly carcinogenic to humans* (Group 2B), on the basis of *limited* evidence for cancer in humans, specifically for HCC (IARC, 2024a). Saccharin and cyclamates were evaluated by IARC as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1999b). Studies of ASBs were considered in the recent evaluation of aspartame only to the extent to which they reflected primarily aspartame exposure (IARC, 2024a).

Exposure characterization

SSBs are any liquids that are sweetened with various forms of added sugar, such as brown sugar, corn sweetener, corn syrup, dextrose, fructose, glucose, high-fructose corn syrup, honey, lactose, malt syrup, maltose, molasses, raw sugar, or sucrose. Examples of SSBs include, but are not limited to, regular soda (not sugar-free), fruit drinks, sports drinks, energy drinks, sweetened waters, and coffee and tea beverages with added sugars (Chevinsky et al., 2021).

ASBs include a large variety of drinks that contain artificial sweeteners, such as aspartame, sucralose, or saccharine (Ruanpeng et al., 2017), either as a replacement of or in combination with sugar. These are mainly of industrial production, often best known on the market as diet sodas, diet soft drinks, etc.

National and international data on the number of consumers and the level of consumption of sweetened beverages per capita are not easy to summarize and compare because of the different types of product involved, such as naturally sweetened beverages (e.g. fruit juices), industrially sweetened drinks and soft drinks, and artificially sweetened drinks.

For the USA, the CDC reported that the prevalence of self-reported intake of SSBs at least once daily among adults, in the period between 2010 and 2015, varied from 44.5% to 76.5% (Chevinsky et al., 2021; CDC, 2022b). In Europe, based on a report from the EU, total sales of soft drinks per country ranged from 130 to over 300 L/person per year. Annual trends indicated a steady increase from 2014 until 2018, and a slight decrease in 2019 (AHFES, 2021). Daily consumption of sugary and diet soft drinks in European adolescents decreased between 2002 (2006 for diet drinks) and 2018 (Chatelan et al., 2022).

With the pervasive presence of these beverages in global markets, human exposure is widespread and occurs mainly through ingestion. Some populations have particularly high levels of consumption, such as children or individuals with specific dietary practices or health conditions.

Cancer in humans

Some epidemiological studies have investigated the possible association between SSB and ASB consumption and a subsequent risk of developing cancer. In several studies, a specific objective was to investigate separately the association of SSB or ASB consumption with cancer. The results of a relatively small number of prospective cohort studies have been published on ASBs or SSBs or both (e.g. Chazelas et al., 2019; Mullee et al., 2019; Debras et al., 2022).

Some of the results suggested that consumption of either ASBs or SSBs, or both, may be associated with an increased risk of certain types of cancer, including breast, prostate, and CRC. In *IARC Monographs* Volume 134 (IARC, 2024a), there was an evaluation of *limited* evidence for a causal association between aspartame consumption and HCC, based on findings from three prospective studies encompassing four large cohorts (Stepien et al., 2016; Jones et al., 2022a; McCullough et al., 2022).

Some cohort studies have investigated the possible association between SSBs and cancer risk. A study conducted in combined USA cohorts (the National Institutes of Health (NIH)-American Association of Retired Persons (AARP) Diet and Health Study, and the PLCO Screening Trial) reported that, among people with diabetes, there were significant associations between consumption of sweetened beverages overall and liver cancer (HR, 1.12; 95% CI, 1.01–1.24) (Jones et al., 2022a).

One of the methodological complexities in this type of investigation is that consumption of SSBs and ASBs tend to be correlated. The NutriNet-Santé cohort collected detailed information on types and brands of foods and drinks, aimed at better classifying the type of sweetener consumed by the study participants. The study found that the consumption of sugary drinks was significantly associated with the risk of cancer overall (2193 cases; HR for 100 mL/day, 1.18; 95% CI, 1.10–1.27; $P < 0.0001$) and the risk of breast cancer (693 cases; HR, 1.22; 95% CI, 1.07–1.39; $P = 0.004$) (Chazelas et al., 2019).

Another methodological complexity for these investigations is that consumption of both SSBs and ASBs may be correlated with obesity, sometimes in complex and different ways, in different population subgroups. Because obesity is a known risk factor for various cancers, there is the possibility of confounding by obesity when analysing the association of ASB and SSB consumption with cancer risk. However, all large and well-conducted prospective cohort studies measured height and weight at baseline and controlled for BMI in the analysis.

Cancer in experimental animals

Adenomatous polyposis coli (APC)-mutant mice (which are predisposed to develop intestinal tumours) treated with daily oral administration of high-fructose corn syrup, the primary sweetener in sweetened sugary beverages, showed a substantial increase in tumour size and tumour grade in the absence of obesity and metabolic syndrome (Goncalves et al., 2019). In another study of APC-mutant mice fed high-fructose corn syrup, dietary fructose led to a more severe intestinal tumour burden (Taylor et al., 2021). In a study of subcutaneous colorectal tumour grafts in mice, consumption of water containing 10% glucose, water, or water containing 10% fructose led to significantly greater tumour growth in vivo compared with controls, with a stronger effect observed for fructose (Cui et al., 2023). In a study of female Sprague-Dawley rats treated with *N*-methyl-*N*-nitrosourea, animals fed a high-fructose diet exhibited decreased latency in mammary tumours and an approximately twofold increase in tumour multiplicity, compared with animals fed a standard diet, without a change in body weight (Kumar et al. 2021).

Mechanistic evidence

Several studies in experimental systems investigated the potential of single exposures to sweeteners including sucrose, molasses, corn syrup, fructose, sucralose, acesulfame potassium, and steviol, to induce genotoxicity, oxidative stress, chronic inflammation, and alteration of the immune system, and, more recently, on the potential to affect gut microbiota or alter metabolism. For example, in human lymphocytes

treated with fructose at varying concentrations, an increase in DNA damage was identified using the alkaline comet assay (Pasqualli et al., 2020b). In a study in Switzerland of female mice fed water with 0%, 10%, or 20% fructose, a dose–response increase in DNA damage was observed (Magenis et al., 2020). A subsequent study in Switzerland of female mice also showed that fructose exposure (versus water only) before and during pregnancy led to higher DNA damage in the PBLs and liver cells, as well as higher levels of micronucleated erythrocytes in bone marrow samples (Magenis et al., 2023). In addition, the offspring of mothers receiving fructose before pregnancy or during pregnancy experienced increases in liver steatosis and genotoxicity. A study of male rats fed a high-fructose diet showed increased mitochondrial DNA (mtDNA) damage in liver cells and reduced mtDNA copy number, a marker of impaired mitochondrial biogenesis (Cioffi et al., 2017). Recently, it was reported that long-term exposure to sucrose solution or commercial SSBs can induce oxidative stress and alter liver metabolism, or modulate receptor-mediated effects in the pancreas in experimental animals, thus altering insulin sensitivity (Schiano et al., 2020; Souza Cruz et al., 2020; Cao et al., 2021; Barzalobre-Geronimo et al., 2023; Wu et al., 2023b). Recently, exposure to SSBs has been associated with alteration of the immune system, including shortening of telomere length in leukocytes in adolescents (Wojcicki et al., 2018).

Summary

Overall, there is evidence that SSBs may be associated with an increased risk of cancer in humans. In addition, there is some evidence that SSBs can induce cancer in experimental animals. Certain SSBs, mainly containing fructose, have been shown to exhibit some of the KCs, including genotoxicity, oxidative stress, and chronic inflammation in experimental systems. Evidence for ASBs is difficult to separate from the recent evaluation of aspartame. Based on the available evidence, the Advisory Group considered an evaluation of SSBs, but not ASBs, to be warranted and suggested its timing during the latter half of the evaluation period.

Recommendations

SSBs: High priority (and ready for evaluation within 5 years)

ASBs: No priority

108 Ultraprocessed food consumption

Current IARC/WHO classification

Ultraprocessed food (UPF) consumption has not been previously evaluated by the *IARC Monographs* programme.

Exposure characterization

The term UPF is generally applied to foods that result from a series of industrial processes. Their chemical and physical definition is not straightforward, as they may contain, in different combinations and proportions, a large number of substances, such as flavours, flavour enhancers, colours, emulsifiers, emulsifying salts, artificial sweeteners, thickeners, foaming, anti-foaming, bulking, carbonating, gelling, and glazing agents, sugars, oils, fats, sodium chloride, and other substances (Monteiro, 2009; Monteiro et al., 2019a). UPFs tend to be ready-to-eat or easy-to-prepare foods, with a prolonged shelf life and high palatability. UPFs generally meet high standards of toxicological and microbiological safety.

The exceptionally large varieties of foods and drinks that meet some of the criteria for being labelled as UPFs represents an objective difficulty for their precise definition and characterization in epidemiological investigations of their relation with the risk of developing cancer or other chronic diseases.

A classification of foods in four categories by level of processing (the Nova classification) has been used in several nutritional and epidemiological studies for the classification of human exposure to UPFs (FAO,

2019); in this classification, group 4 comprises UPFs (i.e., formulations of ingredients of mostly industrial use, created by a series of industrial processes and techniques) (Monteiro et al., 2019b).

Consumption of UPFs has increased over the past decades in many countries around the world. Recent studies indicate that in Canada, the UK, and the USA, UPFs account for approximately 50–70% of an individual's daily total energy intake from food and drinks, while consumption remains much lower (accounting for 10% of energy intake) and is inversely associated with a “Mediterranean" diet in countries such as Italy (Marino et al., 2021).

Cancer in humans

The association between UPF consumption and cancer risk has been investigated in several prospective cohort studies, and findings have been summarized in a recent meta-analysis (Isaksen and Dankel, 2023).

A publication based on the EPIC, a large population-based cohort study, estimated (using food replacement statistical modelling) that a substitution of 10% of UPFs in a participant’s diet with an equal amount of minimally processed foods was associated with a reduced risk of head and neck cancer, colon cancer, and HCC (Kliemann et al., 2023).

In another population-based cohort study in > 100 000 participants from the French NutriNet-Santé cohort, similar statistical modelling found that a 10% increase in the proportion of UPFs consumed in an individual's diet was associated with a significantly increased risk of breast cancer and overall cancer development (Fiolet et al., 2018). A similar study was conducted in the UK Biobank cohort in the UK, and the results indicated that every 10 percentage points increase in UPF consumption was associated with a higher incidence of overall cancer and specifically of ovarian cancer, along with an increased risk of overall, ovarian, and breast cancer-related mortality (Chang et al., 2023a). Additionally, in three large prospective USA-based cohort studies, it was observed that men in the highest fifth percentile of UPF consumption had a 29% higher risk of developing CRC compared with men in the lowest fifth percentile of UPF consumption (Hang et al., 2023). A study in the PLCO Screening Trial cohort observed a positive association between UPF (assessed using the Nova classification) and prostate cancer, with evidence of a linear trend with exposure (P_{trend} = 0.021) (Zhong et al., 2023b).

Cancer in experimental animals

UPFs include processed meats, which were evaluated by the *IARC Monographs* programme in 2015 in Volume 114 (IARC, 2018b). The Working Group deemed that evidence from experimental animals was *inadequate* for the carcinogenicity of consumption of processed meat. No studies of cancer in experimental animals examining the effects of levels of food processing have been identified, but single components have been evaluated for carcinogenicity.

Mechanistic evidence

The 2015 Working Group (IARC, 2018b) concluded that mechanistic evidence for the carcinogenicity of processed meat was *moderate*. Several observational studies of humans have identified associations between UPF consumption and increased markers of inflammation, predominantly C-reactive protein, as measured in blood (Tristan Asensi et al., 2023). Also, some studies in exposed humans have reported increased end-points of disease outcomes related to chronic inflammation, such as increases in inflammatory bowel disease and Crohn disease (Narula et al., 2021; Chen et al., 2023a). Another study in humans also observed evidence of increased oxidative stress (lower activity of antioxidant enzymes and increased activity of oxidizing enzymes) in association with UPF consumption (Quetglas-Llabrés et al., 2023). Similar effects were observed in pregnant women enrolled in the Origen Bioquímico y Epigenético del Sobrepeso y la Obesidad (OBESO) perinatal cohort (Mexico) (Rodríguez-Cano et al., 2022). A study of adolescents

observed that greater consumption of UPF was associated with higher levels of oxidative DNA damage, as measured in urine (Edalati et al., 2021).

Evidence of mechanisms related to the KCs is also available from studies in experimental systems. Specific extracts from processed meat were found to induce micronucleus formation in standard tests (Chamlal et al., 2021), and processed meat has also been observed to promote inflammation in mice (Ahmad et al., 2019). Travinsky-Shmul et al. (2021) have observed that UPF can affect bone quality, adiposity, and inflammation, and induce alteration of gut microbiota of mice.

Summary

The chemical and physical definition of UPFs is not straightforward, as they may contain different combinations and proportions of a large number of added substances. The epidemiological evidence is currently based on three large cohort studies, totalling over 1 million study participants (EPIC, NutriNet-Santé, and UK Biobank). The three studies used similar methodologies for the definition of UPFs and similar statistical approaches for data analyses. The results consistently indicate that an increase in the proportion of UPFs, of the total food and drinks consumption, is associated with a statistically significant increase in the risk of developing various types of cancer.

UPFs include a broad variety of foods; some of their components have been evaluated for carcinogenicity in experimental animals. However, no experimental studies examining UPFs in general, or varied levels of food processing, were identified.

There is evidence that UPFs may exhibit the KCs, including genotoxicity, oxidative stress, and chronic inflammation from studies in exposed humans and experimental systems. The Advisory Group therefore considered an *IARC Monographs* evaluation of UPFs to be warranted, with careful consideration of the UPF constituents.

Recommendation: High priority (and ready for evaluation within 2.5 years)

109 1,2-Dibromo-3-chloropropane (DBCP) (CAS No. 96-12-8)

Current IARC/WHO classification

1,2-Dibromo-3-chloropropane (DBCP) has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Volume 71 in 1998, on the basis of *sufficient* evidence of cancer in experimental animals (IARC, 1999d).

Exposure characterization

DBCP is a pesticide that has been used as a soil fumigant and was an active ingredient of nematicides. Because of its toxic health effects (sterility in men), its use in agriculture was banned in the USA in 1979. It has been extensively used in farming (e.g. bananas and pineapples) in Central America, where it caused sterilization of a large number of workers (Wesseling et al., 1996). Use in Central America was also discontinued at the end of the 1970s (Hofmann et al., 2006). In the occupational context in farming, skin is the major route of exposure (Hofmann et al., 2006). In areas with contaminated soils, oral exposure of the general population via food and drinking-water has been documented even after agricultural use was discontinued (Hart et al., 2018).

Cancer in humans

Few publications from cohort studies are available that report on associations between exposure to DBCP and cancer risk. *Monographs* Volume 71 noted a report of excess lung cancer in a small cohort of DBCP production workers with exposure of > 1 year and a suggestive increased risk of leukaemia in a case–control study in a population exposed to contaminated drinking-water in Fresno County (USA) (IARC,

1999d). Since the last *Monographs* evaluation of DBCP in 1999 (*inadequate* evidence regarding cancer in humans), two new studies have been published. A study conducted within the Nurses' Health Study II assessing associations of air pollutants with breast cancer risk found a hazard ratio (HR) of 1.12 (95% CI, 0.98–1.29; *P* for trend, 0.004) associated with DBCP exposure, which was modelled based on the US EPA's National Air Toxics Assessment (Hart et al., 2018). Hofmann et al. (2006) reported on mortality among a cohort of banana-plantation workers in Costa Rica, which was an update on the same cohort for which cancer incidence had been described earlier and was reviewed in the previous monograph. The authors observed elevated SMRs in men for testicular cancer (SMR, 2.07 based on a local comparison), penile cancer (SMR, 2.23, national comparison), and Hodgkin lymphoma (SMR, 1.17, national comparison), and elevated SMRs in women for cervical cancer (SMR, 1.52, national comparison) and lung cancer (SMR, 1.82, national comparison).

Cancer in experimental animals

In the previous evaluation (IARC, 1999d), there was *sufficient* evidence in experimental animals for the carcinogenicity of DBCP, on the basis of findings in various tissues from two studies by inhalation, one in F344 rats, and one in $B6C3F_1$ mice, along with other positive findings from old NTP studies.

Mechanistic evidence

DBCP is rapidly absorbed when administered orally and distributes in various tissues. Data available, mostly for rats, have shown that it is metabolized via oxidation by CYPs and conjugated with GSH. It can form water-soluble metabolites and metabolites that bind to macromolecules. Several active metabolites, such as *S*-[1-(hydroxymethyl)-2-(*N*7-guanyl)-ethyl] glutathione, have been identified in rat and other species (Søderlund et al., 1995; Weber et al., 1995). Human glutathione-S-transferase has been found to actively metabolize DBCP. Testis is the most sensitive tissue, especially in rats (Bjørge et al., 1995).

DBCP induces genotoxicity in several experimental systems. Most of the data from the classical genotoxicity battery in vitro and in vivo, conducted in the 1980s and 1990s and evaluated in the previous monograph, provided consistent positive findings (IARC, 1999d). In normal Clara cells and type II cells and alveolar macrophages, isolated by lavage from rabbit lungs, an increase of DNA damage measured as alkali-labile sites and/or single-strand breaks was observed after DBCP exposure (Becher et al., 1993).

In addition, increased gene mutagenicity in bacteria expressing human glutathione *S*-transferases (Simula et al., 1993) was observed in *S.typhymurium* T100 transformed strain. DNA damage, in the form of double strand breaks, as measured by alkaline filter elution, was also observed in cells from human testis obtained from 18 organ donors, as well as in cells from rat testis (Bjørge et al., 1996a; Brunborg et al., 1996). Increased DNA damage, assessed using comet assay, was also observed in human lymphocytes and sperm cells from healthy donors (Anderson et al., 1997). Chromosomal aberrations and altered DNA repair responses were described in isolated lymphocytes from a small group of farmers, several with male fertility alterations, at banana plantations in Costa Rica (Au et al., 1999). However, it was reported that workers might have been exposed to other pesticides, so these findings may be of limited relevance. Recently, DBCP was also reported to induce oxidative stress in a spermatogenic in vitro model of WA01 male human embryonic stem cells. Exposure to DBCP or the similar agent 2-bromopropane (Group 2A) generated ROS and promoted gene expression of antioxidants and detoxifying enzymes through Nrf2 (Easley et al., 2015). Evidence for DBCP inducing chronic inflammation is sparse and limited to some histopathology findings associated with nasal cavity tumours in a rat bioassay (Haseman and Hailey, 1997). DBCP has been reported to affect male fertility, causing morphological changes of the testis and affecting sperm count and morphology in rodents in vivo in several studies (IARC, 1999d). Since the previous evaluation, many new studies in both experimental systems and exposed humans have confirmed the potential of DBCP to modulate receptor-mediated effects (Olsen et al., 1990; Anderson et al., 1997; Ye et al., 2011, 2014; Moffit

et al., 2013). DCBP is structurally related to other halogenated propanes such as 2-bromopropane, 1-bromopropane and bromochloromethane (Maeng and Yu, 1997; Takeuchi et al., 1997) with which it might share the KCs of genotoxicity and effects leading to reproductive toxicity.

Summary

There is limited use of DBCP since it was widely banned in the late 1970s; but continuing exposure through contaminated environmental media has been documented. There are sporadic findings of cancer risk associated with employment in occupations with DBCP exposure, such as on banana plantations and in pesticide manufacturing. *Sufficient* evidence is available for cancer in experimental animals and formed the basis of the current Group 2B classification. Since the previous evaluation, evidence of mechanistic end-points associated with the KCs, including genotoxicity, oxidative stress and modulation of receptor-mediated effects, has become available from studies in exposed humans and in human primary cells and tissues in vitro. However, the mechanistic studies seem to have limitations in the exposure assessments. Due to the potential limitations of the mechanistic studies and the sparse epidemiological evidence of cancers in humans, the Advisory Group considered that an *IARC Monographs* re-evaluation of 1,2-dibromo-3-chloropropane is unwarranted at present.

Recommendation: No priority

110 2,4-Dichlorophenol (CAS No. 120-83-2)

Current IARC/WHO classification

2,4-Dichlorophenol (2,4-DCP) as such has not previously been evaluated by the *IARC Monographs* programme. However, in 1999, IARC evaluated combined exposures to polychlorophenols (containing 2,4-DCP) or to their sodium salts as *possibly carcinogenic to humans* (Group 2B) (IARC, 1999d).

Exposure characterization

2,4-DCP is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a).

2,4-DCP has been used in the synthesis of phenoxy acid herbicides, including 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid. It can also be formed as a by-product during the manufacture of various chlorinated chemicals, in chlorination processes involving water treatment and wood-pulp bleaching, and from the incineration or combustion of municipal solid waste, coal, and wood (IARC, 1999d; CDC, 2000; PubChem, 2009; Rooney et al., 2019).

General population exposure to 2,4-DCP can occur by inhalation of contaminated air, ingestion of contaminated water or dermal contact with this lipid-soluble chemical. In addition, other chlorophenols absorbed into the body can be metabolized to 2,4-DCP (CDC, 2017). Occupational exposure may occur through inhalation and/or dermal contact in facilities that produce or use 2,4-DCP (ATSDR, 2022).

Cancer in humans

Two case–control studies, one in northern and one in southern Sweden, showed relative risks of 5.3 (95% CI, 2.4–11.5) (Hardell and Sandström, 1979) and 6.8 (95% CI, 2.6–17.3) for soft-tissue sarcoma, (Eriksson et al., 1981) for men exposed to phenoxy acid herbicides, but the extent of exposure to 2,4-DCP was unclear in these studies. In 1977, in Sweden, a cluster of patients with malignant lymphomas and previous exposure to phenoxy acid herbicides and/or chlorophenols was reported (Hardell, 1977).

Following these reports, a cohort study was developed aimed at clarifying the potential carcinogenicity of phenoxy acid herbicides based on 2,4-DCP and 4-chloro-*ortho*-cresol (Lynge, 1985). The observation in this cohort study of five soft-tissue sarcoma cases in contrast to 1.84 expected among males supports the

Swedish observation of an excess risk of soft-tissue sarcomas after exposure to phenoxy acid herbicides based on 2,4-DCP. However, as with the earlier studies, the role of 2,4-DCP itself in the findings of Lynge (1985) is unclear.

Rooney et al. (2019) evaluated associations of urinary concentrations of 2,4-DCP with prevalence of various medical conditions among 3617 US National Health and Nutrition Examination Survey participants from 2007–2008 and 2009–2010 to test cross-sectional associations between the urinary concentrations with several diseases and cancer. No associations were found between 2,4-DCP and prevalence of any disease. For thyroid cancer, there is evidence from a case–control study in China (Yang et al., 2021b), where urinary concentrations of 2,4-DCP were positively correlated with thyroid cancer and showed evidence of a dose–response relation.

Cancer in experimental animals

In the previous evaluation (IARC, 1999d), there was *evidence suggesting lack of carcinogenicity* in experimental animals for the carcinogenicity of 2,4-dichlorophenol. 2,4-DCP has been tested in two long-term carcinogenesis studies by oral administration (in feed) to B6C3F$_1$ mice and F344/N rats (NTP, 1989b) and in one study by oral administration (in drinking-water) to rats (Exon and Koller, 1985). There were no compound-related increases in the incidence of neoplastic lesions in rats or mice, and it was concluded that there was no evidence of carcinogenicity (NTP, 1989b). No additional studies on cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

The absorption of 2,4-DCP is quite rapid when it is given orally, dermally, or by inhalation. Somani and Khalique (1982) reported that intravenously administered 2,4-DCP was distributed to the kidney, liver, fat, and brain of rats, with the highest concentration in the kidney. 2,4-DCP is metabolized to glucuronide and other conjugates. The parent compound and its conjugates were rapidly eliminated from the body. The half-lives of 2,4-DCP and its conjugates in plasma, fat, brain, liver, and kidney ranged from 4 to 30 minutes. The volume of distribution of 2,4-DCP in plasma was 3.7 L/kg. Tissue/plasma ratios indicated that 2,4-DCP has a greater affinity for kidney than for other major organs (Somani and Khalique, 1982).

A significant increase in the percentage of chromosome aberrations in bone-marrow and spermatocyte cells was observed after intraperitoneal injection of 2,4-DCP in Swiss mice (Amer and Aly, 2001). In cultured CHO cells, 2,4-DCP did not induce chromosomal aberrations but significantly increased the frequency of SCEs in both the presence and absence of metabolic activation (microsome S9) (NTP, 1989b). No mutagenicity of 2,4-DCP was observed in mouse L5178Y lymphoma cells without metabolic activation. Similarly, 2,4-DCP produced no increase in revertant colonies in *S. typhimurium* strains TA98, TA100, or TA1537 with or without exogenous metabolic activation, and equivocal results were observed in strain aTA1535 only in the presence of hamster S9 (NTP, 1989b). In non-mammalian species in contrast, mainly fishes, 2,4-DCP significantly induce DNA strand breaks (detected by neutral comet assay) in erythrocytes and hepatocytes of goldfish in a dose-dependent manner in numerous studies.

2,4-DCP increased ROS formation, lipid peroxidation, and oxidized proteins in human PBMCs (Bukowska et al., 2016). In rats receiving pre- and postnatal treatment with 2,4-DCP in drinking-water, the immune response was affected: cell-mediated immunity (measured as delayed-type hypersensitivity) was decreased, while humoral immunity was enhanced (increased serum antibody production) (Exon and Koller, 1985).

Exposure of H295R human adrenocortical carcinoma cells to 2,4-DCP resulted in lower production of estradiol and alterations in transcript expression of genes involved in steroidogenesis, including CYP (CYP11A, CYP17, CYP19A), 3βHSD, 17βHSD, and StAR (Ma et al., 2012). Recently, 2,4-DCP was reported to induce endocrine-disruptive effects in non-mammalian species, i.e. feminization in fish, by

disrupting the synthesis of sex hormones and downregulating male-related genes through DNA methylation (Yuan et al., 2020; Zhang et al., 2020a; Hu et al., 2021a); induction of global DNA hypermethylation via altered *S*-adenosylmethionine (SAM) level and DNA methyltransferase-expression in fish (Zhang et al., 2014). Huang et al. (2018a) observed significant, dose-dependent oxidative stress (ROS) in fish after exposure to 2,4-DCP (Huang et al., 2018a). 2,4-DCP was considered to induce adverse effects in female sex organs through interruption of ER-mediated processes (Zhang et al., 2008).

Summary

Findings from studies of cancer in humans are minimally informative for 2,4-DCP specifically. No carcinogenic effect was observed in mice and rats after oral treatment with 2,4-DCP. There is sparse evidence that 2,4-DCP exhibits KCs in experimental systems in vivo and in vitro, mainly from non-mammalian species. The Advisory Group therefore considered that an *IARC Monographs* evaluation of 2,4-dichlorophenol is unwarranted at present.

Recommendation: No priority

111 Alachlor (CAS No. 15972-60-8)

Current IARC/WHO classification

Alachlor has not previously been evaluated by the *IARC Monographs* programme. Alachlor was given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of human cancer and mechanistic evidence.

Exposure characterization

Alachlor is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). It is a chloroacetanilide herbicide used primarily on corn and soybeans. It was first registered for use in the USA in 1969 and, at its peak in the 1980s, was one of the most widely used agricultural pesticides (US EPA, 1998). It has been banned in Canada and the EU (European Commission, 2007a) but is still authorized in the USA and subject to consent for importing in many countries in Africa, Asia, and Central and South America (Rotterdam Convention, 2011a). Occupational exposure in pesticide applicators may occur either via the dermal or inhalational routes (Flaherty et al., 1995; Mahaboonpeeti et al., 2018). Wearing long-sleeved shirts and long pants can reduce dermal alachlor exposures by > 80% (Mahaboonpeeti et al., 2018). Alachlor is relatively non-persistent in the environment (Lewis et al., 2016).

Cancer in humans

There are a few studies of cancer in humans for alachlor. In the most recent update of the US NCI Agricultural Health Study (AHS) cohort (Lerro et al., 2018b), there was a strong increased risk of laryngeal cancer and an imprecise elevation in myeloid leukaemia. There was no association with lymphohaematopoietic malignancies overall, nor NHL or its subtypes, although a previous AHS analysis had found suggestive evidence of elevated risk of multiple myeloma (Lee et al., 2004a), which did not persist in the updated analysis. Another AHS analysis suggested an elevated risk for NHL among alachlor users with asthma, but not among those without (Lee et al., 2004b). In the AGRICOH Consortium, there was no association between alachlor and NHL overall or any of its subtypes (Leon et al., 2019). In a pooled study of three population-based case–control studies of NHL conducted by the US NCI, there was no association with alachlor use overall, but there was a statistically significant risk elevation among those who applied both alachlor and the widely used herbicide atrazine (which also showed no risk when considered alone) (De Roos et al., 2003). An analysis of the North American Pooled Project (NAPP) found no association between alachlor and Hodgkin lymphoma (Latifovic et al., 2020). In an industry-conducted study of a small

cohort of workers in alachlor manufacture, there was no elevated risk of cancer mortality or incidence at any site compared with the general population, but there were only 29 cases of incident cancer in total (Acquavella et al., 2004). Healthy-worker biases were likely to be strong in this cohort (the all-cause SMR was 0.64).

Cancer in experimental animals

In a 2-year oral study reviewed by the US EPA, a statistically significant increase in lung bronchiolar tumours was observed in female mice treated with alachlor by oral administration (US EPA, 1998). In a 2-year study in rats treated orally reviewed by the US EPA, statistically significant increases of malignant stomach tumours, follicular tumours of the thyroid (adenomas plus carcinomas), and nasal turbinate adenomas were observed in both sexes (US EPA, 1998). In another study in rats treated orally reviewed by the US EPA, statistically significant increases in thyroid cell adenoma in males, malignant stomach tumours in both sexes, and nasal adenocarcinoma in both sexes were observed. The increases of tumours observed in cancer bioassays of alachlor (nasal tumours, follicular tumours of the thyroid, stomach tumours, liver tumours) are consistent with those observed in similar studies with other structurally related chloroacetanilide herbicides (US EPA, 1998).

Mechanistic evidence

Alachlor belongs to the group of chloroacetanilide herbicides that display a consistent pattern of mutagenic activity (Dearfield et al., 1999). Alachlor metabolites form DNA adducts in vitro (Nelson and Ross, 1998). Genotoxicity and genomic instability studies in human primary cells and cell lines found elevated micronucleus frequency, SCEs, and chromosome aberrations (Ribas et al., 1996; Mattiuzzo et al., 2006). Alachlor induced oxidative stress in in vivo models, particularly in the same target tissues observed in cancer assays (nasal mucosa) (Burman et al., 2003).

Summary

Evidence from studies of cancer in humans is mixed. Most studies of alachlor have focused on NHL and have not shown consistent associations, although some suggestions of increased risk have been found in certain populations (e.g. people with asthma) or along with co-exposures. One study reported strong associations with laryngeal cancer and myeloid leukaemia, but no other studies have evaluated these cancer sites. Carcinogenicity studies in mice and rats found increases of various tumours in both sexes. Mechanistic studies in different models reported that the agent exhibits KCs including electrophilicity, genotoxicity, and oxidative stress. The Advisory Group therefore considered an *IARC Monographs* evaluation of alachlor to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

112 Ametryn (CAS No. 834-12-8)

Current IARC/WHO classification

Ametryn has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Ametryn, one of the triazine family of herbicides, is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). It is used for control of broadleaf weeds and annual grasses, and for general weed control on food crops (PubChem, 2024b). Recognized sources of exposure are dietary intake and drinking-water in the general population (US EPA, 2005); exposure levels may be elevated in (rural) areas that use recycled irrigation water (Msibi et al., 2023) or in close proximity

to agricultural land where ametryn is applied (de Queiroz et al., 2018). Occupational exposure is also documented (US EPA, 2005; Msibi et al., 2021), with relatively high levels of inhalation exposure reported even with use of personal protective equipment (Msibi et al., 2021).

Cancer in humans

No epidemiological data on ametryn specifically or on cancer incidence or mortality were available to the Advisory Group. A 2011 review evaluated triazine herbicides and cancer and suggested a lack of evidence for a causal relationship between these pesticides and cancer (Sathiakumar et al., 2011). This review predominantly included studies that evaluated triazines overall, with no indication of use or proportion of use of ametryn. No other epidemiological studies on triazines overall and cancer were identified.

Cancer in experimental animals

In an oral study in rats reviewed by US EPA (2005, 2018a), a significant increase in tumours in the testes, epididymis, and thyroid in males and both the liver and mammary gland in females were observed. However, these increases were observed only at the highest dose tested, with excessive systemic toxicity. No tumour formation was observed in a carcinogenicity study in mice up to the highest dose tested (US EPA, 2017a).

Mechanistic evidence

Ametryn was reported to bind to DNA in vitro (Oliveira-Brett and da Silva, 2002) and to form micronuclei in vivo (Santos et al., 2015). It gave negative results in a series of regulatory genotoxicity studies in experimental systems (ECHA, 2024a). Ametryn has been screened in the US EPA ToxCast programme for induction of hormone synthesis in the in vitro H295R steroidogenesis assay and was found to cause cells to significantly increase production of estradiol and progesterone, showing that it could modulate receptor-mediated effects (Karmaus et al., 2016; Haggard et al., 2018; Cardona and Rudel, 2021; Kay et al., 2024). Ametryn was reported to alter cell proliferation in in vivo and in vitro cell models (Ohno et al., 1998; Dantas et al., 2015).

Summary

No human cancer studies for ametryn were identified. One carcinogenicity oral study in rats exposed to ametryn reported increases of tumours in the testes, epididymis, and thyroid in males and both the liver and mammary gland in females. There is sparse mechanistic evidence suggesting that ametryn exhibits KCs. The Advisory Group noted that ametryn belongs to the triazine herbicides group (thiomethyl-*s*-triazines) and could be evaluated together with atrazine but considered that an *IARC Monographs* evaluation of ametryn is unwarranted at present on the basis of the available evidence.

Recommendation: No priority

113 Atrazine (CAS No. 1912-24-9) and other 2-chloro-s-triazine herbicides

Current IARC/WHO classification

Atrazine and simazine have previously both been evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in Volume 73 (IARC, 1999b). Propazine has not previously been evaluated. Atrazine was given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a), based on human cancer and mechanistic evidence.

Exposure characterization

Atrazine is a broad-spectrum chlorinated triazine herbicide that has agricultural uses for weed control in the cultivation of corn, soybean, sugarcane, and other crops and can also be used for weed control in recreational spaces and gardens (US EPA, 2018b). Atrazine was listed as a high production volume chemical by the OECD (OECD, 2007) and by the US EPA (US EPA, 2024a). Although it has been banned in the EU since 2004 due to concerns about water contamination, it is still one of the most heavily used herbicides in North America, Africa, and the Asia–Pacific region (Jablonowski et al., 2011). It was also the second most commonly used active ingredient in conventional pesticides in the USA in 2012 (US EPA, 2017b). Atrazine and its metabolites can persist in water and soil for decades (Jablonowski et al., 2011). A study of pregnant women in France found that 5.3% had detectable urinary levels of atrazine and metabolites nearly 20 years after the EU ban (Chevrier et al., 2014). Atrazine has been detected in the urine of pesticide applicators in Croatia (Mendaš et al., 2012). In a study of families in the USA, urinary atrazine metabolites were above the limit of detection for 41% of farm fathers and 18% for non-farm fathers (Curwin et al., 2007), with lower prevalences for mothers and children. Levels of urinary atrazine are largely driven by recent exposure (Bakke et al., 2009).

Other 2-chloro-***s***-triazine herbicides are simazine (CAS No. 122-34-9) and propazine (CAS No. 139-40-2). Simazine is a high production volume chemical in the OECD (2007) list, but propazine is not.

Cancer in humans

In the AHS cohort, the latest evaluation of atrazine showed suggestive associations with lung cancer (RR, 1.24; 95% CI, 1.04–1.46), aggressive prostate cancer (RR, 1.20; 95% CI, 0.95–1.52), and soft-tissue sarcoma (RR, 2.45; 95% CI, 0.97–2.54) (Remigio et al., 2024). Analyses focusing on lagged exposure reaffirmed a previously observed association with renal cell carcinoma (RR, 1.62; 95% CI, 1.15–2.29) and pharyngeal cancer (RR, 3.04; 95% CI, 1.45–6.36). There were suggestions of increased risk of NHL, but only in those diagnosed at younger ages. A pooled analysis of NHL that included the AHS and based on ever-exposure in the AGRICOH Consortium showed no evidence of an association with NHL (Leon et al., 2019).

An industry-conducted cohort study among triazine manufacturing workers found that the risk of death from any cancer, lung cancer or gastrointestinal cancer was not raised compared with the local population (MacLennan et al., 2003). The authors reported a sixfold excess of prostate cancer (SIR, [6.13]; 95% CI, [3.06–10.96]) in the original study; however, a nested case–control study within this cohort attributed this excess to screening (Hessel et al., 2004). This study is limited by potential healthy-worker biases. In a 2011 Canadian case–control study, the OR was 1.51 (95% CI, 0.64–3.35) based on nine exposed cases (Band et al., 2011). A pooled study of case–control studies in the USA demonstrated an OR of 1.6 (95% CI, 1.1–2.5) (De Roos et al., 2003) for NHL with atrazine use. Another study focusing on NHL subtypes with t(14:18) translocations showed an OR of 1.7 (95% CI, 1.0–2.8) for atrazine use (Schroeder et al., 2001). A cohort study of women found no association between atrazine levels in drinking-water and ovarian cancer (Inoue-Choi et al., 2016) and a population-based case–control study found no statistically significant association between atrazine use and epithelial ovarian cancer (Young et al., 2005).

For simazine, the Canadian case–control study found an elevated risk of prostate cancer (Band et al., 2011). No human cancer studies were identified for propazine.

Cancer in experimental animals

When atrazine and simazine were evaluated in 1999 (IARC, 1999b), there was *sufficient* evidence for cancer in experimental animals for atrazine and *limited* evidence for simazine. However, the mechanism by which atrazine increased the incidence of mammary gland tumours in Sprague-Dawley rats was considered not relevant to humans. It is worth noting that use of the criteria in the latest *IARC Monographs* Preamble

(IARC, 2019b) could change the evaluation for atrazine in experimental animals. No long-term cancer bioassays published since the previous *IARC Monographs* evaluation nor any bioassays for propazine were available to the Advisory Group.

Mechanistic evidence

Since the most recent *Monographs* evaluation, some studies have provided new insights into carcinogenic and genotoxic activity of atrazine. Atrazine is an endocrine disruptor with both estrogenic and anti-estrogenic properties, which could modulate receptor-mediated effects that could be related to the etiology of mammary, prostate, and ovarian cancer (Fan et al., 2007; Vandenberg et al., 2012; Huang et al., 2014). There is sparser evidence that other 2-chloro-s-triazine herbicides present similar endocrine-disruptive properties (Sanderson et al., 2001; Zorrilla et al., 2010).

Several studies have indicated that atrazine may be genotoxic, damaging the integrity of DNA and the stability of the cell genome in animal in vivo and in primary human cells in vitro (Singh et al., 2008; Cavas, 2011; Shang et al., 2022). Atrazine induced epigenetic changes in vivo and in human cell lines in vitro (Sánchez et al., 2020) Atrazine alters cell proliferation of primary human cell models (Manske et al., 2004; Liu et al., 2006). Atrazine was found to promote cell proliferation by activating the STAT3 signalling pathway in both RM1 prostate cancer cells in vitro and in the RM1 prostate cell xenograft mouse model in vivo (Hu et al., 2016b). Human liver cell lines treated with atrazine showed repression of *S100A4* gene expression, a biomarker of epithelial–mesenchymal transition, which is crucial for cancer metastasis, and inhibited TPA-induced cell motility, potentially disrupting cell homeostasis through an S100A4-dependent mechanism (Peyre et al., 2014). More recently, an investigation in a subcohort of AHS pesticide applicators observed an association between recent atrazine use and diminished kidney function (Shearer et al., 2021), supporting the biological plausibility of the observed association with renal cell carcinoma.

Summary

There are both cohort and case–control studies of atrazine exposure and cancer risk, with positive, although not entirely consistent, findings for cancers of the prostate and kidney and NHL. When atrazine and simazine were evaluated in 1999 (IARC, 1999b), there was *sufficient* evidence in experimental animals for the carcinogenicity of atrazine and *limited* evidence in experimental animals for the carcinogenicity of simazine. New mechanistic studies on atrazine in various models reported that it can be genotoxic, cause genomic instability, induce epigenetic changes, modulate receptor-mediated effects and alter cell proliferation. The Advisory Group considered a *Monographs* evaluation of atrazine to be warranted but considered that the evidence for propazine and simazine would be unlikely to lead to a new or revised classification at present.

Recommendation: High priority (and ready for evaluation within 2.5 years)

114 Pyrethrins and pyrethroids

Current IARC/WHO classification

Pyrethrins and pyrethroids have previously been evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in Volume 53 in 1990 (IARC, 1991).

"Some pyrethroids (e.g. permethrin, cypermethrin, deltamethrin)" were given a priority rating of *high* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of human cancer findings (for multiple myeloma and childhood leukaemia) and mechanistic evidence for some of the pesticides in this class. Pyrethrins are on the priority list for the JMPR.

Exposure characterization

Pyrethroids are synthetic derivatives of natural pyrethrins from the plant *Chrysanthemum cinerariaefolium*. They comprise esters of chrysanthemic acid (2,2-dimethyl-3-(1-isobutenyl)cyclopropane-1-carboxylic acid) and halogenated derivatives of their acids and alcohols. They are used as insecticides worldwide in agricultural, veterinary, domestic, and public health applications. Of the 42 pyrethroid substances, deltamethrin, permethrin (agent 118) and α-cypermethrin (agent) are commonly used (Chrustek et al., 2018). Other pyrethroids that have been studied include imiprothrin, bifenthrin (agent 115) and cyfluthrin (agent 116). Their public health uses include disinfection of buildings and aircraft and treatment of mosquito nets and army uniforms. Permethrin is also used in shampoo for treatment of head lice and scabies (IARC, 1991). Pyrethrins are also commonly used as insecticides in agricultural and home and garden use (Ensley, 2018). Exposure of the general population has been identified by detection of urinary metabolites of pyrethroids in inhabitants of residential areas (Schettgen et al., 2002).

Cancer in humans

Results specific to permethrin are described in its own section (see agent 118). No human cancer studies of cypermethrin were available to the Advisory Group (see agent 117).

Pyrethroid insecticides as a class were evaluated in the AGRICOH Consortium. There was no association with NHL overall nor with any of its subtypes based on ever-use of the group (Leon et al., 2011). However, exposure to deltamethrin was associated with increased risk of small lymphocytic lymphoma/chronic lymphocytic leukaemia (SLL/CLL) (HR, 1.48; 95% CI, 1.06–2.07). Pyrethroid insecticides were evaluated in the Interlymph Consortium and showed no association with NHL overall or any subtype (De Roos et al., 2021).

In a case–control study of childhood acute lymphocytic leukaemia, higher levels of urinary metabolites of pyrethroid insecticides were associated with increased risk (OR, 2.75; 95% CI; 1.43–5.29) (Ding et al., 2012). In another case–control study of childhood acute leukaemia, there was an increased risk with use of insecticidal shampoos (not specific to pyrethroid insecticides, but pyrethroids are a major component of many insecticidal shampoos) (OR, 1.9; 95% CI, 1.2–3.3); in other analyses focused on shampoos with pyrethroid ingredients the OR was 2.0 (95% CI, 1.1–3.4) (Menegaux et al., 2006). A separate case–control study indicated no association with leukaemia (OR, 0.86, 95% CI, 0.61–1.20) among children whose residences were within 600 m of where pyrethroid insecticides, grouped as a class, were sprayed (Nguyen et al., 2023).

A case–control study of leukaemia among men reported increased risks in those applying natural pyrethrins (Brown et al., 1990). A case–control study in Spain indicated in principal components analysis that one component, including pyrethrin insecticides, accounted for an increased risk of CLL (Benavente et al., 2020).

Within the AHS, lung cancer mortality was increased among non-smokers who reported use of pyrethroids (Shrestha et al., 2022).

Cancer in experimental animals

Since the previous IARC evaluation of *inadequate* evidence for the carcinogenicity of permethrin in experimental animals (IARC, 1991), increases in the incidence of bronchioloalveolar adenoma and carcinoma in female mice, and of hepatocellular adenoma in male and female mice, have been observed in one 2-year study in mice (oral administration) reviewed by the US EPA, and a high-dose study has shown an increased incidence of lung adenoma in female mice (US EPA, 2006a). In a 2-year oral study in mice exposed to imiprothrin, increased incidence of lung adenocarcinomas was observed in males, and females showed an increasing trend in the incidence of lung adenomas and combined lung adenoma/adenocarcinomas (Yamada et al., 2019). The US EPA reported increased incidence of benign lung

adenomas and adenomas plus carcinomas combined in females in a mouse carcinogenicity study of cypermethrin, while there was no evidence of tumours in rats (US EPA, 2023a). In a 1-year study in mice with chronic dermal exposure to cypermethrin, increased incidence of benign skin tumours was observed (Shukla et al., 2002). A combined chronic toxicity/carcinogenicity GLP study in rats administered cyfluthrin orally, reviewed by US EPA (2001), reported increases in mammary gland adenocarcinomas at the highest dose in females. Mammary adenocarcinomas were also reported in males treated by various routes, a rare finding in rats. Although these increases were not statistically significant, the incidence of mammary adenocarcinoma in both males and females was above historical control rates in rats.

Mechanistic evidence

Since the previous IARC evaluation, many mechanistic studies relevant to the KCs have become available for permethrin and other pyrethroids. Permethrin can induce genotoxicity, genomic instability, and DNA damage in animals and in primary human cells in vitro (Gabbianelli et al., 2004; Roma et al., 2012a; Navarrete-Meneses et al., 2017). Permethrin alters the modulation of receptor-mediated and endocrine effects in animals in vivo and cell line models in vitro (Go et al., 1999; Kim et al., 2004; Brander et al., 2012). Permethrin can induce cytotoxicity in vivo (Bath et al., 2009) and in human primary cells in vitro (Das et al., 2008, Roma et al., 2012b).

Cypermethrin can induce genotoxicity, genomic instability, and DNA damage in animals and in primary human cells in vitro (Gabbianelli et al., 2004; Vardavas et al., 2016; Mužinić et al., 2019). Cypermethrin promoted metastasis of lung cancer cells both in vitro and in animal models by inhibiting development of pro-inflammatory M1 macrophages (Huang et al., 2018b). Cypermethrin is an endocrine disruptor with ER activity and could facilitate cell proliferation (Zhang et al., 2021c). AR activity (Ding et al., 2020) and thyroid-receptor activity were also reported (Ha et al., 2021). β-Cypermethrin and the general pyrethroid metabolite 3-phenoxybenzoic acid induce cytotoxicity, block granulocytic cell differentiation (He et al., 2018a), and induce apoptosis in human neuroblastoma cell lines (Raszewski et al., 2016).

Cyfluthrin can induce genotoxicity, genomic instability and DNA damage in animals and in primary human cells in vitro (Ila et al., 2008; Calderón-Segura et al., 2018). Cyfluthrin induced cytotoxicity and oxidative stress in cell line models (Martínez et al., 2019). Cyfluthrin has been screened in the US EPA ToxCast programme for induction of hormone synthesis in the in vitro H295R steroidogenesis assay and was one of the most potent estradiol steroidogens of all chemicals screened in this assay, showing that it could modulate receptor-mediated effects. (Karmaus et al., 2016; Haggard et al., 2018; Cardona and Rudel, 2021)

Summary

Human cancer studies suggest associations of pyrethrin and pyrethroid insecticides with leukaemia in children and, to a lesser extent, adults. Carcinogenicity studies in mice and rats exposed to some pyrethroids reported increases of various tumours in both sexes. Mechanistic studies on some pyrethroids in various models reported that these substances can be genotoxic, cause genomic instability, modulate receptor-mediated effects and alter cell proliferation. The Advisory Group therefore considered an *IARC Monographs* evaluation of pyrethins and pyrethroids to be warranted, and recommended that this agent be evaluated in the same volume as other prioritized pyrethroids (see agents 115–118 in the present report).

Recommendation: High priority (and ready for evaluation within 2.5 years)

115 Bifenthrin (CAS No. 82657-04-3)

Current IARC/WHO classification

Bifenthrin has not previously been evaluated by the *IARC Monographs* programme. Bifenthrin is on the priority list for the Joint FAO/WHO Meeting on Pesticide Residues (JMPR).

Exposure characterization

Bifenthrin is a non-water-soluble insecticide used in consumer (i.e. home-use) and commercial products (PubChem, 2024c) and as an agricultural pesticide (FAO, 2022). Its water insolubility leads to accumulation in soil (half-life, 7 days to 8 months) (PubChem, 2024c). More than 600 bifenthrin-containing products are available in the USA (Johnson et al., 2010). It is part of the widely used pyrethroid-based pesticide group (Ravula and Yenugu, 2021) and is used against insects ranging from termites to agricultural pests, as well as mosquitoes, flies, and fleas. Beyond household and commercial use, it has been used in pesticide-treated clothing (Banks et al., 2014). In the EU it is not authorized either as a pesticide or biocide.

Bifenthrin has been quantified on household surfaces (Starr et al., 2018) and in air (Yoshida et al., 2021). It has been detected in food (reviewed in (Morgan et al., 2018; Morgan, 2020; Ravula and Yenugu, 2021), in breast milk (including samples above the tolerable daily intake (Anand et al., 2021), and in urine samples from the general population (Yoshida et al., 2021; Akyeampong et al., 2022) and workers such as bifenthrin applicators (Kongtip et al., 2013).

Cancer in humans

A case–control study evaluating prenatal and early-childhood exposure (exposure estimated based on address at birth) observed no statistically significant association between bifenthrin and ALL or AML in children aged < 6 years (ALL: OR, 1.18; 95% CI, 0.82, 1.70; AML: OR, 1.20; 95% CI, 0.56, 2.58); the interpretation was unchanged when considering estimates adjusted for exposure to other pesticides (Park et al., 2020). A study on urinary levels of the general pyrethroid metabolite 3-phenoxybenzoic acid observed higher all-cause and cardiovascular mortality with higher metabolite levels, but no association with cancer mortality (Bao et al., 2020b). A second study on pyrethroid use in pesticide applicators observed higher risk of mortality from lung and bronchus cancers among non-smokers with ever use (Shrestha et al., 2022). These studies evaluated permethrin or general pyrethroid exposure and not a measure of bifenthrin directly and thus their informativeness may be limited.

Cancer in experimental animals

Evidence was reported of mesenchymal tumours of the bladder (both epithelial and spindle cells) in mice exposed to bifenthrin at 0, 50, 200, 500, and 600 ppm (no observed adverse effect level (NOAEL) (50 ppm = 7.6 mg/kg bw per day). Tumours were observed in many of the animals, mainly in males (Butler et al., 1997). The findings have been dismissed by a follow-up re-evaluation, but details are not available (FAO, 2009). The FAO (2009) studies in mice revealed only benign tumours at high doses.

Mechanistic evidence

Mechanistic evidence on bifenthrin carcinogenicity derives mainly from studies in experimental systems in vitro and in vivo. No evidence of genotoxicity was reported in studies summarized in INCHEM and more recently in FAO reports (INCHEM, 1992; FAO, 2022).

Bifenthrin induces oxidative stress and alteration of inflammatory markers in human neuroblastoma and colorectal cancer cells (Bouaziz et al., 2020; Gargouri et al., 2020). Increased levels of Il1B protein in liver and kidney were observed in female mice; however, the increase of inflammatory markers was accompanied by liver toxicity (Pylak-Piwko and Nieradko-Iwanicka, 2021). In two other studies in mice, general immunotoxicity, including pro-inflammatory markers and peritoneal macrophages, was observed with

decrease of spleen weight and increase of cytokine levels in the spleen, serum, thymus and other tissues (Jin et al., 2014; Wang et al., 2017a).

Bifenthrin has been considered an endocrine disruptor and exhibits evidence of the key characteristic of modulating receptor-mediated effects in rodents in vivo and in vitro (Liu et al., 2011; Jin et al., 2013). It was shown to have estrogen-disrupting activity in breast cancer cells and tested positive for E-screen model enantiomer-dependent estrogenic activity (Montes-Grajales and Olivero-Verbel, 2020). It was shown to affect calcium ion homeostasis, but this is mostly linked to cytotoxicity effects (Chien et al., 2019). Goto and co-workers showed that bifenthrin has tumour-promoting activity in a cell transformation assay (Goto et al., 2004).

Summary

Evidence regarding cancer in humans is sparse. The evidence of tumour formation in animals, reported in only one study in mice, has been considered negative. Bifenthrin exhibits limited mechanistic evidence of some of the KCs from studies in experimental systems, mainly in vitro. The Advisory Group therefore considered an *IARC Monographs* evaluation of bifenthrin to be warranted, together with other pyrethrins and pyrethroids included in this report (see agents 114, 116–118 in the present report).

Recommendation: Medium priority

116 Cyfluthrin (CAS No. 68359-37-5)

Current IARC/WHO classification

Cyfluthrin has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Cyfluthrin is used as an agricultural and structural pesticide (PubChem, 2024d). The insecticide is part of the widely used pyrethroid-based pesticide group and is used against a range of insects (e.g. cockroaches, houseflies, mosquitoes, rape winter stem weevil, and aphids (Ravula and Yenugu, 2021)). Beyond household and commercial use, cyfluthrin has been used in pesticide-treated clothing (Banks et al., 2014). Cyfluthrin has been detected in household dust in homes with proximate application (Madrigal et al., 2023) and in carpet dust (Deziel et al., 2015). Detectable levels have been measured in urine (Dalsager et al., 2019; Faure et al., 2020; Norén et al., 2020), plasma (Channa et al., 2012), breast milk (Sereda et al., 2009), and meconium (Berton et al., 2014) in general populations.

Cancer in humans

No studies on cancer in humans specifically associated with cyfluthrin were available to the Advisory Group. Studies evaluating cancer associated with pyrethroids more generally are described elsewhere in this report (see agent 114).

Cancer in experimental animals

A combined chronic toxicity/carcinogenicity oral GLP study on cyfluthrin in rats reviewed by the US EPA (US EPA, 2001) reported increases in mammary gland adenocarcinomas at the highest dose in females. Mammary adenocarcinomas were also reported in male rats treated by various routes, a rare finding in rats. Although these increases were not statistically significant, the incidence of mammary adenocarcinoma in both males and females was above historical control rates.

Mechanistic evidence

Many mechanistic studies relevant to the KCs are available for cyfluthrin and other pyrethroids. Cyfluthrin can induce genotoxicity, genomic instability and DNA damage in animals and primary human cells in vitro (Ila et al., 2008; Calderón-Segura et al., 2018). It induced cytotoxicity and oxidative stress in cell line models (Martínez et al., 2019). Cyfluthrin has been screened in the US EPA ToxCast programme for induction of hormone synthesis in the in vitro H295R steroidogenesis assay and was one of the most potent estradiol steroidogens of all chemicals screened in this assay, showing that it could modulate receptor-mediated effects (Karmaus et al., 2016; Haggard et al., 2018; Cardona and Rudel, 2021; Kay et al., 2024).

Summary

There is no direct human cancer evidence on cyfluthrin, and indirect evidence from studies on pyrethroid or permethrin exposure may be of limited informativeness. One carcinogenicity study on rats exposed orally to cyfluthrin reported increases above the historical control rates of mammary adenocarcinoma in both sexes. There is evidence that cyfluthrin exhibits KCs in human primary cells and in experimental systems. The Advisory Group therefore considered an *IARC Monographs* evaluation of cyfluthrin to be warranted, together with other pyrethrins and pyrethroids included in this report (agents 114-118).

Recommendation: High priority (and ready for evaluation within 2.5 years)

117 Cypermethrin (CAS No. 52315-07-8)

Current IARC/WHO classification

Cypermethrin has not previously been evaluated by the *IARC Monographs* programme. "Some pyrethroids (e.g. permethrin, cypermethrin, deltamethrin)" were given a priority rating of *high* by the 2019 Advisory Group on Priorities (IARC, 2019a). For cypermethrin specifically, only mechanistic evidence was described. Cypermethrin is on the priority list for the JMPR.

Exposure characterization

Cypermethrin is a synthetic pyrethroid insecticide. It is widely used in both agricultural and residential settings. It is found in many household ant and cockroach killers. The agent is approved in the EU until 2029, for use on crops only under specific risk mitigation measures.

The routes of exposure for cypermethrin are inhalation and skin contact. However, little information is available on the real level exposure of cypermethrin in biological samples, since biomarkers of exposure for cypermethrin are the metabolites 3-phenoxybenzoic acid (3-PBA), *cis*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (cis-DCCA), and *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (trans-DCCA), which are generally metabolized by many other pyrethroids (Côté et al., 2014). Therefore, it cannot be assumed that the levels of quantified metabolites correspond only to cypermethrin exposure.

Cancer in humans

There were no studies specifically of cypermethrin and cancer risk in humans. However, there are several studies that evaluated pyrethroid insecticides, including cypermethrin. These studies are summarized in the section on Pyrethrins and pyrethroids (see agent 114 in the present report).

Cancer in experimental animals

The US EPA reported the incidence of benign lung adenomas and adenomas plus carcinomas combined in female mice. No evidence was seen of tumours in rats (US EPA, 2023a). In a 1-year study in mice with

chronic dermal exposure to cypermethrin, increased incidence of benign skin tumours was observed (Shukla et al., 2002).

Mechanistic evidence

Cypermethrin can induce genotoxicity, genomic instability, and DNA damage in animals and in primary human cells in vitro (Gabbianelli et al., 2004; Vardavas et al., 2016; Mužinić et al., 2019). Cypermethrin promoted metastasis of lung cancer cells both in vitro and in vivo by inhibiting development of pro-inflammatory M1 macrophages (Huang et al., 2018b). Cypermethrin is an endocrine disruptor, with ER activity, and could facilitate cell proliferation (Zhang et al., 2021c). AR activity (Ding et al., 2020) and thyroid-receptor activity have also been reported (Ha et al., 2021). β-Cypermethrin and the general pyrethroid metabolite 3-PBA induce cytotoxicity, block granulocytic cell differentiation (He et al., 2018a), and induce apoptosis in human neuroblastoma cell lines (Raszewski et al., 2016).

Summary

No studies of cancer in humans were available to the Advisory Group. One carcinogenicity study in mice exposed dermally to cypermethrin reported increases of benign skin tumours and another study in mice exposed to cypermethrin reported increases of benign lung adenomas and adenomas plus carcinomas combined in females. Mechanistic studies on cypermethrin in various models reported that it exhibits KCs, including genotoxicity, genomic instability, modulation of receptor-mediated effects, and alteration of cell proliferation. The Advisory Group therefore considered an *IARC Monographs* evaluation of cypermethrin to be warranted, together with other pyrethrins and pyrethroids included in this report (agents 114-118).

Recommendation: High priority (and ready for evaluation within 2.5 years)

118 Permethrin (CAS No. 52645-53-1)

Current IARC/WHO classification

Permethrin has previously been evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in Volume 53 (IARC, 1991). "Some pyrethroids (e.g. permethrin, cypermethrin, deltamethrin)" were given a priority rating of *high* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of human cancer findings (for multiple myeloma and childhood leukaemia) and mechanistic evidence. Permethrin is on the priority list for the JMPR.

Exposure characterization

Permethrin is a pyrethroid insecticide with widespread agricultural, residential, and commercial use. It is used in agriculture for insect and parasite control in both crop and livestock farming (US EPA, 2009a) and in residential settings for vector control, including fleas and ticks for dogs and medical treatment of lice and scabies. It is also used to impregnate clothing for outdoor use, including military (Kegel et al., 2014). The agent is not authorized in the EU. As a result of its various applications, exposure of workers and the general population is likely.

Cancer in humans

Within the AHS cohort, permethrin has been linked to increased risk of multiple myeloma, a finding that has persisted through several updates of the cohort (Rusiecki et al., 2009; Alavanja et al., 2014a), with RR > 2.0 for ever use and evidence of exposure-related response (*P* for trend, 0.002). Within a sub-study of the AHS, recent and long-term use of permethrin was also associated with monoclonal gammopathy of undetermined significance (MGUS), an obligate precursor of multiple myeloma (Hofmann et al., 2021). In the AGRICOH Consortium pooled analysis based on ever use, there was no association with NHL overall,

nor with multiple myeloma (Leon et al., 2019). The Interlymph pooled study of case–control studies found no association between permethrin exposure and NHL, but there were not enough exposed cases to evaluate multiple myeloma specifically (De Roos et al., 2021). This association was also not evaluated within the NAPP, because there were few exposed multiple myeloma cases (Presutti et al., 2016; Kachuri et al., 2020). A mortality study within the AHS also suggested increased risk of death from multiple myeloma overall and from lung cancer among never-smokers (Shrestha et al., 2022); previous analyses of lung cancer incidence had not identified such an association.

A case–control study of infant and childhood leukaemia conducted in Brazil found that prenatal exposure to permethrin was associated with ALL and AML (Ferreira et al., 2013). However, a case–control study of childhood leukaemia in California found no association between permethrin in house dust and ALL (Madrigal et al., 2021). A more recent case–control study has suggested an increased risk of childhood leukaemia (OR, 1.49, 95% CI, 0.83-2.67) among children who lived within 600 m of where permethrin was being applied (Nguyen et al., 2023).

Other studies have evaluated pyrethroids more generally, and those studies are summarized in the section on pyrethrins and pyrethroids (see agent 114).

Cancer in experimental animals

Since the previous IARC evaluation of *inadequate* evidence for the carcinogenicity of permethrin in experimental animals (IARC, 1991), increases in the incidence of bronchioloalveolar adenoma and carcinoma in female mice and of hepatocellular adenoma in male and female mice have been observed in one 2-year study of oral permethrin in mice reviewed by the US EPA, and a high-dose study has shown an increased incidence of lung adenoma in female mice (US EPA, 2006a).

Mechanistic evidence

Since the previous IARC evaluation, many mechanistic studies relevant to the KCs have been published for permethrin and other pyrethroids. Permethrin can induce genotoxicity, genomic instability and DNA damage in animals and in primary human cells in vitro (Gabbianelli et al., 2004; Roma et al., 2012a; Navarrete-Meneses et al., 2017). In models in vivo and in vitro, permethrin modulates various receptor-mediated and endocrine effects (Go et al., 1999; Kim et al., 2004; Brander et al., 2012). Permethrin can induce cytotoxicity in animals in vivo and primary human cells in vitro (Das et al., 2008; Roma et al., 2012b).

Summary

The human cancer evidence is relatively consistent with respect to the association between permethrin and multiple myeloma, although the evidence comes primarily from the AHS cohort, as the case–control studies have not had enough exposed cases for evaluation. Within the AHS cohort, there is a statistically significant increase in incidence with permethrin exposure, with evidence of exposure-related response. In addition, permethrin was associated with MGUS, an obligate precursor to multiple myeloma, and with mortality from multiple myeloma. There is also some evidence of a positive association with childhood leukaemia, although it is less consistent. Carcinogenicity studies in mice exposed to permethrin reported increases of various tumours in both sexes. There is some mechanistic evidence that permethrin in human primary cells and in various experimental systems in vivo and in vitro exhibits KCs, including genotoxicity, genomic instability, modulation of receptor-mediated effects, and alteration of cell proliferation. The Advisory Group therefore considered an *IARC Monographs* evaluation of permethrin to be warranted, together with other pyrethrins and pyrethroids included in this report (agents 114–117).

Recommendation: High priority **(**and ready for evaluation within 2.5 years)

119 Biphenyl (CAS No. 92-52-4)

Current IARC/WHO classification

Biphenyl has not previously been evaluated by the *IARC Monographs* programme. Biphenyl was given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of cancer bioassay and mechanistic evidence.

Exposure characterization

Biphenyl is listed as a high production volume chemical by the OECD (OECD, 2007) and by the US EPA (US EPA, 2024a). Biphenyl is used in organic syntheses, dye carriers, food preservatives, as an intermediate in the production of polychlorinated biphenyls, and as a fungistat in the packaging of citrus fruits and in plant disease control. Because of its high thermal stability, biphenyl in a mixture with biphenyl oxide is used as a heat transfer fluid (ACGIH, 2005; Li et al., 2016c; NCBI, 2020). Biphenyl is naturally present in coal tar, crude oil, and natural gas (Li et al., 2016c).

Exposure to biphenyl can occur by inhalation, ingestion, and dermal absorption (ILO and WHO, 2006). The general population can be exposed to biphenyl through eating citrus fruits that have been wrapped in paper impregnated with biphenyl or if living near an industrial site where biphenyl is used or has been discarded. At these sites, biphenyl may be carried on dust particles. Workers can be exposed if working in an industry that produces biphenyl, including unintentionally as a by-product, or uses it (Australian Government, 2022).

Cancer in humans

No studies on cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In two 2-year animal bioassays, dietary exposure to biphenyl was associated with increased incidence of urinary bladder tumours in male F344 rats (Umeda et al., 2002) and of liver tumours in female BDF_1 mice (Umeda et al., 2005). Earlier studies of dietary biphenyl in rats and mice did not provide clear evidence of carcinogenicity (Dow Chemical Co., 1953; Ambrose et al., 1960; NTIS, 1968; Imai et al., 1983; Shiraiwa et al., 1989).

Mechanistic evidence

In the human liver, biphenyl is hydroxylated to hydroxybiphenyls (HBPs) (Benford et al., 1981). Powis et al. (1987) showed that the metabolite 4-hydroxybiphenyl (4-HBP) is conjugated with glucuronic acid and sulfate in human liver and kidney tissue slices. Sulfotransferase activity for 2-, 3-, and 4-HBP was detected in various human surgical tissue sample preparations (liver, intestinal mucosa, lung, kidney, bladder, and brain) incubated with one of the hydroxybiphenyl isomers, with the highest activity found in the liver (Pacifici et al., 1991). The genotoxicity of biphenyl has been summarized by Li et al. (2016c) and US EPA (2013b), which concluded that biphenyl and its metabolites may induce genotoxicity, but the overall results were inconsistent. Biphenyl has been reported to be mutagenic and clastogenic in some, but not all, in vitro assays. However, positive results were reported for DNA strand breaks in stomach, blood, liver, bone marrow, kidney, bladder, lung, and brain of mice administered single doses of 2000 mg biphenyl/kg (Sasaki et al., 1997a, 2002). Micronuclei were observed in primary human lymphocytes (US EPA, 2013b). Exposure to biphenyl in the diet for 2 years produced hyperplasia in the urinary bladder of rats (Umeda et al., 2002).

Summary

No studies of human cancer related to biphenyl exposure were available. Recent studies have yielded evidence that biphenyl induces cancer in experimental animals. Some mechanistic evidence suggests that

biphenyl exhibits the KC of genotoxicity. However, some inconsistency was observed across results. The Advisory Group therefore considered an *IARC Monographs* evaluation of biphenyl to be warranted.

Recommendation: Medium priority

120 Boscalid (CAS No. 188425-85-6)

Current IARC/WHO classification

Boscalid has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Boscalid is a broad-spectrum fungicide. It is a biphenyl amide and works by inhibiting succinate dehydrogenase. Because it is active against a wide range of fungi, it is used on a similarly wide range of crops. It is approved in the USA and EU. Boscalid and its metabolites were not detected in urine in a study of the general population in the USA (Hyland et al., 2019) but were detected in 3.9 to 36% of the general population in EU countries (Ottenbros et al., 2023). In South Africa, silicone wrist bands detected boscalid in 56% of study participants, more often in children than adults (Fuhrimann et al., 2022). However, in Belgium, silicone wristbands detected boscalid in only 7% of participants (Aerts et al., 2018).

Cancer in humans

A case–control study of childhood leukaemia in the USA used data on pesticide use and residential history to model exposure to pesticides (Park et al., 2020) and found an association with boscalid in the single-pesticide model (OR, 1.81; 95% CI, 1.10–2.97), which was attenuated in the fully adjusted model (OR, 1.38; 95% CI, 0.78–2.43).

Cancer in experimental animals

Boscalid was reported to induce a slight increase of thyroid follicular cell adenomas in a 2-year rodent study (EFSA, 2008).

Mechanistic evidence

Genotoxicity studies using human peripheral blood lymphocytes showed that boscalid significantly increased micronucleus formation (Çayır et al., 2014). In line with the evidence that boscalid is a succinate dehydrogenase (SDH) inhibitor, boscalid was found to increase the level of mitochondrial superoxide in HepG2 cells and to induce apoptosis (d'Hose et al., 2021). Deficiency in the enzyme SDH has been linked to several tumours in experimental animals and in humans (Duarte-Hospital et al., 2023). Yanicostas et al. summarized the results of toxicity testing with zebrafish, showing the KCs, including oxidative stress and alteration of nutrient supply (Yanicostas and Soussi-Yanicostas, 2021). In addition, Wang et al. found that boscalid might directly induce oxidative stress and alter the activity of ATPase (Wang et al., 2020a). Exposure of *Daphnia magna* to boscalid for 48 hours led to clearly decreased levels of antioxidant enzymes and to lipid peroxidation (Aksakal, 2020). Boscalid induced CYP1A, CYP2B, and CYP3A mRNA and/or increased related activities in primary rat and human hepatocytes (Wiemann et al., 2023), but inhibited prostaglandin D2 synthesis in a concentration-dependent manner in SC5 mouse Sertoli cells (Kugathas et al., 2016). Boscalid induced strong transcriptional upregulation of genes associated with the immune response and encoding enzymes related to oxidative phosphorylation and metabolism, including CYP4c3 and CYP6a2 in the eastern honeybee *Apis cerana* (Hymenoptera) (Huang et al., 2023b). In addition, boscalid showed estrogenic activity in MCF-7 and T47D-KBluc cell lines (Jabłońska-Trypuć et al., 2023), and it has been screened in the US EPA ToxCast programme for induction of various cytochromes, including

CYP2E1, CYP1A1 and CYP1A2 among others notably induced by PAHs, and for mRNA expression of PPARγ (US EPA, 2024g).

Summary

Only one study of cancer in humans is available, with relatively weak exposure assessment and substantial risk attenuation after adjustment for other pesticides. There is some evidence from one experimental animal cancer study showing that boscalid induces benign tumours. There is some evidence that boscalid exhibits KCs, including genotoxicity, alterations in nutrient supply, and receptor-mediated effects, in experimental systems, and in one study in human primary cells. Based on this evidence, the Advisory Group considered that an *IARC Monographs* evaluation of boscalid is unwarranted at present.

Recommendation: No priority

121 Carbaryl (CAS No. 63-25-2)

Current IARC/WHO classification

Carbaryl (1-naphthyl-methylcarbamate) has previously been evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in Supplement 7 (IARC, 1987a). Carbaryl was given a priority rating of *high* by the 2019 Advisory Group on Priorities (IARC, 2019a) on the basis of findings of cancer in humans, cancer bioassays, and mechanistic evidence. Carbaryl is on the priority list for the JMPR.

Exposure characterization

Carbaryl, an *N*-methyl carbamate insecticide, is listed as a high production volume chemical by the OECD (OECD, 2007) and by the US EPA (US EPA, 2024a). In the EU, the use of carbaryl has not been authorized since 2006 (European Commission, 2007b). However, in the USA, carbaryl remains registered for both agricultural and residential uses, including for application to fruit, vegetables, grains, and lawn and garden care (US EPA, 2021). The general population may be exposed to carbaryl from spray drift in regions surrounding agricultural areas. Carbaryl has been detected in both surface water and food (Koshlukova and Reed, 2014). In water samples from both paddy and vegetable fields in Dhamrai Upazila, Bangladesh, carbaryl was the most common pesticide detected at 14.1 and 18.1 μg/L, above the maximum acceptable level of 0.5 μg/L (Chowdhury et al., 2012). A metabolite of carbaryl, 1-naphthol, has been reported in urine samples from the US general population (CDC, 2022c).

Workers are most likely to be exposed to carbaryl dermally or by inhalation during its manufacture, formulation, and application (Koshlukova and Reed, 2014). In a study of workers exposed to carbaryl in greenhouses, 24-hour cumulative 1-naphthol levels ranged from 4.8 to 65.1% of the proposed biological reference value of 32 nmol/kg bw in 24-hour urine (Bouchard et al., 2008).

Cancer in humans

Several epidemiological studies have reported results on carbaryl and cancer. Within the Interlymph Consortium, a pooled analysis of population-based case–control studies, there was an increased risk of NHL overall based on exposure assigned by self-report or expert assessment. Most subtypes, with the exception of CLL, showed some evidence of increased risk (De Roos et al., 2021). In a separate pooled analysis of case–control studies in the NAPP, which do not overlap with those included in Interlymph, there was also an elevation of NHL based on self-reported exposure (Koutros et al., 2019). A separate analysis within the NAPP showed a statistically significant association with multiple myeloma (Presutti et al., 2016). There was no evidence of an association with NHL or any subtype in the AHS cohort (Alavanja et al., 2014a), nor within the AGRICOH Consortium (HR, 0.95, 95% CI, 0.83–1.10 for all NHL combined) (Leon et al., 2019),

the latter based on ever/never exposure. A few studies have reported increased risks for cancer at other sites, including a prostate cancer case–control study (Band et al., 2011), associations with central nervous system (CNS) tumours in the AGRICAN cohort (Piel et al., 2019a) and with cutaneous melanoma within the AHS (Mahajan et al., 2007). New analyses are expected from the AHS, including one on all cancers within the pesticide applicators, and another on associations within the spouses.

Cancer in experimental animals

Mice and rats were fed diets containing carbaryl for 2 years at various concentrations in a GLP study. Carbaryl caused increases in the incidence of haemangioma or haemangiosarcoma (combined) and renal cell adenoma or carcinoma (combined) in male mice, and of haemangiosarcoma and hepatocellular adenoma or carcinoma (combined) in female mice (US EPA, 1993b). In another GLP study, carbaryl caused an increase in the incidence of bladder papilloma and carcinoma in male rats and female rats (INCHEM, 1996). However, tumours in rats were observed only at doses above the maximum tolerated dose.

Mechanistic evidence

The European Food Safety Authority (EFSA) Scientific Report provides insights into the metabolism of carbaryl (EFSA, 2006a). Three main metabolic pathways were identified: arene oxide formation, hydrolysis to form 1-naphthol, and oxidation of the *N*-methyl moiety. Various metabolites were isolated from urine and faeces, with 1-naphthol being the predominant urinary metabolite. Other metabolites include dihydrodihydroxycarbaryl, 5-hydroxycarbaryl, and 4-hydroxycarbaryl. The Environmental Health Criteria monograph on carbaryl notes rapid absorption in the lungs and digestive tract, with metabolism via similar pathways across various mammalian species. Carbaryl and its metabolites are primarily excreted in urine, with some enterohepatic cycling. Under normal exposure conditions, carbaryl is unlikely to accumulate in animals.

Since the previous IARC evaluation (IARC, 1987a), new mechanistic evidence has been published on carbaryl, covering cytotoxic and genotoxic effects. Although carbaryl gave negative results in the Ames test, evidence from studies in vitro and in vivo indicates that carbaryl may have genotoxic effects (EFSA, 2006a). In an NTP study, a COMET assay in Sprague-Dawley rats in vivo revealed a positive result in blood samples (NTP, 2019b). Carbaryl induced SCE, chromatid gaps, chromosomal breaks, translocations, ring formation, and fragmentation in V79 Chinese hamster cells. An increased frequency of aneuploid and polyploid cells was also reported. Carbaryl was screened in ToxCast and gave positive results in assays for cell-cycle and DNA binding and estrogen agonism (US EPA, 2024h).

Ferrucio et al. (2017) investigated the molecular effects of carbaryl and solar radiation on human melanocytes. The findings indicated that carbaryl exposure induced oxidative stress, as evidenced by upregulation of antioxidant genes such as haemoxygenase-1 (HMOX1) and downregulation of microphthalmia-associated transcription factor (MITF), a key regulator of melanocytic activity. Additionally, both carbaryl and solar radiation triggered gene responses indicative of DNA damage and cell-cycle disruption. Combined exposure to carbaryl and solar radiation resulted in a more intense gene response, particularly affecting genes involved in cell-cycle regulation (CDKN1A), DNA repair (BRCA1/2), and apoptosis (MDM2), suggesting a synergistic effect between the two exposures. Flow cytometry assays revealed S-phase cell-cycle arrest, reduced levels of apoptosis, and faster induction of DNA lesions (cyclobutane pyrimidine dimers) in carbaryl-treated groups. Overall, the study suggests that carbaryl is genotoxic to human melanocytes, especially when combined with solar radiation. A study by Saquib et al. (2021) focused on cytotoxic and genotoxic effects of carbaryl in human (HUVEC) umbilical vein endothelial cells. Exposure to carbaryl led to significant proliferation inhibition, lysosomal fragility, increased intracellular ROS levels, DNA damage, and apoptotic cell death, suggesting that carbaryl, along with other

pesticides studied, may adversely affect endothelial cell functions, potentially impacting angiogenesis and vascular biology.

In a long-term study by Tsatsakis et al. (2019), rats were exposed to a mixture of chemicals, including carbaryl, at doses below the no observed adverse effect level (NOAEL). The results indicated genotoxic effects in female rats and dose-dependent cytotoxic effects across various tissues. Specifically, testes exhibited degenerative and cellularity disorders, liver hepatocytes showed decreased glycogen deposition, gastric cells displayed degenerative changes, and lung tissue presented increased inflammatory cell infiltration and enhanced phagocytic activity in alveolar macrophages.

Xia et al. (2005) examined the genotoxic effects of carbaryl exposure on spermatozoa in workers. Carbaryl exposure was associated with increased sperm DNA fragmentation and numerical chromosomal aberrations, particularly aneuploidy. The study indicated a potential link between carbaryl exposure and adverse reproductive outcomes. Several studies of the immunotoxic and carcinogenic effects of carbamate pesticides have particularly focused on their impact on the immune system. Dhouib et al. (2016) examined the transition from immunotoxicity to carcinogenicity caused by carbamate pesticides, emphasizing their detrimental effects on the immune system. Jorsaraei et al. (2014) explored immunotoxic effects of carbaryl, both in vivo and in vitro, shedding light on its potential harm to immune function. Li et al. (2015b) examined how carbamate pesticides induce apoptosis (cell death) in human T lymphocytes. Igarashi et al. (2006) investigated the influence of possible endocrine-disrupting chemicals, including carbamate pesticides, on the activation of NF-κB, a key regulator of immune responses. These studies collectively underscore the immunological risks associated with carbamate pesticide exposure, relevant to discussions regarding KC7.

Several studies explored the metabolism and effects of carbamate insecticides, particularly methiocarb and carbaryl, on liver enzymes and plasma levels in both rats and humans, as well as their influence on nuclear receptors such as pregnane X receptor (PXR), constitutive androstane receptor (CAR), PPARα, estrogenic, and anti-androgenic activities (Klotz et al., 1997; Fujino et al., 2016; Tange et al., 2016). Carbamate insecticides inhibit estrogen and progesterone activity in human breast and endometrial cancer cells by, and persistent binding of these compounds to the aryl hydrocarbon receptor has been reported (Lemaire et al., 2006; Bohonowych and Denison, 2007). Li et al. (2014a) reported that carbamate pesticides, including carbaryl, induced apoptosis and necrosis in human NK cells in a time- and dose-dependent manner. The mechanism involved both the caspase-cascade and mitochondrial cytochrome c pathways.

Summary

There are several studies of carbaryl exposures and NHL in humans. Two separate pooled studies of population-based case-–control studies reported increased risks of NHL with carbaryl exposure, while the AHS cohort demonstrated no evidence, nor did a meta-analysis of three cohorts based on ever/never exposed classification. Single studies have reported suggestive associations with other sites. In experiments with mice and rats, carbaryl increased the incidence of tumours in several tissues, that, according to the criteria in the latest version of the *Monographs* Preamble, could support the evidence for carcinogenicity in experimental animals. There is mechanistic evidence that carbaryl exhibits KCs, including genotoxicity, immunosuppression, modulation of receptor-mediated effects, and alteration of cell proliferation, cell death and nutrient supply. The Advisory Group therefore considered an *IARC Monographs* evaluation of carbaryl to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years).

122 Chlordecone (CAS No. 143-50-0)

Current IARC/WHO classification

Chlordecone has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Supplement 7 (IARC, 1987a), on the basis of *sufficient* evidence for cancer in experimental animals. Chlordecone was given a priority rating of *low* by the 2019 Advisory Group on Priorities (IARC, 2019a).

Exposure characterization

Chlordecone (also known as kepone), a stable and persistent organochlorine insecticide, was extensively used in the French West Indies, Martinique and Guadeloupe, on banana farms between 1973 and 1993. It has been banned globally, and since 2019 it has been listed in Annex A of the Stockholm Convention (Secretariat of the Stockholm Convention, 2009). However, due to its long-term presence in the environment, particularly in waterways and soil, and its capacity to accumulate in the food chain, there is still significant exposure to chlordecone in these regions (Dereumeaux et al., 2020).

Exposure occurs primarily through consuming locally produced foods including root vegetables, meat, and fish, resulting in widespread contamination among both animals and humans. Chlordecone has been measured in body fluids and tissues, including blood, fat, and milk (INSERM Collective Expertise Centre, 2022). In the "Kannari study: Health, Nutrition and Exposition to Chlordecone in French West Indies" (2013–2014), more than 90% of the general population showed some level of contamination, with a general declining trend (Dereumeaux et al., 2020). A recent study has also confirmed this decreasing pattern (El Balkhi and Saint-Marcoux, 2023).

Cancer in humans

A population-based case–control study found a significant positive association between chlordecone concentration in blood and prostate cancer (Multigner et al., 2010). This finding was supported by a reanalysis conducted by Emeville et al. (2015). In addition, a study based on the data from the population-based Martinique Cancer Registry indicated that age-standardized incidence rates for prostate cancer increased by 5.07% annually between 1981 and 2005. However, an aggregate analysis of the same data revealed higher incidence rates of prostate cancer in urban areas with lower levels of soil contamination by chlordecone (Dieye et al., 2014). A cohort mortality study was conducted of banana plantation workers who were employed in polluted areas during the period of authorized chlordecone use from 1973 to 1993. Over a 15-year follow-up period (2000 to 2015), SMRs for cause-specific mortality were computed, comparing the mortality rates in the cohort with those of the general population of the polluted area. While significant excess deaths from stomach cancer were observed in women, no increase was observed for all-cancer mortality or mortality from prostate cancer (Luce et al., 2020). However, the limitations of using cancer-specific mortality data to investigate potential carcinogens, along with the presence of some level of exposure in the general population of the area that may potentially distort SMR results, should be considered. Another cohort study in the region, the Timoun mother–child cohort study in Guadeloupe, focused on the risk of congenital anomalies and early-life development (Costet et al., 2022), but has not yet reported on cancer outcomes.

Cancer in experimental animals

In the previous evaluation (IARC, 1979b, 1987a), there was *sufficient* evidence in experimental animals for the carcinogenicity of chlordecone.

Mechanistic evidence

DNA damage by chlordecone was observed in isolated human and rat testis cells (Bjørge et al., 1996b), but not in Ames tests (Schoeny et al., 1979; Legeay et al., 2018). Epigenetic effects induced by chlordecone exposure in utero on human male cord blood included a global reduction in H3K9me3, which correlated with decreased methylation in LINE-1 promoters and telomere length extension. The expression of genes linked to immune response, the cell cycle, DNA repair, and chromatin organization (genomic instability) was affected in human cord blood (Legoff et al., 2021a). Epigenetic effects were found in prostate and ovarian tissues of mice (Legoff et al., 2019, 2021b).

Chlordecone is an agonist of ER α in vitro (Lemaire et al., 2006). In the 2019 Advisory Group report, studies of the estrogenic properties of chlordecone in vitro were cited (IARC, 2019a). Only one study in exposed humans was cited, in which there were no associations between serum concentrations of various hormones and the level of exposure to chlordecone (Emeville et al., 2013). Since then, new mechanistic studies in exposed humans have become available. Ayhan et al. (2021) investigated the consequences of prenatal exposure to chlordecone on pregnancy and child development at the age of 7 years (Ayhan et al., 2021). They observed a non-monotonic (inverted-U) association between exposure to chlordecone in utero, assessed by concentrations in cord blood, and thyroid-stimulating hormone (TSH) levels in girls and dehydroepiandrosterone, total testosterone, and dihydrotestosterone levels in both boys and girls. Only the third quartile of exposure in utero was associated with significantly increased hormone levels (Ayhan et al. 2021). The same group also found that cord-blood concentrations of chlordecone were monotonically associated with increased TSH levels at 3 months of age in boys only, without modification of free thyroxine (T4) or triiodothyronine (T3) levels (Cordier et al., 2015). Modulatory hormone-related effects of chlordecone in experimental models in vivo have been reported (Das et al., 1998; Lian et al., 2020; Yang et al., 2020b).

In human umbilical vein endothelial cells (HUVECs), chlordecone increases oxidative species and has pro-angiogenic properties (increased VEGF, capillary length, cell proliferation) (Alabed Alibrahim et al., 2018; Legeay et al., 2018; Clere et al., 2012). The angiogenic process is mediated by activation of ER α in vivo (Clere et al., 2012).

Summary

There is new evidence from epidemiological studies of cancer in humans associated with chlordecone exposure. There is already *sufficient* evidence for cancer in experimental animals. Mechanistic data in exposed humans show that chlordecone is probably an endocrine disruptor, modulating receptor-mediated effects, and can exert wide epigenetic effects. These results are supported by studies in experimental systems. In primary human cells, chlordecone can promote cell proliferation and angiogenesis. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of re-evaluation of chlordecone to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years).

123 Chlorpyrifos (CAS No. 2921-88-2)

Current IARC/WHO classification

Chlorpyrifos has not previously been evaluated by the *IARC Monographs* programme. Chlorpyrifos was given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of human cancer and mechanistic evidence. Chlorpyrifos is on the priority list for the JMPR.

Exposure characterization

Chlorpyrifos is listed as a high production volume chemical by the OECD (OECD, 2007) and by the US EPA (US EPA, 2024a). Chlorpyrifos is an organophosphate insecticide, acaricide, and miticide used to control foliage and soil-borne insect pests on a variety of food and feed crops. It is currently still registered for use in the USA (US EPA, 2006b), although use has declined as particular registrations have been cancelled. The European Commission voted to cancel all registrations as of January 2020 (European Commission, 2020a). It was used in the past in many countries for both agricultural and residential applications.

Adults and children in the general population are exposed to chlorpyrifos through consumption of water and food (Bradman et al., 2007; El-Nahhal and Lubbad, 2018). Workers could be exposed to chlorpyrifos through direct transdermal contact and by inhalation during its manufacture, preparation of spraying solutions, loading of sprayer tanks, and application (EFSA, 2019). In low-income countries, exposure to chlorpyrifos can be very high. 3,5,6-Trichloro-2-pyridinol, a chlorpyrifos-specific metabolite, was analysed in urine specimens collected from agricultural workers in Egypt. Concentrations were 6437 µg/g creatinine in sprayers, 184 µg/g in technicians and 157 µg/g in engineers (Farahat et al., 2011).

Cancer in humans

In the NAPP, which includes population-based case–control studies, there was a positive association, but not statistically significant, between ever-use of chlorpyrifos and NHL overall (Koutros et al., 2019). In the Interlymph Consortium, a pooling project of case–control studies not included in the NAPP, there was no apparent association between NHL overall or any subtypes, including with increased duration of use (De Roos et al., 2021). Within the AHS cohort, there have been several evaluations of chlorpyrifos. The most recent publication reported no apparent association with NHL overall; however, there was a suggestion of increased risk of follicular lymphoma with increasing use of chlorpyrifos (Alavanja et al., 2014b). In the AGRICOH Consortium, there was no association of ever use of chlorpyrifos with NHL overall or any of the subtypes (Leon et al., 2019). An analysis of chlorpyrifos and multiple cancer sites within the AHS suggested increased risk of brain cancer and leukaemia (Lee et al., 2004). Among spouses in the AHS, breast cancer risk was elevated among women who ever used chlorpyrifos, primarily in premenopausal women (Engel et al., 2017). A case–control study of postmenopausal breast cancer also demonstrated increased risk among women with estimated occupational and residential chlorpyrifos exposure (Tayour et al., 2019).

Cancer in experimental animals

Yano et al. (2000) evaluated the carcinogenicity of chlorpyrifos in a high-dose, 2-year dietary toxicity study in Fischer 344 rats. Chlorpyrifos administered daily in the feed according to US EPA guidelines was not found to be carcinogenic.

Mechanistic evidence

Chorpyrifos has been generally considered not to be a genotoxic agent. The available studies do not support a concern about mutagenicity; neither gene mutation nor clastogenic effects have been reported for chlorpyrifos (EFSA, 2019; Wołejko et al., 2022). Studies using high doses showed mutagenic results (Sandhu et al., 2013), whereas lower exposures did not. However, several studies on DNA damage in human lymphocytes in vitro and in vivo have shown positive findings (Rahman et al., 2002; Vindas et al., 2004; Ojha and Srivastava, 2014; Ezzi et al., 2016; Zeljezic et al., 2017), and one recent study observed chromosome loss and mis-segregation (Mužinić et al., 2019).

Chlorpyrifos has significant ER and AR activity in high-throughput screening assays (Andersen et al., 2002). In the steroidogenesis assay, at high test concentrations, chlorpyrifos increased estradiol levels and decreased testosterone levels. However, effects seen in vitro were not supported by data on higher mammals

from the uterotrophic assay, the Hershberger assay, and pubertal hormone assays in boys and girls (Kang et al., 2004; US EPA, 2011a; Medithi et al., 2022a).

Chlorpyrifos induces cytotoxicity in human glioblastoma cells through oxidative stress-related apoptosis (Hsu et al., 2023). These authors observed decreased cell viability, morphological changes, and increased production of ROS. Additionally, chlorpyrifos upregulated pro-apoptotic proteins (Bax and cleaved caspases), while downregulating anti-apoptotic protein Bcl-2. Moreover, chlorpyrifos modulated antioxidant response pathways. Importantly, vitamin E ameliorated the cytotoxic effects of chlorpyrifos, suggesting oxidative stress as a critical mechanism in chlorpyrifos-associated glioblastoma.

In studies related to neurotoxicity, Parween et al. (2022) found that chlorpyrifos induces oxidative stress, cytotoxicity, and downregulation of paraoxonase 2 (PON2) expression in human neuroblastoma cells. Combined exposure to pyridostigmine bromide, chlorpyrifos, and *N,N*-diethyl-*meta*-toluamide (DEET) led to profound mitochondrial dysfunction in neuroblastoma cells, although without a significant increase in ROS production (Delic et al., 2021). Moyano et al. (2020) demonstrated that chlorpyrifos promoted cell proliferation in breast cancer cells through estrogen and aryl hydrocarbon receptors, suggesting multiple mechanisms of carcinogenicity. Chlorpyrifos disrupted cholinergic and Wnt/β-catenin signalling pathways, upregulated acetylcholinesterase-R, and induced oxidative stress, contributing to increased cell proliferation (Moyano et al., 2021).

Summary

Although there are a few suggestive associations, the human cancer evidence for chlorpyrifos is inconclusive. Two pooled case–control studies have examined NHL, one showing some suggestive evidence and one showing no evidence of an association. The large prospective AHS cohort showed no association with NHL overall, but a suggestive association with one of its subtypes. An update of the AHS evaluating multiple cancer sites with chlorpyrifos is expected within a couple of years. A case–control and a cohort study suggested an association between chlorpyrifos and breast cancer in women, of particular interest given its estrogenic properties. There is a lack of evidence for cancer in experimental animals.

Mechanistic evidence suggests that chlorpyrifos exhibits KCs, including oxidative stress, modulation of receptor-mediated effects, and cell proliferation and cell death in experimental systems and some evidence in exposed humans. The mechanistic evidence would support an evaluation of the carcinogenicity of chlorpyrifos. The Advisory Group therefore considered an *IARC Monographs* evaluation of chlorpyrifos to be warranted, together with other organophosphates included in this report (fonofos, agent 124; malathion, agent 131; terbufos, agent 127).

Recommendation: High priority (and ready for evaluation within 5 years)

124 Fonofos (CAS No. 944-2-9)

Current IARC/WHO classification

Fonofos has not previously been evaluated by the *IARC Monographs* programme. Fonofos was given a priority rating of *low* by the 2019 Advisory Group on Priorities (IARC, 2019a).

Exposure characterization

Fonofos is an organothiophosphate soil insecticide used on a variety of agricultural crops (e.g. cereals, maize, vegetables, and fruit). In 1997, its registration in the USA was cancelled (US EPA, 1999) and it is no longer approved for use in the EU (European Commission, n.d). While regulatory information is difficult to find in other parts of the world, there is some evidence that fonofos is still being used in LMICs. For example, in a study of pesticide residues on fruits and vegetables in Uganda sold for human consumption, fonofos was

detected in 29% of samples (Ssemugabo et al., 2022). In the US AHS, around 20% of the included licensed pesticide applicators were ever exposed to fonofos (Mahajan et al., 2006).

Cancer in humans

Within the AHS cohort, there was a statistically significant association between fonofos use and aggressive prostate cancer (Koutros et al., 2013). A recent publication from the AHS showed a significant interaction between use of fonofos and a polygenic risk score (PRS) on prostate cancer risk, with men who used fonofos and had a higher PRS having increased risk of prostate cancer overall, which was greater among those with aggressive disease (Hurwitz et al., 2023). Within the AHS, there was no association between fonofos and NHL overall, although there was a suggestive exposure–response relation with multiple myeloma (Alavanja et al., 2014a) and evidence of an association with leukaemia (Mahajan et al., 2006). In the NAPP pooled analysis of US and Canadian population-based case–control studies, there was a statistically significant elevation of NHL overall based on self-reported use of fonofos, with the strongest associations observed for follicular lymphoma and diffuse large B-cell lymphoma (Koutros et al., 2019)

Among spouses of the AHS pesticide applicators, no association was observed with breast cancer for personal use of fonofos (Lerro et al., 2015), but among women who did not apply pesticides, their husband's use was associated with elevated risk (Engel et al., 2017).

Cancer in experimental animals

As noted in the 2019 Advisory Group report (IARC, 2019a), results of chronic cancer rodent bioassays were found to be equivocal by the US EPA (US EPA, 2008a). In a report reviewed by the US EPA, male and female Sprague-Dawley rats fed fonofos in the diet for 24 months had cortical cell adenoma and phaeochromocytoma of the adrenal gland, hepatocellular adenoma, mammary gland carcinoma and adenoma, tumours of the thyroid, pituitary gland carcinoma and adenoma in males, hepatocellular adenoma and carcinoma, tumours of the pituitary gland in both males and females, and HCC in males (US EPA, 1991). However, these tumours were also reported in the control group and there was no significant difference in the incidence of tumours between the control and treated groups at any dose. In male CD-1 mice administered fonofos in diet for 18 months, no differences in the incidence of tumours at any dose compared with controls in either males or females were reported (US EPA, 1996a).

Mechanistic evidence

Furnes and Schlenk (2005) explored the metabolism of fonofos, highlighting its extrahepatic metabolism by flavin-containing monooxygenase (FMO) and CYP enzymes. The study demonstrated that FMO1 plays a significant role in the sulfoxidation of fonofos and other pesticides. This suggested that fonofos may undergo metabolic transformations outside the liver, expanding understanding of its biotransformation pathways. Moreover, Smyser and Hodgson (1985) provided insights into the oxidative desulfuration of fonofos by pig liver microsomal FAD-containing monooxygenase. The study revealed that fonofos acts as a substrate for this enzyme, indicating phosphorus-oxidase activity. The formation of phosphine oxide as the major metabolite underscored the role of microsomal FAD-containing monooxygenase in fonofos metabolism, with implications for its overall biological effects.

Fonofos has been implicated in various mechanistic pathways associated with potential carcinogenicity. Fonofos tested positive in mutagenicity studies, such Ames assay, and in *S. cerevisiae* (Gentile et al., 1982). Zhang et al. (2012b) investigated the epigenetic effects of fonofos, along with parathion and terbufos, on the human haematopoietic K562 cell line and found that exposure to these pesticides induced DNA methylation alterations in the promoter regions of 712 genes. Notably, fonofos, parathion, and terbufos clustered together based on their methylation patterns, indicating similar effects. Functional analysis revealed the involvement of these methylation changes in processes related to carcinogenesis, providing experimental evidence that

pesticides, including fonofos, may modify gene promoter DNA methylation levels. This suggests a potential role for epigenetic mechanisms in pesticide-induced carcinogenesis.

There is evidence that fonofos exhibits the KC "modulates receptor-mediated effects", as Hurwitz et al. (2023) suggested the interaction between fonofos and individual genetic variants occurring in regions associated with variants related to altered AR-driven transcriptional programmes relevant to prostate cancer. In addition, it was reported to alter steroid hormone metabolism (E2) and to inhibit testosterone activity in acellular models of human liver microsomes (Usmani et al., 2003, 2006). Fonofos was reported to induce hyperplasia in the duodenum in an 18-month carcinogenicity study in mice (US EPA, 1996a). Data are also available from the ToxCast and Tox21 programmes.

Summary

There is evidence of human carcinogenicity that may support an evaluation for fonofos. Many epidemiological studies, including those from a large prospective cohort, have been conducted, with the strongest evidence noted for aggressive prostate cancer. Some positive associations with fonofos exposure were found for NHL (including subtypes) and breast cancer. Long-term bioassays in rats and mice fed fonofos in the diet did not show any significant differences in tumour incidence from the control group. Hence, the evidence from experimental animals is considered equivocal. Fonofos appears to exhibit KCs, including "alters DNA repair", "induces epigenetic alterations", and "modulates receptor-mediated effects". The Advisory Group therefore considered an *IARC Monographs* evaluation of fonofos to be warranted, together with other organophosphates included in this report (chlorpyrifos, agent 123; malathion, agent 131; terbufos, agent 127).

Recommendation: High priority (and ready for evaluation within 5 years)

125 Glyphosate (CAS No. 1071-83-6)

Current IARC/WHO classification

Glyphosate was previously evaluated in 2015 by the *IARC Monographs* programme as *probably carcinogenic to humans* (Group 2A) in Volume 112 (IARC, 2017a). The basis of this evaluation was *limited* evidence for cancer in humans (for NHL) and *sufficient* evidence for cancer in experimental animals, supported by *strong* mechanistic evidence for genotoxicity and oxidative stress. Glyphosate was given a priority rating of *no priority* for re-evaluation by the 2019 Advisory Group on Priorities (IARC, 2019a).

Exposure characterization

Glyphosate is listed as a high production volume chemical by the OECD (OECD, 2007) and by the US EPA (US EPA, 2024a). Glyphosate has been for decades one of the most heavily used herbicides globally. Its use was recently reauthorized by the European Commission until 2033 (EUR-Lex, 2023). For the 2015 evaluation, IARC evaluated both "pure" glyphosate and formulations containing glyphosate (IARC 2016). Formulations can vary and may contain glyphosate as the isopropylamine, ammonium, or sodium salt. Additives such as surfactants and impurities such as formaldehyde *N*-nitrosoglyphosate may be present in various concentrations (IARC, 2016).

In recent years, several studies have been conducted worldwide on exposure of the general population, as well as workers, to glyphosate or its main metabolite aminomethylphosphonic acid (AMPA). The National Health and Nutrition Examination Survey (NHANES) in the USA found detectable levels of glyphosate in 81% of the US population aged ≥ 6 years in 2013–2014, with a median (interquartile range) urine concentration of 0.450 (0.266–0.753) μg/g creatinine (Ospina et al., 2022). Some determinants of exposure in the general population include age (with exposures higher among young children in some

studies), diet, and proximity to spraying fields or to open water sources of drinking-water (e.g. Ospina et al., 2022; Berni et al., 2023; Lucia et al., 2023; Liu et al., 2024). A study of children in Japan found an increase in urinary concentrations between 2006 and 2015 (Nomura et al., 2022). Additional studies have recently reported on occupational exposure in a variety of jobs, including those involving direct handling of glyphosate (Boulanger et al., 2023; Dou et al., 2023; Hyland et al., 2024).

Cancer in humans

Since the last evaluation, several studies have examined various cancer outcomes, mainly NHL. Hardell et al. (2023) pooled three Swedish case–control studies of NHL and hairy-cell leukaemia (all of which had been considered in the previous IARC evaluation). Among the few exposed cases (n = 37) and controls (26), ORs of 2.0 (95% CI, 0.96–4.3) and 2.4 (95% CI, 1.2–5.0) were seen with ≤ 13 and > 13 days (respectively) of reported exposure to glyphosate relative to no exposure. A pattern of higher risk with increased latency was observed, but no adjustment was made for exposure to other pesticides.

Increasing attention has focused on risks for subtypes of NHL. In a publication from the AHS that included exposure–response analyses of intensity-weighted lifetime days, there was no association with NHL overall, nor with any subtype in unlagged and lagged analyses (Andreotti et al., 2018). However, in a pooled study of three cohorts, including the AHS, and studies from France and Norway (AGRICOH), a positive association was seen between ever-exposure to glyphosate and diffuse large B-cell lymphoma (DLBCL) (HR, 1.36; 95% CI, 1.00–1.85). (Leon et al., 2019). Elevation was seen only in the Norwegian cohort, although the formal test for heterogeneity was null. For all other subtypes of NHL, the point estimates were below unity (but imprecise) and the HR for NHL overall was 0.95 (95% CI, 0.77–1.33) In the NAPP case–control study, positive associations were observed for handling glyphosate > 2 days per year for NHL overall and for DLBCL (OR, 2.14; 95% CI, 1.07–4.28; *P* for trend, 0.2), but not for duration or overall use (Pahwa et al., 2019). By contrast, no association was seen between glyphosate and DLBCL in the Interlymph pooled case–control study (De Roos et al., 2022), either overall or by exposure duration. A meta-analysis, which found a positive meta-relative risk (meta-RR) for DLBCL (meta-RR, 1.29; 95% CI, 1.02–1.63) but not for NHL overall (meta-RR, 1.05; 95% CI, 0.90–1.24), did not include the recent findings from Interlymph (Boffetta et al., 2021).

Regarding other subtypes of NHL, findings have been mostly null. Exceptions include some evidence of positive associations between SLL and some, but not other, metrics in the NAPP (Pahwa et al., 2019) Positive associations observed in Interlymph for follicular lymphoma using a 10-year lag (OR, 1.48; 95% CI, 0.98–2.25) were robust to multiple sensitivity analyses (De Roos et al., 2022). Positive associations were also observed for follicular lymphoma in a recent case–control study in six centres in Italy (Meloni et al., 2021). No other studies have suggested associations with other NHL subtypes (Andreotti et al., 2018; Pahwa et al., 2019; Leon et al., 2019). In the most recent AHS analysis, there was an increased risk of AML; among applicators in the highest exposure quartile, there was an increased risk of AML compared with never-users (RR, 2.44; 95% CI, 0.94 to 6.32, *P* for trend, 0.11) in unlagged analyses, which became statistically significant in lagged analyses (Andreotti et al., 2018).

Cancer in experimental animals

In the previous evaluation (IARC, 2017a), there was *sufficient* evidence in experimental animals for the carcinogenicity of glyphosate, on the basis of studies in rodents: positive trends of renal tubule carcinoma and of renal tubule adenoma or carcinoma (combined) and haemangiosarcoma in CD-1 mice after dietary exposure (US EPA, 1985a, b, 1986a; Chandra and Frith, 1994; JMPR, 2006). Glyphosate induced adenomas and exerted tumour-promoting activity in several studies in rodents, including a transgenic mouse model for a *MYC* mutation in germinal B cells (George et al., 2010; Wang et al., 2019a).

Mechanistic evidence

Glyphosate is mostly absorbed through the skin and via oral or pulmonary routes: it has been calculated that approximately 2% of glyphosate can penetrate skin. It accumulates in the kidneys, liver, colon, and small intestine and is excreted in the faeces (90%) and urine (JMPR, 2006; EFSA, 2015a). Since the previous evaluation, several studies have looked for effects linked to the KCs in multiple test systems. There is mounting evidence from studies in human cells in vitro and in experimental systems for effects on various KCs. The most recent evidence in exposed humans is summarized below.

One study identified an increase of genotoxicity-associated end-points in exposed humans. Balderrama-Carmona et al. (2020) reported a significant increase of micronucleus formation in agricultural workers from the Valle del Mayo area (Sonora, Mexico). However, the study lacked a proper exposure assessment. Several studies have confirmed previous findings and shown that glyphosate, its metabolite AMPA, and a common formulation induce single-strand breaks in human lymphocytes and PBMCs and at higher concentrations also double strand breaks, which might be repaired after 2 hours except with the formulation (Kwiatkowska et al., 2017; Suárez-Larios et al., 2017; Santovito et al., 2018; Woźniak et al., 2018).

Several studies of exposed humans have found evidence of oxidative stress, including oxidative DNA damage. In a longitudinal pre-post study performed among maize farmers, Sidthilaw et al. (2022) observed in 180 study participants an association of increased levels of urinary glyphosate with serum levels of malondialdehyde (MDA) and decreased serum levels of GSH. Recently, Chang et al. (2023b) identified a positive association between exposure to glyphosate and oxidative damage to DNA in a subcohort of male farmers of the AHS prospective cohort of pesticide applicators in Iowa and North Carolina. Specifically, urinary glyphosate concentration correlated positively with 8-OHdG and MDA (pre- and post-exposure). Also, farmers with high glyphosate exposure in the past year, or with lifetime glyphosate exposure, showed elevated 8-iso-prostaglandin F2α levels compared with controls. Alterations in antioxidant defence mechanisms, i.e. GSH metabolism, by metabolomic analysis, were observed in serum samples of workers from three glyphosate manufacturing facilities in China when compared with control participants (general population) (Zhang et al., 2022b). Makris et al. (2022) identified an increase in markers of oxidative DNA damage but not of lipid peroxidation in a group of 177 children aged 10–11 years from a study in Cyprus (within the HBM4EU project). 8-OHdG was positively associated with the level of the glyphosate metabolite AMPA only.

Glyphosate exposure has been linked to inflammatory effects. In the study by Sidthilaw et al. (2022), participants were tested for lung function parameters: forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC, peak expiratory flow (PEF), and forced expiratory flow 25–75% (FEF25–75%). Glyphosate exposure was associated with decreases in FEV1, FVC, FEV1/FVC, PEF, and FEF25–75%. These results were similar to other epidemiological findings in the Republic of Korea (Cha et al., 2012) and Thailand (Sapbamrer et al., 2020). These findings are concordant with the observation that glyphosate induces inflammatory response in lung and other tissues in vitro and in vivo (Hernández et al., 2008; Kumar et al., 2014; Hao et al., 2019).

There is evidence for receptor-mediated effects in exposed humans. In the 2013–2014 NHANES study mentioned above, the relation between increased urinary levels of glyphosate and blood sex hormone levels (total testosterone, total estradiol, and sex hormone binding globulin (SHBG)) was assessed in 2130 persons. Urinary concentrations of glyphosate were inversely correlated with total estradiol levels and testosterone but not SHBG. The ratios of total testosterone:SHBG and total estradiol:SHBG (representing the fraction of active sex hormones in the blood) were significantly inversely correlated with urinary concentrations of glyphosate (Geier and Geier, 2023). Association of urinary glyphosate with methylation in promoter regions of MSH4, KCNA6, ABAT, and NDUFAF2/ERCC8 ageing genes and of the glyphosate metabolite AMPA with estrogen receptor 1 (ESR1) promoter hypomethylation, was observed in an epigenome-wide

association study conducted on leukocytes from a cohort of 392 postmenopausal women (Lucia et al., 2023). ER mediation of the effects of glyphosate was recently described in human PBMCs obtained from healthy donors, in which a reduction of Th1/Th2 ratio of T-helper (Th) cells was observed along with increased production of IL-4 and IL-17A and reduction of IFNγ. The effects of glyphosate on IL-4 and IFNγ were abolished by inhibition of the nuclear estrogen receptors ERα/ERβ, thus linking the modulation of receptor-mediated effects and the potential immunosuppressive effect of glyphosate (Maddalon et al., 2022).

Acute exposure to glyphosate induced a significant increase in serum levels of T4 hormone in a study in farmers pre- and post-spraying activity (Kongtip et al., 2021). Effects on endocrine systems have been confirmed in a pilot study conducted in 94 mother–infant pairs (45 female and 49 male) from The Infant Development and the Environment Study (TIDES) in the USA. Anogenital distance (AGD) as a marker of the "prenatal hormone milieu" was measured in male and female infants. Urinary levels of glyphosate and its metabolite AMPA were associated with specific AGDs in female infants but not males (Lesseur et al., 2021).

Summary

The findings regarding associations between glyphosate and NHL in humans remain inconsistent, although more recent studies have focused on NHL subtypes. The Advisory Group concluded that it is unlikely that an evaluation of the human cancer evidence since the 2015 evaluation would result in a change in classification. The evidence for cancer in experimental animals was *sufficient* in 2015. Increasing mechanistic evidence that glyphosate exhibits various KCs, including genotoxicity, oxidative stress, chronic inflammation, immunosuppression, and modulation of receptor-mediated effects in exposed humans has become available since the previous evaluation. This is supported by mounting evidence in human cells in vitro and in experimental systems. However, several of the new studies in exposed humans were considered of limited relevance in terms of study design and exposure assessment, because of difficulties in discriminating between exposure to glyphosate and to other pesticides. The Advisory Group also considered the importance of clarifying glyphosate formulations in future evaluations of the mechanistic data in exposed humans. The Advisory Group therefore considered that an *IARC Monographs* re-evaluation of glyphosate is unwarranted at present.

Recommendation: No priority

126 Phosmet (CAS No. 732-11-6)

Current IARC/WHO classification

Phosmet has not previously been evaluated by the *IARC Monographs* programme. Phosmet is on the priority list for the JMPR.

Exposure characterization

Phosmet is an organophosphate pesticide, consisting of a phthalimide group and a dithiophosphate ester group, with two methyl groups. It is a non-systemic organophosphate insecticide used on a wide variety of crops and for ticks and fleas on domestic and farm animals. Approval to use phosmet was withdrawn in the EU in 2022 (European Food Safety Authority (EFSA) et al., 2021; European Commission, 2022). It is still used in the USA, although there are some mitigation actions required by registrants (US EPA, 2023b).

A study of Chilean children calculated that 19% were exposed to phosmet residues in fruit and vegetables (Muñoz-Quezada et al., 2012). Occupational exposure in farming has been documented, but clothing and gloves provide good protection from exposure for applicators (Stewart et al., 1999).

Cancer in humans

A case–control study of childhood leukaemia in the USA used data on pesticide use and residential history to model exposure to pesticides (Park et al., 2020) and found an association with phosmet (OR, 2.10; 95% CI, 1.30–3.39) in the fully adjusted model.

Cancer in experimental animals

Information released by the US EPA Office of Pesticide Programs in 2006 about a carcinogenicity study in mice indicated that phosmet caused increases in liver carcinomas/adenomas in males and increased mammary gland tumours in females, but was not carcinogenic in rats (US EPA, 2016). However, in another study of male rats, phosmet exposure induced lung adenomas (Hasegawa et al., 1993).

Mechanistic evidence

Phosmet induced single-strand breaks in DNA, exhibiting a weak mutagenic effect without metabolic activation but significantly stronger with the S9 fraction (Slamenová et al., 1992). Furthermore, phosmet decreased DNA synthesis independently of cellular death and lowered the cell percentage in the S-phase. Induction of oxidative stress was reported in juvenile rainbow trout (*O. mykiss*) subjected to phosmet treatment (Muhammed and Dogan, 2021). Phosmet exhibited a distinctive toxicity signature, including impairing cell viability and inducing inflammatory response (Guiñazú et al., 2012).

Phosmet increased progesterone activity in human H295R adrenocortical carcinoma cells with reported mammary gland effects (Cardona and Rudel, 2021; Kay et al., 2024). It showed binding activity to the AR, and CYP induction, in a few reporter gene assays, as reported in the ToxCast database (US EPA, 2024i). In the human JEG-3 choriocarcinoma cell line, phosmet exerted concentration- and time-dependent effects on cellular viability, leading to apoptosis and reduced [^{3}H]thymidine incorporation (Guiñazú et al., 2012).

Summary

There is only one study of cancer in humans in relation to phosmet, with relatively weak exposure assessment quality. There is evidence of increased incidence of some benign and malignant tumours in male and female mice and male rats. There is sparse mechanistic evidence that phosmet exhibits some of the KCs, including genotoxicity, oxidative stress, chronic inflammation, alterations in receptor-mediated effects and cell proliferation and cell death, in experimental systems. The Advisory Group therefore considered that an *IARC Monographs* evaluation of phosmet is unwarranted at present.

Recommendation: No priority

127 Terbufos (CAS No. 13071-79-9)

Current IARC/WHO classification

Terbufos has not previously been evaluated by the *IARC Monographs* programme. Terbufos is on the priority list for the JMPR. Terbufos was given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of human cancer and mechanistic evidence.

Exposure characterization

Terbufos is an organothiophosphate insecticide that has historically had widespread agricultural use as an insecticide and nematocide. As of 2023, terbufos is not approved by the EU (ECHA, 2023d). In the USA, it continues to be registered for widespread use (US EPA, 2006c). There are no residential uses registered for terbufos (US EPA, 2015). Exposure is expected to occur mainly in agricultural workers handling and applying the substance (US EPA, 2015).

Cancer in humans

Within the AHS cohort, there was a significant exposure–response relation between terbufos and prostate cancer, particularly aggressive prostate cancer (Koutros et al., 2013). More recent findings in the AHS suggest that terbufos may interact with specific prostate cancer genetic susceptibility variants identified through genome-wide association studies (Hurwitz et al., 2023). The AHS has also evaluated associations with cancer at other sites; of note, while there was no overall association with NHL, there was an exposure–response relation between terbufos and small B-cell lymphocytic lymphoma (SLL)/chronic B-cell lymphocytic leukaemia (CLL)/mantle cell lymphoma (MCL) (Alavanja et al., 2014a). Within the AGRICOH Consortium, which includes the AHS, there was an elevation of NHL overall based on ever use, which seemed to be driven by CLL/SLL and follicular lymphoma (Leon et al., 2019). In the pooled data from the NAPP, results for lymphoma from population-based case–control studies showed no evidence of association with ever use or duration of use (Koutros et al., 2019). Among the spouses of the AHS farmers, there was an association between terbufos and breast cancer based on self-reported personal use (Lerro et al., 2015), and based on use by their husbands (Engel et al., 2017).

Cancer in experimental animals

No studies on carcinogenicity in experimental animals were available to the Advisory Group.

Mechanistic evidence

Wu et al. (2011) reported that terbufos induces DNA damage and apoptosis in HepG2 cells exposed to concentrations of 50–200 µM for 2 hours. Complementing the findings of overall associations between terbufos and aggressive prostate cancer risk (Koutros et al., 2013), Koutros et al. (2010) explored interactions between pesticide use, genetic variants on chromosome 8q24, and prostate cancer risk. They observed significant interactions between certain variants on chromosome 8q24 and exposure to organophosphate and pyrethroid insecticides, particularly fonofos. This suggests that genetic predispositions may modify the association between pesticide exposure and prostate cancer risk.

Moreover, Andreotti et al. (2012) reported findings suggesting that genetic variation in lipid metabolism genes may modify pesticide associations with prostate cancer. Notably, one association was found between ALOXE3 rs3027208 and terbufos, highlighting the potential role of lipid metabolism pathways in mediating the effects of pesticides on prostate cancer risk. These studies collectively underscore the complex interaction between pesticide exposure, genetic factors, and biological pathways involved in prostate and breast carcinogenesis.

Potential mechanisms for carcinogenicity have been reported, including that terbufos may influence risk of prostate cancer by altering signalling pathways involved in cellular adhesion, proliferation, and differentiation (Zhang et al., 2012b; Koutros et al., 2013; Christensen et al., 2016). Terbufos also alters steroid hormone metabolism and inhibits testosterone. The study by Zhang et al. (2012b) identified specific genes and pathways that were affected by terbufos exposure-induced DNA methylation alterations. While the exact genes and pathways affected may vary depending on cell type and context, the study provided insights into some of the potential targets (Christensen et al., 2016).

A genome-wide DNA methylation analysis of samples obtained from human haematopoietic K562 cell lines exposed to several pesticides (including terbufos) revealed that differential methylation was associated with numerous genes that are involved in carcinogenesis-related processes (Zhang et al., 2012b).

Summary

The human cancer evidence, while not entirely consistent, shows evidence of elevated risk of NHL in several studies, both cohort and case–control. In addition, there is consistent evidence within a large cohort of pesticide applicators of increased risk of aggressive prostate cancer, including interaction with prostate

cancer genetic susceptibility loci identified through genome-wide association studies. Two analyses within the AHS, one focused on personal use and one focused on use by pesticide applicator husbands both suggested an increased risk of breast cancer. No studies were available of cancer in experimental animals.

There is some mechanistic evidence from studies in exposed humans and experimental systems that terbufos exhibits KCs, including genotoxicity, epigenetic alterations, modulation of receptor-mediated effects, and alteration of cell proliferation. The Advisory Group, on the basis of emerging evidence of cancers in humans, considered an *IARC Monographs* evaluation of terbufos to be warranted and recommended that this agent be evaluated together with other organophosphates in this report (chlorpyrifos, agent 123; fonofos, agent 124; phosmet, agent126; and malathion, agent 131).

Recommendation: High priority (and ready for evaluation within 5 years).

128 Ethylenedithiocarbamates

Current IARC/WHO classification

Ethylenedithiocarbamates – sodium diethyldithiocarbamate (CAS No. 148-18-5), potassium bis(2-hydroxyethyl)dithiocarbamate (CAS No. 23746-34-1), disulfiram (CAS No. 97-77-8), thiram (CAS No. 97-77-8), nabam (CAS No. 142-59-6), ferbam (CAS No. 14484-64-1), zineb (CAS No. 12122-67-7) and ziram (CAS No. 137-30-4) – have previously been evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in Supplement 7 in 1987 (IARC, 1976a, 1987a). Ethylene thiourea (ETU; the main metabolite of ethylenedithiocarbamates) has previously been evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in Supplement 7 and in Volume 79 in 2001 (IARC, 2001). Ethylenedithiocarbamates are on the priority list for the JMPR. Mancozeb has been nominated for prioritization and is discussed separately in this report (see agent 132).

Exposure characterization

Ethylenedithiocarbamates (also called ethylenebisdithiocarbamates or EBDCs) are complexes of a dithiocarbamate with manganese, zinc or a combination of manganese and zinc. They include disulfiram, thiram, nabam, ferbam, zineb, ziram, maneb (CAS No. 12427-38-2), metiram (CAS No. 9006-42-2), mancozeb (CAS No. 8018-01-7), and propineb (CAS No. 12071-83-9) (Cocco, 2022). The main metabolite of the EBDCs is ethylene thiourea (CAS No. 96-45-7) (Cocco, 2022).

Disulfiram, zineb, maneb, and propineb are listed as high production volume chemicals by the OECD (2007). Mancozeb was one of the most commonly used conventional pesticide active ingredients in the USA in 2012 (US EPA, 2017b) and is widely used in India, with over 28% of the world market being in this country (Industry Data Analytics, 2020). Mancozeb was banned in the EU in 2021 due to its endocrine-disrupting and reproductive effects (FAS, 2020). Various EBDCs have been used as fungicides in agriculture since the 1940s, and some are also used in the vulcanization of rubber (Cocco, 2022). Disulfiram is also used in the pharmaceutical treatment of alcohol dependence (Cocco, 2022). Some EBDCs are soluble in water, and mancozeb and thiourea have been detected in urine in farm workers (Kurttio and Savolainen, 1990; Colosio et al., 2002) and residents of agricultural areas (Castorina et al., 2010; van Wendel de Joode et al., 2014), as well as in adults (Saieva et al., 2004) and children (Castiello et al., 2023) in the general population.

Cancer in humans

A recent review summarized the literature on EBDCs and cancer (Cocco, 2022). A case–control study in Italy and Brazil found an association between fungicide use and melanoma after adjusting for sun

exposure and other variables (OR, 3.88; 95% CI, 1.17–12.9) and the most commonly used fungicides in this study included mancozeb, maneb, zineb and ziram (Fortes et al., 2016).

In a cohort of members of a farmworker union, several nested case–control studies revealed an increased risk for several cancers with mancozeb exposure (described elsewhere) and for maneb and stomach cancer (OR, 1.26; 95% CI, 0.67–2.38). No association was found between various EBDCs and thyroid cancer in the AHS cohort (Lerro et al., 2021). In the AGRICAN cohort, significant associations between EBDCs and primary CNS tumours were observed for thiram (HR, 1.80; 95% CI, 1.19–2.73; $n_{exposed} = 67$), cupreb, ferbam, propineb, zineb and/or ziram (HR, 1.89; 95% CI, 1.21–2.93; $n_{exposed} = 46$) and mancozeb, maneb and/or metiram (HR, 1.84; 95% CI, 1.23–2.74; $n_{exposed} = 70$) (Piel et al., 2019b).

Cancer in experimental animals

In the previous evaluation (IARC, 1987a), there was *limited* evidence of carcinogenicity in animals for potassium bis(2-hydroxyethyl)dithiocarbamate. New studies of cancer in experimental animals exposed to ethylenedithiocarbamates and their main metabolite ETU have been published since the previous monograph (Belpoggi et al., 2002).

Cancer induced in experimental animals by mancozeb is described elsewhere in this report (agent 132). No significant increase in tumours was observed in F344 rats or $B6C3F_1$ mice of either sex treated with sodium diethyldithiocarbamate (NCI, 1979a). However, the study included an unusually low number of animals (16–20) in concurrent control groups compared with treated groups (50) and the incidence of thyroid follicular cell adenoma, a rare tumour, in treated groups of male rats (4/50, 8%, 2/49; 4%) exceeded the range in NTP historical controls during 1984–1997 (7/902, overall incidence 0.78%, range 0–2%) (NTP, 1997a).

A study in rats on thiram (Hasegawa et al., 1988b) and a study in mice and rats on metiram (Charles et al., 2000) did not report any increase in tumours.

Carcinogenicity studies of orally administered ETU were conducted in rats and mice of each sex (NTP, 1992a). The studies were designed to determine the effects of ETU in rats and mice receiving adult exposure only, perinatal exposure only (dietary exposure of dams before breeding and throughout gestation and lactation) or combined perinatal and adult exposure. With adult-only dietary exposures in male and female rats, incidence was increased of thyroid follicular cell neoplasms while in the equivalent groups of male and female mice, increases in the incidence of thyroid follicular cell neoplasms, hepatocellular neoplasms, and adenomas of the pars distalis of the pituitary gland were observed. Perinatal exposure alone had no effect on the incidence of neoplasms in rats or mice after 2 years. Combined perinatal and 2-year adult dietary exposure to ethylene thiourea confirmed the findings for 2-year adult-only exposures regarding the incidence of neoplasms in the thyroid gland of rats and mice and the liver and pituitary gland of mice. In male and female rats, combined perinatal and adult exposure was also associated with increases in Zymbal's gland neoplasms and mononuclear cell leukaemia.

Mechanistic evidence

New mechanistic studies on ethylenedithiocarbamates and their main metabolite ETU have been published since the previous *IARC Monographs* evaluation. Genotoxicity studies in rats exposed to mancozeb revealed elevated micronucleus frequency and DNA damage (Goldoni et al., 2014). In studies using human cell lines and primary human cells in vitro, ethylenedithiocarbamates induced elevated micronucleus frequency, DNA damage, inhibition of DNA repair, cytotoxicity, and oxidative stress (Perocco et al., 1989; Lori et al., 2021). Exposure to the dithiocarbamate fungicide maneb in vitro and in vivo induced neuronal apoptosis and mitochondrial dysfunction, and generated ROS in a dose-dependent manner (Liu et al., 2023c). Thyroid inhibition, with increased TSH levels and decreased T4 levels, was reported in workers exposed to ethylenedithiocarbamates or ETU (Medda et al., 2017; Panganiban et al., 2004; Piccoli et al.,

2016). In the 2-year studies, perinatal and adult exposures of rats and mice to ETU, endocrine, inflammatory and hyperplastic effects involved the thyroid gland. Serum levels of T4 and/or T3 were significantly decreased in rats, while TSH was significantly increased, and the incidence of follicular cell hyperplasia or follicular cell adenoma of the thyroid gland was significantly increased relative to the controls (Kurttio et al., 1986; NTP, 1992a). ETU induced DNA damage and DNA repair synthesis in primary cultures of human thyroid cells (Mattioli et al., 2006).

Summary

These agents constitute a class of related pesticides. While a few studies in humans have looked at various combinations of ethylenedithiocarbamates, the findings are not consistent as to the type of ethylenedithiocarbamate or the tumour site. A few of the positive results concern mancozeb, which is considered separately in this report. Carcinogenicity studies in mice and rats exposed to some ethylenedithiocarbamates or their metabolite ETU reported increases of various tumours in both sexes. Mechanistic studies on some ethylenedithiocarbamates or ETU in various models reported that the group of listed ethylenedithiocarbamates exhibits KCs, including genotoxicity, genomic instability, receptor-mediated effects, and cell proliferation. This mechanistic evidence supports the re-evaluation of several of the agents and ETU. The Advisory Group considered an *IARC Monographs* evaluation of ethylenedithiocarbamates to be warranted together with ETU (see also the recommendation for mancozeb, agent 132).

Recommendation: High priority (and ready for evaluation within 2.5 years)

129 *S*-Ethyl-*N*,*N*,-dipropylthiocarbamate (EPTC) (CAS No. 759-94-4)

Current IARC/WHO classification

S-Ethyl-*N*,*N*-dipropylthiocarbamate (EPTC) has not previously been evaluated by the *IARC Monographs* programme. EPTC was given a priority rating of *low* by the 2019 Advisory Group on Priorities (IARC, 2019a).

Exposure characterization

EPTC is listed as a high production volume chemical by the OECD. As noted in the 2019 Advisory Group report, "EPTC is a thiocarbamate herbicide that is widely used to selectively control annual and perennial grass weeds and some broadleaf in citrus, bean, corn, potato, and pineapple. Occupational and residential exposure to EPTC residues via dermal and inhalation routes can occur during handling activities. In 1999, the US EPA classified EPTC as "not likely to be carcinogenic to humans" (US EPA, 2008b)."

Cancer in humans

As noted by the 2019 Advisory Group (IARC, 2019a), an earlier report of the AHS cohort found a modestly increased risk of NHL among farmers who applied carbamate pesticides, compared with non-farmers. An update of the AHS found an excess risk of cancers of the colorectum and pancreas, with suggestive evidence of an association with leukaemia and NHL (van Bemmel et al., 2008). A case–control study of pancreatic cancer nested in the AHS cohort found statistically significant exposure–response associations for EPTC (Andreotti et al., 2009). No new studies since this report were available to the Advisory Group.

Cancer in experimental animals

The few available studies did not observe carcinogenic activity (US EPA, 1999, 2011b).

Mechanistic evidence

The 2019 Advisory Group noted that "mutagenicity tests such as the in vivo micronucleus test or the Drosophila sex-linked recessive lethal mutation assay were negative. A few studies in experimental animals found that EPTC sulfoxide can form DNA adducts and induces DNA damage. EPTC also has been classified as nitrosatable. Nitrosamine compounds are potent animal carcinogens related to different types of cancer, including pancreatic cancer". Since then, few new data have been published. One study on human epigenetics reported positive findings for EPTC (Alexander et al., 2017).

Summary

The Advisory Group therefore considered that an *IARC Monographs* evaluation of EPTC is unwarranted at present, in view of the few available studies.

Recommendation: No priority

130 Hexythiazox (CAS No. 78587-05-0)

Current IARC/WHO classification

Hexythiazox has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Hexythiazox is an acaricide used in agricultural applications (PubChem, 2024e). Residues have been found on fruit and vegetables and in drinking-water (FAO/WHO, 2020; US EPA, 2020a). Dermal (non-occupational) exposure is possible in areas that may experience overspray from agricultural applications, with possible incidental oral exposure in children (US EPA, 2020a). Occupational exposures are likely to occur during agricultural applications, but no specific data were identified.

Cancer in humans

A case–control study evaluating prenatal and early-childhood exposure to pesticides (exposure estimated based on address at birth) observed no convincing association between hexythiazox and acute lymphocytic leukaemia in children aged < 6 years (OR, 1.09; 95% CI, 0.71–1.69); the interpretation was unchanged when the estimate was adjusted for exposure to other pesticides (Park et al., 2020).

Cancer in experimental animals

Two chronic toxicity and carcinogenicity studies with dietary administration of hexythiazox are summarized in a report from the JMPR (FAO/WHO, 2010). In F344 rats, there were increases in mammary gland fibroadenomas and testicular interstitial cell adenoma in males, but no treatment-related tumour findings in females. In $B6C3F_1$ mice fed hexythiazox, there was increased incidence of hepatocellular adenomas in males and females. A non-significant increased incidence of hepatoblastomas was observed in male mice.

Mechanistic evidence

Hexythiazox has tested negative for genotoxicity in a wide range of assays in vitro and in vivo, including CHO cells, rat primary hepatocytes and mouse bone marrow, and bacteria (FAO/WHO, 2010). Hexythiazox is reported as active in 183 ToxCast assays, including altered signalling of nuclear receptors, e.g. estrogen, androgen, progesterone receptors, and pregnane X receptor (PXR) in human cell lines. In a separate analysis of the public ToxCast data set, hexythiazox was shown to be among the highest efficacy/potency at increasing production of estradiol in a human cell line-based steroidogenesis assay (Cardona and Rudel, 2021).

Summary

Human cancer studies are scarce, with a single epidemiological study identified, which observed no associations. Available data indicate that hexythiazox induces benign tumours in experimental animals. Mechanistic evidence that hexythiazox exhibits KCs is sparse and limited to modulation of receptor-mediated effects in experimental systems in vitro (high-throughput screening).

The Advisory Group therefore considered that an *IARC Monographs* evaluation of hexythiazox is unwarranted at present.

Recommendation: No priority

131 Malathion (CAS No. 121-75-5)

Current IARC/WHO classification

Malathion has previously been evaluated in 2015 by the *IARC Monographs* programme as *probably carcinogenic to humans* (Group 2A) in Volume 112 (IARC, 2017a), on the basis of a combination of *limited* evidence for cancer in humans (for prostate cancer and NHL) and *sufficient* evidence for cancer in experimental animals.

Exposure characterization

Malathion is a broad-spectrum organophosphate insecticide, listed as a high production volume chemical by the OECD (OECD, 2007) and by the US EPA (US EPA, 2024a). In the USA it is the most frequently used organophosphate insecticide (Sergi, 2019). It is formulated as a dust, wettable powder, emulsifiable concentrate, ready-to-use liquid or pressurized liquid. Exposure to malathion may occur through its use in agriculture, residential or public-health applications, notably mosquito control. Occupational exposure occurs mainly via the dermal route. The general population is exposed to malathion from residues on food, from living near areas where malathion is sprayed, or through personal use of products containing malathion. It is a prescription drug approved by the US FDA for the treatment of infestation with head lice (Calaf, 2023; CDC, 2024).

Cancer in humans

In the previous *IARC Monographs* evaluation of malathion in 2015, positive associations were observed with NHL and cancer of the prostate (IARC, 2017a).

Since 2015, one cohort study, two pooled case–control studies, and a meta-analysis on NHL have been published. The cohort study found decreased risk of NHL among spouses of pesticide applicators (Lerro et al., 2015). The meta-analysis showed a statistically non-significant association between NHL and malathion exposure (Hu et al., 2017). The US/Canadian pooled case–control study supported an association between malathion use and NHL overall and provided new information on associations with NHL subtypes (Koutros et al., 2019), while the non-overlapping US/EU/Canadian/Australian pooled case–control study did not find an association between occupational exposure to malathion and NHL (De Roos et al., 2021). The AGRICOH pooled study of three cohorts, including the US AHS plus French and Norwegian cohorts, found no association with NHL overall, based on 1208 cases (Leon et al., 2019). Since 2015, two case–control studies on prostate cancer have been published, one of which found an association of malathion exposure with prostate cancer (Abhishek et al., 2020) and the other did not (Hurwitz et al., 2023).

Since 2015, studies on malathion exposure and other cancers have been published. In the AHS cohort, malathion exposure was associated with increased risk of thyroid cancer among spouses of pesticide applicators (Lerro et al., 2015). In a pooled analysis of US and Canadian population-based studies, among people aged ≤ 40 years, a duration of use of 1–5 years and frequency of use of 1–2 days per year of malathion

was statistically significantly associated with Hodgkin lymphoma (HL) (Latifovic et al., 2020). In a French cohort study, a positive association was found for high exposure to malathion and postmenopausal breast cancer risk among overweight and obese women (Rebouillat et al., 2021). A population-based case–control study in California found that prenatal residential proximity to malathion applications was associated with increased risk of testicular germ cell tumours among Latino adolescents (Swartz et al., 2022).

Cancer in experimental animals

In the previous evaluation (IARC, 2017a), there was *sufficient* evidence in experimental animals for the carcinogenicity of malathion, on the basis of tumours in two species and both sexes in feeding studies, and via subcutaneous injection in one study in females. The metabolite malaoxon has since been reported to induce thyroid gland C-cell adenoma or carcinoma (combined) in males and female rats in one study and leukaemia in males in a second study, both with dietary administration (IARC, 2017a). Malathion was also identified as a tumour promoter of hepatocarcinogenesis in rats in a medium-term bioassay (Hasegawa and Ito, 1992; Ito et al., 1994).

Mechanistic evidence

Malathion exhibits *strong* mechanistic evidence for the KCs, including genotoxicity, oxidative stress, chronic inflammation, modulation of receptor-mediated effects, and alteration of cell proliferation. Specifically, evidence for genotoxicity was found in various test systems including exposed humans (IARC, 2017a). Since the previous evaluation, new studies of exposed humans have further contributed to the mechanistic evidence for malathion. Analysis of genetic variants in farmers from the AHS cohort found positive interactions between pesticides, including malathion, and individual genetic variants occurring in regions associated with DNA damage response (CDH3, EMSY genes) and with variants related to altered AR-driven transcriptional programmes critical for prostate cancer (Hurwitz et al., 2023). In another analysis investigating cellular and genetic effects of pesticide exposure in farmers from a region of Sanghar, Sindh, Pakistan, the authors reported a significant difference in genotypic and allelic frequencies of pesticide-exposed subjects compared with controls (Imran et al., 2022). Increased DNA damage, measured by comet assay, has also been observed in blood samples from a group of workers in a pesticide factory in Multan, Pakistan. The damage, as tail length, correlated with the concentration of malathion in the blood (Arshad et al., 2016). Similar findings were reported in a group of 223 rice field workers in Colombia, exposed to a mixture containing malathion (Varona-Uribe et al., 2016). Studies in exposed humans have identified an association between malathion exposure and alteration of the immune system. Medithi et al. (2022b) observed significant decrease in the levels of CD3+, CD4+, CD8+, CD16+ and CD19+ phenotypes in a group of women and children occupationally exposed in the Rangareddy district (Telangana, India) (Medithi et al., 2022b). In a prospective cohort of pesticide applicators from a study including more than 12 200 farmers (1993–1997; North Carolina and Iowa) and followed for about 12 years, Parks et al. (2021) identified an increased incidence of shingles, the clinical reactivation of varicella-zoster virus, in exposed farmers compared to non-exposed. A case report of generalized sclerosis was also associated with malathion exposure in two exposed children (Sozeri et al., 2012). Recent evidence has confirmed that in exposed humans, mainly occupationally exposed, malathion was associated with modulation of receptor-mediated effects. Alteration of follicle-stimulating hormone (FSH) was observed in the group of occupationally exposed women of the Rangareddy district (Telangana, India) (Medithi et al., 2022b). Long-term exposure (about 20 years) to malathion in pesticide applicators enrolled in the AHS has been linked to increased incidence of altered thyroid functions (Shrestha et al., 2018a). Similar findings were reported in previous studies (Lerro et al., 2015; Goldner et al., 2013). Malathion levels in follicular fluid collected from a group of women aged 20–38 years, affiliated with a university fertility centre in Egypt, were reported to be associated with alteration of endometrial thickness (Al-Hussaini et al., 2018).

Summary

There is new epidemiological evidence for the carcinogenicity of malathion, but it would be unlikely to influence the current classification in Group 2A. The evidence of cancer in experimental animals has already been evaluated as *sufficient*. Malathion exhibits convincing mechanistic evidence of several KCs in exposed humans. The overall evidence could support a change of classification. The Advisory Group therefore considered an *IARC Monographs* evaluation of *malathion* to be warranted, together with other organophosphates prioritized in this report.

Recommendation: High priority (and ready for evaluation within 2.5 years)

132 Mancozeb (CAS No. 8018-01-7)

Current IARC/WHO classification

Mancozeb has not previously been evaluated by the *IARC Monographs* programme. Mancozeb was given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of evidence of skin cancer in humans and malignant tumours seen in animal bioassays. Mancozeb is on the priority list for the JMPR.

Exposure characterization

Mancozeb, an ethylenedithiocarbamate pesticide (see agent 128), is a broad-spectrum contact fungicide that is labelled for use on many fruit, vegetable, nut, and field crops. It provides protection against a wide spectrum of fungal diseases, including potato blight, leaf spot, scab, and rust. It is also used as seed treatment for potatoes, corn, sorghum, tomatoes, and cereal grains (Anastassiadou et al., 2020; Costa et al., 2022). Mancozeb has been listed as a high production volume chemical by the US EPA (US EPA, 2024a).

Occupational exposure to mancozeb occurs mainly in the agriculture and farming industries (in key sectors of mancozeb production and application), through either inhalation or direct skin contact, with dermal absorption representing the main route of exposure (Costa et al., 2022; Tait et al., 2022). Therefore, dermal assessment is considered relevant for exposure evaluation, especially in greenhouses, where the temperature is often very high, creating conditions for high absorption rates of mancozeb (Liu et al., 2003; Abdourahime et al., 2020). The general population can be exposed to mancozeb through ingestion of food containing pesticide residues (Anastassiadou et al., 2020). The use of mancozeb was banned in the EU in 2021 (European Commission, 2020b).

In Matina, a large banana plantation area in Costa Rica, exposure to mancozeb was evaluated in 445 pregnant women with determination of urinary levels of the metabolite ETU; three samples were taken from each woman during pregnancy. Specific gravity-corrected urinary ETU concentration was 3.1 µg/L and creatinine-corrected ETU was 3.0 µg/g creatinine. Dermal exposure in Italian greenhouse workers was evaluated with both skin pads and blood samples. The median level of ETU absorbed was 0.31 µg/kg bw, and the median urinary ETU was 8 µg/g creatinine (Costa et al., 2022).

Cancer in humans

A study examined exposure–response relations for 50 agricultural pesticides and cutaneous melanoma incidence in the AHS cohort of licensed pesticide applicators. Results showed a strong association between cutaneous melanoma and maneb/mancozeb (63 exposure days: OR, 2.4; 95% CI, 1.2–4.9; *P* for trend, 0.006) (Dennis et al., 2010). In a pooled analysis of two case–control studies in Italy and Brazil, the use of fungicides was associated with a high risk of cutaneous melanoma (OR, 3.88; 95% CI, 1.17–12.9). The authors did not evaluate mancozeb in particular but noted that it was the most common fungicide used (Fortes et al., 2016).

The French AGRICAN cohort analyses showed increased risk of CNS tumours with overall exposure to carbamate fungicides, a class that includes mancozeb. Specifically, the study found a RR, 2.17 (95% CI, 1.30–3.62) of CNS tumours for those with > 30 years duration of mancozeb use (Piel et al., 2019b). A nested case–control study of farm workers in California estimated exposure by linking county/month and crop-specific job history information from union records with California Department of Pesticide Regulation pesticide use reports and found that workers with mancozeb exposure had an increased risk of leukaemia compared with those without mancozeb exposure (OR, 2.35; 95% CI, 1.12–4.95) (Mills et al., 2005).

Cancer in experimental animals

Mancozeb administered in diet, at 0–750 ppm, for up to 104 weeks increased the incidence of thyroid adenomas and thyroid carcinomas in a two-year study in Crl:CD®BR rats. No tumorigenic response was seen in another study in rats at doses up to 454 ppm (EFSA, 2018). However, no primary data are available for the regulatory study reports. In Sprague-Dawley rats, mancozeb administered at concentrations of 0–1000 ppm in feed supplied ad libitum for 104 weeks increased occurrences of benign and malignant tumours in several organs compared with controls. Increases were seen in mammary tumours in females; Zymbal gland and ear duct carcinomas in males; head and neck carcinomas in males and in females of all treated groups; HCCs in males; pancreatic malignant tumours in males and females; thyroid gland tumours and haemolymphoreticular neoplasia in both sexes (Belpoggi et al., 2002). Carcinogenicity was not observed in two 18-month dietary oncogenicity studies in CD-1 mice up to the top dose of 1000 ppm (130/180 mg/kg bw per day in males and females), even though signs of toxicity and reduction of T4 were observed (EFSA, 2018). In other studies, mancozeb induced neoplastic alterations (keratinocyte differentiation and proliferation) in mice and promoted the formation of benign squamous cell papillomas and skin keratoacanthomas, as well as promoting transplacental carcinogenesis in TPA-pretreated mice (Tyagi et al., 2011; Shukla et al., 1990; Shukla and Arora, 2001). Of note, the major metabolite of mancozeb, ethylene thiourea (ETU) is also a rodent carcinogen (NTP, 2021a).

Mechanistic evidence

Fifty per cent of mancozeb is absorbed within hours after oral administration in rats. It distributes widely in the thyroid tissues and is excreted in the urine and faeces. It is metabolized (over 95%) through hydrolysis and oxidation to the final product glycine. However, the major metabolites detected in urine and bile of rats are ETU, ethylene urea, ethylenediamine (EDA) and *N*-acetyl-EDA.

Mancozeb was tested in the classical genotoxicity battery, including for gene mutagenicity in various *Salmonella* strains and in mammalian cells, chromosomal aberrations, and micronuclei as well as UDS and SCE in vitro and in vivo, chromosomal aberrations and micronuclei in bone marrow; results were mostly negative (Garrett et al., 1986; Perocco et al., 1989; EFSA, 2018). No primary data are available for the regulatory study reports. However, mancozeb induced DNA damage in various test systems, including in exposed humans. Specifically, Jablonická et al. (1989) observed increases of chromosomal aberrations and SCE in cultures of peripheral lymphocytes of 44 workers exposed to mancozeb during the production of another pesticide. Cytogenetic effects were also observed in a group of 49 farmers from Mexico involved in spraying mixed pesticides. Levels of SCE and chromosomal translocations were increased in cultures of whole blood samples from the farmers compared with control subjects not involved in spraying. Urinary levels of ETU were used to assess exposure to the pesticide mixture; however, a clear measurement of mancozeb was lacking (Steenland et al., 1997). Paz-Trejo and Gómez-Arroyo (2017) observed increased DNA damage and micronuclei in human peripheral blood lymphocytes in vitro. The increase in DNA damage, measured mostly by comet assay, was observed either in vitro or in vivo and was often coupled with concomitant increases of oxidative stress or inflammatory response markers (Saber et al., 2019; Lori et

al., 2021; Stanic et al., 2021). Specifically, Lori et al. (2021) observed altered expression of DNA repair (ERCC1/OGG1) which is involved in the excision of oxidative stress-related damage.

Mancozeb alters antioxidant defence mechanisms in several in vitro and in vivo systems. Mancozeb exposure induced oxidative stress in human primary hepatocytes, HepaRG cells, isolated human erythrocytes and various other tissues in vivo (Bao et al., 2022; Zhang et al., 2022c; Quds et al., 2023; Suarez Uribe et al., 2023; Petitjean et al., 2024). Increases in serum biomarkers of oxidative stress such as lipid peroxidation, reactive oxygen metabolites, advanced oxidation protein products (AOPPs), and biological antioxidant potential were found associated with the levels of ETU measured (pre-post shift work) on the skin and in the urine of 19 greenhouse farmers involved in mancozeb-spraying in eastern Sicily (Italy) (Costa et al., 2022)

Mancozeb modulates receptor-mediated effects, specifically affecting the thyroid pathway in vitro and in vivo in various species (Ksheerasagar and Kaliwal, 2003; Axelstad et al., 2011; Bhaskar and Mohanty, 2014; Hallinger et al., 2017). The effect on the thyroid is mediated by the mancozeb metabolite ETU (Freyberger and Ahr, 2006; Price et al., 2020). The rat has been reported to be the most sensitive species to the effect of mancozeb and ETU on the thyroid (EFSA, 2018). Mancozeb exposure of mice between postnatal days 30 and 60 induced a reduction in plasma levels of T3 and T4 hormones, an increase in TSH, and a reduction in spleen and thymus weight and cellularity (Bano and Mohanty, 2020). Some evidence of thyroid disruption in exposed humans is also available. A small study among farmers from four banana plantations in the Philippines found higher mean TSH measurements among workers exposed to ethylenebisdithiocarbamates compared with non-exposed workers, which were correlated with blood but not urine levels of ETU. In some of the workers, thyroid nodules were also detected and correlated with blood ETU. However, the study failed to define the exposure clearly (Panganiban et al., 2004). Thyroid-disrupting effects, mainly of mild proportions, were reported in a group of 177 workers from two Italian regions, Chianti and Alto Adige, compared with 74 controls. Increased urinary levels of iodine were more pronounced in more exposed workers from the Chianti region, an area with mild iodine deficiency (Medda et al., 2017). Long-term exposure to mancozeb in spouses of farmers in the AHS has been linked to increased incidence of altered thyroid functions (Shrestha et al., 2018b). Apart from effects on the thyroid pathway, mounting evidence from experimental systems indicates that mancozeb may also affect other hormone signalling (Skalny et al., 2021). Alterations to the thyroid pathway were also linked to immune system changes. Almeida Roque et al. (2023) described alterations in human THP-1 leukaemia monocytic cells (Almeida Roque et al., 2023). Parks et al. (2016) described an association between exposure to maneb/mancozeb and rheumatoid arthritis in spouses of farmers from the AHS cohort who were enrolled between 1993 and 1997 and followed up to 2010. An association was identified between prenatal exposure to some pesticides, including mancozeb, as assessed by measuring ETU, and lower respiratory tract infections among 5-year-old children (n = 303) from the Infants' Environmental Health Study in Costa Rica (Islam et al., 2023). Data are available in the US EPA's Toxicity Forecaster (ToxCast) programme.

Summary

Two studies found increased risk of cutaneous melanoma; however, for both studies, the results were not necessarily specific to mancozeb, and may be attributed to other carbamate fungicides such as maneb. One cohort study reported increased risk of CNS tumours with longer duration of exposure to mancozeb, while another study reported an increased risk of leukaemia among farm workers. Given the uncertainties of attributing the melanoma results to mancozeb specifically, and the single reports of other cancer sites, the human cancer evidence may make an uncertain contribution to a future carcinogenicity evaluation. Evidence of cancer in experimental animals is available mainly for thyroid adenomas and thyroid carcinomas in rats and other tumours. Neoplastic alterations and promoting activity were reported in mice. Mancozeb exhibits mechanistic evidence of several KCs, including genotoxicity, oxidative stress, immunosuppression and

modulation of receptor-mediated effects in exposed humans, in primary cells and in several experimental systems. The emerging mechanistic evidence from all three systems supports an evaluation of the agent, although for the studies in humans, there may be limitations in the exposure assessment or other study quality concerns. The Advisory Group therefore considered an *IARC Monographs* evaluation of mancozeb to be warranted, together with other ethylenedithiocarbamates included in this report and their common metabolite, ethylene thiourea (see agent 128).

Recommendation: High priority (and ready for evaluation within 2.5 years)

133 Metyltetraprole (CAS No. 1472649-01-6)

Current IARC/WHO classification

Metyltetraprole has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Metyltetraprole is a relatively new antifungal agent (introduced in 2018) used in agricultural applications, and classified as "a member of tetrazoles, a pyrazole pesticide and a member of monochlorobenzenes" (PubChem, 2024f). It is used on cereals and some other crops. No literature on circulating or excreted levels in humans was found.

Cancer in humans

No studies evaluating cancer in humans were available to the Advisory Group.

Cancer in experimental animals

Two OECD guideline oral chronic toxicity and carcinogenicity studies were summarized in a Draft Assessment Report prepared for EU pesticide registration purposes (ECHA, 2022a). Han Wistar rats fed metyltetraprole in the diet had increased incidence of malignant lymphomas in males and females, and uterine schwannomas and mammary gland adenoma or adenocarcinoma (combined) in females. In CD-1 mice, dietary administration of metyltetraprole led to an increased incidence of malignant lymphomas in males and histiocytic sarcomas in females.

Mechanistic evidence

As summarized in the Draft Assessment Report prepared for EU pesticide registration purposes, metyltetraprole gave negative results in several genotoxicity studies in vitro and in vivo (ECHA, 2022a). Metyltetrapole is extensively metabolized, via *N*-demethylation of the tetrazole ring and oxidation of the 3-methyl group on the phenyl ring, followed by glucuronide conjugation. Increased lymphocyte counts and decreased thymus and spleen weight were observed in rats following chronic oral administration (ECHA, 2022a). No published toxicity studies or bioactivity screening data are available.

Summary

Metyltetraprole was recently introduced and no studies of cancer in humans were identified. Data are available indicating that metyltetraprole is carcinogenic in experimental animals. There is sparse evidence that metyltetraprole exhibits certain KCs, in particular immunosuppression in exposed animals. The Advisory Group noted that, although the aforementioned evidence in experimental animals and mechanistic evidence comes solely from unpublished studies as summarized in publicly available regulatory assessment documents, all the raw data and other needed information are available in these publicly available reports including annexes. The Advisory Group therefore considered an *IARC Monographs* evaluation of metyltetraprole to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

134 Neonicotinoid insecticides

Current IARC/WHO classification

Neonicotinoid insecticides have not previously been evaluated by the *IARC Monographs* programme. Neonicotinoid insecticides are on the priority list for the JMPR.

Exposure characterization

Neonicotinoids are a class of neuro-active insecticides chemically similar to nicotine, which act as agonists on nicotinic acetylcholine receptors.

As of 2011 there were seven neonicotinoid insecticides on the market (Jeschke et al., 2011). Three were cyclic compounds: imidacloprid (CAS No. 138261-41-3) and thiacloprid (CAS No. 111988-49-9) which have a five-ring structure, and thiamethoxam (CAS No. 153719-23-4) which has a six-ring structure. Four were noncyclic compounds: nitenpyram (CAS No. 150824-47-8), acetamiprid (CAS No. 135410-20-7), clothianidin (CAS No. 210880-92-5), and dinotefuran (Jeschke et al., 2011) (CAS No. 165252-70-0). The more recently marketed generation of neonicotinoids includes cycloxaprid (CAS No. 1203791-41-6), imidaclothiz (CAS No. 105843-36-5), paichongding (CAS No. 948994-16-9), sulfoxaflor (CAS No. 946578-00-3), guadipyr (CAS No. 1376342-13-0), and flupyradifurone (CAS No. 951659-40-8) (Giorio et al., 2021; Hou et al., 2021). None of the neonicotinoid insecticides appear on the 2007 OECD list of high production volume chemicals. Large increases in urinary 6-chloronicotinic acid can occur after spraying of imidacloprid (Tao et al., 2019).

Neonicotinoids are the most widely used class of insecticide worldwide, having replaced organophosphates due to their lower toxicity to humans and the environment (Klingelhöfer et al., 2022). They are used in agriculture, veterinary practice, and domestically, and have high persistence in the environment in soils, water, and food. Concern for the effects on bees has led to banning of some neonicotinoids in the EU and the USA, but they are still used widely in other countries (ECHA, 2024b).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

Administration of the neonicotinoid sulfoxaflor increased hepatocellular adenomas and carcinomas after 18 months in male and female CD-1 mice and hepatocellular adenomas increased after 2 years in male F344 rats dosed at 500 ppm (LeBaron et al., 2013, 2014). Nitenpyram significantly increased oesophageal squamous papilloma in male and female rats (Xing et al., 2018). Thiamethoxam induced a dose-related increase of total liver adenoma and adenocarcinoma in male and female Tif:MAGf mice (Green et al., 2005a; Pastoor et al., 2005), but did not induce liver tumours in rats (Green et al., 2005b; Pastoor et al., 2005).

Mechanistic evidence

Recent studies have shown that neonicotinoids exhibit several KCs. Clothianidin induced DNA single-strand breaks, as seen by an increase in alkaline comet parameters in human bronchial epithelial cells (BEAS-2B). Clothianidin also significantly induced the formation of DNA double strand breaks by increasing phosphorylated H2AX protein foci and p53-binding protein 1 foci. Such DNA damage was not repaired in a 24-hour recovery period. Iturburu et al. (2018) demonstrate that imidacloprid, a neonicotinoid, induces DNA damage in fish, specifically through clastogenesis, a mechanism of genotoxicity. Short-term exposure to environmentally relevant concentrations of imidacloprid led to increased damage to the genetic

integrity of fishes, primarily through oxidative damage to DNA bases. de Morais et al. (2017) evaluated the mutagenic, recombinogenic, and carcinogenic potential of thiamethoxam, another neonicotinoid, and its formulated product in somatic cells of *Drosophila melanogaster*. Their findings suggest that thiamethoxam and its product exhibit mutagenic effects at high concentrations, indicating a promutagenic potential. Global DNA methylation levels have been shown to be affected in human cell lines exposed to neonicotinoids (Guler et al., 2023). Observed transgenerational effects of neonicotinoids indicate potential long-lasting impact on gene expression across generations (Dali et al., 2023). Global DNA methylation significantly increased after imidacloprid and thiamethoxam exposure in a human neuroblastoma (SH-SY5Y) cell line. Imidacloprid significantly decreased the expression of DNMT1 and DNMT3a genes (Guler et al., 2023). Gestational exposure to thiacloprid affected epigenetic mechanisms controlling meiosis in male mice (Hartman et al., 2021; Dali et al., 2023).

Neonicotinoids induce oxidative stress, leading to cellular damage (Wang et al., 2018b). Ecological or cross-sectional epidemiological studies have reported oxidative genetic damage after exposure to neonicotinoids (Thompson et al., 2020). Exposure to multiple neonicotinoids has been associated with increased oxidative stress and complications such as gestational diabetes mellitus (Mahai et al., 2023). These pesticides exhibit different immunomodulatory effects on human primary cells, potentially exacerbating oxidative stress (Parny et al., 2022). Clothianidin also induced oxidative stress by decreasing levels of reduced GSH and increasing lipid peroxidation (Atlı Şekeroğlu et al., 2020). Exposure to chlorpyrifos, dithianon, and captan induced immunomodulatory effects in human primary cells (Parny et al., 2022). Chlorpyrifos, dithianon, and captan inhibited production of ROS and of TNFα and IL-1β pro-inflammatory cytokines in human monocyte-derived macrophages (hMDMs). Dithianon and captan induced mRNA expression of NQO1 and HMOX1 antioxidant enzymes. Dithianon also induced mRNA expression of catalase (CAT) and SOD (Parny et al., 2022). Ma et al. (2023) examined the enantioselective metabolism of a novel chiral neonicotinoid insecticide, paichongding, mediated by human CYP3A4. The results indicated that paichongding stereoisomers exhibit different binding affinities to CYP3A4, with specific interactions dictating their metabolic pathways. The metabolism of paichongding stereoisomers generates various chiral metabolites, some of which possess carcinogenic potential, contributing to adverse effects on human health, such as hepatotoxicity, respiratory toxicity, and carcinogenicity (Ma et al., 2023).

Studies of imidacloprid, clothianidin, acetamiprid, thiacloprid, nitenpyram, and thiamethoxam clearly showed that oxidative stress plays a critical role in their various toxicities (Wang et al., 2018b). In humans, exposure to a mixture of neonicotinoid insecticides was associated with increased odds of gestational diabetes mellitus. A possible mechanism underlying this association may involve oxidative damage to nucleic acids (Mahai et al., 2023). Thiamethoxam induced oxidative stress, as evidenced by the significant increases in malondialdehyde levels and antioxidant enzyme (GST and CAT) activities along with a decrease in GSH levels in rabbits (El Okle et al., 2018). Neonicotinoids can disrupt tight junctions in the intestines, leading to increased intestinal permeability and inflammation (Zhao et al., 2021b). Hepatotoxicity and pro-carcinogenic effects linked to neonicotinoid exposure have been observed in vivo, mediated by oxidative stress, inflammation, and anti-apoptotic pathways (El Okle et al., 2018).

Neonicotinoids may act as endocrine disruptors, affecting hormone levels and contributing to conditions such as obesity and diabetes (Miranda et al., 2023). These pesticides have been shown to affect estrogen receptors and aromatase activity, potentially disrupting hormone signalling pathways (Gea et al., 2022). In a sample representative of the US population, exposure to neonicotinoids was associated with decreased serum testosterone levels in humans (Mendy and Pinney, 2022).

The effect of acetamiprid, clothianidin, and thiamethoxam on estrogen signalling was assessed using a gene reporter assay based on MCF-7 cell lines transfected with the ERE-βGlob-Luc-SVNeo plasmid (MELN); no interference with estrogen signalling was detected (Gea et al., 2022). Courjaret and Lapied (2001) studied the regulation of α-bungarotoxin-resistant nicotinic acetylcholine receptors (nAChRs)

expressed in insect neurosecretory cells. They found that the phosphorylation/dephosphorylation of these receptors strongly affects the action of imidacloprid, implying a potential link between nAChR modulation and carcinogenicity.

Li et al. (2022f) demonstrated that neonicotinoid insecticides promoted breast cancer progression via G protein-coupled estrogen receptor (GPER) pathway. Clothianidin, acetamiprid, and dinotefuran were tested by calcium mobilization assay and all activated GPER. Acetamiprid also induced proliferation of mouse 4T1 breast cancer cells and upregulated GPER expression in a dose-dependent manner. Using a mouse 4T1-Luc (breast) cell orthotopic (implanted into the mammary gland tissue) tumour model, Li et al. (2022f) found that ACE also promoted in-situ breast cancer growth and lung metastasis in normal mouse dependent on GPER. Thiamethoxam upregulated the mRNA levels of IL-6 and BCL2 and down-regulated the mRNA level of TNFα, indicating its effects on cell survival and proliferation through the inhibition of apoptosis (El Okle et al., 2018).

Summary

There are no studies of cancer in humans related to neonicotinoid insecticides. Carcinogenicity studies in mice and rats exposed to some neonicotinoids reported increases of various tumours in both sexes. There is mechanistic evidence that neonicotinoids can exhibit several of the KCs, in particular genotoxicity, epigenetic alterations, oxidative stress, chronic inflammation, and receptor-mediated effects in exposed humans and in experimental systems in vivo and in vitro. The Advisory Group therefore considered an *IARC Monographs* evaluation of neonicotinoids to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

135 *para*-Dichlorobenzene (CAS No. 106-47-7)

Current IARC/WHO classification

para-Dichlorobenzene has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Volume 73 in 1998 (IARC, 1999b), based on *sufficient* evidence for cancer in experimental animals.

Exposure characterization

para-Dichlorobenzene (p-DCB) is listed as high production volume chemical by the US EPA (2024a). It is a volatile compound that has been used as a disinfectant and deodorant, for example in air fresheners and moth balls (Cai et al., 2023a). It has also been used in the production of 2,5-dichloroaniline, pharmaceuticals and polyphenylene sulfide resins (IARC, 1999b). It does not occur naturally. Occupational exposure may occur by inhalation or dermally, whereas the general population is mainly exposed via consumer products (e.g. air freshener, moth balls) or air pollution (IARC, 1999b; Heck et al., 2015). The human metabolite 2,5-dichlorophenol (2,5-DCP) has been used as a urinary biomarker of p-DCB exposure (Yoshida et al., 2002a).

Cancer in humans

Heck et al. (2015) reported an increased risk of retinoblastoma associated with exposure to p-DCB during pregnancy among children in a case–control study in California, USA. Pridgen et al. (2023) used urinary concentrations of the metabolite 2,5-DCP as a proxy of p-DCB exposure in a subsample of women within NHANES. They found increased odds of endocrine-related reproductive cancers associated with higher levels of 2,5-DCP. Another study assessed associations of various health outcomes with urinary concentrations of 2,5-DCP in NHANES and found an increased risk of overall cancer associated with urinary levels of the p-DCB metabolite (Rooney et al., 2019).

Cancer in experimental animals

In the previous evaluation (IARC, 1999b), there was *sufficient* evidence in experimental animals for the carcinogenicity of *para*-dichlorobenzene (IARC, 1999b).

Mechanistic evidence

The toxicokinetics of p-DCB in mice and rats were extensively reviewed in Volume 73 of the *IARC Monographs* (IARC, 1999b). p-DCB is rapidly absorbed after exposure and distributed in various organs and tissue, especially in adipose tissue, and the major route of excretion is via the urine, where the main metabolite is 2,5-DCP. In seven exposed humans, inhalation toxicokinetics of chronic low-level exposure to p-DCB agreed approximately with the studies in animals, but the fraction of p-DCB excreted in urine 9–11 hours after exposure was much lower in humans (5–16% of the amount absorbed) than in animals (Yoshida et al., 2002b). Thus p-DCB seems to exhibit a long elimination time from the human body. Urinary 2,5-DCP concentrations, leukocyte count, and serum alanine aminotransferase level were higher in exposed than in unexposed workers (Hsiao et al., 2009). Significant associations between urinary 2,5-DCP and metabolic syndrome were observed in large US cohorts (Wei and Zhu, 2016a; Cai et al., 2023a). In addition, urinary 2,5-DCP concentrations were significantly associated with diabetes and insulin resistance in US adults (Wei and Zhu, 2016a) and associated with thyroid dysfunction in US adolescents (Wei and Zhu, 2016b).

In most studies in vitro and in vivo, p-DCB is not genotoxic (IARC, 1999b; Tegethoff et al., 2000). In mice, p-DCB can induce oxidative stress (Suhua et al., 2010; Henderson et al., 2015). p-DCB induces receptor-mediated effects in mice and rats, having androgenic (Takahashi et al., 2011) and anti-estrogenic (Takahashi et al., 2007) effects and modulating thyroid hormones (den Besten et al., 1991; Elcombe et al., 2002). p-DCB induces cell proliferation in mouse liver and rat kidney (NTP, 1987; IARC, 1999b).

Summary

Studies have shown sporadic associations between p-DCB exposure and cancer risk. Mechanistic studies in exposed humans show associations between the main urinary metabolite of p-DCB, 2,5-DCP, and endocrine disorders. There is also mechanistic evidence that p-DCB exhibits KCs, including inducing oxidative stress, modulation of receptor-mediated effects, and alteration of cell proliferation in experimental systems. However, given the sparse mechanistic evidence in exposed humans and human primary cells, a future classification seems unlikely to change. The Advisory Group therefore considered that an *IARC Monographs* re-evaluation of *para*-dichlorobenzene is unwarranted at present.

Recommendation: No priority

136 Pendimethalin (CAS No. 40487-42-1)

Current IARC/WHO classification

Pendimethalin has not previously been evaluated by the *IARC Monographs* programme. Pendimethalin was given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of findings for human cancer, as well as mechanistic evidence related to oxidative stress.

Exposure characterization

Pendimethalin is listed as a high production volume chemical by the OECD (OECD, 2007). It is a selective dinitroaniline herbicide with both crop and non-crop uses. Very little information has been published on occupational exposure to pendimethalin, and no studies were found on levels in the general population. General population exposure to pendimethalin can occur by the oral route through food and other

sources. Occupational exposure can occur by inhalation and dermal contact (US EPA, 1997). Sixteen Italian farmers were sampled during mixing and loading of pesticides and during application to tomatoes cultivated in open fields; the absorbed doses of pendimethalin (234 µg/kg bw) were lower than the acceptable operator exposure level (AOEL) (Aprea et al., 2016).

Cancer in humans

Analyses from the AHS cohort found associations of pendimethalin with rectal but not colon cancer (Hou et al., 2006). There was also evidence of an association between pendimethalin and pancreatic cancer in the AHS (Andreotti et al., 2009). There was a suggestive exposure–response relation between pendimethalin use and lung cancer (Bonner et al., 2017) and renal cell carcinoma (Andreotti et al., 2020). Evaluations for other cancer sites showed no evidence of an association within the cohort. Two studies have evaluated childhood leukaemia associations. The first, a state-wide records-based case–control study showed a suggestive elevation (Nguyen et al., 2023). In the second study, a case–control study of childhood ALL, there was no evidence of an association with house dust concentrations of pendimethalin (Metayer et al., 2013).

Cancer in experimental animals

Long-term (2-year) studies showed increases in the incidence of thyroid follicular cell adenomas in male and female rats that received a lifetime exposure to pendimethalin in the diet. No evidence of carcinogenicity was noted in two 18-month carcinogenicity studies in mice. Data are summarized in regulatory reports; no primary information is available (US EPA, 1992, 1996b, 1997). No further studies were available.

Mechanistic evidence

Pendimethalin has been reported to exhibit KCs, including genotoxicity, oxidative stress, chronic inflammation, immunosuppression, and alteration of cell proliferation, cell death or nutrient supply (Hurley, 1998; Ahmad, et al., 2018; IARC, 2019a). More recently, pendimethalin was reported to bind to DNA, specifically by DNA covalent bonds with G and C nitrogenous bases, to intercalate with DNA (Karimi-Maleh et al., 2023) and to induce genotoxicity in human lymphocytes, while inducing apoptosis (Ansari et al., 2018). The agent also caused mutagenicity in the Ames test (Ilyushina et al., 2019). In female rats, exposure to pendimethalin caused DNA damage in the liver that was accompanied by oxidative stress and tissue damage (Gad et al., 2022). In porcine trophectoderm and uterine luminal epithelial cells, exposure to pendimethalin caused disruption of mitochondrial membrane potential, Ca^{2+} homeostasis and MAPK signalling through the generation of ROS (Kim et al., 2023). In human umbilical vein endothelial cells, Lee et al. (2022a) observed activation of ER stress-mediated mitochondrial dysfunction leading to apoptosis. Increased thyroid weight, reduced thyroid hormone, and increased TSH levels, accompanied by cellular hypertrophy and hyperplasia were reported in the rat carcinogenicity study (US EPA, 1992). The effects in rodents were previously considered of low relevance to humans (Hurley, 1998). However, two recent studies in humans indicated antithyroid effects of pendimethalin: one reported elevated risk of hypothyroidism in female spouses of private pesticide applicators (Shrestha et al., 2018b) and the other reported that pendimethalin was associated with subclinical hypothyroidism and higher TSH (Lerro et al., 2018a). Pendimethalin is listed in the ToxCast and Tox21 programme and was found to be active in several ER-related and cytokine-related assays, and one ToxCast ER pathway model (US EPA, 2024j).

Summary

The human cancer evidence has shown suggestive associations of pendimethalin with cancer at a few sites. Most analyses were conducted within a large prospective cohort study (the AHS), for which updated findings for colorectal cancer are forthcoming. In two separate case–control studies of childhood leukaemia, one was positive and the other null. Overall, there is some evidence of an increase of benign tumours in

experimental animals. There is some mechanistic evidence that pendimethalin exhibits KCs in experimental systems and in exposed humans. The Advisory Group therefore considered an *IARC Monographs* evaluation of pendimethalin to be warranted.

Recommendation: Medium priority

137 Proquinazid (CAS No. 189278-12-4)

Current IARC/WHO classification

Proquinazid has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Proquinazid is a fungicide used in agricultural applications, including on cereals and some fruits; it is classified as a quinazoline, an organoiodine compound and an aromatic ether (PubChem, 2024g). Dietary intake is a source of exposure (Bellisai et al., 2021). No literature on circulating or excreted levels in humans was found.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

Two OECD guideline oral chronic toxicity and carcinogenicity studies are summarized in a Draft Assessment Report prepared for EU pesticide registration purposes (ECHA, 2022b). Rats administered proquinazid in feed had increased incidence of thyroid adenomas in males and hepatocellular adenomas and cholangiocarcinoma in females. In CD-1 mice, dietary administration of proquinazid led to increased incidence of benign hepatocellular tumours and HCCs in males and thyroid follicular cell tumours in females.

Mechanistic evidence

As summarized in the Draft Assessment Report prepared for EU pesticide registration purposes, proquinazid gave negative results in several in vitro and in vivo OECD guideline genotoxicity studies (EFSA, 2009; ECHA, 2022b). No relevant toxicity studies of proquinazid were identified in the open scientific literature. No bioactivity screening data were available from the US EPA ToxCast/Tox21 programmes.

Summary

No epidemiological studies of cancer in humans were identified. Data are available indicating that proquinazid is carcinogenic in experimental animals. Primary mechanistic data were not identified. The Advisory Group noted that, although the aforementioned evidence in experimental animals comes solely from unpublished studies as summarized in publicly available regulatory assessment documents, all the raw data and other needed information are available in these publicly available reports including annexes. The Advisory Group therefore considered an *IARC Monographs* evaluation of proquinazid to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years).

138 Tebuconazole (CAS No. 107534-96-3)

Current IARC/WHO classification

Tebuconazole has not previously been evaluated by the *IARC Monographs* programme. Tebuconazole is on the priority list for the JMPR.

Exposure characterization

Tebuconazole is a triazole fungicide used in the agricultural industry. It is approved for use as a biocide in the European Economic Area for preservation films, wood preservation, and preservation of construction materials. In a study of over 1000 European residents in five countries, tebuconazole was detected in urine in between 5 and 71% of subjects (Ottenbros et al., 2023) with no difference between agricultural and non-agricultural regions. In a recent study from Mexico, around 20% of the 109 avocado farmers included had measurable hydroxy-tebuconazole (a tebuconazole metabolite) in urine samples (Rosa et al., 2024).

Cancer in humans

A case–control study of childhood leukaemia in the USA using pesticide use data and residential history (Park et al., 2020) found no association with tebuconazole either in the single pesticide model (OR, 1.24; 95% CI, 0.86–1.80) or in the fully adjusted model (OR, 0.80; 95% CI, 0.48–1.32).

Cancer in experimental animals

In a study in mice given tebuconazole in the diet (reviewed by US EPA, 1993a), a significant increase in the incidence of hepatocellular adenoma, carcinoma, and adenoma or carcinoma (combined) was observed in both males and females.

Mechanistic evidence

Tebuconazole is structurally related to at least six other triazole fungicides (triadimefon, triadimenol, uniconazole, propiconazole, cyproconazole, and etaconazole) that also produce hepatocellular tumours in male and/or female mice (US EPA, 1993a). Tebuconazole can induce genotoxicity, genomic instability, and DNA damage in human cells in vitro and in experimental systems (Othmène et al., 2021; Barrón Cuenca et al., 2022; Andrioli et al., 2023; Barut et al., 2023). Tebuconazole has been screened in various experimental systems in vivo and in vitro, including the US EPA ToxCast programme for induction of hormone synthesis in the H295R steroidogenesis assay in vitro. Tebuconazole significantly altered the production of estradiol and testosterone, showing that it could modulate receptor-mediated effects (Taxvig et al., 2007; Chen et al., 2019c; Singh et al., 2021; Ying et al., 2021; Garnovskaya et al., 2023). Tebuconazole was reported to induce oxidative stress and alter cell proliferation in human colon carcinoma cells (HCT116) (Othmène et al., 2021).

Summary

Sparse human cancer evidence has shown no association with childhood leukaemia. One carcinogenicity study in mice exposed orally to tebuconazole reported increases in the incidence of hepatocellular tumours in both males and females. Tebuconazole is structurally related to other triazole fungicides that also induce hepatocellular tumours in male and/or female mice. Mechanistic studies on tebuconazole in various models reported that it can be genotoxic, cause genomic instability, modulate receptor-mediated effects and alter cell proliferation. The evidence from cancer bioassays and the mechanistic evidence could contribute to a future Working Group evaluation. The Advisory Group therefore considered an *IARC Monographs* evaluation of tebuconazole to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

139 Vinclozolin (CAS No. 50471-44-8)

Current IARC/WHO classification

Vinclozolin has not previously been evaluated by the *IARC Monographs* programme. Vinclozolin was given a priority rating of *high* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of evidence of cancer in experimental animal studies and mechanistic evidence (IARC, 2019a).

Exposure characterization

Vinclozolin is a dicarboximide fungicide that has been commonly used on some fruits, nuts, vines, vegetables, and ornamentals, and as a wood preservative. It was introduced in Germany in 1976 and was listed as a high production volume chemical by the OECD (OECD, 2007) and by the US EPA in 2023 (US EPA, 2024a). However, use has declined since then due to concerns about anti-androgenic activity. Vinclozolin's authorization was withdrawn in January 2007 in the EU (including the UK), and its use restricted in the USA (Lewis et al, 2016).

Dermal exposure has been measured in workers manufacturing vinclozolin, those picking fruit treated with vinclozolin, and those handling stored chicory (Zweig et al., 1985; Zober et al., 1995; Spanoghe et al., 2010). No studies of general population exposure were found.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In a study of carcinogenicity in C57BL/6 mice, HCCs were observed (JMPR, 1995). The long-term toxicity and carcinogenicity of vinclozolin in rats has recently been investigated in three studies. An increased incidence of Leydig cell tumours was seen in treated rats, together with atrophy of accessory sex glands. Benign sex cord stromal tumours in the ovaries were seen in treated rats, and uterine adenocarcinomas were detected in rats treated at 3000 ppm (the highest dose tested in the carcinogenicity study). Adrenal tumours were also seen in treated rats. HCCs were seen in male rats (JMPR, 1995).

Mechanistic evidence

Wu et al. (2005) investigated genotoxic effects of vinclozolin in human hepatoma cells, revealing its ability to enhance micronucleus formation when cells were exposed to benzo[*a*]pyrene (BaP). This enhancement was attributed to an increase in CYP1A1 expression induced by vinclozolin, suggesting a mechanism by which it augments genotoxicity.

In aquatic environments, vinclozolin has been found to exert genotoxic effects on freshwater invertebrates (Aquilino et al., 2018). In *Chironomus riparius* larvae exposed to vinclozolin, a dose-dependent increase in DNA damage was seen, along with alterations in the expression of genes involved in DNA repair and apoptosis. Several studies relevant to other KCs have considered whether vinclozolin induces epigenetic alterations and modulates receptor-mediated effects (Hrelia et al., 1996; Lioi et al., 1998a, b; Skinner, 2016; Pietryk et al., 2018; Maddalon et al., 2023). Exposure to vinclozolin during embryonic gonadal sex determination had profound effects on the epigenome of the male germ line (Skinner and Anway, 2007). This alteration leads to the induction of new imprinted-like genes/DNA sequences, which are transmitted transgenerationally and promote the development of adult-onset diseases, including cancer. Notably, these diseases encompass a spectrum of conditions such as testis abnormalities, prostate disease, kidney disease, immune abnormalities, and tumour development. The transgenerational effects of vinclozolin were elucidated by Nilsson et al. (2018), who found that gestational exposure to vinclozolin induced heritable changes in disease susceptibility across generations of rats. The F3 generation exhibited increased susceptibility to various diseases, including testis, prostate, and kidney diseases, along with

alterations in puberty onset and obesity rates. Epigenetic analysis revealed that different DNA methylation regions were associated with specific diseases, suggesting the potential for epigenetic biomarkers of transgenerational disease susceptibility.

In the 2-year carcinogenicity study, vinclozolin at the dose of 3000 ppm induced Leydig cell hyperplasia, which was accompanied by hepatotoxicity, atrophy of accessory sex glands, atrophic uteri, and lipidosis in the corticomedullary region of the adrenals (JMPR, 1995). Data are available in the ToxCast/Tox21 programme for vinclozolin being active on a series of ToxCast androgen and estrogen pathway models (US EPA, 2024k).

Summary

No studies of cancer in humans are available. There is evidence that vinclozolin may induce cancer in experimental animals. The available studies indicate vinclozolin exhibits several KCs, including genotoxicity, epigenetic alterations, modulation of receptor-mediated effects (with transgenerational inheritance of disease susceptibility), and alteration of cell proliferation in experimental systems in vivo and in vitro. The Advisory Group therefore considered an *IARC Monographs* evaluation of vinclozolin to be warranted. on the basis of the cancer bioassay and mechanistic evidence.

Recommendation: High priority (and ready for evaluation within 2.5 years)

140 Cinidon ethyl (CAS No. 142 891-20-1)

Current IARC/WHO classification

Cinidon ethyl has not previously been evaluated by the *IARC Monographs* programme. It was recommended with *low* priority by the 2019 Advisory Group on Priorities (IARC, 2019a).

Exposure characterization

Cinidon ethyl is a dicarboximide herbicide with applications on cereal crops (e.g. wheat and rye). No evidence of human exposure was found for this compound.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In an unpublished 2-year study in rats, dietary cinidon ethyl induced tumours of the liver and parathyroid gland (European Commission, 2002b).

Mechanistic evidence

Only one study was identified for cinidon ethyl (Pasquer et al., 2006).

Summary

There is a lack of evidence of human exposure to cinidon ethyl, no studies of cancer in humans, and a paucity of other published data. The Advisory Group therefore considered that an *IARC Monographs* evaluation of cinidon ethyl is unwarranted at present.

Recommendation: No priority

141 1,1-Dimethylhydrazine (CAS No. 57-14-7)

Current IARC/WHO classification

1,1-Dimethylhydrazine has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B), most recently in Volume 71 (IARC, 1999d), on the basis of *sufficient* evidence for cancer in experimental animals. 1,1-Dimethylhydrazine was recommended with *low* priority by the 2019 Advisory Group on Priorities (IARC, 2019a).

Exposure characterization

As noted in the 2019 Advisory Group report, "1,1-Dimethylhydrazine is in jet fuel and rocket fuel and is a breakdown product of the plant growth regulator daminozide. In the USA and Europe, daminozide is prohibited for use on food crops but not on ornamental plants, and it appears to be prohibited for use on peanuts in China. Use on mangoes and apples may be allowed some countries (Roy et al., 2018). Exposure to 1,1-dimethylhydrazine results from consumption of the whole fruit and juices and other products made from the treated fruit".

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 1999d), there was *sufficient* evidence in experimental animals for the carcinogenicity of 1,1-dimethylhydrazine.

Mechanistic evidence

Mechanistic evidence has emerged since the previous evaluation, from animal studies and experimental systems, suggesting electrophilicity, genotoxicity, induction of epigenetic alterations, and immunosuppression. However, these data do not appear to come from exposed humans or human primary cells.

Summary

The Advisory Group considered that an *IARC Monographs* re-evaluation of 1,1-dimethylhydrazine is unwarranted at present, given that more mechanistic evidence of KCs from human primary cells or in exposed humans would be needed for a change in classification.

Recommendation: No priority

142 Furmecyclox (CAS No. 60568-05-0)

Current IARC/WHO classification

Furmecyclox has not previously been evaluated by the *IARC Monographs* programme. Furmecyclox was given a priority rating of *low* by the 2019 Advisory Group on Priorities (IARC, 2019a).

Exposure characterization

Furmecyclox is a furamide fungicide and a wood preservative. Although, as noted in the 2019 Advisory Group report, furmecyclox has been listed as a "suspected" or "possible" carcinogen by the ECHA and the US EPA, there is little evidence of exposure. The WHO has listed furmecyclox as an active ingredient believed to be obsolete or discontinued for use as a pesticide (WHO, 2019). No data on exposure were

available to the Advisory Group. No data were found in any of the PubMed searches and almost no references found on Google Scholar.

Cancer in humans

No studies on cancer in humans were available to the Advisory Group.

Cancer in experimental animals

As noted in the 2019 Advisory Group report, "in experimental animals, furmecyclox induced a dose-related increased incidence of neoplastic nodules, carcinomas, and neoplastic nodules or carcinomas (combined) in the liver of female Sprague-Dawley rats and an increased incidence of liver nodules and carcinomas and urothelial tumours of the bladder in male Sprague-Dawley rats (US EPA, 1988)."

Mechanistic evidence

Apart from a few negative tests in mentioned in the EPA report, no mechanistic studies were available to the Advisory Group.

Summary

Although there is a positive animal bioassay, there is a lack of evidence of current or past human exposure. The Advisory Group therefore considered that an *IARC Monographs* evaluation of furmecyclox is unwarranted at present.

Recommendation: No priority

143 *ortho*-Benzyl-*para*-chlorophenol (CAS No. 120-32-1)

Current IARC/WHO classification

ortho-Benzyl-*para*-chlorophenol has not previously been evaluated by the *IARC Monographs* programme. It was given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of weak evidence for cancer in experimental animals and for genotoxicity.

Exposure characterization

ortho-Benzyl-*para*-chlorophenol is listed as a high production volume chemical by the OECD (OECD, 2007) and by the US EPA (US EPA, 2024a). As noted in the 2019 Advisory Group report, "*o*-Benzyl-*p*-chlorophenol is used as a broad-spectrum biocide in cleaning solutions and disinfectants in hospitals and households for general cleaning and disinfecting. Its use is widespread. Human exposure to o-benzyl-p-chlorophenol occurs by absorption through the skin and mucous membranes and by ingestion. From the National Occupational Exposure Survey 1981–1983 (NIOSH, 1983), the US NIOSH has statistically estimated that 347 634 workers (244 212 of them female) were potentially exposed to o-benzyl-p-chlorophenol in the USA (NCBI, 2024h). Occupational exposure to o-benzyl-p-chlorophenol may occur through dermal contact with this compound at workplaces where it is produced or used. The general population may be exposed to *o*-benzyl-*p*-chlorophenol through dermal exposure when using this compound as a household disinfectant."

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

Toxicity and carcinogenicity studies were conducted by administering *ortho*-benzyl-*para*-chlorophenol (approximately 97% pure) in corn oil by gavage to male and female F344/N rats and B6C3F_1 mice for

16 days, 13 weeks, or 2 years (NTP, 1994a). Clinical pathology parameters were evaluated during the 2-year study in rats. No increase in tumours was seen in male F344/N rats that received 30, 60 or 120 mg/kg bw for 2 years or in female $B6C3F_1$ mice that received 120, 240, or 480 mg/kg bw for 2 years (NTP, 1994a). In male $B6C3F_1$ mice, the incidence of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) was increased.

In a further NTP study, it was reported that *ortho*-benzyl-*para*-chlorophenol was a cutaneous irritant and a weak skin tumour promoter in a 1-year skin initiation/promotion study in Swiss (CD-l) mice (NTP, 1995a). When 0.1, 1.0, or 3.0 mg dissolved in acetone were applied 3 days per week for 20 weeks, the agent induced skin tumours (papilloma) in Tg.AC mice only at the highest dose (Spalding et al., 1999). A similar dose regimen was used for the NTP's 1-year skin painting study in CD-1 mice (NTP, 1995a).

Mechanistic evidence

Genetic toxicity studies were conducted in various test systems. In tests performed with and without exogenous metabolic activation, *ortho*-benzyl-*para*-chlorophenol did not induce gene mutations in various *S. typhimurium* strains (TA98, TA100, TA1535, or TA1537) and did not induce SCE or chromosomal aberrations in cultured CHO cells (NTP, 1995b). However, positive results were obtained in gene mutation tests conducted with mouse L5178Y lymphoma cells and human TK6 lymphoblast cells in the absence of S9 (NTP, 1995b). *ortho*-Benzyl-*para*-chlorophenol was not genotoxic in studies in vivo: no lethal mutations were observed in the dominant lethal mouse assay and no micronucleus formation was observed in the bone marrow of mice (as reviewed by Stouten and Bessems, 1998). Toxcast data show active hits for KC5, KC8, KC10 (US EPA, 2024l).

Summary

No studies of cancer in humans are available for *ortho*-benzyl-*para*-chlorophenol. There have been a few carcinogenicity studies in rodents conducted by NTP, a study of initiation/promotion in CD-1 mice and another 1-year study in transgenic mice, reporting weak evidence of promotion but not complete carcinogenicity effects. Few studies are available for the KCs, mainly related to genotoxicity and modulation of receptor-mediated effects. However, the few genotoxicity studies available in the NTP report indicated no genotoxicity of the agent. Other studies in vivo, reporting negative findings but with no primary data, were only summarized in a review of unpublished industry regulatory study reports. The Advisory Group therefore considered that an *IARC Monographs* evaluation of *ortho*-benzyl-*para*-chlorophenol is unwarranted at present.

Recommendation: No priority

144 2,4-Diaminotoluene (CAS No. 95-80-7)

Current IARC/WHO classification

2,4-Diaminotoluene (2,4-DAT) has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Supplement 7 in 1987 (IARC, 1987a). The IPCS has published a report on health effects of 2,4-DAT (WHO, 1987).

Exposure characterization

2,4-DAT is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). 2,4-DAT is used mainly to produce 2,4-toluene diisocyanate, which is a reagent in the manufacture of polyurethanes that are widely used in plastics and synthetic fibres (NTP, 2021a). 2,4-DAT has also been used to produce dyes, with a peak in production in the 1970s.

Occupational exposure might occur in the production and use of 2,4-DAT. 2,4-Toluene diisocyanate and the polymers for which it is used can be metabolized to 2,4-DAT (Lind et al., 1996; Luu et al., 1998). Therefore, workers might be exposed internally after inhalation and metabolization of these compounds (NTP, 2021a). Release of 2,4-DAT into the environment might lead to exposure of the general population through air and water (NTP, 2021a). Surgical implants covered with polyurethane coatings such as breast implants or pacemakers are another potential exposure source (Luu et al., 1998), as are consumer products and materials containing polyurethane in contact with food (Wang and Chen, 2009).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 1987a), there was *sufficient* evidence in experimental animals for the carcinogenicity of 2,4-DAT.

Mechanistic evidence

2,4-DAT forms DNA adducts in vitro and in vivo (Furlong et al., 1987; Citro et al., 1993; La and Froines, 1994; Delclos et al., 1996; Wilson et al., 1996). 2,4-DAT appeared to be genotoxic in a reconstructed 3D human epidermal skin model (Reus et al., 2013) and in the human hepatoma cell line HepG2 (Séverin et al., 2005), but not in HepaRG 3D spheroids or 2D cell cultures (liver models) (Mandon et al., 2019). In rats, 2,4-DAT induces DNA damage (Sasaki et al., 1997b; Narumi et al., 2012; De Boeck et al., 2015) and mutations (Toyoda-Hokaiwado et al., 2010) in the liver. 2,4-DAT is mutagenic in the Ames test (Shahin et al., 1985; Cunningham and Matthews, 1990; Cheung et al., 1996) and induces chromosomal aberrations in CHO cells (Bean et al., 1992). Occupational exposure to 2,4-DAT did not induce asthma in workers exposed to polyurethane foams (Candura and Moscato, 1984), and 2,4-DAT did not act as a respiratory sensitizer in mice (Vanoirbeek et al., 2009). Perturbation of the immune system in mice exposed to 2,4-DAT was observed (Burns et al., 1994). Reduced serum testosterone levels were measured in male rats with other signs associated with reproductive toxicity (Thysen et al., 1985a, b), although no reproductive toxic effects were found in exposed male workers (Hamill et al., 1982). Cell proliferation was increased in rat and mouse livers and other organs after chronic exposure to 2,4-DAT (NTP, 1979; Cunningham and Matthews, 1995).

Summary

No studies in humans on the carcinogenicity of 2,4-DAT were available. There is mechanistic information showing that 2,4-DAT exhibits KCs: it is genotoxic, forms DNA adducts and increases cell proliferation in experimental systems. However, no data relative to the key characteristics in exposed humans or in human primary cells or tissues are available. A few studies have reported that 2,4-DAT is immunosuppressive in mice and modulates receptor-mediated effects in male rats. The Advisory Group therefore considered that an *IARC Monographs* evaluation of 2,4-diaminotoluene is unwarranted at present.

Recommendation: No priority

145 3,3′-Dimethoxybenzidine (CAS No. 119-90-4) (ortho-dianisidine, CI Disperse Black 6)

Current IARC/WHO classification

3,3′-Dimethoxybenzidine (*ortho*-dianisidine, CI Disperse Black 6) has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Supplement 7 in 1987 (IARC, 1987a).

Exposure characterization

3,3′-Dimethoxybenzidine is an aromatic amine that is used as an intermediate in the production of various dyes and pigments for colouring of paper, textiles, leather, plastic, and rubber (NTP, 2021a). It is also used in the production of *ortho*-dianisidine diisocyanate for the manufacture of plastics and adhesives. The use of azo dyes that can yield 3,3′-dimethoxybenzidine when they decompose is banned or restricted for textiles and cosmetics in the EU, where it is mainly used for small-scale laboratory applications (European Commission, 2002c). Production and use have declined in Europe and the USA since the 1990s (IARC, 2010a) and little information is available on current levels of use and human exposure. Occupational exposure, mainly via inhalation or dermal contact, is expected in contexts where use has not been restricted. The general public might be exposed via consumer products that contain 3,3′-dimethoxybenzidine as a trace contaminant or in settings where the use of dyes containing 3,3′-dimethoxybenzidine or metabolized to 3,3′-dimethoxybenzidine have not been banned.

Cancer in humans

Workers exposed to 3,3′-dimethoxybenzidine and other azo dyes had elevated risk of bladder cancer (Ouellet-Hellstrom and Rench,1996). However, no studies on human cancer that could single out exposure to 3,3′-dimethoxybenzidine were available to the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 1987a), there was *sufficient* evidence in experimental animals for the carcinogenicity of 3,3′-dimethoxybenzidine in experimental animals. 3,3′-Dimethoxybenzidine produced tumours in rats at various sites, including the bladder, intestine, skin, and Zymbal gland; it induced forestomach papillomas in hamsters. In addition, 3,3′-dimethoxybenzidine dihydrochloride carcinogenicity was confirmed in the toxicity and carcinogenicity studies as part of the NTP's Benzidine Dye Initiative (NTP, 1990). This initiative was designed to evaluate benzidine congeners and benzidine congener-derived and benzidine-derived dyes (NTP, 1990; Morgan et al., 1994).

Mechanistic evidence

3,3′-Dimethoxybenzidine is listed by the California Office of Environmental Health Hazard Assessment as causing cancer (OEHHA, 2024) and as "reasonably anticipated to be a human carcinogen" by the NTP RoC (NTP, 1990). 3,3′-Dimethoxybenzidine is structurally similar to benzidine, a Group 1 carcinogen (IARC, 1972, 2012b). The metabolic conversion of 3,3′-dimethoxybenzidine to carcinogenic aromatic amines has been observed in experimental systems (Lynn et al., 1980) and humans (Lowry et al., 1980). There is evidence in experimental systems that 3,3′-dimethoxybenzidine is genotoxic. It was mutagenic in *S.typhimurium* and induced UDS in rat hepatocyte primary cultures (NTP, 1990). 3,3′-Dimethoxybenzidine dihydrochloride was mutagenic in *Salmonella* and induced SCE and chromosomal aberrations in mammalian cells in vitro (NTP, 1990). These findings, coupled with the observed mutagenic activity of several metabolites of 3,3′-dimethoxybenzidine and structurally similar compounds (NTP, 1990), are strongly suggestive that a genotoxic mode of action is operative. In addition, DNA damage was observed in primary cells from liver and urinary bladder rats and humans (Martelli et al., 2000). Data from high-throughput screening assays in vitro suggested that the chemical may modulate receptor-mediated effects (Haggard et al., 2018; Cardona and Rudel, 2021).

In a recent evaluation of aromatic amines (IARC, 2021) aniline, *ortho*-anisidine and *ortho*-nitroanisole were classified as *probably carcinogenic to humans* (Group 2A) on the basis of *strong* mechanistic evidence. In view of the metabolism and mechanistic considerations for all three agents, they were classified on the basis of belonging to a class of aromatic amines for which several members (i.e. 4-aminobiphenyl, 2-naphthylamine, and *ortho*-toluidine) have been classified as *carcinogenic to humans* (IARC Group 1). These

agents were similar to this class of aromatic amines with respect to the formation of common DNA-reactive moieties, genotoxicity, and target organs of carcinogenicity in animal bioassays for chronic toxicity. Thus, it could be expected that 3,3′-dimethoxybenzidine could also belong to this same class.

Summary

No studies on human cancer that could single out exposure 3,3′-dimethoxybenzidine were available. There is already *sufficient* evidence for cancer in experimental animals. There is evidence that 3,3′-dimethoxybenzidine exhibits KCs. In addition, the metabolism, genotoxicity, and carcinogenicity in experimental animals provide strong evidence that 3,3′-dimethoxybenzidine belongs to the same mechanistic class as other aromatic amines previously classified by IARC in Groups 1 or 2A. This evidence could support a change in the classification of 3,3′-dimethoxybenzidine. The Advisory Group therefore considered an *IARC Monographs* evaluation of 3,3′-dimethoxybenzidine to be warranted, together with 3,3′-dimethylbenzidine (agent 146).

Recommendation: High priority (and ready for evaluation within 2.5 years)

146 3,3′-Dimethylbenzidine (CAS No. 119-93-7) (*ortho*-tolidine)

Current IARC/WHO classification

3,3′-Dimethylbenzidine (*ortho*-tolidine) has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Supplement 7 in 1987 (IARC, 1987a).

Exposure characterization

3,3′-Dimethylbenzidine is an aromatic amine that is used as an intermediate in the production of various dyes and pigments for colouring of paper, textiles, leather, plastic, and rubber (NTP, 2021a). It is also used in the production of polyurethanes as a curing agent. The use of azo dyes that can yield 3,3′-dimethylbenzidine when they decompose is banned or restricted for textiles and cosmetics in the EU (European Commission, 2002c), where it is mainly used for small-scale, laboratory applications. Production and use have declined in Europe and the USA since the 1990s (IARC, 2010a) and little information is available on current levels of use and human exposure. Occupational exposure, mainly via inhalation or dermal contact, is expected in contexts where use has not been banned. The general public might be exposed via consumer products that contain 3,3′-dimethylbenzidine as a trace contaminant or in settings where the use of dyes containing 3,3′-dimethylbenzidine or dyes metabolized to 3,3′-dimethylbenzidine have not been banned.

Cancer in humans

Studies of workers exposed to 3,3′-dimethylbenzidine and other azo dyes have shown elevated risk of bladder cancer (Ouellet-Hellstrom and Rench, 1996). However, no studies on human cancer that could single out exposure to 3,3′-dimethylbenzidine were available to the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 1987a), there was *sufficient* evidence in experimental animals for the carcinogenicity of 3,3′-dimethylbenzidine. In addition, carcinogenicity of 3,3′-dimethylbenzidine dihydrochloride was confirmed in 2-year carcinogenicity and toxicity studies as part of the NTP's Benzidine Dye Initiative. This initiative was designed to evaluate benzidine congeners and benzidine congener-derived and benzidine-derived dyes (NTP, 1990; Morgan et al., 1994).

Mechanistic evidence

The NTP RoC lists 3,3′-dimethylbenzidine as "reasonably anticipated to be a human carcinogen" based on *sufficient* evidence for cancer in animals (NTP, 1990). 3,3′-Dimethylbenzidine is listed as causing cancer by the California Office of Environmental Health Hazard Assessment (OEHHA, 2024). 3,3′-Dimethylbenzidine is structurally similar to benzidine, a well-known Group 1 agent (IARC, 1972, 2012b). Although little information is available on the metabolism of 3,3′-dimethylbenzidine, there is evidence showing metabolic conversion to carcinogenic aromatic amines in experimental systems (Lynn et al., 1980; Cerniglia et al., 1982b) and humans (Cerniglia et al., 1982a; Golka et al., 2004). There is evidence from experimental systems that 3,3′-dimethylbenzidine dihydrochloride is genotoxic. 3,3′-Dimethylbenzidine was mutagenic in *S. typhimurium* strain TA98 with exogenous metabolic activation; it was not mutagenic in strains TA100, TA1535, or TA97 with or without activation. 3,3′-Dimethylbenzidine dihydrochloride induced SCE and chromosomal aberrations in CHO cells only in the absence of exogenous metabolic activation. Sex-linked recessive lethal mutations were induced in germ cells of adult male *Drosophila melanogaster* given 3,3′-dimethylbenzidine dihydrochloride in the feed or by injection. No reciprocal translocations occurred in *D. melanogaster* germ cells following exposure to 3,3′-dimethylbenzidine dihydrochloride (NTP, 1991). In addition, data from high-throughput screening assays in vitro suggested that the chemical may modulate receptor-mediated effects (Judson et al., 2015; Haggard et al., 2018; Cardona and Rudel, 2021).

In a recent evaluation of aromatic amines (IARC, 2021) aniline, *ortho*-anisidine and *ortho*-nitroanisole were classified as *probably carcinogenic to humans* (Group 2A) on the basis of *strong* mechanistic evidence. In view of the metabolism and mechanistic considerations for all three agents, they were classified on the basis of belonging to a class of aromatic amines for which several members (i.e. 4-aminobiphenyl, 2-naphthylamine, and *ortho*-toluidine) have been classified as *carcinogenic to humans* (Group 1). These agents were similar to this class of aromatic amines with respect to the formation of common DNA-reactive moieties, genotoxicity, and target organs of carcinogenicity in animal bioassays for chronic toxicity. Thus, it could be expected that 3,3′-dimethylbenzidine could also belong to this same class.

Summary

No studies on human cancer that could single out exposure to 3,3′-dimethylbenzidine were available. There is evidence that 3,3′-dimethylbenzidine exhibits KCs. In addition, the metabolism, genotoxicity, and carcinogenicity in experimental animals provide strong evidence that 3,3′-dimethylbenzidine belongs to the same mechanistic class as other aromatic amines previously classified by IARC in Groups 1 or 2A. This evidence could support a change in the classification of 3,3′-dimethylbenzidine. The Advisory Group therefore considered an *IARC Monographs* evaluation of 3,3′-dimethylbenzidine to be warranted, together with 3,3′-dimethoxybenzidine (agent 145).

Recommendation: High priority (and ready for evaluation within 2.5 years)

147 5-Nitro-*ortho*-toluidine (CAS No. 99-55-8)

Current IARC/WHO classification

5-Nitro-*ortho*-toluidine has previously been evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in Volume 48 in 1989 (IARC, 1990b).

Exposure characterization

5-Nitro-*ortho*-toluidine has been used as an intermediate in the synthesis of Pigment Red 17 and Pigment Red 22. It has also been used as a precursor in the synthesis of a wide assortment of azo dyes of various red,

yellow, orange, violet, and brown hues (IARC, 1990b). Data for occupational and non-occupational exposure to 5-nitro-*ortho*-toluidine were not available, but because the compound is used in the synthesis of pigments, it is presumed that exposures can occur.

Cancer in humans

No human cancer studies were available in the previous IARC evaluation (IARC, 1990b). Since then, no studies of cancer in humans have been published.

Cancer in experimental animals

5-Nitro-*ortho*-toluidine was tested for carcinogenicity in both rats and mice by oral administration. In mice, it caused HCCs in both sexes, an increase in the incidence of haemangiomas and haemangiosarcomas (combined) in male mice, and an increased incidence of haemangiosarcomas in female mice. The compound was not considered to be carcinogenic in rats (NTP, 1978).

Mechanistic evidence

5-Nitro-*ortho*-toluidine tested positive for genotoxicity in two assay systems: mammalian cell cytogenetics and bacterial mutagenicity (NTP, 2023h). 5-Nitro-*ortho*-toluidine exposure in rats led to haemoglobin adduct formation (Zwirner-Baier et al., 1994). 5-Nitro-*ortho*-toluidine was screened as part of the US EPA ToxCast programme and found to be active in several nuclear hormone receptor assays in human cell lines, including the androgen and progesterone receptors AHR and RXR (US EPA, 2024c).

Summary

No human cancer studies were available for 5-nitro-*ortho*-toluidine. Available data indicate that 5-nitro-*ortho*-toluidine is carcinogenic in experimental animals, according to the criteria in the latest version of the IARC *Monographs* Preamble. There is some evidence that 5-nitro-*ortho*-toluidine exhibits KCs, in particular genotoxicity and receptor-mediated effects in experimental systems. These data could support an evaluation of 5-nitro-*ortho*-toluidine by a *Monographs* Working Group. The Advisory Group therefore considered an *IARC Monographs* evaluation of 5-nitro-*ortho*-toluidine to be warranted, together with other azo dyes included in this report.

Recommendation: High priority (and ready for evaluation within 2.5 years)

148 Congo red (CAS No. 573-58-0)

Current IARC/WHO classification

Congo red has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Congo red is one of the common names for disodium 3,3′-[[1,1′-biphenyl]-4,4′-diylbis(azo)]bis(4-aminonaphthalene-1-sulfonate. It is a synthetic azo dye previously used in textiles, tanneries, cosmetics, pigments, and the food, pharmaceutical, pulp, paper and printing industries (Harja et al., 2022), but it is unclear to what extent it is still used in these industries. Congo red is used for histological staining to detect amyloid structures (Yakupova et al., 2019).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

There is evidence that Congo red is metabolized to benzidine (Reid et al., 1983; Victor et al., 2020). Benzidine and dyes metabolized to benzidine are classified in as *carcinogenic to humans* (Group 1) by IARC (1987a; 2012b). Concerning Congo red, there is evidence for hepatocarcinogenesis of similar dyes (Direct Blue 6, Direct Black 38, and Direct Brown 95, all derived from benzidine) in rats from a subchronic study (Robens et al., 1980; ECHA, 2013). In fact, much of the evidence comes from similar dyes or benzidine with the assumption of similar action and this has led to the hypothesis of their carcinogenicity (Siddiqui et al., 2023). Mutagenicity has been studied, since the benzidine metabolite is a mutagen. The Ames test shows mutagenicity of Congo red in the presence of hamster S9 (azoreduction necessary) (Reid et al., 1983). In vivo, DNA adducts were found in rat liver (intraperitoneal injection) that were similar to benzidine-related adducts. Azo reduction probably occurs in the gut microflora (Reid et al., 1983; Siddiqui et al., 2023).

Summary

No studies in humans regarding the carcinogenicity of Congo red are available. Congo red is metabolized by microflora in the gut to benzidine and derivatives, which form DNA adducts in the liver. There is some mechanistic evidence that Congo red exhibits KCs, and its metabolism to benzidine suggests that it could belong in Group 1 as part of the agent "dyes metabolized to benzidine". The Advisory Group therefore considered an *IARC Monographs* evaluation of Congo red to be warranted, together with other benzidine-related dyes.

Recommendation: High priority (and ready for evaluation within 2.5 years)

149 Ethyl anthranilate (CAS No. 87-25-2)

Current IARC/WHO classification

Ethyl anthranilate has not previously been evaluated by the *IARC Monographs* programme. The JECFA conducted a limited assessment of ethyl anthranilate in 2005 and concluded that there is no safety concern at current levels of intake when used as a flavouring agent (TRS 934-JECFA 65/54).

Exposure characterization

Ethyl anthranilate, a flavouring agent found naturally in citrus fruits, grapes, and starfruit, is used in the food industry. It is used to enhance flavours in a variety of products, including alcoholic and non-alcoholic beverages, baked goods, chewing gum, frozen dairy, gelatin, puddings, and hard and soft candies. In addition to its role in the food industry, ethyl anthranilate is employed in perfumery and as a fragrance component in various consumer products. It also serves as an inert ingredient in pesticides, indicating its use in agricultural applications (Api et al., 2015; NCBI, 2024a). Occupational dermal exposure may occur in workers in production or industrial settings that utilize ethyl anthranilate. General population exposure includes dietary ingestion of ethyl anthranilate-containing foods and potential dermal contact with consumer products containing the compound (NCBI, 2024a). Total systemic exposure (dermal and inhalation) was estimated at 0.0013 mg/kg per day (Api et al., 2015).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

Results on genotoxicity of ethyl anthranilate appear to be negative, from studies by the NTP and the Research Institute for Fragrance Materials (RIFM) (NTP, 1986a; Api et al., 2015). A read-across study using anthranilic acid and methyl anthranilate did not show potential genotoxic effects (Api et al., 2015). However, there are several issues to consider. Anthranilic acid is a metabolite of ethyl anthranilate. The Advisory Group considered that the Ames test may not have been adequate, as the activation of aromatic amines requires phase II biotransformation.

Another anthranilate (cinnamyl anthranilate) shows some effects in experimental animals: hepatocarcinoma in mice and non-statistically significant tumours in various locations in rats (NCI, 1980; Viswalingam and Caldwell, 1997; IARC, 2000; Klaunig et al., 2003). Cinnamyl anthranilate is a PPARα agonist (IARC, 2000) and it is known that rodents are much more sensitive to PPARα agonists than primates (Klaunig et al., 2003); thus, the human relevance of such findings is questionable. Anthranilic acid and cinnamyl anthranilate have been classified as Group 3 by the *IARC Monographs* (IARC, 1978, 1987a, 2000).

Summary

There is no evidence on cancer in humans or in experimental animals and largely negative mechanistic evidence. The Advisory Group therefore considered that an *IARC Monographs* evaluation of ethyl anthranilate is unwarranted at present.

Recommendation: No priority

150 Menthyl anthranilate (CAS No. 134-09-8)

Current IARC/WHO classification

Menthyl anthranilate has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Menthyl anthranilate, primarily known for its function as an absorber of ultraviolet radiation (UVR), is an ingredient in cosmetic and personal care products, particularly in products that offer protection from UVR, for example in sunscreen products and in lip balms (NCBI, 2024b). It is approved for this purpose in the USA but not in Europe or Japan (EWG, 2024; US EPA 2024d). Occupational dermal exposure may occur in workers in production or industrial settings that use menthyl anthranilate. General population exposure includes dermal contact with consumer products containing the compound. However, there is a lack of studies on the degree of dermal penetration and consumer exposure.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

There are very few mechanistic studies of menthyl anthranilate. This compound may have possible pro-oxidant and antioxidant effects in cellular studies (Hofer et al., 2018). It was recently suggested to induce photoallergic contact dermatitis (Battis et al. 2023).

Summary

There is no evidence on cancer in humans or experimental animals and largely negative mechanistic evidence. The Advisory Group therefore considered that an *IARC Monographs* evaluation of menthyl anthranilate is unwarranted at present.

Recommendation: No priority

151 Methyl anthranilate (CAS No. 134-20-3)

Current IARC/WHO classification

Methyl anthranilate has not previously been evaluated by the *IARC Monographs* programme. The JECFA conducted a limited assessment of methyl anthranilate in 2005 and concluded that the acceptable daily intake (ADI) established at the 23rd meeting was to be maintained (TRS 934-JECFA 65/54).

Exposure characterization

Methyl anthranilate is listed as a high production volume chemical by the OECD and the US EPA (OECD, 2007; US EPA, 2024a). The annual volume of production and importation in the European Economic Area is reported to be 100–1000 tonnes per year (ECHA, 2023e).

Methyl anthranilate, widely recognized as a fragrance and flavouring agent, is extensively used in various consumer and industrial products. It is commonly found in foods, personal care items, air fresheners, polishes, waxes, and cleaning products. Additionally, it serves as a pest repellent, particularly in agricultural settings, leading to potential occupational exposure for workers. It is present in essential oils such as neroli, ylang-ylang, bergamot, and jasmine, as well as in grape juice. Exposure to methyl anthranilate can occur through oral, dermal, and inhalation routes. The total systemic 95th percentile exposure via dermal, oral and inhalation routes when used as fragrance ingredient was estimated as 0.0013 mg/kg per day (Api et al., 2017; ECHA, 2023e; NCBI, 2024c).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

A single study did not reveal increased incidence of tumours in mice (Stoner et al., 1973).

Mechanistic evidence

Results on genotoxicity of methyl anthranilate appear to be negative, from studies by the NTP and RIFM (NTP, 2024c; Api et al., 2017). Anthranilic acid, a metabolite of methyl anthranilate (Yamaori et al., 2005), was not found to be genotoxic (Gadupudi and Chung, 2011). However, the Advisory Group noted that the tests may not have been completely adequate, as activation of aromatic amines requires phase II biotransformation.

Another anthranilate (cinnamyl anthranilate) showed positive effects in animal tests: hepatocarcinoma in mice and non-statistically significant tumours in various locations in rats (Viswalingam and Caldwell, 1997; IARC, 2000; Klaunig et al., 2003; NCBI, 2024c). Cinnamyl anthranilate is a PPARα agonist (IARC 2000), and it is known that rodents are much more sensitive to PPARα agonists than primates (Klaunig et al., 2003); thus, the human relevance of such findings is questionable. Both anthranilic acid and cinnamyl anthranilate have been classified as Group 3 by the *IARC Monographs* (IARC, 1978, 1987a, 2000).

Summary

There is no evidence on cancer in humans or experimental animals and largely negative mechanistic evidence. The Advisory Group therefore considered that an *IARC Monographs* evaluation of methyl anthranilate is unwarranted at present.

Recommendation: No priority

152 *ortho*-Aminoazotoluene (CAS No. 97-6-3)

Current IARC/WHO classification

ortho-Aminoazotoluene has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Supplement 7 in 1987 (IARC, 1987a).

Exposure characterization

ortho-Aminoazotoluene has been used to colour oils, fats, and waxes (IARC, 1975). It is also used as a chemical intermediate for the production of the dyes CI Solvent Red 24 and CI Acid Red 115 (HSDB, 2009). It also has a wide range of applications in the laboratory, including as a reagent for the synthesis of a variety of compounds including azo dyes, polymers, and pharmaceuticals. Additionally, it is used in the production of nitrobenzene and other nitro compounds (BenchChem, 2023).

The primary routes of human exposure to *ortho*-aminoazotoluene are dermal absorption and inhalation (NTP, 2021a). It is not used directly in foods, drugs, or cosmetics, so exposure of the general population through consumer products is not likely (IARC, 1975; NTP, 2021a). Occupational exposure may occur through inhalation of dust or by dermal contact during production, formulation or use of *ortho*-aminoazotoluene (HSDB, 2009; NTP, 2021a). The National Occupational Exposure Survey (conducted by NIOSH from 1981 to 1983) estimated that 1449 workers were potentially exposed (in the chemicals and allied products and the transportation equipment industries); none of these workers were women (NIOSH, 1990a).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 1975), there was *sufficient* evidence in experimental animals for the carcinogenicity of *ortho*-aminoazotoluene. It caused tumours in several species of experimental animals, at several different tissue sites, and by several different routes of exposure (IARC, 1975; NTP, 2021a). Since the previous evaluation, *ortho*-aminoazotoluene given by gavage was found to rapidly induce colonic adenocarcinoma in mice after treatment with dextran sulfate sodium (Hakura et al., 2022).

Mechanistic evidence

ortho-Aminoazotoluene induced epithelial hyperplasia in human embryonic lung and kidney tissues (Shabad et al., 1975). It induced gene mutations in the liver and colon in lambda/lacZ transgenic mice (Ohsawa et al., 2000; Kohara et al., 2001). Severe inflammatory infiltration and proliferation of oval cells were found in liver tissue of mice treated with *ortho*-aminoazotoluene (Baginskaya et al., 2007). An immunosuppressive action was observed in DD mice after a single injection of *ortho*-aminoazotoluene (Kaledin et al., 1978). It gave positive results in the Ames test (Zeiger et al., 1992; Ohsawa et al., 2000; Ovchinnikova et al., 2013). Urothelial hyperplasia was observed in rats after oral administration of *ortho*-aminoazotoluene (Toyoda et al., 2023). *ortho*-Aminoazotoluene has been screened in the US EPA ToxCast programme for induction of hormone synthesis in the in vitro H295R steroidogenesis assay and was found

to cause cells to significantly increase production of estradiol and progesterone. It was one of the most potent inducers of estrogen and progesterone synthesis screened in the assay (Cardona and Rudel, 2021). It was also screened for evidence of activity at the estrogen receptor using a computational model that integrates the concentration–response results from 18 in vitro assays that measure activity related to the ER pathway. According to this model, which is now the EPA's preferred method for identifying ER agonists, this chemical is significantly ER agonistic (Judson et al., 2015; Haggard et al., 2018; Cardona and Rudel, 2021; Kay et al., 2024).

Summary

No studies of cancer in humans were available. There is already *sufficient* evidence that *ortho*-aminoazotoluene causes cancer in experimental animals, at various tissue sites and by several different routes of exposure. Several studies have shown evidence of multiple KCs in experimental systems. However, the lack of new studies in human primary cells or tissues or in exposed humans suggests that an updated evaluation would not lead to a change in classification. The Advisory Group therefore considered that an *IARC Monographs* evaluation of *ortho*-aminoazotoluene is unwarranted at present.

Recommendation: No priority

153 *para*-Cresidine (CAS No. 120-71-8) (2-methoxy-5-methylaniline)

Current IARC/WHO classification

para-Cresidine (*p*-cresidine, 2-methoxy-5-methylaniline) has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Supplement 7 in 1987 (IARC, 1987a).

Exposure characterization

para-Cresidine is used exclusively as a synthetic chemical intermediate to produce azo dyes and pigments. The dyes made with *para*-cresidine have been produced commercially and are used in the food and textile industries (NCI, 1979c, NTP 2021a; IARC, 1982). *para*-Cresidine has been identified as a contaminant in FD&C red dye No. 40, which is used in gelatins, puddings, dairy products, confections, beverages, and condiments (Richfield-Fratz et al., 1989; Food Additives World, 2006).

The routes of potential human exposure to *para*-cresidine are inhalation, ingestion, and dermal contact (HSDB, 2009; NTP, 2021a). Measurements of *para*-cresidine in a longitudinal biomonitoring study involving 15 participants residing in the USA suggested that the sources of exposure were not related to tobacco smoke (Chinthakindi and Kannan, 2022). In a study analysing primary aromatic amines in 256 house dust samples collected from 10 countries, *para*-cresidine was one of the more prevalent (Chinthakindi and Kannan, 2021). Occupational exposure to *para*-cresidine may occur through inhalation and dermal contact at workplaces where *para*-cresidine is produced or used (HSDB, 2009).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 1987a), there was *sufficient* evidence for carcinogenicity in experimental animals, on the basis of the bioassay conducted by NCI (1979c) that evaluated carcinogenicity of *para*-cresidine in F344 rats and B6C3F$_1$ mice. Since that evaluation, new studies have been published. In a study by Petruska et al. (2002) in p53-heterozygous mice, *para*-cresidine administered at a dose of 400 mg/kg bw for 26 weeks showed bladder epithelial cell carcinomas, SCCs, and transitional epithelial

hyperplasia and metaplasia in both males and females. There was also a report of urinary bladder leiomyosarcoma in female mice treated with *para*-crsidine. Transitional cell carcinoma of the urinary bladder was reported in female BK5.IGF-1 TG transgenic mice fed 0.5% *para*-cresidine in the diet (Hursting et al., 2009).

Mechanistic evidence

There is evidence that *para*-cresidine is mutagenic in experimental systems. Sasaki et al. (1998) observed significant DNA damage in tissues of mice fed *para*-cresidine at 595 mg/kg bw for 3 hours and 24 hours. In mice and rats exposed to either oral administration or intraperitoneal injection of *para*-cresidine, UDS, DNA strand breaks, and micronucleus induction were reported (Ashby et al., 1991). BK5.IGF-1 TG mice with urothelial IGF-1 overexpression were more susceptible to *para*-cresidine-induced bladder cancer (Hursting et al., 2009). The agent has been screened in the US EPA ToxCast programme for induction of hormone synthesis in the in vitro H295R steroidogenesis assay and was found to cause cells to significantly increase production of progesterone (Cardona and Rudel, 2021; Kay et al., 2024).

Summary

No studies of cancer in humans were available. There is already *sufficient* evidence that *para*-cresidine causes cancer in experimental animals. There is mechanistic evidence that *para*-cresidine exhibits KCs, mainly genotoxicity, in experimental systems. However, the lack of evidence in human primary cells or tissues or in exposed humans suggests that an updated evaluation would not lead to a change in classification for *para*-cresidine. The Advisory Group therefore considered that an *IARC Monographs* re-evaluation of *para*-cresidine is unwarranted at present.

Recommendation: No priority

154 *para*-Phenylenediamine (CAS No. 106-50-3) (1,4-benzenediamine)

Current IARC/WHO classification

para-Phenylenediamine (*p*-phenylenediamine, 1,4-benzenediamine) has previously been evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in Supplement 7 in 1987 (IARC, 1987a).

Exposure characterization

para-Phenylenediamine is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). *para*-Phenylenediamine is an aniline derivative that is widely used as a dye intermediate and as a photographic developing agent, as an antioxidant and accelerator, and in the production of rubber and of some polymers such as kevlar (US EPA, 2000a; NCBI, 2024d).

para-Phenylenediamine and other arylamines or *para*-aminophenols are used as primary intermediates in permanent hair dyes (IARC, 2010a). These compounds are oxidized and react with couplers in or on the hair to form the final hair dye after another oxidation step. Hair dyes usually contain a mix of different couplers and intermediates and a range of concentrations to achieve the specific tone. Colourant concentrations below 1% or in the low per cent range are applied. For hairdressers and barbers, occupational exposure occurs mainly via inhalation, whereas exposure during personal use of hair dyes is mainly via the dermal route (IARC, 2010a). Occupational exposure during the uses of *para*-phenylenediamine other than as hair dyes is expected to occur but is poorly documented. Consumer exposure due to the illegal addition of *para*-phenylenediamine to non-permanent henna tattoo colours has been documented (Jacob and Brod, 2011; Krüger et al., 2013).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In rats treated subcutaneously with *para*-phenylenediamine at 12 mg/kg bw, fibrosarcoma was observed 7 months after administration of the agent (Saruta et al., 1958). Another study reported no carcinogenic effects in either sex in F344 rats treated with *para*-phenylenediamine for 80 weeks (Imaida et al., 1983). Dermal exposure of female Wistar rats to *para*-phenylenediamine induced mammary gland tumours and subcutaneous injection induced uterine tumours and soft-tissue tumours, whereas tumours of the thyroid, adrenal gland, liver, lung, and urinary bladder were observed in male rats (Rojanapo et al., 1986).

Mechanistic evidence

Although *para*-phenylenediamine by itself has been shown to be non-mutagenic, an oxidation product of *para*-phenylenediamine had mutagenic effects when tested on *S. typhimurium* TA98 (Rojanapo et al., 1986). *para*-Phenylenediamine has been reported to induce apoptosis in melanoma cells in mice (Bhowmick et al., 2016). Inflammatory response is elicited (induction of several interleukins and cytokines) in *para*-phenylenediamine-treated mice (Van Belle et al., 2019). However, this response represents acute contact dermatitis and its relevance to carcinogenicity is not clear. Kasi et al. (2015) reported that *para*-phenylenediamine induces apoptosis via alteration of JNK and Akt cell signalling pathways which are implicated in carcinogenesis. The agent was active in a series of assays linked to KC2, KC5, KC8, and KC10 (ToxCast data, analysed with the software "KC-hits", key characteristics of carcinogens, high-throughput screening discovery tool; Reisfeld et al., 2022), and it was reported to highly increase estradiol levels specifically in the in vitro steroidogenesis assay (Cardona and Rudel, 2021).

Summary

No studies on human cancer were available. There is evidence that *para*-phenylenediamine induces cancer in experimental animals. There is some mechanistic evidence suggesting that *para*-phenylenediamine exhibits several KCs, including genotoxicity in experimental animals. The Advisory Group therefore considered an *IARC Monographs* evaluation of *para*-phenylenediamine to be warranted. This agent should be evaluated in the same volume as hair dyes (agent 157).

Recommendation: High priority (and ready for evaluation within 2.5 years)

155 4-Nitrotoluene (CAS No. 99-99-0)

Current IARC/WHO classification

4-Nitrotoluene has previously been evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in Volume 65 in 1995 (IARC, 1996). 4-Nitrotoluene was given a priority rating of *medium* by the 2019 Advisory Group on Priorities, on the basis of its similarity to *ortho*-toluidine (IARC, 2019a).

Exposure characterization

4-Nitrotoluene, also known as *para*-nitrotoluene, is an organic compound that is a solid at room temperature. 4-Nitrotoluene is listed as a high production volume chemical by the OECD and the US EPA (OECD, 2007; US EPA, 2024a). It is used as an intermediate in the production of dyes, agricultural and rubber chemicals and explosives (NIH, 2024b). It is also used in the production of medications including *para*-aminobenzoic acid, benzocaine, procaine hydrochloride, thioacetazone and folic acid (NIH, 2024b).

Air concentrations in a factory manufacturing dinitrotoluene and 2,4,6-trinitrotoluene were well below the US Occupational Safety and Health Administration (OSHA) permissible exposure limit and UK occupational 8-hour TWA exposure limits set at 11 mg/m^3 (Jones et al., 2005). However, previous smaller studies had suggested that dermal exposure was more important than inhalational exposure in relation to nitrotoluenes generally (Levine et al., 1985; Woollen et al., 1985).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In an NTP study conducted under GLP, there was an increase in bronchioloalveolar adenoma or carcinoma (combined) in male mice (NTP, 2002). In rats, there was a modest increase in the incidence of clitoral gland adenoma or carcinoma (combined) in females, and slight increases in the incidence of subcutaneous skin fibroma or fibrosarcoma (combined) in males. When actual data were examined (NTP, 2002), there was a clear increase at intermediate doses and no increase at the highest dose. The conclusion of the NTP report was "equivocal evidence" because of the dose–response curve pattern. However, the Advisory Group noted that positive findings in male and female rats and in male mice were described in a well-conducted GLP study (NTP, 2002) and suggested furthermore that the non-monotonic dose–response should not be considered as "equivocal" evidence for a *Monographs* evaluation.

Mechanistic evidence

Haemoglobin adducts, but not DNA adducts, were formed in rats dosed with 4-nitrotoluene (Jones and Sabbioni, 2003). The NTP report shows positive mutagenic effects in the L5178Y mouse lymphoma cell assay in trials with S9 and increased SCE frequencies in cultured CHO cells with and without S9 (NTP, 2002). Another study observed evidence of genotoxicity in germ cells of Kunming male rats (Yang et al., 2005), but not in Ames tests (Haworth et al., 1983). Chromosomal aberrations were observed in CHO cells treated with 4-nitrotoluene in the presence of S9, but not without S9 (NTP, 2002). In addition, Burns et al. (1994) showed clear immunosuppression with a decrease in resistance to *Listeria* and a decrease in CD4+ T lymphocytes in the spleen and monocytes in blood (Yang et al., 2005), and spleen toxicity was found in the 13-week NTP study (Dunnick, 1992). Finally, 4-nitrotoluene showed uterotropic effects in rats and may have estrogenic activity (Smith and Quinn, 1992), and the incidence of oncocytic renal tubule and endometrial hyperplasia of the uterus in female rats and alveolar epithelial hyperplasia in male mice was increased in a well-conducted GLP study (NTP, 2002).

Summary

No studies of exposure to 4-nitrotoluene and cancer in humans are available. Since the 2019 Advisory Group review, no new data on carcinogenicity of 4-nitrotoluene in experimental animals have been published; however, the Advisory Group considered the available data to support a reconsideration of the evidence of cancer in experimental animals. In addition, 4-nitrotoluene exhibits several KCs in experimental systems. The Advisory Group therefore considered an *IARC Monographs* evaluation of 4-nitrotoluene to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

156 Red dye No. 3 (CAS No. 16423-68-0) (erythrosine)

Current IARC/WHO classification

Red dye No. 3 (erythrosine) has not previously been evaluated by the *IARC Monographs* programme. The JECFA conducted an assessment of erythrosine in 2018 and, in light of new data, confirmed the previous ADI of 0–0.1 mg/kg bw (FAO/WHO, 2019).

Exposure characterization

Erythrosine is used as a colourant in toothpaste products with a maximum concentration of 0.0025% (25 ppm) (European Commission, 2010). Erythrosine is used in household and commercial or institutional products (e.g. personal care and pet care). It is used as a red colouring in some foods (cherries, fish), for disclosure of dental plaque, and as a stain of some cell types (PubChem, 2024h). Aggregate exposure to erythrosine is possible from other uses (e.g. food, medical products). No studies on occupational exposure have been identified. In Europe, erythrosine is exclusively authorized for use in cocktail and specific cherries specified by the EU Commission Directive 2008/128/EC (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2011). Its use may also be restricted elsewhere, e.g. in the UK and USA.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

Several reports indicated an effect of erythrosine on thyroid hypertrophy or adenoma in rats at high doses (Borzelleca et al., 1987). Another report indicated a promoting role of erythrosine in rats, with a tumorigenic effect on the thyroid seen only after partial thyroidectomy and treatment with *N*-bis(2-hydroxypropyl)nitrosamine (Hiasa et al., 1988).

Mechanistic evidence

The EFSA report concluded, on the basis of human studies, that only a small fraction of erythrosine is absorbed from the gastrointestinal tract (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2011). Positive comet assays were observed in mice (Sasaki et al., 2002). However, previous studies did not find evidence for genotoxicity in vivo, leading the EFSA panel to conclude that erythrosine is not genotoxic in vivo (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2011). A positive comet assay was also observed at high concentration, and micronuclei were observed at several concentrations in HepG2 cells (Chequer et al., 2012). The conclusion from the cytokinesis-block micronucleus cytome (CBMN-Cyt) assay favoured an aneugenic effect, but this was not clear from the in vivo data (Chequer et al., 2012). Ames tests were negative, and erythrosine was found to be antimutagenic in some assays (Lakdawalla and Netrawali, 1988). In another study, there was no clear evidence for genotoxicity in human lymphocytes, but there was evidence of erythrosine binding to calf thymus DNA in vitro (Mpountoukas et al., 2010).

Receptor-mediated effects (and endocrine-disrupting effects) were observed in human and experimental systems. Interventional human studies did not show an effect on T3 and T4 levels, but there was a slight increase of TSH levels, in particular after TSH-releasing hormone stimulation (summarized in European Commission, 2010). In experimental animals, erythrosine increased thyroid hormone and TSH concentrations (summarized in European Commission, 2010). One report suggested that this may be due to increased sensitivity of TSH secretion to TSH-releasing hormone, possibly related to iodine content and interference with thyroid hormone regulation, which could lead to a continued stimulation of the thyroid gland (Jennings et al., 1990).

Summary

No data on cancer in humans are available. Animal studies indicate that there are promoting tumorigenic effects on the thyroid, but the evidence is sparse. Mechanistic data on genotoxicity are inconclusive and cancer-promoting effects may be possible through receptor-mediated mechanisms. The Advisory Group therefore considered that an *IARC Monographs* evaluation of erythrosine is unwarranted at present.

Recommendation: No priority

157 Hair colouring products (personal use of)

Current IARC/WHO classification

Hair colouring products (personal use of) has previously been evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in Volume 99 in 2008 (IARC, 2010a).

Exposure characterization

In the mid- to late 1970s, manufacturers changed the components of permanent hair dye products to eliminate some of the carcinogenic chemicals previously evaluated by IARC. It has been estimated that 50–80% of women in the USA, Japan, and the EU have used hair dyes (IARC, 2010a), and of those, the majority use permanent oxidizing dyes, where frequently used intermediates are aromatic amines together with an oxidizing agent. Semi-permanent and temporary hair dyes include coloured compounds that stain hair directly. Thus, hair colouring products are a broad category of agents and may be mixtures of carcinogenic and non-carcinogenic agents. Skin contact is the primary route of human exposure, but inhalation might also be of importance. Information on exposure in epidemiological studies is based on questionnaire and interview data.

Cancer in humans

Since the last evaluation, several large-scale epidemiological studies in various countries have been conducted, including meta-analysis and prospective follow-up studies focusing on various cancer outcomes including breast cancer, NHL, leukaemia, ovarian cancer, BCC, and bladder cancer. Some of the larger and better studies suggest exposure–response associations. Taken together, the studies provide abundant new information about the association between personal hair dye use and cancer, even though the results overall are not consistent. As an example, for breast cancer a recent meta-analysis found a weak association between ever-use of hair dyes and breast cancer occurrence (pooled OR, 1.07; 95% CI, 1.01–1.13), with a similar estimate for permanent and semi-permanent hair dyes (Xu et al., 2021b). Another meta-analysis on hair dyes and breast cancer estimated an adjusted combined RR of 1.19 (95% CI, 1.03–1.37) (Gera et al., 2018). In the prospective US Nurses' Health Study, with 117 200 women followed up for 36 years having 47 000 incident cancers and over 4800 cancer-related deaths, the strongest association was between cumulative exposure to permanent hair dyes and risk of ER-negative, progesterone-receptor negative (ER^-/PR^-) breast cancer (HR, 1.28; 95% CI, 1.08–1.52) (Zhang et al., 2020b). In the Sister Study cohort, a prospective study of 45 000 White and Black women in the USA and Puerto Rico, an association was observed between history of any use of permanent (but not semi-permanent or temporary) hair dyes in adolescence (age 10–13 years) and breast cancer in Black women (HR, 1.77; 95% CI, 1.01–3.11) (White et al., 2021a). A previous analysis based on the same cohort found use of permanent hair dye 12 months before enrolment to be associated with 45% higher breast cancer risk in Black women and 7% higher risk in White women. In addition, nonprofessional application of semi-permanent dye to others was associated with breast cancer risk (HR, 1.28; 95% CI, 1.05–1.56) (Eberle et al., 2020). Another report from the Sister Study found ever-use of

permanent hair dye in the 12 months before enrolment to be associated with non-serous ovarian cancer (HR, 1.94; 95% CI, 1.12–3.37) but inversely associated with serous ovarian cancer (HR, 0.65; 95% CI, 0.43–0.99) (*P* for heterogeneity, 0.002) (White et al., 2021b). In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort of male Finnish smokers, men who used hair dyes experienced higher prostate cancer risk than men who did not (HR, 1.77; 95% CI, 1.03–3.05) (Lim et al., 2022). A meta-analysis revealed an OR of 1.14 (95% CI, 1.01–1.29) for use of hair dye and NHL (Qin et al., 2019). The highest OR (1.34; 95% CI, 1.04–1.92) was seen for persons who had used hair dye for > 20 years, but there was some indication of publication bias. The OR was clearly higher for women (1.38; 95% CI, 1.01–2.20) than for men (1.04; 95% CI, 0.95–1.43).

Another meta-analysis reported a slightly elevated risk of leukaemia with ever-use of hair dye (meta-RR, 1.09; 95% CI, 0.97–1.22), but a null association when restricted to the five studies that adjusted for smoking (meta-RR, 0.99; 95% CI, 0.76–1.29). In subgroup analyses, leukaemia was elevated in several strata; e.g. permanent hair-dye use (meta-RR, 1.19; 95% CI, 1.07–1.33), hair dye use pre-1980 (meta-RR, 1.49; 95% CI, 1.21–1.83]), and hair dye use for ≥ 15 years (meta-RR, 1.35; 95% CI, 1.13–1.62) (Towle et al., 2017).

Cancer in experimental animals

As previously reviewed by IARC (2010a), several commercially available hair dye formulations have been tested for carcinogenicity by skin application in mice or rats and by subcutaneous injection in a single study in rats. In mice, skin application with five different formulations significantly increased the incidence of lymphoma in females when compared with concurrent controls, yet not when compared with historical controls. In three studies in rats, a significant increase in the incidence of mammary adenomas in females was observed for skin painting of two formulations, and a significant increase in pituitary adenomas was seen in females for one formulation and in males for a different formulation. In the single study of subcutaneous injection in rats, increased incidence in mammary and uterine tumours was observed (IARC, 2010a). No experimental carcinogenicity studies of hair dye formulations have been identified since the previous IARC review.

Mechanistic evidence

Numerous studies investigating cytogenetic alterations or DNA damage in professional hairdressers and hair dye users are available. Previous reviews concluded that evidence of genotoxicity was not consistent (IARC, 2010a; Preston et al., 2010). In a recent systematic review, 13 studies evaluating genotoxic end-points in hairdressers were identified. In the seven out of 13 studies judged to be of moderate or strong quality, five reported positive associations, with effects including increased micronuclei and DNA strand breaks (Guedes Pinto et al., 2023).

Associations with contact dermatitis, asthma, and other allergic conditions in both hairdressers and consumers suggest the possibility of chronic inflammation after long-term use (Helaskoski et al., 2014; He et al., 2022c). A metabolomics study showed that serum levels of several compounds related to antioxidation/ROS pathways differed significantly between hair dye users and non-users (Lim et al., 2023b).

Another recent review briefly summarized toxicity and carcinogenicity information for common ingredients found in permanent hair dye formulations and epidemiological links between hair dye exposure and cancer risk (He et al., 2022c). While some ingredients previously used in hair dyes, such as 4-methoxy-*meta*-phenylenediamine which is a recognized mutagen and rodent carcinogen, for many other ingredients the evidence appears to be limited.

Summary

Hair colouring products are a diverse category of agents and may be mixtures of carcinogenic and non-carcinogenic agents, with changes over time. Since the last evaluation of personal use of hair dyes, several large-scale epidemiological studies have been conducted in various countries, including meta-analysis and prospective follow-up studies focusing on various cancer outcomes. Despite the limitations in the exposure assessment (self-reported data) and heterogeneity in the exposure itself (permanent versus semi-permanent, dark dyes versus light dyes), these new epidemiological findings could lead to a change in classification.

Data are available that indicate that hair dye formulations and certain hair dye ingredients are carcinogenic in experimental animals. There is some evidence that hair dyes exhibit certain KCs, in particular genotoxicity, oxidative stress, and chronic inflammation in exposed humans. Many of these studies were conducted among hairdressers (occupational exposure as a hairdresser or barber has been evaluated separately and is classified in Group 2A). The extent to which these mechanistic data could support an evaluation of personal use of hair dyes requires consideration by an *IARC Monographs* Working Group. Further exploration of commonly used hair dye formulations and ingredients, particularly those identified in epidemiological studies reporting positive cancer findings, could yield additional supporting evidence. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of hair colouring products (personal use of) to be warranted and considered it would be efficient for personal use of hair dyes to be evaluated in the same volume with hair straightening products (agent 158), because they involve many of the same studies.

Recommendation: High priority (and ready for evaluation within 2.5 years)

158 Hair straightening products

Current IARC/WHO classification

Hair straightening products have not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Hair straightening products are used by millions of persons worldwide. Permanent straightening of hair alters the disulphide bonds of keratin by a variety of chemicals including alkaline hydroxides (Miranda-Vilela et al., 2014). Chemical straightening can be also accomplished by ammonium or ethanolamine thioglycolate, sodium thioglycolate, methylene glycol, and other formaldehyde-releasing chemicals, or bisulphite creams. Some formulations contain formaldehyde (evaluated in Group 1 by IARC (2006a)) as an active ingredient, and recently also glutaraldehyde has been used. Skin contact and inhalation are the primary routes of exposure. NIOSH conducted a Health Hazard Evaluation to evaluate exposures to formaldehyde for hair-salon workers during hair straightening procedures and determined exposures to be above occupational exposure ceiling limits (NIOSH, 2011). The US Occupational Safety and Health Administration (OSHA) also issued a hazard alert for exposure to formaldehyde during hair straightening procedures, targeted to hair-salon workers (OSHA, 2011). Information on exposure in epidemiological studies is based on questionnaire and interview data. Use of hair straighteners is higher among Black women than in other ethnic groups (Edwards et al., 2023).

Cancer in humans

There are only a few case–control and cohort studies that have evaluated cancer in relation to use of hair straighteners. Studies have focused mainly on breast cancer, but there are also one or more cohort studies on uterine and ovarian cancer. In the prospective Black Women's Health Study cohort (including 44 798 US Black women with an intact uterus who were followed up from 1997 to 2019), significant positive

associations were observed between moderate or heavy use of hair straighteners and incidence of uterine cancer in postmenopausal women compared with never or light use (HR, 1.60; 95% CI, 1.01–2.53, and HR, 1.64; 95% CI, 1.01–2.64, respectively) and the HR for ≥ 20 years of use regardless of frequency was 1.71 (95% CI, 1.08– 2.72) (Bertrand et al., 2023). In a previous study of the same cohort, duration, frequency, age at first use, and number of scalp burns were not associated with overall breast cancer risk (Coogan et al., 2021). For heavy use of hair relaxers containing lye, the corresponding HR for ER+ breast cancer was 1.32 (95% CI, 0.97–1.80); there was no association for non-lye products.

In the prospective Sister Study cohort, which includes women in the USA and Puerto Rico, White et al. (2021a) found an exposure–response association between frequency of hair straightening products in adolescence and premenopausal breast cancer (HR, 2.11; 95% CI, 1.26–3.55 in the highest exposed group). In a separate report, frequent use (> 4 times/year) of straighteners/relaxers or pressing products in the past year was associated with an increased risk of ovarian cancer (HR, 2.19; 95% CI, 1.12–4.27) (White et al., 2021b). In an earlier study of the same cohort, personal hair straightener use in the 12 months before enrolment was associated with overall breast cancer risk (HR, 1.18; 95% CI, 0.99–1.41), with higher risk associated with increased frequency. Nonprofessional application of straighteners (HR, 1.27; 95% CI, 0.99–1.62) to others was associated with breast cancer risk (Eberle et al., 2020). Another analysis within the Sister Study found that women who had used any straightening product in the previous 12 months before enrolment had an HR of 1.80 (95% CI, 1.12–2.88) for developing uterine cancer compared with never-users, with a stronger association for frequent use (> 4 times in the past 12 months: HR, 2.55; 95% CI, 1.46–4.45; *P* for trend, 0.002) (Chang et al., 2022).

In Ghana, a case–control study with detailed information on personal use of hair straighteners among 1131 invasive breast cancer cases and 2106 population controls found an OR of 1.58 (95% CI, 1.15–2.18) for use of hair relaxers, with higher risks for former users (OR, 2.22; 95% CI, 1.56–3.16) than current users (OR, 1.39; 95% CI, 1.00–1.93) (Brinton et al., 2018).

Cancer in experimental animals

No studies of cancer in experimental animals exposed to hair straightening products were available to the Advisory Group. However, studies on some substances contained in hair straightening products are available.

Mechanistic evidence

There is evidence related to genotoxicity for hair straighteners. A hair straightening cream containing formaldehyde yielded concentration-dependent evidence of genotoxicity: it was positive for mutagenicity in the *S. typhimurium* TA100 microsome test and induced a DNA damage response using the SOS chromotest (Mazzei et al., 2010). Sodium thioglycolate was not mutagenic in *S. typhimurium* strains tested with or without liver S9 activation enzymes (NTP, 2016f). In genetic toxicity investigations, glutaraldehyde was mutagenic in *S. typhimurium* and mouse L5178Y lymphoma cells and induced chromosomal aberrations in mouse bone marrow cells in vivo after intraperitoneal injection (NTP, 1999). In a study of female hairstylists in Cairo, Egypt, women who had worked with hair straighteners containing formaldehyde ($n = 60$) had significantly higher levels of micronuclei in both buccal cells and peripheral blood lymphocytes compared with a control group of hairstylists who did not handle hair straighteners ($n = 60$) (Aglan and Mansour, 2020). In this study, where measured formaldehyde concentrations during hair straightening procedures exceeded regulatory limits, the difference in micronucleus frequency was greater for women who had worked with hair straighteners for > 5 years ($n = 29$) than for those with < 5 years of exposure ($n = 31$). A study of 50 beauty salon workers in Brazil demonstrated elevated levels of urinary formic acid (a metabolite of formaldehyde) and genetic damage in peripheral blood lymphocytes, as measured by the comet assay, in post- versus pre-exposure samples (Peteffi et al., 2016). Another study in Brazil also observed elevated

genetic damage by comet assay among hairdressers (n = 69) versus blood donors (n = 55), although no data regarding use of hair straighteners were reported (Galiotte et al., 2008). A case report from Israel described three cases of female teenagers with acute kidney injury arising soon after hair straightening procedures (Kaidar et al., 2021).

There is evidence related to induction of epigenetic alterations. A study of 49 beauty salon workers in Brazil observed a positive correlation between formaldehyde exposure, measured using personal passive samplers, and global DNA methylation. The correlation was stronger for the subset of workers who worked with hair straightening creams (Barbosa et al., 2019).

There is also mechanistic evidence related to modulation of receptor-mediated effects. In a study of 11 274 participants in a North American preconception cohort study, fecundability was lower among women reporting use of hair straighteners, with the strongest effect observed among those with 10 or more years of use, although there was not a clear monotonic relationship for many of the measures (Wise et al., 2023). Among 585 postmenopausal Ghanaian women, weak positive associations were seen between ever-use of hair relaxers and serum concentrations of estriol and 16-epiestriol. In additional analyses, these results were stronger for lye- versus non-lye-based formulations, although no differences between former and current hair straightener use was observed. Positive associations were also observed between an increasing number of scalp burns from hair relaxer use and circulating unconjugated estrogens (Geczik et al., 2023).

Summary

There are rather few epidemiological studies of cancer in humans associated with personal use of hair straighteners, including from two well-conducted cohort studies that showed consistent positive findings for uterine cancer. No studies of cancer in experimental animals were available. There is convincing evidence that formaldehyde-containing hair straightening products exhibit KCs (genotoxicity, epigenetic alterations) in exposed humans. For non-formaldehyde hair straightening agents, there are few studies, and the overall mechanistic evidence is sparse. The Advisory Group therefore considered an *IARC Monographs* evaluation of hair straightening products to be warranted and recommended evaluating this agent in the same volume as hair dyes (agent 157).

Recommendation: High priority (and ready for evaluation within 2.5 years)

159 Tattoos and permanent make-up

Current IARC/WHO classification

Tattoos and permanent make-up have not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Tattooing is an ancient body art during which tattoo ink, consisting of solid colour pigments diluted in a carrier liquid, is injected into the upper layers of the dermis with the aim of lifelong visibility. The prevalence of tattoos is increasing. In an international survey, the current prevalence has been estimated to range from 12% in the Russian Federation up to 32% in the USA (Kluger et al. 2019).

Tattoo inks are chemical mixtures of organic (e.g. PAH, carbon black) and inorganic pigments (e.g. various metals, titanium oxide) and/or azo dyes diluted in a carrier liquid that may consist of water, alcohol, preservatives, and softeners. Agents classified in Groups 1, 2A, and 2B by the *IARC Monographs* are repeatedly found in tattoo inks. Human exposure assessment in epidemiological studies is based on questionnaires. Recently an effort was made to create and validate a questionnaire-based "epidemiological tattoo assessment tool" for use in future epidemiological studies (Foerster et al., 2023).

Cancer in humans

Multiple case studies describe malignant melanoma on tattoos (Ricci et al., 2022). However, only a few epidemiological studies have been published. A population-based case–control analysis by Warner et al. (2020) included 1518 participants from the NHL study (737 cases) and 742 participants from the multiple myeloma study (373 cases). The authors did not find any clear associations between tattoos and NHL (OR, 1.04) or multiple myeloma (OR, 1.08). In a US nested case–control study with participants identified from a state-wide surveillance system, 156 cases with early onset BCC and 213 controls reported tattoos. Among those with tattoos, the OR of BCC at the tattoo site compared with another site was 1.8 (Barton et al., 2020). More large-scale epidemiological studies are in progress in the USA, Sweden, France, and Germany (IARC, 2024c; Nielsen et al., 2023).

Cancer in experimental animals

A study of immunocompetent mice evaluated the effects of tattooing with a black ink containing BaP and a regimen of exposure to UVR (Lerche et al., 2015). The groups of tattooed and non-tattooed mice receiving no UVR developed no skin tumours after 1 year. In the tattooed and UVR-exposed group, the development of skin SCCs was significantly delayed compared with the irradiated non-tattooed mice, suggesting a potential protective effect. The same investigators conducted a subsequent study using a similar design to evaluate red-ink tattoos, using an ink containing the suspected carcinogen 2-anisidine (Lerche et al., 2017). As before, tattooed mice receiving no UVR did not develop any skin tumours. The time to onset of an animal's first and second SCC did not differ between the tattooed and non-tattooed control groups exposed to UVR. However, the onset of the third SCC and the growth rates of the second and third tumours were slightly faster among the tattooed mice versus controls. In a third study to evaluate the effects of red and black tattoos and UVR on the incidence of internal organ cancers (Sepehri et al., 2017), no internal cancers were detected in any of the animals across all groups (including controls) after 1 year.

Mechanistic evidence

The cytotoxicity of tattoo inks of various colours was assessed using a panel of bacterial and mammalian cell-based bioassays for cytotoxicity, oxidative stress, genotoxicity, and the p53 response (Neale et al., 2015): the studied tattoo inks induced effects in all assays, with stronger effects observed for red and yellow inks. Overproduction of ROS from exposure to tattoo inks was also shown in a study of immortalized human keratinocyte (HaCat) cells and in a cell-free experimental system (Høgsberg et al., 2013; Arl et al., 2019).

To assess cytotoxicity and sensitization potential, 16 different tattoo inks were injected into a three-dimensional model of human skin (reconstructed epidermis on a fibroblast-populated collagen hydrogel). Four inks induced evidence of cytotoxicity and exhibited skin sensitization potential, suggesting a potential to trigger allergic contact dermatitis in tattooed individuals (Karregat et al., 2021). In another study of HaCaT cells, treatment with tattoo inks induced elevated expression of Il-18 (Sozer Karadagli et al., 2024). Several other studies have reported elevated frequencies of chronic inflammatory reactions, sometimes systemic, arising as complications of tattoos (Vagefi et al., 2006; Ruocco et al., 2015; van der Bent et al., 2021).

Investigations of chemicals found in tattoos have identified effects relevant to cancer. In studies of chemical exposures combined with UVR exposure in HaCaT cells, benzo[*ghi*]perylene (Group 3, IARC, 2010b), when photoactivated by UVR-A reduced cell viability and increased apoptotic cell death (Negi et al., 2023); while carbazole (Group 2B, IARC, 2013b), if photoactivated by UVR-B produced elevated levels of ROS and genetic damage as measured by the comet assay (Srivastav et al., 2020). 3,3′-Dichlorobenzidine (Group 2B, IARC, 1987a), which is used in tattoo inks, also caused dose-dependent DNA fragmentation and cell death in human Jurkat T-cells under UVR-A irradiation and was photomutagenic for *S. typhimurium* TA102 cells (Wang et al., 2005).

Summary

Tattoo inks and permanent make-up are a heterogeneous mixture of agents, including some agents classified by IARC in Group 2B or higher. Overall, there is very limited available epidemiological evidence, but more large-scale epidemiological studies are in progress. Experimental evidence suggesting carcinogenicity from tattooing has been reported. There is some mechanistic evidence that tattoos and permanent make-up, or specific chemical constituents, exhibit KCs (e.g. genotoxicity, induction of oxidative stress and chronic inflammation). The Advisory Group therefore considered an *IARC Monographs* evaluation of tattoos and permanent make-up to be warranted.

Recommendation: Medium priority

160 Bisphenol A (CAS No. 80-05-7)

Current IARC/WHO classification

Bisphenol A (BPA) has not previously been evaluated by the *IARC Monographs* programme. Bisphenol A was given a priority rating of *high* by the 2019 Advisory Group on Priorities (IARC, 2019a). A report from the JECFA describes the toxicological and health aspects of bisphenol A (WHO, 2011)

Exposure characterization

BPA is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (OEHHA, 2022a). BPA is a synthetic organic compound, and its major uses are in the production of polycarbonate plastics and epoxy resins, as well as phenolic resins and polyester. Humans are exposed to BPA predominantly through contaminated food (e.g. via food packaging) and drinking-water. Levels of BPA are higher in occupational cohorts than in the general population, according mainly to studies in China (Ribeiro et al., 2017; Bousoumah et al., 2021). The level of BPA in the body varies over time due to its short biological half-life. Long-term exposure to BPA has been estimated through questionnaires combined with literature on BPA levels or by a job–exposure matrix in a few studies.

Cancer in humans

Since 2018, more than 20 epidemiological studies have been conducted, mostly case–control studies but also at least three cohort studies. Most studies failed to support an association between BPA and various cancer outcomes. A prospective analysis from the NHANES cohort, with urinary BPA measured between 2003 and 2008 and follow-up until 2015, found a positive dose–response association for all-cause mortality, but not for cancer mortality (Bao et al., 2020a). The majority of the epidemiological studies on the carcinogenicity of BPA investigated breast cancer. Meta-analyses from 2021 and 2023, respectively, including nine case–control studies did not support an association between BPA and breast cancer (Liu et al., 2021b; Fauconnier et al., 2023). Two prospective analyses did not support an association between BPA and breast cancer (Parada et al., 2019; Salamanca-Fernández et al., 2021).

There are a few studies on prostate cancer. One prospective analysis of BPA and prostate cancer within the Spanish EPIC cohort found an HR of 1.40 for tertile 1, HR 1.37 for tertile 2 and HR 1.31 for tertile 3 compared with persons with BPA levels below the limit of detection (Salamanca-Fernández et al., 2021). A Chinese case–control study of prostate cancer, which included a cumulative BPA index, reported a positive dose–response association with BPA (Tse et al., 2017). One or two studies are available on other cancer sites.

Most studies estimated BPA exposure from a single biological sample collected at a single point in time.

Cancer in experimental animals

There is convincing evidence for tumorigenic effects in certain tissues (mammary and prostate) in Sprague-Dawley rats (reviewed in Heindel et al., 2020 and Prins et al., 2019). Concerning the mammary gland, a statistically significant effect of BPA administered non-stop was seen on the incidence of adenoma or adenocarcinoma in rats in the regulatory core GLP study (Camacho et al., 2019). In collaboration with academic and federal government scientists, organized by the NTP, NIEHS, and the FDA's National Center for Toxicological Research (NCTR), exploratory and confirmatory analyses were conducted to enhance data interpretation, particularly regarding dose–response effects in a biological context. The study used Sprague-Dawley rats, with five BPA doses, a vehicle control, and two doses of ethinyl estradiol (EE2) as a positive control. Administration was by oral gavage starting on day 6 of gestation, followed by direct dosing of the pups after birth. Two studies were conducted: a subchronic and a chronic study. In the chronic study, two exposure regimens were used: one ending at postnatal day (PND) 21 (stop-dose), and the other continuing until tissue collection (continuous). Three hypotheses were considered: (i) BPA effects were qualitatively similar to the effects of EE2 at 0.5 μg/kg bw per day (0.5EE2); (ii) BPA impacted different features and/or had opposite effects to 0.5 EE2; and (iii) BPA had no effect on mammary gland development. Semiquantitative analysis of the subchronic study showed no significant differences at PND21, while at PND90 significant differences in the incidence of adenocarcinoma of the mammary gland were seen between the control and the lowest BPA dose in animals in estrus. In contrast, quantitative analysis of chronic PND21 samples revealed non-monotonic BPA effects, with a breakpoint between 25 and 250 μg/kg per day, confirmed by global analysis at PND90 and 6 months. (Montévil et al., 2020). Other studies showed that BPA increased the propensity to develop mammary lesions in mice and rats (Durando et al., 2007; Murray et al., 2007a; Jenkins et al., 2011; Lamartiniere et al., 2011).

Concerning the prostate, the core study showed that BPA alone did not drive prostate tumorigenesis (Camacho et al., 2019). However, the academic study, while agreeing with these results, found that BPA at the low doses increased susceptibility to develop prostate cancer in rats co-treated with ethinyl estradiol, but BPA alone at any dose did not drive carcinogenesis (Prins et al., 2018). Other general effects found in the core study lacked consistency.

Mechanistic evidence

A detailed analysis of the association of BPA with the 10 KCs was recently conducted by the Carcinogen Identification Committee (CIC) of the state of California (Ricker et al., 2024). The evidence for electrophilicity comes from the considerable knowledge on the metabolism of BPA which leads to formation of electrophilic compounds (OEHHA, 2022a) in vitro and in vivo (reviewed in Ricker et al., 2024). This evidence is supported by the formation of ROS and electrophilic metabolites that induce oxidative DNA damage in exposed human (8-OHdG) and animal models (reviewed in Ricker et al., 2024). In general, BPA is not considered as a genotoxic agent. However, the CIC identified several studies showing genotoxicity in human cells (both primary cells and cell lines), but not in bacteria and yeast. Despite some evidence, genotoxicity in vivo remains inconclusive (summarized in Ricker et al., 2024). In addition, a few studies show that BPA alters DNA repair or causes genomic instability (Ricker et al., 2024). The CIC review described consistent evidence for epigenetic effects in several systems but found the interpretation of such effects to be difficult. Additional studies are discussed here. Concerning prostate cancer and epigenetics in rats, a study showed that developmental exposure to BPA led to methylation profiles that correlated with increased risk of prostate cancer (Cheong et al., 2016). A recent review summarized the epigenetic effects of BPA in human and rodents and highlighted their links to the male reproductive system (Cariati et al., 2020). There is evidence suggesting that BPA induces oxidative stress, which is linked to the induction of oxidative DNA damage (measured as 8-OHdG) in exposed humans and experimental systems and the

formation of reactive oxygen and nitrogen species in experimental systems (Steffensen et al., 2020; Ricker et al., 2024).

There are data suggesting chronic inflammation in animals (Ricker et al., 2024), but the data regarding exposed humans should be carefully analysed. Some studies have shown a decrease in immune function, but the data are sparse and insufficient (Ricker et al., 2024). This is an important point, since EFSA used the increase in TH17 in spleen as a biological test for the revision of the tolerable daily intake of BPA (EFSA Panel on Food Contact Materials, Enzymes and Processing Aids et al., 2023). The literature concerning the effects of BPA on a variety of receptors is considerable, addressing receptors that are relevant for cancer such as the estrogen receptor, the androgen receptor and the aryl hydrocarbon receptor. These studies were summarized by Ricker et al. (2024), who considered the data on estrogen-related receptors highly supportive of KC8.

Finally, the evidence for increased cell proliferation was found to be moderate to strong (Ricker et al., 2024). Several significant studies have described the effects of BPA on cell morphology, particularly in estrogen-sensitive organs. Concerning breast cancer and morphological effects, a study in non-human primates indicated that prenatal treatment of monkeys induced morphological changes in the breast (Tharp et al., 2012).

Summary

Since 2018, more than 20 epidemiological studies have been conducted, and quite consistently no associations have been found for BPA and breast cancer, whereas some studies on BPA and prostate cancer (with relatively weak exposure assessment quality) have suggested an association. There are presumed to be challenges in assessing long-term BPA exposure in cancer epidemiology studies due to its short biological half-lives. There was an increase in the incidence of malignant tumours in both sexes of one species (rat) in a well-conducted GLP study. There is mechanistic evidence indicating that BPA exhibits several KCs in experimental systems and exposed humans. In particular, there are clear receptor-mediated and epigenetic effects. These could account for an implication in tumorigenesis, particularly in hormone-sensitive tissues. The Advisory Group therefore considered an *IARC Monographs* evaluation of bisphenol A to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

161 Bisphenol S and bisphenol F (CAS Nos 80-09-1 and 620-92-8)

Current IARC/WHO classification

Bisphenol S and bisphenol F have not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Bisphenol S (BPS) is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). Bisphenol F (BPF) is not listed in the latest US EPA high production volume chemical list. Both BPS and BPF have been used for more than a decade (Rosenmai et al., 2014), partly as a replacement for BPA in the production of polycarbonate plastics, epoxy resins and thermal papers. Humans are exposed to BPS and BPF predominantly through contaminated food (e.g. via food packaging) and drinking-water. Few occupational exposure data are available, mainly among cashiers (BPS) and incinerator workers (BPF) (Bousoumah et al., 2021). BPF and BPS are found abundantly in urine in population-based studies among children and adults, but in general in lower concentrations compared with BPA (Stillwater et al., 2020; Catenza et al., 2021). The level of BPA in the body varies over time due to its short biological half-life.

Cancer in humans

A few epidemiological case–control studies on BPS and BPF are available (breast cancer, lung cancer, thyroid cancer). In all studies, BPA and BPF were assessed from a single biological sample collected at diagnosis. In a case–control study in China, a dose-dependent positive association was seen between urinary levels of BPS and thyroid cancer (OR per natural log-unit change of 2.40), whereas inverse associations were seen for BPA and BPF (Zhang et al., 2023e). Another case–control study in China found urinary BPS to be associated with lung cancer (OR, 1.23; high versus low exposure). The same tendency was seen for BPF (Qu et al., 2022). No association was seen between serum BPS and breast cancer in a case–control study in Mexico (Segovia-Mendoza et al., 2022)

Cancer in experimental animals

There are few studies on the carcinogenicity of BPF and BPS in experimental animals, and no long-term studies. A 28-day study on BPS by Yue et al. (2023b) in mice focused on uterus and ovary. Histological alterations were observed in the uterus. Gene expression analysis showed correlation with cancer pathways. An NTP systematic analysis of available studies in 2017 identified few animal studies (including subchronic studies) with primary focus on uterotrophic and mechanistic effects. No study provided evidence for carcinogenicity (NTP, 2017).

Mechanistic evidence

Several studies have concluded that BPS and BPF has overall similar estrogenic effects to BPA. They displayed anti-estrogenic, androgenic, and anti-androgenic effects. BPS also showed estrogenic membrane-mediated pathways (Rosenmai et al., 2014; Rochester and Bolden, 2015; NTP, 2017). There is evidence from human studies that urinary BPS and BPF may alter free testosterone levels, albeit in different directions (NHANES study, Zhang et al., 2022d). In another study, both urinary BPS and BPF concentrations negatively correlated with serum estrogen E2 levels and the E2/testosterone (total testosterone) ratio in men (Zeng et al., 2022). Regarding effects on the thyroid, there is evidence that BPF leads to increased thyroid weight and T4 in plasma (T3 decreased) in rodents (NTP, 2017). In a cohort study of pregnant women, BPS levels correlated with a decrease in T3 in the first semester, while BPF levels correlated with an increase in free T4 in the second semester (Huang et al., 2022c). In children, urinary BPF was associated with a higher free T4 level in girls only, but BPS did not show any correlation (Jang et al., 2021). Different genotoxicity activities have been reported (NTP, 2017). In human PBMCs, genotoxic effects were found for both BPF and BPS, as assessed by either micronucleus assay or comet assay (Mokra et al., 2017; Ruberto et al., 2022). Genotoxicity of BPF has been observed in HepG2 cells (Hercog et al., 2019; Audebert et al., 2011) and of BPS in human epithelial bronchial cells (George and Rupasinghe, 2018), using γH2AX assay. In RWPE-1 cells, both BPS and BPF were genotoxic (BPS more than BPF) in a comet assay (Kose et al., 2020). In a systematic review of studies in humans, associations of BPS and BPF with biomarkers of oxidative stress were inconsistent (Steffensen et al., 2020). Ferguson et al. (2019) and Wang et al. (2019b) described consistent associations between BPS and BPF with some markers of oxidative stress. In PBMCs in vitro, BPF and BPS induced oxidative DNA damage, BPS being the least efficient (Mokra et al., 2018). In vivo, BPF increased oxidative stress in rat liver (Linillos-Pradillo et al., 2023a) and both BPS and BPF increased ROS in rat ovaries (Ijaz et al., 2020). In conclusion, BPS and BPF can induce oxidative stress, but the evidence is weak to moderate.

Several studies of exposed humans showed associations between bisphenols and epigenomic markers such as methylation, but the biological significance is unclear (Lu et al., 2020c; Navarro-Lafuente et al., 2022). Studies with human cells also found effects on expression of microRNAs and DNA methylation (Verbanck et al., 2017; Huang et al., 2019).

In women with unexplained recurrent spontaneous abortion, the effect of BPS on inflammatory markers was not clear (Liang et al., 2020). Another study in exposed humans showed an association of urinary BPF with neutrophil to lymphocyte ratio (Zhou et al., 2023b). A study on human cells in vitro indicated an effect of BPF on intestinal inflammation (Liu et al., 2022f). In a study using human macrophages, BPS had little effect compared with BPA (Chen et al., 2018). In vivo, BPS increased intestinal inflammation, and the effect was transgenerational in mice (Brulport et al., 2021), while BPF increased liver inflammation in rats (Linillos-Pradillo et al., 2023b). Evidence for general inflammatory response is somewhat contradictory but it is possible that tissue-specific effects are present.

Summary

Only few sporadic and positive findings on associations in humans between BPS and BPF exposure and cancer risk for different sites are available. Assessment of long-term BPS and BPF exposure in cancer epidemiology studies is difficult due to their short biological half-lives. There are no long-term carcinogenesis studies on bisphenols S and F, but long-term studies have been identified for bisphenol A. BPS and BPF exhibit several KCs, including receptor-mediated and epigenetic effects, in exposed humans and/or experimental systems. This evidence can support a classification of carcinogenicity of BPS and BPF. The Advisory Group therefore considered an *IARC Monographs* evaluation of bisphenol S and bisphenol F to be warranted and suggested that they be evaluated in the same volume as BPA (agent 160).

Recommendation: High priority (and ready for evaluation within 2.5 years)

162 Chlorinated paraffins

Current IARC/WHO classification

Chlorinated paraffins have not previously been evaluated by the *IARC Monographs* programme. Chlorinated paraffins were given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of cancer in experimental animals and mechanistic evidence.

Exposure characterization

Chlorinated paraffins are listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a).

Current use of chlorinated paraffins (short-chain (C10–13), medium-chain (C14–17), and long-chain (C18–28)) in the USA is 150 million pounds per year (100 million pounds (short- and medium-chain chlorinated paraffins) US EPA (2009b). In the EU, less than 1000 tonnes of short-chain chlorinated paraffins were used in 2007, mainly for rubber, sealants and adhesives (ECHA, 2008). The term "chlorinated alkanes" is also used (Government of Canada, 2024), but might be ambiguous, because some solvents that are not chlorinated paraffins have been described as chlorinated alkanes in some studies (e.g. tetrachloroethane). Short-chain chlorinated paraffins are widely used as a component of lubricants and coolants in metal-cutting and metal-forming operations. Their use as secondary plasticizers and flame retardants in plastics, especially polyvinyl chloride (PVC), is frequent, including domestically, as well as in rubber formulations, paints and other coatings, and adhesives and sealants. Medium- and long-chain chlorinated paraffins are used as alternatives for short-chain chlorinated paraffins (US EPA, 2009b). Chlorinated paraffin C23 (a long-chain chlorinated paraffin) is an extreme-pressure lubricant and flame retardant (NTP, 1986b).

Short-chain chlorinated paraffins are found worldwide in the environment, wildlife, and humans (US EPA, 2009b). They are bioaccumulative in wildlife and humans, are persistent and are transported globally in the environment, and are toxic to aquatic organisms at low concentrations (IARC, 1990b).

Medium- and long-chain chlorinated paraffins are also regarded as bioaccumulative and persistent (US EPA, 2009b).

Cancer in humans

In a study based on registry data focusing on hepatobiliary cancer (involving the liver and biliary tract) within a cohort of workers at three automobile manufacturing plants in Michigan who were potentially exposed to metalworking fluids, there were indications of elevated risk of biliary tract cancer from exposure to chlorinated paraffins (OR, 3.9; 95% CI, 0.9–17), which was studied as an additive in metalworking fluids used in extreme-pressure operations with straight oils. No other studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

A 2-year bioassay in rats and mice was conducted by the NTP (NTP, 1986b). Neoplastic lesions associated with chlorinated paraffins (C12, 60% chlorine) administration were found in the liver of rats and mice of both sexes. Dosed male rats showed increased incidence of tubular cell adenomas and two low-dose males had tubular cell adenocarcinomas. The incidence of mononuclear cell leukaemia was increased in dosed male rats and in low-dose female rats. Pancreatic acinar cell tumours occurred at increased incidence in low-dose male rats. Follicular cell adenomas or carcinomas (combined) of the thyroid gland were found at increased incidence in both female rats and female mice.

In addition, in two recent scoping reviews, liver tumours and phaeochromocytoma of the adrenal medulla were also highlighted (Chen et al., 2023b; Huang et al., 2023c).

Mechanistic evidence

The NTP report stated that chlorinated paraffins (C12, 60% chlorine) were not mutagenic in *S. typhimurium* TA97, TA98, TA100, or TA1535 in the presence or absence of liver S9 (NTP, 1986b). There is indirect evidence for a genotoxic pathway through transcriptomic analysis in zebrafish embryos (Peng et al., 2020). There is evidence of oxidative stress from studies in vitro (reviewed by Chen et al., 2023b). Immunomodulation effects in mice include increased splenic T lymphocytes and modulations of TH17 and other inflammatory pathways. It is unclear, however, whether this leads to chronic inflammation (Wang et al., 2019c; Chen et al., 2023b).

Regarding receptor-mediated effects, there is a possible interaction between ERα and short-chain chlorinated paraffins (Zainab et al., 2021; Chen et al., 2023b). Changes in the levels of thyroid hormones, such as T3 and T4, were observed in animal studies (Chen et al., 2023b). Activation of PPARα was also observed in rodents (Klaunig et al., 2003). Short-chain chlorinated paraffins increased kidney toxicity in male rats (Warnasuriya et al., 2010).

Summary

One well-conducted study has assessed associations between exposure to chlorinated paraffins and cancer risk in humans. An increased risk of biliary tract cancer was reported in both sexes of one species (rat). Thus, there are clear carcinogenic effects in experimental animals. Mechanistic data are available, including receptor-mediated effects and immunomodulation in rodents. The Advisory Group therefore considered an *IARC Monographs* evaluation of chlorinated paraffins to be warranted

Recommendation: High priority (and ready for evaluation within 2.5 years)

163 Pentabromodiphenyl ethers (CAS No. 32534-81-9)

Current IARC/WHO classification

Pentabromodiphenyl ethers (PBDEs) have not previously been evaluated by the *IARC Monographs* programme. PBDEs were given a priority rating of *high* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of animal cancer and mechanistic evidence. The IPCS has published an evaluation of health effects of brominated diphenyl ethers, including PBDE (INCHEM, 1994)

Exposure characterization

PBDEs have often been used as flame retardants in furniture materials. The use of PBDEs has been discontinued in the EU and in the USA, but they have been found in the environment, in humans, and in various food products. Potential routes of exposure include inhalation, ingestion, and dermal exposure through soil/water waste, air pollution, and indoor air and dust (Renzelli et al., 2023). PBDEs have been widely detected in human samples, but levels are generally declining as they have been phased out of use and production (Wu et al., 2020b). Occupational exposures have been noted in several industries including in long-term use of foam mats (e.g. gymnastics workers), in electronic scrap recycling, and in carpet installers (Estill et al., 2020; Zhang et al., 2019c). DE-71 is a technical PBDE mixture containing 52% PBDEs and 43% tetra- and hexabromodiphenyl ethers. At least one of the compounds in this mixture, 1,2,4-tribromo-5-(2,4-dibromophenoxy)benzene, is listed as a high production volume chemical by the US EPA (US EPA, 2024a).

Cancer in humans

No epidemiological studies of cancer in relation to PBDEs were available to the Advisory Group. Studies have recently been conducted of exposures to polybrominated diphenyl ethers more generally. For example, a recent case–control study in China found significant positive associations, including positive trends, between cancer of the breast and various brominated diphenyl ether congeners in adipose tissue (He et al., 2018b). In small case–control studies, no association was observed between polybrominated diphenyl ethers and cancers of the prostate (Pi et al., 2016), thyroid (Aschebrook-Kilfoy et al., 2015; Deziel et al., 2019), or breast (Hurley et al., 2019; Mancini et al., 2020a). Zhang et al. (2021d) found a statistically significant positive correlation of serum concentrations of BDE-047 and BDE-099 in a case–control study of thyroid cancer in China. Other pentabromodiphenyl ethers (BDE-100, -153, -154) were not associated with development of thyroid cancer in this study (Zhang et al., 2021d).

Cancer in experimental animals

In chronic toxicity and carcinogenicity studies performed by the US NTP, oral administration of DE-71 increased the incidence of various liver tumour types in male and female rats and mice. Increased incidence of thyroid gland follicular cell adenoma or carcinoma and increased incidence of pituitary gland (pars distalis) adenoma were also observed in male rats, and increased incidence of stromal polyp or stromal sarcoma (combined) of the uterus in female rats was observed (NTP, 2016b; Dunnick et al., 2018).

Mechanistic evidence

DE-71 gave negative results in bacterial mutagenicity assays and a micronucleus test in vivo in mice (NTP, 2016a), consistent with other studies reporting a lack of genotoxicity for PBDEs. Many studies relevant to KCs are available (Azizi et al., 2023), showing that PBDEs can induce oxidative stress (Montalbano et al., 2020) and DNA damage (Pereira et al., 2016), increase cell proliferation and have receptor-mediated effects in human cells (Kanaya et al., 2019). Higher maternal exposure to PBDE-47 (a tetrabromodiphenyl ether present in DE-71) was associated with decreased TNFα methylation in cord blood of exposed humans (Dao et al., 2015). Ding et al. (2021) evaluated DNA methylation changes associated

with PBDEs (BDE-47, -100, -153) in a case–control study of women with breast cancer (versus controls) and found a statistically significant relation between changes in DNA methylation and serum PBDE levels, suggesting a mechanism for increased breast cancer risk. Relevant studies with structurally related polybrominated diphenyl ether mixtures and/or individual components (e.g. tetra-, hexa- and decabromodiphenyl ethers) may also contribute to the body of mechanistic evidence.

Summary

Though the use of PBDEs has been discontinued in the EU and the USA, these compounds have been found to be persistent pollutants in the environment, in humans, and in various food products. There is mixed evidence of cancer development in humans with exposures to specific polybromodiphenyl ethers or mixtures of congeners. Data are available indicating that PBDEs are carcinogenic in experimental animals. There is abundant evidence that PBDEs exhibit many of the KCs in experimental animals and human cell lines, and epigenetic effects have been observed in exposed humans. The Advisory Group therefore considered an *IARC Monographs* evaluation of pentabromodiphenyl ethers to be warranted and recommended considering additional polybrominated diphenyl ethers in the future evaluation.

Recommendation: High priority (and ready for evaluation within 2.5 years)

164 2,3,3,3-Tetrafluoro-2-(heptafluoropropoxy)propanoic acid (HFPO-DA) (CAS No. 13252-13-6)

Current IARC/WHO classification

2,3,3,3-Tetrafluoro-2-(heptafluoropropoxy)propanoic acid, commonly known as hexafluoropropylene oxide dimer acid (HFPO-DA or GenX), has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

HFPO-DA is used mainly as a replacement for perfluorooctanoic acid (PFOA) in industrial processes, as well as in consumer products. HFPO-DA is used to manufacture fluoropolymers. Since it is a substitute for PFOA, products such as some nonstick coatings and aqueous film-forming foam (AFFF) that were previously made using PFOA may now rely on HFPO-DA (US EPA, 2022).

Published data on environmental occurrence of HFPO-DA showed higher concentrations in surface water, groundwater, soil, and vegetation samples taken close to highly polluted areas (emissions and waste incineration). Published data on HFPO-DA concentrations in food (fruit and vegetables, fish, dairy products, drinking-water) are inconsistent (Gebbink and van Leeuwen, 2020).

Cancer in humans

No studies on cancer in humans were available to the Advisory Group.

Cancer in experimental animals

A two-year carcinogenicity study of HFPO-DA in Sprague-Dawley rats identified associations with hepatocellular adenomas and carcinomas in females and elevated counts of pancreatic acinar adenomas and carcinomas in males, as well as a non-significant increase in Leydig cell tumours (Caverly Rae et al., 2015).

Mechanistic evidence

The tumour findings observed in the rodent carcinogenicity study are characteristic of PPARα agonists. The relevance of these findings to humans is unclear given species differences in PPARα activation. HFPO-DA showed genotoxicity in a study of rat thyroid cells by comet assay and micronucleus assay (Coperchini

et al., 2020), while results with other cell types and species were mainly negative (US EPA, 2022). HFPO-DA induced oxidative stress in zebrafish embryos and HepG2 cells (Yoo et al., 2021; Ivantsova et al., 2023) and is a potent activator of PPARα signalling (Evans et al., 2022; US EPA, 2022), although not estrogenic (Conley et al., 2019; Evans et al., 2022; Villeneuve et al., 2023). Most animal experimental studies have shown strong evidence of HFPO-DA-induced liver toxicity (e.g. hepatocellular hypertrophy and liver necrosis); additional findings include haematological effects (e.g. decreases in erythrocytes and haemoglobin), kidney toxicity (e.g. increased kidney weight and blood urea nitrogen), thyroid effects (e.g. lower T3 and T4 levels), gut toxicity (colonic inflammation and changes in microbiota), reproductive/developmental effects (lower gestational weight gain and pup weight, neonatal mortality), and immunotoxicity (e.g. suppression of T-dependent antibody response; decreased globulin levels and spleen weight) (ECHA, 2019a; Xie et al., 2021; US EPA, 2022).

Fewer studies have investigated HFPO-DA effects in human cells. HFPO-DA induced dose-dependent reductions in thyroid cell viability and proliferation rate, and alterations in gene expression in both a rat thyroid cell line and primary normal human thyroid cells (Zhang et al., 2021c). A study of human bone marrow mesenchymal stem cells found HFPO-DA exposure to disturb transcriptomic profiles, enhance cell proliferation, and repress stem multipotency (Pan et al., 2022). Exposure of primary human hepatocytes to HFPO-DA has been reported to increase expression of genes involved in proliferation, inflammation, and fibrosis, as well as lipid transport, metabolism, and synthesis (Marques et al., 2022; Robarts et al., 2022). HFPO-DA induced suppression of the neutrophil respiratory burst (a component of the innate immune response) in larval zebrafish, a human neutrophil-like cell line and primary human neutrophils (Phelps et al., 2023).

Summary

No published information about cancer risk and HFPO-DA in humans is available. The only experimental carcinogenicity study of HFPO-DA conducted to date identified statistically significant exposure-related increases in hepatocellular and pancreatic tumours among rats of both sexes. There is mechanistic evidence demonstrating KCs such as oxidative stress, immunosuppression, and modulation of receptor-mediated effects (e.g. PPARα). The Advisory Group therefore considered an *IARC Monographs* evaluation of HFPO-DA to be warranted and recommended that it be evaluated in the same volume as perfluorohexanesulfonic acid (agent 165).

Recommendation: High priority (and ready for evaluation within 2.5 years)

165 Perfluorohexanesulfonic acid (PFHxS) (CAS No. 355-6-4)

Current IARC/WHO classification

Perfluorohexanesulfonic acid (PFHxS) has not previously been evaluated by the *IARC Monographs* programme. PFHxS is scheduled for evaluation by the JECFA in 2027 or 2028.

Exposure characterization

PFHxS is used as a surfactant in a variety of industrial and consumer products such as food packaging, stain- and water-resistant materials, firefighting foams, and paint additives (Minnesota Pollution Control Agency, 2023; US EPA, 2024e). Exposure of the general population to PFHxS occurs by consumption of food and drinking-water, inhalation of indoor air, and respiratory and oral uptake of dust containing PFHxS, its salts and PFHxS-related compounds. PFHxS has been detected in human blood and breast milk in many regions and is, together with perfluorooctanesulfonic acid (PFOS; agent 166 below), PFOA and perfluorononanoic acid (PFNA), one of the most frequently detected and predominant per- and

polyfluoroalkyl substances (PFAS) in human blood. The fetus is exposed to PFHxS via the umbilical cord blood, and breast milk may be an important source of exposure for infants. In women post-menarche and males, PFHxS levels increase with age, and in general, the highest levels have been observed in men (ECHA, 2019b). The US EPA has not classified PFHxS as a carcinogen (Illinois EPA, 2021).

Cancer in humans

A scoping review has recently been conducted on epidemiological evidence about PFAS and cancer in humans, including PFHxS (Steenland and Winquist, 2021). Sparse positive associations were noted for cancers of breast (Tsai et al., 2020), prostate (Hardell et al., 2014), and kidney (Shearer et al., 2020) with PFHxS.

In a large Swedish cohort exposed to high contamination levels of PFAS, primarily PFHxS and PFOS, there was no overall evidence of increased cancer risk. However, a slight increase in kidney cancer risk was noted. Additionally, there was a modestly elevated risk of bladder cancer (HR, 1.32; 95% CI, 1.01–1.72) and a decreased risk of prostate cancer (HR, 0.83; 95% CI, 0.71–0.98). Among individuals residing in the area with contaminated water during 2005–2013, when exposure was highest, there were elevated risks for kidney cancer (HR, 1.84; 95% CI, 1.00–3.37) but decreased risks for prostate cancer (HR, 0.76; 95% CI, 0.59–0.98) (Li et al., 2022c).

No association with testicular cancer was found in the US Air Force cohort (Purdue et al., 2023). In the American Cancer Society's Cancer Prevention Study II LifeLink Cohort, exposure to background PFHxS levels was associated with CLL/SLL in men (Winquist et al., 2023). Additional results are pending from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

Cancer in experimental animals

No studies evaluating cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

Many studies have reported PFHxS dose-dependent reductions in cell viability across liver cell lines in vitro (Amstutz et al., 2022; Ojo et al., 2022; Solan et al., 2022). Studies evaluating the effects of PFHxS on the generation of ROS and DNA damage in HepG2 cells have yielded conflicting findings (Wielsøe et al., 2015; Ojo et al., 2021; Ojo et al., 2022), although PFHxS-induced associations with measures of oxidative stress have been observed in other experimental systems (zebrafish embryos, mouse oocyte maturation in vitro) (Xu et al., 2023b; Ulhaq and Tse, 2023; Feng et al., 2023). A 28-day toxicity study conducted by the NTP did not observe differences in micronucleated reticulocytes in male or female Sprague-Dawley rats (NTP, 2022). Normal human breast epithelial cells (MCF-10A) treated with 100 µM PFHxS had higher cell proliferation than cells treated at lower concentrations, followed by a drop in cell proliferation at 500 µM; no dose–response relation was observed (Pierozan et al., 2022). Treatment with PFHxS in that study was also reported to increase cell-cycle protein expression, alter histone modifications, and promote cell migration and invasion, although data from treatments at a range of concentrations were not presented.

Several cohort and cross-sectional studies in humans have found increasing serum concentrations of PFHxS to be associated with decreased antibody levels in response to vaccination, suggesting immunosuppressive effects (OEHHA, 2022b). This inverse association was supported by summary results from a meta-analysis of 14 studies (Crawford et al., 2023). In a study of deer mice, increasing PFHxS exposure was associated with decreased plaque-forming cells (suggesting a decreased humoral immune response) (Narizzano et al., 2023). PFHxS administration had no effect on the weight of immune organs in Sprague-Dawley rats and CD-1 mice (Chang et al., 2018a; NTP, 2022).

There is consistent evidence of an association between PFHxS and liver toxicity. Exposure caused increased liver weight in rats and mice (He et al., 2022d; Narizzano et al., 2023), as well as liver steatosis

symptoms resembling non-alcoholic fatty liver disease (NAFLD) in mice and zebrafish embryos (Bijland et al., 2011; Das et al., 2017; Ulhaq and Tse, 2024). Many effects of PFHxS in the liver appear to be mediated through PPARα signalling (Das et al., 2017) and PFHxS exposure has been shown to activate PPARα in both human and animal in vitro assays (Rosenmai et al., 2018; Evans et al., 2022). A positive association between serum PFHxS concentration and risk of NAFLD was observed in cross-sectional epidemiological studies of children and adults (Jin et al., 2020; Zhang et al., 2023a).

Regarding receptor-mediated effects, increasing PFHxS exposure was associated with lower thyroid hormone levels (T3 and T4) in two studies of rats (Ramhøj et al., 2020; NTP, 2022). In contrast, the totality of the evidence from epidemiological studies investigating associations of PFHxS with thyroid hormone or thyroid disease is inconclusive (OEHHA, 2022b). PFHxS exposure of pregnant mice has been reported to induce reproductive effects such as defects in estrous cycle and oocyte maturation, intrauterine growth restriction, and fetal death (Adyeni et al., 2023; Narizzano et al., 2023; Yao et al., 2023a; Zhang et al., 2023b).

Summary

A few human cancer studies suggest positive associations with PFHxS exposure. No experimental evidence of animal carcinogenicity has been reported. There is evidence that PFHxS exhibits KCs, in particular immunosuppression and modulation of PPARα receptor-mediated effects. The Advisory Group therefore considered an *IARC Monographs* evaluation of perfluorohexanesulfonic acid to be warranted and recommended that it be evaluated in the same volume as HFPO-DA (agent 164).

Recommendation: High priority (and ready for evaluation within 2.5 years)

166 Perfluorooctanesulfonic acid (PFOS) (CAS No. 1763-23-1)

Current IARC/WHO classification

Perfluorooctanesulfonic acid (PFOS) has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Volume 135 in 2023 (Zahm et al., 2023). This classification was based on *strong* mechanistic evidence. The evidence for cancer in experimental animals was *limited* for PFOS, and the evidence regarding cancer in humans was *inadequate*. PFOS is scheduled for evaluation by the JECFA in 2027 or 2028.

Exposure characterization

PFOS is part of the large group of PFAS. Due to its hydrophobicity, lipophobicity, surface active properties, and chemical stability, it has been used in various applications including oil-, water-, and stain-repellent surface treatments, AFFF used in firefighting, as a mist suppressant in industrial processes, and in the production of semiconductors and electronics, and in electroplating and printing. The use of PFOS has been phased out in North America and Europe since the 2000s by agreements and guidelines such as the Stockholm Convention (Zahm et al., 2023). PFOS is extremely resistant to chemical degradation and highly mobile in the environment and has been detected in various environmental samples worldwide, including water, air, plants, crops, and animal-based foods (Schrenk et al., 2020b).

Occupational exposure in settings where the use of PFOS is not banned is expected to occur via inhalation or dermal contact. Firefighters might be exposed when using legacy stocks of AFFF. The general population is exposed mainly via the diet and drinking-water and potentially via legacy consumer products. In communities near sources of pollution, the general population is exposed mainly via drinking-water (Zahm et al., 2023).

Cancer in humans

A few dozen studies have assessed the association between PFOS exposure and cancer risk. These were conducted in: (i) populations of workers, with relatively high exposure; (ii) cohorts of residents of areas with PFOS contamination and potentially high exposure, mainly via drinking-water; and (iii) the general population with lower (background) exposure. The evidence is strongest for testis, breast, and thyroid cancer, as described in the forthcoming *IARC Monographs* Volume 135 (summarized in Zahm et al., 2023), but for all cancer types, the evidence was considered *inadequate*.

No studies showed increased risk for breast cancer overall, but two informative prospective studies showed an increased risk of hormone receptor-positive breast cancers associated with higher levels of PFOS (Mancini et al., 2020b; Chang et al., 2023c). Ten other studies reported null findings, but these generally did not evaluate hormonal subtypes. For testicular cancer, the two most informative, conducted within a cohort of Air Force servicemen (Purdue et al., 2023) and among residents of a contaminated area in Sweden (Li et al., 2022c), showed an imprecise positive correlation and a positive correlation, respectively.

For thyroid cancer, some positive evidence related to PFOS exposure came from occupational studies (Leonard et al., 2008; Barry et al., 2013) among women in the Rønneby Register cohort study in Sweden (Li et al., 2022c) and in a hospital-based case–control study in New York, USA, exposed to background levels (van Gerwen et al., 2023). However, in a well-conducted population-based study among women in Finland who were exposed at background levels, findings for PFOS were null after adjusting for other PFAS compounds (Madrigal et al. 2024). There were many other studies on other cancer sites, but associations were largely null. Since the previous evaluation in November 2023, a cohort study of fluorochemical production workers found a significant increase of risk for lung cancer associated with PFOS exposure and some indicative findings for an increased risk of colorectal, bladder, and pancreatic cancer (Alexander et al., 2024). A study of childhood ALL in the Finnish Maternity Cohort (Jones et al., 2024) found no association overall, but found a positive association for samples collected during a time period (1986–1995) of high exposure to PFOS.

Cancer in experimental animals

In the last evaluation of PFOS (IARC, 2024b; Zahm et al., 2023) there was *limited* evidence in experimental animals for the carcinogenicity of PFOS, based on an increase in the incidence of an appropriate combination of benign and malignant neoplasms in one sex (female) of a single species (rat) in a well-conducted study that complied with GLP. Since then, no new studies became available to the Advisory Group.

Mechanistic evidence

In the last evaluation of PFOS (IARC, 2024b; Zahm et al., 2023) there was *strong* evidence that PFOS exhibits multiple KCs in exposed humans, in human primary cells, and in experimental systems. There is evidence that PFOS induces epigenetic mechanisms and that PFOS is immunosuppressive, from a number of studies in exposed humans and experimental systems. In addition, there is strong evidence that PFOS modulates receptor-mediated effects. PFOS also modulates thyroid- and androgen-mediated effects in experimental systems, and PPARα and CAR/PXR in both human primary cells and experimental systems. The pattern of KCs showing strong evidence was very similar between PFOS and PFOA (Group 1).

Summary

Few new human cancer studies have been published on PFOS since the last evaluation, with no new data on the cancer sites with the most positive findings in the previous evaluation (breast, prostate, and thyroid). No new carcinogenesis studies in experimental animals have been identified. The available mechanistic evidence on the key characteristics would not support a re-evaluation of PFOS on the basis of

mechanistic class. The Advisory Group therefore considered that an *IARC Monographs* evaluation of perfluorooctanesulfonic acid is unwarranted at present.

Recommendation: No priority

167 Di(2-ethylhexyl) phthalate (DEHP) (CAS No. 117-81-7)

Current IARC/WHO classification

Di(2-ethylhexyl) phthalate (DEHP) has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Volume 101 in 2011 (IARC, 2013c), on the basis of *sufficient* evidence for cancer in experimental animals. The IPCS has published an evaluation of health effects of DEHP (WHO, 1992).

Exposure characterization

DEHP is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). DEHP is a plasticizer mainly used in PVC products and present in various types of (soft) plastic products, but also in some pesticides, wire and cable, food packaging materials, and children's toys. Although DEHP and a few other phthalates have been regulated in Europe (Boucher, 2021), urinary metabolites from DEHP and other phthalates are still widely present in the population (Kang et al., 2021b), including in children and adolescents (Vogel et al., 2023b). Urinary levels of DEHP and its metabolites have been found in a few studies to be higher in occupationally exposed people compared with unexposed workers (IARC, 2013c).

Cancer in humans

This section is primarily based on DEHP and its metabolites. Since the last evaluation, where there was *inadequate* evidence regarding cancer in humans, at least two meta-analyses, mainly based on case–control studies, have been performed for breast cancer. A meta-analysis including nine case–control studies did not observe an association between phthalate metabolites (including from DEHP) and breast cancer (Liu et al., 2021b). A meta-analysis including four studies (Fu et al., 2017b) found no indication of an increased risk associated with phthalate metabolites in general, but an OR for breast cancer of 1.24 for the highest versus the lowest categories of urinary levels of DEHP metabolites.

In a nested case–control study within the WHI cohort, 13 phthalate metabolites (including those of DEHP) were analysed in 2–3 urine samples per participant (Reeves et al., 2019). ORs for breast cancer risk associated with each phthalate metabolite up to 19 years of follow-up was estimated. Overall, no significant positive association between phthalate biomarkers and breast cancer risk was seen. In one of the few case–control studies where DEHP metabolites were measured before diagnosis Wu et al. (2021b) found in a nested case–control study that breast cancer risk was higher for those in tertile 2 (OR, 1.32) and tertile 3 (OR, 1.26) of primary and secondary metabolites of DEHP, compared with those in tertile 1.

One or two case–control or cross-sectional studies have considered other outcomes, including prostate and colorectal cancer. For thyroid cancer, at least four studies are available, including one paper in Chinese, which was difficult to judge from the English abstract (Mao et al., 2023a). In a small, hospital-based case–control study, also conducted in China, Liu et al. (2020) found urinary levels of DEHP metabolites to be positively associated with both thyroid cancer and benign thyroid nodules. In a case–control study, Miao et al. (2020) found urinary DEHP metabolites to be positively associated with papillary thyroid cancer (OR, 5.35) in an analysis that included mutual adjustment for other phthalate metabolites. In a small case–control study, Marotta et al. (2019) compared 27 patients with benign thyroid nodules and 28 with thyroid cancer.

Patients with serum DEHP above the limit of detection had a much higher odds for thyroid cancer compared with patients with benign nodules (OR, 15.1).

Cancer in experimental animals

In the previous evaluation, there was *sufficient* evidence that DEHP induces cancer in experimental animals, based on increased incidence of hepatocellular adenoma and HCC (and some other tumours) in rats and mice (IARC, 2013c). Since then, an NTP study evaluating the carcinogenicity of DEHP in rats following dietary administration of DEHP confirmed the previous findings on increased incidence of hepatocellular and pancreatic tumours in rats (NTP, 2021c). Additionally, the study found increases in the incidence of uterine (including cervix) adenoma, adenocarcinoma, SCCs, and squamous cell papilloma (combined) in female rats.

Mechanistic evidence

DEHP has been extensively tested in bacterial mutagenicity and mammalian cell genotoxicity assays, which have generally given negative results (IARC, 2013c). A large number of studies have shown DEHP and other phthalates to affect other end-points related to the KCs, including disruption of steroidogenesis, increased oxidative stress and apoptosis, and modulation of nuclear receptor signalling in animals and experimental systems including human cells (IARC, 2013c). Several more recent studies reporting associations of DEHP exposure with markers of oxidative stress (and other relevant end-points) in exposed humans (Huang et al., 2020b; Waits et al., 2020) could be informative for understanding the carcinogenic hazard of DEHP and other co-occurring phthalates.

Summary

Meta-analyses performed since the previous evaluation do not suggest a positive association between DEHP and breast cancer in humans, but in one of the higher-quality studies an exposure–response relation was observed. One study on DEHP and thyroid cancer suggested a positive association, but with several limitations. Evidence is already *sufficient* for cancer in experimental animals. There is evidence that DEHP exhibits KCs in exposed humans, particularly oxidative stress and epigenetic effects; however, in studies in exposed humans it is difficult to separate effects of DEHP from those of other co-occurring phthalates. No mechanistic studies in human primary cells or tissues were identified. The Advisory Group therefore considered that an *IARC Monographs* evaluation of di(2-ethylhexyl) phthalate is unwarranted at present.

Recommendation: No priority

168 Butyl benzyl phthalate (CAS No. 85-68-7)

Current IARC/WHO classification

Butyl benzyl phthalate (BBP) has previously been evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in Volume 73 in 1998 (IARC, 1999b). The IPCS has published an evaluation of health effects of BBP (WHO, 1999a).

Exposure characterization

BBP is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). BBP acts as a plasticizer used mainly in PVC products and present in various types of (soft) plastic products including vinyl floor tiles, vinyl foam and carpet backing, and cellulosic resins; it is also used as an organic intermediate (IARC, 1999b). Although BBP and a few other phthalates have been regulated in the EU (Boucher, 2021), urinary metabolites from BBP and other phthalates are still widely present in the population (Kang et al., 2021b), including in children and adolescents (Vogel et al., 2023b).

According to the 1981–1983 National Occupational Exposure Survey conducted by NIOSH, approximately 330 000 workers in the USA were potentially exposed to BBP (IARC, 1999b).

Cancer in humans

Since the previous evaluation, at least two meta-analyses mainly based on case–control studies have been performed for BBP (or its metabolites) and breast cancer. A meta-analysis including nine case–control studies did not suggest an association between BBP metabolites and breast cancer (Liu et al., 2021b). A meta-analysis including four studies (Fu et al., 2017b) found no indication of an increased risk of breast cancer for the BBP metabolite monobenzyl phthalate (MBzP). In a nested case–control study within the WHI cohort, 13 phthalate metabolites (including the MBzP) were analysed in two or three urine samples per participant (Reeves et al., 2019). ORs were estimated for breast cancer risk associated with each phthalate metabolite after up to 19 years of follow-up, and MBzP was found to be inversely associated with breast cancer. In one of the few studies in which BBP metabolites were measured before diagnosis, Wu et al. (2021b) found no association between MBzP and breast cancer in a nested case–control study. Few studies are available for other cancer outcomes.

Cancer in experimental animals

In the previous evaluation (IARC, 1999b), there was *limited* evidence for cancer in experimental animals. BBP has been tested in several long-term carcinogenicity studies in rats and mice. In female rats, BBP administered in the feed caused an increase in the incidence of mononuclear cell leukaemia (NTP, 1982b). In a separate study with BBP in the feed, pancreatic acinar cell adenoma or carcinoma (combined) was observed in male rats, and increases in the incidence of pancreatic acinar cell adenoma and urinary bladder transitional epithelial papilloma were observed in female rats (NTP, 1997b). BBP administration was not associated with increased incidence of tumours in male or female mice (NTP, 1982b).

Mechanistic evidence

In mutagenicity tests with BBP, the NTP (1997b) reported negative results from studies in mammalian cells and bacteria in vitro, and positive results in two mouse studies in vivo. Other studies have shown that BBP can induce oxidative stress and DNA damage in human primary cells (Sicińska et al., 2021) and increased cell proliferation in human cancer cell lines (Zhu et al., 2019).

In a wide variety of test systems including high-throughput screening conducted as part of the Tox21 programme, BBP increased cell proliferation, demonstrated activity at several nuclear hormone receptors, and altered the expression of genes associated with potential carcinogenic mechanisms in human cancer cells (OEHHA, 2013a; NTP, 2023d).

Summary

Since the last evaluation, meta-analyses have not identified an association between BBP and breast cancer in humans, and this was supported by two of the better studies. Available data indicate that BBP is carcinogenic in experimental animals. BBP administered orally (in feed) caused tumours at several tissue sites in two different long-term studies in female rats (study 1) and in male and female rats (study 2). The evaluation of the evidence from experimental animals may change based on the criteria in the latest version of the *IARC Monographs* Preamble (IARC, 2019b). There is evidence that BBP exhibits several KCs, in particular increased cell proliferation and receptor-mediated effects in experimental systems. BBP has a similar structure to other carcinogenic phthalates, including DEHP, which is currently classified in Group 2B by the *Monographs* programme. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of BBP to be warranted and recommended that this agent be evaluated in the same volume as other phthalates in this report (see agents 169 and 170).

Recommendation: High priority (and ready for evaluation within 2.5 years)

169 Dibutyl phthalate (CAS No. 84-72-2)

Current IARC/WHO classification

Dibutyl phthalate (DBP) has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

DBP is listed as a high production volume chemical by the OECD and the US EPA (US EPA, 2024a). DBP is one of the six phthalic acid esters found on the Priority Pollutant List, which consists of pollutants regulated by the US EPA (US EPA, 2014). DBP acts as a plasticizer used mainly in PVC products and present in various types of (soft) plastic products. It is used in consumer products, e.g. as a coalescing aid in latex adhesives, as a solvent, and in personal care products (e.g. cosmetics). It is also used in pharmaceutical capsules (Ennis et al., 2018).

Even though DBP and a few other phthalates have been regulated in the EU (Boucher, 2021), urinary metabolites from DBP and other phthalates are still widely present in the population (Kang et al., 2021b), including in children and adolescents (Vogel et al., 2023b). Occupational exposure to DBP has been documented, for example in urine samples among manicurists (Kwapniewski et al., 2008).

Cancer in humans

At least two meta-analyses mainly based on case–control studies have been performed for phthalates as a group and breast cancer. A meta-analysis including nine case–control studies did not suggest an association between DBP metabolites and breast cancer (Liu et al., 2021b). In a meta-analysis including four studies, Fu et al. (2017b) found no increased risk of breast cancer for the metabolite monobutyl phthalate. In a nationwide prospective study in Denmark (Ahern et al., 2019), DBP exposure was estimated from the DBP content of drugs, using data from a prescription registry. For nearly 10 million woman-years of follow-up, very high DBP exposure (> 10 cumulative g) was associated with an HR of 1.9 for ER-positive breast cancer.

In a case–control study nested within the WHI cohort, DBP metabolites were analysed in two or three urine samples per participant (Reeves et al., 2019). ORs were estimated for breast cancer risk associated with each phthalate metabolite after up to 19 years of follow-up, and no association between DBP metabolites and breast cancer risk was seen. In one of the few studies where DBP metabolites were measured before diagnosis, Wu et al. (2021b) found no association between DBP metabolites and breast cancer in a nested case–control study. In a study from the same cohort, prediagnostic urinary DBP metabolites were associated with endometrial cancer, OR: 2.09 (tertile 2) and OR: 1.77 (tertile 3) compared to tertile 1 (Sarink et al., 2021). Few studies are available for other cancer outcomes.

Cancer in experimental animals

In 2-year studies with DBP in feed conducted by the NTP, marginal increases in the incidence of pancreatic acinus adenomas were observed in male rats. There was no evidence of carcinogenic activity of DBP in female rats or in male or female mice (NTP, 2021d).

Mechanistic evidence

DBP has tested positive in some mammalian cell mutagenicity assays (NTP, 2024b) and induces oxidative stress and DNA strand breaks in primary human cells (Sicińska et al., 2021). Oxidative stress and DNA damage (Binder et al., 2021) and increased cell proliferation (Bu et al., 2023) have been observed in human cancer cell lines exposed to DBP. DBP is structurally related to other phthalates, e.g. DEHP (see agent 167) and BBP (see agent 168).

Summary

Meta-analyses have not identified an association between DBP and breast cancer in humans, a finding supported by two of the higher-quality case–control studies. A register-based prospective cohort study found an association for highly exposed individuals with ER-positive breast cancer. Information on other cancer sites is very sparse. Data are available indicating that in experimental animals DBP is carcinogenic in one sex of one species (rat). There is evidence that DBP exhibits several KCs, in particular genotoxicity and increased cell proliferation in experimental systems, and induction of oxidative stress and DNA damage in primary human cells. The Advisory Group therefore considered an *IARC Monographs* evaluation of dibutyl phthalate to be warranted and recommended that this agent be evaluated in the same volume as other phthalates in this report (see agents 168 and 170).

Recommendation: High priority (and ready for evaluation within 2.5 years)

170 Diisononyl phthalate (CAS No. 28553-12-0)

Current IARC/WHO classification

Diisononyl phthalate (DINP) has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

DINP is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). DINP is usually described as part of the subgroup of "high molecular weight" phthalates, in contrast to "low molecular weight" phthalates such as DEHP, DBP and BBP (OECD, 2007). DINP acts as a plasticizer used mainly in PVC products and present in various types of (soft) plastic products, but also in children's toys. Other reported uses are in shoe soles, sealants, paints, and lacquers, as for DEHP. According to the DINP industry, the substance was, together with DEHP, the phthalate of highest commercial interest in Europe in the early 2000s (ECHA, 2010). Urinary metabolites from DINP and other phthalates are widely present in the population (ECHA, 2010) and have been detected in at least 65% of children and adolescents (Vogel et al., 2023b). Occupational exposure to DINP has been indicated in a study among plastics workers in Finland (Porras et al., 2020).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

DINP has been tested in several long-term carcinogenicity studies in rats and mice (reviewed in CPSC, 2001; OEHHA, 2013b). Increases in the incidence of hepatocellular tumours (malignant and combined malignant and benign) and mononuclear cell leukaemia were observed in male and female rats. In one study, increases in the incidence of renal tubule cell carcinomas were also observed in male rats. In male and female mice, DINP administration led to increases in the incidence of hepatocellular adenomas and carcinomas.

Mechanistic evidence

Diisononyl phthalate (DINP) tested negative in assays for bacterial mutagenicity and mammalian genotoxicity in vitro and in vivo (OEHHA, 2013b). DINP is anti-androgenic in vitro and in vivo and shows activity towards several nuclear receptors, including PPAR, CAR, and PXR, in human and rodent cells (OEHHA, 2013b; NTP, 2023e). Short-term oral toxicity studies in mice have demonstrated that DINP can induce oxidative damage and inflammatory responses in liver and kidney (Ma et al., 2014) and increase ROS and DNA–protein cross-links in liver and kidney (Liang and Yan, 2020).

Summary

No studies of cancer in humans were identified. Data are available from multiple studies indicating that DINP is carcinogenic in experimental animals. There is evidence that DINP exhibits certain KCs, in particular receptor-mediated effects, oxidative stress, and DNA damage in experimental systems including human cells. These data could support an evaluation of carcinogenicity of DINP. The Advisory Group therefore considered an *IARC Monographs* evaluation of diisononyl phthalate to be warranted and recommended that this agent be evaluated in the same volume as other phthalates in this report (see agents 168 and 169).

Recommendation: High priority (and ready for evaluation within 2.5 years)

171 Tris(chloropropyl) phosphate (CAS No. 13674-84-5)

Current IARC/WHO classification

Tris(chloropropyl) phosphate (TCPP) has not previously been evaluated by the *IARC Monographs* programme. TCPP was given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of evidence for cancer in experimental animals and mechanistic evidence.

Exposure characterization

TCPP is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). TCPP is a flame retardant that is used primarily in polyurethane foams but also in paint, adhesives and coating, and as a plasticizer in polymers used in aerospace equipment and products.

Processing, distribution, use, and disposal of TCPP can result in releases to the environment. TCPP has been identified in surface water, groundwater, sediment, fish samples, public swimming pools, and human milk (Sundkvist et al., 2010; Lee et al., 2016b; Teo et al., 2016; Khairy and Lohmann, 2019). The general population could be exposed by inhalation of vapour, direct skin contact with furniture fabrics, and incidental ingestion of contaminated water or seafood. Children could be exposed by breast feeding or by mouth contact with furniture fabrics and other objects. In some studies, the possibility of skin absorption of cosmetic products and household dust has been noted (Pawar et al., 2017).

There is potential for occupational exposure during the manufacture and industrial or commercial use of TCPP, including handling, recycling, and disposal of waste. Bello et al. (2018) demonstrated the relevance of dermal occupational exposure in a study with workers using spray polyurethane foam. In this study, high levels of urinary biomarkers for TCPP were found in workers. Other exposed occupations are carpet installation, chemical manufacturing, foam manufacturing, electronic scrap work, gymnastics, rigid board installation, nail salons, and roofing (Estill et al., 2020).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In 2-year studies with TCPP in feed conducted by the NTP, there was an increased incidence of hepatocellular tumours (adenoma or carcinoma combined) in male rats, and an increased incidence of uterine tumours (adenoma or adenocarcinoma combined) in females. Dietary administration of TCPP also caused liver tumours in mice, with increased incidence of HCC in males and of hepatocellular adenoma and HCC in females (NTP, 2023a).

Mechanistic evidence

Numerous genotoxicity studies have been conducted for TCPP and are summarized in reports from the European Commission, ECHA, and Health Canada. Most of these studies gave negative or equivocal results, and very few showed weakly positive results. In genetic toxicology tests performed by the NTP, TCPP showed no mutagenic effects in several bacterial strains and in rodent assays in vivo, except for a small but significant increase in micronuclei in male mice (NTP, 2023a). In addition, higher incidence of endometrial hyperplasia was observed in rats (NTP, 2023a).

In Tox21 high-throughput screening assays, TCPP was a weak activator of the CAR and PXR. TCPP was active in several assays that are mapped to KCs, including alteration of DNA repair and genomic stability (NTP, 2023b). Additionally, some compounds structurally similar to TCPP, including tris(2-chloroethyl) phosphate, are carcinogenic to rodents.

Summary

No studies of cancer in humans were identified. Available data indicate that TCPP is carcinogenic in rats and mice. There are inconclusive results on the genotoxicity of TCPP accompanied by a few other positive findings on KC8 and KC10 in experimental systems. The Advisory Group therefore considered an *IARC Monographs* evaluation of tris(chloropropyl) phosphate to be warranted, in view of the evidence for cancer in experimental animals.

Recommendation: High priority (and ready for evaluation within 2.5 years)

172 Tris(2-chloroethyl) phosphate (TCEP) (CAS No. 115-96-8)

Current IARC/WHO classification

Tris(2-chloroethyl) phosphate (TCEP) was evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) in Volume 71 in 1998 (IARC, 1999a). TCEP was given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of its structural similarity to TCPP (agent No. 171 in this report).

Exposure characterization

TCEP is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). As noted in the 2019 Advisory Group report, "TCEP is an organophosphate flame retardant and plasticizer and is used in a variety of industrial and household products. Because of its many uses, it occurs in multiple environmental media. Residential indoor air and dust are important exposure pathways."

Cancer in humans

A small case–control study observed higher levels of TCEP in household dust from homes of participants with papillary thyroid cancer than from those of controls (Hoffman et al., 2017).

Cancer in experimental animals

In a bioassay using F344/N rats, there was increased incidence of renal tubule adenoma in male and female rats. Thyroid follicular cell neoplasms and mononuclear cell leukaemia in male and female rats may have been related to chemical administration. In $B6C3F_1$ mice, there was equivocal evidence of carcinogenic activity in male mice, shown by a marginally increased incidence of renal tubule cell neoplasms. Equivocal evidence of carcinogenic activity in female mice was shown by a marginally increased incidence of Harderian gland adenomas (NTP, 1991).

Mechanistic evidence

As noted in the 2019 Advisory Group report, **"**TCEP was not mutagenic in bacterial assays and caused equivocal or no effect on chromosomal aberrations and SCE in CHO cells. Evidence beyond the NTP studies is sparse. TCEP was active in a PXR nuclear receptor assay in US EPA ToxCast programme (ToxCast/Tox21: two active assays, Attagene PXR cis, PXR trans) (Bajard et al., 2019). There is one report on in vitro cytotoxicity mediated by oxidative stress (Yu et al., 2019c)." Few new data have appeared since then.

Summary

The Advisory Group considered that an *IARC Monographs* evaluation of tris(2-chloroethyl) phosphate is unwarranted at present.

Recommendation: No priority

173 Allyl alcohol (CAS No. 107-18-6)

Current IARC/WHO classification

Allyl alcohol has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Allyl alcohol is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). Allyl alcohol is a colourless liquid with a mustard-like odour (New Jersey Department of Health, 2017). It is used in the manufacture of detergents, plastics, resins, pharmaceuticals, and chemicals and as an agricultural agent and food additive (NTP, 2006; NCBI, 2024e). It is presumed that occupational and non-occupational exposures to allyl alcohol could occur from the uses described above.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

A chronic toxicity study in hamsters and rats observed no exposure-related differences in any type of tumour (Lijinsky and Reuber, 1987). A 2009 EPA report noted deficiencies in the design of this study, including the use of a single dose level, a small number of tested animals, and the exclusion of female hamsters (US EPA, 2009c). A recent chronic study of mice and rats has been conducted at the Japan Bioassay Research Center, although no English-language report is available. Tables available online that summarize the results from rats do not indicate any tumour increase (JBRC, 2022c).

Mechanistic evidence

Allyl alcohol is metabolized to acrolein (Group 2A). Genotoxicity testing of allyl alcohol has yielded inconsistent findings (US EPA, 2009c). Mutagenicity tests of *S. typhimurium* were negative for most evaluated strains, although a positive test for one strain was reported, as well as a test of Chinese hamster V79 cells. Mutagenicity tests of *Streptomyces coelicolor* and *Aspergillus nidulans* were negative (US EPA, 2009c). No differences in bone marrow and peripheral blood micronucleated erythryocytes were observed across exposures in a subchronic study for male or female mice (NTP, 2006).

Summary

No studies on cancer in humans were available. There is no evidence that allyl alcohol is carcinogenic in experimental animal studies or that it demonstrates KCs. The Advisory Group therefore considered that an *IARC Monographs* evaluation of allyl alcohol is unwarranted at present.

Recommendation: No priority

174 Carbon tetrachloride (CAS No. 56-23-5)

Current IARC/WHO classification

Carbon tetrachloride has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Volume 71 in 1998 (IARC, 1999d). The IPCS has published an evaluation of health effects of carbon tetrachloride (WHO, 1999b).

Exposure characterization

Carbon tetrachloride is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). Carbon tetrachloride has been used widely as a solvent in dry cleaning, primarily from the 1930s until the 1960s, after which it was gradually replaced first with trichloroethylene and then tetrachloroethylene (IARC, 1995; Callahan et al., 2019). Another major application has been as a solvent in metal degreasing. It has also been used as an agricultural fumigant and in the production of refrigerants and propellants (McDuffie et al., 2001; Callahan et al., 2018). The production and use of carbon tetrachloride have been restricted in many parts of the world, but it may still be used in laboratories and some industrial processes (production of chlorine, caustic soda, or chlorinated rubber) (NHS UK, 2022). The main route for occupational exposure is via inhalation. The general population is exposed primarily via the air, with higher levels in urban areas and near industrial sites (Garcia et al., 2015).

Cancer in humans

In the last *Monographs* evaluation of carbon tetrachloride in 1998, the evidence for cancer in humans was assessed as *inadequate*. Several new studies of the association between cancer and carbon tetrachloride exposure have been published. For NHL, several studies show consistent associations. Three out of the four cohort studies with results on NHL and carbon tetrachloride exposure showed positive associations. All three new population-based case–control studies in Canada and the USA also found positive associations (McDuffie et al., 2001; Wang et al., 2009; Callahan et al., 2018).

Some studies have found associations of carbon tetrachloride exposure with brain cancers. In a cohort of Japanese-American men in Hawaii, USA, Nelson et al. (2012) found an association of glioblastoma multiforme with occupational exposure to carbon tetrachloride, as assessed using questionnaire data that also included information on co-exposures such as smoking; however, it was not clear whether these co-exposures were considered in the models. In a hospital-based case–control study, Neta et al. (2012) found a significant association between risk of glioma and occupational carbon tetrachloride exposure when restricting to exposed workers only. However, Ruder et al. (2013) found an inverse association between estimated occupational carbon tetrachloride exposure and glioma in a registry-based case–control study. In a population-based case–control study, Heck et al. (2013) found an association between neuroblastoma in children and maternal carbon tetrachloride exposure during pregnancy, based on modelled air exposure. There is potential for confounding in most of these studies, as co-exposure to other (chlorinated) solvents in the occupational setting and other carcinogens is likely and only some of the studies had detailed information on lifestyle factors, precluding adjustment for factors such as cigarette smoking. For cancer sites such as lung, breast, and head and neck cancers, there were a lower number of studies and only some sporadic

findings for other cancer sites. The Advisory Group noted that some potentially informative studies are in progress in populations exposed in the USA.

Cancer in experimental animals

In the previous evaluation (IARC, 1999b), there was *sufficient* evidence in experimental animals for the carcinogenicity of carbon tetrachloride, based on findings of tumours in several species of experimental animals, at two different tissue sites (liver and adrenal gland), and by several different routes of exposure (IARC, 1999b). Since carbon tetrachloride was evaluated by IARC, additional studies in mice have been reported. Inhalation exposure to carbon tetrachloride caused benign and malignant liver tumours (hepatocellular adenoma and carcinoma) and benign adrenal-gland tumours (phaeochromocytoma) in mice of both sexes (Nagano et al., 2007; reporting the JBRC, 1998).

Mechanistic evidence

Carbon tetrachloride enters the body through inhalation, ingestion, and dermal absorption. Respiration is the primary route of exposure, and pulmonary absorption is estimated to be 60% in humans. Carbon tetrachloride is activated by cytochrome CYP2E1, CYP2B1 or CYP2B2, and possibly CYP3A, to form the trichloromethyl radical, $CCl_3^{\bullet}$, which can react with oxygen to form the trichloromethylperoxy radical $CCl_3OO^{\bullet}$, a highly reactive species. Both metabolites are capable of covalent binding locally to cellular macromolecules, with preference for fatty acids from membrane phospholipids (Raucy et al., 1993; Gruebele et al., 1996; McGregor and Lang, 1996; Manibusan et al., 2007; Unsal et al., 2020). Regarding the KCs, new studies have been published since the 1998 evaluation. In peripheral blood lymphocytes taken from four non-smoking healthy individuals, exposure to carbon tetrachloride induced a significant increase in SCE frequency, a significant reduction in the activities of antioxidant enzymes SOD and GPx, and a reduction of GSH levels (Alpsoy et al., 2011). In human TK6 cells, exposure to carbon tetrachloride induced DNA hypomethylation (Tabish et al., 2012). In mice treated by intraperitoneal injections, carbon tetrachloride induced testicular DNA damage, as evidenced by a significant increase of chromosomal aberrations in primary spermatocytes (Diab et al., 2018); it also increased serum levels of pro-inflammatory cytokines and chemokines Il-6, Il-1β, Ifng, and Tnfa (Sun et al., 2022b; Xu et al., 2022a; Wei et al., 2023). In rats, carbon tetrachloride administered by gavage induced oxidative stress in erythrocytes, spleen, liver, and kidney; in addition, it decreased the enzymatic activities of SOD, GPx, and CAT in these tissues (Rahmouni et al., 2018; 2019). Carbon tetrachloride induced genotoxicity by increasing the frequency of both chromosomal aberrations and SCE; it induced a massive proliferation and hypertrophy of reticulo-endothelial cells as well as an inflammation oedema in rat spleen (Rahmouni et al., 2018). The same alterations (decreased activities of CAT, GPx, SOD, and glutathione-*S*-transferase) and DNA damage were observed in the liver when carbon tetrachloride was given intraperitoneally to rats (Alkreathy et al., 2014; Batool et al., 2017). Administration of carbon tetrachloride to rats for 3 weeks resulted in hypomethylation of liver DNA (Varela-Moreiras et al., 1995).

Summary

Several studies show consistent associations between carbon tetrachloride exposure and risk of NHL in humans. Additionally, a few studies show associations with brain cancer. In all studies, there is potential for confounding due to co-exposure to other solvents. Some potentially informative studies may be forthcoming. Carbon tetrachloride caused tumours in several species of experimental animals exposed by several routes. It exhibits several of the KCs (e.g. genotoxicity, oxidative stress, and inflammation) in human cells and in rodents. There is limited available mechanistic evidence from exposed humans or human primary cells or tissues. The Advisory Group therefore considered an *IARC Monographs* evaluation of carbon tetrachloride to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

175 Cumene (CAS No. 98-82-8)

Current IARC/WHO classification

Cumene has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Volume 101 in 2011 (IARC, 2013c), on the basis of *sufficient* evidence in experimental animals for the carcinogenicity of cumene. Cumene was given a priority rating of *low* by the 2019 by the Advisory Group on Priorities (IARC, 2019a).

Exposure characterization

Cumene is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). Cumene is a phenyl compound that is mainly used in the production of phenol, phenol derivatives, and acetone. To a lesser extent, it is used as a thinner in paints and lacquers and it is part of petroleum-based solvents (NTP, 2013; Bauer and Buettner, 2023). It is naturally present in petroleum and therefore in gasoline and might be added in gasoline blending. Environmental occurrence is mainly in air; it has been reported to be released from fires (Austin et al., 2001). The general population is mainly exposed via the air and, to a much lesser extent, via consumer products and food or water (Martins et al., 2010; NTP, 2013). The NTP RoC found that overall reported urban atmospheric cumene levels were 14.7 $\mu g/m^3$, while reported levels in workers performing various tasks in manufacturing and processing cumene could be as high as 150 000 $\mu g/m^3$ (NTP, 2013).

Cancer in humans

No studies on cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In the last evaluation of cumene (IARC, 2013c), there was *sufficient* evidence in experimental animals for the carcinogenicity of cumene. In addition, there was *sufficient* evidence in experimental animals for the carcinogenicity of its metabolite, α-methylstyrene. Cumene was tested for carcinogenicity in a 2-year study conducted by the NTP in both sexes of mice and rats exposed by inhalation (NTP, 2009).

Mechanistic evidence

In the last evaluation of cumene (IARC, 2013c), there was *moderate* evidence that a mutational mechanism underlies the development of cumene-induced lung tumours in rodents (Rosman et al., 1986; Hong et al., 2008; Wakamatsu et al., 2008). This conclusion was based on the findings that mouse lung tumours had an elevated frequency of mutations in the KRAS and TRP53 genes, and at least one mutagenic metabolite of cumene (α-methylstyrene oxide) has been found in rats and mice (Gollapudi et al., 2021). Additional studies evaluated in the NTP RoC (NTP, 2013), which listed cumene as "reasonably anticipated to be a human carcinogen", showed that although cumene was not mutagenic or genotoxic in most of the standard assays in vitro and in vivo, single-cell gel electrophoresis provided evidence that cumene caused DNA damage in the liver of male rats and the lungs of female mice (NTP, 2012a). α-Methylstyrene was not mutagenic in bacteria (NTP, 2007b), but there is evidence that it causes chromosomal damage in rodents and cultured cells, and its proposed metabolite, α-methylstyrene oxide, is mutagenic in bacteria. Therefore, some evidence exists for a genotoxic mechanism of action for cumene (presumably via its conversion to α-methylstyrene or to other metabolites). Other evidence suggests that cumene can cause cell proliferation and epigenetic effects, as observed through microarray analysis in tumour and normal tissues from mice

(Wakamatsu et al., 2008). No other data on human primary cells or exposed humans relating to cumene were identified.

Summary

No studies on cancer in humans and cumene exposure were available. New mechanistic evidence relevant to the KCs in experimental systems is available. However, the lack of mechanistic information from human primary cells or tissues or exposed humans would probably preclude a reclassification of the agent. The Advisory Group therefore considered that an *IARC Monographs* evaluation of cumene is unwarranted at present.

Recommendation: No priority

176 Dichloromethane (CAS No. 75-09-2)

Current IARC/WHO classification

Dichloromethane (methylene chloride) has been evaluated previously by the *IARC Monographs* programme (IARC, 1987a, 1999d, 2017b) and is classified as *probably carcinogenic to humans* (Group 2A), on the basis of *sufficient* evidence for cancer in experimental animals and *limited* evidence for cancer in humans, specifically of cancer of the biliary tract and NHL. FAO/WHO (1992) recommended that dichloromethane should be limited to its current uses (as an extraction solvent for spice oleoresins and the decaffeination of coffee and tea, and for food additives in which previous specifications drawn up by the Committee covered residues of dichloromethane). WHO has also made an assessment in relation to dichloromethane in drinking-water (WHO, 1993).

Dichloromethane was given a priority rating of *low* by the 2019 Advisory Group on Priorities (IARC, 2019a).

Exposure characterization

As noted in the 2019 Advisory Group report, there remains extensive use of and exposure to dichloromethane, particularly in occupational settings. For example, dichloromethane has been extensively used as a paint stripper, but this use is currently being restricted due to acute poisonings via inhalation. Dichloromethane is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a).

Cancer in humans

As noted in the 2019 Advisory Group report, there are new studies available for several cancer types, but the evidence does not appear to have changed substantially since the previous evaluation.

Cancer in experimental animals

In *Monographs* Volume 110 (IARC, 2017b), there was *sufficient* evidence for cancer in experimental animals.

Mechanistic evidence

New studies relevant to KCs are available, particularly on whether dichloromethane is genotoxic and induces oxidative stress. However, there are few such studies in exposed humans (e.g. Mimaki et al., 2016; Zeljezic et al., 2016).

Summary

Bearing in mind the current classification of dichloromethane in Group 2A, the Advisory Group concluded that the evidence published since the previous evaluation in 2017 would be unlikely to lead to a change in classification and therefore considered that an *IARC Monographs* re-evaluation of dichloromethane is unwarranted at present.

Recommendation: No priority

177 Isoprene (CAS No. 78-79-5)

Current IARC/WHO classification

Isoprene has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Volume 71 in 1998 (IARC, 1999d). Isoprene was given a priority rating of *high* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of cancer in several tissues in mice and rats, its chemical structural similarity to 1,3-butadiene (a Group 1 carcinogen), and mechanistic evidence of adduct formation and genotoxicity.

Exposure characterization

Isoprene is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). Isoprene is used as a chemical intermediate to manufacture primarily polymers, which occurs in closed production systems. Greater than 95% of high-purity isoprene is used as a monomer to manufacture elastomers such as polyisoprene, styrenic thermoplastic elastomer block copolymers (styrene-isoprene-styrene), and butyl rubber (IARC, 1994c; ECHA, 2021a). In 2020, the isoprene market was expanding due to its increasing use in the synthetic rubber industry to produce tyres, conveyor belts, hoses, moulded rubber, and in medical equipment such as gloves and balloons (ECHA, 2021a). Isoprene is also used to manufacture specialty chemicals, intermediates, and derivatives, which are then used in the production of vitamins, pharmaceuticals, flavourings and perfumes, epoxy hardeners, and fuels (IARC, 1994c; Asghar and Masoon, 2020; ECHA, 2021a).

Isoprene--derived polymers are used in paint resins, tyres, footwear, adhesives, and motor oil viscosity improvers and an unknown percentage of unreacted monomer is present in the end-products. Exposure of the general population to isoprene is thought to be minimal (OECD, 2005; ECHA, 2021a). Occupational exposure to isoprene through inhalation (primarily) and dermal absorption could potentially occur at workplaces where isoprene or synthetic rubber is produced or used (ECHA, 2021a).

Cancer in humans

In published studies, only risk estimates for rubber industry work as such were reported, and no risk estimates for isoprene could be assessed (ECHA, 2021a). No studies of workers exposed in the isoprene chemical industry or other cohort or case–control studies were available to the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 1999d), there was *sufficient* evidence in experimental animals for the carcinogenicity of isoprene.

Mechanistic evidence

Isoprene is the 2-methyl analogue of 1,3-butadiene (a Group 1 carcinogen; IARC, 2012b). Similarly, to 1,3-butadiene, isoprene is metabolized to monoepoxide and diepoxide intermediates by hepatic CYP enzymes (particularly CYP2E1) of several species, including humans (IARC, 1999d).

Isoprene exhibits several KCs. In experimental systems, DNA adducts (2'-deoxyadenosine adducts and *N*7-guanine adducts) were measured in vitro (Begemann et al., 2004, 2011) and haemoglobin adducts in mice and rats (Anderson, 2001; Fred et al., 2005). In human primary cells, genotoxicity in human PBMCs (Fabiani et al., 2007, 2012) and formation of haemoglobin adducts in human erythrocytes (Tareke et al., 1998) have been reported. Genotoxicity was also described in human cell lines (Fabiani et al., 2012; Li et al., 2014b), and genetic alterations in the KRAS and HRAS proto-oncogenes were observed in isoprene-induced tumours of the Harderian gland and forestomach in mice (IARC, 2019a). In particular, tumours of the Harderian gland had a high frequency of KRAS A→T transversion mutations (Hong et al., 1997; Sills et al., 2001). The mutation profile was similar to that induced by 1,3-butadiene (Hong et al., 1997; Sills et al., 2001). Epigenetic changes were associated with inflammatory/oxidative stress response in human lung cells (BEAS-2B cells) exposed to secondary organic aerosols derived from isomeric isoprene epoxydiols (Eaves et al., 2020).

Summary

No studies on isoprene exposure and human cancer were available. Isoprene is genotoxic and forms haemoglobin adducts in human primary cells and experimental systems, and it has a similar mutation profile to that of 1,3-butadiene (Group 1) in experimental animals. The Advisory Group therefore considered an *IARC Monographs* evaluation of isoprene to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

178 Methanol (CAS No. 67-56-1)

Current IARC/WHO classification

Methanol has not previously been evaluated by the *IARC Monographs* programme. Methanol was given a priority rating of *low* by the 2019 Advisory Group on Priorities (IARC, 2019a). The IPCS has published an evaluation of health effects of methanol (WHO, 1997).

Exposure characterization

Methanol is a water-soluble compound used as a precursor in the production of various essential chemicals and consumer products. It serves as an industrial chemical with varied uses, e.g. as an additive in fuel and antifreeze, industrial solvent, denaturant, and paint stripper (IPCS 1988). It is also used in the synthesis of compounds such as formaldehyde, acetic acid, and methyl tertiary butyl ether (Samoto et al., 2006; IHS Chemical, 2016; Tabibian and Sharifzadeh, 2023). Methanol is listed as high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). Methanol has been detected in workplace samples from a biodiesel manufacturing facility (Law et al., 2007) and plastics manufacturing (Kawai et al., 1992). In the general population, exposure occurs mainly through consumption of fermented beverages, fruits, fruit-based products, vegetables, which naturally contain methanol, and as a metabolite of the artificial sweetener aspartame (Group 2B). Children who consume substantial amounts of fruit purées may be particularly exposed to methanol (Gürler and Bayram, 2023). The daily exposure to methanol from all sources based on blood levels was estimated to be 0.13–1.03 g per day (Dhareshwar and Stella, 2008). The methanol content of some foods, such as alcoholic beverages, is regulated in many countries. Human exposure may also occur from methanol admixture in counterfeited or illegally manufactured alcohol products (unrecorded alcohol), which has regularly led to poisoning outbreaks with high morbidity and mortality (Lachenmeier et al., 2021).

Cancer in humans

The only informative epidemiological study is a cancer mortality cohort study of 25 000 workers in the Republic of Korea exposed to methanol in their occupations (Min et al., 2019). Exposure metrics based on categorical job duration and workplace methanol exposure levels found lower cancer mortality rates among exposed workers compared with the general population, but with concern about healthy-worker bias. Furthermore, exposure was not individually measured but represented the median exposure level of all workers within the workplace.

Cancer in experimental animals

A 2-year study with drinking-water containing methanol was conducted in Sprague-Dawley rats (Soffritti et al., 2002a). Dose-related increases of carcinomas of the head and neck, mainly in the ear ducts, in both sexes were reported. In addition, there were statistically significant increases of testicular interstitial cell hyperplasias and adenomas at the highest dose, an increase in sarcomas of the uterus at the highest dose, a dose-related increase in osteosarcomas of the head, and in haemolymphoreticular neoplasias in both sexes. In another study with oral administration (Apaja, 1980), increased incidence of malignant lymphoma was reported in both sexes in mice (IARC, 2019a). In studies of inhaled methanol in rat and mouse, no increase in neoplasms was found, even at high air levels that caused 10-fold increased blood methanol levels (NEDO, 1985a, b).

Mechanistic evidence

Methanol is readily absorbed by all routes (inhalation, ingestion, or dermal exposure) and distributed in the body water (~0.7 L/kg) in exposed humans (Ashurst and Nappe, 2023). It undergoes extensive metabolism, and the majority is excreted as carbon dioxide, with small quantities excreted unchanged by the lungs and in the urine. In the liver, alcohol dehydrogenase oxidizes around 70–80% of methanol into formaldehyde, which is oxidized by aldehyde dehydrogenase to formic acid (WHO, 1997; Moon, 2017). Formic acid is not easily eliminated but mostly accumulates, and a small amount of formate interacts with folate to create carbon dioxide and water for exhalation (Ashurst and Nappe, 2023). In humans and primates, the toxicity of methanol is mediated through metabolites and not the parent molecule, because methanol is metabolized and does not accumulate as in rodents. Formic acid is considered to be the key toxicant, especially in the CNS.

Methanol is not considered to be a mutagen in humans (Public Health England, 2016). In contrast, formaldehyde, the main metabolite of methanol, increased the levels of chromosomal aberrations and DNA damage in a group of workers exposed to formaldehyde (Costa et al., 2015). Methanol can cause acute toxicity if ingested or inhaled, and dermal exposure can cause systemic toxicity in humans (Public Health England, 2016). Intraperitoneal administration of methanol does not lead to accumulation of oxidative DNA damage in bone marrow and spleen of mice, rabbits, or primates (McCallum et al., 2011). One study described decreases in various antioxidant enzymes after 15 and 30 days of methanol exposure in rats, suggesting that oxidative stress could occur in the hypothalamic–pituitary–adrenal axis (Parthasarathy et al., 2006).

Some acute inflammatory markers in nasal secretions (IL-8 and IL-1β) were significantly increased after exposure of 12 healthy volunteers to 200 ppm of methanol for 4 hours (Mann et al., 2002). Soffritti et al. (2002a) reported lung inflammation present in dying rats. Immunosuppressive properties of methanol were investigated in experimental animals. In rats, an acute intoxication with methanol (1.0 LD_{50}) reduced cellular and humoral immune responses and the blood concentration of immunoregulatory (IFNγ , IL-2, IL-4) and pro-inflammatory (TNF, IL-1 β, IL-6) cytokines (Zabrodskii et al., 2016). Another study in rats showed a huge decrease in corticosterone levels, a decrease of the cell-mediated immune response of footpad thickness, decreased neutrophil functions, and increased leukocyte migration inhibition (Parthasarathy et al.,

2006). Workers exposed to methanol had increased prevalence of a homozygous type of *TNF* gene and a heterozygous variant of the *CYP* gene (Dolgikh et al., 2013). These genetic changes were associated with decreased transcription of p53 protein and TNF receptor (Dolgikh et al., 2013).

Methanol perturbed the programmed cellular death pathway in workers exposed to methanol (Dolgikh et al., 2013). Methanol intoxication for 30 days induced apoptosis, measured as DNA fragmentation in rat hypothalamus, adrenal gland, and spleen (Parthasarathy et al., 2006). Methanol can inhibit cell differentiation and proliferation in the retina at the early developmental stage of zebrafish embryos exposed for 24 hours (Fu et al., 2017a). Finally, one study in exposed humans has reported chronic blood serum proteome changes in patients with methanol poisoning (Cejnar et al., 2022). The most important proteins were associated with blood coagulation, metabolism of vitamin A (increased retinol-binding protein), immune response (increased complement factors I, C3 and C5), and lipid transport (increased apolipoprotein A I and II, adiponectin).

Summary

No evidence of human cancer was found for methanol. However, 70–80% of methanol absorbed is metabolized as formaldehyde, which is carcinogenic to humans (Group 1) (IARC, 2006a). There are data supporting potential carcinogenicity in experimental animals. There is evidence that methanol exhibits KCs, in particular immunosuppressive properties in exposed humans and experimental systems. The Advisory Group therefore considered an *IARC Monographs* evaluation of methanol to be warranted.

Recommendation: High priority (and ready for evaluation within 2.5 years)

179 *para*-Cresol (CAS No. 106-44-5)

Current IARC/WHO classification

para-Cresol has not previously been evaluated by the *IARC Monographs* programme. The IPCS has published an evaluation of health effects of cresols (WHO, 1995a).

Exposure characterization

para-Cresol (4-hydroxytoluene, 4-methylphenol) is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). Cresols are used as industrial solvents, to make synthetic resins, and in disinfectants and deodorizers, as well as to make other chemicals. They occur in foods, wood, tobacco smoke, crude oil, and coal tar. They are part of chemical mixtures such as creosote that can be used as wood preservatives. They also occur as bioproducts from organisms in soil and water (NCBI, 2024f). There is evidence that *para*-cresol may be formed by gut microbial flora (Al Hinai et al., 2019). Cresols are obtained by chemical synthesis or distillation from petroleum or coal tar (Dietz, 1991). They are widely used as disinfectants (Chang et al., 2014) and may also be found in some resins, pesticides, industrial solvents, wood preservatives, and tobacco smoke (Dietz, 1991). Occupational exposure may occur during production, and the general population may be exposed mainly via tobacco smoke, air pollution or contaminated water or soil (Dietz, 1991).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

An increased incidence of skin papilloma was observed among mice dermally exposed to any of the three cresol isomers following an initial application of dimethylbenzanthracene (Boutwell and Bosch, 1959). A 2-year study investigating a 60:40 mixture of *meta*- and *para*-cresol (selected to mimic the ratio of isomers

distilled from coke-oven tars) fed to rats and mice found no clear evidence of carcinogenicity; the only notable finding was an elevated incidence of forestomach squamous cell papilloma in female mice exposed at the highest concentration (10 000 ppm) (Sanders et al., 2009).

Mechanistic evidence

As summarized in a Health Canada report (Health Canada, 2016), *para*-cresol was not mutagenic across strains of *S. typhimurium* with or without hamster or rat S9 (NTP, 1992b), increased chromosome aberrations in CHO cells (Anonymous, 2012), and did not increase SCE in human fibroblasts (Cheng and Kligerman, 1984). A 60:40 mixture of *meta*- and *para*-cresol did not affect the frequencies of micronucleated erythrocytes in peripheral blood from male or female mice in 13-week studies conducted by the NTP (NTP, 1992b). On the other hand, there is evidence that *para*-cresol is genotoxic in HT-29 and Caco-2 colorectal carcinoma cell lines (Al Hinai et al., 2019). A study of *para*-cresol in the human hepatocyte cell line HepaRG demonstrated exposure-dependent changes in measures of oxidative stress, GSH depletion, and cellular necrosis (Zhu et al., 2021c). A 2-year study with male rats and female mice observed exposure-related kidney and thyroid toxicity, as well as non-neoplastic lesions in the respiratory tract and liver (NTP, 2008). *para*-Cresol also promoted the invasion and migration of human bladder cancer TSGH830 cells (Hsu et al., 2019) and HepG2 human liver cancer cells (Chen et al., 2023c).

Summary

No studies on cancer in humans were available. There is sparse evidence of cancer in experimental animals and mechanistic evidence of carcinogenicity for *para*-cresol. The Advisory Group therefore considered that an *IARC Monographs* evaluation of *para*-cresol is unwarranted at present.

Recommendation: No priority

180 Sulfolane (CAS No. 126-33-0)

Current IARC/WHO classification

Sulfolane has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Sulfolane is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). In 2003, it was estimated that global production was approximately 13 300 tons per year (OECD, 2004). Other estimates suggest global production of 18 000–36 000 tonnes per year (Thompson et al., 2013). Sulfolane is primarily used in the oil and gas industry and acid gas purification, as a solvent to extract aromatic hydrocarbons (80% of usage). It is used in several other processes including hydrocarbon fractionation, electronics, and textiles manufacturing, as a plasticizer, pharmaceutical industry, jet ink printing, and component in hydraulic fluid and as a curing agent for epoxy resins (OECD, 2004). A newer use has been noted in the manufacture of lithium-ion batteries (Li et al., 2023b). It is a metabolite of the drug busulfane, which is used for the treatment of myelofibrosis (Dadkhah et al., 2022). OECD (2004) noted occupational exposures during drum filling as part of the production of the chemical and potential exposures for downstream users. It was also noted that sulfolane has been found in "significant amounts in water, groundwater and vegetation" near production areas, suggesting exposure via drinking-water and food crop ingestion from environmental releases (OECD, 2004).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group. A chronic toxicity study involving rats and mice is in progress at the US NTP (NTP, 2024d).

Mechanistic evidence

The genotoxicity of sulfolane has been evaluated in various experimental systems in vitro, yielding predominantly negative results (US EPA, 2012a). Animal studies have identified reproductive/developmental and immunological effects related to sulfolane exposure. A study of rats exposed to sulfolane during preconception, gestation, and lactation identified increased litter loss, reduced litter size and lower pup weights at doses ≥ 200 mg/kg per day (OECD, 2004). Increased fetal resorptions and skeletal anomalies in prenatal mice with exposure have also been reported (Zhu et al., 1987). Mild to moderate decreases in leukocyte count with exposure have been observed in several animal studies (ATSDR, 2011). In Sprague-Dawley rats, evidence of decreased NK cell activity in spleen cells from F1 females but not males was seen after developmental exposure (Watson et al., 2021).

Summary

No studies on cancer in humans were available. No evidence of carcinogenicity of sulfolane in experimental animals was identified and there is no clear mechanistic evidence for any KCs. The Advisory Group recommended that the priority of this chemical be reconsidered after the NTP bioassay data become available.

Recommendation: Medium priority

181 Tetrachloroethylene (perchloroethylene) (CAS No. 127-18-4)

Current IARC/WHO classification

Tetrachloroethylene (perchloroethylene) has previously been evaluated by the *IARC Monographs* programme as *probably carcinogenic to humans* (Group 2A) in Volume 106 in 2012 (IARC, 2014b), on the basis of *limited* evidence for cancer in humans (for bladder cancer) and *sufficient* evidence for cancer in experimental animals. Tetrachloroethylene was given a priority rating of *high* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of new human cancer evidence. The IPCS has published an evaluation of health effects of tetrachloroethylene (WHO, 1984).

Exposure characterization

Tetrachloroethylene is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). Tetrachloroethylene is a chlorinated solvent which has been used in degreasing in the metal industry and other industries (IARC, 2014b). It has been widely used as a solvent in dry cleaning. Co-exposure to other solvents might occur; for example, trichloroethylene was also used in dry cleaning before being phased out due to health concerns (Callahan et al., 2019). Tetrachloroethylene does not occur naturally but is a widespread environmental contaminant due to its uses, including industrial releases (IARC, 2014b). Occupational exposure occurs mainly via inhalation, while the general population may be exposed via the air and contaminated drinking-water or food.

A review of exposure levels (Gold et al., 2008) found that the overall arithmetic mean exposure in workers undertaking degreasing tasks was 95 ppm (range 0–1800, $n = 206$). The mean for personal tetrachloroethylene exposures in the dry-cleaning industry was 59 ppm (range: 0–4636, $n = 1395$), with the highest levels found in machine operators who transferred wet garments to a dryer (arithmetic mean = 150 ppm, range 0–1000, $n = 441$). High levels of tetrachloroethylene exposure were also seen in

cleaning mining equipment, testing coal, cleaning animal coats in taxidermy, and cleaning and duplicating film.

Cancer in humans

Since the most recent *Monographs* evaluation of tetrachloroethylene, some additional studies on tetrachloroethylene exposure and various cancer sites have been published. Concerning bladder cancer, an extended follow-up of a cohort of dry cleaners in the USA found an exposure–response relation with solvent exposure and bladder cancer. HRs were 4.2 (95% CI, 0.7–24.5) in the medium exposure group and 9.2 (95% CI, 1.1–76.7) for high exposure, based on 5 and 3 cases, respectively (Callahan et al., 2019). One additional new study assessed health outcomes in a cohort of microelectronic and business machine manufacturing workers in the USA (Silver et al., 2014). There was no association between tetrachloroethylene exposure and bladder cancer. In a new case–control study performed using the Nordic Occupational Cancer Database, Hadkhale et al. (2017) estimated cumulative occupational exposures using a job–exposure matrix and found a significant positive association between tetrachloroethylene exposure (measured based on job titles) and bladder cancer in the medium but not the highest exposure category (HR, 1.12; 95% CI, 1.02–1.23 and HR, 0.94; 95% CI, 0.73–1.22, respectively).

More than a dozen new studies for other cancer sites such as liver, kidney, breast, and head and neck, and for NHL and CLL, for which the evidence had been evaluated as *inadequate* by the previous Working Group, have been published. There are few new studies for each cancer site, with mixed results of some positive and some null associations between tetrachloroethylene exposure and cancer risk.

Cancer in experimental animals

In the last evaluation of tetrachloroethylene (IARC, 2014b), there was *sufficient* evidence in experimental animals for the carcinogenicity of tetrachloroethylene.

Mechanistic evidence

In the last evaluation of tetrachloroethylene, it was noted that its metabolic activation via the GSH-conjugation pathway leads to the formation of genotoxic metabolites. Since then, the genotoxicity of tetrachloroethylene has been intensively investigated (Lovell, 2010), with several studies in exposed humans.

Azimi et al. (2017) examined 33 dry cleaners and 26 controls, conducting comet assay on peripheral blood lymphocyte samples. A significant increase in primary DNA damage was seen among the exposed individuals (dry cleaners) versus the non-exposed. However, no correlation was determined between the duration of employment and DNA damage (Azimi et al., 2017). One biomonitoring study collected personal air samples and peripheral blood from 59 volunteers (30 exposed dry-cleaning workers and 29 controls) and showed that dry cleaners had higher micronucleus frequency and DNA damage, measured by comet assay, compared with the control group. Also, there was a significant association between chromosome aberrations and employment duration and frequency of exposure (Everatt et al., 2013). A smaller study with 18 dry-cleaning workers and 18 laundry workers (unexposed controls) showed no significant difference between the tetrachloroethylene-exposed dry cleaners and the laundry workers for chromosome translocation frequencies, but tetrachloroethylene levels were significantly correlated with percentage of cells with acentric fragments (Tucker et al., 2011). However, another study found that women exposed to tetrachloroethylene while working in dry-cleaning shops had lower levels of oxidative DNA damage than launderers without tetrachloroethylene exposure, although the exposure levels in this study were well below recommended exposure limits (Toraason, et al., 2003).

Summary

A growing number of studies show associations between occupational exposure to tetrachloroethylene and bladder cancer, with new studies since the last evaluation. Most studies mainly include dry cleaners or other workers, and one recent study shows a dose–response relation. Some informative studies that are in progress may not become available within 5 years. (Any evaluation of tetrachloroethylene may also benefit from a re-evaluation of dry cleaning as an occupation, which is currently classified in Group 2B). For all other cancer sites, results are inconclusive. A small number of mechanistic studies suggest that tetrachloroethylene is genotoxic in exposed humans. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of tetrachloroethylene to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

182 Xylenes (CAS No. 1330-20-7)

Current IARC/WHO classification

Xylenes have previously been evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in Volume 71 in 1998 (IARC, 1999d).

Exposure characterization

Xylenes are listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). Xylenes are a group of aromatic hydrocarbons consisting of *ortho*-, *meta*- and *para*-xylene, and these compounds are often quantified as part of the group of "benzene, toluene, xylene" (BTX). Xylenes are colourless liquids occurring naturally in petroleum and coal (ATSDR, 2007).

Xylene is widely used in industry and medical technology as a solvent. The main applications are in the printing, rubber, and leather industries. It is also used as a cleaning agent, a thinner for paint, and in paints and varnishes. It is found in small amounts in aeroplane fuel, gasoline, and cigarette smoke (Kandyala et al., 2010). In the biomedical field, xylene is used in histological laboratories for tissue-processing, tissue-staining, and coverslipping, and also in endodontic retreatment as a guttapercha solvent (Kandyala et al., 2010). In addition to occupational exposure, human contact may result from soil contaminated by leaking underground storage tanks containing petroleum products. Xylene can leak into the soil, surface water or groundwater (Kandyala et al., 2010). Xylene is present in combustion emissions (Alberta Environment, 2004). The general population can be exposed via air pollution from combustion emissions.

Cancer in humans

There was *inadequate* evidence for cancer in humans in the previous IARC evaluation of xylene (IARC, 1999d). Data from a retrospective cross-sectional study from NHANES, investigating the relation between volatile organic aromatic compounds in the blood across adulthood and mortality, identified a higher risk of cancer among participants with exposure to benzene, ethylbenzene, and *ortho*-xylene (Malik et al., 2022; and Li et al., 2022d). Other population-based case–control studies have provided suggestive evidence that occupational exposure to one or more of the BTX agents may be associated with cancers of the lung, prostate, and bladder (Blanc-Lapierre et al., 2018; Warden et al., 2018; Xie et al., 2024b). Sporadic positive associations have been reported for other cancer sites and exposure to xylenes.

Cancer in experimental animals

In 1985 the NTP conducted a carcinogenicity study of technical-grade xylenes (60% *meta*-xylene, 14% *para*-xylene, 9% *ortho*-xylene, 17% ethylbenzene) administered by oral gavage to rats and mice. No increased incidence of tumours with exposure was observed in either mice or rats (NTP, 1986c). No

additional carcinogenicity studies were available to the Advisory Group, but another NTP bioassay is underway with a different route of administration.

Mechanistic evidence

A Substance Evaluation Conclusion document published by the ECHA in 2021 provided a summary of the findings from 30 studies investigating the genotoxicity of xylenes across a range of test systems in vitro and in vivo (ECHA, 2021b). Most studies suggested no evidence of genotoxicity. One exception was a study that conducted comet assay testing of human peripheral blood lymphocytes in vitro and observed exposure-related increases in DNA damage for *meta*-xylene, *para*-xylene, and *ortho*-xylene (Chen et al., 2008). The ECHA report noted some limitations in the design of this study, including the lack of a standardized evaluation of comet tail length, lack of use of a metabolic activation system, and absence of historical controls. In a genotoxicity study of xylenes in human promyelocytic leukaemia cells, not included in the ECHA report, dose-related increases in cell apoptosis, ROS generation, and DNA damage were observed. Pre-treatment with the ROS scavenger *N*-acetylcysteine weakened the effects of xylenes, suggesting that ROS play a major role in inducing xylene-related cell damage (Sarma et al., 2011).

Summary

Positive findings for human cancer are only sporadic, and the exposure was not specific to xylene. There is no evidence of cancer in experimental animals and no sufficient mechanistic evidence of genotoxicity or other KCs. The evidence to date is unlikely to support a change in classification, but the Advisory Group recommended that the priority of this chemical should be reconsidered after the NTP bioassay data become available.

Recommendation: Medium priority

183 Diisononyl cyclohexane-1,2-dicarboxylate (DINCH) (CAS No. 166412-78-8)

Current IARC/WHO classification

Diisononyl cyclohexane-1,2-dicarboxylate (DINCH) has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

DINCH is commonly used as a plasticizer and is found in products ranging from food packaging and children's toys to medical materials such as infusion tubes and blood bags, as well as in printing inks, paints, and textile coatings. DINCH has been increasingly used as a substitute for traditional phthalates following regulatory restrictions for these compounds (Schaffert et al., 2021). Since its introduction in 2002, the production of DINCH has seen a noticeable growth (200 000 tonnes per year in 2014 (BASF SE, 2014)), reflecting its rising adoption across various industries. This widespread application in everyday products has led to frequent detection of DINCH metabolites in human urine samples, suggesting extensive exposure among the general population (Vogel et al., 2023a, b).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

A series of studies with intravenous injection or intravenous infusion of DINCH to rats did not reveal any apparent systemic effects (David et al., 2015). In addition, several unpublished GLP studies were

conducted according to the most recent OECD guidelines. Exposure of rats to DINCH at various doses and exposure regimes did not cause any pathology related to increased cancer risk (EFSA, 2006b; Bhat, et al., 2014).

Mechanistic evidence

One prospective cohort study suggested that urinary concentrations of a DINCH metabolite was inversely correlated with estradiol levels among women undergoing in vitro fertilization treatments (Mínguez-Alarcón et al., 2016). In experimental systems, DINCH activates the human nuclear receptors ERα, ERβ, AR, PPARα, and PPARγ (Engel et al., 2018; Campioli et al., 2019). The naturally occurring metabolite of DINCH, the monoisononyl ester known as MINCH, induced cellular stress and pro-inflammatory effects in human macrophages (Schaffert et al., 2021).

DINCH and MINCH did not directly affect differentiation of rat cells in vitro, while in these cells MINCH affected the expression of Cebpa and Fabp4, inducing preadipocytes to accumulate lipids and fully differentiate into mature adipocytes (Campioli et al., 2015).

DINCH induced oxidative DNA damage in HepG2 liver cells. No marked chromosomal damage was noted after short-term or longer treatment of liver and kidney cell lines, estimated by micronuclei (Vasconcelos et al., 2019). DINCH and MINCH induced mitochondrial dysfunction, increased ROS, and enhanced inflammatory responses in human THP-1 macrophages (Schaffert et al., 2021). DINCH was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP2 *uvrA* with or without rat liver S9 (Bhat et al., 2014). Results were also negative in a forward gene mutation assay at the HPRT locus in CHO cells with or without rat liver S9 mix. DINCH failed to induce structural chromosomal aberrations in V79 Chinese hamster lung cells with or without rat liver S9 mix (Bhat et al., 2014). Micronucleated polychromatic erythrocytes (PCE) were not observed in the bone marrow of male NMRI mice given a single intraperitoneal injection of DINCH (Bhat et al., 2014).

Summary

No human cancer studies were available, and the existing studies of cancer in animals did not show carcinogenic effects for DINCH. There is sparse mechanistic evidence for DINCH and its metabolite MINCH in experimental systems. The Advisory Group therefore considered that an *IARC Monographs* evaluation of diisononyl cyclohexane-1,2-dicarboxylate is unwarranted at present.

Recommendation: No priority

184 1,2-Dihydroxybenzene (pyrocatechol) (CAS No. 120-80-9)

Current IARC/WHO classification

1,2-Dihydroxybenzene (pyrocatechol) has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Volume 71 in 1998 (IARC, 1999d).

Exposure characterization

1,2-Dihydroxybenzene is listed as a high production volume chemical by the OECD and the US EPA (OECD, 2007; US EPA, 2024a). 1,2-Dihydroxybenzene is used as a photographic developer, a developer for fur dyes, as an intermediate for antioxidants in rubber and lubricating oils, in polymerization inhibitors, and in the pharmaceuticals industry mainly in small quantities as a laboratory reagent for raw material testing (IARC, 1999d; Environment Canada, 2007a). It is also used as an antioxidant in electroplating baths, where it is destroyed (oxidized) during the process (Environment Canada, 2007b). 1,2-Dihydroxybenzene also has cosmetic applications such as in hair dyes, perfumes, and essential oils (IARC, 1999d; NICNAS, 2014).

1,2-Dihydroxybenzene can be absorbed by inhalation of an aerosol, by ingestion and through the skin. The major exposure routes for the general population are consumption of contaminated drinking-water and ingestion of contaminated food (US EPA, 2000b). Occupational exposure to 1,2-dihydroxybenzene may occur during its manufacture and use, if adequate control measures to minimize exposure to the chemical are not implemented (NICNAS, 2014).

Cancer in humans

In an untargeted metabolomic analysis performed on prediagnostic plasma samples from a case–cohort study of 1695 incident breast cancer cases and a subcohort of 1983 women drawn from the Cancer Prevention Study, an association was found between catechol glucuronide (a 1,2-dihydroxybenzene metabolite) and increased breast cancer risk (Stevens et al., 2023).

Cancer in experimental animals

In the previous evaluation (IARC, 1999d), there was *sufficient* evidence in experimental animals for the carcinogenicity of 1,2-dihydroxybenzene. Since then, additional carcinogenesis studies with 1,2-dihydroxybenzene in rats have been conducted, in which glandular stomach tumours were observed (Hirose et al., 1999; Hagiwara et al., 2001). 1,2-Dihydroxybenzene co-administered with *N*-diethylnitrosamine induced forestomach and glandular tumours (Kobayashi et al., 1997, 1999; Yafune et al., 2014), and forestomach initiation treatment followed by 1,2-dihydroxybenzene caused forestomach tumours (Taniai et al., 2012; Kobayashi et al., 1999).

Mechanistic evidence

1,2-Dihydroxybenzene induces oxidative DNA damage in human HL-60 and HP100 cells (Oikawa et al., 2001). Dietary catechol caused increased oxidative DNA damage in livers of mice treated with acetaminophen (Ishii et al., 2009). Subacute co-exposure to 1,2-dihydroxybenzene and sodium nitrite increased levels of 8-OHdG in rat forestomach epithelium, followed by epithelial injury and hyperplasia (Ishii et al., 2006). 1,2-Dihydroxybenzene alters cell proliferation and the cell cycle. In vivo cell-cycle fluctuations, cell proliferation, and hyperplasia have been observed in rats (Hirose et al., 1999; Hagiwara et al., 2001; Taniai et al., 2012).

Summary

Little evidence of cancer in humans is available. There is already *sufficient* evidence that 1,2-dihydroxybenzene causes cancer in experimental animals. Several studies show data for genotoxicity, oxidative DNA damage, and cell proliferation in experimental systems in vitro and in vivo. However, no evidence is available for exposed humans or human primary cells or tissues. Thus, a change in classification is unlikely, and the Advisory Group therefore considered that an *IARC Monographs* re-evaluation of 1,2-dihydroxybenzene is unwarranted at present

Recommendation: No priority

185 1,4-Dioxane (CAS No. 123-91-1)

Current IARC/WHO classification

1,4-Dioxane has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Volume 71 in 1998 (IARC, 1999d), on the basis of *sufficient* evidence for cancer in experimental animals.

Exposure characterization

1,4-Dioxane is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). 1,4-Dioxane is a clear, colourless liquid with a faint sweet odour. It can dissolve a wide range of substances and is primarily used as a solvent stabilizer for chlorinated solvents in various industries (IARC, 1999d). It is used mainly in the production of rubber and plastics. Moreover, 1,4-dioxane can be produced as a by-product and impurity in certain chemical processes, including the production of polyethylene terephthalate, consumer detergents, industrial detergents, and cleaning compounds. Environmental presence of dioxane is primarily attributed to wastewater and air discharges at sites involved in its production, processing, and utilization (Godri Pollitt et al., 2019; Adamson et al., 2017). Elevated levels of 1,4-dioxane have been detected in landfill leachates arising from materials containing this compound in landfills (Mohr, 2020). Exposure to 1,4-dioxane occurs through occupational exposure, consumer products, or contact with water, land, or air where 1,4-dioxane has been released (Doherty et al., 2023).

Cancer in humans

No new informative epidemiological studies have been conducted since *IARC Monographs* Supplement 7 (IARC, 1987a). The only study in humans with cancer data is Buffler et al. (1978).

Cancer in experimental animals

In the previous evaluation (IARC, 1999d), there was *sufficient* evidence in experimental animals for the carcinogenicity of 1,4-dioxane. Since that evaluation, two cancer bioassays on the carcinogenicity of 1,4-dioxane by oral administration in mice and rats (Kano et al., 2009), and one by inhalation in rats (Kasai et al., 2009) have been published.

Mechanistic evidence

Mechanistic data are available only in experimental systems, not in human primary cells (or tissue) or exposed humans. The US EPA reviewed more than 40 studies on genotoxicity of 1,4-dioxane and concluded that "there is some evidence for genotoxicity in vivo at high doses, but there is insufficient evidence to conclude that 1,4-dioxane is mutagenic or induces cancer through a mutagenic mode of action" (US EPA, 2020b). 1,4-Dioxane forms DNA adducts in the liver of gpt-deficient rats (Totsuka et al., 2020). In a recent review, Lafranconi et al. (2023) concluded that the mode of carcinogenic action of 1,4-dioxane in rodents is dependent on metabolic or clearance saturation of absorbed 1,4-dioxane, direct mitotic response, and induction of Cyp2E1 activity and oxidative stress that led to some genotoxicity and cytotoxicity followed by sustained proliferation. A number of studies have investigated non-genotoxic mechanisms of 1,4-dioxane in experimental systems (e.g. Gi et al., 2018; Chappell et al., 2021).

Summary

No new evidence from epidemiological studies of cancer in humans was found. There is *sufficient* evidence that 1,4-dioxane causes tumours in experimental animals supporting its Group 2B classification. There is no new mechanistic information related to the KCs in studies in exposed humans or human primary cells or tissues. The Advisory Group therefore considered that an *IARC Monographs* re-evaluation of 1,4-dioxane is unwarranted at present.

Recommendation: No priority

186 2,3-Butanedione (CAS No. 431-03-8)

Current IARC/WHO classification

2,3-Butanedione (commonly known as diacetyl) has not previously been evaluated by the *IARC Monographs* programme. 2,3-Butanedione was evaluated in 1998 by the JECFA, which determined that there was no safety concern at current levels of intake when it is used as a flavouring agent (FAO/WHO, 1998b). 2,3-Butanedione was given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of bioassay and mechanistic evidence.

Exposure characterization

2,3-Butanedione is commonly used in the production of artificial flavour formulations, the production of which exceeds 18 tonnes per year in Europe and 42 tonnes per year in the USA (WHO TRS 891, 2000). Examples of flavoured food products containing the compound include cake mixes, flour, beer, wine, margarines and soft spreads, cheese, confectionery, bakery products, crackers, popcorn, cookies, ice cream, and frozen foods. 2,3-Butanedione is "generally recognized as safe (GRAS)" by the US FDA for use in foods. It also occurs naturally in butter, various fruits, coffee, honey, and other foods and as a fermentation by-product in wine, beer, and dairy products. Non-occupational exposure to 2,3-butanedione is primarily by ingestion, whereas occupational exposure to 2,3-butanedione occurs mainly by inhalation of vapours (NIOSH, 2016a). Inhalation exposure may also occur from tobacco smoking, and use of electronic cigarettes and flavoured tobacco products (NTP, 2018d; IARC, 2019a).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

2,3-Butanedione exposure by inhalation induced SCCs of the nasal mucosa in male and female rats, while in female mice it induced a non-significant number of nasal adenocarcinomas (NTP, 2018d). In female mice, intraperitoneal injection of 2,3-butanedione led to a dose-dependent increase in the incidence and multiplicity of lung tumours, an effect not observed in male mice (Stoner et al., 1973). In a mouse model of progression of non-alcoholic steatohepatitis to HCC, 2,3-butanedione, identified by non-target profiling analysis among faecal volatile organic compounds, was associated with tumour appearance (Kato et al., 2023).

Mechanistic evidence

There is evidence that 2,3-butanedione is electrophilic. When incubated with *N*-α-acetylarginine, 2,3-butanedione formed ring-opened and cyclic adducts with the guanidine nitrogens (Mathews et al., 2010). There is evidence that 2,3-butanedione is genotoxic. It induced a highly mutagenic response in the L5178Y mouse lymphoma mutation assay in the presence of human liver S9 for activation: there was an increased frequency of small colonies with multiple loci on chromosome 11 in addition to functional loss of the thymidine kinase locus (Whittaker et al., 2008). Exposure of human liver THLE2 cells to 2,3-butanedione caused DNA damage, indicated by an increase in tail length, tail DNA%, and tail moment (Salama et al., 2023). 2,3-Butanedione was mutagenic in *S. typhimurium* strains TA100, TA102, and TA104 (with and without rat liver S9 activation). It is also mutagenic in mouse lymphoma L5178 $tk^{+/-}$ cells in the presence of human liver S9 (NTP, 2018d). Mitotic chromosome loss was induced by 2,3-butanedione in *S.cerevisiae*, but only when combined with subacute concentrations of propionitrile, which is a strong inducer of chromosomal segregation (Zimmermann and Mohr, 1992).

Ingestion of 2,3-butanedione by rats disrupted the liver oxidant/antioxidant balance, as shown by alterations in levels of GSH, SOD, CAT, GPX, GR, MDA, NO, and peroxynitrite, and increased levels of inflammatory cytokines (Salama et al., 2023). Administration of 2,3-butanedione by inhalation to male and female mice induced significant increases in neutrophil counts consistent with inflammation, squamous metaplasia of the respiratory epithelium, atypical hyperplasia and atypical squamous metaplasia of the bronchial epithelium, and metaplasia of the olfactory epithelium (NTP, 2018d). Using primary human airway epithelial cells and single-cell sequencing, it was shown that 2,3-butanedione decreased the proportion of basal cells expressing keratin 5, whereas the proportion of cells aligned to secretory cell clusters increased, that is associated with bronchiolitis obliterans, a fibrotic lung disease and thus relevant to KC6 (chronic inflammation) (Chu et al., 2024). In mice and rats treated with 2,3-butanedione, binding to albumin and haemoglobin through arginine caused bronchiolitis obliterans (Fennell et al., 2015). 2,3-Butanedione induced several pro-inflammatory molecules, including TNFα, cyclooxygenase-2, monocyte chemoattractant protein-1, and transforming growth factor-β, in mouse macrophage RAW264.7 and Kupfer KPU5 cells (Kato et al., 2023). In addition, 2,3-butanedione increased EGFR-dependent IL-8 production in human lung mucoepidermoid carcinoma cells (Kelly et al., 2019), increased the EGFR ligand amphiregulin in the pulmonary epithelial cell line NCI-H292 and in primary human airway epithelial cells inhibiting a TNFα-converting enzyme by specific small inhibitor RNA (Kelly et al., 2014).

Summary

There is no evidence for cancer in humans. There is evidence that 2,3-butanedione causes tumours in male and female rats and in female mice. There is substantial evidence that 2,3-butanedione exhibits KCs in experimental systems and in human primary cells. The Advisory Group therefore considered an *IARC Monographs* evaluation of 2,3-butanedione to be warranted.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

187 2,4-Dihydroxybenzophenone (benzophenone-1) (CAS No. 131-56-6)

Current IARC/WHO classification

2,4-Dihydroxybenzophenone (commonly known as benzophenone-1) has not previously been evaluated by the *IARC Monographs* programme. 2,4-Dihydroxybenzophenone was given a priority rating of *low* by the 2019 Advisory Group on Priorities (IARC, 2019a). Benzophenone was classified by IARC as *possibly carcinogenic to humans* (Group 2B), with no data in humans and *sufficient* evidence of carcinogenicity in experimental animals (IARC, 2013c).

Exposure characterization

2,4-Dihydroxybenzophenone is a UVR blocker that is used in many cosmetic products (e.g. sunscreens, hair products, lipsticks, toothpastes, and nail polishes) as well as in paints and plastics, because it helps to prevent the degradation and discolouration of materials caused by UVR exposure (Yao et al., 2023b).

The following information concerns the group of benzophenones, because little specific information on 2,4-dihydroxybenzophenone exposure was available to the Advisory Group. Benzophenones can be absorbed by the human body through various routes, including dermal absorption, inhalation, and oral ingestion. Studies have reported the occurrence of benzophenones in drinking-water, seafood, and packaged foods. Indoor air and indoor dust can also contribute to inhalation exposure to benzophenones (Yao et al., 2023b). According to Lu et al. (2018), the estimated average dermal intake of benzophenones (including

2,4-dihydroxybenzophenone) from personal care products in 280 schoolchildren in China was as high as 283 ng/kg bw per day.

Some studies have shown that benzophenones are present in human urine and blood (Zhang et al., 2022e), breast milk (Hines et al., 2015; Iribarne-Durán et al., 2022), semen (Hines et al., 2015), and adipose tissue (Wang et al., 2015). In a review of 158 studies, concentrations of 2,4-dihydroxybenzophenone were up to 92.7 mg/L in urine, followed by blood (up to 0.9 mg/L) and milk (up to 0.8 mg L^{-1}) (Mao et al., 2022). In analyses of maternal and fetal samples from China, Denmark, Spain, and the USA, 2,4-dihydroxybenzophenone was widely found (Yao et al., 2023b).

Cancer in humans

No studies of cancer in humans, for either 2,4-dihydroxybenzophenone or benzophenones as a group, were available to the Advisory Group.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

2,4-Dihydroxybenzophenone has been reported to induce mutations in the TA97 and TA100 *S. typhimurium* strains in the absence of metabolic activation (S9 microsomes) (Wang et al., 2018c). There is some evidence that it disrupts the ER and AR signalling pathways in vitro. 2,4-Dihydroxybenzophenone was also identified as a potent inhibitor of 17β-HSD3-dependent testosterone formation. It acts as a direct AR antagonist, suggesting that the agent causes synergistic effects in vivo by inhibiting testosterone synthesis and blocking AR activation (Nashev et al., 2010). 2,4-Dihydroxybenzophenone inhibits human, rat, and mouse gonadal 3β-hydroxysteroid dehydrogenases (Wang et al., 2023h). Liu et al. (2022g) observed dissemination of SKOV3 ovarian cancer cells in vitro after exposure to 2,4-dihydroxybenzophenone. In fact, the agent promotes proliferation, migration, and invasion of SKOV3 cells by regulating epithelial–mesenchymal transitions (EMT), i.e. downregulating the ZO-1 gene and upregulating the MMP9 gene. The abnormal stimulation and progression of human SKOV3 ovarian cancer cells induced by 2,4-dihydroxybenzophenone were mediated by activation of ERα which triggered crosstalk between the ERα and Wnt/β-catenin pathways (Liu et al., 2022g). In addition, 2,4-dihydroxybenzophenone significantly promoted the growth of human ovarian cancer cells (BG-1 – an estrogen-dependent cell line) similarly to 17β-estradiol, as shown in a cell viability assay. The mechanism underlying BG-1 cell proliferation was proved to be related to the upregulation of cyclin D1 through ERα signalling, a cell cycle progressor. The agent also stimulated BG-1 (ovarian cancer cell) tumour growth in a xenograft mouse model (Park et al., 2013). In addition, Shin et al. (2016) showed that 2,4-dihydroxybenzophenone promoted wound healing, presumably mediated by the ER-dependent pathway, in a migration assay in a BG-1 cell culture. In another study, In et al. (2015) observed migration of MCF-7 breast cancer cells after treatment with 2,4-dihydroxybenzophenone, which was associated with increased expression of cyclin D1 and cathepsin and decreased expression of the senescence marker p21.

Summary

No studies of cancer in humans or of cancer in experimental animals were available in relation to carcinogenicity of 2,4-dihydroxybenzophenone. There is mechanistic evidence suggesting that 2,4-dihydroxybenzophenone exhibits KCs, including genotoxicity, modulation of receptor-mediated effects and cell proliferation in experimental systems. The Advisory Group therefore considered an *IARC Monographs* evaluation of 2,4-dihydroxybenzophenone to be warranted.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

188 2,4-Dimethylphenol (CAS No. 105-67-9)

Current IARC/WHO classification

2,4-Dimethylphenol has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

2,4-Dimethylphenol (also named 2,4-xylenol, *meta*-xylenol or *meta*-4-xylenol) is a fungicide and disinfectant with a variety of agricultural uses as well as many industrial applications (solvent, disinfectant, bactericide) (Lewis et al., 2016). 2,4-Dimethylphenol is also used in making wetting agents, dyestuffs, phenolic antioxidants, pharmaceuticals, rubber chemicals, lubricants, gasoline additives, plasticizers, and a perfuming agent in the cosmetics industry. It is also used in the production of high-viscosity phosphate esters, as a feedstock for hindered phenol antioxidant and specialty modified phenolic resin manufacture (US EPA, 2007; ChemicalBook, 2023).

2,4-Dimethylphenol is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). In 2019, the volume of this chemical that was produced or imported into the USA was reported to be between 10 and 50 million pounds [4536–22 680 tonnes], under the Toxic Substances Control Act's Chemical Data Reporting mechanism (US EPA, 2024a).

2,4-Dimethylphenol is volatile and highly soluble in water. It is not expected to be persistent in soils (Lewis et al., 2016). The main routes of exposure are inhalation of ambient air, ingestion of fish, and dermal exposure by contact with products containing 2,4-dimethylphenol (US EPA, 2007; ChemicalBook, 2023). No information was available on environmental and occupational exposure levels.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

2,4-Dimethylphenol was tested for clastogenicity and for the ability to have spindle poison effects in NMRI mice using the micronucleus test method after oral administration (OECD, 2014). A single oral dose of 2,4-dimethylphenol did not increase the number of polychromatic erythrocytes containing small or large micronuclei. The rate of micronucleus formation was always in the same range as that of the negative controls in all dose groups and at all sacrifice intervals. No inhibition of erythropoiesis, determined from the ratio of polychromatic to normochromatic erythrocytes, was observed (ECHA, 2023f). 2,4-Dimethylphenol was assayed by the NTP in the Ames *Salmonella*/microsome mutagenicity assay and tested weakly positive in two of the tests and negative in one (Mortelmans et al., 1986, NTP, 2023f).

Bukowska et al. (2007) investigated potential effects of various phenols in generating oxidative stress and observed that 2,4-dimethylphenol induced an increase in the concentration- and time-dependent oxidation of H_2DCFDA (fluorescent label 6-carboxy-2′,7′-dichlorodihydrofluorescein diacetate) in human erythrocytes. The agent also induced an increase in carbonyl group content and changes in the denaturation of haemoglobin (parameter T), but not lipid peroxidation in human erythrocytes (Bukowska et al., 2007).

2,4-Dimethylphenol has been screened in the US EPA ToxCast programme for induction of hormone synthesis in the in vitro H295R steroidogenesis assay (OECD, 2023), and was found to cause cells to significantly increase production of estradiol and progesterone (Cardona and Rudel, 2021). Increased production of these hormones can raise the risk of breast cancer and other types of hormone-responsive

cancers. The relation between hormone exposure—especially of E2 and progesterone—and breast cancer in experimental animals is well documented (Cogliano et al., 2011; Rudel et al., 2014).

Summary

There is no evidence for cancer in humans or cancer in experimental animals. There is only sparse mechanistic evidence that 2,4-dimethylphenol exhibits KCs, including genotoxicity, oxidative stress, and modulation of receptor-mediated effects; however, findings come mainly from a few experimental systems in vitro. The Advisory Group therefore considered that an *IARC Monographs* evaluation 2,4-dimethylphenol is unwarranted at present.

Recommendation: No priority

189 2,4,6-Tribromophenol (CAS No. 118-79-6)

Current IARC/WHO classification

2,4,6-Tribromophenol (TBP) has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

TBP is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). TBP is the most widely produced brominated phenol (Koch and Sures, 2018). It is used as an antiseptic and germicide; as a chemical intermediate in the production of its bismuth salt (antiseptic), pentachlorophenol, 2,4,6-tribromophenoxy compounds, and 2,4,6-tribromophenyl allyl ether; as a wood preservative; as a flame retardant intermediate; and as a reactive flame retardant.

Occupational exposure may occur in various workplaces, for example at electronics dismantling facilities, in the production of printed circuit boards, or among laboratory personnel (Thomsen et al., 2001). There is potential for consumer exposure to TBP through the consumption of foods (e.g. fish) and beverages that may contain it. There is potential for environmental exposure to TBP through its occurrence in ambient air (from combustion sources) and wastewater. The European Chemicals Agency noted that consumer exposure includes exposure from house dust and indoor air, as well as dermal or oral contact with consumer products (ECHA, 2016).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

In humans, TBP has been detected in blood serum, adipose tissue, placenta, breast milk and urine of environmentally and occupationally exposed individuals (Michałowicz et al., 2022). In a study of human PBMCs using the comet assay to assess DNA damage, TBP was found to exhibit moderate genotoxicity (Cardona and Rudel, 2021), and TBP was also observed to induce chromosome aberrations in a study of human lymphocytes (Alexander et al., 2012). It decreased the activity of antioxidant enzymes SOD and CAT in human erythrocytes (Jarosiewicz et al., 2019). TBP also induced the generation of ROS, as well as lipid and protein oxidation in human PBMCs (Włuka et al., 2020). In a study of Asian freshwater clams, exposure to TBP was observed to inhibit two antioxidant enzymes, *Gsts1* and *Gstm1* (Yan et al., 2017), suggesting an impact on oxidative stress. In mouse splenic lymphocytes, TBP was cytotoxic to B- and T-cell mitogenesis, suggesting potential immunosuppressive effects (Sakazaki et al., 2001). Data from a high-throughput assay

measuring hormone concentrations following exposure of human H295R adrenocortical carcinoma cells to TBP indicated increases in estradiol and progesterone. TBP had estrogen-like activity in a human MCF-7 breast cancer cell line (Olsen et al., 2002; Kay et al., 2024). TBP was also reported to bind to nuclear receptors, causing disturbance in thyroid hormone metabolism and transport in a human choriocarcinoma placenta cell line (Leonetti et al., 2018). Despite binding to estrogen receptors, TBP did not elicit any notable downstream effects, including stimulation of cell growth. However, it was reported to alter transduction pathways, including cellular calcium ion or transforming growth factor-β signalling (Chen et al., 2017).

Summary

Although TBP was nominated as a water disinfection by-product, the Advisory Group noted that this is not the main use or source of human exposure, as described above. There is no available evidence for cancer in humans or in experimental animals. There is only sparse evidence that the agent exhibits KCs including genotoxicity, induction of oxidative stress, immunosuppression, and modulation of receptor-mediated effects, mainly in experimental systems. The Advisory Group therefore considered that an *IARC Monographs* evaluation of 2,4,6-tribromophenol is unwarranted at present.

Recommendation: No priority

190 2-Hydroxy-4-methoxybenzophenone (CAS No. 131-57-7)

Current IARC/WHO classification

2-Hydroxy-4-methoxybenzophenone (HMBP) (also known as oxybenzone) has not previously been evaluated by the *IARC Monographs* programme. It was given a priority rating of *low* by the 2019 Advisory Group on Priorities (IARC, 2019a).

Exposure characterization

HMBP is widely used as a UVR filter in sunscreen formulations and in some industrial processes involving plastics. Human biomonitoring has shown high frequency of detection of HMBP in urine in the general population.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

The US NTP has conducted 2-year chronic toxicity and carcinogenicity studies of HMBP in rats and mice. These studies yielded equivocal evidence of carcinogenic activity of HMBP exposure in male Sprague-Dawley rats with incidence of brain and spinal cord malignant meningiomas. In female rats there was increased incidence of thyroid C-cell adenomas and increased incidence of uterine stromal polyps at only one of the intermediate doses. There was no evidence of carcinogenic activity in male or female $B6C3F_1$/N mice at any of the exposure concentrations tested (NTP, 2020b).

Mechanistic evidence

No evidence of genotoxic potential of HMBP is available. HMBP was included in the Tox21 and ToxCast programmes. The NTP 2020 technical report on HMBP toxicity mentions that cytotoxic concentrations of HMBP induced nuclear receptor activation (ER, PXR) and also showed induction of inflammatory cytokines (IL-1α, CCL26).

Summary

The Advisory Group noted that the newly available cancer bioassay from the NTP shows equivocal evidence of carcinogenicity. No studies were available of cancer in humans, and there is only sparse mechanistic evidence at present. The Advisory Group therefore considered that an *IARC Monographs* evaluation of 2-hydroxy-4-methoxybenzophenone is unwarranted at present.

Recommendation: No priority

191 Acetaldehyde (CAS No. 75-07-0)

Current IARC/WHO classification

Acetaldehyde has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Volume 71 in 1998 (IARC, 1999d), on the basis of *sufficient* evidence for cancer in experimental animals. In 2009, acetaldehyde associated with consumption of alcoholic beverages was classified in Group 1 (IARC, 2012f). The IPCS has published an Environmental Health Criteria document on acetaldehyde (WHO, 1995b). Acetaldehyde was given a priority rating of *high* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of new epidemiological evidence on the association of acetaldehyde (as a metabolite of alcohol consumption) with gastric and hepatocellular cancers.

Exposure characterization

Acetaldehyde is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). A major source of population exposure to acetaldehyde is its endogenous formation during alcohol metabolism by microbial flora in the oral cavity and digestive tract and as the first metabolite of ethanol oxidation in the liver and other tissues. The general population is exposed by ingestion of acetaldehyde as a natural compound in various foods and beverages, especially alcoholic beverages, and from use of consumer products such as alcohol-based mouthwash. Other important exposures include inhalation of polluted outdoor air (e.g. Xu et al., 2022b), indoor air (Chen et al., 2021b; Lunderberg et al., 2021; Villanueva et al., 2022; Yen et al., 2023), and tobacco smoke and vaping products (Landmesser et al., 2021; Nyakutsikwa et al., 2021; Zhou et al., 2021; Noël and Ghosh, 2022). Occupational inhalation exposure occurs in industrial manufacturing (Stefaniak et al., 2021), firefighting (Navarro et al., 2023a), restaurants (Le et al., 2022b), sewage and food waste treatment (Zhang et al., 2022f; Wang et al., 2023i; Zhang et al., 2023f), beauty salons (Choi et al., 2023), offices (Jung et al., 2022), and bakeries and pastry producers (Chang et al., 2018b; Miligi et al., 2023).

Cancer in humans

In 2009, acetaldehyde associated with consumption of alcoholic beverages was classified in Group 1, with causal associations noted for cancers of the oesophagus and upper aerodigestive tract (oral cavity, pharynx, larynx) combined (IARC, 2012f). A pooled analysis of 12 case–control studies showed positive associations of head and neck cancer with long-term and frequent use of mouthwash (Boffetta et al., 2016). Another meta-analysis of 17 studies, which included Boffetta et al. (2016), showed a statistically significant correlation between frequent mouthwash use and squamous cell head and neck carcinoma (Hostiuc et al., 2021). Several studies found positive associations between early-life exposure to acetaldehyde as a component of air pollution and several childhood cancers (Shrestha et al., 2014; Heck et al., 2015; von Ehrenstein et al., 2016). A recent meta-analysis showed an exposure–response association (based on duration of use > 35 years and frequency of more than three times daily) between use of alcohol-containing mouthwash and risk of oral cancer (Carr and Aslam-Pervez, 2022). However, the use of alcohol-containing mouthwashes alone in the absence of other known risk factors such as smoking and drinking did not increase

the risk of oral cancer or lead to increased levels of salivary acetaldehyde. However, where other risk factors for oral cancer are present, the use of an alcohol-containing mouthwash may further increase this risk (Carr and Aslam-Pervez, 2022).

Cancer in experimental animals

In the previous evaluation (IARC, 1999d), there was *sufficient* evidence in experimental animals for the carcinogenicity of acetaldehyde. An additional long-term study in rats has been published (Soffritti et al., 2002b). Administration of acetaldehyde to male and female rats in drinking-water increased the incidence of haemolymphoreticular cancer (leukaemia or lymphoma (combined)), benign tumours of the pancreas (islet-cell adenoma), and cancer of the bone (osteosarcoma) and nasal cavity (carcinoma) in male rats and benign mammary gland tumours (fibroma or fibroadenoma) in females. Increases in the incidence of tumours at other sites were observed only at one of the lower doses tested.

Mechanistic evidence

Acetaldehyde-specific DNA adducts have been characterized in experimental systems (Matsuda et al., 2007; Balbo et al., 2016), in human primary cells (Fang and Vaca, 1997), and in exposed humans (Wang et al., 2006; Balbo et al., 2012; Guidolin et al., 2021). For instance, ingestion of a moderate dose of alcohol led to a significant increase in *N*2-ethylidene-dG levels of up to 100 times the baseline value in cells of the oral cavity (Balbo et al., 2012); these authors pointed out the high intraindividual variability in DNA adduct formation induced by alcohol. The genotoxicity of acetaldehyde has recently been reviewed and indicates that acetaldehyde is genotoxic in experimental systems (ECHA, 2015; Rietjens et al., 2022).

The metabolism of alcohol via the CYP2E1 pathway leads to hepatic oxidative stress through the generation of ROS, including superoxide anion radicals and hydrogen peroxide. Acetaldehyde induces oxidative stress in experimental systems (Tamura et al., 2014; Srinivasan et al., 2021), human primary cells (Waris et al., 2020), and exposed humans (Tsermpini et al., 2022).

A recent evaluation of acetaldehyde as food-flavouring agent concluded that, in contrast to exposure to acetaldehyde via alcohol consumption, insufficient toxicokinetic, toxicity, and exposure data are available related to oral intake of acetaldehyde via food (Cartus et al., 2023). Also, it should be borne in mind that acetaldehyde is a product of normal metabolism in all living organisms, including humans, and that endogenous exposure may account for a major part of the overall exposome (Cheng et al., 2003; Rietjens et al., 2022).

Summary

The evaluation for acetaldehyde is dichotomized by its association (or not) with alcohol consumption. For alcohol-associated acetaldehyde exposure, the classification has advanced to Group 1, and a robust body of research continues to explore the role of acetaldehyde from alcoholic beverage consumption in causing cancer. Some studies have evaluated acetaldehyde as part of air pollution and childhood leukaemia. Otherwise, no studies were identified of acetaldehyde exposure outside that associated with alcohol consumption or use of mouthwash. Use of alcohol-containing mouthwash is not independently associated with oral cancer in the absence of other known risk factors. If an evaluation is carried out, it may be advisable to separate the evaluation of direct acetaldehyde exposure from indirect exposure from use of mouthwash. There is already *sufficient* evidence that acetaldehyde causes tumours in experimental animals. There is mechanistic evidence that acetaldehyde exhibits KCs in exposed humans. As such, the mechanistic evidence could lead to a change of the current classification of acetaldehyde not associated with alcohol consumption, but a careful review would be needed to determine if the mechanistic evidence informs this exposure scenario. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of acetaldehyde to be warranted

Recommendation: High priority (and ready for evaluation within < 2.5 years)

192 Acrylamide (CAS No. 79-06-1)

Current IARC/WHO classification

Acrylamide has previously been evaluated by the *IARC Monographs* programme as *probably carcinogenic to humans* (Group 2A) in Volume 60 in 1994 (IARC, 1994c), on the basis of *inadequate* evidence of carcinogenicity in humans and *sufficient* evidence of carcinogenicity in animals. The JECFA conducted a risk assessment of acrylamide in food in 2011 and did not calculate an ADI, concluding that it is a genotoxic carcinogen (FAO/WHO, 2011c). Acrylamide was given a priority rating of *high* by the 2019 Advisory Group on Priorities, on the basis of new evidence on cancers of the kidney, endometrium, and ovary in humans (IARC, 2019a).

Exposure characterization

Acrylamide is listed as a high production volume chemical by the OECD and the US EPA (OECD, 2007; US EPA, 2024a). Occupational exposure may occur via the dermal and inhalation routes in acrylamide, polyacrylamide and acrylamide copolymer production and in various industrial processes (e.g. production of paper, dyes, and plastics; drinking-water and wastewater treatment; grouting) (NCI, 2017). Acrylamide forms naturally in carbohydrate-rich foods during high-temperature cooking (e.g. frying, roasting, and baking) (EFSA, 2015b). High levels of acrylamide have been detected in fried potato products, in potato chips and snacks, and in dry coffee and coffee substitute products (EFSA, 2015b). Acrylamide is also present in cigarette smoke (EFSA, 2015b). For smokers, tobacco smoking is a greater source of exposure to acrylamide than food (NCI, 2017). The daily intake of acrylamide is estimated to range from 14 to 70 µg per day for adults in European, American, and Asian countries (Nehlig and Cunha, 2020). In Europe, average acrylamide exposure among adults did not increase significantly between 2000 and 2021 but still exceeded suggested benchmark levels. An increasing trend of acrylamide biomarker concentrations was found in children over the years 2014–2017 (Poteser et al., 2022).

Cancer in humans

Since the most recent *IARC Monographs* evaluation in 1994, several epidemiological studies have examined the relation between estimated dietary consumption of acrylamide and specific cancer types, mostly with inconclusive or inconsistent results (Filippini et al., 2022; Başaran et al., 2023; Guth et al., 2023; Iwasaki et al., 2023). These results are subject to non-differential exposure misclassification, because of the difficulty in estimating dietary intake of acrylamide (as evidenced by non-concordance with estimates from biomarker-based methods of exposure assessment), resulting in likely bias of estimated effects towards the null. The evidence is suggestive of modest associations for cancers of the kidney (Pelucchi et al., 2015) and premenopausal breast (Adani et al., 2020; Bellicha et al., 2022); and for cancers of the oesophagus (SCC), endometrium, and ovary in never-smokers (Lin et al., 2011; Pelucchi et al., 2015; Adani et al., 2020; Bellicha et al., 2022), including in two meta-analyses (Pelucchi et al., 2015; Adani et al., 2020). Another recent meta-analysis found no association between dietary acrylamide and renal cell carcinoma among never-smokers (Jiang et al., 2020a). As smoking affects the metabolism of acrylamide to its carcinogenic metabolite glycidamide, never-smokers could experience a slightly positive association between dietary acrylamide and cancer risk that is not detectable in smokers (Schettgen et al., 2004; Filippini et al., 2022). Haemoglobin adducts of acrylamide or glycidamide were not associated with risks of cancer of the ovary or endometrium in non-smoking postmenopausal women in the USA (Xie et al., 2013) and in European cohort studies (Obón-Santacana et al., 2016), but were associated with risk of breast cancer in Japan (Iwasaki et al., 2023). Levels

of acrylamide and glycidamide haemoglobin adducts were positively associated with cancer mortality in the adult American population in an analysis of NHANES 2003–2014 data (Gu et al., 2022).

Cancer in experimental animals

In the previous evaluation (IARC, 1994c), there was *sufficient* evidence of carcinogenicity in experimental animals.

Mechanistic evidence

In the previous *IARC Monographs* evaluation (IARC, 1994c), there was *strong evidence* that acrylamide and its active metabolite glycidamide form covalent adducts with DNA and are genotoxic in experimental animals. Since then, several new studies have reported positive results on the clastogenic and mutagenic properties of acrylamide and glycidamide (Benford et al., 2022). In addition, further insight into the mechanisms underlying the mutagenic effects of acrylamide and glycinamide in exposed humans is available. Acrylamide is metabolized to glycidamide, which forms an *N*7-glycidamideguanine DNA adduct in rodents. These adducts in the blood DNA of healthy human volunteers have been identified and quantified (Hemgesberg et al., 2021; Jones et al., 2022b). A unique mutational signature imprinted by acrylamide through the effects of its reactive metabolite glycidamide was found in one third of approximately 1600 tumour genomes corresponding to 19 human tumour types from 14 organs (Zhivagui et al., 2019). Hogervorst et al. (2007) observed statistically significant interactions between several SNPs in the HSD3B1/B2 gene cluster and acrylamide intake for ovarian cancer risk, suggesting that acrylamide may cause ovarian cancer through effects on sex hormones. There is evidence that acrylamide induces oxidative stress in experimental systems (Zhang et al., 2023g) and exposed humans (Piwowar et al., 2023).

Other studies have shown acrylamide-induced adipogenesis in cell cultures and various metabolic-related outcomes such as metabolic syndrome and increased prevalence of overweight in early childhood (Kadawathagedara et al., 2018; Wan et al., 2022).

Summary

Since the previous classification, new evidence has been published of an association between non-occupational, mainly dietary, exposure to acrylamide and cancers of the breast, kidney, endometrium, and ovary in humans, but it is unclear whether this would reach *sufficient* evidence. There is already *sufficient* evidence that acrylamide causes tumours in experimental animals. There is evidence that acrylamide exhibits KCs in exposed humans. However, the available mechanistic evidence would support a re-evaluation only if additional mechanistic studies in exposed humans are published. Although the classification may not change overall, a determination of even *limited* evidence for some cancer types could have important public health implications. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of acrylamide to be warranted and recommended that it be evaluated together with glycidamide (agent 204).

Recommendation: High priority (and ready for evaluation within < 2.5 years)

193 Atraric acid (methyl 3-methylorsellinate) (CAS No. 4707-47-5)

Current IARC/WHO classification

Atraric acid (methyl 3-methylorsellinate; methyl 2,4-dihydroxy-3,6-dimethylbenzoate) has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Atraric acid is an anti-androgenic phenolic compound that is naturally derived from the bark of the African Plum tree *Prunus africana* (previously known as *Pygeum africanum*) or from *Stereocaulon japonicum* lichen (Bourgeois et al., 1999; Hoffman et al., 2013; Pulat et al., 2023). Atraric acid is used in perfumes (Li et al., 2022e), air fresheners, and food flavouring. *Prunus africana* has been used in African traditional medicine for the treatment of prostate cancer (Komakech et al., 2017). Extracts from the bark of the plant are also used in Europe and the USA as phytotherapeutic preparations to treat lower urinary tract symptoms and benign prostatic hyperplasia (Papaioannou et al., 2009). However, while the primary exposure to humans is in fragrances (Li et al., 2022e), there are no studies quantifying human exposure to atraric acid.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

Atraric acid was identified as an AR antagonist in an AR-responsive MMTV-Luc reporter gene assay, inducing repression of AR-mediated transactivation (Schleich et al., 2006). Atraric acid also has an agonistic effect on both the α- and β-estrogen receptors (Hoffman et al., 2013).

Atraric acid has been screened in the US EPA ToxCast programme for induction of hormone synthesis in the in vitro H295R steroidogenesis assay (OECD, 2023) and was found to cause cells to significantly increase production of estradiol (E2) and weakly increase production of progesterone (Cardona and Rudel, 2021). Increased production of these hormones can raise the risk of breast cancer and other types of hormone-responsive cancers. The relation between hormone exposure—especially of E2 and progesterone—and breast cancer in experimental animals is well documented (Cogliano et al., 2011; Rudel et al., 2014).

Summary

Human exposure to atraric acid is primarily through perfumes, although no quantitative data on this exposure exist. There are no human or animal cancer bioassay studies for atraric acid. There is little mechanistic evidence associating atraric acid with KCs. The Advisory Group therefore considered that an *IARC Monographs* evaluation of atraric acid is unwarranted at present.

Recommendation: No priority

194 Bromate compounds (including CAS No. 7758-01-2)

Current IARC/WHO classification

Potassium bromate has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Volume 73 in 1998 (IARC, 1999b), on the basis of *sufficient* evidence for cancer in experimental animals. WHO has assessed bromate in its drinking-water quality guidelines (WHO, 2005). The JECFA concluded that use of potassium bromate as a flour treatment agent is not acceptable (see FAO/WHO, 1995b). Bromate compounds were given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of mechanistic evidence.

Exposure characterization

Bromate is a disinfection by-product that can be formed from the reaction of ozone or other oxidizing disinfectants with bromide present in water (Fawell and Walker, 2006). Bromate has been measured in both drinking-water and swimming-pool water and guideline values have been established by several national and international bodies, including WHO (2005). Bromate is added to flour to improve texture and volume of loaves (El Ati-Hellal et al., 2018). It is expected to be broken down when used in small quantities and proper baking practices are followed, but some countries have banned or limited the use of bromate compounds in flour. Bromate also has minor uses as a laboratory reagent and in explosives (IARC, 1999b). In a report on potassium bromate, Health Canada (2018) estimated that drinking-water is the main exposure source of bromate compounds in the Canadian general population and expected other sources such as food or cosmetics to be negligible.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 1999b), there was *sufficient* evidence in experimental animals for the carcinogenicity of potassium bromate, based on findings of malignant tumours in both sexes of rats.

Mechanistic evidence

In the previous evaluation (IARC, 1999b) it was concluded that potassium bromate is genotoxic in experimental systems in vivo and in rodent cells in vitro. No conclusion could be drawn with respect to its mutagenicity to bacteria. Since then, the genotoxicity of potassium bromate has been more intensively investigated (Spassova et al., 2013). Potassium bromate induced chromosomal aberrations and micronucleus formation in human peripheral blood lymphocytes (Kaya and Topaktaş, 2007). Potassium bromate has been considered a suitable positive assay control for the Fpg- and hOGG1-modified comet assay because it produces high levels of oxidatively damaged DNA (Møller et al., 2020). In addition, potassium bromate induces oxidative DNA base damage in whole blood or lymphocytes ex vivo (Bausinger and Speit, 2016) and in fresh or stored leukocytes collected from salivary samples from healthy non-smokers (Fernández-Bertólez et al., 2021); in these studies, potassium bromate was used as a reference inducer of oxidative DNA damage. In addition, potassium bromate induces oxidative stress in human erythrocytes through the generation of ROS and alteration of the cellular antioxidant defence system (Ahmad et al., 2014).

Summary

No studies on bromate exposure and human cancer were available. There is already *sufficient* evidence that potassium bromate causes cancer in experimental animals. There is evidence that potassium bromate induces KCs, including genotoxicity and induction of oxidative stress in human primary cells. These data could support a possible change in the current classification; the Advisory Group therefore considered that an *IARC Monographs* re-evaluation of bromate compounds is warranted.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

195 Butyraldehyde (butanal) (CAS No. 123-72-8)

Current IARC/WHO classification

Butyraldehyde (also known as butanal) has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Butyraldehyde is listed as a high production volume chemical by the OECD (OECD, 2009a) and the US EPA (NCBI, 2024g). Japanese exports and imports in 2020 totalled 7887 and 5103 tonnes, respectively (JBRC, 2022a). Butyraldehyde is used primarily in the manufacture of various industrial products such as rubber accelerators, solvents, synthetic resins, high polymers, and plasticizers. It is also used as a flavouring agent in food products such as alcoholic beverages, baked goods, dairy products, gelatines, puddings, gravies, meat products, non-alcoholic beverages, and soft candies (NCBI, 2024g).

Workers are likely to encounter butyraldehyde in various industries, including health services and scientific research and development, where it is used in products such as pH regulators, water treatment products, and laboratory chemicals. Occupational exposure to butyraldehyde can occur through inhalation and dermal routes, primarily at manufacturing and user sites (ECHA, 2023a). Release to the environment of butyraldehyde is likely to occur from its use in consumer and industrial products (e.g. machine wash liquids, detergents, automotive care products, paints, coating or adhesives, fragrances, and air fresheners) (ECHA, 2023b).

Cancer in humans

There are equivocal findings for oral cavity and respiratory cancers (all among smokers) in a small study of 150 workers (during 1967–1972) who were exposed to butyraldehyde and other aldehydes at a chemical plant in former East Germany (IARC, 1985). No other studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In a two-year study in rats with whole-body inhalation, butyraldehyde induced SCC of the nasal cavity in males and females; SCC, carcinosarcoma or adenosquamous cell carcinoma (combined) of the nasal cavity in males; and squamous cell papilloma or SCC (combined) of the nasal cavity, spleen mononuclear cell leukaemia, mammary gland fibroadenoma, and mammary gland adenoma, fibroadenoma or adenocarcinoma (combined) in females (JBRC, 2022a, b).

Mechanistic evidence

Butyraldehyde induced chromosomal aberrations in Chinese hamster lung cells CHL/IU after short and continuous treatment (Ministry of Health, Labour, and Welfare Japan, no date.). Special meiotic anomalies consisting of degenerative nuclei, multi-spindle cells, and polyploid cells were observed at all stages of spermatogenesis in male mice after treatment with butyraldehyde (Moutschen-Dahmen et al., 1975); this was included in the OECD Existing Chemicals Database as a positive result for genotoxicity (OECD, 2009a). Butyraldehyde did not induce micronuclei in blood cells of male and female B6C3F$_1$ mice fed by gavage at doses ranging from 75 to 1200 mg/kg bw once per day for 65 days (Witt et al., 2000) and it did not increase the frequencies of chromosomal aberration, but did induce a statistically significant increase in the frequency of SCE in a dose-dependent manner in CHO cells (Galloway et al., 1987). Butyraldehyde did not influence the frequency of wild-type males in a sex-linked recessive lethal test in *Drosophila melanogaster* (Valencia et al., 1985). Butyraldehyde was not mutagenic at dose ranges between 10 and 1000 mg per plate in *S. typhimurium* strains TA98, TA100, TA102, TA104, TA1535, and TA1537 without or with rat-, hamster-, or mouse-induced liver S9 microsomes (Dillon et al., 1998; OECD, 2009a; NTP, 2023g).

In an analysis of large-scale population data, butyraldehyde exposure was associated with markers of chronic inflammation and oxidative stress (Zang et al., 2023). Genome-wide transcriptome and microRNA sequencing in human A549 alveolar epithelial cells exposed to butyraldehyde showed changes in 25 microRNA expression, and integrated analyses of miRNA and mRNA expression profiles revealed

significant correlations. Analysis of target genes (2166 genes for butyraldehyde) provided evidence that it affected cytokine-induced toxicity signalling. Butyraldehyde increased levels of IL-6 and IL-8 (Song et al., 2015). Butyraldehyde was found to upregulate human immunodeficiency viral long-terminal repeat-, SV40 early gene promoter-, and glucocerebrosidase promoter-directed expression of heterologous genes stably integrated into murine NIH 3T3 fibroblast cells (Carstea et al., 1993).

Summary

There is minimal evidence of cancer in humans. In a long-term cancer bioassay in rats, butyraldehyde administered by inhalation caused tumours in males and females at various tissue sites. There is some evidence that butyraldehyde exhibits KCs, including genotoxicity, chronic inflammation, and epigenetic alterations involved in the immune response, mainly from experimental systems. On the basis of the evidence of cancers in experimental animals, the Advisory Group considered an *IARC Monographs* evaluation of butyraldehyde to be warranted, possibly together with other aldehydes included in this report.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

196 Carbon disulfide (CAS No. 75-15-0)

Current IARC/WHO classification

Carbon disulfide has not previously been evaluated by the *IARC Monographs* programme. The IPCS has published an evaluation of health effects of carbon disulfide (WHO, 2002a). Carbon disulfide was given a priority rating of *low* by the 2019 Advisory Group on Priorities (IARC, 2019a).

Exposure characterization

Carbon disulfide is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). Carbon disulfide is used to manufacture rayon and cellophane, in the production of rubber, and as a fumigant for grain, spaces, and materials, (Newhook et al., 2002; ACGIH, 2020; Encyclopaedia Britannica, 2022). It is also used to produce other chemicals, in the manufacture of electronic vacuum tubes, and as a solvent for resins, fats, oils, waxes, and other chemicals.

Exposure to carbon disulfide occurs mainly in the workplace. In the production of viscous rayon, heavy occupational exposures may occur during the opening of spinning machines and while cutting and drying (La Dou and Harrison, 2013). As carbon disulfide is volatile, the general population might be exposed via polluted air (Newhook et al., 2002; Wofford et al., 2014). It is present in cigarette smoke (CDC, 2010). It can also be an impurity in pharmaceutical products. Carbon disulfide or its metabolite 2-thiothiazolidine-4-carboxylic acid have been widely detected in blood and urine of workers (Vermeulen et al., 2005) and the general population (Brugnone et al., 1994; Newhook et al., 2002).

Cancer in humans

Few studies have assessed the association of carbon disulfide exposure and cancer risk, and there are only sporadic findings. In a cohort of rubber workers at one plant in Ohio, USA, Wilcosky et al. (1984) reported a significantly increased risk of lympho-sarcoma and lymphatic leukaemia associated with carbon disulfide exposure. An increased risk of lymphatic leukaemia associated with carbon disulfide exposure was also reported in a case–control study of rubber workers in the USA and the UK (Checkoway et al., 1984).

In another cohort of chemical production workers, many of whom were exposed to carbon disulfide along with other chemicals and shift work, an excess of NHL was observed, which was however not associated with employment duration (Carreón et al., 2014). Results for cancer risk in workers exposed to carbon disulfide only were not presented. In a cohort of workers with reported carbon disulfide poisoning in Poland between 1970 and 1990, an excess of death from colon cancer compared with the national population

was reported (Pepłońska et al., 1996). Other studies of cohorts of chemical production workers have found no association between carbon disulfide exposure and cancer risk (Nurminen and Hernberg, 1984; Pepłlońska et al., 2001). Co-exposure to other chemicals and healthy-worker biases were common in all cohorts.

Cancer in experimental animals

No evidence of carcinogenicity has been reported in long-term studies with laboratory animals. One study reported an increase of pulmonary adenoma in A/J strain mice exposed to carbon disulfide for 6 months (Adkins et al., 1986). A review on toxicity of carbon disulfide reported that there was minimal evidence after administration by gavage to rats and mice due to poor survival of the animals (Beauchamp et al., 1983).

Mechanistic evidence

Carbon disulfide is metabolized by two main routes: by reaction with amino acids or reduced GSH to form thiocarbamates or conjugated GSH, and by CYP-mediated reaction to form reactive sulfur (US EPA, 1986b). DNA damage in human buccal cells of workers occupationally exposed long-term to carbon disulfide was monitored with comet assay, and DNA damage was significantly higher in the exposed group than in control group (Chen and Tan, 2004; Pappuswamy et al., 2023). Carton et al. (2007) identified *TP53* CGT > CTT transversions in buccal cell DNA of production workers (n = 76) at a viscose factory exposed to carbon disulfide (among other pollutants) and in the DNA of non-exposed office workers (n = 67). The mutation appeared more frequently in the exposed than in the non-exposed workers who were smokers. In human sperm exposed to carbon disulfide in vitro, there was a significant increase in the frequency of chromosomal aberrations and in the frequency of chromosomal breaks. However, carbon disulfide was not mutagenic to *S. typhimurium* strains TA98 and TA100 at 300–1000 µmol nor to *E.coli* strain WP2 *uvrA* at 20–600 µmol with or without metabolic activation, nor in *D.melanogaster* at 200–800 ppm. DNA damage in mouse sperm was detected by single-cell gel electrophoresis assay.

It has been reported that carbon disulfide exposure in urban areas is associated with oxidative stress markers and risk of diabetes (Xu et al., 2021c). Increased risk of infections has been observed in farmers using carbon disulfide (Parks et al., 2021). There are several reports of decreased libido and/or impotence among males occupationally exposed to high concentrations of carbon disulfide. Reproductive health hazards for women chronically exposed to carbon disulfide in the workplace include menstrual disorders, earlier average age at menopause, and complex disturbances in the neurohormonal system including diminished secretion of estrogens and progesterone in ovaries and dehydroepiandrosterone sulfate in the adrenal gland (Cirla et al., 1978; Franco et al., 1982; LaDou and Harrison, 2013). Renal injury and hyperplasia in renal biopsy following long-term exposure to carbon disulfide have been reported (Ou et al., 2017; Yan et al., 2019). Carbon disulfide also affects liver enzymes, particularly those related to lipid metabolism. The increases in serum cholesterol that are sometimes seen following carbon disulfide exposure may be a result of increased hepatic cholesterol synthesis (Kotseva, 2001; Navaneethan et al., 2014, 2015).

Summary

There is sparse evidence for carcinogenicity in both humans and experimental animals. There is mechanistic evidence suggesting that carbon disulfide exhibits KCs in experimental systems and in exposed humans. The Advisory Group therefore considered an *IARC Monographs* evaluation of carbon disulfide to be warranted.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

197 Catechol (CAS No. 120-80-9)

Current IARC/WHO classification

Catechol (1,2-dihydroxybenzene) has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Volume 71 in 1999 (IARC, 1999d), on the basis of *sufficient* evidence of carcinogenicity in animals. Catechol was given a priority rating for re-evaluation of *low* by the 2019 Advisory Group on Priorities (IARC, 2019a)

Exposure characterization

Catechol is used in the production of pesticides, perfumes, flavours, and pharmaceuticals and has various specialty uses in certain hair dyes. It occurs naturally in certain foods and is present in tobacco smoke.

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

There is already *sufficient* evidence for cancer in experimental animals.

Mechanistic evidence

Most of the mechanistic evidence identified in the literature search was related to catechol-*O*-methyltransferase. The few mechanistic studies on pure catechol indicated protective effects.

Summary

There is little new evidence to suggest a change in classification is likely for catechol. The Advisory Group therefore considered that an *IARC Monographs* re-evaluation of catechol is unwarranted at present.

Recommendation: No priority

198 Cumyl hydroperoxide (CAS No. 80-15-9)

Current IARC/WHO classification

Cumyl hydroperoxide has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Cumyl hydroperoxide (also known as cumene hydroperoxide) is an organic hydroperoxide used primarily in industrial settings as a polymerization initiator in the production of certain plastics and rubbers and in producing phenol and acetone by catalytic cleavage (Wang et al., 2001; Gooch, 2011; Rider et al., 2016). It is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). Human exposures to cumyl hydroperoxide are primarily occupational through skin contact and inhalation during manufacturing processes (Rider et al., 2016). Persons involved in industrial manufacturing of polymers, plastics, and rubbers or in the handling, transportation, or storage of cumyl hydroperoxide in industrial settings may be exposed (Gooch, 2011; Rider et al., 2016). Pollution of water systems with cumyl hydroperoxide is a potential route of exposure to the general public (Gooch, 2011; Rider et al., 2016).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

The evidence for carcinogenicity of cumyl hydroperoxide in experimental animals was reviewed by NIES, (1998). Kotin and Falk (1963) reported a single subcutaneous sarcoma, and 11 malignant lymphomas in a group of 50 C57B1 mice treated with 50 µM cumyl hydroperoxide by subcutaneous injection, with a 14-month time to appearance of first tumour. However, concurrent controls were not included in this study. In a lifetime carcinogenicity study with dermal application of cumyl hydroperoxide in Swiss Millerton mice, no increase in tumour incidence was reported (Van Duuren et al., 1965). However, a subcutaneous injection of cumyl hydroperoxide once per week for 76 weeks in the left axillary area of mice induced one fibrosarcoma, while no tumours were present at the injection site among control mice (Van Duuren et al., 1966). Similar treatment of rats induced no tumours (Van Duuren et al., 1967). Cumene hydroperoxide is believed to be an active promoter in the initiation–promotion model of the mouse epidermis due to its ability to generate free radicals (Trush and Kensler, 1991).

Cumyl hydroperoxide induced the formation of skin papillomas and carcinomas in AP-1-luciferase reporter transgenic mice primed with dimethylbenz[*a*]anthracene (DMBA-Cum-OOH) exposed for 29 weeks (Murray et al., 2007b).

In a DMBA-initiated SENCAR mouse strain treated for 20 weeks, cumyl hydroperoxide induced the formation of skin papillomas and carcinomas (Shvedova et al., 2004).

Mechanistic evidence

There is evidence that cumyl peroxide is genotoxic (NIES, 1998). In L5178Y $tk^{+/-}$ mouse lymphoma cells, cumyl hydroperoxide induced DNA damage as measured by the comet assay, and micronuclei; it also induced gene mutations at the Tk locus in these cells (Brink et al. 2009). In contrast to these positive results, cumyl hydroperoxide did not induce DNA adducts (i.e. 8-oxo-7,8-dihydro-2-deoxyguanosine or 1,*N*6-etheno-2-deoxyadenosine) in L5178Y $tk^{+/-}$ cells (Brink et al., 2009). Cumyl hydroperoxide is a known oxidant. It induced cellular ROS in human 3D-gingival tissue equivalents. The generation of ROS was observed in the nuclei of keratinocytes, as detected by two species of ROS-staining dyes such as CellROXGreen Reagent and dihydroethidium (Xiao and Miwa, 2017). Accumulation of thiobarbituric acid-reactive substances, inflammation, and decreased levels of GSH and total antioxidant reserves were also observed in the skin of DMBA–Cum-OOH-exposed mice (Murray et al., 2007b). Cumyl hydroperoxide induces higher levels of oxidative stress and inflammation (as indicated by the accumulation of peroxidative products, antioxidant depletion, and oedema formation) in the skin of a DMBA-initiated SENCAR mouse strain (Shvedova et al., 2004).

Cumyl hydroperoxide induced cell death in C6 glioma cells, preceded by lipid peroxidation measured by TBARS, malondialdehyde, and hexanal (Linden et al., 2008). Swiss albino female mice given topical applications of cumyl hydroperoxide showed increased cutaneous microsomal lipid peroxidation and induction of xanthine oxidase activity, accompanied by decreased activities of cutaneous antioxidant enzymes and depletion in the level of GSH. Parallel to these changes, a sharp decrease in the activities of phase II metabolizing enzymes was observed. Cumyl hydroperoxide treatment also induced ornithine decarboxylase activity and enhanced the [^{3}H]thymidine uptake in DNA synthesis in murine skin (Sultana et al., 2003).

Lymphocytes from healthy donors were exposed to cumyl hydroperoxide (at concentrations of 5–40 mM) and malondialdehyde, and cellular viability and growth, ROS, and protein oxidation were measured. Time-dependent increases were observed in the production of all these markers after incubation for 12–48 hours. Cumyl hydroperoxide (25 mM) initiated substantial micronucleus formation assayed 48 hours after incubation compared with DMSO controls (Onaran et al., 2001).

Summary

Human exposure to cumyl hydroperoxide is primarily occupational in industrial settings, and occasionally contamination of water systems may lead to exposure in the general population. No studies of cancer in humans were available, and the evidence of cancer in experimental animals is restricted to promotion studies. There is mechanistic evidence in human primary cells and experimental systems suggesting that cumyl hydroperoxide exhibits KCs. The Advisory Group therefore considered an *IARC Monographs* evaluation of cumyl hydroperoxide to be warranted.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

199 Ethylene oxide (CAS No. 75-21-8)

Current IARC/WHO classification

Ethylene oxide (EtO) has previously been evaluated by the *IARC Monographs* programme as *carcinogenic to humans* (Group 1) in Volume 100F in 2009 (IARC, 2012b). The basis of the classification was a finding of *sufficient* evidence for cancer in experimental animals, *limited* evidence for cancer in humans (specifically for breast cancer and lymphatic neoplasms including NHL, multiple myeloma, and CLL), and *strong* evidence of electrophilicity, genotoxicity, mutagenicity, and clastogenicity in exposed humans and across experimental systems, including in rodents.

Exposure characterization

EtO is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). A major use of EtO is as a sterilant gas in industrial and hospital settings (IARC, 2012b). EtO gas is also used in some countries, such as Canada, the USA and India, as a fungicide, bactericide, and insecticide in foods (Dudkiewicz et al., 2022). According to the EU CARcinogen EXposure (CAREX) database, most workers exposed to EtO worked in medical, other health, and veterinary services. In the NIOSH National Occupational Exposure System database, during 1981–1983, women comprised 44% of the workforce exposed to EtO. Heavy use of EtO has continued globally, and concerns have increased about environmental exposures, especially near facilities that manufacture or use EtO. EtO is also present in tobacco smoke (Yuan et al., 2012) and has been used as a pesticide (Ambroise et al., 2005). The US EPA (2024f) has recently proposed new EtO emission standards and mitigation measures.

Cancer in humans

Since the previous evaluation, new studies have examined the risk of breast cancer and lymphatic and haematopoietic neoplasms in relation to occupational or environmental exposure to EtO (Mikoczy et al., 2011; Park, 2020; Jones et al., 2023b). A relatively small study of cancer in sterilant workers exposed to EtO in Sweden found increased risk of breast cancer incidence in women in the two highest exposure quartiles compared with those exposed at less than the median, as well as evidence of a strong healthy-worker bias (Mikoczy et al., 2011). No clear exposure–response relation was observed for all haematolymphoid cancers combined. In a study of environmental exposure, researchers linked the US EPA Toxics Release Inventory to residences of participants in the NIH-AARP Diet and Health Study to develop quantitative metrics of exposure (emissions weighted for distance and/or wind direction) from EtO-emitting facilities (Jones et al., 2023b). Positive associations were seen for some of these metrics and breast cancer (particularly in situ), with risk declining as distance from the facility increased, but no clear increase in NHL risk was observed.

A large cohort study (pooled across many workplaces) of workers using EtO to sterilize medical supplies or spices was informative in the previous *IARC Monographs* evaluation (Steenland et al., 2003, 2004). A reanalysis of this cohort found evidence of a strong HWSB (Park, 2020). Partial adjustment for this bias by

adjusting for employment duration led to stronger associations between cumulative EtO exposure and cancers of lung, female breast, and haematopoietic cancer. In the next few years, NIOSH aims to publish updated follow-up of this cohort, including information on breast cancer mortality and incidence. Use of the new Virtual Pooled Registry Cancer Linkage System (NCI, 2022) should overcome the main limitation of cancer underascertainment in the previous cancer incidence analysis by Steenland et al. (2003).

An industry-funded meta-analysis estimated an overall meta-relative risk of 1.48 (95% CI, 1.07–2.05) for haematolymphoid cancers and 0.97 (95% CI, 0.80–1.18) for breast cancer, with higher risk seen for the former in earlier studies (Marsh et al., 2019).

Summary

There is growing evidence of an association between EtO exposure and risk of breast cancer, with mixed evidence for lymphatic and haematopoietic cancers. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of ethylene oxide to be warranted but recommended delaying the evaluation pending completion of the highly informative NIOSH study update for cancer mortality and incidence.

Recommendation: High priority (and ready for evaluation within 5 years)

200 Fluoranthene (CAS No. 206-44-0)

Current IARC/WHO classification

Fluoranthene has previously been evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in Volume 92 in 2005 (IARC, 2010b).

Exposure characterization

Fluoranthene is present in mixtures PAHs as part of the incomplete combustion of organic matter. It is also a component of coal tars and petroleum-based asphalts and is present in coke-oven emissions. Minor uses include as a component in plastic composite manufacturing and electrical insulation oils, as a precursor in drug and dye manufacturing, as a stabilizer in epoxy resins, waste tyre retreading processing, and in emission of 3D printers (US EPA, 2012b; Steinle, 2016; Fu et al., 2018; PubChem, 2024i). Sources of exposure include food and breast milk, urban air and water pollution, gasoline and diesel exhaust, and tobacco smoke (IARC, 1983, 2010b; US EPA, 2012b; Acharya et al., 2019).

Cancer in humans

The previous *IARC Monographs* evaluation of fluoranthene (IARC, 2010b) did not identify any human cancer studies specifically examining fluoranthene, and no such subsequent studies were identified by the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 2010b), there was *limited* evidence in experimental animals for the carcinogenicity of fluoranthene. Four studies demonstrated carcinogenicity of fluoranthene in newborn mice. In newborn male and female Swiss-Webster BLU:ha (ICR) mice, three intraperitoneal injections of fluoranthene during two postnatal weeks increased the incidence of lung tumours (primarily adenomas) in both males and females (Busby et al., 1984, 1989). Incidence of lung tumours (primarily adenomas) was increased in both sexes of CD-1 mice after three intraperitoneal injections of fluoranthene during two postnatal weeks (Wang and Busby, 1993; LaVoie et al., 1994). In male mice a low incidence of liver tumours was noted at 6 months, but much higher incidence at 9 months (Wang and Busby, 1993). Fluoranthene was inactive as an initiator in the mouse skin initiation–promotion assay. However, when co-administered with BaP, fluoranthene significantly increased the incidence of tumours in mice, produced an excess number of

skin tumours (primarily squamous cell carcinomas), and shortened their time to occurrence compared with those induced by the same dose of BaP alone (Van Duuren and Goldschmidt, 1976).

Mechanistic evidence

Fluoranthene exhibited mutagenic activity in *S. typhimurium*: in the strain TM677 with S9 liver fraction from rat pretreated with Arochlor 1254 (Kaden et al., 1979); in the strain TA98 with S9 fraction of rat pretreated with phenobarbital and 5,6-benzoflavone (Nagai et al., 2002); in the strain TA100 in the presence of rat liver homogenate (LaVoie et al., 1982); and in the strains TA98 and NA100 in the presence of rat liver S9 fraction (Mossanda et al., 1979). However, fluoranthene did not show mutagenic activity in other studies using *S. typhimurium* with or without rat S9 activation, with strains TA1537 and TA1538 (Gatehouse, 1980) and strains TA98, TA100, TA1535, and TA1537 (Florin et al., 1980). Fluoranthene did not significantly influence the frequency of micronucleated mouse erythrocytes induced by other PAHs in FVB and BALB/c mice (Abramsson-Zetterberg and Maurer, 2015). Chronic administration of fluoranthene in the diet resulted in DNA adduct formation in most examined tissues, including liver, kidney, lung, small intestine, heart, spleen, and lymphocytes (Gorelick et al., 1989; Gorelick and Wogan, 1989; Wang et al., 1995). Fluoranthene influenced the cell cycle in human colon adenocarcinoma cells HT29 in vitro, increasing the proportions of cells in S- and G2-phases (Harris et al., 2013). It inhibited gap junctional intercellular communication (GJIC) and activated MAPKs in human HBE1 bronchial epithelial cell line (Brózman et al., 2020). Exposure of human A549 lung cells to fluoranthene caused significant induction of CYP1B1 and addition of a binary mixture (fluoranthene and 1-methylanthracene) to BaP-treated human EAS-2B lung cells resulted in significant increases in micronucleus formation, dysregulation of GJIC, and changes in the cell cycle (Bauer et al., 2022). Chemical structure analysis led to proposals on how certain features of fluoranthene enable its interaction with gap junctions (Weis et al., 1998).

In a subchronic toxicity study in F344 rats, fluoranthene induced renal and haematological changes including a decrease in leukocytes of up to 40% (Knuckles et al., 2004). In CD-1 mice, subchronic exposure to fluoranthene caused nephropathy and haematological alterations and increased levels of liver enzymes (US EPA, 2012b). In rat H4IIE hepatoma cells, fluoranthene inhibited CYP1A1 activity (Willett et al., 1998). In rat WB-F344 liver epithelial cells, fluoranthene caused aryl hydrocarbon receptor-mediated connexin-43 downregulation and inhibited GJIC (Upham et al., 1994; Bláha et al., 2002; Nováková et al., 2012; Andrysík et al., 2013; Babica et al., 2016). It also induced expression of most AhR gene targets, such as CYP1A1, AHRR, or TIPARP (Kabátková et al., 2015). In the C10 mouse cell line (model systems of alveolar type II cells), fluoranthene inhibited gap junctions and cell communications and activated pro-inflammatory and MAPK pathways (Osgood et al., 2017).

Summary

Fluoranthene is present in PAH mixtures as part of the incomplete combustion of organic matter and is commonly found in pollution and in some occupational environments. No studies of cancer in humans were identified. Fluoranthene was shown in four studies on newborn mice of both sexes to possess carcinogenic activity and demonstrated promoter activity in one study in mice. There is mechanistic evidence suggesting that fluoranthene exhibits KCs in experimental systems. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of fluoranthene to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

201 Formaldehyde (CAS No. 50-00-0)

Current IARC/WHO classification

Formaldehyde has previously been evaluated by the *IARC Monographs* programme as *carcinogenic to humans* (Group 1) in Volume 100F in 2009 (IARC, 2012b), on the basis of *sufficient* evidence for cancer in humans (for nasopharyngeal cancer and leukaemia). There is also *limited* evidence for sinonasal cancer in humans. The IPCS has published an evaluation of health effects of formaldehyde (WHO, 2002b).

Exposure characterization

Formaldehyde is listed as a high production volume chemical by the OECD (OECD, 2007) and the US EPA (US EPA, 2024a). Formaldehyde is used in the production of a variety of polymers and other chemicals, including ethylene glycol, pentaerythritol, and hexamethylene tetramine. Formaldehyde-containing resins, in turn, form raw materials for fertilizer, plywood, insulation, casting cores, and other uses. Occupational exposure may occur in various industries, as formaldehyde is used in the manufacture of furniture adhesives, photographic films, leather, dyes, cosmetics, explosives, pesticides, disinfectants, and preservatives. It remains commonly used as an embalming fluid, for fixation of tissue samples, and as a hair straightener (see agent 158), resulting in short-term higher exposure of workers. Formaldehyde is also present in automobile exhaust, wood smoke, tobacco smoke, and air pollution, resulting in exposure of the general population (IARC, 2012b).

Cancer in humans

There have been relatively few studies of formaldehyde exposure in relation to cancer sites other than leukaemia and nasopharynx since the previous evaluation in 2009. For sinonasal cancer, a meta-analysis observed an increased risk for ever-exposure to formaldehyde (meta-RR, 1.68; 95% CI, 1.37–2.06 for four case–control studies and 1.09; 95% CI, 0.66–1.79 for three cohort studies), with some evidence of an exposure–response relation (Binazzi et al., 2015). All but one of the case–control studies (Mayr et al., 2010) were published before the previous evaluation. In the previous *IARC Monographs* evaluation, it was noted that results for brain tumours were inconsistent. Since then, a meta-analysis has evaluated occupational studies of brain tumours (Rana et al., 2021), including five studies of professional workers and seven studies of industrial workers. In total, there were ten cohort studies and two case–control studies. Using highest peak exposure category as the preferred metric, a meta-RR of 1.71 (95% CI, 1.07–2.73) was observed. Use of alternative exposure metrics (highest average intensity, highest cumulative exposure, and longest duration categories) changed the meta-RR only slightly (meta-RR, 1.77; 95% CI, 1.11–2.83 for average; meta-RR, 1.72; 95% CI, 1.09–2.70 for cumulative; meta-RR, 1.75; 95% CI, 1.07–2.84 for duration). Using the "ever exposure" category, the meta-RR was 1.82 (95% CI, 1.20–2.75). These patterns were robust across sensitivity analyses. Higher meta-RR estimates were seen among the professional workers (meta-RR, 2.42; 95% CI, 1.41–4.17) than among industrial workers (meta-RR, 1.32; 95% CI, 0.72–2.44). These patterns were thought to be consistent with higher exposure levels observed among embalmers and pathologists, compared with garment workers. The authors did not conduct analyses stratified by brain tumour type, and most available studies could not clearly distinguish histopathological subtypes. In the large INTEROCC case–control study (not included in the meta-analysis), an elevated risk of meningioma was observed among the highest cumulative formaldehyde exposure category for women, but not men (McElvenny et al., 2018).

A meta-analysis for cancer of the larynx found meta-RRs of 1.12 (95% CI, 0.97–1.29) for low and 1.13 (95% CI, 0.98–1.31) for high exposure to formaldehyde, combining results from 11 studies (Paget-Bailly et al., 2012).

Mechanistic evidence

The potential for induction of sinonasal cancer after exposure to formaldehyde via the inhalation exposure route seems plausible. Formaldehyde can cause neural damage to the olfactory bulb, but whether and how inhalation or dermal exposure relates to brain tissue exposure remains unknown. The meta-analysis of Rana et al. (2021) explored candidate genes that may be associated with brain tumour development due to formaldehyde exposure. Enriched genes for brain tumours included those related to oxidative stress and pro-inflammatory markers.

Summary

With additional cohort follow-up and publication of new case–control studies since the previous evaluation of formaldehyde, there appears to be evidence that could support a determination of cancer at additional sites. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of formaldehyde to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

202 Furan (CAS No. 110-00-9)

Current IARC/WHO classification

Furan has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Volume 63 in 1995 (IARC, 1995), on the basis of *inadequate* evidence regarding cancer in humans and *sufficient* evidence for cancer in experimental animals. Furan was given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a).

Exposure characterization

Furan is listed as a high production volume chemical by the OECD and the US EPA. As noted in the 2019 Advisory Group report, "furan is used as a synthetic intermediate in the preparation of tetrahydrofuran, pyrrole, and thiophene. It is also used in the production of pesticides, stabilizers, and pharmaceuticals. The major sources of exposure to furan for the general public are tobacco products and food. Mainstream cigarette smoke is estimated to contain up to 65 µg of furan per cigarette. Furan is produced during the cooking of many common foods, including coffee, baked or fried cereal products, canned and jarred foods, baby food, and infant formula. Coffee contributes approximately 50% of the total population-based furan exposure in the USA in individuals aged 2 years and older."

Cancer in humans

No studies were available to the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 1995), there was *sufficient* evidence for cancer in experimental animals.

Mechanistic evidence

As noted in the 2019 Advisory Group report, there is ample evidence that furan is electrophilic and genotoxic, and that it causes epigenetic changes. However, these data derive primarily from experimental systems, with very little evidence from exposed humans or human primary cells.

Summary

The Advisory Group considered that mechanistic studies relevant to the KCs for furan in human systems are still sparse and would be unlikely to lead to a change in classification for furan from Group 2B. The Advisory Group therefore considered that an *IARC Monographs* re-evaluation of furan is unwarranted at present.

Recommendation: No priority

203 Glutathione (CAS No. 70-18-8)

Current IARC/WHO classification

Glutathione has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Glutathione is a tripeptide composed of three amino acids: cysteine, glutamic acid, and glycine (Pizzorno, 2014). It occurs naturally in human cells and functions as an antioxidant to mop up ROS or free radicals (Bansal and Simon, 2018). Glutathione occurs in cells in two states; reduced GSH and also as oxidized glutathione (glutathione disulfide or GSSG), that is formed on interaction with ROS. The GSH/GSSG ratio is a measure of the cell's redox status and oxidative stress (Pizzorno, 2014). Ways of increasing intracellular endogenous glutathione include a balanced diet, reducing alcohol intake and reducing exposure to persistent organic pollutants (Pizzorno, 2014). Exogenous glutathione supplements may be administered orally, intravenously, or by inhalation (Pizzorno, 2014).

Cancer in humans

No studies were identified that examined external exposure to glutathione and cancer in humans. Several reviews highlight the dual role of glutathione in cancer, but it is not clear from these studies that glutathione was from exogenous sources. The null genotype of glutathione *S*-transferase T1 (GSTT1) has been associated with gastric cancer (e.g. Lai et al., 2005; Zhang et al., 2013c; Zeng et al., 2016) and glutathione *S*-transferase M1 (GSTM1) polymorphism has been associated with oesophageal cancer in Asian populations (Lu et al., 2016).

Cancer in experimental animals

No studies of cancer in experimental animals were available to the Advisory Group.

Mechanistic evidence

No studies are available on the potential of glutathione to exhibit the KCs. Altered cellular glutathione homeostasis has been shown to increase cell proliferation and prevent cell death (Hatem et al., 2017; Bansal and Simon, 2018). Differences in expression and/or function of glutathione-dependent enzymes, e.g. due to genetic polymorphism, have been associated with increased tumour growth and/or incidence in mice and humans, while enzyme inhibition has been shown to exacerbate the toxicity of carcinogenic agents (Kennedy et al., 2020). Glutathione was inactive in over 200 ToxCast assays.

Summary

No studies of exogenous glutathione exposure in relation to cancer in humans or experimental animals were identified. Sparse mechanistic information is available indicating that factors altering endogenous glutathione levels or glutathione-dependent enzyme activity influence carcinogenic processes or outcomes in humans, animals, and in vitro human systems. Considering that either an excess of glutathione or a deficiency of glutathione could protect against or induce carcinogenesis, and considering also that alterations

of glutathione homeostasis or cancer susceptibility due to genetic polymorphisms may not be a suitable topic for the *IARC Monographs* programme, the Advisory Group considered that an IARC *Monographs* evaluation of glutathione is unwarranted.

Recommendation: No priority

204 Glycidamide (CAS No. 5694-00-8)

Current IARC/WHO classification

Glycidamide has not previously been evaluated by the *IARC Monographs* programme. Glycidamide was given a priority rating of *high* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of cancer bioassay and mechanistic evidence.

Exposure characterization

Glycidamide is a major metabolite of acrylamide (agent 192). Therefore, the major source of human exposure to glycidamide is through exposure to acrylamide in occupational situations (especially in acrylamide monomer production; Moorman et al., 2012), through the diet (Delatour and Stadler, 2023), or use of tobacco products. Glycidamide has also been reported to be present in certain processed foods at a level of 0.3–1.5 µg/kg, or less than 1% of that of acrylamide (Granvogl et al., 2008; NTP, 2014).

Cancer in humans

There are no data pertaining to the carcinogenicity of glycidamide, independently from acrylamide, in humans (NTP, 2014), although glycidamide biomarker levels were associated with increased cancer mortality risk (Gu et al., 2022).

Cancer in experimental animals

The carcinogenicity of glycidamide has been demonstrated in experimental animals. C57BL/6J *Min*/+ mice, a strain susceptible to intestinal neoplasia, and their wild-type littermates were administered subcutaneous injections of glycidamide at 1 week and 2 weeks after birth. In both strains, there was a dose-related induction of tumours of the small intestine, and the increase was significant at the highest dose (Olstørn et al., 2007). In another study, male B6C3F$_1$ mice injected intraperitoneally with glycidamide on postnatal days 1, 8, and 15 had a significant increase in hepatocellular tumours (Von Tungeln et al., 2012). Male and female B6C3F$_1$ mice exposed to glycidamide in the drinking-water had significant dose-related increases in tumours of the Harderian gland, lung, forestomach, and skin. Female B6C3F$_1$ mice also had significantly increased incidence of tumours of the mammary gland and ovary. In male and female F344/N rats, there were significant increases in neoplasms of the thyroid and the oral cavity and mononuclear cell leukaemia. Male F344/N rats also had significant dose-related increases in tumours of the epididymis or testis and heart, and female F344/N rats had significant increases in tumours of the mammary gland, clitoral gland, and forestomach (NTP, 2014; Beland et al., 2015).

Mechanistic evidence

There is evidence that glycidamide is electrophilic. DNA adducts from its reactions with deoxyguanosine and deoxyadenosine have been detected in mice and rats treated with glycidamide. The same DNA adducts have been detected in Chinese hamster V79 lung cells, mouse L5178Y kk$^{+/-}$ lymphoma cells, and primary mouse embryonic fibroblasts treated in vitro with glycidamide. Glycidamide reacts with cysteine residues in haemoglobin and other proteins and with the N-terminal valine of haemoglobin (NTP, 2014).

There is evidence that glycidamide is genotoxic. Glycidamide induced mutations in *S. typhimurium* (various strains), mouse L5178Y $tk^{+/-}$ lymphoma cells (attributed to a clastogenic mode of action), Chinese hamster V79 lung cells (chromosomal aberrations), CHO cells, Big Blue mouse embryo fibroblasts (primarily substitutions), and human TK6 lymphoid cells (primarily point mutations). Strand breaks were detected in human peripheral blood lymphocytes incubated with glycidamide. Increased mutant frequencies have been detected in male and female mice and rats treated with glycidamide (NTP, 2014).

As reported for acrylamide (see agent 192), in the previous *IARC Monographs* evaluation (IARC, 1994c), there was *strong* evidence that acrylamide and its active metabolite glycidamide form covalent adducts with DNA and are genotoxic in experimental animals. Since then, several new studies have reported positive results on the clastogenic and mutagenic properties of acrylamide and glycidamide (Benford et al., 2022). In addition, further information on the mechanisms underlying the mutagenic effects of acrylamide and glycidamide in exposed humans is available.

Metabolic conversion of acrylamide leads to glycidamide, which forms an *N*7-glycidamide–guanine DNA adduct in rodents. *N*7-Glycidamide–guanine adducts in the blood DNA of healthy volunteers have been identified and quantified (Hemgesberg et al., 2021; Jones et al., 2022b). A unique mutational signature imprinted by acrylamide through the effects of its reactive metabolite glycidamide has been identified. This mutational signature was found in one-third of approximately 1600 tumour genomes corresponding to 19 human tumour types from 14 organs (Zhivagui et al., 2019). In addition, Hogervorst et al. (2017) investigated whether genetic make-up modifies the association between acrylamide and ovarian cancer risk, thereby contributing to evidence on acrylamide's mechanism of action and the causality of the observed association in humans. The authors observed statistically significant interactions between several SNPs in the HSD3B1/B2 gene cluster and acrylamide intake for ovarian cancer risk, suggesting that acrylamide may cause ovarian cancer through effects on sex hormones (Hogervorst et al., 2017). There is evidence that acrylamide induces oxidative stress in experimental systems (Zhang et al., 2023g) and exposed humans (Piwowar et al., 2023).

Summary

No studies of exogenous exposure to glycidamide and cancer in humans were available. There is evidence that glycidamide, when administered orally in drinking-water, causes tumours in two rodent species, at several different tissue sites. There is substantial evidence that glycidamide exhibits KCs in experimental animals and some evidence in exposed humans. The Advisory Group therefore considered an *IARC Monographs* evaluation of glycidamide to be warranted, and that glycidamide should be evaluated together with acrylamide (agent 192).

Recommendation: High priority (and ready for evaluation within < 2.5 years)

205 Ingested nitrate (CAS No. 14 797-55-8)

Current IARC/WHO classification

Nitrate or nitrite (ingested) under conditions that result in endogenous nitrosation has previously been evaluated by the *IARC Monographs* programme as *probably carcinogenic to humans* (Group 2A) in Volume 94 in 2006 (IARC, 2010c), with *limited* evidence in humans for stomach cancer. IARC (2010c) noted that: (1) the endogenous nitrogen cycle in humans includes interconversion of nitrate and nitrite; (2) nitrite-derived nitrosating agents produced in the acid stomach environment can react with nitrosating compounds such as secondary amines and amides to generate *N*-nitroso compounds; (3) nitrosating conditions are enhanced upon ingestion of additional nitrate, nitrite, or nitrosatable compounds; and (4) some *N*-nitroso

compounds are known carcinogens. The WHO has published a drinking-water quality guideline for nitrate (see WHO, 2016).

Exposure characterization

Nitrate is a naturally occurring ion that is ubiquitous in the environment. It is a product of the oxidation of nitrogen, as part of the cycle required by all living systems to produce complex organic molecules, such as enzymes and other proteins. Human exposure to nitrate is through ingested food and water.

Ingested nitrate from food

The main sources of ingested nitrate from food are vegetables, especially leafy vegetables (> 1000 mg/kg), bakery goods and cereal products (mean, about 10 mg/kg, up to about 20 mg/kg) and cured meat (mean, 60 mg/kg; up to 450 mg/kg). For an average adult living in an area with low drinking-water contamination, total exposure to ingested nitrate is estimated to be about 60–90 mg per person per day. For high consumers of vegetables, the intake of nitrate may reach 200 mg per person per day. An ADI of 3.7 mg nitrate ion/kg bw per day was adopted by the European Commission. It was estimated that the exposure resulting from its use as a food additive (sodium nitrate, E 251 and potassium nitrate, E 252) did not exceed this ADI. If all sources of dietary nitrate exposure were considered together, the ADI would be exceeded for all age groups at the mean and the highest exposure. The contribution of nitrates used as food additives represented approximately 2% of the overall exposure of nitrates as food additives (European Commission, 2023).

Ingested nitrate from drinking-water

When the concentration of nitrate in drinking-water is greater than 10 mg/L, water becomes an important source of exposure and then is generally the principal source of ingested nitrate (IARC, 2010c). In most countries, nitrate concentrations in drinking-water derived from surface water do not exceed 10 mg/L. In 15 European countries, the percentage of the population exposed to nitrate concentrations in drinking-water above 50 mg/L (as nitrate ion) ranged from 0.5% to 10% (WHO, 2016). Nitrate levels in water resources have increased worldwide as a result of applications of inorganic fertilizer and animal manure in agricultural areas. Nitrogen fertilizers, as the major source of nitrate in the soil, can contaminate groundwater, surface water and drinking-water. Contamination sources also include septic systems that do not effectively remove nitrogen, and discharges from wastewater treatment plants, as well as atmospheric deposition of nitrogen oxides and fertilizer use on lawns, golf courses, and parks. In areas with nitrate-contaminated drinking-water, this source may account for most human nitrate exposure. In the USA, the highest reported nitrate concentration was in a domestic well (> 1200 mg/L as nitrate-nitrogen) (WHO, 2016). WHO guidelines on safe concentrations of nitrate compounds in water for human use are regularly exceeded in many countries, especially in shallow waters and wells, in both high-income and low- and middle-income countries (WHO, 2016; Picetti et al., 2022; Clemmensen et al., 2023; Levin et al., 2023). The German Federal Institute of Risk Assessment (2009) estimated that in Germany the median nitrate intake for adults from water and other beverages was 28.3 mg per day – about [18%] of the median nitrate intake from all sources (159.8 mg per day).

Cancer in humans

In a recent review, an association of nitrate in drinking-water with gastric cancer – but with no other cancer site – was identified. The meta-analysis included four case–control studies with a total population of 19 874. Two case–control and two cohort studies not included in the meta-analysis found no evidence of an association (Picetti et al., 2022).

The most consistent associations with drinking-water nitrate ingestion were shown for colon cancer (Espejo-Herrera et al., 2016; Ward et al., 2018). A meta-analysis of 48 publications with 13 different cancer

sites showed an association with colon cancer (Essien et al., 2022). A meta-analysis of six recent case–control and cohort studies showed high exposure levels to be associated with increased risk for colon cancer and colorectal cancer, but not for rectal cancer alone (Chambers et al., 2022). Another meta-analysis suggested that the association with nitrate concentration was stronger for colon cancer than for rectal cancer (Elwood and Werf, 2022). A meta-analysis of three cohort studies and seven case–control studies found no significant association; however, a separate meta-analysis of two case–control studies that reported results on well water observed a significant association only between nitrate and colorectal cancer (Picetti et al., 2022). A nationwide population-based cohort study in Denmark found an increased colorectal cancer risk at drinking-water nitrate concentrations well below the European drinking-water standard of 50 mg/L (Schullehner et al., 2018).

In a US cohort of postmenopausal women (the Iowa Women's Health Study), high nitrate levels in drinking-water were associated with bladder cancer (Jones et al., 2016), thyroid cancer (Ward et al., 2010b), ovarian cancer (Inoue-Choi et al., 2015), and kidney cancer (Jones et al., 2017b), while no association was found with breast cancer (Inoue-Choi et al., 2012), colon and rectal cancers (Jones et al., 2019), pancreatic cancer (Quist et al., 2018), digestive system cancers (Buller et al., 2021), or endometrial cancer (Medgyesi et al., 2022). In European studies, where nitrate ingestion levels were lower, weaker associations were found for these cancer sites and some positive findings for colon cancer in some of the cohorts (Ward et al., 2018). However, a recent study observed a positive association between preconception/prenatal average nitrate ingestion with childhood cancer in Denmark (Stayner et al., 2021).

Cancer in experimental animals

In the last evaluation in the *IARC Monographs* (IARC, 2010c), there was *inadequate* evidence in experimental animals for the carcinogenicity of nitrate; there was *limited* evidence in experimental animals for the carcinogenicity of nitrite; and there was *sufficient* evidence in experimental animals for the carcinogenicity of nitrite in combination with amines or amides.

Mechanistic evidence

There is some evidence of genotoxicity in exposed humans associated with ingested nitrate through drinking-water, although the results are equivocal. Increased micronucleus formation was observed in lymphocytes of women living in Mexico with chronic exposure to nitrate in drinking-water (Gandarilla-Esparza, et al., 2021) and in humans exposed to chronic long-term nitrate therapy by oral or transdermal administration (Andreassi et al., 2001). A significant increase in the mean number of chromosome breaks was observed in children exposed to high nitrate concentrations, but there was no significant increase in the mean number of SCEs per cell (Tsezou et al., 1996). There was no mutagenicity in nitrate-contaminated water from a region in China (Cao et al., 2016). Nitrate contamination in drinking-water was not associated with increased frequencies of SCE in peripheral lymphocyte (Kleinjans et al., 1991).

Several studies of exposed humans observed association of nitrate in drinking-water with thyroid disease. A study of women in the Netherlands consuming water with high nitrate levels found increased prevalence of thyroid hypertrophy (van Maanen et al., 1994). In women, high nitrate exposure was significantly associated with subclinical hypothyroidism (Aschebrook-Kilfoy et al., 2012). A study of school-age children in Slovakia found increased prevalence of subclinical hypothyroidism among children in an area with high nitrate levels in water supplies. In Bulgarian villages with high nitrate levels, clinical examinations of the thyroids of pregnant women and schoolchildren revealed approximately four- and threefold increased prevalences of goitre, respectively (Tajtáková et al., 2006; Rádiková et al., 2008).

Summary

There is new evidence regarding the association between nitrate in drinking-water and cancer in humans, particularly for colon cancer. The Advisory Group was aware of other potentially informative studies of cancer in humans that should be published in the next few years. There is some evidence that nitrate in drinking-water exhibits KCs in exposed humans and experimental animals. The Advisory Group therefore considered an *IARC Monographs* evaluation of ingested nitrate to be warranted, towards the latter half of the next 5 years.

Recommendation: Medium priority

206 Nitrilotriacetic acid (CAS No. 139-13-9)

Current IARC/WHO classification

Nitrilotriacetic acid and its salts (evaluated as a group) have previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Volume 73 in 1998 (IARC, 1999b), on the basis of *sufficient* evidence for carcinogenicity in experimental animals.

Exposure characterization

Nitrilotriacetic acid (NTA) is a tertiary amino-polycarboxylic acid with the chemical formula $C_6H_9NO_6$ and exists as a white crystalline powder at room temperature. It is used as a metal chelating agent in laundry and dishwashing detergents and related cleaning products (IARC, 1999b). It is also widely used in industry as a boiler feedwater additive and in water treatment, textile treatment and metal plating and in pulp and paper processing (Khan and Sultana, 2004; NTP, 2011).

Workers in industries involved in the production or utilization of NTA, such as detergent manufacturing, may have occupational exposure to NTA (NTP, 2011). The environmental presence of NTA is primarily attributed to industrial wastewater and agricultural areas where NTA-containing products are used as a chelating agent to improve the quality of soil (Pinto et al., 2014; Mehrab et al., 2023). Individuals are mainly exposed to NTA through household cleaning products, detergents, or personal care items that contain NTA (Bucheli-Witschel and Egli, 2001). Exposure can occur by oral exposure from consuming water or residues on dishes washed with detergents containing NTA, skin contact during bathing or wearing clothes laundered with NTA-containing detergents, and inhalation of detergents during laundry or hand-washing activities (Anderson et al., 1985; NTP, 2011; Gupta and Sekhri, 2014).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 1999b), there was *sufficient* evidence in experimental animals for the carcinogenicity of nitrilotriacetic acid, on the basis of studies of mice and rats that showed tumours in both sexes after oral administration (NTP, 1977).

Mechanistic evidence

No data were available to the previous Working Group on the genetic and related effects of nitrilotriacetic acid in exposed humans (IARC, 1999b). Since the last evaluation, studies have shown a dose-dependent increase in the frequency of both DNA breaks and micronucleated cells in primary cultures of kidney cells from human donors which were exposed to nitrilotriacetic acid (Robbiano et al., 1999). Moreover, the same genotoxic effects have been observed in the kidney of rats treated orally with a single dose or three successive daily doses of nitrilotriacetic acid, or in primary cultures of rat kidney cells exposed

to nitrilotriacetic acid (Robbiano et al., 1999). In another study, Robbiano et al. (2002) observed a modest but significant amount of DNA fragmentation in both urinary bladder and kidney of rats treated with nitrilotriacetic acid. In addition, a dose-dependent increase has been observed in the frequency of DNA single-strand breaks and alkali-labile sites in primary cultures of rat urinary bladder mucosa. Nitrilotriacetic acid induced DNA primary damage in isolated kidney cells from rats treated orally (Nesslany et al., 2008). Nitrilotriacetic acid gave positive results in a high-throughput in vitro steroidogenesis assay (increase of estradiol and progesterone synthesis) in human H295R adrenocortical carcinoma cells (Cardona and Rudel, 2021; Kay et al., 2024). Nitrilotriacetic acid is known to dissolve heavy metals and therefore to increase their genotoxicity (Celotti et al., 1987; Lanfranchi et al., 1988).

Summary

Nitrilotriacetic acid, given by oral administration, caused tumours in mice and rats at several different tissue sites. Several studies have shown mechanistic evidence of KCs, mainly genotoxicity in experimental systems: human cells in vitro, and in rodents in vivo and in vitro. However, based on sparse mechanistic data on human primary cells (only one study) and no studies in exposed humans, it is unlikely that the classification would change. The Advisory Group therefore considered that an *IARC Monographs* re-evaluation of nitrilotriacetic acid is unwarranted at present.

Recommendation: No priority

207 Palmitic acid (CAS No. 57-10-3)

Current IARC/WHO classification

Palmitic acid has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Palmitic acid is listed as a high production volume chemical by the OECD and the US EPA (OECD, 2009b; US EPA, 2024a). Palmitic acid is manufactured in and/or imported to the European Economic Area in quantities ranging from 10 000 to under 100 000 tonnes annually (ECHA, 2023g). Palmitic acid, a saturated fatty acid, is both a dietary component and an endogenously synthesized substance in the human body. It constitutes 20–30% of total fatty acids in membrane phospholipids and adipose triacylglycerols. Palmitic acid is a significant dietary component of palm oil (where it accounts for 44% of total fats), meat and dairy products, cocoa butter, and olive oil. It is used in a wide array of consumer products such as washing and cleaning products, coating products, polishes, waxes, and air care products, as well as in industrial applications such as leather treatment and textile processing, and as an ingredient in polymers, lubricants, and greases. Additionally, palmitic acid is present in various articles used in everyday life, including automotive care products, furniture, clothing, and electronic equipment. Its release into the environment can occur through various industrial processes, and it is found in long-life materials with varying release rates (Carta et al., 2017; ECHA, 2023g). Exposure occurs predominantly via the diet, as it is present in staple foods.

Cancer in humans

The relation between circulating palmitic acid levels and development of cancer, particularly breast cancer, is the subject of continuing debate, because of conflicting results (Carta et al., 2017). A meta-analysis by Saadatian-Elahi et al. (2004) and a prospective study by Bassett et al. (2016) both reported an association between palmitic acid levels in blood and increased risk of breast cancer. In contrast, a prospective study conducted in northern Italy by Pala et al. (2001) did not find a notable association between saturated fatty acids, including palmitic acid, and breast cancer risk.

Cancer in experimental animals

Palmitic acid was administered subcutaneously to sixteen Swiss-Webster female mice at a dose of 1.0 mg three times per week for a total of 10 injections (total dose, 10 mg palmitic acid/1 ml tricaprylin). Eight mice were alive after 12 months, and six were alive after 18 months. One subcutaneous sarcoma was found after 19 months, two pulmonary neoplasms were found after 19 and 22 months, and one breast carcinoma was found after 22 months. Another group of 16 female Swiss-Webster mice received two subcutaneous injections of 5.0 mg palmitic acid per week for a total of 25 injections (total dose, 125 mg palmitic acid/2.5 ml tricaprylin). Eight mice were alive after 12 months and five were alive after 18 months. A subcutaneous sarcoma was found after 8 months, two breast carcinomas were found after 18 months, and one "leukaemia-lymphoma" was found after 12 months (Swern et al., 1970).

The EFSA Panel on Food Additives and Nutrient Sources Added to Food evaluated the effects of a series of fatty acids (lauric acid, oleic acid, myristic acid, capric acid, caprylic acid, stearic acid, and palmitic acid) on the development of cancer in animal models treated with an initiating agent. Except for linoleic acid at high doses, most of these studies reported protective effects of free fatty acids (Mortensen et al., 2017).

Mechanistic evidence

Palmitic acid induced DNA damage in RINm5F insulin-secreting cells and in primary normal human fibroblasts (Beeharry et al., 2003). By contrast, it tested negative in three assays for genotoxicity (the bacterial reverse mutation assay, the in vitro mammalian mouse lymphoma gene mutation assay and the rat micronucleus test) (Paskaleva et al., 2014). Numerous studies have investigated the inflammatory effects of palmitic acid. While some studies observed pro-inflammatory effects on macrophages (reviewed in Hidalgo et al., 2021), others found anti-inflammatory effects (Zhu et al., 2021d; He et al., 2023; Wang et al., 2023j; Yu et al., 2023). With regard to cell proliferation, some studies observed that palmitic acid increased the proliferation of colorectal cancer cells (Fatima et al., 2019) and of prostate cancer cell lines in vitro (Landim et al., 2018; Binker-Cosen et al., 2017) and in vivo (Kim et al., 2019); it also promoted metastasis in several human oral cancer cell lines (Pascual et al., 2017). However, other studies showed that palmitic acid inhibited proliferation, impaired cell invasiveness, suppressed hepatocarcinoma growth in vitro and in mouse xenograft models (Lin et al., 2017), and inhibited cell proliferation of human colon cancer cell lines (Hu et al., 2021b) and breast cancer cells (Baumann et al., 2016).

Summary

Data regarding cancer in humans and animal experiments are few and equivocal. In addition, there is inconsistent mechanistic evidence suggesting that palmitic acid exhibits KCs in experimental systems. There is also substantial evidence showing anti-carcinogenic proprieties of palmitic acid in experimental animals. In view of the limitations in the available data from all three evidence streams, the Advisory Group considered that an *IARC Monographs* evaluation of palmitic acid is unwarranted at present.

Recommendation: No priority

208 Parabens

Current IARC/WHO classification

Parabens have not previously been evaluated by the *IARC Monographs* programme. Parabens were given a priority rating of *high* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of mechanistic evidence.

Exposure characterization

Parabens are a group of alkyl esters of *para*-hydroxybenzoic acid, commonly used as preservatives in cosmetics, pharmaceuticals, and personal care products for their antimicrobial and antifungal effects (Giulivo et al., 2016; Parada et al., 2019). Parabens are added to prevent the growth of bacteria and fungi in these products to extend their shelf life. Common parabens include methylparaben, ethylparaben, propylparaben, and butylparaben (Giulivo et al., 2016; Parada et al., 2019). Human exposure is ubiquitous through use of products such as deodorants, creams, lotions, make-up, toothpaste, toiletries, shaving products, sanitary wipes, and food packaging. Parabens are also used as food additives (Giulivo et al., 2016). The general population is continuously exposed to parabens through skin absorption (paraben-containing personal care products), ingestion (paraben-containing food and water), inhalation (paraben-contaminated indoor dust), and environmental exposures (paraben-contaminated soil, sediment or sludge) (Giulivo et al., 2016). Parabens are excreted in urine, and their urinary concentration is a valid measure of exposure (Hager et al., 2022). People living in Europe and the USA have higher exposure to parabens than people in other regions such as Asia; females have higher exposure than males, and pregnant women have higher exposure than the general population (Wei et al., 2021b; Calafat et al., 2010).

Cancer in humans

A few studies have evaluated paraben exposure and breast cancer risk in humans. In the Long Island Breast Cancer Study Project (a case–control study), the highest quintiles of urinary methyl-, propyl-, and total parabens were found to be associated with increased risks of breast cancer (Parada et al., 2019). The Multiethnic Cohort Study found a weakly inverse relationship between paraben exposure and breast cancer (Wu et al., 2021c). Other studies have evaluated associations between paraben exposure and other cancers. Urinary concentrations of parabens were found to be associated with the risk of lung cancer in adults (Mao et al., 2023b) and exposure to individual parabens to be associated with the risk of thyroid cancer and benign nodules in Wuhan, China (Wu et al., 2022c). Epidemiological studies have tended to rely on a single measurement of parabens in the urine, often after cancer was detected, making misclassification, reverse causality, and confounding a serious concern (Hager et al., 2022).

Cancer in experimental animals

No carcinogenic effect was noted in several chronic toxicity studies on rodents when parabens were administrated orally or subcutaneously (SCCS, 2021).

Mechanistic evidence

With regard to genotoxicity, parabens were inactive in classical assays for mutagenicity (SCCS, 2021). Assessment of genotoxic effects of various parabens by the Drosophila Wing Spot Test (SMART) gave negative or insignificant results (Ayar and Uysal, 2013). Treatment of keratinocytes with UVR in combination with parabens revealed oxidative stress induction, ROS and nitric oxide production, and lipid peroxidation in vitro. Positive associations were seen between exposure to parabens and levels of some inflammatory biomarkers in exposed humans (Aung et al., 2019; Peinado et al., 2023). Methylparaben (0.003%) had little or no effect on cellular viability, oxidative stress, nitric oxide production, lipid peroxidation, and activation of nuclear transcription factors in HaCaT keratinocytes. Low-dose UVB also had little or no effect on these parameters in HaCaT keratinocytes. However, UVB exposure significantly increased cell death, oxidative stress, nitric oxide production, lipid peroxidation, and activation of transcription factors in methylparaben-treated HaCaT keratinocytes (Handa et al., 2006; van Meeuwen et al., 2008).

Parabens, together with their common metabolite *para*-hydroxybenzoic acid, possess estrogen agonist properties and androgen antagonist activity (Darbre and Harvey, 2008). Parabens interfered with the

homeostasis of the thyroid gland, affecting the levels of synthesis and secretion of thyroid hormones (Aker et al., 2018; Azeredo et al., 2023). Estrogenic activity of parabens was demonstrated in MCF-7 human breast cancer cells at concentrations that could be found in vivo (Byford et al., 2002; Fransway et al., 2019). Methyl-, propyl-, and butylparaben increased *GPR30* gene and protein expression in both breast cancer MCF-7 and immortalized MCF-10A cells. Propylparaben affected cAMP levels in MCF-10A cells (Wróbel and Gregoraszczuk, 2015).

In MCF-7 cells in vitro, methylparaben increased proliferation and induced canonical estrogen-responsive genes (pS2 and progesterone receptor). Mammospheres obtained using cells of MCF-7 and patient-derived xenografts exhibited increased size and upregulation of canonical stem cell markers (Lillo et al., 2017). The estrogenic activity of parabens measured in human breast carcinoma cells by luciferase reporter assay demonstrated its dependence on the length of the alkyl chain (Tong et al., 2023). Propylparabens promoted glycolysis in MCF-7 cells and enhanced the tricarboxylic acid cycle in mitochondria, inducing an increase in cell proliferation, which is also stimulated via a mitogen-activated protein kinase pathway of MCF-7 cells (Hager et al., 2022; Chen et al., 2023d). In addition to nuclear receptors ERα and ERβ, parabens also bind to estrogens and activate downstream signalling events (Zimmerman et al., 2016; Xu et al., 2019b). In MCF-7 cells, parabens inhibited aromatase, an enzyme involved in a rate-limiting step in steroidogenesis (van Meeuwen et al., 2008). In a reporter luciferase assay, a paraben mixture exhibited significant anti-androgenic activity, which exceeded the sum of the mixture components; only isobutylparaben produced a significant effect when applied alone (Chen et al., 2007; Kjaerstad et al., 2010).

Methylparaben and propylparaben significantly enhanced mammary tumour growth and pulmonary metastasis in female mice exposed to parabens (Tong et al., 2023). Moreover, methylparaben increased tumour size of MCF-7 xenografts and a patient-derived xenograft tumour expressing estrogen receptors (Lillo et al., 2017).

Parabens caused no effect on testosterone production in male ICR mice (Oishi, 2002). In male rats exposed to parabens orally, no effects on testosterone production and induced sperm DNA hypermethylation were observed (Park et al., 2012).

Summary

Parabens are widely used as a component of cosmetics. Their carcinogenicity has not been demonstrated in humans or experimental animals; however, parabens stimulate breast cancer growth and metastasis. As endocrine disruptors, parabens exhibit KCs in experimental systems and in exposed humans. The Advisory Group therefore considered an *IARC Monographs* evaluation of parabens to be warranted.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

209 Piperonyl butoxide (CAS No. 51-03-6)

Current IARC/WHO classification

Piperonyl butoxide (PBO) has previously been evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) in Supplement 7 in 1987 (IARC, 1987a). The WHO has published a risk assessment for PBO, as a synergist in insecticide-treated bed nets (WHO, 2021d).

Exposure characterization

PBO is used synergistically in enhancing the efficacy of insecticides (such as pyrethrins) in pest control. PBO-enhanced long-lasting pyrethroid-treated mosquito nets were recommended by the WHO in 2017 for malaria prevention in areas with insecticide-resistant mosquito populations and have been used with great

success for malaria vector control in Africa (Gleave et al., 2017). Exposure to PBO in humans occurs in domestic, agricultural, industrial, and commercial settings. Specifically, exposure occurs through contact with pyrethroid–PBO-treated nets (Gleave et al., 2017), inhalation of PBO-containing sprays in aircraft (Berger-Preiss et al., 2004), aerial applications for malaria control (Macedo et al., 2010), inhalation of PBO-contaminated dust in agricultural areas (Navarro et al., 2023b), and prenatal exposure of children when pregnant women inhale PBO-contaminated dust (Liu et al., 2012). Residential exposure may be accidental (especially in children) through contact with insecticide formulations stored within the reach of children (Osimitz et al., 2009).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 1987a), there was *inadequate* evidence in experimental animals for the carcinogenicity of PBO. At that time, the few studies of long-term toxicity on PBO showed no significant increase of the incidence of any tumour type in (C57BL/6 × C3H/Anf)F1 or (C57BL/6 × AKR)F1 mice given 464 mg/kg orally for 7 to 28 days followed by 1112 ppm in the diet for 17 months (Innes at al., 1969). There was no significant carcinogenic effect in Fischer 344 rats to which PBO was administered in the diet (NCI, 1979b), nor in $B6C3F_1$ mice (NCI, 1979b).

Since the last evaluation, numerous studies have been conducted using mice and rats. In CD-1 mice, PBO treatment in the diet increased the incidence of eosinophilic adenoma in males and in females (Butler et al., 1998). PBO administered in the diet for 1 year induced significant increases in the incidence of hepatocellular adenoma, HCC, and haemangioendothelial sarcoma in male CD-1 mice in a dose-dependent manner (Takahashi et al., 1994a) and of HCC in both sexes of CD-1 mice (Takahashi et al., 1997). PBO treatment of male and female CD-1 mice in the diet for 79 weeks significantly increased the incidence of hepatocellular adenoma, but not HCC (Lake et al., 2020).

After treatment of Sprague-Dawley rats with PBO for 104/105 weeks, there was no increased incidence of neoplasia at any site (Butler et al., 1998). In male and female F344 rats, PBO treatment in the diet significantly increased the incidence of hepatocellular adenoma, HCCs, hepatocellular adenoma or HCC (combined), and haemangiosarcoma in both sexes, and in a dose-dependent manner (Takahashi et al., 1994b). A promoting effect of PBO was demonstrated using a two-stage liver carcinogenesis protocol in rats, combined with intraperitoneal injection of *N*-diethylnitrosamine (Muguruma et al., 2009).

Mechanistic evidence

PBO lacked genotoxicity in bacterial mutation assays and in the CHO/HGPRT assay, both with and without metabolic activation. PBO was not found to be genotoxic when tested for chromosomal aberrations in CHO cells and for effects on UDS in rat liver primary cell cultures in vitro (Butler et al., 1996). Lack of effect of PBO on UDS was also demonstrated in precision-cut human liver slices (Beamand et al., 1996). PBO increased DNA methylation in the promoter region of Wdr6 and Cmtm6 genes, and decreased expression of these genes in non-neoplastic liver cells, in contrast to the effects in the majority of proliferative lesions (Yafune et al., 2013). PBO induced oxidative stress in several animal models. In a liver carcinogenesis model using male F344 rats, treatment with PBO in the diet significantly increased oxidative stress and the level of 8-OHdG (Muguruma et al., 2007). In a two-stage liver carcinogenesis model, combining *N*-diethylnitrosamine intraperitoneal injection and hepatectomy, piperonyl butoxide induced a significant increase in ROS (Muguruma et al., 2009). Treatment of p53-proficient and p53-deficient *gpt* mice with PBO caused significant increases in 8-OHdG levels in liver DNA (Tasaki et al., 2013). PBO also increased ROS production in microsomes but did not induce oxidative DNA damage (Kawai et al., 2010b).

Possible involvement of CAR activation associated with PBO was shown in some animal studies (Lake et al., 2020; Sakamoto et al., 2013). Piperonyl butoxide induced replicative DNA synthesis in human primary hepatocytes (Lake et al., 2020) and increased cell proliferation in rodents (Okamiya et al., 1998; Phillips et al., 1997; Kawai et al., 2010a). Piperonyl butoxide also increased expression of genes associated with activation of cell growth pathways, such as the Myc and E2F1 pathways (Kawai et al., 2009; Kawai et al., 2010b).

Summary

There is significant exposure of humans to piperonyl butoxide, particularly through pesticides used for malaria control. No studies of cancer in humans were available. There is new evidence from cancer bioassays that piperonyl butoxide induces hepatic tumours in mice and rats. There is mechanistic evidence suggesting that piperonyl butoxide exhibits KCs, including epigenetic alterations, oxidative stress, modulation of receptor-mediated effects, and cell proliferation, but not genotoxicity in several studies in experimental systems. The Advisory Group therefore considered an *IARC Monographs* re-evaluation of piperonyl butoxide to be warranted.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

210 Polyhexamethylene guanidine (CAS No. 31961-54-3)

Current IARC/WHO classification

Polyhexamethylene guanidine (PHMG) has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

PHMG is a biocide used in humidifier disinfectants, household and industrial cleaning disinfectants, paints, paper, plastics, fabric softeners, shampoos, wet wipes, and water purification (National Industrial Chemicals Notification and Assessment Scheme, 1989; Song et al., 2014b; Yoon et al., 2017). Exposure can be through inhalation, skin contact, and handling treated water. PHMG is approved by the US FDA for disinfecting medical devices (Song et al., 2014b). Exposure to PHMG in humidifier disinfectants and the associated lung injury, particularly in children in the Republic of Korea, are well documented (Yoon et al., 2017; Song et al., 2022b).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

Intratracheal treatment of rats with polyhexamethylene guanidine phosphate (PHMG-p) for 52 weeks induced the formation of bronchioloalveolar adenomas and bronchioloalveolar carcinomas (Kim et al., 2021a, b).

Mechanistic evidence

PHMG-p promoted ROS generation and increased the expression of DNA markers such as ATM and H2AX phosphorylation in human A549 and BEAS-2B cell lines (Park et al., 2019; Kang et al., 2022a). PHMG-p induced lung injury and transcriptomic changes that varied with the number of weeks after intratracheal exposure in rats, suggesting that PHMG may induce cell damage in lung tissue over time (Kim et al., 2021a). PHMG-p induced lung fibrosis after intratracheal instillation to experimental animals (Kim et al., 2021a, b; Kang et al., 2022a). Alveolar hyperplasia developed at 6 weeks after PHMG-p intratracheal

administration to rats and then decreased. Several studies show that PHMG-p induces apoptosis in human lung epithelial A549 cells (Jung et al., 2014; Park et al., 2019).

Long-term exposure of human pulmonary normal alveolar epithelial cells to low-dose PHMG-p caused transcriptional changes, mainly in lung cancer-associated genes, in a time-dependent manner (Lee et al., 2022b).

Summary

No studies of cancer in humans were available for polyhexamethylene guanidine. There is sparse evidence for carcinogenesis in experimental animals. There is mechanistic evidence suggesting that polyhexamethylene guanidine phosphate exhibits KCs in experimental systems, which could support a classification of carcinogenicity of PHMG. The Advisory Group therefore considered an *IARC Monographs* Working Group evaluation of polyhexamethylene guanidine to be warranted.

Recommendation: High priority (and ready for evaluation within 5 years)

211 Styrene–acrylonitrile (SAN) trimer

Current IARC/WHO classification

Styrene–acrylonitrile (SAN) trimer has not previously been evaluated by the *IARC Monographs* programme. SAN trimer was given a priority rating of *medium* by the 2019 Advisory Group on Priorities (IARC, 2019a), on the basis of human cancer evidence.

Exposure characterization

SAN trimer exists as a mixture of isomers comprising two structural forms: 4-cyano-1,2,3,4-tetrahydro-α-methyl-1-naphthaleneacetonitrile (THNA; CAS No. 57 964-39-3) and 4-cyano-1,2,3,4-tetrahydro-1-naphthalenepropionitrile (THNP; CAS No. 57 964-40-6). These, in turn, consist of four and two stereoisomers, respectively. As noted in the 2019 Advisory Group report, "SAN Trimer is a by-product of specific manufacturing processes for polymers of styrene and acrylonitrile, but it is currently not considered commercially useful (NTP, 2012b). SAN trimer has been found to contaminate soil and drinking-water in the USA (e.g. in New Jersey) (US EPA, 2014)." SAN trimer and acrylonitrile–butadiene–styrene copolymer are gaining in importance as food contact materials.

Cancer in humans

The 2019 Advisory Group noted that there were a few epidemiological studies on the incidence of childhood cancer in New Jersey, USA, including three ecological studies and a case–control study (ATSDR, 2008). One study found increased incidence of soft-tissue sarcomas in a subgroup (females aged ≤ 19 years in 2004–2005) in two areas with contaminated drinking-water containing SAN trimer; however, exposure to other mutagens occurred in the drinking-water.

Cancer in experimental animals

The one available study of cancer in experimental animals, in male and female F344 rats exposed to SAN trimer during gestation, during nursing through their mothers' milk, and throughout their lifetimes through feed, did not find a significant increase in the incidence of any tumours (NTP, 2012b).

Mechanistic evidence

As noted in the 2019 Advisory Group report, "A few studies relevant to key characteristics of carcinogens are available. SAN trimer was tested for genotoxicity by the US NTP. It was negative in bacterial tests but induced DNA damage in the combined micronucleus/comet assay in brain cells and in

leukocytes in juvenile rats (Hobbs et al., 2012). In the same study, SAN trimer also increased micronucleated reticulocytes in rat peripheral blood. It increased the incidence of chronic active inflammation in the liver of male F344/N rats)". No subsequent persuasive mechanistic evidence has been reported.

Summary

With little human cancer evidence, one negative bioassay and very few mechanistic data, the Advisory Group considered that an *IARC Monographs* evaluation of SAN trimer is unwarranted at present.

Recommendation: No priority

212 Thioacetamide (CAS No. 62-55-5)

Current IARC/WHO classification

Thioacetamide has previously been evaluated by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) in Supplement 7 in 1987 (IARC, 1987a), on the basis of *sufficient* evidence for cancer in experimental animals.

Exposure characterization

Thioacetamide is a colourless, crystalline material with a slight sulfur-like odour, capable of dissolving in both water and ethanol. It was formerly used in various industries, but since the 1970s its application has mostly been confined to laboratory settings for specific tests and in the manufacturing of metal salt nanoparticles (Zhou et al., 2006; HSDB, 2009). In 2009, thioacetamide was manufactured primarily in India and used mainly in the USA (NTP, 2021a). Clinical laboratory technicians are the primary population at risk of exposure, primarily through inhalation and skin contact (NIOSH, 1990b; HSDB, 2009).

Cancer in humans

No studies of cancer in humans were available to the Advisory Group.

Cancer in experimental animals

In the previous evaluation (IARC, 1987a), there was *sufficient* evidence in experimental animals for the carcinogenicity of thioacetamide. Since that evaluation, numerous studies in mice and rats have been published, many with positive findings (Kuroda et al., 1987; Yang et al., 1997; Park et al., 2001; Lim, 2002; Yeh et al., 2004, 2008; Liu et al., 2008; El Sadda et al., 2023). There were also several new initiation–promotion studies (Kobayashi et al., 1999; Taniai et al., 2009; Mizukami et al., 2010; Kimura et al., 2013; Omura et al., 2014; Dwivedi and Jena, 2020).

Mechanistic evidence

Several studies have investigated the molecular mechanisms of the toxicity of thioacetamide (Clawson et al., 1997; El-Ashmawy et al., 2014). Thioacetamide did not increase the proportion of micronucleated hepatocytes in treated rats; bone marrow micronucleus assays with thioacetamide also yielded negative results. The liver micronucleus assay using young adult rats singly dosed with thioacetamide also produced negative results. Thioacetamide gave positive results only in mouse bone marrow micronucleus assays (Sui et al., 2015). KRAS mutations have been observed in thioacetamide-induced tumours in rats (Colyn et al., 2022). Thioacetamide gave positive results in the mouse L5178Y lymphoma cell mutagenesis assay (Mitchell et al., 1988; Myhr and Caspary, 1988). Thioacetamide increased oxidative DNA damage, with increased generation of 8-OHdG; it also increased levels of cytokines IL-4, TNFα, and IFNγ in rats treated orally with thioacetamide (Zargar et al., 2019; Purnomo et al., 2023). In thioacetamide-induced tumours in rats, activation of inflammatory pathways (e.g. upregulation of Il6 and NFκB gene expression and IL-6

protein levels), leading to hepatic fibrosis (Dwivedi and Jena, 2020; Colyn et al., 2022; Ezhilarasan, 2023), as well as oxidative stress (e.g. elevation of Nrf2, hydrogen peroxide, and superoxide anion) (Dwivedi and Jena, 2020; El-Far et al., 2020) have been observed. Thioacetamide-treated rats showed significant variations in hepatic oxidative stress markers such as reduced hepatic levels of GSH, SOD, and CAT, and increased levels of hepatic malondialdehyde, nitric oxide, hydroxyproline, and plasma TNFα (Bashandy et al., 2018).

Summary

No studies of cancer in humans were available. There is already *sufficient* evidence that thioacetamide causes cancer in experimental animals. Mechanistic data show evidence for several KCs. When tested in vivo, thioacetamide was genotoxic in mice and increased oxidative DNA damage, oxidative stress, and inflammation in rats. However, considering the current classification of thioacetamide in Group 2B, without mechanistic evidence in human primary cells or in exposed humans the Advisory Group considered it unlikely that the evaluation would change and therefore considered an *IARC Monographs* re-evaluation of thioacetamide to be unwarranted.

Recommendation: No priority

213 Triclosan (CAS No. 3380-34-5)

Current IARC/WHO classification

Triclosan has not previously been evaluated by the *IARC Monographs* programme.

Exposure characterization

Triclosan is an antimicrobial agent that has been commonly used in a variety of personal care and household products, such as soaps, toothpaste, deodorants, and hand sanitizers, due to its ability to inhibit the growth of bacteria (Fang et al., 2010). Triclosan is listed as a high production volume chemical by the US EPA (US EPA, 2024a). The worldwide production of triclosan has recently been estimated as 1500 tonnes per year, and 132 million litres of triclosan-containing products are used annually in the USA alone (Alfhili and Lee, 2019). Human exposure to triclosan is through personal care, household, and medical products. Triclosan is absorbed via the skin, mouth, gastrointestinal tract, and mucous membranes. Triclosan exposure can be measured in human biospecimens, such as urine, serum, milk, and adipose tissue (Cai et al., 2023b). Its ubiquitous use exposes the general population through contact with triclosan-containing consumer products and through the consumption of food and drinking-water contaminated with triclosan (Fang et al., 2010). Triclosan-coated sutures have applications for infection-control in surgery (Yamashita et al., 2016).

Cancer in humans

A few epidemiological studies have investigated the association between triclosan and breast cancer. In a case–control study that included 302 breast cancer patients and 302 healthy individuals in Wuhan, China, triclosan level in urine was associated with breast cancer risk (Cai et al., 2023b). However, in the Multiethnic Cohort Study, urinary triclosan was inversely associated with breast cancer (OR, 0.83; 95% CI, 0.66–1.04) (Wu et al., 2021c).

Cancer in experimental animals

Triclosan has been examined for carcinogenicity in several species. There was no evidence of carcinogenicity in the rat and hamster. In mice, there was evidence of carcinogenicity (US EPA, 2018c; SCCS, 2022). The incidence of liver tumours in groups of CD-1 mice treated with triclosan for 18 months was statistically significantly greater than that in controls for both sexes (Rodricks et al., 2010). In male

$B6C3F_1$ mice receiving dermal applications of triclosan for 104 weeks, there were positive trends in the incidence of HCC and hepatocellular adenoma or carcinoma (combined), with the incidence being significantly increased for both. The same treatment of female $B6C3F_1$ caused a positive trend in the incidence of pancreatic islet adenoma (Fang et al., 2024).

Triclosan substantially accelerates HCC development, acting as a liver tumour promoter of *N*-diethylnitrosamine-induced carcinogenesis. Six-month exposure of homozygous null $Car^{-/-}$ or heterozygous Car ($Car^{+/-}$) mice to triclosan in drinking-water after a single intraperitonel injection of *N*-diethylnitrosamine at the age of 15 days increased the number of detectable HCCs up to 4.5-fold; 25% of mice treated with *N*-diethylnitrosamine only exhibited small nodules, whereas > 80% of those treated with both *N*-diethylnitrosamine and triclosan developed tumours. Maximal tumour diameter was also 3.5-fold larger in mice treated with triclosan (Yueh et al., 2014).

Mechanistic evidence

Triclosan did not exhibit positive responses for mutagenicity in the microplate Ames test when *S. typhimurium* strains TA98, TA100, TA1535, TA1537 were employed with and without activation with rat S9 fraction according to OECD TG 471 (Chrz et al., 2024; SCCS, 2022). In the comet assay on HaCaT cells in vitro, performed according to OECD TG 489, the percentage of DNA in the tail significantly increased at the highest tested non-cytotoxic concentration (10 µg/mL) of triclosan, and a clear concentration-dependent positive response was observed (Chrz et al., 2024). In the mammalian chromosome aberration test in vitro, performed using human peripheral lymphocytes according OECD TG 473, triclosan was clearly positive at the highest tested non-cytotoxic concentration (10 µg/mL) after treatment for 4 hours (Chrz et al., 2024). DNA fragmentation was quantified by the comet assay after exposure to various concentrations of triclosan in cells of macroinvertebrate *Chironomus riparius* larvae (Martínez-Paz et al., 2013).

In the breast cancer case–control study described above, exposure to triclosan was significantly positively correlated with relative telomere length and with 8-iso-prostaglandin F2α (8-isoPGF2α) and 4-hydroxy-2-nonenal-mercapturic acid (HNE-MA) (Cai et al., 2023b).

Triclosan influenced epigenetic enzyme regulation: treatment of the SCC-15 cell line decreased mRNA expression of DNMT3A and DNMT3B after 24- and 48-hour treatment (Sinicropi et al., 2022; Szychowski et al., 2022).

In both CD-1 and C57BL/6 mice, triclosan induced a dose-dependent increase in relative liver weight and centrilobular hypertrophy; hepatocyte DNA synthesis was also increased in a dose-related pattern and a significant increase in CAR/PXR and PPARα responsive genes was observed (Wang et al., 2017b). After treatment of male C57BL/6 mice with triclosan for 8 months, higher expression of several markers and genes, including Ki-67, c-Myc, and Cyclin D1, increased levels of superoxide and a marked increase in expression of oxidative stress responsive genes, including haem oxygenase 1, NADPH hydrogenase quinone 1, and glutathione-*S*-transferase were observed in livers of animals (Yueh et al., 2014).

Triclosan caused adverse effects on immune system function (Barros et al., 2010; Clayton et al., 2011; Anderson et al., 2016).

Triclosan in mice has been classified as a peroxisome proliferator (Rodricks et al., 2010; Lee et al., 2019). Subcutaneous injections of triclosan upregulated ER-dependent signalling pathways in MCF-7 xenografts (Lee et al., 2014). Triclosan stimulated ovarian cancer growth by regulating cell-cycle- and apoptosis-related genes via an ER-dependent pathway (Kim et al., 2014b).

Triclosan enhanced LNCaP prostate cancer cell proliferation and migration, regulating cell-cycle- and metastasis-related genes via the AR signalling pathway (Kim et al., 2015b). Proliferation of MCF-7 breast cancer cells in vitro was enhanced by triclosan via an ER-dependent signalling pathway (Lee et al., 2014). In BG-1 cells, triclosan induced cell-growth-regulating genes encoding cyclin D1, p21, and BAX, related to the cell cycle and apoptosis, via an ER-dependent pathway (Kim et al., 2014b). Triclosan promoted

epithelial–mesenchymal transition in H460 lung cancer cells, along with migratory and invasive abilities (Winitthana et al., 2014).

Triclosan interacted with several nuclear receptors, including hPXR, hCAR1, hCAR3, and rCAR to regulate hepatic catabolism and downstream thyroid hormone homeostasis in both rat and human (Paul et al., 2013). Triclosan demonstrated anticancer activity against prostate cancer cells via inhibition of fatty acid synthase (Sadowski et al., 2014).

Summary

Two studies in humans found inconsistent evidence of an association of triclosan with breast cancer. There is evidence from studies of cancer in experimental animals suggesting that triclosan has carcinogenic activity in mice. In addition, there is mechanistic evidence that triclosan exhibits KCs. The Advisory Group therefore considered an *IARC Monographs* evaluation of triclosan to be warranted.

Recommendation: High priority (and ready for evaluation within < 2.5 years)

214 Diabetes

The Advisory Group considered the agent to be an endogenous condition and therefore ineligible for evaluation.

Recommendation: No priority

215 Reduction of sex hormones in people older than 35–40 years

The Advisory Group considered the agent to be an endogenous condition and therefore ineligible for evaluation.

Recommendation: No priority

216 Violation of tissue renewal (regeneration) in people older than 35–40 years

The Advisory Group considered the agent to be an endogenous condition and therefore ineligible for evaluation.

Recommendation: No priority

References

Abassi H, Ayed-Boussema I, Shirley S, Abid S, Bacha H, Micheau O (2016). The mycotoxin zearalenone enhances cell proliferation, colony formation and promotes cell migration in the human colon carcinoma cell line HCT116. Toxicol Lett. 254:1–7. https://doi.org/10.1016/j.toxlet.2016.04.012 PMID:27084041

Abbasian N, Momtaz S, Baeeri M, Navaei-Nigjeh M, Hosseini R, Abdollahi M (2018). Molecular and biochemical evidence on the role of zearalenone in rat polycystic ovary. Toxicon. 154:7–14. https://doi.org/10.1016/j.toxicon.2018.07.022 PMID:30055260

Abdollahi A, Razavian I, Razavian E, Ghodsian S, Almukhtar M, Marhoommirzabak E, et al. (2022). Toxoplasma gondii infection/exposure and the risk of brain tumors: a systematic review and meta-analysis. Cancer Epidemiol. 77:102119. https://doi.org/10.1016/j.canep.2022.102119 PMID:35152168

Abdourahime H, Anastassiadou M, Arena M, Auteri D, Barmaz S, Brancato A, et al.; European Food Safety Authority (EFSA) (2020). Peer review of the pesticide risk assessment of the active substance mancozeb. EFSA J. 18(12):e05755.

Abe M, Asada N, Kimura M, Fukui C, Yamada D, Wang Z, et al. (2024). Antitumor activity of α-pinene in T-cell tumors. Cancer Sci. 115(4):1317–32. https://doi.org/10.1111/cas.16086 PMID:38279512

Abhishek A, Ansari NG, Singh V, Sinha RJ, Mishra P, Mishra A (2020). Genetic susceptibility of CYP1A1 gene and risk of pesticide exposure in prostate cancer. Cancer Biomark. 29(4):429–40. https://doi.org/10.3233/CBM-190636 PMID:31929142

Abraham J, Diller K (2019). A review of hot beverage temperatures – satisfying consumer preference and safety. J Food Sci. 84(8):2011–4. https://doi.org/10.1111/1750-3841.14699 PMID:31294834

Abramsson-Zetterberg L, Maurer BM (2015). Fluoranthene and phenantrene, two predominant PAHs in heat-prepared food, do not influence the frequency of micronucleated mouse erythrocytes induced by other PAHs. Toxicol Rep. 2:1057–63. https://doi.org/10.1016/j.toxrep.2015.07.016 PMID:28962447

Accardi R, Dong W, Smet A, Cui R, Hautefeuille A, Gabet AS, et al. (2006). Skin human papillomavirus type 38 alters p53 functions by accumulation of deltaNp73. EMBO Rep. 7(3):334–40. https://doi.org/10.1038/sj.embor.7400615 PMID:16397624

ACGIH (2005). Biphenyl. Documentation of threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati (OH), USA: American Conference of Governmental Industrial Hygienists. Available from: https://www.acgih.org/biphenyl/, accessed February 2024.

ACGIH (2020). ACGIH – Documentation of the TLVs and BEIs. 7th ed. Cincinnati (OH), USA: American Conference of Governmental Industrial Hygienists Worldwide.

Acharya N, Gautam B, Subbiah S, Rogge MM, Anderson TA, Gao W (2019). Polycyclic aromatic hydrocarbons in breast milk of obese vs normal women: infant exposure and risk assessment. Sci Total Environ. 668:658–67. https://doi.org/10.1016/j.scitotenv.2019.02.381 PMID:30856574

Acquavella JF, Delzell E, Cheng H, Lynch CF, Johnson G (2004). Mortality and cancer incidence among alachlor manufacturing workers 1968–99. Occup Environ Med. 61(8):680–5. https://doi.org/10.1136/oem.2003.010934 PMID:15258274

ACR (2023). ACR Manual on Contrast Media 2023. Reston (VA), USA: American College of Radiology, Committee on Drugs and Contrast Media. Available from: https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf, accessed March 2024. ISBN:978–1-55903–012–0

Adamson DT, Piña EA, Cartwright AE, Rauch SR, Hunter Anderson R, Mohr T, et al. (2017). 1,4-Dioxane drinking water occurrence data from the third unregulated contaminant monitoring rule. Sci Total Environ. 596–597:236–45. https://doi.org/10.1016/j.scitotenv.2017.04.085 PMID:28433766

Adani G, Filippini T, Wise LA, Halldorsson TI, Blaha L, Vinceti M (2020). Dietary intake of acrylamide and risk of breast, endometrial, and ovarian cancers: a systematic review and dose–response meta-analysis. Cancer Epidemiol Biomarkers Prev. 29(6):1095–106. https://doi.org/10.1158/1055-9965.EPI-19-1628 PMID:32169997

AdisInsight (2023). Alefacept – Astellas Pharma. Released 1994 August 17, Updated 2023 November 05. London, UK: Springer Nature. Available from: https://adis.springer.com/drugs/800003883, accessed December 2023.

Adkins B Jr, Van Stee EW, Simmons JE, Eustis SL (1986). Oncogenic response of strain A/J mice to inhaled chemicals. J Toxicol Environ Health. 17(2–3):311–22. https://doi.org/10.1080/15287398609530825 PMID:3083111

Adyeni BS, Carlos U, Tatiana HM, Luisa G, Jessica T, Eduardo C, et al. (2023). Perfluorohexane sulfonate (PFHxS) disturbs the estrous cycle, ovulation rate, oocyte cell communication and calcium homeostasis in mice. Reprod Biol. 23(2):100768. https://doi.org/10.1016/j.repbio.2023.100768 PMID:37163972

Aerts R, Joly L, Szternfeld P, Tsilikas K, De Cremer K, Castelain P, et al. (2018). Silicone wristband passive samplers yield highly individualized pesticide residue exposure profiles. Environ Sci Technol. 52(1):298–307. https://doi.org/10.1021/acs.est.7b05039 PMID:29185731

Africander D, Verhoog N, Hapgood JP (2011). Molecular mechanisms of steroid receptor-mediated actions by synthetic progestins used in HRT and contraception. Steroids. 76(7):636–52. https://doi.org/10.1016/j.steroids.2011.03.001 PMID:21414337

Afsah-Hejri L, Jinap S, Hajeb P, Radu S, Shakibazadeh S (2013). A review on mycotoxins in food and feed: Malaysia case study. Compr Rev Food Sci Food Saf. 12(6):629–51. https://doi.org/10.1111/1541-4337.12029 PMID:33412719

Agalliu I, Chen Z, Wang T, Hayes RB, Freedman ND, Gapstur SM, et al. (2018). Oral alpha, beta, and gamma HPV types and risk of incident esophageal cancer. Cancer Epidemiol Biomarkers Prev. 27(10):1168–75. https://doi.org/10.1158/1055-9965.EPI-18-0287 PMID:30087123

Agalliu I, Costello S, Applebaum KM, Ray RM, Astrakianakis G, Gao DL, et al. (2011). Risk of lung cancer in relation to contiguous windows of endotoxin exposure among female textile workers in Shanghai. Cancer Causes Control. 22(10):1397–404. https://doi.org/10.1007/s10552-011-9812-x PMID:21732048

Agalliu I, Kriebel D, Quinn MM, Wegman DH, Eisen EA (2005). Prostate cancer incidence in relation to time windows of exposure to metalworking fluids in the auto industry. Epidemiology. 16(5):664–71. https://doi.org/10.1097/01.ede.0000173266.49104.bb PMID:16135943

Agbaria S, Haim A, Fares F, Zubidat AE (2019). Epigenetic modification in 4T1 mouse breast cancer model by artificial light at night and melatonin – the role of DNA-methyltransferase. Chronobiol Int. 36(5):629–43. https://doi.org/10.1080/07420528.2019.1574265 PMID:30746962

Aghajanshakeri S, Salmanmahiny A, Aghajanshakeri S, Babaei A, Alishahi F, Babayani E, et al. (2023). Modulatory effect of amifostine (WR-1065) against genotoxicity and oxidative stress induced by methotrexate in human umbilical vein endothelial cells (HUVECs). Toxicol Mech Methods. 33(9):755–65. https://doi.org/10.1080/15376516.2023.2238069 PMID:37537746

Aglan MA, Mansour GN (2020). Hair straightening products and the risk of occupational formaldehyde exposure in hairstylists. Drug Chem Toxicol. 43(5):488–95. https://doi.org/10.1080/01480545.2018.1508215 PMID:30208743

Aguayo-Guerrero JA, Méndez-García LA, Manjarrez-Reyna AN, Esquivel-Velázquez M, León-Cabrera S, Meléndez G, et al. (2023). Newborns from mothers who intensely consumed sucralose during pregnancy are heavier and exhibit markers of metabolic alteration and low-grade systemic inflammation: a cross-sectional, prospective study. Biomedicines. 11(3):650. https://doi.org/10.3390/biomedicines11030650 PMID:36979631

Ahern TP, Broe A, Lash TL, Cronin-Fenton DP, Ulrichsen SP, Christiansen PM, et al. (2019). Phthalate exposure and breast cancer incidence: a Danish nationwide cohort study. J Clin Oncol. 37(21):1800–9. https://doi.org/10.1200/JCO.18.02202 PMID:30995175

AHFES (2021). Soft drinks: European market, consumer trends, and innovation. Belfast, UK: Atlantic Area Healthy Food Eco-System. Available from: https://www.ahfesproject.com/research/soft-drinks-european-market-consumer-trends-and-innovation/, accessed August 2024.

Ahmad MI, Zafeer MF, Javed M, Ahmad M (2018). Pendimethalin-induced oxidative stress, DNA damage and activation of anti-inflammatory and apoptotic markers in male rats. Sci Rep. 8(1):17139. https://doi.org/10.1038/s41598-018-35484-3 PMID:30459330

Ahmad MI, Zou X, Ijaz MU, Hussain M, Liu C, Xu X, et al. (2019). Processed meat protein promoted inflammation and hepatic lipogenesis by upregulating Nrf2/Keap1 signalling pathway in Glrx-deficient mice. J Agric Food Chem. 67(32):8794–809. https://doi.org/10.1021/acs.jafc.9b03136 PMID:31345023

Ahmad MK, Amani S, Mahmood R (2014). Potassium bromate causes cell lysis and induces oxidative stress in human erythrocytes. Environ Toxicol. 29(2):138–45. https://doi.org/10.1002/tox.20780 PMID:22012894

Ahmed MM, Cushman CH, DeCaprio JA (2021). Merkel cell polyomavirus: oncogenesis in a stable genome. Viruses. 14(1):58. PMID:35062263

Ahn YH, Imaida K, Kim YB, Han KH, Pack JK, Kim N, et al. (2022). An international collaborative animal study of the carcinogenicity of mobile phone radiofrequency radiation: considerations for preparation of a global project. Bioelectromagnetics. 43(4):218–24. https://doi.org/10.1002/bem.22407 PMID:35476263

Aiello I, Fedele MLM, Román F, Marpegan L, Caldart C, Chiesa JJ, et al. (2020). Circadian disruption promotes tumor-immune microenvironment remodeling favoring tumor cell proliferation. Sci Adv. 6(42):eaaz4530. https://doi.org/10.1126/sciadv.aaz4530

Ajrawat P, Yang Y, Wasilewski E, Leroux T, Ladha KS, Bhatia A, et al. (2022). Medical cannabis use and inflammatory cytokines and chemokines among adult chronic pain patients. Cannabis Cannabinoid Res. 9(1):267–81. https://doi.org/10.1089/can.2022.0143 PMID:36342776

Aker AM, Johns L, McElrath TF, Cantonwine DE, Mukherjee B, Meeker JD (2018). Associations between maternal phenol and paraben urinary biomarkers and maternal hormones during pregnancy: a repeated measures study. Environ Int. 113:341–9. https://doi.org/10.1016/j.envint.2018.01.006https://doi.org/10.1016/j.envint.2018.01.006 PMID:29366524

Åkerlund E, Cappellini F, Di Bucchianico S, Islam S, Skoglund S, Derr R, et al. (2018). Genotoxic and mutagenic properties of Ni and NiO nanoparticles investigated by comet assay, γ-H2AX staining, Hprt mutation assay and ToxTracker reporter cell lines. Environ Mol Mutagen. 59(3):211–22. https://doi.org/10.1002/em.22163 PMID:29243303

Åkerlund E, Islam MS, McCarrick S, Alfaro-Moreno E, Karlsson HL (2019). Inflammation and (secondary) genotoxicity of Ni and NiO nanoparticles. Nanotoxicology. 13(8):1060–72. https://doi.org/10.1080/17435390.2019.1640908 PMID:31322448

Akre S, Sharma K, Chakole S, Wanjari MB (2022). Recent advances in the management of polycystic ovary syndrome: a review article. Cureus. 14(8):e27689. https://doi.org/10.7759/cureus.27689 PMID:36072214

Aksakal FI (2020). Evaluation of boscalid toxicity on *Daphnia magna* by using antioxidant enzyme activities, the expression of genes related to antioxidant and detoxification systems, and life-history parameters. Comp Biochem Physiol C Toxicol Pharmacol. 237:108830. https://doi.org/10.1016/j.cbpc.2020.108830 PMID:32535132

Akyeampong E, Bend JR, Luginaah I, Yawson DO, Cobbina SJ, Armah FA, et al. (2022). Urinary pesticide residual levels and acute respiratory infections in children under 5 years of age: findings from the Offinso North Farm Health Study. Environ Health Insights. 16:11786302221094418. https://doi.org/10.1177/11786302221094418 PMID:35521362

Al Hinai EA, Kullamethee P, Rowland IR, Swann J, Walton GE, Commane DM (2019). Modelling the role of microbial p-cresol in colorectal genotoxicity. Gut Microbes. 10(3):398–411. https://doi.org/10.1080/19490976.2018.1534514 PMID:30359553

Al-Hussaini TK, Abdelaleem AA, Elnashar I, Shabaan OM, Mostafa R, El-Baz MAH, et al. (2018). The effect of follicullar fluid pesticides and polychlorinated biphenyls concentrations on intracytoplasmic sperm injection (ICSI) embryological and clinical outcome. Eur J Obstet Gynecol Reprod Biol. 220:39–43. https://doi.org/10.1016/j.ejogrb.2017.11.003 PMID:29154179

Al-Saleh I, Al-Sedairi A, Elkhatib R (2012). Effect of mercury (Hg) dental amalgam fillings on renal and oxidative stress biomarkers in children. Sci Total Environ. 431:188–96. https://doi.org/10.1016/j.scitotenv.2012.05.036 PMID:22683759

Al-Soneidar WA, Harper S, Coutlée F, Gheit T, Tommasino M, Nicolau B (2023). Prevalence of alpha, beta, and hamma human papillomaviruses (HPV) in head and neck cancer patients and non-cancer controls and relation to behavioral factors. J Infect Dis. 229(4):1088–96. https://doi.org/10.1093/infdis/jiad335 PMID:37584283

Alabed Alibrahim E, Andriantsitohaina R, Hardonnière K, Soleti R, Faure S, Simard G (2018). A redox-sensitive signalling pathway mediates pro-angiogenic effect of chlordecone via estrogen receptor activation. Int J Biochem Cell Biol. 97:83–97. https://doi.org/10.1016/j.biocel.2018.02.008 PMID:29452237

Alabi OA, Adeoluwa YM, Bakare AA (2020). Elevated serum Pb, Ni, Cd, and Cr levels and DNA damage in exfoliated buccal cells of teenage scavengers at a major electronic waste dumpsite in Lagos, Nigeria. Biol Trace Elem Res. 194(1):24–33. https://doi.org/10.1007/s12011-019-01745-z PMID:31104299

Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. (2022). The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. Leukemia. 36(7):1720–48. https://doi.org/10.1038/s41375-022-01620-2 PMID:35732829

Alavanja M, Hofmann J, Lynch C, Hines C, Barry K, Barker J, et al. (2014b). Occupational use of insecticides, fungicides and fumigants and risk of non-Hodgkin lymphoma and multiple myeloma in the Agricultural Health Study. Occup Environ Med. 71 Suppl 1:A36. https://doi.org/10.1136/oemed-2014-102362.111

Alavanja MC, Hofmann JN, Lynch CF, Hines CJ, Barry KH, Barker J, et al. (2014a). Non-Hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the Agricultural Health Study. PLoS One. 9(10):e109332. https://doi.org/10.1371/journal.pone.0109332 PMID:25337994

Albert GC, McNamee JP, Marro L, Bellier PV, Prato FS, Thomas AW (2009). Assessment of genetic damage in peripheral blood of human volunteers exposed (whole-body) to a 200 muT, 60 Hz magnetic field. Int J Radiat Biol. 85(2):144–52. https://doi.org/10.1080/09553000802641169 PMID:19280467

Alberta Environment (2004). Assessment report on xylenes for developing ambient air quality objectives. Prepared by Cantox Environmental Inc. Edmonton (AL), Canada: Alberta Environment. Available from: https://open.alberta.ca/dataset/2a18a23d-2136-48e8-8c62-bf3bbf9a3e62/resource/3b0fa971-b33e-491c-b1f4-bf006b1e61f6/download/2004-assessmentreport-xylenes-nov2004.pdf, accessed August 2024.

Albrecht T, Deng CZ, Abdel-Rahman SZ, Fons M, Cinciripini P, El-Zein RA (2004). Differential mutagen sensitivity of peripheral blood lymphocytes from smokers and nonsmokers: effect of human cytomegalovirus infection. Environ Mol Mutagen. 43(3):169–78. https://doi.org/10.1002/em.20012 PMID:15065204

Alexander BH, Checkoway H, Nagahama SI, Domino KB (2000). Cause-specific mortality risks of anesthesiologists. Anesthesiology. 93(4):922–30. https://doi.org/10.1097/00000542-200010000-00008https://doi.org/10.1097/00000542-200010000-00008 PMID:11020740

Alexander BH, Ryan A, Church TR, Kim H, Olsen GW, Logan PW (2024). Mortality and cancer incidence in perfluorooctanesulfonyl fluoride production workers. Am J Ind Med. 67(4):321–33. https://doi.org/10.1002/ajim.23568 PMID:38345456

Alexander J, Benford D, Boobis A, Ceccotelli S, Cottrill B, Cravedi J-P (2012). European Food Safety Authority, scientific opinion on brominated flame retardants (BFRs) in food: brominated phenols and their derivatives. EFSA J. 10(4):2634–76. https://doi.org/10.2903/j.efsa.2012.2634

Alexander M, Koutros S, Bonner MR, Barry KH, Alavanja MCR, Andreotti G, et al. (2017). Pesticide use and LINE-1 methylation among male private pesticide applicators in the Agricultural Health Study. Environ Epigenet. 3(2):dvx005. https://doi.org/10.1093/eep/dvx005 PMID:29492307

Alfaiate D, Clément S, Gomes D, Goossens N, Negro F (2020). Chronic hepatitis D and hepatocellular carcinoma: a systematic review and meta-analysis of observational studies. J Hepatol. 73(3):533–9. https://doi.org/10.1016/j.jhep.2020.02.030 PMID:32151618

Alfheim I, Ramdahl T (1984). Contribution of wood combustion to indoor air pollution as measured by mutagenicity in *Salmonella* and polycyclic aromatic hydrocarbon concentration. Environ Mutagen. 6(2):121–30. https://doi.org/10.1002/em.2860060203 PMID:6368216

Alfhili MA, Lee MH (2019). Triclosan: an update on biochemical and molecular mechanisms. Oxid Med Cell Longev. 2019:1607304. https://doi.org/10.1155/2019/1607304 PMID:31191794

Alhusainy W, Paini A, van den Berg JH, Punt A, Scholz G, Schilter B, et al. (2013). In vivo validation and physiologically based biokinetic modeling of the inhibition of SULT-mediated estragole DNA adduct formation in the liver of male Sprague-Dawley rats by the basil flavonoid nevadensin. Mol Nutr Food Res. 57(11):1969–78. https://doi.org/10.1002/mnfr.201300144 PMID:23894034

Alif SM, Sim MR, Ho C, Glass DC (2022). Cancer and mortality in coal mine workers: a systematic review and meta-analysis. Occup Environ Med. 79(5):347–57. https://doi.org/10.1136/oemed-2021-107498

Alkayyali T, Ochuba O, Srivastava K, Sandhu JK, Joseph C, Ruo SW, et al. (2021). An exploration of the effects of radiofrequency radiation emitted by mobile phones and extremely low frequency radiation on thyroid hormones and thyroid gland histopathology. Cureus. 13(8):e17329. https://doi.org/10.7759/cureus.17329 PMID:34567874

Alkreathy HM, Khan RA, Khan MR, Sahreen S (2014). CCl4 induced genotoxicity and DNA oxidative damages in rats: hepatoprotective effect of *Sonchus arvensis.* BMC Complement Altern Med. 14(1):452. https://doi.org/10.1186/1472-6882-14-452 PMID:25412679

Allemang A, Mahony C, Lester C, Pfuhler S (2018). Relative potency of fifteen pyrrolizidine alkaloids to induce DNA damage as measured by micronucleus induction in HepaRG human liver cells. Food Chem Toxicol. 121:72–81. https://doi.org/10.1016/j.fct.2018.08.003 PMID:30125636

Allemang A, Mahony C, Pfuhler S (2022). The in vitro genotoxicity potency of mixtures of pyrrolizidine alkaloids can be explained by dose addition of the individual mixture components. Environ Mol Mutagen. 63(8–9):400–7. https://doi.org/10.1002/em.22512https://doi.org/10.1002/em.22512 PMID:36258291

Allen EM, Alexander BH, MacLehose RF, Nelson HH, Ramachandran G, Mandel JH (2015). Cancer incidence among Minnesota taconite mining industry workers. Ann Epidemiol. 25(11):811–5. https://doi.org/10.1016/j.annepidem.2015.08.003 PMID:26381550

Allenspach M, Steuer C (2021). α-Pinene: a never-ending story. Phytochemistry. 190:112857. https://doi.org/10.1016/j.phytochem.2021.112857https://doi.org/10.1016/j.phytochem.2021.112857 PMID:34365295

Almanzar G, Kienle F, Schmalzing M, Maas A, Tony H-P, Prelog M (2019). Tofacitinib modulates the VZV-specific CD4+ T cell immune response in vitro in lymphocytes of patients with rheumatoid arthritis. Rheumatology (Oxford). 58(11):2051–60. https://doi.org/10.1093/rheumatology/kez175 PMID:31106368

Almberg KS, Halldin CN, Friedman LS, Go LHT, Rose CS, Hall NB, et al. (2023). Increased odds of mortality from non-malignant respiratory disease and lung cancer are highest among US coal miners born after 1939. Occup Environ Med. 80(3):121–8. https://doi.org/10.1136/oemed-2022-108539

Almeida Roque A, Filipak Neto F, Cosio C, Barjhoux I, Oliveira Ribeiro CA, Rioult D (2023). Immunotoxicity of relevant mixtures of pesticides and metabolites on THP-1 cells. Toxicology. 493:153557. https://doi.org/10.1016/j.tox.2023.153557 PMID:37236337

Alon-Maimon T, Mandelboim O, Bachrach G (2022). *Fusobacterium nucleatum* and cancer. Periodontol 2000. 89(1):166–80. https://doi.org/10.1111/prd.12426 PMID:35244982

Alpsoy L, Akcayoglu G, Sahin H (2011). Anti-oxidative and anti-genotoxic effects of carnosine on human lymphocyte culture. Hum Exp Toxicol. 30(12):1979–85. https://doi.org/10.1177/0960327111404908 PMID:21464095

Alvito P, Assunção RM, Bajard L, Martins C, Mengelers MJB, Mol H, et al. (2022). Current advances, research needs and gaps in mycotoxins biomonitoring under the HBM4EU-lessons learned and future trends. Toxins (Basel). 14(12):826. https://doi.org/10.3390/toxins14120826 PMID:36548723

Amadou A, Praud D, Coudon T, Deygas F, Grassot L, Dubuis M, et al. (2023). Long-term exposure to nitrogen dioxide air pollution and breast cancer risk: a nested case–control within the French E3N cohort study. Environ Pollut. 317:120719. https://doi.org/10.1016/j.envpol.2022.120719 PMID:36435283

Ambroise D, Moulin JJ, Squinazi F, Protois JC, Fontana JM, Wild P (2005). Cancer mortality among municipal pest-control workers. Int Arch Occup Environ Health. 78(5):387–93. https://doi.org/10.1007/s00420-004-0599-x PMID:15846500

Ambrose AM, Booth A, DeEds F, Cox J Jr (1960). A toxicological study of biphenyl, a citrus fungistat. J Food Sci. 25(3):328–36. https://doi.org/10.1111/j.1365-2621.1960.tb00338.x

Amer AS, Othman AA, Dawood LM, El-Nouby KA, Gobert GN, Abou Rayia DM (2023). The interaction of *Schistosoma mansoni* infection with diabetes mellitus and obesity in mice. Sci Rep. 13(1):9417. https://doi.org/10.1038/s41598-023-36112-5 PMID:37296126

Amer SM, Aly FA (2001). Genotoxic effect of 2,4-dichlorophenoxy acetic acid and its metabolite 2,4-dichlorophenol in mouse. Mutat Res. 494(1–2):1–12. PMID:11423340

Amoon AT, Swanson J, Magnani C, Johansen C, Kheifets L (2022). Pooled analysis of recent studies of magnetic fields and childhood leukemia. Environ Res. 204 Pt A:111993. https://doi.org/10.1016/j.envres.2021.111993 PMID:34481821

Amorrortu RP, Zhao Y, Messina JL, Schell MJ, Fenske NA, Cherpelis BS, et al. (2021). Association between human polyomaviruses and keratinocyte carcinomas: a prospective cohort study. Cancer Epidemiol Biomarkers Prev. 30(9):1761–4. https://doi.org/10.1158/1055-9965.EPI-21-0332 PMID:34187857

Amstutz VH, Cengo A, Gehres F, Sijm DTHM, Vrolijk MF (2022). Investigating the cytotoxicity of per- and polyfluoroalkyl substances in HepG2 cells: a structure-activity relationship approach. Toxicology. 480:153312. https://doi.org/10.1016/j.tox.2022.153312https://doi.org/10.1016/j.tox.2022.153312 PMID:36075290

Anand N, Chakraborty P, Ray S (2021). Human exposure to organochlorine, pyrethroid and neonicotinoid pesticides: comparison between urban and semi-urban regions of India. Environ Pollut. 270:116156. https://doi.org/10.1016/j.envpol.2020.116156 PMID:33321437

Anastassiadou M, Bernasconi G, Brancato A, Carrasco Cabrera L, Greco L, Jarrah S, et al.; European Food Safety Authority (EFSA) (2020). Modification of the existing maximum residue levels for mancozeb in various crops. EFSA J. 18(8):e06108. https://doi.org/10.2903/j.efsa.2020.6108 PMID:32831945

Andersen HR, Vinggaard AM, Rasmussen TH, Gjermandsen IM, Bonefeld-Jørgensen EC (2002). Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity in vitro. Toxicol Appl Pharmacol. 179(1):1–12. https://doi.org/10.1006/taap.2001.9347 PMID:11884232

Andersen L, Friis S, Hallas J, Ravn P, Kristensen BW, Gaist D (2015). Hormonal contraceptive use and risk of glioma among younger women: a nationwide case–control study. Br J Clin Pharmacol. 79(4):677–84. https://doi.org/10.1111/bcp.12535 PMID:25345919

Andersen ML, Ribeiro DA, Bergamaschi CT, Alvarenga TA, Silva A, Zager A, et al. (2009). Distinct effects of acute and chronic sleep loss on DNA damage in rats. Prog Neuropsychopharmacol Biol Psychiatry. 33(3):562–7. https://doi.org/10.1016/j.pnpbp.2009.02.014 PMID:19258023

Anderson D (2001). Genetic and reproductive toxicity of butadiene and isoprene. Chem Biol Interact. 135:65–80. https://doi.org/10.1016/S0009-2797(01)00171-5PMID:11397382

Anderson D, Dobrzyńska MM, Basaran N (1997). Effect of various genotoxins and reproductive toxins in human lymphocytes and sperm in the comet assay. Teratog Carcinog Mutagen. 17(1):29–43. https://doi.org/10.1002/(SICI)1520-6866(1997)17:1<29::AID-TCM5>3.0.CO;2-H PMID:9249928

Anderson RL, Bishop WE, Campbell RL, Becking GC (1985). A review of the environmental and mammalian toxicology of nitrilotriacetic acid. Crit Rev Toxicol. 15(1):1–102. https://doi.org/10.3109/10408448509023766 PMID:3899518

Anderson SE, Meade BJ, Long CM, Lukomska E, Marshall NB (2016). Investigations of immunotoxicity and allergic potential induced by topical application of triclosan in mice. J Immunotoxicol. 13(2):165–72. https://doi.org/10.3109/1547691X.2015.1029146 PMID:25812624

Anderson TJ, Battersby S, King RJB, McPherson K, Going JJ (1989). Oral contraceptive use influences resting breast proliferation. Hum Pathol. 20(12):1139–44. https://doi.org/10.1016/S0046-8177(89)80003-6 PMID:2591943

Andrade ACDSP, Campolina-Silva GH, Queiroz-Junior CM, de Oliveira LC, Lacerda LSB, Pimenta JC, et al. (2021). A biosafety level 2 mouse model for studying betacoronavirus-induced acute lung damage and systemic manifestations. J Virol. 95(22):e0127621. https://doi.org/10.1128/jvi.01276-21 PMID:34495692

Andreassi MG, Picano E, Del Ry S, Botto N, Colombo MG, Giannessi D, et al. (2001). Chronic long-term nitrate therapy: possible cytogenetic effect in humans? Mutagenesis. 16(6):517–21. https://doi.org/10.1093/mutage/16.6.517 PMID:11682643

Andreotti G, Beane Freeman LE, Shearer JJ, Lerro CC, Koutros S, Parks CG, et al. (2020). Occupational pesticide use and risk of renal cell carcinoma in the Agricultural Health Study. Environ Health Perspect. 128(6):67011. https://doi.org/10.1289/EHP6334 PMID:32692250

Andreotti G, Freeman LE, Hou L, Coble J, Rusiecki J, Hoppin JA, et al. (2009). Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort. Int J Cancer. 124(10):2495–500. https://doi.org/10.1002/ijc.24185 PMID:19142867

Andreotti G, Hoppin JA, Hou L, Koutros S, Gadalla SM, Savage SA, et al. (2015). Pesticide use and relative leukocyte telomere length in the Agricultural Health Study. PLoS One. 10(7):e0133382. https://doi.org/10.1371/journal.pone.0133382 PMID:26196902

Andreotti G, Koutros S, Berndt SI, Hughes Barry K, Hou L, Hoppin JA, et al. (2012). The interaction between pesticide use and genetic variants involved in lipid metabolism on prostate cancer risk. J Cancer Epidemiol. 2012:358076. https://doi.org/10.1155/2012/358076 PMID:22919386

Andreotti G, Koutros S, Hofmann JN, Sandler DP, Lubin JH, Lynch CF, et al. (2018). Glyphosate use and cancer incidence in the Agricultural Health Study. J Natl Cancer Inst. 110(5):509–16. https://doi.org/10.1093/jnci/djx233 PMID:29136183

Andrioli NB, Nieves M, Poltronieri M, Bonzon C, Chaufan G (2023). Genotoxic effects induced for sub-cytotoxic concentrations of tebuconazole fungicide in HEp-2 cell line. Chem Biol Interact. 373:110385. https://doi.org/10.1016/j.cbi.2023.110385 PMID:36754225

Andrysík Z, Procházková J, Kabátková M, Umannová L, Simečková P, Kohoutek J, et al. (2013). Aryl hydrocarbon receptor-mediated disruption of contact inhibition is associated with connexin43 downregulation and inhibition of gap junctional intercellular communication. Arch Toxicol. 87(3):491–503. https://doi.org/10.1007/s00204-012-0963-7 PMID:23085979

Anisimov VN, Baturin DA, Popovich IG, Zabezhinski MA, Manton KG, Semenchenko AV, et al. (2004). Effect of exposure to light at night on life span and spontaneous carcinogenesis in female CBA mice. Int J Cancer. 111(4):475–9. https://doi.org/10.1002/ijc.20298 PMID:15239122

Ankerst J, Sjögren HO (1982). Effect of selenium on the induction of breast fibroadenomas by adenovirus type 9 and 1,2-dimethylhydrazine-induced bowel carcinogenesis in rats. Int J Cancer. 29(6):707–10. https://doi.org/10.1002/ijc.2910290618 PMID:7107071

Anonymous (2003). *Cimicifuga racemosa*. Monograph. Altern Med Rev. 8(2):186–9. PMID:12777164

Anonymous (2012). Cresol (all isomers) [MAK Value Documentation, 2000]. In: The MAK-Collection for Occupational Health and Safety. Weinheim, Germany: Wiley-VCH Verlag GmbH Co. KGaA. , accessed October 2024.

Anonymous (2021). Gene therapy needs a long-term approach. Nat Med. 27(4):563. https://doi.org/10.1038/s41591-021-01333-6 PMID:33859432

Ansari SM, Saquib Q, Attia SM, Abdel-Salam EM, Alwathnani HA, Faisal M, et al. (2018). Pendimethalin induces oxidative stress, DNA damage, and mitochondrial dysfunction to trigger apoptosis in human lymphocytes and rat bone-marrow cells. Histochem Cell Biol. 149(2):127–41. https://doi.org/10.1007/s00418-017-1622-0 PMID:29151145

ANSES (2021). Opinion of the French Agency for Food, Environment, and Occupational Safety and Health on the "Risks associated with intense pulsed light (IPL) hair removal devices". Request No: 2019-SA-0124. Maisons-Alfort, France: Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail. Available from: https://www.anses.fr/en/system/files/AP2019SA0124EN.pdf, accessed January 2024.

Antonsson A, Erfurt C, Hazard K, Holmgren V, Simon M, Kataoka A, et al. (2003). Prevalence and type spectrum of human papillomaviruses in healthy skin samples collected in three continents. J Gen Virol. 84(Pt 7):1881–6. https://doi.org/10.1099/vir.0.18836-0 PMID:12810883

Anttila A, Uuksulainen S, Rantanen M, Sallmén M (2022). Lung cancer incidence among workers biologically monitored for occupational exposure to lead: a cohort study. Scand J Work Environ Health. 48(7):540–8. https://doi.org/10.5271/sjweh.4046 PMID:35753006

Apaja M (1980). Evaluation of toxicity and carcinogenicity of malonaldehyde: an experimental study in Swiss mice [thesis]. Oulu, Finland: University of Oulu.

Api AM, Belsito D, Bhatia S, Bruze M, Calow P, Dagli ML, et al. (2015). RIFM fragrance ingredient safety assessment, ethyl anthranilate, CAS registry number 87-25-2. Food Chem Toxicol. 82 Suppl:S97–104. https://doi.org/10.1016/j.fct.2015.03.017 PMID:25818467

Api AM, Belsito D, Botelho D, Browne D, Bruze M, Burton GA Jr, et al. (2017). RIFM fragrance ingredient safety assessment, methyl anthranilate, CAS registry number 134-20-3. Food Chem Toxicol. 110 Suppl 1:S290–8. https://doi.org/10.1016/j.fct.2017.06.003 PMID:28595957

Api AM, Belsito D, Botelho D, Bruze M, Burton GA Jr, Buschmann J, et al. (2022). RIFM fragrance ingredient safety assessment, α-pinene, CAS registry number 80-56-8. Food Chem Toxicol. 159 Suppl 1:112702. https://doi.org/10.1016/j.fct.2021.112702https://doi.org/10.1016/j.fct.2021.112702 PMID:34838673

Applebaum KM, Ray RM, Astrakianakis G, Gao DL, Thomas DB, Christiani DC, et al. (2013). Evidence of a paradoxical relationship between endotoxin and lung cancer after accounting for left truncation in a study of Chinese female textile workers. Occup Environ Med. 70(10):709–15. https://doi.org/10.1136/oemed-2012-101240 PMID:23759537

Applegate CC, Rowles JL 3rd, Ranard KM, Jeon S, Erdman JW (2018). Soy consumption and the risk of prostate cancer: an updated systematic review and meta-analysis. Nutrients. 10(1):E40. https://doi.org/10.3390/nu10010040 PMID:29300347

Aprea MC, Bosi A, Manara M, Mazzocchi B, Pompini A, Sormani F, et al. (2016). Assessment of exposure to pesticides during mixing/loading and spraying of tomatoes in the open field. J Occup Environ Hyg. 13(6):476–89. https://doi.org/10.1080/15459624.2016.1143948 PMID:26853603

Aquilino M, Sánchez-Argüello P, Martínez-Guitarte JL (2018). Genotoxic effects of vinclozolin on the aquatic insect *Chironomus riparius* (Diptera, Chironomidae). Environ Pollut. 232:563–70. https://doi.org/10.1016/j.envpol.2017.09.088 PMID:28987565

Arafa A, Eshak ES, Iso H, Muraki I, Tamakoshi A (2021). Night work, rotating shift work, and the risk of cancer in Japanese men and women: the JACC study. J Epidemiol. 31(12):585–92. https://doi.org/10.2188/jea.JE20200208 PMID:32801280

Arena VC, Sussman NB, Redmond CK, Costantino JP, Trauth JM (1998). Using alternative comparison populations to assess occupation-related mortality risk. Results for the high nickel alloys workers cohort. J Occup Environ Med. 40(10):907–16. https://doi.org/10.1097/00043764-199810000-00012 PMID:9800177

Arfianti A, Pok S, Barn V, Haigh WG, Yeh MM, Ioannou GN, et al. (2020). Exercise retards hepatocarcinogenesis in obese mice independently of weight control. J Hepatol. 73(1):140–8. https://doi.org/10.1016/j.jhep.2020.02.006https://doi.org/10.1016/j.jhep.2020.02.006 PMID:32302728

Arita A, Niu J, Qu Q, Zhao N, Ruan Y, Nadas A, et al. (2012b). Global levels of histone modifications in peripheral blood mononuclear cells of subjects with exposure to nickel. Environ Health Perspect. 120(2):198–203. https://doi.org/10.1289/ehp.1104140 PMID:22024396

Arita A, Shamy MY, Chervona Y, Clancy HA, Sun H, Hall MN, et al. (2012a). The effect of exposure to carcinogenic metals on histone tail modifications and gene expression in human subjects. J Trace Elem Med Biol. 26(2–3):174–8. https://doi.org/10.1016/j.jtemb.2012.03.012 PMID:22633395

Arl M, Nogueira DJ, Schveitzer Köerich J, Mottim Justino N, Schulz Vicentini D, Gerson Matias W (2019). Tattoo inks: characterization and in vivo and in vitro toxicological evaluation. J Hazard Mater. 364:548–61. https://doi.org/10.1016/j.jhazmat.2018.10.072 PMID:30388639

Armenian HK, Hoover DR, Rubb S, Metz S, Martinez-Maza O, Chmiel J, et al. (1996). Risk factors for non-Hodgkin's lymphomas in acquired immunodeficiency syndrome (AIDS). Am J Epidemiol. 143(4):374–9. https://doi.org/10.1093/oxfordjournals.aje.a008751 PMID:8633621

Arshad M, Siddiqa M, Rashid S, Hashmi I, Awan MA, Ali MA (2016). Biomonitoring of toxic effects of pesticides in occupationally exposed individuals. Saf Health Work. 7(2):156–60. https://doi.org/10.1016/j.shaw.2015.11.001 PMID:27340604

Arthur JC, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, et al. (2012). Intestinal inflammation targets cancer-inducing activity of the microbiota. Science. 338(6103):120–3. https://doi.org/10.1126/science.1224820 PMID:22903521

Aschebrook-Kilfoy B, DellaValle CT, Purdue M, Kim C, Zhang Y, Sjodin A, et al. (2015). Polybrominated diphenyl ethers and thyroid cancer risk in the Prostate, Colorectal, Lung, and Ovarian Cancer Screening Trial cohort. Am J Epidemiol. 181(11):883–8. https://doi.org/10.1093/aje/kwu358 PMID:25939348

Aschebrook-Kilfoy B, Heltshe SL, Nuckols JR, Sabra MM, Shuldiner AR, Mitchell BD, et al. (2012). Modeled nitrate levels in well water supplies and prevalence of abnormal thyroid conditions among the Old Order Amish in

Pennsylvania. Environ Health. 11(1):6. https://doi.org/10.1186/1476-069X-11-6https://doi.org/10.1186/1476-069X-11-6 PMID:22339761

Asghar U, Masoon A (2020). Economic analysis of isoprene production from good year scientific process. Am J Chem Eng. 8(3):1. https://doi.org/10.11648/j.ajche.20200803.12

ASH (2023). Fact sheet: Use of e-cigarettes (vapes) among adults in Great Britain. London, UK: Action on Smoking and Health. Available from: https://ash.org.uk/uploads/Use-of-e-cigarettes-among-adults-in-Great-Britain-2023.pdf?v=1691058248, accessed August 2024

Ashby J, Lefevre PA, Tinwell H, Brunborg G, Schmezer P, Pool-Zobel B, et al. (1991). The non-genotoxicity to rodents of the potent rodent bladder carcinogens *o*-anisidine and *p*-cresidine. Mutat Res. 250(1–2):115–33. https://doi.org/10.1016/0027-5107(91)90168-Nhttps://doi.org/10.1016/0027-5107(91)90168-N PMID:1719389

Ashurst JV, Nappe TM (2023). Methanol toxicity. Treasure Island (FL), USA: StatPearls Publishing.

Assa A, Vong L, Pinnell LJ, Avitzur N, Johnson-Henry KC, Sherman PM (2014). Vitamin D deficiency promotes epithelial barrier dysfunction and intestinal inflammation. J Infect Dis. 210(8):1296–305. https://doi.org/10.1093/infdis/jiu235 PMID:24755435

Assa A, Vong L, Pinnell LJ, Rautava J, Avitzur N, Johnson-Henry KC, et al. (2015). Vitamin D deficiency predisposes to adherent-invasive *Escherichia coli*-induced barrier dysfunction and experimental colonic injury. Inflamm Bowel Dis. 21(2):297–306. https://doi.org/10.1097/MIB.0000000000000282 PMID:25590952

Astrakianakis G, Seixas NS, Ray R, Camp JE, Gao DL, Feng Z, et al. (2007). Lung cancer risk among female textile workers exposed to endotoxin. J Natl Cancer Inst. 99(5):357–64. https://doi.org/10.1093/jnci/djk063 PMID:17341727

Atkinson RW, Butland BK, Anderson HR, Maynard RL (2018). Long-term concentrations of nitrogen dioxide and mortality: a meta-analysis of cohort studies. Epidemiology. 29(4):460–72. https://doi.org/10.1097/EDE.0000000000000847 PMID:29746370

Atkinson RW, Butland BK, Dimitroulopoulou C, Heal MR, Stedman JR, Carslaw N, et al. (2016). Long-term exposure to ambient ozone and mortality: a quantitative systematic review and meta-analysis of evidence from cohort studies. BMJ Open. 6(2):e009493. https://doi.org/10.1136/bmjopen-2015-009493 PMID:26908518

Atlı Şekeroğlu Z, Şekeroğlu V, Aydın B, Kontaş Yedier S, İlkun E (2020). Clothianidin induces DNA damage and oxidative stress in bronchial epithelial cells. Environ Mol Mutagen. 61(6):647–55. https://doi.org/10.1002/em.22376 PMID:32285515

ATSDR (2007). Toxicological profile for xylene. Atlanta (GA), USA: Agency for Toxic Substances and Disease Registry. Available from: https://www.ncbi.nlm.nih.gov/books/NBK600781/, accessed December 2023.

ATSDR (2008). Childhood cancer incidence update: a review and analysis of cancer registry data, 2001–2005 for Township of Toms River, Ocean County, New Jersey. Atlanta (GA), USA: Agency for Toxic Substances and Disease Registry. Available from: https://www.state.nj.us/health/ceohs/documents/eohap/haz_sites/ocean/toms_river/toms_river_dover_twp/toms_river_childhood_cancer_update.pdf, accessed August 2024.

ATSDR (2011). Health Consultation. Sulfolane. Atlanta (GA), USA: Agency for Toxic Substances and Disease Registry. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/noms/support_docs/atsdrsulfolanehc_2011_508.pdf, accessed December 2023.

ATSDR (2022). Toxicological profile for chlorophenols. Atlanta (GA), USA: Agency for Toxic Substances and Disease Registry. Available from: https://www.atsdr.cdc.gov/ToxProfiles/tp107.pdf, accessed December 2023.

Atwood ST, Lunn RM, Garner SC, Jahnke GD (2019). New perspectives for cancer hazard evaluation by the report on carcinogens: a case study using read-across methods in the evaluation of haloacetic acids found as water disinfection by-products. Environ Health Perspect. 127(12):125003. https://doi.org/10.1289/EHP5672 PMID:31854200

Au WW, Sierra-Torres CH, Cajas-Salazar N, Shipp BK, Legator MS (1999). Cytogenetic effects from exposure to mixed pesticides and the influence from genetic susceptibility. Environ Health Perspect. 107(6):501–5. https://doi.org/10.1289/ehp.99107501 PMID:10339452

Audebert M, Dolo L, Perdu E, Cravedi JP, Zalko D (2011). Use of the γH2AX assay for assessing the genotoxicity of bisphenol A and bisphenol F in human cell lines. Arch Toxicol. 85(11):1463–73. https://doi.org/10.1007/s00204-011-0721-2 PMID:21656223

Auerbach SS, Shah RR, Mav D, Smith CS, Walker NJ, Vallant MK, et al. (2010). Predicting the hepatocarcinogenic potential of alkenylbenzene flavoring agents using toxicogenomics and machine learning. Toxicol Appl Pharmacol. 243(3):300–14. https://doi.org/10.1016/j.taap.2009.11.021 PMID:20004213

Auger N, Laverdière C, Ayoub A, Lo E, Luu TM (2019). Neonatal phototherapy and future risk of childhood cancer. Int J Cancer. 145(8):2061–9. https://doi.org/10.1002/ijc.32158 PMID:30684392

Aung MT, Ferguson KK, Cantonwine DE, Bakulski KM, Mukherjee B, Loch-Caruso R, et al. (2019). Associations between maternal plasma measurements of inflammatory markers and urinary levels of phenols and parabens during pregnancy: a repeated measures study. Sci Total Environ. 650(Pt 1):1131–40. https://doi.org/10.1016/j.scitotenv.2018.08.356 PMID:30308801

Aung WW, Wang C, Xibei J, Horii M, Mizumaki K, Kano M, et al. (2021). Immunomodulating role of the JAKs inhibitor tofacitinib in a mouse model of bleomycin-induced scleroderma. J Dermatol Sci. 101(3):174–84. https://doi.org/10.1016/j.jdermsci.2020.12.007 PMID:33451905

Austin CC, Wang D, Ecobichon DJ, Dussault G (2001). Characterization of volatile organic compounds in smoke at municipal structural fires. J Toxicol Environ Health A. 63(6):437–58. https://doi.org/10.1080/15287390130034347https://doi.org/10.1080/15287390130034347 PMID:11482799

Australian Government (2022). Biphenyl (1,1-biphenyl). Canberra (ACT), Australia: Department of Climate Change, Energy, the Environment, and Water, Australian Government. Available from: https://www.dcceew.gov.au/environment/protection/npi/substances/fact-sheets/biphenyl-11-biphenyl, accessed December 2023.

Axelstad M, Boberg J, Nellemann C, Kiersgaard M, Jacobsen PR, Christiansen S, et al. (2011). Exposure to the widely used fungicide mancozeb causes thyroid hormone disruption in rat dams but no behavioral effects in the offspring. Toxicol Sci. 120(2):439–46. https://doi.org/10.1093/toxsci/kfr006https://doi.org/10.1093/toxsci/kfr006 PMID:21266532

Ayar A, Uysal H (2013). Examination of the genotoxic effects of various parabens used as food additives with the drosophila wing spot test (SMART). J Appl Biol Sci. 7(2): 83–8. https://www.jabsonline.org/index.php/jabs/article/view/326

Aycicek A, Kocyigit A, Erel O, Senturk H (2008). Phototherapy causes DNA damage in peripheral mononuclear leukocytes in term infants. J Pediatr (Rio J). 84(2):141–6. https://doi.org/10.2223/JPED.1765 PMID:18350230

Ayed Y, Ayed-Boussema I, Ouanes Z, Bacha H (2011). In vitro and in vivo induction of chromosome aberrations by alpha- and beta-zearalenols: comparison with zearalenone. Mutat Res. 726(1):42–6. https://doi.org/10.1016/j.mrgentox.2011.08.003 PMID:21889607

Ayhan G, Rouget F, Giton F, Costet N, Michineau L, Monfort C, et al. (2021). In utero chlordecone exposure and thyroid, metabolic, and sex-steroid hormones at the age of seven years: a study from the TIMOUN Mother–Child Cohort in Guadeloupe. Front Endocrinol (Lausanne). 12:771641. https://doi.org/10.3389/fendo.2021.771641 PMID:34880833

Azadnajafabad S, Saeedi Moghaddam S, Mohammadi E, Rezaei N, Rashidi MM, Rezaei N, et al.; GBD 2019 NAME Breast Cancer Collaborators (2023). Burden of breast cancer and attributable risk factors in the North Africa and Middle East region, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Front Oncol. 13:1132816. https://doi.org/10.3389/fonc.2023.1132816 PMID:37593096

Azar A, Trochimowicz HJ, Maxfield ME (1973) Review of lead studies in animals carried out at Haskell Laboratory: two-year feeding study and response to hemorrhage study. In: Environmental health aspects of lead. In: Proceedings of an International Symposium, 2–6 October 1972. Amsterdam, Netherlands; pp. 199–210.

Azeredo DBC, de Sousa Anselmo D, Soares P, Graceli JB, Magliano DC, Miranda-Alves L (2023). Environmental endocrinology: parabens hazardous effects on hypothalamic-pituitary-thyroid axis. Int J Mol Sci. 24(20):15246. https://doi.org/10.3390/ijms242015246https://doi.org/10.3390/ijms242015246 PMID:37894927

Azimi M, Bahrami MR, Rezaei Hachesu V, Zavar Reza J, Mihanpour H, Zare Sakhvidi MJ, et al. (2017). Primary DNA damage in dry cleaners with perchlorethylene exposure. Int J Occup Environ Med. 8(4):224–31. https://doi.org/10.15171/ijoem.2017.1089 PMID:28970597

Azimi P, Zhao D, Pouzet C, Crain NE, Stephens B (2016). Emissions of ultrafine particles and volatile organic compounds from commercially available desktop threedimensional printers with multiple filaments. Environ Sci Technol. 50(3):1260–8. https://doi.org/10.1021/acs.est.5b04983 PMID:26741485

Azizi M, Mami S, Noorimotlagh Z, Mirzaee SA, Silva Martinez S, Bazgir N (2023). The role of polybrominated diphenyl ethers in the induction of cancer: a systematic review of insight into their mechanisms. Environ Sci Pollut Res Int. 30(4):9271–89. https://doi.org/10.1007/s11356-022-24538-9 PMID:36469279

Babica P, Čtveráčková L, Lenčešová Z, Trosko JE, Upham BL (2016). Chemopreventive agents attenuate rapid inhibition of gap junctional intercellular communication induced by environmental toxicants. Nutr Cancer. 68(5):827–37. https://doi.org/10.1080/01635581.2016.1180409 PMID:27266532

Baden JM, Kundomal YR, Mazze RI, Kosek JC (1988). Carcinogen bioassay of isoflurane in mice. Anesthesiology. 69(5):750–3. https://doi.org/10.1097/00000542-198811000-00018https://doi.org/10.1097/00000542-198811000-00018 PMID:3189921

Baena A, Paolino M, Villarreal-Garza C, Torres G, Delgado L, Ruiz R, et al. (2023). Latin America and the Caribbean Code Against Cancer 1st Edition: medical interventions including hormone replacement therapy and cancer screening. Cancer Epidemiol. 86 Suppl 1:102446. https://doi.org/10.1016/j.canep.2023.102446 PMID:37852728

Baena Ruiz R, Salinas Hernández P (2016). Cancer chemoprevention by dietary phytochemicals: epidemiological evidence. Maturitas. 94:13–9. https://doi.org/10.1016/j.maturitas.2016.08.004 PMID:27823732

Baenas N, Suárez-Martínez C, García-Viguera C, Moreno DA (2017). Bioavailability and new biomarkers of cruciferous sprouts consumption. Food Res Int. 100(Pt 1):497–503. https://doi.org/10.1016/j.foodres.2017.07.049 PMID:28873713

Báez-Saldaña R, Canseco-Raymundo A, Ixcot-Mejía B, Juárez-Verdugo I, Escobar-Rojas A, Rumbo-Nava U, et al. (2021). Case–control study about magnitude of exposure to wood smoke and risk of developing lung cancer. Eur J Cancer Prev. 30(6):462–8. https://doi.org/10.1097/CEJ.0000000000000644 PMID:34115693

Baggio LL, Drucker DJ (2007). Biology of incretins: GLP-1 and GIP. Gastroenterology. 132(6):2131–57. https://doi.org/10.1053/j.gastro.2007.03.054 PMID:17498508

Baginskaya NV, Il'nitskaya SI, Nikitenko EV, Kaledin VI (2007). Promoting effect of o-aminoazotoluene on hepatocarcinogenesis is accompanied by the increase in inflammatory and proliferative processes in liver tissue and decrease in the concentration of free thyroxin in the blood. Bull Exp Biol Med. 144(6):821–4. https://doi.org/10.1007/s10517-007-0440-0https://doi.org/10.1007/s10517-007-0440-0 PMID:18856210

Baglietto L, Severi G, English DR, Krishnan K, Hopper JL, McLean C, et al. (2010). Circulating steroid hormone levels and risk of breast cancer for postmenopausal women. Cancer Epidemiol Biomarkers Prev. 19(2):492–502. https://doi.org/10.1158/1055-9965.EPI-09-0532 PMID:20086116

Bai B, Wang X, Chen E, Zhu H (2016). Human cytomegalovirus infection and colorectal cancer risk: a meta-analysis. Oncotarget. 7(47):76735–42. https://doi.org/10.18632/oncotarget.12523 PMID:27732934

Bai F, Wang DY, Fan YJ, Qiu J, Wang L, Dai Y, et al. (2020). Assisted reproductive technology service availability, efficacy and safety in mainland China: 2016. Hum Reprod. 35(2):446–52. https://doi.org/10.1093/humrep/dez245 PMID:32020190

Bai X, Cui C, Yin J, Li H, Gong Q, Wei B, et al. (2023). The association between oral hygiene and head and neck cancer: a meta-analysis. Acta Odontol Scand. 81(5):374–95. https://doi.org/10.1080/00016357.2022.2158129 PMID:36538375

Baibergenova AT, Weinstock MA; VATTC Trial Group (2012). Oral prednisone use and risk of keratinocyte carcinoma in non-transplant population. The VATTC trial. J Eur Acad Dermatol Venereol. 26(9):1109–15. https://doi.org/10.1111/j.1468-3083.2011.04226.x PMID:21923839

Bailey KL, Wyatt TA, Katafiasz DM, Taylor KW, Heires AJ, Sisson JH, et al. (2019). Alcohol and cannabis use alter pulmonary innate immunity. Alcohol. 80:131–8. https://doi.org/10.1016/j.alcohol.2018.11.002 PMID:30419300

Bailly-Maitre B, de Sousa G, Zucchini N, Gugenheim J, Boulukos KE, Rahmani R (2002). Spontaneous apoptosis in primary cultures of human and rat hepatocytes: molecular mechanisms and regulation by dexamethasone. Cell Death Differ. 9(9):945–55. https://doi.org/10.1038/sj.cdd.4401043 PMID:12181745

Baj J, Dring JC, Czeczelewski M, Kozyra P, Forma A, Flieger J, et al. (2022). Derivatives of plastics as potential carcinogenic factors: the current state of knowledge. Cancers (Basel). 14(19):4637. https://doi.org/10.3390/cancers14194637 PMID:36230560

Bajard L, Melymuk L, Blaha L (2019). Prioritization of hazards of novel flame retardants using the mechanistic toxicology information from ToxCast and adverse outcome pathways. Environ Sci Eur. 31(1):14. https://doi.org/10.1186/s12302-019-0195-z

Bakke B, De Roos AJ, Barr DB, Stewart PA, Blair A, Freeman LB, et al. (2009). Exposure to atrazine and selected non-persistent pesticides among corn farmers during a growing season. J Expo Sci Environ Epidemiol. 19(6):544–54. https://doi.org/10.1038/jes.2008.53 PMID:19052531

Bakken K, Alsaker E, Eggen AE, Lund E (2004). Hormone replacement therapy and incidence of hormone-dependent cancers in the Norwegian Women and Cancer study. Int J Cancer. 112(1):130–4. https://doi.org/10.1002/ijc.20389 PMID:15305384

Balbo S, Juanes RC, Khariwala S, Baker EJ, Daunais JB, Grant KA (2016). Increased levels of the acetaldehyde-derived DNA adduct N 2-ethyldeoxyguanosine in oral mucosa DNA from Rhesus monkeys exposed to alcohol. Mutagenesis. 31(5):553–8. https://doi.org/10.1093/mutage/gew016 PMID:27056945

Balbo S, Meng L, Bliss RL, Jensen JA, Hatsukami DK, Hecht SS (2012). Kinetics of DNA adduct formation in the oral cavity after drinking alcohol. Cancer Epidemiol Biomarkers Prev. 21(4):601–8. https://doi.org/10.1158/1055-9965.EPI-11-1175 PMID:22301829

Balderrama-Carmona AP, Valenzuela-Rincón M, Zamora-Álvarez LA, Adan-Bante NP, Leyva-Soto LA, Silva-Beltrán NP, et al. (2020). Herbicide biomonitoring in agricultural workers in Valle del Mayo, Sonora Mexico. Environ Sci Pollut Res Int. 27(23):28480–9. https://doi.org/10.1007/s11356-019-07087-6 PMID:31832947

Balduzzi A, Castiglione-Gertsch M (2005). Leukemia risk after adjuvant treatment of early breast cancer. Womens Health (Lond Engl). 1(1):73–85. https://doi.org/10.1517/17455057.1.1.073 PMID:19803948

Balmes JR, Speizer FE (2012). Occupational and Environmental Lung Disease. Harrison's principles of internal medicine. 18th ed. New York, USA: McGraw-Hill.

Baló J, Bajtai A, Szende B (1965). [Experimental adenomas of the kidney produced by chronic administration of lead phosphate]. Skagyar Onkol. 9:144–51. [Hungarian]

Baluku JB, Olum R, Sanya RE, Ocama P (2023). Respiratory morbidity in *Schistosoma mansoni* infection: a rapid review of literature. Ther Adv Infect Dis. 10:20499361231220152. https://doi.org/10.1177/20499361231220152 PMID:38152611

Band PR, Abanto Z, Bert J, Lang B, Fang R, Gallagher RP, et al. (2011). Prostate cancer risk and exposure to pesticides in British Columbia farmers. Prostate. 71(2):168–83. https://doi.org/10.1002/pros.21232 PMID:20799287

Bandolin L, Borsetto D, Fussey J, Da Mosto MC, Nicolai P, Menegaldo A, et al. (2020). Beta human papillomaviruses infection and skin carcinogenesis. Rev Med Virol. 30(4):e2104. https://doi.org/10.1002/rmv.2104 PMID:32232924

Banerjee A, Shelver WL (2021). Micro- and nanoplastic induced cellular toxicity in mammals: a review. Sci Total Environ. 755(Pt 2):142518. https://doi.org/10.1016/j.scitotenv.2020.142518 PMID:33065507

Banks SD, Murray N, Wilder-Smith A, Logan JG (2014). Insecticide-treated clothes for the control of vector-borne diseases: a review on effectiveness and safety. Med Vet Entomol. 28 Suppl 1:14–25. https://doi.org/10.1111/mve.12068 PMID:24912919

Bano F, Mohanty B (2020). Thyroxine modulation of immune toxicity induced by mixture pesticides mancozeb and fipronil in mice. Life Sci. 240:117078. https://doi.org/10.1016/j.lfs.2019.117078https://doi.org/10.1016/j.lfs.2019.117078 PMID:31759041

Bansal A, Simon MC (2018). Glutathione metabolism in cancer progression and treatment resistance. J Cell Biol. 217(7):2291–8. https://doi.org/10.1083/jcb.201804161 PMID:29915025

Bao J, Zhang Y, Wen R, Zhang L, Wang X (2022). Low level of mancozeb exposure affects ovary in mice. Ecotoxicol Environ Saf. 239:113670. https://doi.org/10.1016/j.ecoenv.2022.113670https://doi.org/10.1016/j.ecoenv.2022.113670 PMID:35617905

Bao W, Liu B, Rong S, Dai SY, Trasande L, Lehmler HJ (2020a). Association between bisphenol A exposure and risk of all-cause and cause-specific mortality in US adults. JAMA Netw Open. 3(8):e2011620. https://doi.org/10.1001/jamanetworkopen.2020.11620 PMID:32804211

Bao W, Liu B, Simonsen DW, Lehmler HJ (2020b). Association between exposure to pyrethroid insecticides and risk of all-cause and cause-specific mortality in the general US adult population. JAMA Intern Med. 180(3):367–74. https://doi.org/10.1001/jamainternmed.2019.6019 PMID:31886824

Bará S, Falchi F (2023). Artificial light at night: a global disruptor of the night-time environment. Philos Trans R Soc Lond B Biol Sci. 378(1892):20220352. https://doi.org/10.1098/rstb.2022.0352 PMID:37899010

Barati M, Darvishi B, Javidi MA, Mohammadian A, Shariatpanahi SP, Eisavand MR, et al. (2021). Cellular stress response to extremely low-frequency electromagnetic fields (ELF-EMF): an explanation for controversial effects of ELF-EMF on apoptosis. Cell Prolif. 54(12):e13154. https://doi.org/10.1111/cpr.13154 PMID:34741480

Barber LE, VoPham T, White LF, Roy HK, Palmer JR, Bertrand KA (2023). Circadian disruption and colorectal cancer incidence in black women. Cancer Epidemiol Biomarkers Prev. 32(7):927–35. https://doi.org/10.1158/1055-9965.EPI-22-0808

Barberet J, Ducreux B, Guilleman M, Simon E, Bruno C, Fauque P (2022). DNA methylation profiles after ART during human lifespan: a systematic review and meta-analysis. Hum Reprod Update. 28(5):629–55. https://doi.org/10.1093/humupd/dmac010 PMID:35259267

Barbosa E, Dos Santos ALA, Peteffi GP, Schneider A, Müller D, Rovaris D, et al. (2019). Increase of global DNA methylation patterns in beauty salon workers exposed to low levels of formaldehyde. Environ Sci Pollut Res Int. 26(2):1304–14. https://doi.org/10.1007/s11356-018-3674-7 PMID:30421373

Barbosa de Sousa A, Rohr P, Silveira HCS (2023). Analysis of mitochondrial DNA copy number variation in Brazilian farmers occupationally exposed to pesticides. Int J Environ Health Res. 15:1–10. PMID:37967258

Barcroft JF, Galazis N, Jones BP, Getreu N, Bracewell-Milnes T, Grewal KJ, et al. (2021). Fertility treatment and cancers – the eternal conundrum: a systematic review and meta-analysis. Hum Reprod. 36(4):1093–107. https://doi.org/10.1093/humrep/deaa293 PMID:33586777

Bardin JA, Eisen EA, Tolbert PE, Hallock MF, Hammond SK, Woskie SR, et al. (1997). Mortality studies of machining fluid exposure in the automobile industry. V: A case–control study of pancreatic cancer. Am J Ind Med. 32(3):240–7. https://doi.org/10.1002/(SICI)1097-0274(199709)32:3<240::AID-AJIM9>3.0.CO;2-0https://doi.org/10.1002/(SICI)1097-0274(199709)32:3<240::AID-AJIM9>3.0.CO;2-0 PMID:9219653

Barguilla I, Domenech J, Ballesteros S, Rubio L, Marcos R, Hernández A (2022). Long-term exposure to nanoplastics alters molecular and functional traits related to the carcinogenic process. J Hazard Mater. 438:129470. https://doi.org/10.1016/j.jhazmat.2022.129470 PMID:35785738

Barros SP, Wirojchanasak S, Barrow DA, Panagakos FS, Devizio W, Offenbacher S (2010). Triclosan inhibition of acute and chronic inflammatory gene pathways. J Clin Periodontol. 37(5):412–8. https://doi.org/10.1111/j.1600-051X.2010.01548.x PMID:20507366

Barry V, Steenland K (2019). Lead exposure and mortality among U.S. workers in a surveillance program: results from 10 additional years of follow-up. Environ Res. 177:108625. https://doi.org/10.1016/j.envres.2019.108625 PMID:31401374

Barry V, Winquist A, Steenland K (2013). Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ Health Perspect. 121(11–12):1313–8. https://doi.org/10.1289/ehp.1306615https://doi.org/10.1289/ehp.1306615 PMID:24007715

Bartholomew RM, Ryan DS (1980). Lack of mutagenicity of some phytoestrogens in the salmonella/mammalian microsome assay. Mutat Res. 78(4):317–21. https://doi.org/10.1016/0165-1218(80)90036-1 PMID:6449666

Barton DT, Zens MS, Marmarelis EL, Gilbert-Diamond D, Karagas MR (2020). Cosmetic tattooing and early onset basal cell carcinoma: a population-based case–control study from New Hampshire. Epidemiology. 31(3):448–50. https://doi.org/10.1097/EDE.0000000000001179 PMID:32079835

Barut BB, Erkmen C, İpek S, Yıldırım S, Üstündağ A, Uslu B (2023). Analytical studies on some pesticides with antifungal effects: simultaneous determination by HPLC, investigation of interactions with DNA and DNA damages. J Chromatogr B Analyt Technol Biomed Life Sci. 1229:123862. https://doi.org/10.1016/j.jchromb.2023.123862 PMID:37696115

Barzalobre-Geronimo R, Contreras-Ramos A, Cervantes-Cruz AI, Cruz M, Suárez-Sánchez F, Goméz-Zamudio J, et al. (2023). Pancreatic β-cell apoptosis in normoglycemic rats is due to mitochondrial translocation of p53-induced by the consumption of sugar-sweetened beverages. Cell Biochem Biophys. 81(3):503–14. https://doi.org/10.1007/s12013-023-01147-y PMID:37392315

Başaran B, Çuvalcı B, Kaban G (2023). Dietary acrylamide exposure and cancer risk: a systematic approach to human epidemiological studies. Foods. 12(2):346. https://doi.org/10.3390/foods12020346 PMID:36673439

BASF (2014). BASF doubles production capacity of Hexamoll® DINCH® to 200,000 metric tons. Ludwigshafen, Germany: BASF. Available from: https://www.basf.com/ru/ru/media/news-releases/2014/05/p-14-231.html, accessed February 2024.

Bashandy SAE, Ebaid H, Abdelmottaleb Moussa SA, Alhazza IM, Hassan I, Alaamer A, et al. (2018). Potential effects of the combination of nicotinamide, vitamin B2 and vitamin C on oxidative-mediated hepatotoxicity induced by thioacetamide. Lipids Health Dis. 17(1):29. https://doi.org/10.1186/s12944-018-0674-z PMID:29444683

Bassett JK, Hodge AM, English DR, MacInnis RJ, Giles GG (2016). Plasma phospholipids fatty acids, dietary fatty acids, and breast cancer risk. Cancer Causes Control. 27(6):759–73. https://doi.org/10.1007/s10552-016-0753-2https://doi.org/10.1007/s10552-016-0753-2 PMID:27146840

Basu A, Krishnamurthy S (2010). Cellular responses to cisplatin-induced DNA damage. J Nucleic Acids. 2010(1):201367. https://doi.org/10.4061/2010/201367 PMID:20811617

Bates MN (2006). Mercury amalgam dental fillings: an epidemiologic assessment. Int J Hyg Environ Health. 209(4):309–16. https://doi.org/10.1016/j.ijheh.2005.11.006 PMID:16448848

Bates MN, Fawcett J, Garrett N, Cutress T, Kjellstrom T (2004). Health effects of dental amalgam exposure: a retrospective cohort study. Int J Epidemiol. 33(4):894–902. https://doi.org/10.1093/ije/dyh164 PMID:15155698

Bath PM, Gray LJ, Bath AJ, Buchan A, Miyata T, Green AR; NXY-059 Efficacy Meta-analysis in Individual Animals with Stroke investigators (2009). Effects of NXY-059 in experimental stroke: an individual animal meta-analysis. Br J Pharmacol. 157(7):1157–71. https://doi.org/10.1111/j.1476-5381.2009.00196.x PMID:19422398

Batool R, Khan MR, Majid M (2017). *Euphorbia dracunculoides* L. abrogates carbon tetrachloride induced liver and DNA damage in rats. BMC Complement Altern Med. 17(1):223. https://doi.org/10.1186/s12906-017-1744-x PMID:28427398

Battilani P, Toscano P, Van der Fels-Klerx HJ, Moretti A, Camardo Leggieri M, Brera C, et al. (2016). Aflatoxin B1 contamination in maize in Europe increases due to climate change. Sci Rep. 6(1):24328. https://doi.org/10.1038/srep24328 PMID:27066906

Battis N, Ekstein SF, Neeley AB (2023). Photoallergic contact dermatitis to menthyl anthranilate (meradimate). Dermatitis. 34(2):153. https://doi.org/10.1089/derm.2022.0048 PMID:36917525

Bauer AK, Siegrist KJ, Wolff M, Nield L, Brüning T, Upham BL, et al. (2022). The carcinogenic properties of overlooked yet prevalent polycyclic aromatic hydrocarbons in human lung epithelial cells. Toxics. 10(1):28. https://doi.org/10.3390/toxics10010028 PMID:35051070

Bauer P, Buettner A (2023). Quantification of odorous and potentially harmful substances in acrylic paint. Ecotoxicol Environ Saf. 262:115329. https://doi.org/10.1016/j.ecoenv.2023.115329https://doi.org/10.1016/j.ecoenv.2023.115329 PMID:37562174

Bauer SE, Wagner SE, Burch J, Bayakly R, Vena JE (2013). A case-referent study: light at night and breast cancer risk in Georgia. Int J Health Geogr. 12(1):23. https://doi.org/10.1186/1476-072X-12-23 PMID:23594790

Baumann AE, Petersen CB, Blond K, Rangul V, Hardy LL (2017). The descriptive epidemiology of sedentary behaviour. In: Leitzmann MF, Jochem C, Schmid D, editors. Sedentary behaviour epidemiology. Cham, Switzerland: Springer; pp. 73–109.

Baumann J, Wong J, Sun Y, Conklin DS (2016). Palmitate-induced ER stress increases trastuzumab sensitivity in HER2/neu-positive breast cancer cells. BMC Cancer. 16(1):551. https://doi.org/10.1186/s12885-016-2611-8https://doi.org/10.1186/s12885-016-2611-8 PMID:27464732

Bausinger J, Speit G (2016). The impact of lymphocyte isolation on induced DNA damage in human blood samples measured by the comet assay. Mutagenesis. 31(5):567–72. https://doi.org/10.1093/mutage/gew021 PMID:27154923

Beamand JA, Price RJ, Phillips JC, Butler WH, Jones GD, Osimitz TG, et al. (1996). Lack of effect of piperonyl butoxide on unscheduled DNA synthesis in precision-cut human liver slices. Mutat Res. 371(3–4):273–82. https://doi.org/10.1016/S0165-1218(96)90116-0 PMID:9008729

Bean CL, Armstrong MJ, Galloway SM (1992). Effect of sampling time on chromosome aberration yield for 7 chemicals in Chinese hamster ovary cells. Mutat Res. 265(1):31–44. https://doi.org/10.1016/0027-5107(92)90037-3 PMID:1370241

Beane Freeman LE, Kogevinas M, Cantor KP, Villanueva CM, Prokunina-Olsson L, Florez-Vargas O, et al. (2022). Disinfection by-products in drinking water and bladder cancer: evaluation of risk modification by common genetic polymorphisms in two case–control studies. Environ Health Perspect. 130(5):57006. https://doi.org/10.1289/EHP9895 PMID:35536285

Beard JD, Erdely A, Dahm MM, de Perio MA, Birch ME, Evans DE, et al. (2018). Carbon nanotube and nanofiber exposure and sputum and blood biomarkers of early effect among US workers. Environ Int. 116:214–28. https://doi.org/10.1016/j.envint.2018.04.004 PMID:29698898

Beauchamp RO Jr, Bus JS, Popp JA, Boreiko CJ, Goldberg L, McKenna MJ (1983). A critical review of the literature on carbon disulfide toxicity. Crit Rev Toxicol. 11(3):169–278. https://doi.org/10.3109/10408448309128255 PMID:6349939

Becci PJ, Hess FG, Johnson WD, Gallo MA, Babish JG, Dailey RE, et al. (1981). Long-term carcinogenicity and toxicity studies of patulin in the rat. J Appl Toxicol. 1(5):256–61. https://doi.org/10.1002/jat.2550010504 PMID:6821081

Becher R, Låg M, Schwarze PE, Brunborg G, Søderlund EJ, Holme JA (1993). Chemically induced DNA damage in isolated rabbit lung cells. Mutat Res. 285(2):303–11. https://doi.org/10.1016/0027-5107(93)90119-Z PMID:7678904

Becherer BE, de Boer M, Spronk PER, Bruggink AH, de Boer JP, van Leeuwen FE, et al. (2019). The Dutch breast implant registry: registration of breast implant-associated anaplastic large cell lymphoma – a proof of concept. Plast Reconstr Surg. 143(5):1298–306. https://doi.org/10.1097/PRS.0000000000005501 PMID:31033810

Becherer BE, Hopper I, Cooter RD, Couturaud B, von Fritschen U, Mullen E, et al. (2023). Comparing 200 000 breast implants and 85000 patients over four national breast implant registries. Plast Reconstr Surg. 152(2):307–18. PMID:36728275

Becker H, Herzberg F, Schulte A, Kolossa-Gehring M (2011). The carcinogenic potential of nanomaterials, their release from products and options for regulating them. Int J Hyg Environ Health. 214(3):231–8. https://doi.org/10.1016/j.ijheh.2010.11.004 PMID:21168363

Beeharry N, Lowe JE, Hernandez AR, Chambers JA, Fucassi F, Cragg PJ, et al. (2003). Linoleic acid and antioxidants protect against DNA damage and apoptosis induced by palmitic acid. Mutat Res. 530(1–2):27–33. https://doi.org/10.1016/S0027-5107(03)00134-9https://doi.org/10.1016/S0027-5107(03)00134-9 PMID:14563528

Begemann P, Boysen G, Georgieva NI, Sangaiah R, Koshlap KM, Koc H, et al. (2011). Identification and characterization of 2′-deoxyadenosine adducts formed by isoprene monoepoxides in vitro. Chem Res Toxicol. 24(7):1048–61. https://doi.org/10.1021/tx200055c PMID:21548641

Begemann P, Christova-Georgieva NI, Sangaiah R, Koc H, Zhang D, Golding BT, et al. (2004). Synthesis, characterization, and identification of N7-guanine adducts of isoprene monoepoxides in vitro. Chem Res Toxicol. 17(7):929–36. https://doi.org/10.1021/tx0342565 PMID:15257618

Béguelin C, Atkinson A, Boyd A, Falconer K, Kirkby N, Suter-Riniker F, et al.; for EuroSIDA and SHCS (2023). Hepatitis delta infection among persons living with HIV in Europe. Liver Int. 43(4):819–28. https://doi.org/10.1111/liv.15519 PMID:36625770

Behrens T, Ge C, Vermeulen R, Kendzia B, Olsson A, Schüz J, et al. (2023). Occupational exposure to nickel and hexavalent chromium and the risk of lung cancer in a pooled analysis of case–control studies (SYNERGY). Int J Cancer. 152(4):645–60. https://doi.org/10.1002/ijc.34272 PMID:36054442

Bekki K, Uchiyama S, Ohta K, Inaba Y, Nakagome H, Kunugita N (2014). Carbonyl compounds generated from electronic cigarettes. Int J Environ Res Public Health. 11(11):11192–200. https://doi.org/10.3390/ijerph111111192 PMID:25353061

Beland FA, Olson GR, Mendoza MC, Marques MM, Doerge DR (2015). Carcinogenicity of glycidamide in B6C3F1 mice and F344/N rats from a two-year drinking water exposure. Food Chem Toxicol. 86:104–15. https://doi.org/10.1016/j.fct.2015.09.017 PMID:26429628

Belhassen H, Jiménez-Díaz I, Arrebola JP, Ghali R, Ghorbel H, Olea N, et al. (2015). Zearalenone and its metabolites in urine and breast cancer risk: a case–control study in Tunisia. Chemosphere. 128:1–6. https://doi.org/10.1016/j.chemosphere.2014.12.055 PMID:25602441

Bell DA, Kamens RM (1990). Evaluation of the mutagenicity of combustion particles from several common biomass fuels in the Ames/*Salmonella* microsome test. Mutat Res. 245(3):177–83. https://doi.org/10.1016/0165-7992(90)90047-N PMID:2233838

Bellicha A, Wendeu-Foyet G, Coumoul X, Koual M, Pierre F, Guéraud F, et al. (2022). Dietary exposure to acrylamide and breast cancer risk: results from the NutriNet-Santé cohort. Am J Clin Nutr. 116(4):911–9. https://doi.org/10.1093/ajcn/nqac167 PMID:36055962

Bellisai G, Bernasconi G, Brancato A, Carrasco Cabrera L, Ferreira L, Giner G, et al.; EFSA (European Food Safety Authority) (2021). Modification of the existing maximum residue levels for proquinazid in blueberries and cranberries. EFSA J. 19(9):e06835. PMID:34531929

Bello A, Carignan CC, Xue Y, Stapleton HM, Bello D (2018). Exposure to organophosphate flame retardants in spray polyurethane foam applicators: role of dermal exposure. Environ Int. 113:55–65. https://doi.org/10.1016/j.envint.2018.01.020 PMID:29421408

Belpoggi F, Soffritti M, Guarino M, Lambertini L, Cevolani D, Maltoni C (2002). Results of long-term experimental studies on the carcinogenicity of ethylene-bis-dithiocarbamate (Mancozeb) in rats. Ann N Y Acad Sci. 982(1):123–36. https://doi.org/10.1111/j.1749-6632.2002.tb04928.x PMID:12562632

Beltrán-Aguilar ED, Thornton-Evans G, Wei L, Bernal J (2023). Prevalence and mean number of teeth with amalgam and nonamalgam restorations, United States, 2015 through 2018. J Am Dent Assoc. 154(5):417–26. https://doi.org/10.1016/j.adaj.2023.02.016 PMID:37105669

Ben Salah-Abbès J, Abbès S, Ouanes Z, Abdel-Wahhab MA, Bacha H, Oueslati R (2009). Isothiocyanate from the Tunisian radish (*Raphanus sativus*) prevents genotoxicity of zearalenone in vivo and in vitro. Mutat Res. 677(1–2):59–65. https://doi.org/10.1016/j.mrgentox.2009.05.017 PMID:19501672

Benavente Y, Costas L, Rodríguez-Suarez MM, Alguacil J, Santibáñez M, Vila J, et al. (2020). Occupational exposure to pesticides and chronic lymphocytic leukaemia in the MCC–Spain Study. Int J Environ Res Public Health. 17(14):5174. https://doi.org/10.3390/ijerph17145174 PMID:32709095

BenchChem (2023). o-Aminoazotoluene. Pasadena (CA), USA: BenchChem. Available from: https://www.benchchem.com/product/b045844, accessed August 2024.

Benedetti D, Lopes Alderete B, de Souza CT, Ferraz Dias J, Niekraszewicz L, Cappetta M, et al. (2018). DNA damage

and epigenetic alteration in soybean farmers exposed to complex mixture of pesticides. Mutagenesis. 33(1):87–95. https://doi.org/10.1093/mutage/gex035 PMID:29244183

Benegiamo G, Vinciguerra M, Guarnieri V, Niro GA, Andriulli A, Pazienza V (2013). Hepatitis delta virus induces specific DNA methylation processes in Huh-7 liver cancer cells. FEBS Lett. 587(9):1424–8. https://doi.org/10.1016/j.febslet.2013.03.021 PMID:23523924

Benford D, Bignami M, Chipman JK, Ramos Bordajandi L; European Food Safety Authority (EFSA) (2022). Assessment of the genotoxicity of acrylamide. EFSA J. 20(5):e07293. PMID:35540797

Benford DJ, Bridges JW, Boobis AR, Kahn GC, Brodie MJ, Davies DS (1981). The selective activation of cytochrome P-450 dependent microsomal hydroxylases in human and rat liver microsomes. Biochem Pharmacol. 30(12):1702–3. https://doi.org/10.1016/0006-2952(81)90401-9 PMID:7271855

Benninghoff AD, Williams DE (2013). The role of estrogen receptor β in transplacental cancer prevention by indole-3-carbinol. Cancer Prev Res (Phila). 6(4):339–48. https://doi.org/10.1158/1940-6207.CAPR-12-0311 PMID:23447562

Benson VS, Pirie K, Schüz J, Reeves GK, Beral V, Green J; Million Women Study Collaborators (2013). Mobile phone use and risk of brain neoplasms and other cancers: prospective study. Int J Epidemiol. 42(3):792–802. https://doi.org/10.1093/ije/dyt072 PMID:23657200

Berame JS, Lapada AA, Miguel FF, Noguera EC, Alam ZF (2020). Micronucleus evaluation in exfoliated human buccal epithelium cells among e-waste workers in Payatas, the Philippines. J Health Pollut. 10(28):201213. https://doi.org/10.5696/2156-9614-10.28.201213 PMID:33324510

Berger-Preiss E, Koch W, Behnke W, Gerling S, Kock H, Elflein L, et al. (2004). In-flight spraying in aircrafts: determination of the exposure scenario. Int J Hyg Environ Health. 207(5):419–30. https://doi.org/10.1078/1438-4639-00310 PMID:15575556

Bergin IL, Sheppard BJ, Fox JG (2003). *Helicobacter pylori* infection and high dietary salt independently induce atrophic gastritis and intestinal metaplasia in commercially available outbred Mongolian gerbils. Dig Dis Sci. 48(3):475–85. https://doi.org/10.1023/A:1022524313355 PMID:12757158

Bergman K, Müller L, Teigen SW (1996). Series: current issues in mutagenesis and carcinogenesis, No. 65. The genotoxicity and carcinogenicity of paracetamol: a regulatory (re)view. Mutat Res. 349(2):263–88. https://doi.org/10.1016/0027-5107(95)00185-9 PMID:8600357

Bermingham K, Stensrud S, Valdes A, Franks P, Chan A, Wolf J, et al. (2022). Social jetlag is associated with poor diet and increased inflammation in the ZOE PREDICT 1 cohort. Curr Dev Nutr. 6 Suppl 1:413. https://doi.org/10.1093/cdn/nzac055.002

Bernacki DT, Bryce SM, Bemis JC, Dertinger SD, Witt KL, Smith-Roe SL (2019). Evidence for an aneugenic mechanism of action for micronucleus induction by black cohosh extract. Environ Mol Mutagen. 60(9):845–56. https://doi.org/10.1002/em.22334https://doi.org/10.1002/em.22334 PMID:31569270

Berni I, Menouni A, Creta M, El Ghazi I, Duca RC, Godderis L, et al. (2023). Exposure of children to glyphosate in Morocco: urinary levels and predictors of exposure. Environ Res. 217:114868. https://doi.org/10.1016/j.envres.2022.114868 PMID:36417941

Berrios C, Padi M, Keibler MA, Park DE, Molla V, Cheng J, et al. (2016). Merkel cell polyomavirus small T antigen promotes pro-glycolytic metabolic perturbations required for transformation. PLoS Pathog. 12(11):e1006020. https://doi.org/10.1371/journal.ppat.1006020 PMID:27880818

Berry C, Brusick D, Cohen SM, Hardisty JF, Grotz VL, Williams GM (2016). Sucralose non-carcinogenicity: a review of the scientific and regulatory rationale. Nutr Cancer. 68(8):1247–61. https://doi.org/10.1080/01635581.2016.1224366 PMID:27652616

Berry JP, Galle P, Poupon MF, Pot-Deprun J, Chouroulinkov I, Judde JG, et al. (1984). Electron microprobe in vitro study of interaction of carcinogenic nickel compounds with tumour cells. IARC Sci Publ. 53(53):153–64. PMID:6099827

Berry TG, Nicholson J, Troendle K (1994). Almost two centuries with amalgam: where are we today? J Am Dent Assoc. 125(4):392–9. https://doi.org/10.14219/jada.archive.1994.0053 PMID:8176074

Bertazzoli C, Chieli T, Solcia E (1971). Different incidence of breast carcinomas or fibroadenomas in daunomycin or adriamycin treated rats. Experientia. 27(10):1209–10. https://doi.org/10.1007/BF02286933 PMID:5127885

Berton T, Mayhoub F, Chardon K, Duca RC, Lestremau F, Bach V, et al. (2014). Development of an analytical strategy based on LC–MS/MS for the measurement of different classes of pesticides and their metabolites in meconium: application and characterisation of foetal exposure in France. Environ Res. 132:311–20. https://doi.org/10.1016/j.envres.2014.03.034 PMID:24834827

Bertrand KA, Delp L, Coogan PF, Cozier YC, Lenzy YM, Rosenberg L, et al. (2023). Hair relaxer use and risk of uterine cancer in the Black Women's Health Study. Environ Res. 239(Pt 1):117228. https://doi.org/10.1016/j.envres.2023.117228 PMID:37821068

Bessler H, Djaldetti M (2019). The impact of three commercial sweeteners on cytokine expression by mononuclears impelled by colon carcinoma cells. Int J Food Sci Nutr. 70(8):970–6. https://doi.org/10.1080/09637486.2019.1605337 PMID:31066319

Betenia N, Costello S, Eisen EA (2012). Risk of cervical cancer among female autoworkers exposed to metalworking fluids. Scand J Work Environ Health. 38(1):78–83. https://doi.org/10.5271/sjweh.3193https://doi.org/10.5271/sjweh.3193 PMID:21901243

Bezin J, Gouverneur A, Pénichon M, Mathieu C, Garrel R, Hillaire-Buys D, et al. (2023). GLP-1 receptor agonists and the risk of thyroid cancer. Diabetes Care. 46(2):384–90. https://doi.org/10.2337/dc22-1148 PMID:36356111

BfR (2020). Updated risk assessment on levels of 1,2-unsaturated pyrrolizidine alkaloids (PAs) in foods. BfR Opinion 026/2020, issued 17 June 2020. German Federal Institute for Risk Assessment (BfR). Available from: https://mobil.bfr.bund.de/cm/349/updated-risk-assessment-on-levels-of-1-2-unsaturated-pyrrolizidine-alkaloids-pas-in-foods.pdf, accessed September 2024.

Bhaskar R, Mohanty B (2014). Pesticides in mixture disrupt metabolic regulation: in silico and in vivo analysis of cumulative toxicity of mancozeb and imidacloprid on body weight of mice. Gen Comp Endocrinol. 205:226–34. https://doi.org/10.1016/j.ygcen.2014.02.007 PMID:24530807

Bhat TA, Kalathil SG, Goniewicz ML, Hutson A, Thanavala Y (2023). Not all vaping is the same: differential pulmonary effects of vaping cannabidiol versus nicotine. Thorax. 78(9):922–32. https://doi.org/10.1136/thorax-2022-218743 PMID:36823163

Bhat VS, Durham JL, Ball GL, English JC (2014). Derivation of an oral reference dose (RfD) for the nonphthalate alternative plasticizer 1,2-cyclohexane dicarboxylic acid, di-isononyl ester (DINCH). J Toxicol Environ Health B Crit Rev. 17(2):63–94. https://doi.org/10.1080/10937404.2013.876288 PMID:24627975

Bhattacharya K, Davoren M, Boertz J, Schins RP, Hoffmann E, Dopp E (2009). Titanium dioxide nanoparticles induce oxidative stress and DNA-adduct formation but not DNA-breakage in human lung cells. Part Fibre Toxicol. 6(1):17. https://doi.org/10.1186/1743-8977-6-17 PMID:19545397

Bhowmick D, Bhar K, Mallick SK, Das S, Chatterjee N, Sarkar TS, et al. (2016). *Para*-phenylenediamine induces apoptotic death of melanoma cells and reduces melanoma tumour growth in mice. Biochem Res Int. 2016:3137010. https://doi.org/10.1155/2016/3137010https://doi.org/10.1155/2016/3137010 PMID:27293892

Bhuyan BK, Zimmer DM, Mazurek JH, Trzos RJ, Harbach PR, Shu VS, et al. (1983). Comparative genotoxicity of adriamycin and menogarol, two anthracycline antitumor agents. Cancer Res. 43(11):5293–7. PMID: 6225515

Bian X, Chi L, Gao B, Tu P, Ru H, Lu K (2017). Gut microbiome response to sucralose and its potential role in inducing liver inflammation in mice. Front Physiol. 8:487. https://doi.org/10.3389/fphys.2017.00487 PMID:28790923

Bijland S, Rensen PC, Pieterman EJ, Maas AC, van der Hoorn JW, van Erk MJ, et al. (2011). Perfluoroalkyl sulfonates cause alkyl chain length-dependent hepatic steatosis and hypolipidemia mainly by impairing lipoprotein production in APOE*3-Leiden CETP mice. Toxicol Sci. 123(1):290–303. https://doi.org/10.1093/toxsci/kfr142https://doi.org/10.1093/toxsci/kfr142 PMID:21705711

Binazzi A, Corfiati M, Di Marzio D, Cacciatore AM, Zajacovà J, Mensi C, et al. (2018). Sinonasal cancer in the Italian national surveillance system: epidemiology, occupation, and public health implications. Am J Ind Med. 61(3):239–50. https://doi.org/10.1002/ajim.22789 PMID:29114957

Binazzi A, Ferrante P, Marinaccio A (2015). Occupational exposure and sinonasal cancer: a systematic review and

meta-analysis. Am J Ind Med. 15(1):49. https://doi.org/10.1186/s12885-015-1042-2

Binder S, Cao X, Bauer S, Rastak N, Kuhn E, Dragan GC, et al. (2021). In vitro genotoxicity of dibutyl phthalate on A549 lung cells at air–liquid interface in exposure concentrations relevant at workplaces. Environ Mol Mutagen. 62(9):490–501. https://doi.org/10.1002/em.22464 PMID:34636079

Binker-Cosen MJ, Richards D, Oliver B, Gaisano HY, Binker MG, Cosen-Binker LI (2017). Palmitic acid increases invasiveness of pancreatic cancer cells AsPC-1 through TLR4/ROS/NF-κB/MMP-9 signalling pathway. Biochem Biophys Res Commun. 484(1):152–8. https://doi.org/10.1016/j.bbrc.2017.01.051https://doi.org/10.1016/j.bbrc.2017.01.051 PMID:28088520

Birka M, Roscher J, Holtkamp M, Sperling M, Karst U (2016a). Investigating the stability of gadolinium based contrast agents towards UV radiation. Water Res. 91:244–50. https://doi.org/10.1016/j.watres.2016.01.012 PMID:26802476

Birka M, Wehe CA, Hachmöller O, Sperling M, Karst U (2016b). Tracing gadolinium-based contrast agents from surface water to drinking water by means of speciation analysis. J Chromatogr A. 1440:105–11. https://doi.org/10.1016/j.chroma.2016.02.050 PMID:26931429

Birt DF, Julius AD, Runice CE, White LT, Lawson T, Pour PM (1988). Enhancement of BOP-induced pancreatic carcinogenesis in selenium-fed Syrian golden hamsters under specific dietary conditions. Nutr Cancer. 11(1):21–33. https://doi.org/10.1080/01635588809513966 PMID:2832833

Birt DF, Pour PM, Pelling JC (1989). The influence of dietary selenium on colon, pancreas, and skin tumorigenesis. In: Wendel A, editor. Selenium in biology and medicine. Berlin, Germany: Springer-Verlag; pp. 297–304. https://doi.org/10.1007/978-3-642-74421-1_57

Biswas A, Petnicki-Ocwieja T, Kobayashi KS (2012). Nod2: a key regulator linking microbiota to intestinal mucosal immunity. J Mol Med (Berl). 90(1):15–24. https://doi.org/10.1007/s00109-011-0802-y PMID:21861185

Bizjak M, Selmi C, Praprotnik S, Bruck O, Perricone C, Ehrenfeld M, et al. (2015). Silicone implants and lymphoma: the role of inflammation. J Autoimmun. 65:64–73. https://doi.org/10.1016/j.jaut.2015.08.009 PMID:26330346

Bizzarri D, Dollé MET, Loef B, van den Akker EB, van Kerkhof LWM (2022). GlycA, a biomarker of low-grade inflammation, is increased in male night shift workers. Metabolites. 12(12):1172. https://doi.org/10.3390/metabo12121172

Bjerre Knudsen L, Madsen LW, Andersen S, Almholt K, de Boer AS, Drucker DJ, et al. (2010). Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology. 151(4):1473–86. https://doi.org/10.1210/en.2009-1272 PMID:20203154

Bjørge C, Brunborg G, Wiger R, Holme JA, Scholz T, Dybing E, et al. (1996b). A comparative study of chemically induced DNA damage in isolated human and rat testicular cells. Reprod Toxicol. 10(6):509–19. https://doi.org/10.1016/S0890-6238(96)00138-4 PMID:8946565

Bjørge C, Wiger R, Holme JA, Brunborg G, Andersen R, Dybing E, et al. (1995). In vitro toxicity of 1,2-dibromo-3-chloropropane (DBCP) in different testicular cell types from rats. Reprod Toxicol. 9(5):461–73. https://doi.org/10.1016/0890-6238(95)00038-C PMID:8563189

Bjørge C, Wiger R, Holme JA, Brunborg G, Scholz T, Dybing E, et al. (1996a). DNA strand breaks in testicular cells from humans and rats following in vitro exposure to 1,2-dibromo-3-chloropropane (DBCP). Reprod Toxicol. 10(1):51–9. https://doi.org/10.1016/0890-6238(95)02018-7 PMID:8998386

Bjørklund G, Shanaida M, Lysiuk R, Antonyak H, Klishch I, Shanaida V, et al. (2022). Selenium: an antioxidant with a critical role in anti-aging. Molecules. 27(19):6613. https://doi.org/10.3390/molecules27196613 PMID:36235150

Bláha L, Kapplová P, Vondrácek J, Upham B, Machala M (2002). Inhibition of gap-junctional intercellular communication by environmentally occurring polycyclic aromatic hydrocarbons. Toxicol Sci. 65(1):43–51. https://doi.org/10.1093/toxsci/65.1.43 PMID:11752684

Blakely KM, Drucker AM, Rosen CF (2019). Drug-induced photosensitivity – an update: culprit drugs, prevention and management. Drug Saf. 42(7):827–47. https://doi.org/10.1007/s40264-019-00806-5 PMID:30888626

Blanc-Lapierre A, Sauvé JF, Parent ME (2018). Occupational exposure to benzene, toluene, xylene and styrene and risk of prostate cancer in a population-based study. Occup Environ Med. 75(8):562–72. https://doi.org/10.1136/oemed-2018-105058 PMID:29980583

Blanchard KT, Barthel C, French JE, Holden HE, Moretz R, Pack FD, et al. (1999). Transponder-induced sarcoma in the heterozygous p53+/− mouse. Toxicol Pathol. 27(5):519–27. https://doi.org/10.1177/019262339902700505 PMID:10528631

Blanco-Muñoz J, Lacasaña M, López-Flores I, Rodríguez-Barranco M, González-Alzaga B, Bassol S, et al. (2016). Association between organochlorine pesticide exposure and thyroid hormones in floriculture workers. Environ Res. 150:357–63. https://doi.org/10.1016/j.envres.2016.05.054 PMID:27344267

Blanco-Pérez JJ, Blanco-Dorado S, Rodríguez-García J, Gonzalez-Bello ME, Salgado-Barreira Á, Caldera-Díaz AC, et al. (2021). Serum levels of inflammatory mediators as prognostic biomarker in silica exposed workers. Sci Rep. 11(1):13348. https://doi.org/10.1038/s41598-021-92587-0 PMID:34172787

Blask DE, Brainard GC, Dauchy RT, Hanifin JP, Davidson LK, Krause JA, et al. (2005). Melatonin-depleted blood from premenopausal woman exposed to light at night stimulates growth of human breast cancer xenografts in nude rats. Cancer Res. 65(23):11174–84. https://doi.org/10.1158/0008-5472.CAN-05-1945 PMID:16322268

Bliss B, Tran KI, Sioutas C, Campbell A (2018). Ambient ultrafine particles activate human monocytes: effect of dose, differentiation state and age of donors. Environ Res. 161:314–20. https://doi.org/10.1016/j.envres.2017.11.019 PMID:29178980

Bloching M, Reich W, Schubert J, Grummt T, Sandner A (2008). Micronucleus rate of buccal mucosal epithelial cells in relation to oral hygiene and dental factors. Oral Oncol. 44(3):220–6. https://doi.org/10.1016/j.oraloncology.2007.02.002 PMID:17434785

Boffetta P, Ciocan C, Zunarelli C, Pira E (2021). Exposure to glyphosate and risk of non-Hodgkin lymphoma: an updated meta-analysis. Med Lav. 112(3):194–9. https://www.mattioli1885journals.com/index.php/lamedicinadellavoro/article/view/11123/9704 PMID:34142676

Boffetta P, Hayes RB, Sartori S, Lee YC, Muscat J, Olshan A, et al. (2016). Mouthwash use and cancer of the head and neck: a pooled analysis from the International Head and Neck Cancer Epidemiology Consortium. Eur J Cancer Prev. 25(4):344–8. https://doi.org/10.1097/CEJ.0000000000000179 PMID:26275006

Bohonowych JE, Denison MS (2007). Persistent binding of ligands to the aryl hydrocarbon receptor. Toxicol Sci. 98(1):99–109. https://doi.org/10.1093/toxsci/kfm085 PMID:17431010

Boland S, Baeza-Squiban A, Fournier T, Houcine O, Gendron MC, Chévrier M, et al. (1999). Diesel exhaust particles are taken up by human airway epithelial cells in vitro and alter cytokine production. Am J Physiol. 276(4):L604–13. PMID:10198358

Bolton KL, Ptashkin RN, Gao T, Braunstein L, Devlin SM, Kelly D, et al. (2020). Cancer therapy shapes the fitness landscape of clonal hematopoiesis. Nat Genet. 52(11):1219–26. https://doi.org/10.1038/s41588-020-00710-0 PMID:33106634

Bomhard EM (2018). The toxicology of indium oxide. Environ Toxicol Pharmacol. 58:250–8. https://doi.org/10.1016/j.etap.2018.02.003 PMID:29448164

Bondurant S, Ernster V, Herdman R, editors. (2000). Safety of silicone breast implants. Washington (DC), USA: Committee on the Safety of Silicone Breast Implants, Division of Health Promotion and Disease Prevention. Available from: https://www.nap.edu/read/9602/chapter/1, accessed September 2024.

Bondy G, Mehta R, Caldwell D, Coady L, Armstrong C, Savard M, et al. (2012). Effects of long term exposure to the mycotoxin fumonisin B1 in p53 heterozygous and p53 homozygous transgenic mice. Food Chem Toxicol. 50(10):3604–13. https://doi.org/10.1016/j.fct.2012.07.024 PMID:22841953

Bonner MR, Freeman LE, Hoppin JA, Koutros S, Sandler DP, Lynch CF, et al. (2017). Occupational exposure to pesticides and the incidence of lung cancer in the Agricultural Health Study. Environ Health Perspect. 125(4):544–51. https://doi.org/10.1289/EHP456 PMID:27384818

Boor PPC, de Ruiter PE, Asmawidjaja PS, Lubberts E, van der Laan LJW, Kwekkeboom J (2017). JAK-inhibitor tofacitinib suppresses interferon alfa production by plasmacytoid dendritic cells and inhibits arthrogenic and

antiviral effects of interferon alfa. Transl Res. 188:67–79. https://doi.org/10.1016/j.trsl.2016.11.006 PMID:27931982

Boot A, Huang MN, Ng AWT, Ho SC, Lim JQ, Kawakami Y, et al. (2018). In-depth characterization of the cisplatin mutational signature in human cell lines and in esophageal and liver tumors. Genome Res. 28(5):654–65. https://doi.org/10.1101/gr.230219.117 PMID:29632087

Bopp L, Wieland U, Hellmich M, Kreuter A, Pfister H, Silling S (2021). Natural history of cutaneous human polyomavirus infection in healthy individuals. Front Microbiol. 12:740947. https://doi.org/10.3389/fmicb.2021.740947 PMID:34733257

Bornholdt J, Dybdahl M, Vogel U, Hansen M, Loft S, Wallin H (2002). Inhalation of ozone induces DNA strand breaks and inflammation in mice. Mutat Res. 520(1–2):63–71. https://doi.org/10.1016/S1383-5718(02)00176-6 PMID:12297145

Borzelleca JF, Capen CC, Hallagan JB (1987). Lifetime toxicity/carcinogenicity study of FD & C Red No. 3 (erythrosine) in rats. Food Chem Toxicol. 25(10):723–33. https://doi.org/10.1016/0278-6915(87)90226-2 PMID:2824305

Botelho MC, Costa C, Silva S, Costa S, Dhawan A, Oliveira PA, et al. (2014). Effects of titanium dioxide nanoparticles in human gastric epithelial cells in vitro. Biomed Pharmacother. 68(1):59–64. https://doi.org/10.1016/j.biopha.2013.08.006 PMID:24051123

Bouaoun L, Byrnes G, Lagorio S, Feychting M, Beranger AABR, Schüz J (2024). Effects of recall and selection biases on modeling cancer risk from mobile phone use: results from a case–control simulation study. Epidemiology. 35(4):437–46. https://doi.org/10.1097/EDE.0000000000001749 PMID:38771708

Bouaziz C, Graiet I, Salah A, Ben Salem I, Abid S (2020). Influence of bifentrin, a pyrethriod pesticide, on human colorectal HCT-116 cells attributed to alterations in oxidative stress involving mitochondrial apoptotic processes. J Toxicol Environ Health A. 83(9):331–40. https://doi.org/10.1080/15287394.2020.1755756 PMID:32364034

Bouchard M, Carrier G, Brunet RC (2008). Assessment of absorbed doses of carbaryl and associated health risks in a group of horticultural greenhouse workers. Int Arch Occup Environ Health. 81(3):355–70. https://doi.org/10.1007/s00420-007-0220-1 PMID:17638006

Boucher J (2021). ECHA regulation updates limits of DEHP in FCMs. Zurich, Switzerland: Food Packaging Forum. Available from: https://www.foodpackagingforum.org/news/echa-regulation-updates-limits-of-dehp-in-fcms#:~:text=On%20November%2023%2C%202021%2C%20the%20European%20Commission%20announced,Regulation%2C%20which%20is%20known%20as%20the%20Authorization%20List, accessed February 2024.

Boulanger M, de Graaf L, Pons R, Bouchart V, Bureau M, Lecluse Y, et al. (2023). Herbicide exposure during occupational knapsack spraying in French gardeners and municipal workers. Ann Work Expo Health. 67(8):965–78. https://doi.org/10.1093/annweh/wxad045 PMID:37619214

Bouma F, Janssen NA, Wesseling J, van Ratingen S, Strak M, Kerckhoffs J, et al. (2023). Long-term exposure to ultrafine particles and natural and cause-specific mortality. Environ Int. 175:107960. https://doi.org/10.1016/j.envint.2023.107960 PMID:37178608

Bourdon JA, Halappanavar S, Saber AT, Jacobsen NR, Williams A, Wallin H, et al. (2012). Hepatic and pulmonary toxicogenomic profiles in mice intratracheally instilled with carbon black nanoparticles reveal pulmonary inflammation, acute phase response, and alterations in lipid homeostasis. Toxicol Sci. 127(2):474–84. https://doi.org/10.1093/toxsci/kfs119 PMID:22461453

Bourgeois G, Suire C, Vivas N, Benoist F, Vitry C (1999). Atraric acid, a marker for epiphytic lichens in the wood used in cooperage: identification and quantification by GC/MS/(MS). Analusis. 27(3):281–3. https://doi.org/10.1051/analusis:1999100https://doi.org/10.1051/analusis:1999100

Bousoumah R, Leso V, Iavicoli I, Huuskonen P, Viegas S, Porras SP, et al. (2021). Biomonitoring of occupational exposure to bisphenol A, bisphenol S and bisphenol F: a systematic review. Sci Total Environ. 783:146905. https://doi.org/10.1016/j.scitotenv.2021.146905 PMID:33865140

Boussabbeh M, Ben Salem I, Prola A, Guilbert A, Bacha H, Abid-Essefi S, et al. (2015). Patulin induces apoptosis through ROS-mediated endoplasmic reticulum stress pathway. Toxicol Sci. 144(2):328–37. https://doi.org/10.1093/toxsci/kfu319 PMID:25577197

Boussemart L, Girault I, Malka-Mahieu H, Mateus C, Routier E, Rubington M, et al. (2016). Secondary tumors arising in patients undergoing BRAF inhibitor therapy exhibit increased BRAF–CRAF heterodimerization. Cancer Res. 76(6):1476–84. https://doi.org/10.1158/0008-5472.CAN-15-2900-T PMID:26825172

Boutwell RK, Bosch DK (1959). The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res. 19(4):413–24. https://aacrjournals.org/cancerres/article/19/4/413/473978/The-Tumor-promoting-Action-of-Phenol-and-Related PMID:13652126

Boxman IL, Russell A, Mulder LH, Bavinck JN, Schegget JT, Green A; The Nambour Skin Cancer Prevention Study Group (2000). Case–control study in a subtropical Australian population to assess the relation between non-melanoma skin cancer and epidermodysplasia verruciformis human papillomavirus DNA in plucked eyebrow hairs. Int J Cancer. 86(1):118–21. https://doi.org/10.1002/(SICI)1097-0215(20000401)86:1<118::AID-IJC18>3.0.CO;2-2 PMID:10728604

Brabant C, Geerinck A, Beaudart C, Tirelli E, Geuzaine C, Bruyère O (2022). Exposure to magnetic fields and childhood leukemia: a systematic review and meta-analysis of case–control and cohort studies. Rev Environ Health. 38(2):229–53. https://doi.org/10.1515/reveh-2021-0112 PMID:35302721

Bradley F, Franzén Boger M, Kaldhusdal V, Åhlberg A, Edfeldt G, Lajoie J, et al. (2022). Multi-omics analysis of the cervical epithelial integrity of women using depot medroxyprogesterone acetate. PLoS Pathog. 18(5):e1010494. https://doi.org/10.1371/journal.ppat.1010494 PMID:35533147

Bradman A, Whitaker D, Quirós L, Castorina R, Claus Henn B, Nishioka M, et al. (2007). Pesticides and their metabolites in the homes and urine of farmworker children living in the Salinas Valley, CA. J Expo Sci Environ Epidemiol. 17(4):331–49. https://doi.org/10.1038/sj.jes.7500507 PMID:16736054

Brander SM, He G, Smalling KL, Denison MS, Cherr GN (2012). The in vivo estrogenic and in vitro anti-estrogenic activity of permethrin and bifenthrin. Environ Toxicol Chem. 31(12):2848–55. https://doi.org/10.1002/etc.2019 PMID:23007834

Brandi G, Di Girolamo S, Farioli A, de Rosa F, Curti S, Pinna AD, et al. (2013). Asbestos: a hidden player behind the cholangiocarcinoma increase? Findings from a case–control analysis. Cancer Causes Control. 24(5):911–8. https://doi.org/10.1007/s10552-013-0167-3 PMID:23408245

Brandi G, Tavolari S (2020). Asbestos and intrahepatic cholangiocarcinoma. Cells. 9(2):421. https://doi.org/10.3390/cells9020421 PMID:32059499

Brasky TM, Lampe JW, Potter JD, Patterson RE, White E (2010). Specialty supplements and breast cancer risk in the VITamins And Lifestyle (VITAL) Cohort. Cancer Epidemiol Biomarkers Prev. 19(7):1696–708. https://doi.org/10.1158/1055-9965.EPI-10-0318 PMID:20615886

Bräuner EV, Andersen CE, Andersen HP, Gravesen P, Lind M, Ulbak K, et al. (2010). Is there any interaction between domestic radon exposure and air pollution from traffic in relation to childhood leukemia risk? Cancer Causes Control. 21(11):1961–4. https://doi.org/10.1007/s10552-010-9608-4 PMID:20607382

Brennan CA, Garrett WS (2019). *Fusobacterium nucleatum* – symbiont, opportunist and oncobacterium. Nat Rev Microbiol. 17(3):156–66. https://doi.org/10.1038/s41579-018-0129-6 PMID:30546113

BRIMP (2020) Breast implant register annual report. Stockholm, Sweden: Swedish Breast Implant Registry. Available from: https://registercentrum.blob.core.windows.net/brimp/r/BRIMP-Annual-Report-2020--SkgiRSNRXF.pdf, accessed September 2024.

Brina KR, Carvalho TS, Ardenghi PG, Basso da Silva L (2018). Micronuclei and other nuclear anomalies in exfoliated buccal cells of urban solid waste collectors and recyclers in southern Brazil. Chemosphere. 193:1058–62. https://doi.org/10.1016/j.chemosphere.2017.11.119 PMID:29874732

Brink A, Richter I, Lutz U, Wanek P, Stopper H, Lutz WK (2009). Biological significance of DNA adducts: comparison of increments over background for various biomarkers of genotoxicity in L5178Y tk(+/−) mouse lymphoma cells treated with hydrogen peroxide and cumene hydroperoxide. Mutat Res. 678(2):123–8. https://doi.org/10.1016/j.mrgentox.2009.06.001 PMID:19539047

Brinton LA, Figueroa JD, Ansong D, Nyarko KM, Wiafe S, Yarney J, et al. (2018). Skin lighteners and hair relaxers as risk factors for breast cancer: results from the Ghana Breast Health Study. Carcinogenesis. 39(4):571–9. https://doi.org/10.1093/carcin/bgy002 PMID:29324997

Brinton LA, Moghissi KS, Scoccia B, Lamb EJ, Trabert B, Niwa S, et al. (2015). Effects of fertility drugs on cancers other than breast and gynecologic malignancies. Fertil Steril. 104(4):980–8. https://doi.org/10.1016/j.fertnstert.2015.06.045 PMID:26232746

Brinton LA, Westhoff CL, Scoccia B, Lamb EJ, Trabert B, Niwa S, et al. (2013). Fertility drugs and endometrial cancer risk: results from an extended follow-up of a large infertility cohort. Hum Reprod. 28(10):2813–21. https://doi.org/10.1093/humrep/det323 PMID:23943795

Bristol DW (2011). NTP 3-month toxicity studies of estragole (CAS no. 140-67-0) administered by gavage to F344/N rats and $B6C3F_1$ mice. Toxic Rep Ser. 82(82):1–111. https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/st_rpts/tox082.pdf PMID:21445103

Encyclopaedia Britannica (2022). Carbon disulfide. Chicago (IL), USA: Britannica Group. Available from: https://www.britannica.com/science/carbon-disulfide, accessed February 2024.

Brockmann PE, Gozal D, Villarroel L, Damiani F, Nuñez F, Cajochen C (2017). Geographic latitude and sleep duration: a population-based survey from the Tropic of Capricorn to the Antarctic Circle. Chronobiol Int. 34(3):373–81. https://doi.org/10.1080/07420528.2016.1277735 PMID:28128998

Broen K, Dickens J, Trangucci R, Ogwang MD, Tenge CN, Masalu N, et al. (2023). Burkitt lymphoma risk shows geographic and temporal associations with *Plasmodium falciparum* infections in Uganda, Tanzania, and Kenya. Proc Natl Acad Sci USA. 120(2):e2211055120. https://doi.org/10.1073/pnas.2211055120 PMID:36595676

Bronzato JD, Bomfim RA, Edwards DH, Crouch D, Hector MP, Gomes BPFA (2020). Detection of *Fusobacterium* in oral and head and neck cancer samples: a systematic review and meta-analysis. Arch Oral Biol. 112:104669. https://doi.org/10.1016/j.archoralbio.2020.104669 PMID:32028171

Brooks AM, Vornoli A, Kovi RC, Ton TVT, Xu M, Mashal A, et al. (2024). Genetic profiling of rat gliomas and cardiac schwannomas from life-time radiofrequency radiation exposure study using a targeted next-generation sequencing gene panel. PLoS One. 19(1):e0296699. https://doi.org/10.1371/journal.pone.0296699

Brouwers EE, Huitema AD, Beijnen JH, Schellens JH (2008). Long-term platinum retention after treatment with cisplatin and oxaliplatin. BMC Clin Pharmacol. 8(1):7. https://doi.org/10.1186/1472-6904-8-7 PMID:18796166

Brown LM, Blair A, Gibson R, Everett GD, Cantor KP, Schuman LM, et al. (1990). Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. Cancer Res. 50(20):6585–91. PMID: 2208120

Brózman O, Novák J, Bauer AK, Babica P (2020). Airborne PAHs inhibit gap junctional intercellular communication and activate MAPKs in human bronchial epithelial cell line. Environ Toxicol Pharmacol. 79:103422. https://doi.org/10.1016/j.etap.2020.103422 PMID:32492535

Brozmanová J, Mániková D, Vlčková V, Chovanec M (2010). Selenium: a double-edged sword for defense and offence in cancer. Arch Toxicol. 84(12):919–38. https://doi.org/10.1007/s00204-010-0595-8 PMID:20871980

Bruce N, Dherani M, Liu R, Hosgood HD 3rd, Sapkota A, Smith KR, et al. (2015). Does household use of biomass fuel cause lung cancer? A systematic review and evaluation of the evidence for the GBD 2010 study. Thorax. 70(5):433–41. https://doi.org/10.1136/thoraxjnl-2014-206625 PMID:25758120

Brugnone F, Perbellini L, Giuliari C, Cerpelloni M, Soave M (1994). Blood and urine concentrations of chemical pollutants in the general population. Med Lav. 85(5):370–89. PMID:7885292

Brulport A, Lencina C, Chagnon MC, Le Corre L, Guzylack-Piriou L (2021). Transgenerational effects on intestinal inflammation status in mice perinatally exposed to bisphenol S. Chemosphere. 262:128009. https://doi.org/10.1016/j.chemosphere.2020.128009 PMID:33182144

Brunborg G, Søderlund EJ, Holme JA, Dybing E (1996). Organ-specific and transplacental DNA damage and its repair in rats treated with 1,2-dibromo-3-chloropropane. Chem Biol Interact. 101(1):33–48. https://doi.org/10.1016/0009-2797(96)03709-X PMID:8665617

Brunekreef B, Strak M, Chen J, Andersen ZJ, Atkinson R, Bauwelinck M, et al. (2021). Mortality and morbidity effects of long-term exposure to low-level $PM_{2.5}$, BC, NO_2, and O_3: an analysis of European cohorts in the ELAPSE project. Res Rep Health Eff Inst. 2021(208):1–127. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9476567/ PMID:36106702

Brusick D, Grotz VL, Slesinski R, Kruger CL, Hayes AW (2010). The absence of genotoxicity of sucralose. Food Chem Toxicol. 48(11):3067–72. https://doi.org/10.1016/j.fct.2010.07.047 PMID:20691239

Bu H, Tang S, Liu G, Miao C, Zhou X, Yang H, et al. (2023). In silico, in vitro and in vivo studies: dibutyl phthalate promotes prostate cancer cell proliferation by activating forkhead box M1 and remission after natura-α pretreatment. Toxicology. 488:153465. https://doi.org/10.1016/j.tox.2023.153465 PMID:36828243

Bua L, Tibaldi E, Falcioni L, Lauriola M, De Angelis L, Gnudi F, et al. (2018). Results of lifespan exposure to continuous and intermittent extremely low frequency electromagnetic fields (ELFEMF) administered alone to Sprague Dawley rats. Environ Res. 164:271–9. https://doi.org/10.1016/j.envres.2018.02.036 PMID:29549848

Bucclarelli E (1981). Mammary tumor induction in male and female Sprague-Dawley rats by adriamycin and daunomycin. J Natl Cancer Inst. 66(1):81–4. https://academic.oup.com/jnci/article-abstract/66/1/81/921352?redirectedFrom=PDF PMID:6935469

Bucheli-Witschel M, Egli T (2001). Environmental fate and microbial degradation of aminopolycarboxylic acids. FEMS Microbiol Rev. 25(1):69–106. https://doi.org/10.1111/j.1574-6976.2001.tb00572.x PMID:11152941

Budiu RA, Vlad AM, Nazario L, Bathula C, Cooper KL, Edmed J, et al. (2017). Restraint and social isolation stressors differentially regulate adaptive immunity and tumor angiogenesis in a breast cancer mouse model. Cancer Clin Oncol. 6(1):12–24. https://doi.org/10.5539/cco.v6n1p12https://doi.org/10.5539/cco.v6n1p12 PMID:28603578

Buffler PA, Wood SM, Suarez L, Kilian DJ (1978). Mortality follow-up of workers exposed to 1,4-dioxane. J Occup Med. 20(4):255–9. https://journals.lww.com/joem/abstract/1978/04000/mortality_follow_up_of_workers_exposed_to.6.aspx PMID:641607

Bugaiski-Shaked A, Shany E, Mesner O, Sergienko R, Wainstock T (2022). Association between neonatal phototherapy exposure and childhood neoplasm. J Pediatr. 245:111–6. https://doi.org/10.1016/j.jpeds.2022.01.046 PMID:35120988

Bukowska B, Michałowicz J, Krokosz A, Sicińska P (2007). Comparison of the effect of phenol and its derivatives on protein and free radical formation in human erythrocytes (in vitro). Blood Cells Mol Dis. 39(3):238–44. https://doi.org/10.1016/j.bcmd.2007.06.003https://doi.org/10.1016/j.bcmd.2007.06.003 PMID:17651993

Bukowska B, Wieteska P, Kwiatkowska M, Sicińska P, Michalowicz J (2016). Evaluation of the effect of 2,4-dichlorophenol on oxidative parameters and viability of human blood mononuclear cells (in vitro). Hum Exp Toxicol. 35(7):775–84. https://doi.org/10.1177/0960327115606789 PMID:26391574

Buller ID, Patel DM, Weyer PJ, Prizment A, Jones RR, Ward MH (2021). Ingestion of nitrate and nitrite and risk of stomach and other digestive system cancers in the Iowa Women's Health Study. Int J Environ Res Public Health. 18(13):6822. https://doi.org/10.3390/ijerph18136822https://doi.org/10.3390/ijerph18136822 PMID:34202037

Bullman S, Pedamallu CS, Sicinska E, Clancy TE, Zhang X, Cai D, et al. (2017). Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer. Science. 358(6369):1443–8. https://doi.org/10.1126/science.aal5240 PMID:29170280

Bunch KJ, Swanson J, Vincent TJ, Murphy MF (2016). Epidemiological study of power lines and childhood cancer in the UK: further analyses. J Radiol Prot. 36(3):437–55. https://doi.org/10.1088/0952-4746/36/3/437 PMID:27356108

Burdock GA (2010). Fenaroli's handbook of flavor ingredients. Sixth edition. Boca Raton (FL), USA: CRC Press, Taylor & Francis Group. Available from: https://www.taylorfrancis.com/books/mono/10.1201/9781439847503/fenaroli-handbook-flavor-ingredients-george-burdock.

Burkey JL, Sauer JM, McQueen CA, Sipes IG (2000). Cytotoxicity and genotoxicity of methyleugenol and related congeners – a mechanism of activation for methyleugenol. Mutat Res. 453(1):25–33. https://doi.org/10.1016/S0027-5107(00)00070-1 PMID:11006409

Burman DM, Shertzer HG, Senft AP, Dalton TP, Genter MB (2003). Antioxidant perturbations in the olfactory mucosa of alachlor-treated rats. Biochem Pharmacol. 66(9):1707–15. https://doi.org/10.1016/S0006-2952(03)00475-1 PMID:14563481

Burns LA, Bradley SG, White KL, McCay JA, Fuchs BA, Stern M, et al. (1994). Immunotoxicity of 2,4-diaminotoluene in female $B6C3F_1$ mice. Drug Chem Toxicol. 17(3):401–36. https://doi.org/10.3109/01480549409017865 PMID:7988388

Bury F, Iguyovwe V, Trivett M, Baraitser P (2023). Patterns of use of emergency and oral contraceptives from an online service in the United Kingdom during the COVID-19 pandemic: a quantitative study of routinely collected data. Contraception. 122:109992. https://doi.org/10.1016/j.contraception.2023.109992 PMID:36849031

Busby WF Jr, Goldman ME, Newberne PM, Wogan GN (1984). Tumorigenicity of fluoranthene in a newborn mouse lung adenoma bioassay. Carcinogenesis. 5(10):1311–6. https://doi.org/10.1093/carcin/5.10.1311 PMID:6488452

Busby WF Jr, Stevens EK, Martin CN, Chow FL, Garner RC (1989). Comparative lung tumorigenicity of parent and mononitro-polynuclear aromatic hydrocarbons in the BLU:Ha newborn mouse assay. Toxicol Appl Pharmacol. 99(3):555–63. https://doi.org/10.1016/0041-008X(89)90162-2 PMID:2749740

Busch RH, Filipy RE, Karagianes MT, Palmer RF (1981). Pathologic changes associated with experimental exposure of rats to coal dust. Environ Res. 24(1):53–60. https://doi.org/10.1016/0013-9351(81)90131-6 PMID:7215328

Buss LA, Hock B, Merry TL, Ang AD, Robinson BA, Currie MJ, et al. (2021). Effect of immune modulation on the skeletal muscle mitochondrial exercise response: an exploratory study in mice with cancer. PLoS One. 16(10):e0258831. https://doi.org/10.1371/journal.pone.0258831https://doi.org/10.1371/journal.pone.0258831 PMID:34665826

Bustamante J, Dock L, Vahter M, Fowler B, Orrenius S (1997). The semiconductor elements arsenic and indium induce apoptosis in rat thymocytes. Toxicology. 118(2–3):129–36. https://doi.org/10.1016/S0300-483X(96)03607-4 PMID:9129167

Bustami RT, Ojo AO, Wolfe RA, Merion RM, Bennett WM, McDiarmid SV, et al. (2004). Immunosuppression and the risk of post-transplant malignancy among cadaveric first kidney transplant recipients. Am J Transplant. 4(1):87–93. https://doi.org/10.1046/j.1600-6135.2003.00274.x PMID:14678038

Busund M, Bugge NS, Braaten T, Waaseth M, Rylander C, Lund E (2018). Progestin-only and combined oral contraceptives and receptor-defined premenopausal breast cancer risk: The Norwegian Women and Cancer Study. Int J Cancer. 142(11):2293–302. https://doi.org/10.1002/ijc.31266 PMID:29349773

Butler WH, Cohen SH, Squire RA (1997). Mesenchymal tumors of the mouse urinary bladder with vascular and smooth muscle differentiation. Toxicol Pathol. 25(3):268–74. https://doi.org/10.1177/019262339702500304 PMID:9210258

Butler WH, Gabriel KL, Osimitz TG, Preiss FJ (1998). Oncogenicity studies of piperonyl butoxide in rats and mice. Hum Exp Toxicol. 17(6):323–30. https://doi.org/10.1177/096032719801700607https://doi.org/10.1177/096032719801700607 PMID:9688356

Butler WH, Gabriel KL, Preiss FJ, Osimitz TG (1996). Lack of genotoxicity of piperonyl butoxide. Mutat Res. 371(3–4):249–58. https://doi.org/10.1016/S0165-1218(96)90113-5https://doi.org/10.1016/S0165-1218(96)90113-5 PMID:9008726

Byford JR, Shaw LE, Drew MG, Pope GS, Sauer MJ, Darbre PD (2002). Oestrogenic activity of parabens in MCF7 human breast cancer cells. J Steroid Biochem Mol Biol. 80(1):49–60. https://doi.org/10.1016/S0960-0760(01)00174-1https://doi.org/10.1016/S0960-0760(01)00174-1 PMID:11867263

Byrd RA, Sorden SD, Ryan T, Pienkowski T, LaRock R, Quander R, et al. (2015). Chronic toxicity and carcinogenicity studies of the long-acting GLP-1 receptor agonist dulaglutide in rodents. Endocrinology. 156(7):2417–28. https://doi.org/10.1210/en.2014-1722 PMID:25860029

Byrley P, Boyes WK, Rogers K, Jarabek AM (2021). 3D printer particle emissions: translation to internal dose in adults and children. J Aerosol Sci. 154:1–12. https://doi.org/10.1016/j.jaerosci.2021.105765 PMID:35999899

Byrley P, George BJ, Boyes WK, Rogers K (2019). Particle emissions from fused deposition modeling 3D printers: evaluation and meta-analysis. Sci Total Environ. 655:395–407. https://doi.org/10.1016/j.scitotenv.2018.11.070 PMID:30471608

Cabantous S, Hou X, Louis L, He H, Mariani O, Sastre X, et al. (2017). Evidence for an important role of host microRNAs in regulating hepatic fibrosis in humans infected with *Schistosoma japonicum.* Int J Parasitol.

47(13):823–30. https://doi.org/10.1016/j.ijpara.2017.05.007 PMID:28739251

Cadet JL, Jayanthi S, McCoy MT, Ladenheim B, Saint-Preux F, Lehrmann E, et al. (2013). Genome-wide profiling identifies a subset of methamphetamine (METH)-induced genes associated with METH-induced increased H4K5Ac binding in the rat striatum. BMC Genomics. 14(1):545. https://doi.org/10.1186/1471-2164-14-545https://doi.org/10.1186/1471-2164-14-545 PMID:23937714

Cadwell K, Liu JY, Brown SL, Miyoshi H, Loh J, Lennerz JK, et al. (2008). A key role for autophagy and the autophagy gene Atg16l1 in mouse and human intestinal Paneth cells. Nature. 456(7219):259–63. https://doi.org/10.1038/nature07416 PMID:18849966

Cahoon EK, Kitahara CM, Ntowe E, Bowen EM, Doody MM, Alexander BH, et al. (2015). Female estrogen-related factors and incidence of basal cell carcinoma in a nationwide US cohort. J Clin Oncol. 33(34):4058–65. https://doi.org/10.1200/JCO.2015.62.0625 PMID:26527779

Cai J, Yang Z, Zhao S, Ke X (2023a). Associations of dichlorophenol with metabolic syndrome based on multivariate-adjusted logistic regression: a US nationwide population-based study 2003–2016. Environ Health. 22(1):88. https://doi.org/10.1186/s12940-023-01037-z PMID:38102676

Cai M, Sun S, Wang J, Dong B, Yang Q, Tian L, et al. (2021). Sevoflurane preconditioning protects experimental ischemic stroke by enhancing anti-inflammatory microglia/macrophages phenotype polarization through GSK-3β/Nrf2 pathway. CNS Neurosci Ther. 27(11):1348–65. https://doi.org/10.1111/cns.13715https://doi.org/10.1111/cns.13715 PMID:34370899

Cai X, Ning C, Fan L, Li Y, Wang L, He H, et al. (2023b). Triclosan is associated with breast cancer via oxidative stress and relative telomere length. Front Public Health. 11:1163965. https://doi.org/10.3389/fpubh.2023.1163965 PMID:37213605

Caillard S, Dharnidharka V, Agodoa L, Bohen E, Abbott K (2005). Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation. 80(9):1233–43. https://doi.org/10.1097/01.tp.0000179639.98338.39 PMID:16314791

Cairat M, Al Rahmoun M, Gunter MJ, Heudel PE, Severi G, Dossus L, et al. (2021). Use of systemic glucocorticoids and risk of breast cancer in a prospective cohort of postmenopausal women. BMC Med. 19(1):186. https://doi.org/10.1186/s12916-021-02004-6 PMID:34340701

Cajochen C, Frey S, Anders D, Späti J, Bues M, Pross A, et al. (2011). Evening exposure to a light-emitting diodes (LED)-backlit computer screen affects circadian physiology and cognitive performance. J Appl Physiol. 110(5):1432–8. https://doi.org/10.1152/japplphysiol.00165.2011 PMID:21415172

Calafat AM, Ye X, Wong L-Y, Bishop AM, Needham LL (2010). Urinary concentrations of four parabens in the U.S. population: NHANES 2005–2006. Environ Health Perspect. 118(5):679–85. https://doi.org/10.1289/ehp.0901560https://doi.org/10.1289/ehp.0901560 PMID:20056562

Caldeira S, Zehbe I, Accardi R, Malanchi I, Dong W, Giarrè M, et al. (2003). The E6 and E7 proteins of the cutaneous human papillomavirus type 38 display transforming properties. J Virol. 77(3):2195–206. https://doi.org/10.1128/JVI.77.3.2195-2206.2003 PMID:12525654

Calderón-Segura ME, Gómez-Arroyo S, Cortés-Eslava J, Martínez-Valenzuela C, Mojica-Vázquez LH, Sosa-López M, et al. (2018). In vitro cytotoxicity and genotoxicity of Furia®180 SC (zeta-cypermethrin) and Bulldock 125®SC (β-cyfluthrin) pyrethroid insecticides in human peripheral blood lymphocytes. Toxicol Mech Methods. 28(4):268–78. https://doi.org/10.1080/15376516.2017.1402977 PMID:29129129

Calip GS, Malmgren JA, Lee WJ, Schwartz SM, Kaplan HG (2015). Myelodysplastic syndrome and acute myeloid leukemia following adjuvant chemotherapy with and without granulocyte colony-stimulating factors for breast cancer. Breast Cancer Res Treat. 154(1):133–43. https://doi.org/10.1007/s10549-015-3590-1 PMID:26450505

Callaghan RC, Allebeck P, Akre O, McGlynn KA, Sidorchuk A (2017). Cannabis use and incidence of testicular cancer: a 42-year follow-up of Swedish men between 1970 and 2011. Cancer Epidemiol Biomarkers Prev. 26(11):1644–52. https://doi.org/10.1158/1055-9965.EPI-17-0428 PMID:29093004

Callahan CL, Stewart PA, Blair A, Purdue MP (2019). Extended mortality follow-up of a cohort of dry cleaners. Epidemiology. 30(2):285–90. https://doi.org/10.1097/EDE.0000000000000951 PMID:30721169

Callahan CL, Stewart PA, Friesen MC, Locke S, De Roos AJ, Cerhan JR, et al. (2018). Case–control investigation of occupational exposure to chlorinated solvents and non-Hodgkin's lymphoma. Occup Environ Med. 75(6):415–20. https://doi.org/10.1136/oemed-2017-104890 PMID:29588333

Camacho L, Lewis SM, Vanlandingham MM, Olson GR, Davis KJ, Patton RE, et al. (2019). A two-year toxicology study of bisphenol A (BPA) in Sprague-Dawley rats: CLARITY-BPA core study results. Food Chem Toxicol. 132:110728. https://doi.org/10.1016/j.fct.2019.110728 PMID:31365888

Campioli E, Duong TB, Deschamps F, Papadopoulos V (2015). Cyclohexane-1,2-dicarboxylic acid diisononyl ester and metabolite effects on rat epididymal stromal vascular fraction differentiation of adipose tissue. Environ Res. 140:145–56. https://doi.org/10.1016/j.envres.2015.03.036 PMID:25863588

Campioli E, Lau M, Papadopoulos V (2019). Effect of subacute and prenatal DINCH plasticizer exposure on rat dams and male offspring hepatic function: the role of PPAR-α. Environ Res. 179 Pt A:108773. https://doi.org/10.1016/j.envres.2019.108773 PMID:31605871

Campos-Rodriguez F, Martinez-Garcia MA, Martinez M, Duran-Cantolla J, Peña ML, Masdeu MJ, et al.; Spanish Sleep Network (2013). Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort. Am J Respir Crit Care Med. 187(1):99–105. https://doi.org/10.1164/rccm.201209-1671OC PMID:23155146

Candura F, Moscato G (1984). Do amines induce occupational asthma in workers manufacturing polyurethane foams? Br J Ind Med. 41(4):552–3. https://doi.org/10.1136/oem.41.4.552 PMID:6093853

Caner A (2021). *Toxoplasma gondii* could have a possible role in the cancer mechanism by modulating the host's cell response. Acta Trop. 220:105966. https://doi.org/10.1016/j.actatropica.2021.105966 PMID:34023305

Cannella D, Brenier-Pinchart MP, Braun L, van Rooyen JM, Bougdour A, Bastien O, et al. (2014). miR-146a and miR-155 delineate a microRNA fingerprint associated with *Toxoplasma* persistence in the host brain. Cell Rep. 6(5):928–37. https://doi.org/10.1016/j.celrep.2014.02.002 PMID:24582962

Cantor KP, Villanueva CM, Silverman DT, Figueroa JD, Real FX, Garcia-Closas M, et al. (2010). Polymorphisms in GSTT1, GSTZ1, and CYP2E1, disinfection by-products, and risk of bladder cancer in Spain. Environ Health Perspect. 118(11):1545–50. https://doi.org/10.1289/ehp.1002206 PMID:20675267

Cao G, González J, Ortiz Fragola JP, Muller A, Tumarkin M, Moriondo M, et al. (2021). Structural changes in endocrine pancreas of male Wistar rats due to chronic cola drink consumption. Role of PDX-1. PLoS One. 16(6):e0243340. https://doi.org/10.1371/journal.pone.0243340 PMID:34115756

Cao M, Pan C, Tian Y, Wang L, Zhao Z, Zhu B (2023). Glucagon-like peptide 1 receptor agonists and the potential risk of pancreatic carcinoma: a pharmacovigilance study using the FDA Adverse Event Reporting System and literature visualization analysis. Int J Clin Pharm. 45(3):689–97. https://doi.org/10.1007/s11096-023-01556-2https://doi.org/10.1007/s11096-023-01556-2 PMID:36977858

Cao W, Han J, Yuan Y, Xu Z, Yang S, He W (2016). Drinking water: a risk factor for high incidence of esophageal cancer in Anyang, China. Environ Geochem Health. 38(3):773–82. https://doi.org/10.1007/s10653-015-9760-6https://doi.org/10.1007/s10653-015-9760-6 PMID:26399884

Cao Y, Lu J, Lu J (2020). Paternal smoking before conception and during pregnancy is associated with an increased risk of childhood acute lymphoblastic leukemia: a systematic review and meta-analysis of 17 case–control studies. J Pediatr Hematol Oncol. 42(1):32–40. https://doi.org/10.1097/MPH.0000000000001657 PMID:31743318

Caraballo-Arias Y, Roccuzzo F, Graziosi F, Danilevskaia N, Rota S, Zunarellli C, et al. (2023). Quantitative assessment of asbestos fibers in abdominal organs: a scoping review. Med Lav. 114(6):e2023048. PMID:38060208

Cardona B, Rudel RA (2021). Application of an *in vitro* assay to identify chemicals that increase estradiol and progesterone synthesis and are potential breast cancer risk factors. Environ Health Perspect. 129(7):77003. https://doi.org/10.1289/EHP8608 PMID:34287026

Cariati F, Carbone L, Conforti A, Bagnulo F, Peluso SR, Carotenuto C, et al. (2020). Bisphenol A-induced epigenetic changes and its effects on the male reproductive system. Front Endocrinol (Lausanne). 11:453. https://doi.org/10.3389/fendo.2020.00453 PMID:32849263

Carles C, Esquirol Y, Turuban M, Piel C, Migault L, Pouchieu C, et al. (2020). Residential proximity to power lines

and risk of brain tumor in the general population. Environ Res. 185:109473. https://doi.org/10.1016/j.envres.2020.109473 PMID:32278161

Carmen JC, Sinai AP (2007). Suicide prevention: disruption of apoptotic pathways by protozoan parasites. Mol Microbiol. 64(4):904–16. https://doi.org/10.1111/j.1365-2958.2007.05714.x PMID:17501916

Carpenter LM, Swerdlow AJ, Fear NT (1997). Mortality of doctors in different specialties: findings from a cohort of 20000 NHS hospital consultants. Occup Environ Med. 54(6):388–95. https://doi.org/10.1136/oem.54.6.388https://doi.org/10.1136/oem.54.6.388 PMID:9245944

Carr E, Aslam-Pervez B (2022). Does the use of alcohol mouthwash increase the risk of developing oral cancer? Evid Based Dent. 23(1):28–9. https://doi.org/10.1038/s41432-022-0236-0 PMID:35338325

Carr MJ, Sun J, Eroglu Z, Zager JS (2020). An evaluation of encorafenib for the treatment of melanoma. Expert Opin Pharmacother. 21(2):155–61. https://doi.org/10.1080/14656566.2019.1694664 PMID:31790307

Carreón T, Hein MJ, Hanley KW, Viet SM, Ruder AM (2014). Coronary artery disease and cancer mortality in a cohort of workers exposed to vinyl chloride, carbon disulfide, rotating shift work, and o-toluidine at a chemical manufacturing plant. Am J Ind Med. 57(4):398–411. https://doi.org/10.1002/ajim.22299 PMID:24464642

Carson SA, Kallen AN (2021). Diagnosis and management of infertility: a review. JAMA. 326(1):65–76. https://doi.org/10.1001/jama.2021.4788 PMID:34228062

Carstea ED, Miller SP, Christakis H, O'Neill RR (1993). Analogues of butyric acid that increase the expression of transfected DNAs. Biochem Biophys Res Commun. 192(2):649–56. https://doi.org/10.1006/bbrc.1993.1464https://doi.org/10.1006/bbrc.1993.1464 PMID:8484774

Carta G, Murru E, Banni S, Manca C (2017). Palmitic acid: physiological role, metabolism and nutritional implications. Front Physiol. 8:902. https://doi.org/10.3389/fphys.2017.00902https://doi.org/10.3389/fphys.2017.00902 PMID:29167646

Carter JJ, Paulson KG, Wipf GC, Miranda D, Madeleine MM, Johnson LG, et al. (2009). Association of Merkel cell polyomavirus-specific antibodies with Merkel cell carcinoma. J Natl Cancer Inst. 101(21):1510–22. https://doi.org/10.1093/jnci/djp332 PMID:19776382

Carton T, Tan XD, Hartemann P, Joyeux M (2007). Use of genotypic selection to detect P53 codon 273 CGT>CTT transversion: application to an occupationally exposed population. Int J Hyg Environ Health. 210(1):69–77. https://doi.org/10.1016/j.ijheh.2006.07.001 PMID:16949342

Cartus AT, Lachenmeier DW, Guth S, Roth A, Baum M, Diel P, et al. (2023). Acetaldehyde as a food flavoring substance: aspects of risk assessment. Mol Nutr Food Res. 67(23):e2200661. https://doi.org/10.1002/mnfr.202200661 PMID:37840378

Castaño-Vinyals G, Sadetzki S, Vermeulen R, Momoli F, Kundi M, Merletti F, et al. (2022). Wireless phone use in childhood and adolescence and neuroepithelial brain tumours: Results from the international MOBI-Kids study. Environ Int. 160:107069. https://doi.org/10.1016/j.envint.2021.107069 PMID:34974237

Castiello F, Suárez B, Beneito A, Lopez-Espinosa MJ, Santa-Marina L, Lertxundi A, et al. (2023). Childhood exposure to non-persistent pesticides and pubertal development in Spanish girls and boys: evidence from the INMA (Environment and Childhood) cohort. Environ Pollut. 316(Pt 2):120571. https://doi.org/10.1016/j.envpol.2022.120571 PMID:36356884

Castorina R, Bradman A, Fenster L, Barr DB, Bravo R, Vedar MG, et al. (2010). Comparison of current-use pesticide and other toxicant urinary metabolite levels among pregnant women in the CHAMACOS cohort and NHANES. Environ Health Perspect. 118(6):856–63. https://doi.org/10.1289/ehp.0901568 PMID:20129873

Catalano T, Selvaggi F, Esposito DL, Cotellese R, Aceto GM (2023). Infectious agents induce Wnt/β-catenin pathway deregulation in primary liver cancers. Microorganisms. 11(7):1632. https://doi.org/10.3390/microorganisms11071632 PMID:37512809

Catanzaro I, Caradonna F, Barbata G, Saverini M, Mauro M, Sciandrello G (2012). Genomic instability induced by α-pinene in Chinese hamster cell line. Mutagenesis. 27(4):463–9. https://doi.org/10.1093/mutage/ges005 PMID:22379123

Catenza CJ, Farooq A, Shubear NS, Donkor KK (2021). A targeted review on fate, occurrence, risk and health

implications of bisphenol analogues. Chemosphere. 268:129273. https://doi.org/10.1016/j.chemosphere.2020.129273 PMID:33352513

Cavas T (2011). In vivo genotoxicity evaluation of atrazine and atrazine-based herbicide on fish *Carassius auratus* using the micronucleus test and the comet assay. Food Chem Toxicol. 49(6):1431–5. https://doi.org/10.1016/j.fct.2011.03.038 PMID:21443921

Caverly Rae JM, Craig L, Slone TW, Frame SR, Buxton LW, Kennedy GL (2015). Evaluation of chronic toxicity and carcinogenicity of ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate in Sprague-Dawley rats. Toxicol Rep. 2:939–49. https://doi.org/10.1016/j.toxrep.2015.06.001 PMID:28962433

Çayır A, Coskun M, Coskun M (2014). Micronuclei, nucleoplasmic bridges, and nuclear buds induced in human lymphocytes by the fungicide signum and its active ingredients (boscalid and pyraclostrobin). Environ Toxicol. 29(7):723–32. https://doi.org/10.1002/tox.21789 PMID:22730168

CDC (2000). Occupational fatalities associated with 2,4-dichlorophenol (2,4-DCP) exposure, 1980—1998. Atlanta (GA), USA: Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4923a3.htm, accessed September 2024.

CDC (2010). How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the Surgeon General. 3, Chemistry and Toxicology of Cigarette Smoke and Biomarkers of Exposure and Harm. Atlanta (GA), USA: Centers for Disease Control and Prevention. Available from: https://www.ncbi.nlm.nih.gov/books/NBK53014/, accessed March 2024.

CDC (2017). 2,4-Dichlorophenol. Biomonitoring Summary. Atlanta (GA), USA: National Biomonitoring Program, Centers for Disease Control and Prevention. Available from https://downloads.regulations.gov/EPA-HQ-OPP-2012-0330-0019/attachment_3.pdf , accessed December 2023.

CDC (2019a). E-cigarette, or vaping, products visual dictionary. Atlanta (GA), USA: Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/pdfs/ecigarette-or-vaping-products-visual-dictionary-508.pdf, accessed March 2024.

CDC (2019b). Fourth national report on human exposure to environmental chemicals, updated tables, January 2019. Atlanta (GA), USA: National Center for Environmental Health (U.S.) Division of Laboratory Sciences, Centers for Disease Control and Prevention. Available from: https://stacks.cdc.gov/view/cdc/75822

CDC (2021). 2021 Assisted reproductive technology (ART) fertility clinic and national summary report. Atlanta (GA), USA: Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/art/reports/2021/index.html, accessed March 2024.

CDC (2022a). Cannabis and public health. Atlanta (GA), USA: Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/marijuana/featured-topics/CBD.html, accessed October 2024.

CDC (2022b). Nutrition. Get the facts: sugar-sweetened beverages and consumption. Atlanta (GA), USA: Division of Nutrition, Physical Activity, and Obesity, National Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/nutrition/data-statistics/sugar-sweetened-beverages-intake.html, accessed March 2024.

CDC (2022c). National report on human exposure to environmental chemicals. Atlanta (GA), USA: National Center for Environmental Health (NCEH), Centers for Disease Control and Prevention. Available from: , accessed March 2024.

CDC (2024). Clinical care of head lice. Atlanta (GA), USA: Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/lice/hcp/clinical-care/, accessed October 2024.

Cejnar P, Smirnova TA, Kuckova S, Prochazka A, Zak I, Harant K, et al. (2022). Acute and chronic blood serum proteome changes in patients with methanol poisoning. Sci Rep. 12(1):21379. https://doi.org/10.1038/s41598-022-25492-9 PMID:36494437

Celotti L, Furlan D, Seccati L, Levis AG (1987). Interactions of nitrilotriacetic acid (NTA) with Cr(VI) compounds in the induction of gene mutations in cultured mammalian cells. Mutat Res. 190(1):35–9. https://doi.org/10.1016/0165-7992(87)90079-0 PMID:3796669

Cemeli E, Marcos R, Anderson D (2006). Genotoxic and antigenotoxic properties of selenium compounds in the in vitro micronucleus assay with human whole blood lymphocytes and TK6 lymphoblastoid cells. ScientificWorldJournal. 6:1202–10. https://doi.org/10.1100/tsw.2006.204 PMID:17013525

Cendoya E, Chiotta ML, Zachetti V, Chulze SN, Ramirez ML (2018). Fumonisins and fumonisin-producing *Fusarium* occurrence in wheat and wheat by products: a review. J Cereal Sci. 80:158–66. https://doi.org/10.1016/j.jcs.2018.02.010

Cerniglia CE, Freeman JP, Franklin W, Pack LD (1982a). Metabolism of azo dyes derived from benzidine, 3,3′-dimethyl-benzidine and 3,3′-dimethoxybenzidine to potentially carcinogenic aromatic amines by intestinal bacteria. Carcinogenesis. 3(11):1255–60. https://doi.org/10.1093/carcin/3.11.1255 PMID:7151244

Cerniglia CE, Freeman JP, Franklin W, Pack LD (1982b). Metabolism of benzidine and benzidine-congener based dyes by human, monkey and rat intestinal bacteria. Biochem Biophys Res Commun. 107(4):1224–9. https://doi.org/10.1016/S0006-291X(82)80128-9 PMID:6814437

Cestonaro LV, Marcolan AM, Rossato-Grando LG, Anzolin AP, Goethel G, Vilani A, et al. (2017). Ozone generated by air purifier in low concentrations: friend or foe? Environ Sci Pollut Res Int. 24(28):22673–8. https://doi.org/10.1007/s11356-017-9887-3 PMID:28812184

CFR (2024). 21 CFR Ch. I (4–1–23 Edition). Code of Federal Regulations. Washington (DC), USA: US Government Publishing Office. Available from: https://www.govinfo.gov/content/pkg/CFR-2023-title21-vol3/pdf/CFR-2023-title21-vol3-sec189-180.pdf, accessed March 2024.

Cha ES, Lee YK, Moon EK, Kim YB, Lee YJ, Jeong WC, et al. (2012). Paraquat application and respiratory health effects among South Korean farmers. Occup Environ Med. 69(6):398–403. https://doi.org/10.1136/oemed-2011-100244 PMID:22213838

Chahoud J, Semaan A, Chen Y, Cao M, Rieber AG, Rady P, et al. (2016). Association between β-genus human papillomavirus and cutaneous squamous cell carcinoma in immunocompetent individuals – a meta-analysis. JAMA Dermatol. 152(12):1354–64. https://doi.org/10.1001/jamadermatol.2015.4530 PMID:26720285

Chambers GM, Dyer S, Zegers-Hochschild F, de Mouzon J, Ishihara O, Banker M, et al. (2021). International Committee for Monitoring Assisted Reproductive Technologies world report: assisted reproductive technology, 2014. Hum Reprod. 36(11):2921–34. https://doi.org/10.1093/humrep/deab198 PMID:34601605

Chambers T, Douwes J, Mannetje A, Woodward A, Baker M, Wilson N, et al. (2022). Nitrate in drinking water and cancer risk: the biological mechanism, epidemiological evidence and future research. Aust N Z J Public Health. 46(2):105–8. https://doi.org/10.1111/1753-6405.13222https://doi.org/10.1111/1753-6405.13222 PMID:35238441

Chamian F, Lowes MA, Lin SL, Lee E, Kikuchi T, Gilleaudeau P, et al. (2005). Alefacept reduces infiltrating T cells, activated dendritic cells, and inflammatory genes in psoriasis vulgaris. Proc Natl Acad Sci USA. 102(6):2075–80. https://doi.org/10.1073/pnas.0409569102 PMID:15671179

Chamlal N, Benouareth DE, Khallef M, Simar-Mentières S, Nesslany F (2021). Mutagenicity and genotoxicity assessments of some industrially processed meat products in Algeria. Toxicol In Vitro. 73:105145. https://doi.org/10.1016/j.tiv.2021.105145 PMID:33737049

Champion WM, Warren SH, Kooter IM, Preston W, Krantz QT, DeMarini DM, et al. (2020). Mutagenicity- and pollutant-emission factors of pellet-fueled gasifier cookstoves: comparison with other combustion sources. Sci Total Environ. 739:139488. https://doi.org/10.1016/j.scitotenv.2020.139488 PMID:32526531

Chan DSM, Abar L, Cariolou M, Nanu N, Greenwood DC, Bandera EV, et al. (2019). World Cancer Research Fund International: Continuous Update Project – systematic literature review and meta-analysis of observational cohort studies on physical activity, sedentary behavior, adiposity, and weight change and breast cancer risk. Cancer Causes Control. 30(11):1183–200. https://doi.org/10.1007/s10552-019-01223-w PMID:31471762

Chan HH, Yang CH, Leung JC, Wei WI, Lai KN (2007). An animal study of the effects on p16 and PCNA expression of repeated treatment with high-energy laser and intense pulsed light exposure. Lasers Surg Med. 39(1):8–13. https://doi.org/10.1002/lsm.20447 PMID:17115383

Chandra M, Frith CH (1994). Spontaneous renal lesions in CD-1 and B6C3F_1 mice. Exp Toxicol Pathol. 46(3):189–98. https://doi.org/10.1016/S0940-2993(11)80080-1 PMID:8000238

Chandwani ND, Pawar MG, Tupkari JV, Yuwanati M (2014). Histological evaluation to study the effects of dental amalgam and composite restoration on human dental pulp: an in vivo study. Med Princ Pract. 23(1):40–4. https://doi.org/10.1159/000355607 PMID:24217468

Chang CJ, O'Brien KM, Keil AP, Gaston SA, Jackson CL, Sandler DP, et al. (2022). Use of straighteners and other hair products and incident uterine cancer. J Natl Cancer Inst. 114(12):1636–45. https://doi.org/10.1093/jnci/djac165 PMID:36245087

Chang K, Gunter MJ, Rauber F, Levy RB, Huybrechts I, Kliemann N, et al. (2023a). Ultra-processed food consumption, cancer risk and cancer mortality: a large-scale prospective analysis within the UK Biobank. EClinicalMedicine. 56:101840. https://doi.org/10.1016/j.eclinm.2023.101840 PMID:36880051

Chang MC, Chang HH, Chan CP, Yeung SY, Hsien HC, Lin BR, et al. (2014). *p*-Cresol affects reactive oxygen species generation, cell cycle arrest, cytotoxicity and inflammation/atherosclerosis-related modulators production in endothelial cells and mononuclear cells. PLoS One. 9(12):e114446. https://doi.org/10.1371/journal.pone.0114446 PMID:25517907

Chang PT, Hung PC, Tsai SW (2018b). Occupational exposures of flour dust and airborne chemicals at bakeries in Taiwan. J Occup Environ Hyg. 15(8):580–7. https://doi.org/10.1080/15459624.2018.1470634 PMID:29708861

Chang S, Butenhoff JL, Parker GA, Coder PS, Zitzow JD, Krisko RM, et al. (2018a). Reproductive and developmental toxicity of potassium perfluorohexanesulfonate in CD-1 mice. Toxicol Sci. 78:150–68. https://doi.org/10.1016/j.reprotox.2018.04.007https://doi.org/10.1016/j.reprotox.2018.04.007PMID:29694846

Chang VC, Andreotti G, Ospina M, Parks CG, Liu D, Shearer JJ, et al. (2023b). Glyphosate exposure and urinary oxidative stress biomarkers in the Agricultural Health Study. J Natl Cancer Inst. 115(4):394–404. https://doi.org/10.1093/jnci/djac242 PMID:36629488

Chang VC, Rhee J, Berndt SI, Moore SC, Freedman ND, Jones RR, et al. (2023c). Serum perfluorooctane sulfonate and perfluorooctanoate and risk of postmenopausal breast cancer according to hormone receptor status: an analysis in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Int J Cancer. 153(4):775–82. https://doi.org/10.1002/ijc.34487https://doi.org/10.1002/ijc.34487 PMID:36843273

Channa KR, Röllin HB, Wilson KS, Nøst TH, Odland JO, Naik I, et al. (2012). Regional variation in pesticide concentrations in plasma of delivering women residing in rural Indian Ocean coastal regions of South Africa. J Environ Monit. 14(11):2952–60. https://doi.org/10.1039/c2em30264k PMID:23047303

Chao C, Jacobson LP, Tashkin D, Martínez-Maza O, Roth MD, Margolick JB, et al. (2009). Recreational amphetamine use and risk of HIV-related non-Hodgkin lymphoma. Cancer Causes Control. 20(5):509–16. https://doi.org/10.1007/s10552-008-9258-y PMID:19011979

Chappell GA, Borghoff SJ, Pham LL, Doepker CL, Wikoff DS (2020). Lack of potential carcinogenicity for sucralose – systematic evaluation and integration of mechanistic data into the totality of the evidence. Food Chem Toxicol. 135:110898. https://doi.org/10.1016/j.fct.2019.110898 PMID:31654706

Chappell GA, Heintz MM, Haws LC (2021). Transcriptomic analyses of livers from mice exposed to 1,4-dioxane for up to 90 days to assess potential mode(s) of action underlying liver tumor development. Curr Res Toxicol. 2:30–41. https://doi.org/10.1016/j.crtox.2021.01.003 PMID:34345848

Charles JM, Tobia A, van Ravenzwaay B (2000). Subchronic and chronic toxicological investigations on metiram: the lack of a carcinogenic response in rodents. Toxicol Sci. 54(2):481–92. https://doi.org/10.1093/toxsci/54.2.481 PMID:10774831

Chatelan A, Lebacq T, Rouche M, Kelly C, Fismen AS, Kalman M, et al. (2022). Long-term trends in the consumption of sugary and diet soft drinks among adolescents: a cross-national survey in 21 European countries. Eur J Nutr. 61(5):2799–813. https://doi.org/10.1007/s00394-022-02851-w PMID:35290478

Chaube SK, Prasad PV, Thakur SC, Shrivastav TG (2005). Estradiol protects clomiphene citrate-induced apoptosis in ovarian follicular cells and ovulated cumulus-oocyte complexes. Fertil Steril. 84 Suppl 2:1163–72. https://doi.org/10.1016/j.fertnstert.2005.03.073 PMID:16210008

Chaurasia M, Singh R, Sur S, Flora SJS (2023). A review of FDA approved drugs and their formulations for the treatment of breast cancer. Front Pharmacol. 14:1184472. https://doi.org/10.3389/fphar.2023.1184472 PMID:37576816

Chazelas E, Srour B, Desmetz E, Kesse-Guyot E, Julia C, Deschamps V, et al. (2019). Sugary drink consumption and risk of cancer: results from NutriNet-Santé prospective cohort. BMJ. 366:l2408. https://doi.org/10.1136/bmj.l2408 PMID:31292122

Checkoway H, Ray RM, Lundin JI, Astrakianakis G, Seixas NS, Camp JE, et al. (2011). Lung cancer and occupational exposures other than cotton dust and endotoxin among women textile workers in Shanghai, China. Occup Environ Med. 68(6):425–9. https://doi.org/10.1136/oem.2010.059519 PMID:21131604

Checkoway H, Wilcosky T, Wolf P, Tyroler H (1984). An evaluation of the associations of leukemia and rubber industry solvent exposures. Am J Ind Med. 5(3):239–49. https://doi.org/10.1002/ajim.4700050307 PMID:6702828

ChemicalBook (2023). 2,4-Dimethylphenol. CAS database list. Beijing, China: ChemicalBook. Available from: https://www.chemicalbook.com/ChemicalProductProperty_EN_CB6125178.htm, accessed February 2024.

Chen C, Arjomandi M, Qin H, Balmes J, Tager I, Holland N (2006a). Cytogenetic damage in buccal epithelia and peripheral lymphocytes of young healthy individuals exposed to ozone. Mutagenesis. 21(2):131–7. https://doi.org/10.1093/mutage/gel007 PMID:16513656

Chen CL, Chi CW, Chang KW, Liu TY (1999). Safrole-like DNA adducts in oral tissue from oral cancer patients with a betel quid chewing history. Carcinogenesis. 20(12):2331–4. https://doi.org/10.1093/carcin/20.12.2331 PMID:10590228

Chen CL, Yang PH, Kao YC, Chen PY, Chung CL, Wang SW (2017). Pentabromophenol suppresses TGF-β signaling by accelerating degradation of type II TGF-β receptors via caveolae-mediated endocytosis. Sci Rep. 7(1):43206. https://doi.org/10.1038/srep43206 PMID:28230093

Chen CS, Hseu YC, Liang SH, Kuo JY, Chen SC (2008). Assessment of genotoxicity of methyl-tert-butyl ether, benzene, toluene, ethylbenzene, and xylene to human lymphocytes using comet assay. J Hazard Mater. 153(1–2):351–6. https://doi.org/10.1016/j.jhazmat.2007.08.053 PMID:17900805

Chen HW, Su SF, Chien CT, Lin WH, Yu SL, Chou CC, et al. (2006b). Titanium dioxide nanoparticles induce emphysema-like lung injury in mice. FASEB J. 20(13):2393–5. https://doi.org/10.1096/fj.06-6485fje PMID:17023518

Chen J, Ahn KC, Gee NA, Gee SJ, Hammock BD, Lasley BL (2007). Antiandrogenic properties of parabens and other phenolic containing small molecules in personal care products. Toxicol Appl Pharmacol. 221(3):278–84. https://doi.org/10.1016/j.taap.2007.03.015https://doi.org/10.1016/j.taap.2007.03.015 PMID:17481686

Chen J, Wellens J, Kalla R, Fu T, Deng M, Zhang H, et al. (2023a). Intake of ultra-processed foods is associated with an increased risk of Crohn's disease: a cross-sectional and prospective analysis of 187 154 participants in the UK Biobank. J Crohns Colitis. 17(4):535–52. https://doi.org/10.1093/ecco-jcc/jjac167 PMID:36305857

Chen J, Wen J, Tang Y, Shi J, Mu G, Yan R, et al. (2021a). Research progress on fumonisin B1 contamination and toxicity: a review. Molecules. 26(17):5238. https://doi.org/10.3390/molecules26175238 PMID:34500671

Chen KF, Tsai YP, Lai CH, Xiang YK, Chuang KY, Zhu ZH (2021b). Human health-risk assessment based on chronic exposure to the carbonyl compounds and metals emitted by burning incense at temples. Environ Sci Pollut Res Int. 28(30):40640–52. https://doi.org/10.1007/s11356-020-10313-1 PMID:32743699

Chen L, Gibbons DL, Goswami S, Cortez MA, Ahn YH, Byers LA, et al. (2014a). Metastasis is regulated via microRNA-200/ZEB1 axis control of tumour cell PD-L1 expression and intratumoral immunosuppression. Nat Commun. 5(1):5241. https://doi.org/10.1038/ncomms6241 PMID:25348003

Chen L, Liu WQ, Lei JH, Guan F, Li MJ, Song WJ, et al. (2012). Chronic *Schistosoma japonicum* infection reduces immune response to vaccine against hepatitis B in mice. PLoS One. 7(12):e51512. https://doi.org/10.1371/journal.pone.0051512 PMID:23272112

Chen M, Tse LA (2012). Laryngeal cancer and silica dust exposure: a systematic review and meta-analysis. Am J Ind Med. 55(8):669–76. https://doi.org/10.1002/ajim.22037 PMID:22457229

Chen P, Chen F, Zhou B (2019b). Systematic review and meta-analysis of prevalence of dermatological toxicities associated with vemurafenib treatment in patients with melanoma. Clin Exp Dermatol. 44(3):243–51. https://doi.org/10.1111/ced.13751 PMID:30280426

Chen QY, Costa M (2017). A comprehensive review of metal-induced cellular transformation studies. Toxicol Appl Pharmacol. 331:33–40. https://doi.org/10.1016/j.taap.2017.05.004 PMID:28506836

Chen QY, DesMarais T, Costa M (2019a). Metals and mechanisms of carcinogenesis. Annu Rev Pharmacol Toxicol. 59(1):537–54. https://doi.org/10.1146/annurev-pharmtox-010818-021031 PMID:30625284

Chen S, Gong Y, Luo Y, Cao R, Yang J, Cheng L, et al. (2023b). Toxic effects and toxicological mechanisms of chlorinated paraffins: a review for insight into species sensitivity and toxicity difference. Environ Int. 178:108020. https://doi.org/10.1016/j.envint.2023.108020https://doi.org/10.1016/j.envint.2023.108020 PMID:37354881

Chen T, Mei N, Fu PP (2010). Genotoxicity of pyrrolizidine alkaloids. J Appl Toxicol. 30(3):183–96. https://doi.org/10.1002/jat.1504 PMID:20112250

Chen T, Surcel HM, Lundin E, Kaasila M, Lakso HA, Schock H, et al. (2011). Circulating sex steroids during pregnancy and maternal risk of non-epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev. 20(2):324–36. https://doi.org/10.1158/1055-9965.EPI-10-0857 PMID:21177423

Chen W, Liu Y, Li M, Mao J, Zhang L, Huang R, et al. (2015). Anti-tumor effect of α-pinene on human hepatoma cell lines through inducing G2/M cell cycle arrest. J Pharmacol Sci. 127(3):332–8. https://doi.org/10.1016/j.jphs.2015.01.008https://doi.org/10.1016/j.jphs.2015.01.008 PMID:25837931

Chen WQ, Xu B, Mao JW, Wei FX, Li M, Liu T, et al. (2014b). Inhibitory effects of α-pinene on hepatoma carcinoma cell proliferation. Asian Pac J Cancer Prev. 15(7):3293–7. https://doi.org/10.7314/APJCP.2014.15.7.3293https://doi.org/10.7314/APJCP.2014.15.7.3293 PMID:24815485

Chen X, Mikhail SS, Ding YW, Yang G, Bondoc F, Yang CS (2000). Effects of vitamin E and selenium supplementation on esophageal adenocarcinogenesis in a surgical model with rats. Carcinogenesis. 21(8):1531–6. https://doi.org/10.1093/carcin/21.8.1531 PMID:10910955

Chen X, Xiang F, Cao X, Zou J, Zhang B, Ding X (2023c). Effects of *p*-cresol, a uremic toxin, on cancer cells. Transl Cancer Res. 12(2):367–74. https://doi.org/10.21037/tcr-22-2042 PMID:36915599

Chen X, Zhu Q, Li X, Huang T, Wang S, Wang Y, et al. (2019c). Pubertal exposure to tebuconazole increases testosterone production via inhibiting testicular aromatase activity in rats. Chemosphere. 230:519–26. https://doi.org/10.1016/j.chemosphere.2019.05.122 PMID:31125880

Chen XQ, Tan XD (2004). [Studies on DNA damage in workers with long-term exposure to lower concentration of carbon disulfide]. Zhonghua Yu Fang Yi Xue Za Zhi. 38(1):36–8. PMID:14989902 [Chinese]

Chen Y, Xu HS, Guo TL (2018). Modulation of cytokine/chemokine production in human macrophages by bisphenol A: a comparison to analogues and interactions with genistein. J Immunotoxicol. 15(1):96–103. https://doi.org/10.1080/1547691X.2018.1476629 PMID:29847185

Chen Y, Zhao C, Zheng J, Su N, Ji H (2023d). Discovery of the mechanism of *n*-propylparaben-promoting the proliferation of human breast adenocarcinoma cells by activating human estrogen receptors via metabolomics analysis. Hum Exp Toxicol. 42:9603271231171648. https://doi.org/10.1177/09603271231171648https://doi.org/10.1177/09603271231171648 PMID:37121592

Cheng G, Shi Y, Sturla SJ, Jalas JR, McIntee EJ, Villalta PW, et al. (2003). Reactions of formaldehyde plus acetaldehyde with deoxyguanosine and DNA: formation of cyclic deoxyguanosine adducts and formaldehyde cross-links. Chem Res Toxicol. 16(2):145–52. https://doi.org/10.1021/tx025614r PMID:12588185

Cheng M, Kligerman AD (1984). Evaluation of the genotoxicity of cresols using sister-chromatid exchange (SCE). Mutat Res. 137(1):51–5. https://doi.org/10.1016/0165-1218(84)90112-5https://doi.org/10.1016/0165-1218(84)90112-5 PMID:6749167

Cheng Y, Ling Z, Li L (2020). The intestinal microbiota and colorectal cancer. Front Immunol. 11:615056. https://doi.org/10.3389/fimmu.2020.615056 PMID:33329610

Cheong A, Zhang X, Cheung YY, Tang WY, Chen J, Ye SH, et al. (2016). DNA methylome changes by estradiol benzoate and bisphenol A links early-life environmental exposures to prostate cancer risk. Epigenetics. 11(9):674–89. https://doi.org/10.1080/15592294.2016.1208891https://doi.org/10.1080/15592294.2016.1208891 PMID:27415467

Chequer FM, Venâncio VP, Bianchi ML, Antunes LM (2012). Genotoxic and mutagenic effects of erythrosine B, a xanthene food dye, on HepG2 cells. Food Chem Toxicol. 50(10):3447–51. https://doi.org/10.1016/j.fct.2012.07.042 PMID:22847138

Cheung V, Yuen VM, Wong GTC, Choi SW (2019). The effect of sleep deprivation and disruption on DNA damage and health of doctors. Anaesthesia. 74(4):434–40. https://doi.org/10.1111/anae.14533 PMID:30675716

Cheung YL, Snelling J, Mohammed NN, Gray TJ, Ioannides C (1996). Interaction with the aromatic hydrocarbon receptor, CYP1A induction, and mutagenicity of a series of diaminotoluenes: implications for their carcinogenicity. Toxicol Appl Pharmacol. 139(1):203–11. https://doi.org/10.1006/taap.1996.0159 PMID:8685904

Chevinsky JR, Lee SH, Blanck HM, Park S (2021). Prevalence of self-reported intake of sugar-sweetened beverages among US adults in 50 states and the District of Columbia, 2010 and 2015. Prev Chronic Dis. 18:E35. https://doi.org/10.5888/pcd18.200434 PMID:33856977

Chevrier C, Serrano T, Lecerf R, Limon G, Petit C, Monfort C, et al. (2014). Environmental determinants of the urinary concentrations of herbicides during pregnancy: the PELAGIE mother–child cohort (France). Environ Int. 63:11–8. https://doi.org/10.1016/j.envint.2013.10.010 PMID:24246238

Chiang HC, Hughes M, Chang WL (2023a). The role of microbiota in esophageal squamous cell carcinoma: a review of the literature. Thorac Cancer. 14(28):2821–9. https://doi.org/10.1111/1759-7714.15096 PMID:37675608

Chiang PL, Hao WR, Hong HJ, Chen CC, Chiu CC, Fang YA, et al. (2023b). The effects of different types of sleep disorder on colorectal cancer: a nationwide population-based cohort study. Cancers (Basel). 15(19):4728. https://doi.org/10.3390/cancers15194728 PMID:37835421

Chien JM, Liang WZ, Liao WC, Kuo CC, Chou CT, Hao LJ, et al. (2019). Ca^{2+} movement and cytotoxicity induced by the pyrethroid pesticide bifenthrin in human prostate cancer cells. Hum Exp Toxicol. 38(10):1145–54. https://doi.org/10.1177/0960327119855129 PMID:31204517

Chinthakindi S, Kannan K (2021). Primary aromatic amines in indoor dust from 10 countries and associated human exposure. Environ Int. 157:106840. https://doi.org/10.1016/j.envint.2021.106840https://doi.org/10.1016/j.envint.2021.106840 PMID:34450547

Chinthakindi S, Kannan K (2022). Variability in urinary concentrations of primary aromatic amines. Sci Total Environ. 831:154768. https://doi.org/10.1016/j.scitotenv.2022.154768https://doi.org/10.1016/j.scitotenv.2022.154768 PMID:35341833

Chitsulo L, Engels D, Montresor A, Savioli L (2000). The global status of schistosomiasis and its control. Acta Trop. 77(1):41–51. https://doi.org/10.1016/S0001-706X(00)00122-4 PMID:10996119

Chiu HW, Xia T, Lee YH, Chen CW, Tsai JC, Wang YJ (2015). Cationic polystyrene nanospheres induce autophagic cell death through the induction of endoplasmic reticulum stress. Nanoscale. 7(2):736–46. https://doi.org/10.1039/C4NR05509H PMID:25429417

Chiu WY, Shih SR, Tseng CH (2012). A review on the association between glucagon-like peptide-1 receptor agonists and thyroid cancer. Exp Diabetes Res. 2012:924168. https://doi.org/10.1155/2012/924168https://doi.org/10.1155/2012/924168 PMID:22693487

Chlebowski RT, Anderson GL, Aragaki AK, Manson JE, Stefanick ML, Pan K, et al. (2020). Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the women's health initiative randomized clinical trials. JAMA. 324(4):369–80. https://doi.org/10.1001/jama.2020.9482 PMID:32721007

Cho S, Lee Y, Lee S, Choi YJ, Chung HW (2014). Enhanced cytotoxic and genotoxic effects of gadolinium following ELF–EMF irradiation in human lymphocytes. Drug Chem Toxicol. 37(4):440–7. https://doi.org/10.3109/01480545.2013.879662 PMID:24479558

Choi S, Yoon C, Kim S, Kim W, Ha K, Jeong J, et al. (2018). Comprehensive evaluation of hazardous chemical exposure control system at a semiconductor manufacturing company in South Korea. Int J Environ Res Public Health. 15(6):1162. https://doi.org/10.3390/ijerph15061162 PMID:29865268

Choi YH, Kim HJ, Sohn JR, Seo JH (2023). Occupational exposure to VOCs and carbonyl compounds in beauty salons and health risks associated with it in South Korea. Ecotoxicol Environ Saf. 256:114873. https://doi.org/10.1016/j.ecoenv.2023.114873 PMID:37043945

Choi YJ, Kim BS, Choi CY (2015). Effect of long-after glow phosphorescent pigment on reproductive parameters and ovarian maturation in the yellowtail damselfish, *Chrysiptera parasema*. Comp Biochem Physiol A Mol Integr Physiol. 182:113–20. https://doi.org/10.1016/j.cbpa.2014.12.012 PMID:25498352

Choi YJ, Park JW, Lim Y, Seo S, Hwang DY (2021). *In vivo* impact assessment of orally administered polystyrene nanoplastics: biodistribution, toxicity, and inflammatory response in mice. Nanotoxicology. 15(9):1180–98. https://doi.org/10.1080/17435390.2021.1996650 PMID:34731582

Chou MW, Fu PP (2006). Formation of DHP-derived DNA adducts in vivo from dietary supplements and Chinese herbal plant extracts containing carcinogenic pyrrolizidine alkaloids. Toxicol Ind Health. 22(8):321–7. https://doi.org/10.1177/0748233706071765https://doi.org/10.1177/0748233706071765 PMID:17120530

Chowdhury MA, Banik S, Uddin B, Moniruzzaman M, Karim N, Gan SH (2012). Organophosphorus and carbamate pesticide residues detected in water samples collected from paddy and vegetable fields of the Savar and Dhamrai Upazilas in Bangladesh. Int J Environ Res Public Health. 9(9):3318–29. https://doi.org/10.3390/ijerph9093318 PMID:23202689

Chowdhury R, Sarnat SE, Darrow L, McClellan W, Steenland K (2014). Mortality among participants in a lead surveillance program. Environ Res. 132:100–4. https://doi.org/10.1016/j.envres.2014.03.008 PMID:24769120

Chowdhury-Paulino IM, Hart JE, James P, Iyer HS, Wilt GE, Booker BD, et al. (2023). Association between outdoor light at night and prostate cancer in the Health Professionals Follow-up Study. Cancer Epidemiol Biomarkers Prev. 32(10):1444–50. https://doi.org/10.1158/1055-9965.EPI-23-0208 PMID:37462694

Christensen CH, Barry KH, Andreotti G, Alavanja MC, Cook MB, Kelly SP, et al. (2016). Sex steroid hormone single-nucleotide polymorphisms, pesticide use, and the risk of prostate cancer: a nested case–control study within the Agricultural Health Study. Front Oncol. 6:237. https://doi.org/10.3389/fonc.2016.00237 PMID:27917368

Chrustek A, Hołyńska-Iwan I, Dziembowska I, Bogusiewicz J, Wróblewski M, Cwynar A, et al. (2018). Current research on the safety of pyrethroids used as insecticides. Medicina (Kaunas). 54(4):61. https://doi.org/10.3390/medicina54040061 PMID:30344292

Chrz J, Dvořáková M, Kejlová K, Očadlíková D, Svobodová L, Malina L, et al. (2024). The potential for genotoxicity, mutagenicity and endocrine disruption in triclosan and triclocarban assessed through a combination of in vitro methods. J Xenobiot. 14(1):15–30. https://doi.org/10.3390/jox14010002PMID:38535491

Chteinberg E, Klufah F, Rennspiess D, Mannheims MF, Abdul-Hamid MA, Losen M, et al. (2019). Low prevalence of Merkel cell polyomavirus in human epithelial thymic tumors. Thorac Cancer. 10(3):445–51. https://doi.org/10.1111/1759-7714.12953 PMID:30628176

Chu FS, Li GY (1994). Simultaneous occurrence of fumonisin B1 and other mycotoxins in moldy corn collected from the People's Republic of China in regions with high incidences of esophageal cancer. Appl Environ Microbiol. 60(3):847–52. https://doi.org/10.1128/aem.60.3.847-852.1994 PMID:8161178

Chu H, Chan JF, Yuen KY (2022). Animal models in SARS-CoV-2 research. Nat Methods. 19(4):392–4. https://doi.org/10.1038/s41592-022-01447-w PMID:35396468

Chu CY, Kim SY, Pryhuber GS, Mariani TJ, McGraw MD (2024). Single-cell resolution of human airway epithelial cells exposed to bronchiolitis obliterans-associated chemicals. Am J Physiol Lung Cell Mol Physiol. 326(2):L135–48. https://doi.org/10.1152/ajplung.00304.2023 PMID:38084407

Chun YS, Yoshida T, Mori T, Huso DL, Zhang Z, Stearns V, et al. (2012). Intraductally administered pegylated liposomal doxorubicin reduces mammary stem cell function in the mammary gland but in the long term, induces malignant tumors. Breast Cancer Res Treat. 135(1):201–8. https://doi.org/10.1007/s10549-012-2138-x PMID:22752247

Chung YT, Chen CL, Wu CC, Chan SA, Chi CW, Liu TY (2008). Safrole-DNA adduct in hepatocellular carcinoma associated with betel quid chewing. Toxicol Lett. 183(1–3):21–7. https://doi.org/10.1016/j.toxlet.2008.09.013 PMID:18938230

Cioffi F, Senese R, Lasala P, Ziello A, Mazzoli A, Crescenzo R, et al. (2017). Fructose-rich diet affects mitochondrial DNA damage and repair in rats. Nutrients. 9(4):323. https://doi.org/10.3390/nu9040323 PMID:28338610

Cirla AM, Bertazzi PA, Tomasini M, Villa A, Graziano C, Invernizzi R, et al. (1978). Study of endocrinological functions and sexual behaviour in carbon disulphide workers. Med Lav. 69(2):118–29. PMID:661737

Citro G, Galati R, Verdina A, Marini S, Zito R, Giardina B (1993). Activation of 2,4-diaminotoluene to proximate carcinogens in vitro, and assay of DNA adducts. Xenobiotica. 23(3):317–25. https://doi.org/10.3109/00498259309059385 PMID:8498094

Clark JH, McCormack S (1977). Clomid or nafoxidine administered to neonatal rats causes reproductive tract abnormalities. Science. 197(4299):164–5. https://doi.org/10.1126/science.877546 PMID:877546

Clarke RB, Amini H, James P, von Euler-Chelpin M, Jørgensen JT, Mehta A, et al. (2021). Outdoor light at night and breast cancer incidence in the Danish Nurse Cohort. Environ Res. 194:110631. https://doi.org/10.1016/j.envres.2020.110631 PMID:33345898

Clavo B, Martínez-Sánchez G, Rodríguez-Esparragón F, Rodríguez-Abreu D, Galván S, Aguiar-Bujanda D, et al. (2021). Modulation by ozone therapy of oxidative stress in chemotherapy-induced peripheral neuropathy: the background for a randomized clinical trial. Int J Mol Sci. 22(6):2802. https://doi.org/10.3390/ijms22062802 PMID:33802143

Clawson GA, Benedict CM, Kelley MR, Weisz J (1997). Focal nuclear hepatocyte response to oxidative damage following low dose thioacetamide intoxication. Carcinogenesis. 18(8):1663–8. https://doi.org/10.1093/carcin/18.8.1663 PMID:9276646

Clayton EM, Todd M, Dowd JB, Aiello AE (2011). The impact of bisphenol A and triclosan on immune parameters in the U.S. population, NHANES 2003–2006. Environ Health Perspect. 119(3):390–6. https://doi.org/10.1289/ehp.1002883 PMID:21062687

Clemmensen PJ, Schullehner J, Brix N, Sigsgaard T, Stayner LT, Kolstad HA, et al. (2023). Prenatal exposure to nitrate in drinking water and adverse health outcomes in the offspring: a review of current epidemiological research. Curr Environ Health Rep. 10(3):250–63. https://doi.org/10.1007/s40572-023-00404-9https://doi.org/10.1007/s40572-023-00404-9 PMID:37453984

Clere N, Lauret E, Malthiery Y, Andriantsitohaina R, Faure S (2012). Estrogen receptor alpha as a key target of organochlorines to promote angiogenesis. Angiogenesis. 15(4):745–60. https://doi.org/10.1007/s10456-012-9288-7 PMID:22829064

Cobanoglu H (2022). Assessment of genetic damage induced by gadolinium-based radiocontrast agents. J Trace Elem Med Biol. 70:126914. https://doi.org/10.1016/j.jtemb.2021.126914 PMID:34953388

Cocco P (2022). Time for re-evaluating the human carcinogenicity of ethylenedithiocarbamate fungicides? A systematic review. Int J Environ Res Public Health. 19(5):2632. https://doi.org/10.3390/ijerph19052632PMID:35270318

Cogliano VJ, Baan R, Straif K, Grosse Y, Lauby-Secretan B, El Ghissassi F, et al. (2011). Preventable exposures associated with human cancers. J Natl Cancer Inst. 103(24):1827–39. https://doi.org/10.1093/jnci/djr483 PMID:22158127

Cohn AM, Abudayyeh H, Perreras L, Peters EN (2019). Patterns and correlates of the co-use of marijuana with any tobacco and individual tobacco products in young adults from Wave 2 of the PATH Study. Addict Behav. 92:122–7. https://doi.org/10.1016/j.addbeh.2018.12.025 PMID:30623805

Cohn AM, Blount BC, Hashibe M (2021). Nonmedical cannabis use: patterns and correlates of use, exposure, and harm, and cancer risk. J Natl Cancer Inst Monogr. 2021(58):53–67. https://doi.org/10.1093/jncimonographs/lgab006 PMID:34850898

Colbeth HL, Chen KT, Picciotto S, Costello S, Eisen EA (2023). Exposure to metalworking fluids and cancer incidence in the United Auto Workers–General Motors Cohort. Am J Epidemiol. 192(2):171–81. https://doi.org/10.1093/aje/kwac190https://doi.org/10.1093/aje/kwac190 PMID:36305635

Cold S, Cold F, Jensen MB, Cronin-Fenton D, Christiansen P, Ejlertsen B (2022). Systemic or vaginal hormone therapy after early breast cancer: a Danish observational cohort study. J Natl Cancer Inst. 114(10):1347–54. https://doi.org/10.1093/jnci/djac112 PMID:35854422

Colin R, Grzebyk M, Wild P, Hédelin G, Bourgkard È (2018). Bladder cancer and occupational exposure to metalworking fluid mist: a counter-matched case–control study in French steel-producing factories. Occup Environ Med. 75(5):328–36. https://doi.org/10.1136/oemed-2017-104666https://doi.org/10.1136/oemed-2017-104666 PMID:29374095

Colinot DL, Garbuz T, Bosland MC, Wang L, Rice SE, Sullivan WJ Jr, et al. (2017). The common parasite *Toxoplasma gondii* induces prostatic inflammation and microglandular hyperplasia in a mouse model. Prostate. 77(10):1066–75. https://doi.org/10.1002/pros.23362 PMID:28497488

Collaborative Group on Hormonal Factors in Breast Cancer (2019). Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 394(10204):1159–68. https://doi.org/10.1016/S0140-6736(19)31709-X PMID:31474332

Collao N, Sanders O, Caminiti T, Messeiller L, De Lisio M (2023). Resistance and endurance exercise training improves muscle mass and the inflammatory/fibrotic transcriptome in a rhabdomyosarcoma model. J Cachexia Sarcopenia Muscle. 14(2):781–93. https://doi.org/10.1002/jcsm.13185 PMID:36797054

Collatuzzo G, Pelucchi C, Negri E, Kogevinas M, Huerta JM, Vioque J, et al. (2023). Sleep duration and stress level in the risk of gastric cancer: a pooled analysis of case–control studies in the stomach cancer pooling (StoP) project. Cancers (Basel). 15(17):4319. https://doi.org/10.3390/cancers15174319 PMID:37686594

Collinge M, Ball DJ, Bowman CJ, Nilson AL, Radi ZA, Vogel WM (2018). Immunologic effects of chronic administration of tofacitinib, a janus kinase inhibitor, in cynomolgus monkeys and rats – comparison of juvenile and adult responses. Regul Toxicol Pharmacol. 94:306–22. https://doi.org/10.1016/j.yrtph.2018.02.006 PMID:29454012

Colosio C, Fustinoni S, Birindelli S, Bonomi I, De Paschale G, Mammone T, et al. (2002). Ethylenethiourea in urine as an indicator of exposure to mancozeb in vineyard workers. Toxicol Lett. 134(1-3):133–40. https://doi.org/10.1016/S0378-4274(02)00182-0 PMID:12191871

Colović MB, Krstić DZ, Lazarević-Pašti TD, Bondžić AM, Vasić VM (2013). Acetylcholinesterase inhibitors: pharmacology and toxicology. Curr Neuropharmacol. 11(3):315–35. https://doi.org/10.2174/1570159X11311030006 PMID:24179466

Colt JS, Friesen MC, Stewart PA, Donguk P, Johnson A, Schwenn M, et al. (2014). A case–control study of occupational exposure to metalworking fluids and bladder cancer risk among men. Occup Environ Med. 71(10):667–74. https://doi.org/10.1136/oemed-2013-102056https://doi.org/10.1136/oemed-2013-102056 PMID:25201311

Colt JS, Karagas MR, Schwenn M, Baris D, Johnson A, Stewart P, et al. (2011). Occupation and bladder cancer in a population-based case–control study in northern New England. Occup Environ Med. 68(4):239–49. https://doi.org/10.1136/oem.2009.052571 PMID:20864470

Colyn L, Alvarez-Sola G, Latasa MU, Uriarte I, Herranz JM, Arechederra M, et al. (2022). New molecular mechanisms in cholangiocarcinoma: signals triggering interleukin-6 production in tumor cells and KRAS co-opted epigenetic mediators driving metabolic reprogramming. J Exp Clin Cancer Res. 41(1):183. https://doi.org/10.1186/s13046-022-02386-2 PMID:35619118

Conley JM, Lambright CS, Evans N, Strynar MJ, McCord J, McIntyre BS, et al. (2019). Adverse maternal, fetal, and postnatal effects of hexafluoropropylene oxide dimer acid (GenX) from oral gestational exposure in Sprague-Dawley rats. Environ Health Perspect. 127(3):37008. https://doi.org/10.1289/EHP4372 PMID:30920876

Connor TH, Theiss JC, Hanna HA, Monteith DK, Matney TS (1985). Genotoxicity of organic chemicals frequently found in the air of mobile homes. Toxicol Lett. 25(1):33–40. https://doi.org/10.1016/0378-4274(85)90097-9 PMID:3887653

Coogan PF, Rosenberg L, Palmer JR, Cozier YC, Lenzy YM, Bertrand KA (2021). Hair product use and breast cancer incidence in the Black Women's Health Study. Carcinogenesis. 42(7):924–30. https://doi.org/10.1093/carcin/bgab041 PMID:34013957

Cook S, Hirschtick JL, Barnes G, Arenberg D, Bondarenko I, Patel A, et al. (2023). Time-varying association between cigarette and ENDS use on incident hypertension among US adults: a prospective longitudinal study. BMJ Open. 13(4):e062297. https://doi.org/10.1136/bmjopen-2022-062297 PMID:37085311

Coperchini F, Croce L, Denegri M, Pignatti P, Agozzino M, Netti GS, et al. (2020). Adverse effects of in vitro GenX exposure on rat thyroid cell viability, DNA integrity and thyroid-related genes expression. Environ Pollut. 264:114778. https://doi.org/10.1016/j.envpol.2020.114778 PMID:32417585

Cora MC, Gwinn W, Wilson R, King D, Waidyanatha S, Kissling GE, et al. (2017). A black cohosh extract causes hematologic and biochemical changes consistent with a functional cobalamin deficiency in female B6C3F$_1$/N mice. Toxicol Pathol. 45(5):614–23. https://doi.org/10.1177/0192623317714343https://doi.org/10.1177/0192623317714343 PMID:28618975

Corbella S, Veronesi P, Galimberti V, Weinstein R, Del Fabbro M, Francetti L (2018). Is periodontitis a risk indicator for cancer? A meta-analysis. PLoS One. 13(4):e0195683. https://doi.org/10.1371/journal.pone.0195683 PMID:29664916

Cordelli E, Keller J, Eleuteri P, Villani P, Ma-Hock L, Schulz M, et al. (2017). No genotoxicity in rat blood cells upon 3- or 6-month inhalation exposure to CeO2 or BaSO4 nanomaterials. Mutagenesis. 32(1):13–22. https://doi.org/10.1093/mutage/gew005 PMID:26861493

Cordier S, Bouquet E, Warembourg C, Massart C, Rouget F, Kadhel P, et al. (2015). Perinatal exposure to chlordecone, thyroid hormone status and neurodevelopment in infants: the Timoun cohort study in Guadeloupe (French West Indies). Environ Res. 138:271–8. https://doi.org/10.1016/j.envres.2015.02.021 PMID:25747818

Cornet I, Bouvard V, Campo MS, Thomas M, Banks L, Gissmann L, et al. (2012). Comparative analysis of transforming properties of E6 and E7 from different beta human papillomavirus types. J Virol. 86(4):2366–70. https://doi.org/10.1128/JVI.06579-11 PMID:22171257

Costa C, Teodoro M, Giambò F, Catania S, Vivarelli S, Fenga C (2022). Assessment of mancozeb exposure, absorbed dose, and oxidative damage in greenhouse farmers. Int J Environ Res Public Health. 19(17):10486. https://doi.org/10.3390/ijerph191710486 PMID:36078202

Costa S, Carvalho S, Costa C, Coelho P, Silva S, Santos LS, et al. (2015). Increased levels of chromosomal aberrations and DNA damage in a group of workers exposed to formaldehyde. Mutagenesis. 30(4):463–73. https://doi.org/10.1093/mutage/gev002 PMID:25711496

Costanzo M, De Giglio MAR, Roviello GN (2023). Deciphering the relationship between SARS-CoV-2 and cancer. Int J Mol Sci. 24(9):7803. https://doi.org/10.3390/ijms24097803 PMID:37175509

Costello S, Chen K, Picciotto S, Lutzker L, Eisen E (2020). Metalworking fluids and cancer mortality in a US autoworker cohort (1941–2015). Scand J Work Environ Health. 46(5):525–32. https://doi.org/10.5271/sjweh.3898https://doi.org/10.5271/sjweh.3898 PMID:32406514

Costello S, Friesen MC, Christiani DC, Eisen EA (2011). Metalworking fluids and malignant melanoma in autoworkers. Epidemiology. 22(1):90–7. https://doi.org/10.1097/EDE.0b013e3181fce4b8https://doi.org/10.1097/EDE.0b013e3181fce4b8 PMID:20975563

Costet N, Lafontaine A, Rouget F, Michineau L, Monfort C, Thomé JP, et al. (2022). Prenatal and childhood exposure to chlordecone and adiposity of seven-year-old children in the Timoun mother-child cohort study in Guadeloupe (French West Indies). Environ Health. 21(1):42. https://doi.org/10.1186/s12940-022-00850-2 PMID:35439992

Costet N, Villanueva CM, Jaakkola JJ, Kogevinas M, Cantor KP, King WD, et al. (2011). Water disinfection by-products and bladder cancer: is there a European specificity? A pooled and meta-analysis of European case–control studies. Occup Environ Med. 68(5):379–85. https://doi.org/10.1136/oem.2010.062703 PMID:21389011

Côté J, Bonvalot Y, Carrier G, Lapointe C, Fuhr U, Tomalik-Scharte D, et al. (2014). A novel toxicokinetic modeling of cypermethrin and permethrin and their metabolites in humans for dose reconstruction from biomarker data. PLoS One. 9(2):e88517. https://doi.org/10.1371/journal.pone.0088517 PMID:24586336

Council of Europe (2022). Black cohosh. Cimicifugae rhizoma. 04/2014:2069. European Pharmacopoeia 11.0. Strasbourg, France: Council of Europe. Available from: https://pheur.edqm.eu/home

Coureau G, Bouvier G, Lebailly P, Fabbro-Peray P, Gruber A, Leffondre K, et al. (2014). Mobile phone use and brain tumours in the CERENAT case–control study. Occup Environ Med. 71(7):514–22. https://doi.org/10.1136/oemed-2013-101754 PMID:24816517

Courjaret R, Lapied B (2001). Complex intracellular messenger pathways regulate one type of neuronal alpha-bungarotoxin-resistant nicotinic acetylcholine receptors expressed in insect neurosecretory cells (dorsal unpaired median neurons). Mol Pharmacol. 60(1):80–91. https://doi.org/10.1124/mol.60.1.80 PMID:11408603

Courtney KE, Ray LA (2014). Methamphetamine: an update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. Drug Alcohol Depend. 143:11–21. https://doi.org/10.1016/j.drugalcdep.2014.08.003 PMID:25176528

Couturier-Maillard A, Secher T, Rehman A, Normand S, De Arcangelis A, Haesler R, et al. (2013). NOD2-mediated dysbiosis predisposes mice to transmissible colitis and colorectal cancer. J Clin Invest. 123(2):700–11. https://doi.org/10.1172/JCI62236 PMID:23281400

Cox DTC, Sánchez de Miguel A, Bennie J, Dzurjak SA, Gaston KJ (2022). Majority of artificially lit Earth surface associated with the non-urban population. Sci Total Environ. 841:156782. https://doi.org/10.1016/j.scitotenv.2022.156782 PMID:35724779

CPSC (2001). Report to the US Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Diisononyl Phthalate (DINP) June 2001. Bethesda (MA), USA: US Consumer Product Safety Commission. Available from: https://www.cpsc.gov/s3fs-public/pdfs/dinp.pdf, accessed December 2023.

Cragle DL, Hollis DR, Newport TH, Shy CM (1984). A retrospective cohort mortality study among workers occupationally exposed to metallic nickel powder at the Oak Ridge Gaseous Diffusion Plant. IARC Sci Publ. 53(53):57–63. PMID:6532993

Crawford L, Halperin SA, Dzierlenga MW, Skidmore B, Linakis MW, Nakagawa S, et al. (2023). Systematic review and meta-analysis of epidemiologic data on vaccine response in relation to exposure to five principal perfluoroalkyl substances. Environ Int. 172:107734. https://doi.org/10.1016/j.envint.2023.107734https://doi.org/10.1016/j.envint.2023.107734 PMID:36764183

Crespi CM, Sudan M, Juutilainen J, Roivainen P, Hareuveny R, Huss A, et al. (2024). International study of childhood leukemia in residences near electrical transformer rooms. Environ Res. 249:118459. https://doi.org/10.1016/j.envres.2024.118459 PMID:38346482

Crump JA, Luby SP, Mintz ED (2004). The global burden of typhoid fever. Bull World Health Organ. 82(5):346–53. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622843/pdf/15298225.pdf PMID:15298225

Crump M, Tu D, Shepherd L, Levine M, Bramwell V, Pritchard K (2003). Risk of acute leukemia following epirubicin-based adjuvant chemotherapy: a report from the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 21(16):3066–71. https://doi.org/10.1200/JCO.2003.08.137 PMID:12915595

Cuenca JB, de Oliveira Galvão MF, Endirlik BU, Tirado N, Dreij K (2022). In vitro cytotoxicity and genotoxicity of single and combined pesticides used by Bolivian farmers. Environ Mol Mutagen. 63(1):4–17. https://doi.org/10.1002/em.22468 PMID:34881454

Cuevas-Ramos G, Petit CR, Marcq I, Boury M, Oswald E, Nougayrède JP (2010). *Escherichia coli* induces DNA damage in vivo and triggers genomic instability in mammalian cells. Proc Natl Acad Sci USA. 107(25):11537–42. https://doi.org/10.1073/pnas.1001261107 PMID:20534522

Cui Y, Liu H, Wang Z, Zhang H, Tian J, Wang Z, et al. (2023). Fructose promotes angiogenesis by improving vascular endothelial cell function and upregulating VEGF expression in cancer cells. J Exp Clin Cancer Res. 42(1):184. https://doi.org/10.1186/s13046-023-02765-3 PMID:37507736

Culvenor CCJ (1983). Estimated intakes of pyrrolizidine alkaloids by humans. A comparison with dose rates causing tumors in rats. J Toxicol Environ Health. 11(4–6):625–35. https://doi.org/10.1080/15287398309530372 PMID:6620404

Cunningham ML, Matthews HB (1990). Evidence for an acetoxyarylamine as the ultimate mutagenic reactive intermediate of the carcinogenic aromatic amine 2,4-diaminotoluene. Mutat Res. 242(2):101–10. https://doi.org/10.1016/0165-1218(90)90035-Z PMID:2233826

Cunningham ML, Matthews HB (1995). Cell proliferation as a determining factor for the carcinogenicity of chemicals: studies with mutagenic carcinogens and mutagenic noncarcinogens. Toxicol Lett. 82–83:9–14. https://doi.org/10.1016/0378-4274(95)03464-1 PMID:8597159

Curwin BD, Hein MJ, Sanderson WT, Striley C, Heederik D, Kromhout H, et al. (2007). Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in iowa. Ann Occup Hyg. 51(1):53–65. https://doi.org/10.1093/annhyg/mel062 PMID:16984946

d'Hose D, Isenborghs P, Brusa D, Jordan BF, Gallez B (2021). The short-term exposure to SDHI fungicides boscalid and bixafen induces a mitochondrial dysfunction in selective human cell lines. Molecules. 26(19):5842. https://doi.org/10.3390/molecules26195842 PMID:34641386

da Silva Júnior F, Tavella RA, Fernandes C, Soares M, de Almeida KA, Garcia EM, et al. (2018). Genotoxicity in Brazilian coal miners and its associated factors. Hum Exp Toxicol. 37(9):891–900. https://doi.org/10.1177/0960327117745692 PMID:29226719

Dadhania VP, Tripathi DN, Vikram A, Ramarao P, Jena GB (2010). Intervention of alpha-lipoic acid ameliorates methotrexate-induced oxidative stress and genotoxicity: a study in rat intestine. Chem Biol Interact. 183(1):85–97. https://doi.org/10.1016/j.cbi.2009.10.020 PMID:19900424

Dadkhah A, Wicha SG, Kröger N, Müller A, Pfaffendorf C, Riedner M, et al. (2022). Population pharmacokinetics of busulfan and its metabolite sulfolane in patients with myelofibrosis undergoing hematopoietic stem cell transplantation. Pharmaceutics. 14(6):1145. https://doi.org/10.3390/pharmaceutics14061145 PMID:35745718

Dahle JT, Arai Y (2015). Environmental geochemistry of cerium: applications and toxicology of cerium oxide nanoparticles. Int J Environ Res Public Health. 12(2):1253–78. https://doi.org/10.3390/ijerph120201253 PMID:25625406

Dahlman-Höglund A, Schiöler L, Andersson M, Mattsby-Baltzer I, Lindgren Å (2022). Endotoxin in aerosol particles from metalworking fluids measured with a sioutas cascade impactor. Ann Work Expo Health. 66(2):260–8. https://doi.org/10.1093/annweh/wxab077 PMID:34595500

Dahm MM, Schubauer-Berigan MK, Evans DE, Birch ME, Bertke S, Beard JD, et al. (2018). Exposure assessments for a cross-sectional epidemiologic study of US carbon nanotube and nanofiber workers. Int J Hyg Environ Health. 221(3):429–40. https://doi.org/10.1016/j.ijheh.2018.01.006 PMID:29339022

Dali O, D'Cruz S, Legoff L, Diba Lahmidi M, Heitz C, Merret PE, et al. (2023). Transgenerational epigenetic effects imposed by neonicotinoid thiacloprid exposure. Life Sci Alliance. 7(2):e202302237. https://doi.org/10.26508/lsa.202302237 PMID:37973188

Dalsager L, Fage-Larsen B, Bilenberg N, Jensen TK, Nielsen F, Kyhl HB, et al. (2019). Maternal urinary concentrations of pyrethroid and chlorpyrifos metabolites and attention deficit hyperactivity disorder (ADHD) symptoms in 2–4-year-old children from the Odense Child Cohort. Environ Res. 176:108533. https://doi.org/10.1016/j.envres.2019.108533 PMID:31229776

Daniels RD, Schubauer-Berigan MK (2017). Radon in US workplaces: a review. Radiat Prot Dosimetry. 176(3):278–86. https://doi.org/10.1093/rpd/ncx007 PMID:28204795

Dankner R, Murad H, Agay N, Olmer L, Freedman LS (2024). Glucagon-like peptide-1 receptor agonists and pancreatic cancer risk in patients with type 2 diabetes. JAMA Netw Open. 7(1):e2350408. https://doi.org/10.1001/jamanetworkopen.2023.50408https://doi.org/10.1001/jamanetworkopen.2023.50408 PMID:38175642

Dantas TA, Cancian G, Neodini DN, Mano DR, Capucho C, Predes FS, et al. (2015). Leydig cell number and sperm production decrease induced by chronic ametryn exposure: a negative impact on animal reproductive health. Environ Sci Pollut Res Int. 22(11):8526–35. https://doi.org/10.1007/s11356-014-4010-5 PMID:25561257

Dao T, Hong X, Wang X, Tang WY (2015). Aberrant 5′-CpG methylation of cord blood TNFα associated with maternal exposure to polybrominated diphenyl ethers. PLoS One. 10(9):e0138815. https://doi.org/10.1371/journal.pone.0138815 PMID:26406892

Darbre PD (2016). Aluminium and the human breast. Morphologie. 100(329):65–74. https://doi.org/10.1016/j.morpho.2016.02.001 PMID:26997127

Darbre PD, Harvey PW (2008). Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks. J Appl Toxicol. 28(5):561–78. https://doi.org/10.1002/jat.1358https://doi.org/10.1002/jat.1358 PMID:18484575

Darbre PD, Mannello F, Exley C (2013). Aluminium and breast cancer: sources of exposure, tissue measurements and mechanisms of toxicological actions on breast biology. J Inorg Biochem. 128:257–61. https://doi.org/10.1016/j.jinorgbio.2013.07.005 PMID:23899626

Darby SC, Whitley E, Howe GR, Hutchings SJ, Kusiak RA, Lubin JH, et al. (1995). Radon and cancers other than lung cancer in underground miners: a collaborative analysis of 11 studies. J Natl Cancer Inst. 87(5):378–84. https://doi.org/10.1093/jnci/87.5.378 PMID:7853419

Das KP, Wood CR, Lin MT, Starkov AA, Lau C, Wallace KB, et al. (2017). Perfluoroalkyl acids-induced liver steatosis: effects on genes controlling lipid homeostasis. Toxicology. 378:37–52. https://doi.org/10.1016/j.tox.2016.12.007https://doi.org/10.1016/j.tox.2016.12.007 PMID:28049043

Das PC, Streit TM, Cao Y, Rose RL, Cherrington N, Ross MK, et al. (2008). Pyrethroids: cytotoxicity and induction of CYP isoforms in human hepatocytes. Drug Metabol Drug Interact. 23(3–4):211–36. https://doi.org/10.1515/DMDI.2008.23.3-4.211 PMID:19326768

Das SK, Tan J, Johnson DC, Dey SK (1998). Differential spatiotemporal regulation of lactoferrin and progesterone receptor genes in the mouse uterus by primary estrogen, catechol estrogen, and xenoestrogen. Endocrinology. 139(6):2905–15. https://doi.org/10.1210/endo.139.6.6051 PMID:9607801

Dasari S, Tchounwou PB (2014). Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol. 740:364–78. https://doi.org/10.1016/j.ejphar.2014.07.025 PMID:25058905

Datzmann T, Markevych I, Trautmann F, Heinrich J, Schmitt J, Tesch F (2018). Outdoor air pollution, green space, and cancer incidence in Saxony: a semi-individual cohort study. BMC Public Health. 18(1):715. https://doi.org/10.1186/s12889-018-5615-2 PMID:29884153

Dauchy RT, Blask DE, Sauer LA, Brainard GC, Krause JA (1999). Dim light during darkness stimulates tumor progression by enhancing tumor fatty acid uptake and metabolism. Cancer Lett. 144(2):131–6. https://doi.org/10.1016/S0304-3835(99)00207-4 PMID:10529012

David RM, White RD, Larson MJ, Herman JK, Otter R (2015). Toxicity of Hexamoll(®) DINCH(®) following intravenous administration. Toxicol Lett. 238(2):100–9. https://doi.org/10.1016/j.toxlet.2015.07.013 PMID:26211741

Davidsen JM, Cohen SM, Eisenbrand G, Fukushima S, Gooderham NJ, Guengerich FP, et al. (2023). FEMA GRAS assessment of derivatives of basil, nutmeg, parsley, tarragon and related allylalkoxybenzene-containing natural flavor complexes. Food Chem Toxicol. 175:113646. https://doi.org/10.1016/j.fct.2023.113646 PMID:36804339

Davidson M, Mayer M, Habib A, Rashidi N, Filippone RT, Fraser S, et al. (2022). Methamphetamine induces systemic inflammation and anxiety: the role of the gut–immune–brain axis. Int J Mol Sci. 23(19):11224. https://doi.org/10.3390/ijms231911224 PMID:36232524

Davis S, Mirick DK, Stevens RG (2001). Night shift work, light at night, and risk of breast cancer. J Natl Cancer Inst. 93(20):1557–62. https://doi.org/10.1093/jnci/93.20.1557 PMID:11604479

De Andrea M, Mondini M, Azzimonti B, Dell'Oste V, Germano S, Gaudino G, et al. (2007). Alpha- and betapapillomavirus E6/E7 genes differentially modulate pro-inflammatory gene expression. Virus Res. 124(1–2):220–5. https://doi.org/10.1016/j.virusres.2006.09.010

de Aquino T, Zenkner FF, Ellwanger JH, Prá D, Rieger A (2016). DNA damage and cytotoxicity in pathology laboratory technicians exposed to organic solvents. An Acad Bras Cienc. 88(1):227–36. https://doi.org/10.1590/0001-3765201620150194 PMID:26871490

De Boeck M, van der Leede BJ, De Vlieger K, Geys H, Vynckier A, Van Gompel J (2015). Evaluation of p-phenylenediamine, o-phenylphenol sodium salt, and 2,4-diaminotoluene in the rat comet assay as part of the Japanese Center for the Validation of Alternative Methods (JaCVAM)-initiated international validation study of in vivo rat alkaline comet assay. Mutat Res Genet Toxicol Environ Mutagen. 786–788:151–7. https://doi.org/10.1016/j.mrgentox.2015.04.002 PMID:26212306

de Boer M, van Leeuwen FE, Hauptmann M, Overbeek LIH, de Boer JP, Hijmering NJ, et al. (2018). Breast implants and the risk of anaplastic large-cell lymphoma in the breast. JAMA Oncol. 4(3):335–41. https://doi.org/10.1001/jamaoncol.2017.4510 PMID:29302687

de Faria Junior GM, Murata FHA, Lorenzi HA, Castro BBP, Assoni LCP, Ayo CM, et al. (2021). The role of microRNAs in the infection by *T. gondii* in Humans. Front Cell Infect Microbiol. 11:670548. https://doi.org/10.3389/fcimb.2021.670548 PMID:34055667

de Hoogh K, Chen J, Gulliver J, Hoffmann B, Hertel O, Ketzel M, et al. (2018). Spatial $PM_{2.5}$, NO_2, O_3 and BC models for Western Europe – evaluation of spatiotemporal stability. Environ Int. 120:81–92. https://doi.org/10.1016/j.envint.2018.07.036 PMID:30075373

de Jong D, Vasmel WL, de Boer JP, Verhave G, Barbé E, Casparie MK, et al. (2008). Anaplastic large-cell lymphoma in women with breast implants. JAMA. 300(17):2030–5. https://doi.org/10.1001/jama.2008.585 PMID:18984890

de Lima JM, Macedo CCS, Barbosa GV, Castellano LRC, Hier MP, Alaoui-Jamali MA, et al. (2023). E-liquid alters oral epithelial cell function to promote epithelial to mesenchymal transition and invasiveness in preclinical oral squamous cell carcinoma. Sci Rep. 13(1):3330. https://doi.org/10.1038/s41598-023-30016-0 PMID:36849550

de Melo FT, de Oliveira IM, Greggio S, Dacosta JC, Guecheva TN, Saffi J, et al. (2012). DNA damage in organs of mice treated acutely with patulin, a known mycotoxin. Food Chem Toxicol. 50(10):3548–55. https://doi.org/10.1016/j.fct.2011.12.022 PMID:22222931

de Melo Silva J, Pinheiro-Silva R, Costa de Oliveira R, de Castro Alves CE, Barbosa AN, Pontes GS (2021). Prevalence and recurrence rates of cytomegalovirus infection among patients with hematological diseases in the western Brazilian Amazon: a cross-sectional study. Front Public Health. 9:692226. https://doi.org/10.3389/fpubh.2021.692226 PMID:34692617

de Morais CR, Carvalho SM, Carvalho Naves MP, Araujo G, de Rezende AAA, Bonetti AM, et al. (2017). Mutagenic, recombinogenic and carcinogenic potential of thiamethoxam insecticide and formulated product in somatic cells of *Drosophila melanogaster*. Chemosphere. 187:163–72. https://doi.org/10.1016/j.chemosphere.2017.08.108 PMID:28846972

de Moura NA, Caetano BFR, de Moraes LN, Carvalho RF, Rodrigues MAM, Barbisan LF (2018). Enhancement of colon carcinogenesis by the combination of indole-3 carbinol and synbiotics in hemin-fed rats. Food Chem Toxicol. 112:11–8. https://doi.org/10.1016/j.fct.2017.12.029 PMID:29269057

de Oliveira FM, Carmona AM, Ladeira C (2017). Is mobile phone radiation genotoxic? An analysis of micronucleus frequency in exfoliated buccal cells. Mutat Res Genet Toxicol Environ Mutagen. 822:41–6. https://doi.org/10.1016/j.mrgentox.2017.08.001 PMID:28844241

de Oliveira Galvão MF, Sadiktsis I, Batistuzzo de Medeiros SR, Dreij K (2020). Genotoxicity and DNA damage signalling in response to complex mixtures of PAHs in biomass burning particulate matter from cashew nut roasting. Environ Pollut. 256:113381. https://doi.org/10.1016/j.envpol.2019.113381 PMID:31662259

de Queiroz VT, Azevedo MM, da Silva Quadros IP, Costa AV, do Amaral AA, Dos Santos GMADA, et al. (2018). Environmental risk assessment for sustainable pesticide use in coffee production. J Contam Hydrol. 219:18–27. https://doi.org/10.1016/j.jconhyd.2018.08.008 PMID:30342837

De Roos AJ, Fritschi L, Ward MH, Monnereau A, Hofmann J, Bernstein L, et al. (2022). Herbicide use in farming and other jobs in relation to non-Hodgkin's lymphoma (NHL) risk. Occup Environ Med. 79(12):795–806. https://doi.org/10.1136/oemed-2022-108371 PMID:36207110

De Roos AJ, Schinasi LH, Miligi L, Cerhan JR, Bhatti P, 't Mannetje A, et al. (2021). Occupational insecticide exposure and risk of non-Hodgkin lymphoma: a pooled case–control study from the InterLymph Consortium. Int J Cancer. 149(10):1768–86. https://doi.org/10.1002/ijc.33740 PMID:34270795

De Roos AJ, Zahm SH, Cantor KP, Weisenburger DD, Holmes FF, Burmeister LF, et al. (2003). Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occup Environ Med. 60(9):E11. https://doi.org/10.1136/oem.60.9.e11 PMID:12937207

de Waal E, Vrooman LA, Fischer E, Ord T, Mainigi MA, Coutifaris C, et al. (2015). The cumulative effect of assisted reproduction procedures on placental development and epigenetic perturbations in a mouse model. Hum Mol Genet. 24(24):6975–85. https://doi.org/10.1093/hmg/ddv400 PMID:26401051

DEA (2020). Methamphetamine. Drug fact sheet. Springfield (VA), USA: Department of Justice, Drug Enforcement Administration. Available from: https://www.dea.gov/sites/default/files/2020-06/Methamphetamine-2020_0.pdf, accessed September 2024.

Dearfield KL, McCarroll NE, Protzel A, Stack HF, Jackson MA, Waters MD (1999). A survey of EPA/OPP and open literature on selected pesticide chemicals. II. Mutagenicity and carcinogenicity of selected chloroacetanilides and related compounds. Mutat Res. 443(1–2):183–221. https://doi.org/10.1016/S1383-5742(99)00019-8 PMID:10415440

Debertin J, Teles F, Martin LM, Lu J, Koestler DC, Kelsey KT, et al. (2023). Antibodies to oral pathobionts and colon cancer risk in the CLUE I cohort study. Int J Cancer. 153(2):302–11. https://doi.org/10.1002/ijc.34527 PMID:36971101

Debras C, Chazelas E, Srour B, Druesne-Pecollo N, Esseddik Y, Szabo de Edelenyi F, et al. (2022). Artificial sweeteners and cancer risk: results from the NutriNet-Santé population-based cohort study. PLoS Med. 19(3):e1003950. https://doi.org/10.1371/journal.pmed.1003950 PMID:35324894

DeCoster RC, Clemens MW, Di Napoli A, Lynch EB, Bonaroti AR, Rinker BD, et al. (2021). Cellular and molecular mechanisms of breast implant-associated anaplastic large cell lymphoma. Plast Reconstr Surg. 147(1):30e–41e. https://doi.org/10.1097/PRS.0000000000007423 PMID:33370049

Del Risco Kollerud R, Blaasaas KG, Claussen B (2014). Risk of leukaemia or cancer in the central nervous system among children living in an area with high indoor radon concentrations: results from a cohort study in Norway. Br J Cancer. 111(7):1413–20. https://doi.org/10.1038/bjc.2014.400 PMID:25117818

Delatour T, Stadler RH (2023). Two decades of research in dietary acrylamide: what do we know today. Crit Rev Food Sci Nutr. 63(33):12169–77. https://doi.org/10.1080/10408398.2022.2099344 PMID:35852101

Delclos KB, Blaydes B, Heflich RH, Smith BA (1996). Assessment of DNA adducts and the frequency of 6-thioguanine resistant T-lymphocytes in F344 rats fed 2,4-toluenediamine or implanted with a toluenediisocyanate-containing polyester polyurethane foam. Mutat Res. 367(4):210–8. PMID:8628327

Delic V, Karp J, Klein J, Stalnaker KJ, Murray KE, Ratliff WA, et al. (2021). Pyridostigmine bromide, chlorpyrifos, and DEET combined Gulf War exposure insult depresses mitochondrial function in neuroblastoma cells. J Biochem Mol Toxicol. 35(12):e22913. https://doi.org/10.1002/jbt.22913 PMID:34528356

Dell LD, Gallagher AE, Crawford L, Jones RM, Mundt KA (2015). Cohort study of carbon black exposure and risk of malignant and nonmalignant respiratory disease mortality in the US carbon black industry. J Occup Environ Med. 57(9):984–97. https://doi.org/10.1097/JOM.0000000000000511 PMID:26340287

DeMarini DM, Shelton ML, Warren SH, Ross TM, Shim JY, Richard AM, et al. (1997). Glutathione S-transferase-mediated induction of GC–>AT transitions by halomethanes in *Salmonella.* Environ Mol Mutagen. 30(4):440–7. https://doi.org/10.1002/(SICI)1098-2280(1997)30:4<440::AID-EM9>3.0.CO;2-M PMID:9435885

Demoury C, Marquant F, Ielsch G, Goujon S, Debayle C, Faure L, et al. (2017). Residential exposure to natural background radiation and risk of childhood acute leukemia in France, 1990–2009. Environ Health Perspect. 125(4):714–20. https://doi.org/10.1289/EHP296 PMID:27483500

den Besten C, Vet JJ, Besselink HT, Kiel GS, van Berkel BJ, Beems R, et al. (1991). The liver, kidney, and thyroid toxicity of chlorinated benzenes. Toxicol Appl Pharmacol. 111(1):69–81. https://doi.org/10.1016/0041-008X(91)90135-2 PMID:1949037

Deng Q, Wang X, Wang M, Lan Y (2012). Exposure-response relationship between chrysotile exposure and mortality from lung cancer and asbestosis. Occup Environ Med. 69(2):81–6. https://doi.org/10.1136/oem.2011.064899 PMID:21742741

Deng S, Yan T, Jendrny C, Nemecek A, Vincetic M, Gödtel-Armbrust U, et al. (2014). Dexrazoxane may prevent doxorubicin-induced DNA damage via depleting both topoisomerase II isoforms. BMC Cancer. 14(1):842. https://doi.org/10.1186/1471-2407-14-842 PMID:25406834

Dennis LK, Lynch CF, Sandler DP, Alavanja MC (2010). Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural heath study. Environ Health Perspect. 118(6):812–7. https://doi.org/10.1289/ehp.0901518https://doi.org/10.1289/ehp.0901518 PMID:20164001

Dereumeaux C, Saoudi A, Guldner L, Pecheux M, Chesneau J, Thomé JP, et al. (2020). Chlordecone and organochlorine compound levels in the French West Indies population in 2013–2014. Environ Sci Pollut Res Int. 27(33):41033–45. https://doi.org/10.1007/s11356-019-07181-9 PMID:31884530

Deschamps F, Deambrogio V (2023). Calculated residential exposure to power frequency magnetic fields for an epidemiological study in France and comparison to measurements. J Radiol Prot. 43(2):021507. https://doi.org/10.1088/1361-6498/acd0b9 PMID:37105165

Deshayes-Pinçon F, Morlais F, Roth-Delgado O, Merckel O, Lacour B, Launoy G, et al. (2023). Estimation of the general population and children under five years of age in France exposed to magnetic field from high or very high voltage power line using geographic information system and extrapolated field data. Environ Res. 232:116425. https://doi.org/10.1016/j.envres.2023.116425 PMID:37327843

Dessinioti C, Tsiakou A, Christodoulou A, Stratigos AJ (2023). Clinical and dermoscopic findings of nevi after photoepilation: a review. Life (Basel). 13(9):1832. https://doi.org/10.3390/life13091832 PMID:37763236

Detoni MB, Bortoleti BTDS, Tomiotto-Pellissier F, Concato VM, Gonçalves MD, Silva TF, et al. (2023). Biogenic silver nanoparticle exhibits schistosomicidal activity in vitro and reduces the parasitic burden in experimental *schistosomiasis mansoni*. Microbes Infect. 25(7):105145. https://doi.org/10.1016/j.micinf.2023.105145 PMID:37120010

Deziel NC, Alfonso-Garrido J, Warren JL, Huang H, Sjodin A, Zhang Y (2019). Exposure to polybrominated diphenyl ethers and a polybrominated biphenyl and risk of thyroid cancer in women: single and multi-pollutant approaches. Cancer Epidemiol Biomarkers Prev. 28(10):1755–64. https://doi.org/10.1158/1055-9965.EPI-19-0526 PMID:31387967

Deziel NC, Colt JS, Kent EE, Gunier RB, Reynolds P, Booth B, et al. (2015). Associations between self-reported pest treatments and pesticide concentrations in carpet dust. Environ Health. 14(1):27. https://doi.org/10.1186/s12940-015-0015-x PMID:25889489

Dhakal S, Ruiz-Bedoya CA, Zhou R, Creisher PS, Villano JS, Littlefield K, et al.; Johns Hopkins COVID-19 Hamster Study Group (2021). Sex differences in lung imaging and SARS-CoV-2 antibody responses in a COVID-19 Golden Syrian Hamster model. MBio. 12(4):e0097421. https://doi.org/10.1128/mBio.00974-21 PMID:34253053

Dhareshwar SS, Stella VJ (2008). Your prodrug releases formaldehyde: should you be concerned? No! J Pharm Sci. 97(10):4184–93. https://doi.org/10.1002/jps.21319 PMID:18288723

Dharnidharka VR, Stevens G (2005). Risk for post-transplant lymphoproliferative disorder after polyclonal antibody induction in kidney transplantation. Pediatr Transplant. 9(5):622–6. https://doi.org/10.1111/j.1399-3046.2005.00361.x PMID:16176420

Dhillon S (2016). Dabrafenib plus trametinib: a review in advanced melanoma with a BRAF (V600) mutation. Target Oncol. 11(3):417–28. https://doi.org/10.1007/s11523-016-0443-8 PMID:27246822

Dhouib I, Jallouli M, Annabi A, Marzouki S, Gharbi N, Elfazaa S, et al. (2016). From immunotoxicity to carcinogenicity: the effects of carbamate pesticides on the immune system. Environ Sci Pollut Res Int. 23(10):9448–58. https://doi.org/10.1007/s11356-016-6418-6 PMID:26988364

Dhurandhar D, Bharihoke V, Kalra S (2018). A histological assessment of effects of sucralose on liver of albino rats. Morphologie. 102(338):197–204. https://doi.org/10.1016/j.morpho.2018.07.003 PMID:30078469

Di Bucchianico S, Gliga AR, Åkerlund E, Skoglund S, Wallinder IO, Fadeel B, et al. (2018). Calcium-dependent cyto- and genotoxicity of nickel metal and nickel oxide nanoparticles in human lung cells. Part Fibre Toxicol. 15(1):32. https://doi.org/10.1186/s12989-018-0268-y PMID:30016969

Di Domenico EG, Cavallo I, Pontone M, Toma L, Ensoli F (2017). Biofilm producing *Salmonella typhi*: chronic colonization and development of gallbladder cancer. Int J Mol Sci. 18(9):1887. https://doi.org/10.3390/ijms18091887 PMID:28858232

Di Mauro R, Cantarella G, Bernardini R, Di Rosa M, Barbagallo I, Distefano A, et al. (2019). The biochemical and pharmacological properties of ozone: the smell of protection in acute and chronic diseases. Int J Mol Sci. 20(3):634. https://doi.org/10.3390/ijms20030634 PMID:30717203

Di Pietro A, Visalli G, La Maestra S, Micale R, Baluce B, Matarese G, et al. (2008). Biomonitoring of DNA damage in peripheral blood lymphocytes of subjects with dental restorative fillings. Mutat Res. 650(2):115–22. https://doi.org/10.1016/j.mrgentox.2007.10.023 PMID:18178127

Diab KA, Fahmy MA, Hassan ZM, Hassan EM, Salama AB, Omara EA (2018). Genotoxicity of carbon tetrachloride and the protective role of essential oil of *Salvia officinalis* L. in mice using chromosomal aberration, micronuclei formation, and comet assay. Environ Sci Pollut Res Int. 25(2):1621–36. https://doi.org/10.1007/s11356-017-0601-2 PMID:29098592

Diamond B, Ziccheddu B, Maclachlan K, Taylor J, Boyle E, Ossa JA, et al. (2023). Tracking the evolution of therapy-related myeloid neoplasms using chemotherapy signatures. Blood. 141(19):2359–71. https://doi.org/10.1182/blood.2022018244 PMID:36626250

Dietz D (1991). NTP technical report on the toxicity studies of cresols in F344/N rats and B6C3F$_1$ mice (Feed studies). Toxic Rep Ser. 9:1–128. PMID:12209177

Dieye M, Banydeen R, Macni J, Michel S, Veronique-Baudin J, Sasco A, et al. (2014). Geographic variations and temporal trends in prostate cancer in Martinique over a 25-year period. BMC Res Notes. 7(1):262. https://doi.org/10.1186/1756-0500-7-262 PMID:24758582

Digitale JC, Kim MO, Kuzniewicz MW, Newman TB (2021). Update on phototherapy and childhood cancer in a Northern California cohort. Pediatrics. 148(5):e2021051033. https://doi.org/10.1542/peds.2021-051033 PMID:34716218

Dika E, Fanti PA, Vaccari S, Capizzi E, Degiovanni A, Gobbi A, et al. (2017). Oestrogen and progesterone receptors in melanoma and nevi: an immunohistochemical study. Eur J Dermatol. 27(3):254–9. https://doi.org/10.1684/ejd.2017.3019 PMID:28524047

Diler SB, Çelik A (2011). Cytogenetic biomonitoring of carpet fabric workers using micronucleus frequency, nuclear changes, and the calculation of risk assessment by repair index in exfoliated mucosa cells. DNA Cell Biol. 30(10):821–7. https://doi.org/10.1089/dna.2011.1216 PMID:21495858

Dillon D, Combes R, Zeiger E (1998). The effectiveness of *Salmonella* strains TA100, TA102 and TA104 for detecting mutagenicity of some aldehydes and peroxides. Mutagenesis. 13(1):19–26. https://doi.org/10.1093/mutage/13.1.19https://doi.org/10.1093/mutage/13.1.19 PMID:9491389

Ding G, Shi R, Gao Y, Zhang Y, Kamijima M, Sakai K, et al. (2012). Pyrethroid pesticide exposure and risk of childhood acute lymphocytic leukemia in Shanghai. Environ Sci Technol. 46(24):13480–7. https://doi.org/10.1021/es303362a PMID:23153377

Ding W, Levy DD, Bishop ME, Pearce MG, Davis KJ, Jeffrey AM, et al. (2015). In vivo genotoxicity of estragole in male F344 rats. Environ Mol Mutagen. 56(4):356–65. https://doi.org/10.1002/em.21918 PMID:25361439

Ding YC, Hurley S, Park JS, Steele L, Rakoff M, Zhu Y, et al. (2021). Methylation biomarkers of polybrominated diphenyl ethers (PBDEs) and association with breast cancer risk at the time of menopause. Environ Int. 156:106772. https://doi.org/10.1016/j.envint.2021.106772 PMID:34425644

Ding Z, Shen JY, Hong JW, Zhang R, Li Z, Wang Q, et al. (2020). Inhibitory effects of cypermethrin on interactions of the androgen receptor with coactivators ARA70 and ARA55. Biomed Environ Sci. 33(3):158–64. PMID:32209174

Dinh A, Sriprasert I, Williams AR, Archer DF (2015). A review of the endometrial histologic effects of progestins and progesterone receptor modulators in reproductive age women. Contraception. 91(5):360–7. https://doi.org/10.1016/j.contraception.2015.01.008 PMID:25596512

Diwan BA, Anderson LM, Rehm S, Rice JM (1993). Transplacental carcinogenicity of cisplatin: initiation of skin tumors and induction of other preneoplastic and neoplastic lesions in SENCAR mice. Cancer Res. 53(17):3874–6. PMID:8358711

Diwan BA, Anderson LM, Ward JM, Henneman JR, Rice JM (1995). Transplacental carcinogenesis by cisplatin in F344/NCr rats: promotion of kidney tumors by postnatal administration of sodium barbital. Toxicol Appl Pharmacol. 132(1):115–21. https://doi.org/10.1006/taap.1995.1092 PMID:7747274

Dodmane PR, Arnold LL, Pennington KL, Cohen SM (2014). Orally administered nicotine induces urothelial hyperplasia in rats and mice. Toxicology. 315:49–54. https://doi.org/10.1016/j.tox.2013.11.002 PMID:24269753

Doherty A-C, Lee C-S, Mengl O, Sakano Y, Noble AE, Grant KA, et al. (2023). Contribution of household and personal care products to 1,4-dioxane contamination of drinking water. Curr Opin Environ Sci Health. 2023(31):100414. https://doi.org/10.1016/j.coesh.2022.100414

Dolgikh OV, Krivtsov AV, Bubnova OA, Predeina RA, Dianova DG, Sinitsyna OO, et al. (2013). [Immunogenetic features of apoptosis in workers engaged in methanol production]. Med Tr Prom Ekol. 11(11):9–12. PMID:24640084 [Russian]

Domenech J, Annangi B, Marcos R, Hernández A, Catalán J (2023). Insights into the potential carcinogenicity of micro- and nano-plastics. Mutat Res Rev Mutat Res. 791:108453. https://doi.org/10.1016/j.mrrev.2023.108453 PMID:36739075

Domijan AM, Hercog K, Štampar M, Gajski G, Gerić M, Sokolović M, et al. (2023). Impact of deoxynivalenol and zearalenone as single and combined treatment on DNA, cell cycle and cell proliferation in HepG2 cells. Int J Mol Sci. 24(4):4082. https://doi.org/10.3390/ijms24044082 PMID:36835492

Dommasch E, Gelfand JM (2009). Is there truly a risk of lymphoma from biologic therapies? Dermatol Ther. 22(5):418–30. https://doi.org/10.1111/j.1529-8019.2009.01258.x PMID:19845719

Don Porto Carero A, Hoet PH, Verschaeve L, Schoeters G, Nemery B (2001). Genotoxic effects of carbon black particles, diesel exhaust particles, and urban air particulates and their extracts on a human alveolar epithelial cell line (A549) and a human monocytic cell line (THP-1). Environ Mol Mutagen. 37(2):155–63. https://doi.org/10.1002/em.1023 PMID:11246222

Dores GM, Linet MS, Curtis RE, Morton LM (2023). Risks of therapy-related hematologic neoplasms beyond myelodysplastic syndromes and acute myeloid leukemia. Blood. 141(8):951–5. https://doi.org/10.1182/blood.2022018051 PMID:36379026

Dorfer S, Handisurya A (2020). Model systems for papillomavirus-associated skin disease. Drug Discov Today Dis Models. 32:7–16. https://doi.org/10.1016/j.ddmod.2020.10.002

Dos Santos IC, da Silva JT, Rohr P, Lengert AVH, de Lima MA, Kahl VFS, et al. (2022). Genomic instability evaluation by BMCyt and telomere length in Brazilian family farmers exposed to pesticides. Mutat Res Genet Toxicol Environ Mutagen. 878:503479. https://doi.org/10.1016/j.mrgentox.2022.503479 PMID:35649672

Dos Santos MAL, de Santana FS, Soares AF, de Sousa SF, Menezes LS, Takeshita WM (2020). Genotoxic and cytotoxic effects of mobile phone use on the oral epithelium: a systematic review with meta-analysis. Gen Dent. 68(6):70–4. PMID:33136050

Dou JR, Zhou X, Pan XY, Miao RF, Zhou ML, Zhang F (2023). [Investigation on health status of workers exposed to glyphosate]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 41(7):517–22. https://rs.yiigle.com/cmaid/1468061 PMID:37524675 [Chinese]

Dow Chemical Co. (1953). Toxicological study of diphenyl in citrus wraps with cover letter. Stanford Research Institute. Midland (MI), USA: Dow Chemical Company. Available from: https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0206456, accessed March 2024.

Druckmann R (2003). Progestins and their effects on the breast. Maturitas. 46 Suppl 1:S59–69. https://doi.org/10.1016/j.maturitas.2003.09.020 PMID:14670647

DrugBank Online (2024a). Alefacept. Edmonton (AL), Canada: DrugBank. Available from: https://go.drugbank.com/drugs/DB00092, accessed March 2024.

DrugBank Online (2024b). 5-Androstenedione. Edmonton (AL), Canada: DrugBank. Available from: https://go.drugbank.com/drugs/DB01456, accessed June 2024.

Duarte-Hospital C, Tête A, Debizet K, Imler J, Tomkiewicz-Raulet C, Blanc EB, et al. (2023). SDHi fungicides: an example of mitotoxic pesticides targeting the succinate dehydrogenase complex. Environ Int. 180:108219. https://doi.org/10.1016/j.envint.2023.108219

Dudkiewicz A, Dutta P, Kołożyn-Krajewska D (2022). Ethylene oxide in foods: current approach to the risk assessment and practical considerations based on the European food business operator perspective. Eur Food Res Technol. 248(7):1951–8. https://doi.org/10.1007/s00217-022-04018-7 PMID:37778286

Duijster JW, Franz E, Neefjes J, Mughini-Gras L (2021). Bacterial and parasitic pathogens as risk factors for cancers in

the gastrointestinal tract: a review of current epidemiological knowledge. Front Microbiol. 12:790256. https://doi.org/10.3389/fmicb.2021.790256 PMID:34956157

Dunford R, Salinaro A, Cai L, Serpone N, Horikoshi S, Hidaka H, et al. (1997). Chemical oxidation and DNA damage catalysed by inorganic sunscreen ingredients. FEBS Lett. 418(1–2):87–90. https://doi.org/10.1016/S0014-5793(97)01356-2 PMID:9414101

Dunnick J (1992). NTP technical report on the toxicity studies of ortho-, meta-, and para-nitrotoluenes (CAS nos. 88-72-2, 99-08-1, 99-99-0) administered in dosed feed to F344/N rats and B6C3F$_1$ mice. Toxic Rep Ser. 23:1–E4. https://ntp.niehs.nih.gov/publications/reports/tox/000s/tox023 PMID:12209183

Dunnick JK, Pandiri AR, Merrick BA, Kissling GE, Cunny H, Mutlu E, et al. (2018). Carcinogenic activity of pentabrominated diphenyl ether mixture (DE-71) in rats and mice. Toxicol Rep. 5:615–24. https://doi.org/10.1016/j.toxrep.2018.05.010 PMID:29868454

Dupont D, Robert MG, Brenier-Pinchart MP, Lefevre A, Wallon M, Pelloux H (2023). *Toxoplasma gondii*, a plea for a thorough investigation of its oncogenic potential. Heliyon. 9(11):e22147. https://doi.org/10.1016/j.heliyon.2023.e22147 PMID:38034818

Duran B, Ozdemir I, Demirel Y, Ozdemir O, Cetin A, Guven A (2006). In vivo evaluation of the genotoxic effects of clomiphene citrate on rat reticulocytes: a micronucleus genotoxicity. Gynecol Obstet Invest. 61(4):228–31. https://doi.org/10.1159/000091739 PMID:16508321

Durando M, Kass L, Piva J, Sonnenschein C, Soto AM, Luque EH, et al. (2007). Prenatal bisphenol A exposure induces preneoplastic lesions in the mammary gland in Wistar rats. Environ Health Perspect. 115(1):80–6, 1289, 9282. https://doi.org/10.1289/ehp.9282 PMID:17366824

Dwivedi DK, Jena GB (2020). Diethylnitrosamine and thioacetamide-induced hepatic damage and early carcinogenesis in rats: role of Nrf2 activator dimethyl fumarate and NLRP3 inhibitor glibenclamide. Biochem Biophys Res Commun. 522(2):381–7. https://doi.org/10.1016/j.bbrc.2019.11.100 PMID:31761320

Eakin AJ, Mc Erlain T, Burke A, Eaton A, Tipping N, Allocca G, et al. (2020). Circulating levels of epirubicin cause endothelial senescence while compromising metabolic activity and vascular function. Front Cell Dev Biol. 8:799. https://doi.org/10.3389/fcell.2020.00799 PMID:32974345

Easley CA 4th, Bradner JM, Moser A, Rickman CA, McEachin ZT, Merritt MM, et al. (2015). Assessing reproductive toxicity of two environmental toxicants with a novel in vitro human spermatogenic model. Stem Cell Res. 14(3):347–55. https://doi.org/10.1016/j.scr.2015.03.002 PMID:25863443

Easton DF, Peto J, Morgan LG, Metcalfe LP, Usher V, Doll R (1992). Respiratory cancer mortality in Welsh nickel refiners: which nickel compounds are responsible? In: Nieboer E, Nriagu JO, editors. Nickel and human health: current perspectives. New York (NY), USA: Wiley and Sons; pp. 603–19.

Eaves LA, Smeester L, Hartwell HJ, Lin YH, Arashiro M, Zhang Z, et al. (2020). Isoprene-derived secondary organic aerosol induces the expression of microRNAs associated with inflammatory/oxidative stress response in lung cells. Chem Res Toxicol. 33(2):381–7. https://doi.org/10.1021/acs.chemrestox.9b00322 PMID:31765140

Eberle CE, Sandler DP, Taylor KW, White AJ (2020). Hair dye and chemical straightener use and breast cancer risk in a large US population of black and white women. Int J Cancer. 147(2):383–91. https://doi.org/10.1002/ijc.32738 PMID:31797377

Ebmeyer J, Rasinger JD, Hengstler JG, Schaudien D, Creutzenberg O, Lampen A, et al. (2020). Hepatotoxic pyrrolizidine alkaloids induce DNA damage response in rat liver in a 28-day feeding study. Arch Toxicol. 94(5):1739–51. https://doi.org/10.1007/s00204-020-02779-2https://doi.org/10.1007/s00204-020-02779-2 PMID:32419051

ECHA (2008). Data on manufacture, import, export, uses and releases of alkanes, C10-13, Chloro (SCCPS) as well as information on potential alternatives to its use. Helsinki, Finland: European Chemical Agency. Available from: https://echa.europa.eu/documents/10162/354d4bac-d3b0-aca9-bd59-79f4d058fb22, accessed June 2024.

ECHA (2010). Evaluation of new scientific evidence concerning the restrictions contained in Annex XVII to regulation. Review of new available information for di-'isononyl' phthalate (DINP). Helsinki, Finland: European Chemical Agency.

ECHA (2013). Support document for identification of disodium 3,3′-[[1,1'-biphenyl]-4,4' diylbis(azo)]bis(4-aminonaphthalene-1-sulphonate) (c.i. direct red 28) as a substance of very high concern because of its CMR properties. Helsinki, Finland: European Chemical Agency. Available from: https://echa.europa.eu/documents/10162/cf3a4398-3305-424e-ab1e-a02fbc548431, accessed January 2024.

ECHA (2015). Acetaldehyde Working Group. Comments on the CLH report on acetaldehyde; proposal for harmonised classification and labeling (June 2015). Helsinki, Finland: European Chemical Agency. Available from: https://echa.europa.eu/documents/10162/b9885f2c-b491-4ad4-8900-8cba349b15a0, accessed January 2024.

ECHA (2016). Substance evaluation conclusion as required by reach article 48 and evaluation report for 2,4,6-tribromophenol. EC No 204–278–6. CAS no 118-79-6. Helsinki, Finland: European Chemical Agency. Available from: https://echa.europa.eu/documents/10162/fd19d44e-7365-c189-d263-d3b0f4cc7dd9, accessed January 2024.

ECHA (2019a). Annex XV report. Proposal for identification of very high concern on the basis of the criteria set out in reach article 57. Substance name(s): 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoic acid, its salts and its acyl halides (covering any of their individual isomers and combinations thereof). Helsinki, Finland: European Chemical Agency. Available from: https://www.echa.europa.eu/documents/10162/ef1b1606-b234-2ce5-e159-2ab89d61bfbc, accessed January 2024.

ECHA (2019b). Annex XV restriction report. Proposal for a restriction. Substance name(s): Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related substances. Helsinki, Finland: European Chemical Agency. Available from: https://echa.europa.eu/documents/10162/a22da803-0749-81d8-bc6d-ef551fc24e19, accessed March 2024.

ECHA (2021a). Draft ECHA scientific report for evaluation of limit values for isoprene at the workplace. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/documents/10162/431f6bc0-a4b3-a1a1-4e8f-6c8eb48ab64a, accessed January 2024.

ECHA (2021b). Substance evaluation conclusion as required by EACH article 48 and evaluation report for p-xylene and o-xylene and m-xylene. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/documents/10162/2525f5e6-5f59-59bc-2f61-5efaeb4c700d, accessed January 2024.

ECHA (2022a). Combined draft assessment report prepared according to Regulation (EC) N° 1107/2009 and proposal for harmonised classification and labelling (CLH Report) according to Regulation (EC) N° 1272/2008, metyltetraprole (ISO); 1-[2-({[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy}thyl)-3-methylphenyl]-4-methyl-1,4-dihydro-5H-tetrazol-5-one. ECHA Registry of CLH intentions, CAS no. 1472649-01-6. Helsinki, Finland: European Chemical Agency. Available from: https://echa.europa.eu/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e1829d36fc, accessed January 2024.

ECHA (2022b). Combined draft assessment report prepared according to Regulation (EC) N° 1107/2009 and proposal for harmonised classification and labelling (CLH Report) according to Regulation (EC) no 1272/2008, proquinazid. Available from ECHA Registry of CLH intentions, CAS no. 1472649-01-6. Helsinki, Finland: European Chemical Agency. Available from: https://echa.europa.eu/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e180a10e0b, accessed January 2024.

ECHA (2023a). Butyraldehyde. Brief profile. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/de/brief-profile/-/briefprofile/100.004.225, accessed January 2024.

ECHA (2023b). Butyraldehyde. Substance infocard. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.004.225, accessed January 2024.

ECHA (2023c). Pin-2(3)-ene. Brief profile. Helsinki, Finland: European Chemical Agency. Available from: https://echa.europa.eu/brief-profile/-/briefprofile/100.001.175, accessed January 2024.

ECHA (2023d). Active substances, safeners and synergists. Helsinki, Finland: European Chemical Agency. Available from: https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/start/screen/active-substances, accessed January 2024.

ECHA (2023e). Methyl anthranilate. Brief profile. Helsinki, Finland: European Chemical Agency. Available from: https://echa.europa.eu/de/brief-profile/-/briefprofile/100.004.667, accessed January 2024.

ECHA (2023f). Xylenol. CAS number: 1300-71-6. EC number: 215–089–3. Registration dossier. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/registration-dossier/-/registered-dossier/17240, accessed February 2024.

ECHA (2023g). Palmitic acid. Brief profile. Helsinki, Finland: European Chemical Agency. Available from: https://echa.europa.eu/de/brief-profile/-/briefprofile/100.000.284, accessed January 2024.

ECHA (2024a). Ametryn. Endpoint summary. Registered dossier. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/registration-dossier/-/registered-dossier/2171/7/7/1, accessed March 2024.

ECHA (2024b). Classification and labelling inventory. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/regulations/clp/cl-inventory, accessed January 2024.

Edalati S, Bagherzadeh F, Asghari Jafarabadi M, Ebrahimi-Mamaghani M (2021). Higher ultra-processed food intake is associated with higher DNA damage in healthy adolescents. Br J Nutr. 125(5):568–76. https://doi.org/10.1017/S0007114520001981 PMID:32513316

Edwards L, Ahmed L, Martinez L, Huda S, Shamasunder B, McDonald JA, et al. (2023). Beauty inside out: examining beauty product use among diverse women and femme-identifying individuals in Northern Manhattan and South Bronx through an environmental justice framework. Environ Justice. 16(6):449–60. https://doi.org/10.1089/env.2022.0053 PMID:38074851

Edwards M, Can AS (2023). Progestin. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK563211/

EFSA (2006a). Conclusion regarding the peer review of the pesticide risk assessment of the active substance carbaryl. EFSA J. 2006(80):1–71.

EFSA (2006b). Opinion of the scientific panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to the 12th list of substances for food contact materials. Question number: EFSA-Q-2004–073, EFSA-Q-2006–024, EFSA-Q-2005–238a, EFSA-Q-2005–238b, EFSA-Q-2005–238c, EFSA-Q-2006–012, EFSA-Q-2006–027. EFSA J. 395–401:1–21. https://doi.org/10.2903/j.efsa.2006.395

EFSA (2008). Active substance: boscalid (formerly nicobifen). Status under Reg. (EC) No 1107/2009. Parma, Italy: European Food Safety Authority. Available from: https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/start/screen/active-substances/details/472, accessed February 2024.

EFSA (2009). Conclusion on the peer review of the pesticide risk assessment of the active substance proquinazid on request from the European Commission. EFSA J. 7(10):1350. https://doi.org/10.2903/j.efsa.2009.1350

EFSA (2015a). Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA J. 13(11):4302. .

EFSA (2015b). Scientific opinion on acrylamide in food. EFSA Panel on Contaminants in the Food Chain (CONTAM). Parma, Italy: European Food Safety Authority. Available from: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2015.4104, accessed February 2024.

EFSA (2018). Renewal Assessment Report (RAR) on the active substance mancozeb. Parma, Italy: European Food Safety Authority. Available from: https://www.efsa.europa.eu/en/consultations/call/180226-0, accessed February 2024.

EFSA (2019). Statement on the available outcomes of the human health assessment in the context of the pesticides peer review of the active substance chlorpyrifos. EFSA J. 17(8):e05809. PMID:32626415

EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain); Knutsen HK, Alexander J, Barregård L, Bignami M, Brüschweiler B, Ceccatelli S, et al. (2017). Risks for human health related to the presence of pyrrolizidine alkaloids in honey, tea, herbal infusions and food supplements. EFSA J. 15(7):e04908. https://doi.org/10.2903/j.efsa.2017.4908 PMID:32625569

EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain); Schrenk D, Bignami M, Bodin L, Chipman JK, del Mazo J, Grasl-Kraupp B, et al. (2020) Scientific opinion on the update of the risk assessment of nickel in food and drinking water. EFSA J. 18(11):6268. PMID:33193868

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) (2011). Scientific opinion on the re-evaluation of erythrosine (E 127) as a food additive. EFSA J. 9(1):1854. https://doi.org/10.2903/j.efsa.2011.1854

EFSA Panel on Food Contact Materials, Enzymes and Processing Aids; Lambré C, Barat Baviera JM, Bolognesi C, Chesson A, Cocconcelli PS, Crebelli R, et al. (2023) Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. EFSA J. 21(4):e06857. https://doi.org/10.2903/j.efsa.2023.6857

PMID:37089179

EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA); Turck D, Bohn T, Castenmiller J, de Henauw S, Hirsch-Ernst K-I, Knutsen HK (2023). Scientific opinion on the tolerable upper intake level for selenium. EFSA J. 21(1):7704. PMID:36698500

Egan KM, Kim Y, Bender N, Hodge JM, Coghill AE, Smith-Warner SA, et al. (2021). Prospective investigation of polyomavirus infection and the risk of adult glioma. Sci Rep. 11(1):9642. https://doi.org/10.1038/s41598-021-89133-3 PMID:33953301

Ehrlich A, Gordon RE, Dikman SH (1991). Carcinoma of the colon in asbestos-exposed workers: analysis of asbestos content in colon tissue. Am J Ind Med. 19(5):629–36. https://doi.org/10.1002/ajim.4700190507 PMID:1647135

Eigeliene N, Härkönen P, Erkkola R (2006). Effects of estradiol and medroxyprogesterone acetate on morphology, proliferation and apoptosis of human breast tissue in organ cultures. BMC Cancer. 6(1):246. https://doi.org/10.1186/1471-2407-6-246 PMID:17044944

Eisen EA, Bardin J, Gore R, Woskie SR, Hallock MF, Monson RR (2001). Exposure–response models based on extended follow-up of a cohort mortality study in the automobile industry. Scand J Work Environ Health. 27(4):240–9. https://doi.org/10.5271/sjweh.611https://doi.org/10.5271/sjweh.611 PMID:11560338

Eisen EA, Tolbert PE, Hallock MF, Monson RR, Smith TJ, Woskie SR (1994). Mortality studies of machining fluid exposure in the automobile industry. III: A case–control study of larynx cancer. Am J Ind Med. 26(2):185–202. https://doi.org/10.1002/ajim.4700260205 PMID:7977395

El-Ashmawy NE, El-Bahrawy HA, Shamloula MM, El-Feky OA (2014). Biochemical/metabolic changes associated with hepatocellular carcinoma development in mice. Tumour Biol. 35(6):5459–66. https://doi.org/10.1007/s13277-014-1714-6 PMID:24523022

El Ati-Hellal M, Doggui R, Krifa Y, El Ati J (2018). Potassium bromate as a food additive: a case study of Tunisian breads. Environ Sci Pollut Res Int. 25(3):2702–6. https://doi.org/10.1007/s11356-017-0712-9 PMID:29134528

El Balkhi S, Saint-Marcoux F (2023). Chlordecone determination in serum by LC–MS/MS and the importance of low limit of detection. J Chromatogr B Analyt Technol Biomed Life Sci. 1230:123915. https://doi.org/10.1016/j.jchromb.2023.123915 PMID:37925903

El-Domyati M, El-Ammawi TS, Medhat W, Moawad O, Mahoney MG, Uitto J (2013). Expression of p53 protein after nonablative rejuvenation: the other side of the coin. Dermatol Surg. 39(6):934–43. https://doi.org/10.1111/dsu.12145 PMID:23458347

El-Far YM, Khodir AE, Noor AO, Almasri DM, Bagalagel AA, Diri RM, et al. (2020). Selective cytotoxic activity and protective effects of sodium ascorbate against hepatocellular carcinoma through its effect on oxidative stress and apoptosis *in vivo* and *in vitro*. Redox Rep. 25(1):17–25. https://doi.org/10.1080/13510002.2020.1739870 PMID:32172678

El-Farrash RA, El-Shimy MS, Tawfik S, Nada AS, Salem DAD, M Gallo MS, et al. (2019). Effect of phototherapy on oxidant/antioxidant status: a randomized controlled trial. Free Radic Res. 53(2):179–86. https://doi.org/10.1080/10715762.2018.1549364 PMID:30458636

El Golli-Bennour E, Timoumi R, Koroit M, Bacha H, Abid-Essefi S (2019). Protective effects of kefir against zearalenone toxicity mediated by oxidative stress in cultured HCT-116 cells. Toxicon. 157:25–34. https://doi.org/10.1016/j.toxicon.2018.11.296 PMID:30448289

El-Nahhal Y, Lubbad R (2018). Acute and single repeated dose effects of low concentrations of chlorpyrifos, diuron, and their combination on chicken. Environ Sci Pollut Res Int. 25(11):10837–47. https://doi.org/10.1007/s11356-018-1313-y PMID:29397503

El Okle OS, El Euony OI, Khafaga AF, Lebda MA (2018). Thiamethoxam induced hepatotoxicity and pro-carcinogenicity in rabbits via motivation of oxidative stress, inflammation, and anti-apoptotic pathway. Environ Sci Pollut Res Int. 25(5):4678–89. https://doi.org/10.1007/s11356-017-0850-0 PMID:29197058

El Sadda RR, Elshahawy ZR, Saad EA (2023). Biochemical and pathophysiological improvements in rats with thioacetamide induced-hepatocellular carcinoma using aspirin plus vitamin C. BMC Cancer. 23(1):175. https://doi.org/10.1186/s12885-023-10644-5 PMID:36809998

El Saie A, Fu C, Grimm SL, Robertson MJ, Hoffman K, Putluri V, et al. (2022). Metabolome and microbiome multi-omics integration from a murine lung inflammation model of bronchopulmonary dysplasia. Pediatr Res. 92(6):1580–9. https://doi.org/10.1038/s41390-022-02002-1 PMID:35338351

El Skhawy N, Eissa MM (2023). Shedding light on a mysterious link between *Toxoplasma gondii* and cancer: a review. Exp Parasitol. 250:108544. https://doi.org/10.1016/j.exppara.2023.108544 PMID:37149210

El-Tonsy MM, Hussein HM, Helal T-S, Tawfik RA, Koriem KM, Hussein HM (2013). *Schistosoma mansoni* infection: is it a risk factor for development of hepatocellular carcinoma? Acta Trop. 128(3):542–7. https://doi.org/10.1016/j.actatropica.2013.07.024 PMID:23932944

Elcombe CR, Odum J, Foster JR, Stone S, Hasmall S, Soames AR, et al. (2002). Prediction of rodent nongenotoxic carcinogenesis: evaluation of biochemical and tissue changes in rodents following exposure to nine nongenotoxic NTP carcinogens. Environ Health Perspect. 110(4):363–75. https://doi.org/10.1289/ehp.02110363 PMID:11940454

Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA (2013). Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer. 13(11):759–71. https://doi.org/10.1038/nrc3611 PMID:24154716

Elliott L, Loomis D, Dement J, Hein MJ, Richardson D, Stayner L (2012). Lung cancer mortality in North Carolina and South Carolina chrysotile asbestos textile workers. Occup Environ Med. 69(6):385–90. https://doi.org/10.1136/oemed-2011-100229 PMID:22267448

Ellis CN, Krueger GG; Alefacept Clinical Study Group (2001). Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. N Engl J Med. 345(4):248–55. https://doi.org/10.1056/NEJM200107263450403 PMID:11474662

Elloumi-Mseddi J, Jemel-Oualha I, Beji A, Hakim B, Aifa S (2015). Effect of estradiol and clomiphene citrate on Erk activation in breast cancer cells. J Recept Signal Transduct Res. 35(2):202–6. https://doi.org/10.3109/10799893.2014.951895 PMID:25319474

Elwood JM, Werf BV (2022). Nitrates in drinking water and cancers of the colon and rectum: a meta-analysis of epidemiological studies. Cancer Epidemiol. 78:102148. https://doi.org/10.1016/j.canep.2022.102148https://doi.org/10.1016/j.canep.2022.102148 PMID:35429892

EMA (2018). Assessment report on *Cimicifuga racemosa* (L.) Nutt., rhizome. London, UK: Committee on Herbal Medicinal Products, European Medicines Agency. Available from: https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-cimicifuga-racemosa-l-nutt-rhizome-revision-1_en.pdf, accessed January 2024.

Emeville E, Giton F, Giusti A, Oliva A, Fiet J, Thomé JP, et al. (2013). Persistent organochlorine pollutants with endocrine activity and blood steroid hormone levels in middle-aged men. PLoS One. 8(6):e66460. https://doi.org/10.1371/journal.pone.0066460 PMID:23785499

Emeville E, Giusti A, Coumoul X, Thomé JP, Blanchet P, Multigner L (2015). Associations of plasma concentrations of dichlorodiphenyldichloroethylene and polychlorinated biphenyls with prostate cancer: a case–control study in Guadeloupe (French West Indies). Environ Health Perspect. 123(4):317–23. https://doi.org/10.1289/ehp.1408407 PMID:25493337

Emmer KM, Russart KLG, Walker WH, Nelson RJ, DeVries AC (2018). Effects of light at night on laboratory animals and research outcomes. Behav Neurosci. 132(4):302–14. https://doi.org/10.1037/bne0000252 PMID:29952608

Engel A, Buhrke T, Kasper S, Behr AC, Braeuning A, Jessel S, et al. (2018). The urinary metabolites of DINCH® have an impact on the activities of the human nuclear receptors ERα, ERβ, AR, PPARα and PPARγ. Toxicol Lett. 287:83–91. https://doi.org/10.1016/j.toxlet.2018.02.006 PMID:29421333

Engel LS, Werder E, Satagopan J, Blair A, Hoppin JA, Koutros S, et al. (2017). Insecticide use and breast cancer risk among farmers' wives in the Agricultural Health Study. Environ Health Perspect. 125(9):097002. https://doi.org/10.1289/EHP1295 PMID:28934092

Ennis ZN, Broe A, Pottegård A, Ahern TP, Hallas J, Damkier P (2018). Cumulative exposure to phthalates from phthalate-containing drug products: a Danish population-wide study. Br J Clin Pharmacol. 84(8):1798–805. https://doi.org/10.1111/bcp.13614 PMID:29688578

Ensley SM (2018). Pyrethrins and pyrethroids. Chapter 39. In: Gupta RC, editor. Veterinary Toxicology. Third edition. Cambridge (MA), USA: Academic Press; pp. 515-520.

Environment Canada (2007a). Challenge Questionnaire [voluntary data submitted by industry]. Gatineau (QC), Canada: Environment Canada, Existing Substances Division. Available upon request from: Existing Substances Division, Environment Canada, Ottawa, K1A 0H3.

Environment Canada (2007b). Additional voluntary information on substance CAS no. 120-80-9 submitted by industry. Gatineau (QC), Canada: Environment Canada, Existing Substances Division. Available upon request from: Existing Substances Division, Environment Canada, Ottawa, K1A 0H3.

Eriksson M, Hardell L, Berg NO, Möller T, Axelson O (1981). Soft-tissue sarcomas and exposure to chemical substances: a case-referent study. Br J Ind Med. 38(1):27–33. https://doi.org/10.1136/oem.38.1.27 PMID:7470401

Ernst B, Setayesh T, Nersesyan A, Kundi M, Fenech M, Bolognesi C, et al. (2021). Investigations concerning the impact of consumption of hot beverages on acute cytotoxic and genotoxic effects in oral mucosa cells. Sci Rep. 11(1):23014. https://doi.org/10.1038/s41598-021-01995-9 PMID:34836993

Escoula L, Bourdiol D, Linas MD, Recco P, Seguela JP (1988b). Enhancing resistance and modulation of humoral immune response to experimental *Candida albicans* infection by patulin. Mycopathologia. 103(3):153–6. https://doi.org/10.1007/BF00436814 PMID:3057378

Escoula L, Thomsen M, Bourdiol D, Pipy B, Peuriere S, Roubinet F (1988a). Patulin immunotoxicology: effect on phagocyte activation and the cellular and humoral immune system of mice and rabbits. Int J Immunopharmacol. 10(8):983–9. https://doi.org/10.1016/0192-0561(88)90045-8 PMID:3265132

Escutia B, Ledesma E, Serra-Guillen C, Gimeno C, Vilata JJ, Guillén C, et al. (2011). Detection of human papilloma virus in normal skin and in superficial and nodular basal cell carcinomas in immunocompetent subjects. J Eur Acad Dermatol Venereol. 25(7):832–8. https://doi.org/10.1111/j.1468-3083.2010.03875.x PMID:21054564

Espejo-Herrera N, Gràcia-Lavedan E, Boldo E, Aragonés N, Pérez-Gómez B, Pollán M, et al. (2016). Colorectal cancer risk and nitrate exposure through drinking water and diet. Int J Cancer. 139(2):334–46. https://doi.org/10.1002/ijc.30083 PMID:26954527

Essien EE, Said Abasse K, Côté A, Mohamed KS, Baig MMFA, Habib M, et al. (2022). Drinking-water nitrate and cancer risk: a systematic review and meta-analysis. Arch Environ Occup Health. 77(1):51–67. https://doi.org/10.1080/19338244.2020.1842313https://doi.org/10.1080/19338244.2020.1842313 PMID:33138742

Esteban-Jurado C, Garre P, Vila M, Lozano JJ, Pristoupilova A, Beltrán S, et al. (2014). New genes emerging for colorectal cancer predisposition. World J Gastroenterol. 20(8):1961–71. https://doi.org/10.3748/wjg.v20.i8.1961 PMID:24587672

Esteves M, Silva C, Bovolini A, Pereira SS, Morais T, Moreira Â, et al. (2023). Regular voluntary running is associated with increased tumor vascularization and immune cell infiltration and decreased tumor growth in mice. Int J Sports Med. 44(6):427–37. https://doi.org/10.1055/a-2008-7732 PMID:36931293

Esteves M, Silva C, Pereira SS, Morais T, Moreira Â, Costa MM, et al. (2021). Regular voluntary running inhibits androgen-independent prostate cancer growth in mice. J Phys Act Health. 18(6):653–9. https://doi.org/10.1123/jpah.2020-0761 PMID:33848979

Estill CF, Slone J, Mayer A, Chen IC, La Guardia MJ (2020). Worker exposure to flame retardants in manufacturing, construction and service industries. Environ Int. 135:105349. https://doi.org/10.1016/j.envint.2019.105349 PMID:31810010

Eubanks A (2023). Hormone therapy: menopausal hormone therapy. FP Essent. 531:15–21. PMID:37603881

EUR-Lex (2023). Commission Implementing Regulation (EU) 2023/2660 of 28 November 2023 renewing the approval of the active substance glyphosate in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council and amending Commission Implementing Regulation (EU) No 540/2011. Brussels, Belgium: European Union. Available from: https://eur-lex.europa.eu/eli/reg_impl/2023/2660/oj, accessed June 2024.

European Commission (2002a). Opinion of the Scientific Committee on Food on the safety of the presence of safrole (1-allyl-3,4-methylene dioxy benzene) in flavourings and other food ingredients with flavouring properties.

(adopted on 12 December 2001). Brussels, Belgium: European Commission, Health & Consumer Protection Directorate-General, Scientific Committee on Food. Available from: https://food.ec.europa.eu/system/files/2016-10/fs_food-improvement-agents_flavourings-out116.pdf, accessed June 2024.

European Commission (2002b). Review report for the active substance cinidon ethyl. EU pesticides database. Brussels, Belgium: European Commission. Available from: https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/start/screen/active-substances/details/555, accessed February 2019.

European Commission (2002c). Directive 2002/61/EC of the European Parliament and of the Council of 19 July 2002 amending for the nineteenth time Council Directive 76/769/EEC relating to restrictions on the marketing and use of certain dangerous substances and preparations (azocolourants). L243/15. Brussels, Belgium: European Commission. Available from: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:243:0015:0018:en:PDF, accessed June 2024.

European Commission (2006). Commission regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. Brussels, Belgium: European Commission. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006R1881-20140701, accessed June 2024.

European Commission (2007a). Review report for the active substance alachlor. EU pesticides database. Brussels, Belgium: European Commission. Available from: http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=homepage&language=EN

European Commission (2007b). Health and Consumer Protection Directorate-General (HaCPD). Review report for the active substance carbaryl. SANCO/10049/06 – rev 02006. Brussels, Belgium: European Commission.

European Commission (2010). Opinion on CI 45430 (Erythrosine). Brussels, Belgium: Scientific Committee on Consumer Safety, Public Health and Risk Assessment, Health & Consumers Directorate C, European Commission. Available from: https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_030.pdf, accessed June 2024.

European Commission (2020a). Food Safety. Chlorpyrifos and chlorpyrifos-methyl. Brussels, Belgium, European Commission. Available from: https://food.ec.europa.eu/plants/pesticides/approval-active-substances/renewal-approval/chlorpyrifos-chlorpyrifos-methyl_en, accessed June 2024.

European Commission (2020b). EC Final renewal report for the active substance mancozeb finalised by the Standing Committee on Plants, Animals, Food and Feed on 23 October 2020 in view of the non-renewal of the approval of mancozeb as an active substance in accordance with Regulation (EC) No 1107/2009. SANTE/10326/2020 Rev 1. Brussels, Belgium, European Commission. Available from: https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/backend/api/active_substance/download/1115, accessed June 2024.

European Commission (2022). Commission Implementing Regulation (EU) 2022/94 of 24 January 2022 concerning the non-renewal of the approval of the active substance phosmet, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011. Brussels, Belgium: European Commission. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32022R0094, accessed June 2024.

European Commission (2023). Commission Regulation (EU) 2023/2108 of 6 October 2023 amending Annex II to Regulation (EC) No 1333/2008 of the European Parliament and of the Council and the Annex to Commission Regulation (EU) No 231/2012 as regards food additives nitrites (E 249–250) and nitrates (E 251–252). 2023. Brussels, Belgium: European Commission. Available from: https://eur-lex.europa.eu/eli/reg/2023/2108/oj, accessed December 2023.

European Commission (2024). EU Pesticides Database. Active substances, safeners and synergists. Brussels, Belgium: European Commission. Available from: https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/start/screen/active-substances, accessed October 2024.

European Food Safety Authority (EFSA); Anastassiadou M, Arena M, Auteri D, Brancato A, Bura L, Cabrera LC, et al. (2021). Peer review of the pesticide risk assessment of the active substance phosmet. EFSA J. 19(3):e06237. PMID:33747228

European Medicines Agency (2011). Ablavar. Gadofosveset trisodium. EPAR summary for the public. London, UK: European Medicines Agency. EMA/CHMP/54085/2011 Available from:

https://www.ema.europa.eu/en/documents/overview/ablavar-epar-summary-public_en.pdf, accessed March 2024.

European Medicines Agency (2012). European Medicines Agency recommends first gene therapy for approval. Press release EMA/CHMP/474664/2012. 20 July 2012. London, UK: European Medicines Agency. Available from: https://www.ema.europa.eu/en/documents/press-release/european-medicines-agency-recommends-first-gene-therapy-approval_en.pdf#:~:text=The%20European%20Medicines%20Agency%E2%80%99s%20Committee%20for%20Medicinal%20Products,or%20multiple%20pancreatitis%20attacks%2C%20despite%20dietary%20fat%20restrictions, accessed May 2024.

European Medicines Agency (2020a). New gene therapy to treat spinal muscular atrophy. Press release EMA/163207/2020. 27 March 2020. Amsterdam, Netherlands: European Medicines Agency. Available from: https://www.ema.europa.eu/en/documents/press-release/new-gene-therapy-treat-spinal-muscular-atrophy_en.pdf, accessed May 2024.

European Medicines Agency (2020b). Libmeldy (autologous CD34+ cell enriched population that contains haematopoietic stem and progenitor cells transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A gene). An overview of Libmeldy and why it is authorised in the EU. Amsterdam, Netherlands: European Medicines Agency. Available from: https://www.ema.europa.eu/en/documents/overview/libmeldy-epar-medicine-overview_en.pdf, accessed May 2024.

European Medicines Agency (2021). First gene therapy to treat children with rare inherited neurological disease. Amsterdam, Netherlands: European Medicines Agency. Available from: https://www.ema.europa.eu/en/news/first-gene-therapy-treat-children-rare-inherited-neurological-disease, accessed June 2024.

European Medicines Agency (2022a). First therapy to treat rare genetic nervous system disorder AADC deficiency. Amsterdam, Netherlands: European Medicines Agency. Available from: https://www.ema.europa.eu/en/news/first-therapy-treat-rare-genetic-nervous-system-disorder-aadc-deficiency, accessed May 2024.

European Medicines Agency (2022b). First gene therapy to treat haemophilia B. Amsterdam, Netherlands: European Medicines Agency. Available from: https://www.ema.europa.eu/en/news/first-gene-therapy-treat-haemophilia-b, accessed May 2024.

European Medicines Agency (2024a). Dabrafenib. Summary of product characteristics. Amsterdam, Netherlands: European Medicines Agency. Available from: https://www.ema.europa.eu/en/documents/product-information/tafinlar-epar-product-information_en.pdf, accessed January 2024.

European Medicines Agency (2024b). Encorafenib. Summary of product characteristics. Amsterdam, Netherlands: European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/braftovi-epar-product-information_en.pdf, accessed January 2024.

European Medicines Agency (2024c). Vemurafenib. Summary of product characteristics. Amsterdam, Netherlands: European Medicines Agency. Available from: https://www.ema.europa.eu/en/documents/product-information/zelboraf-epar-product-information_en.pdf, accessed January 2024.

European Parliament (2008). Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. Annex III. Brussels, Belgium, European Union. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2008:354:FULL&from=CS, accessed June 2024.

European Union (1998). Commission regulation (EC) No 2788/98 of 22 December 1998 amending Council Directive 70/524/EEC concerning additives in feeding stuffs as regards the withdrawal of authorisation for certain growth promoters. Official Journal of the European Communities L 347/31. Brussels, Belgium: European Union. Available from: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:347:0031:0032:EN:PDF

Eusebi LH, Zagari RM, Bazzoli F (2014). Epidemiology of *Helicobacter pylori* infection. Helicobacter. 19 Suppl 1:1–5. https://doi.org/10.1111/hel.12165 PMID:25167938

Evans N, Conley JM, Cardon M, Hartig P, Medlock-Kakaley E, Gray LE Jr (2022). In vitro activity of a panel of per- and polyfluoroalkyl substances (PFAS), fatty acids, and pharmaceuticals in peroxisome proliferator-activated

receptor (PPAR) alpha, PPAR gamma, and estrogen receptor assays. Toxicol Appl Pharmacol. 449:116136. https://doi.org/10.1016/j.taap.2022.116136https://doi.org/10.1016/j.taap.2022.116136 PMID:35752307

Everatt R, Slapšytė G, Mierauskienė J, Dedonytė V, Bakienė L (2013). Biomonitoring study of dry cleaning workers using cytogenetic tests and the comet assay. J Occup Environ Hyg. 10(11):609–21. https://doi.org/10.1080/15459624.2013.818238 PMID:24116666

Evlampidou I, Font-Ribera L, Rojas-Rueda D, Gracia-Lavedan E, Costet N, Pearce N, et al. (2020). Trihalomethanes in drinking water and bladder cancer burden in the European Union. Environ Health Perspect. 128(1):17001. https://doi.org/10.1289/EHP4495 PMID:31939704

EWG (2024). Menthyl anthranilate. Washington (DC), USA: Environmental Working Group. Available from: https://www.ewg.org/skindeep/ingredients/703863-MENTHYL_ANTHRANILATE/, accessed June 2024.

Exley C, Siesjö P, Eriksson H (2010). The immunobiology of aluminium adjuvants: how do they really work? Trends Immunol. 31(3):103–9. https://doi.org/10.1016/j.it.2009.12.009 PMID:20153253

Exon JH, Koller LD (1985). Toxicity of 2-chlorophenol, 2,4-dichlorophenol, and 2,4,6-trichlorophenol. In: Jolley RL, Bull RJ, Davis WP, Katz S, Roberts MH Jr, Jacobs VA, editors. Water chlorination, environmental impact and health effects. Volume 5. Chelsea (MI): Lewis Publishers; pp. 307–30.

Ezhilarasan D (2021). Hepatotoxic potentials of methotrexate: understanding the possible toxicological molecular mechanisms. Toxicology. 458:152840. https://doi.org/10.1016/j.tox.2021.152840 PMID:34175381

Ezhilarasan D (2023). Molecular mechanisms in thioacetamide-induced acute and chronic liver injury models. Environ Toxicol Pharmacol. 99:104093. https://doi.org/10.1016/j.etap.2023.104093 PMID:36870405

Ezzi L, Belhadj Salah I, Haouas Z, Sakly A, Grissa I, Chakroun S, et al. (2016). Histopathological and genotoxic effects of chlorpyrifos in rats. Environ Sci Pollut Res Int. 23(5):4859–67. https://doi.org/10.1007/s11356-015-5722-x PMID:26545888

Fabiani R, Rosignoli P, De Bartolomeo A, Fuccelli R, Morozzi G (2007). DNA-damaging ability of isoprene and isoprene mono-epoxide (EPOX I) in human cells evaluated with the comet assay. Mutat Res. 629(1):7–13. https://doi.org/10.1016/j.mrgentox.2006.12.007 PMID:17317274

Fabiani R, Rosignoli P, De Bartolomeo A, Fuccelli R, Morozzi G (2012). Genotoxicity of alkene epoxides in human peripheral blood mononuclear cells and HL60 leukaemia cells evaluated with the comet assay. Mutat Res. 747(1):1–6. https://doi.org/10.1016/j.mrgentox.2012.01.004 PMID:22285587

Falchi F, Bará S (2023). Light pollution is skyrocketing. Science. 379(6629):234–5. https://doi.org/10.1126/science.adf4952 PMID:36656943

Falchi F, Cinzano P, Duriscoe D, Kyba CCM, Elvidge CD, Baugh K, et al. (2016). The new world atlas of artificial night sky brightness. Sci Adv. 2(6):e1600377. https://doi.org/10.1126/sciadv.1600377 PMID:27386582

Falcioni L, Bua L, Tibaldi E, Lauriola M, De Angelis L, Gnudi F, et al. (2018). Report of final results regarding brain and heart tumors in Sprague-Dawley rats exposed from prenatal life until natural death to mobile phone radiofrequency field representative of a 1.8 GHz GSM base station environmental emission. Environ Res. 165:496–503. https://doi.org/10.1016/j.envres.2018.01.037 PMID:29530389

Fan W, Yanase T, Morinaga H, Gondo S, Okabe T, Nomura M, et al. (2007). Atrazine-induced aromatase expression is SF-1 dependent: implications for endocrine disruption in wildlife and reproductive cancers in humans. Environ Health Perspect. 115(5):720–7. https://doi.org/10.1289/ehp.9758 PMID:17520059

Fang H, Tong W, Shi LM, Blair R, Perkins R, Branham W, et al. (2001). Structure–activity relationships for a large diverse set of natural, synthetic, and environmental estrogens. Chem Res Toxicol. 14(3):280–94. https://doi.org/10.1021/tx000208y PMID:11258977

Fang JL, Stingley RL, Beland FA, Harrouk W, Lumpkins DL, Howard P (2010). Occurrence, efficacy, metabolism, and toxicity of triclosan. J Environ Sci Health Part C Environ Carcinog Ecotoxicol Rev. 28(3):147–71. https://doi.org/10.1080/10590501.2010.504978 PMID:20859822

Fang JL, Vaca CE (1997). Detection of DNA adducts of acetaldehyde in peripheral white blood cells of alcohol abusers. Carcinogenesis. 18(4):627–32. https://doi.org/10.1093/carcin/18.4.627 PMID:9111191

Fang JL, Vanlandingham MM, Olson GR, Maisha MP, Felton R, Beland FA (2024). Two-year dermal carcinogenicity bioassay of triclosan in B6C3F1 mice. Arch Toxicol. 98(1):335–45. https://doi.org/10.1007/s00204-023-03613-1 PMID:37874342

Fang L, Fehse B, Engel M, Zander A, Kröger N (2005). Antithymocyte globulin induces ex vivo and in vivo depletion of myeloid and plasmacytoid dendritic cells. Transplantation. 79(3):369–71. https://doi.org/10.1097/01.TP.0000150210.77543.1B PMID:15699773

Fang SC, Mehta AJ, Hang JQ, Eisen EA, Dai HL, Zhang HX, et al. (2013). Cotton dust, endotoxin and cancer mortality among the Shanghai textile workers cohort: a 30-year analysis. Occup Environ Med. 70(10):722–9. https://doi.org/10.1136/oemed-2012-100950 PMID:23828454

Fanlo A, Sinuès B, Mayayo E, Bernal L, Soriano A, Martínez-Jarreta B, et al. (2004). Urinary mutagenicity, CYP1A2 and NAT2 activity in textile industry workers. J Occup Health. 46(6):440–7. https://doi.org/10.1539/joh.46.440 PMID:15613766

Fantauzzi MF, Cass SP, McGrath JJC, Thayaparan D, Wang P, Stampfli MR, et al. (2021). Development and validation of a mouse model of contemporary cannabis smoke exposure. ERJ Open Res. 7(3):00107–02021. https://doi.org/10.1183/23120541.00107-2021 PMID:34291110

FAO (2009). Bifenthrin. FAO specifications and evaluations for agricultural pesticides. Rome, Italy: Food and Agricultural Organization of the United Nations. Available from: https://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Report09/bifenthrin.pdf, accessed September 2024.

FAO (2019). Ultra-processed foods, diet quality, and health using the NOVA classification system. Prepared by Monteiro CA, Cannon G, Lawrence M, da Costa Louzada ML, Machado PP. Rome, Italy: Food and Agriculture Organization of the United Nations. Available from: https://openknowledge.fao.org/3/ca5644en/ca5644en.pdf, accessed September 2024.

FAO (2022). Bifenthrin. FAO specifications and evaluations for agricultural pesticides. Rome, Italy: Food and Agricultural Organization of the United Nations. Available from: https://openknowledge.fao.org/3/ca9605en/ca9605en.pdf, accessed February 2024

FAO/WHO (1986). Evaluation of certain food additives and contaminants. Twenty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO technical report series No. 733. Geneva, Switzerland: World Health Organization. Available from: https://iris.who.int/bitstream/handle/10665/37285/WHO_TRS_733.pdf?sequence=1, accessed June 2024.

FAO/WHO (1992). Evaluation of certain food additives and naturally occurring toxicants: thirty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO technical report series, No. 828. Geneva, Switzerland: World Health Organization. Available from: https:// iris/bitstream/handle/10665/40033/WHO_TRS_828.pdf?sequence=1, accessed June 2024.

FAO/WHO (1995a). Patulin. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/food-additives-contaminants-jecfa-database/Home/Chemical/3345, accessed March 2024.

FAO/WHO (1995b). Evaluation of certain food additives and contaminants. WHO technical report series, No. 859. Geneva, Switzerland: World Health Organization, Joint FAO/WHO Expert Committee on Food Additives. Available from: https://iris/bitstream/handle/10665/37246/WHO_TRS_859.pdf?sequence=1, accessed June 2024.

FAO/WHO (1998a). Joint FAO/WHO Expert Committee on Food Additives (JECFA). Position paper on patulin, 30th session, The Hague, The Netherlands, 9–13 March, 1998.

FAO/WHO (1998b). Evaluation of certain food additives. WHO Technical Report Series No. 891. Geneva, Switzerland: World Health Organization. Available from: https://iris.who.int/bitstream/10665/42245/1/WHO_TRS_891.pdf, accessed March 2024.

FAO/WHO (2000). Zeralenone. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/food-additives-contaminants-jecfa-database/Home/Chemical/2730, accessed March 2024.

FAO/WHO (2010). Pesticide residues in food – 2008: toxicological evaluations. / Joint Meeting of the FAO Panel of

Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group, Rome, Italy, Switzerland, 9–18 September 2008. Geneva, Switzerland: World Health Organization. Available from: https://www.inchem.org/documents/jmpr/jmpmono/v2008pr01.pdf, accessed September 2024.

FAO/WHO (2011a). Evaluation of certain food additives and contaminants. Seventy-third report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series No. 960. Geneva, Switzerland: World Health Organization. Available from: https://iris.who.int/bitstream/10665/44515/1/WHO_TRS_960_eng.pdf, accessed September 2024.

FAO/WHO (2011b). Evaluation of certain food additives and contaminants. Seventy-fourth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO technical report series No. 966. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/bitstream/handle/10665/44788/WHO_TRS_966_eng.pdf?sequence=1#page=18, accessed June 2024.

FAO/WHO (2011c). Evaluation of certain contaminants in food. Seventy-second report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series No. 959. Geneva, Switzerland: World Health Organization. Available from: https://iris.who.int/bitstream/10665/44514/1/WHO_TRS_959_eng.pdf, accessed March 2024.

FAO/WHO (2015). Joint FAO/WHO expert committee on food additives. Eightieth meeting Rome, 16–25 June 2015. Geneva, Switzerland: World Health Organization. Available from: http://www.fao.org/fileadmin/user_upload/agns/pdf/jecfa/Summary_report_of_the_80th_JECFA_meeting.pdf, accessed March 2024.

FAO/WHO (2016). Joint FAO/WHO expert committee on food additives (JECFA). Eighty-third meeting. Rome, 8–17 November 2016. Geneva, Switzerland: World Health Organization. Available from: https://cdn.who.int/media/docs/default-source/food-safety/jecfa/summary-and-conclusions/jecfa83_8-17-november-2016_summary-and-conclusion.pdf?sfvrsn=ca027114_5, accessed March 2024.

FAO/WHO (2017). Evaluation of certain contaminants in food. Eighty-third report of the Joint FAO/WHO committee on food additives (JECFA). Geneva, Switzerland: World Health Organization. Available from: https://iris.who.int/bitstream/handle/10665/254893/9789241210027-eng.pdf?sequence=1, accessed March 2024.

FAO/WHO (2018). Aflatoxins. Safety evaluation of certain contaminants in food: prepared by the eighty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series, No 74; 2-280.

FAO/WHO (2019). Evaluation of certain food additives. Eighty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO technical report series; no. 1014. Geneva, Switzerland: World Health Organization. Available from: https://iris.who.int/bitstream/handle/10665/279832/9789241210232-eng.pdf, accessed June 2024.

FAO/WHO (2020). Pesticide residues in food 2019 – Report 2019 – Joint FAO/WHO Meeting on Pesticide Residues, Rome. Geneva, Switzerland: World Health Organization. Available from: https://openknowledge.fao.org/handle/20.500.14283/ca7455en, accessed September 2024.

FAO/WHO (2022). Maximum levels for aflatoxins in certain cereals and cereal-based products including foods for infants and young children. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/news-room/events/detail/2022/11/21/default-calendar/fao-who-45th-session-of-the-codex-alimentarius-commission-adopts-new-standards, accessed June 2024.

Farahat FM, Ellison CA, Bonner MR, McGarrigle BP, Crane AL, Fenske RA, et al. (2011). Biomarkers of chlorpyrifos exposure and effect in Egyptian cotton field workers. Environ Health Perspect. 119(6):801–6. https://doi.org/10.1289/ehp.1002873 PMID:21224175

Farber E, Kwiecien JM, Bojic D, Ngu M, Akohene-Mensah P, Vanhie JJ, et al. (2021). Exercise improves cancer-free survival and health span in a model of radiation-induced cancer. Med Sci Sports Exerc. 53(11):2254–63. https://doi.org/10.1249/MSS.0000000000002711 PMID:34081060

Farbstein D, Hollander N, Peled O, Apter A, Fennig S, Haberman Y, et al. (2021). Social isolation in mice: behavior, immunity, and tumor growth. Stress. 24(2):229–38. https://doi.org/10.1080/10253890.2020.1777976 PMID:32510284

Farcas MT, McKinney W, Coyle J, Orandle M, Mandler WK, Stefaniak AB, et al. (2022). Evaluation of pulmonary effects of 3-D printer emissions from acrylonitrile butadiene styrene using an air–liquid interface model of primary normal human-derived bronchial epithelial cells. Int J Toxicol. 41(4):312–28. https://doi.org/10.1177/10915818221093605 PMID:35586871

Farcas MT, Stefaniak AB, Knepp AK, Bowers L, Mandler WK, Kashon M, et al. (2019). Acrylonitrile butadiene styrene (ABS) and polycarbonate (PC) filaments three-dimensional (3-D) printer emissions-induced cell toxicity. Toxicol Lett. 317:1–12. https://doi.org/10.1016/j.toxlet.2019.09.013 PMID:31562913

Farias KPRA, Moreli ML, Floriano VG, da Costa VG (2019). Evidence based on a meta-analysis of human cytomegalovirus infection in glioma. Arch Virol. 164(5):1249–57. https://doi.org/10.1007/s00705-019-04206-z PMID:30888562

Farioli A, Straif K, Brandi G, Curti S, Kjaerheim K, Martinsen JI, et al. (2018). Occupational exposure to asbestos and risk of cholangiocarcinoma: a population-based case–control study in four Nordic countries. Occup Environ Med. 75(3):191–8. https://doi.org/10.1136/oemed-2017-104603 PMID:29133597

FAS (2020). European Union: mancozeb non-renewal and MRL review. Washington (DC), USA: Foreign Agricultural Service, US Department of Agriculture. Available from: https://fas.usda.gov/data/european-union-mancozeb-non-renewal-and-mrl-review, accessed June 2024.

Fatima S, Hu X, Huang C, Zhang W, Cai J, Huang M, et al. (2019). High-fat diet feeding and palmitic acid increase CRC growth in β2AR-dependent manner. Cell Death Dis. 10(10):711. https://doi.org/10.1038/s41419-019-1958-6https://doi.org/10.1038/s41419-019-1958-6 PMID:31558710

Fatkhutdinova LM, Gabidinova GF, Daminova AG, Dimiev AM, Khamidullin TL, Valeeva EV, et al. (2024). Mechanisms related to carbon nanotubes genotoxicity in human cell lines of respiratory origin. Toxicol Appl Pharmacol. 482:116784. https://doi.org/10.1016/j.taap.2023.116784 PMID:38070752

Fatkhutdinova LM, Khaliullin TO, Vasil'yeva OL, Zalyalov RR, Mustafin IG, Kisin ER, et al. (2016a). Fibrosis biomarkers in workers exposed to MWCNTs. Toxicol Appl Pharmacol. 299:125–31. https://doi.org/10.1016/j.taap.2016.02.016 PMID:26902652

Fatkhutdinova LM, Khaliullin TO, Zalyalov RR, Tkachev AG, Birch ME, Shvedova AA (2016b). Assessment of airborne multiwalled carbon nanotubes in a manufacturing environment. Nanotechnol Russ. 11(1):110–6. https://doi.org/10.1134/S1995078016010055 PMID:28603597

Fauconnier MB, Albert C, Tondreau A, Maumy L, Rouzier R, Bonneau C (2023). Bisphénol A et cancer du sein: état des lieux des connaissances et méta-analyse. [Bisphenol A and breast cancer: State of knowledge and meta-analysis]. Bull Cancer. 110(2):151–9. https://doi.org/10.1016/j.bulcan.2022.11.011 PMID:36543681

Faure S, Noisel N, Werry K, Karthikeyan S, Aylward LL, St-Amand A (2020). Evaluation of human biomonitoring data in a health risk based context: an updated analysis of population level data from the Canadian Health Measures Survey. Int J Hyg Environ Health. 223(1):267–80. https://doi.org/10.1016/j.ijheh.2019.07.009 PMID:31523017

Faust H, Andersson K, Ekström J, Hortlund M, Robsahm TE, Dillner J (2014). Prospective study of Merkel cell polyomavirus and risk of Merkel cell carcinoma. Int J Cancer. 134(4):844–8. https://doi.org/10.1002/ijc.28419 PMID:23922031

Faustino-Rocha AI, Rodrigues D, Ferreira R, Colaço B, Gomes PS, Pires MJ, et al. (2016). The effects of intense pulsed light in a mouse model of skin carcinogenesis. Br J Dermatol. 174(1):216–8. https://doi.org/10.1111/bjd.14010 PMID:26147791

Fawell J, Walker M (2006). Approaches to determining regulatory values for carcinogens with particular reference to bromate. Toxicology. 221(2–3):149–53. https://doi.org/10.1016/j.tox.2005.12.019 PMID:16466841

Fears TR, Elashoff RM, Schneiderman MA (1989). The statistical analysis of a carcinogen mixture experiment. III. Carcinogens with different target systems, aflatoxin B1, N-butyl-N-(4-hydroxybutyl)nitrosamine, lead acetate, and thiouracil. Toxicol Ind Health. 5(1):1–23. https://doi.org/10.1177/074823378900500101 PMID:2497557

Federal Institute of Risk Assessment (2009). Bundesinstitut für Risikobewertung. [Nitrate in rocket, spinach, and salad. Revised statement No. 032/2009.] Berlin, Germany: Federal Institute of Risk Assessment. [German]

Fedorova OS, Kovshirina AE, Kovshirina YV, Hattendorf J, Onishchenko SV, Katanakhova LL, et al. (2023).

Opisthorchis felineus infection is a risk factor for cholangiocarcinoma in Western Siberia: a hospital-based case–control study. Clin Infect Dis. 76(3):e1392–8. https://doi.org/10.1093/cid/ciac497 PMID:35723279

Fedotcheva TA (2021). Clinical use of progestins and their mechanisms of action: present and future (review). Sovrem Tekhnologii Med. 13(1):93–106. https://doi.org/10.17691/stm2021.13.1.11 PMID:34513071

Fedrowitz M, Löscher W (2008). Exposure of Fischer 344 rats to a weak power frequency magnetic field facilitates mammary tumorigenesis in the DMBA model of breast cancer. Carcinogenesis. 29(1):186–93. https://doi.org/10.1093/carcin/bgm217 PMID:17916910

Feng J, Soto-Moreno EJ, Prakash A, Balboula AZ, Qiao H (2023). Adverse PFAS effects on mouse oocyte in vitro maturation are associated with carbon-chain length and inclusion of a sulfonate group. Cell Prolif. 56(2):e13353. https://doi.org/10.1111/cpr.13353https://doi.org/10.1111/cpr.13353 PMID:36305033

Feng X, Xia Q, Yuan L, Yang X, Wang K (2010). Impaired mitochondrial function and oxidative stress in rat cortical neurons: implications for gadolinium-induced neurotoxicity. Neurotoxicology. 31(4):391–8. https://doi.org/10.1016/j.neuro.2010.04.003 PMID:20398695

Fennell TR, Morgan DL, Watson SL, Dhungana S, Waidyanatha S (2015). Systemic uptake, albumin and hemoglobin binding of [(14)C]2,3-butanedione administered by intratracheal instillation in male Harlan Sprague Dawley rats and oropharyngeal aspiration in male B6C3F$_1$/N mice. Chem Biol Interact. 227:112–9. https://doi.org/10.1016/j.cbi.2014.12.029https://doi.org/10.1016/j.cbi.2014.12.029 PMID:25559854

Ferguson KK, Lan Z, Yu Y, Mukherjee B, McElrath TF, Meeker JD (2019). Urinary concentrations of phenols in association with biomarkers of oxidative stress in pregnancy: assessment of effects independent of phthalates. Environ Int. 131:104903. https://doi.org/10.1016/j.envint.2019.104903 PMID:31288179

Ferin J, Oberdörster G, Penney DP (1992). Pulmonary retention of ultrafine and fine particles in rats. Am J Respir Cell Mol Biol. 6(5):535–42. https://doi.org/10.1165/ajrcmb/6.5.535 PMID:1581076

Fernández-Bertólez N, Azqueta A, Pásaro E, Laffon B, Valdiglesias V (2021). Salivary leucocytes as suitable biomatrix for the comet assay in human biomonitoring studies. Arch Toxicol. 95(6):2179–87. https://doi.org/10.1007/s00204-021-03038-8 PMID:33787950

Ferng SF, Castro CE, Afifi AA, Bermúdez E, Mustafa MG (1997). Ozone-induced DNA strand breaks in guinea pig tracheobronchial epithelial cells. J Toxicol Environ Health. 51(4):353–67. https://doi.org/10.1080/00984109708984030 PMID:9202716

Ferrante D, Angelini A, Barbiero F, Barbone F, Bauleo L, Binazzi A, et al. (2024). Cause specific mortality in an Italian pool of asbestos workers cohorts. Am J Ind Med. 67(1):31–43. https://doi.org/10.1002/ajim.23546 PMID:37855384

Ferreira JD, Couto AC, Pombo-de-Oliveira MS, Koifman S; Brazilian Collaborative Study Group of Infant Acute Leukemia (2013). In utero pesticide exposure and leukemia in Brazilian children < 2 years of age. Environ Health Perspect. 121(2):269–75. https://doi.org/10.1289/ehp.1103942 PMID:23092909

Ferrey ML, Heiskary S, Grace R, Hamilton MC, Lueck A (2015). Pharmaceuticals and other anthropogenic tracers in surface water: a randomized survey of 50 Minnesota lakes. Environ Toxicol Chem. 34(11):2475–88. https://doi.org/10.1002/etc.3125https://doi.org/10.1002/etc.3125 PMID:26468892

Ferrucio B, Tiago M, Fannin RD, Liu L, Gerrish K, Maria-Engler SS, et al. (2017). Molecular effects of 1-naphthyl-methylcarbamate and solar radiation exposures on human melanocytes. Toxicol In Vitro. 38:67–76. https://doi.org/10.1016/j.tiv.2016.11.005 PMID:27829164

Feychting M, Schüz J, Toledano MB, Vermeulen R, Auvinen A, Poulsen AH, et al. (2024). Mobile phone use and brain tumour risk – COSMOS, a prospective cohort study. Environ Int. 185:108552. https://doi.org/10.1016/j.envint.2024.108552 PMID:38458118

Figueroa JD, Koutros S, Colt JS, Kogevinas M, Garcia-Closas M, Real FX, et al. (2015). Modification of occupational exposures on bladder cancer risk by common genetic polymorphisms. J Natl Cancer Inst. 107(11):djv223. https://doi.org/10.1093/jnci/djv223 PMID:26374428

Figueroa-Romero C, Monteagudo A, Murdock BJ, Famie JP, Webber-Davis IF, Piecuch CE, et al. (2022). Tofacitinib suppresses natural killer cells *in vitro* and *in vivo*: implications for amyotrophic lateral sclerosis. Front Immunol.

13:773288. https://doi.org/10.3389/fimmu.2022.773288 PMID:35197969

Filippini T, Halldorsson TI, Capitão C, Martins R, Giannakou K, Hogervorst J, et al. (2022). Dietary acrylamide exposure and risk of site-specific cancer: a systematic review and dose-response meta-analysis of epidemiological studies. Front Nutr. 9:875607. https://doi.org/10.3389/fnut.2022.875607 PMID:35548558

Filippini T, Hatch EE, Rothman KJ, Heck JE, Park AS, Crippa A, et al. (2019). Association between outdoor air pollution and childhood leukemia: a systematic review and dose-response meta-analysis. Environ Health Perspect. 127(4):46002. https://doi.org/10.1289/EHP4381 PMID:31017485

Finkeldey L, Schmitz E, Ellinger S (2021). Effect of the intake of isoflavones on risk factors of breast cancer – a systematic review of randomized controlled intervention studies. Nutrients. 13(7):2309. https://doi.org/10.3390/nu13072309 PMID:34371819

Fiolet T, Srour B, Sellem L, Kesse-Guyot E, Allès B, Méjean C, et al. (2018). Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. BMJ. 360:k322. https://doi.org/10.1136/bmj.k322 PMID:29444771

Fischer D, Seidu F, Yang J, Felten MK, Garus C, Kraus T, et al. (2020). Health consequences for e-waste workers and bystanders-a comparative cross-sectional study. Int J Environ Res Public Health. 17(5):1534. https://doi.org/10.3390/ijerph17051534 PMID:32120921

Fitzpatrick D, Pirie K, Reeves G, Green J, Beral V (2023). Combined and progestagen-only hormonal contraceptives and breast cancer risk: a UK nested case–control study and meta-analysis. PLoS Med. 20(3):e1004188. https://doi.org/10.1371/journal.pmed.1004188 PMID:36943819

Flach S, Maniam P, Manickavasagam J (2019). E-cigarettes and head and neck cancers: a systematic review of the current literature. Clin Otolaryngol. 44(5):749–56. https://doi.org/10.1111/coa.13384 PMID:31148389

Flaherty DK, Taylor PM, Hopkins WE 2nd, Holland ME, Schlueter DP (1995). A new mask filter cartridge used to determine applicator inhalation exposure to an alachlor herbicide (Lasso) during normal spraying operations. J Occup Environ Med. 37(9):1116–21. https://doi.org/10.1097/00043764-199509000-00013 PMID:8528720

Flaks A, Flaks B (1983). Induction of liver cell tumours in IF mice by paracetamol. Carcinogenesis. 4(4):363–8. https://doi.org/10.1093/carcin/4.4.363-a PMID:6839410

Flaks B, Flaks A, Shaw AP (1985). Induction by paracetamol of bladder and liver tumours in the rat. Effects on hepatocyte fine structure. Acta Pathol Microbiol Immunol Scand [A]. 93(6):367–77. https://doi.org/10.1111/j.1699-0463.1985.tb03964.x PMID:4090988

Fleisch AF, Rokoff LB, Garshick E, Grady ST, Chipman JW, Baker ER, et al. (2020). Residential wood stove use and indoor exposure to $PM_{2.5}$ and its components in northern New England. J Expo Sci Environ Epidemiol. 30(2):350–61. https://doi.org/10.1038/s41370-019-0151-4 PMID:31253828

Fleisch Marcus A, Illescas AH, Hohl BC, Llanos AA (2017). Relationships between social isolation, neighborhood poverty, and cancer mortality in a population-based study of US adults. PLoS One. 12(3):e0173370. https://doi.org/10.1371/journal.pone.0173370 PMID:28273125

Fleurant E, Mokashi M, Simon MA (2023). Over-the-counter progestin-only oral contraceptives. JAMA. 330(18):1810. https://doi.org/10.1001/jama.2023.17781 PMID:37713188

Florin I, Rutberg L, Curvall M, Enzell CR (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology. 15(3):219–32. https://doi.org/10.1016/0300-483X(80)90055-4 PMID:7008261

Foerster M, Dufour L, Bäumler W, Schreiver I, Goldberg M, Zins M, et al. (2023). Development and validation of the epidemiological tattoo assessment tool to assess ink exposure and related factors in tattooed populations for medical research: cross-sectional validation study. JMIR Form Res. 7:e42158. https://doi.org/10.2196/42158 PMID:36630184

Folkmann JK, Risom L, Jacobsen NR, Wallin H, Loft S, Møller P (2009). Oxidatively damaged DNA in rats exposed by oral gavage to C60 fullerenes and single-walled carbon nanotubes. Environ Health Perspect. 117(5):703–8. https://doi.org/10.1289/ehp.11922 PMID:19479010

Food Additives World (2006). FD&C Red No. 40. Food Additives World. Available from: http://www.foodadditivesworld.com/fdc-red-no40.html, accessed April 2006.

Forouzanfar MH, Afshin A, Alexander LT, Anderson HR, Bhutta ZA, Biryukov S, et al.; GBD 2015 Risk Factors Collaborators (2016). Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 388(10053):1659–724. https://doi.org/10.1016/S0140-6736(16)31679-8https://doi.org/10.1016/S0140-6736(16)31679-8 PMID:27733284

Forte M, Iachetta G, Tussellino M, Carotenuto R, Prisco M, De Falco M, et al. (2016). Polystyrene nanoparticles internalization in human gastric adenocarcinoma cells. Toxicol In Vitro. 31:126–36. https://doi.org/10.1016/j.tiv.2015.11.006 PMID:26585375

Fortes C, Mastroeni S, Segatto M M, Hohmann C, Miligi L, Bakos L, et al. (2016). Occupational exposure to pesticides with occupational sun exposure increases the risk for cutaneous melanoma. J Occup Environ Med. 58(4):370–5. https://doi.org/10.1097/JOM.0000000000000665 PMID:27058477

Fourkala EO, Blyuss O, Field H, Gunu R, Ryan A, Barth J, et al. (2016). Sex hormone measurements using mass spectrometry and sensitive extraction radioimmunoassay and risk of estrogen receptor negative and positive breast cancer: case control study in UK Collaborative Cancer Trial of Ovarian Cancer Screening (UKCTOCS). Steroids. 110:62–9. https://doi.org/10.1016/j.steroids.2016.04.003 PMID:27091764

Fournier A, Cairat M, Severi G, Gunter MJ, Rinaldi S, Dossus L (2023). Use of menopausal hormone therapy and ovarian cancer risk in a French cohort study. J Natl Cancer Inst. 115(6):671–9. https://doi.org/10.1093/jnci/djad035 PMID:36809347

Fowler K, Mucha J, Neumann M, Lewandowski W, Kaczanowska M, Grys M, et al. (2022). A systematic literature review of the global seroprevalence of cytomegalovirus: possible implications for treatment, screening, and vaccine development. BMC Public Health. 22(1):1659. https://doi.org/10.1186/s12889-022-13971-7 PMID:36050659

Fox JG, Dangler CA, Taylor NS, King A, Koh TJ, Wang TC (1999). High-salt diet induces gastric epithelial hyperplasia and parietal cell loss, and enhances *Helicobacter pylori* colonization in C57BL/6 mice. Cancer Res. 59(19):4823–8. https://www.academia.edu/100589735/High_salt_diet_induces_gastric_epithelial_hyperplasia_and_parietal_cell_loss_and_enhances_Helicobacter_pylori_colonization_in_C57BL_6_mice PMID:10519391

Francescangeli F, De Angelis ML, Zeuner A (2020). COVID-19: a potential driver of immune-mediated breast cancer recurrence? Breast Cancer Res. 22(1):117. https://doi.org/10.1186/s13058-020-01360-0 PMID:33126915

Francisco LFV, da Silva RN, Oliveira MA, Dos Santos Neto MF, Gonçalves IZ, Marques MMC, et al. (2023). Occupational exposures and risks of non-Hodgkin lymphoma: a meta-analysis. Cancers (Basel). 15(9):2600. https://doi.org/10.3390/cancers15092600 PMID:37174074

Franco G, Malamani T, Germani L, Candura F (1982). Assessment of coronary heart disease risk among viscose rayon workers exposed to carbon disulfide at concentrations of about 30 mg/m^3. Scand J Work Environ Health. 8(2):113–20. https://doi.org/10.5271/sjweh.2487 PMID:7134928

Franco de Diana D, Segovia Abreu J, Castiglioni Serafini D, Ortíz JF, Samaniego MJ, Aranda AC, et al. (2018). Increased genetic damage found in waste picker women in a landfill in Paraguay measured by comet assay and the micronucleus test. Mutat Res Genet Toxicol Environ Mutagen. 836 Pt B:19–23. https://doi.org/10.1016/j.mrgentox.2018.06.011 PMID:30442339

Fransway AF, Fransway PJ, Belsito DV, Yiannias JA (2019). Paraben toxicology. Dermatitis. 30(1):32–45. https://doi.org/10.1097/DER.0000000000000428https://doi.org/10.1097/DER.0000000000000428 PMID:30570577

Franz T, Negele J, Bruno P, Böttcher M, Mitchell-Flack M, Reemts L, et al. (2022). Pleiotropic effects of antibiotics on T cell metabolism and T cell-mediated immunity. Front Microbiol. 13:975436. https://doi.org/10.3389/fmicb.2022.975436 PMID:36329851

Fraser K, Kodali V, Yanamala N, Birch ME, Cena L, Casuccio G, et al. (2020). Physicochemical characterization and genotoxicity of the broad class of carbon nanotubes and nanofibers used or produced in US facilities. Part Fibre Toxicol. 17(1):62. https://doi.org/10.1186/s12989-020-00392-w PMID:33287860

Fraum TJ, Ludwig DR, Bashir MR, Fowler KJ (2017). Gadolinium-based contrast agents: a comprehensive risk assessment. J Magn Reson Imaging. 46(2):338–53. https://doi.org/10.1002/jmri.25625 PMID:28083913

Fred C, Grawé J, Törnqvist M (2005). Hemoglobin adducts and micronuclei in rodents after treatment with isoprene monoxide or butadiene monoxide. Mutat Res. 585(1–2):21–32. https://doi.org/10.1016/j.mrgentox.2005.03.009 PMID:15925539

Frederiksen LE, Erdmann F, Wesseling C, Winther JF, Mora AM (2020). Parental tobacco smoking and risk of childhood leukemia in Costa Rica: a population-based case–control study. Environ Res. 180:108827. https://doi.org/10.1016/j.envres.2019.108827 PMID:31655332

Freedman RA, Seisler DK, Foster JC, Sloan JA, Lafky JM, Kimmick GG, et al. (2017). Risk of acute myeloid leukemia and myelodysplastic syndrome among older women receiving anthracycline-based adjuvant chemotherapy for breast cancer on Modern Cooperative Group Trials (Alliance A151511). Breast Cancer Res Treat. 161(2):363–73. https://doi.org/10.1007/s10549-016-4051-1 PMID:27866278

Freni-Sterrantino A, Fiorito G, D'Errico A, Robinson O, Virtanen M, Ala-Mursula L, et al. (2022). Work-related stress and well-being in association with epigenetic age acceleration: a Northern Finland Birth Cohort 1966 Study. Aging (Albany NY). 14(3):1128–56. https://doi.org/10.18632/aging.203872 PMID:35113041

Freyberger A, Ahr HJ (2006). Studies on the goitrogenic mechanism of action of *N,N,N′,N′*-tetramethylthiourea. Toxicology. 217(2–3):169–75. https://doi.org/10.1016/j.tox.2005.09.005https://doi.org/10.1016/j.tox.2005.09.005 PMID:16297522

Frickhofen N, Heimpel H, Kaltwasser JP, Schrezenmeier H; German Aplastic Anemia Study Group (2003). Antithymocyte globulin with or without cyclosporin A: 11-year follow-up of a randomized trial comparing treatments of aplastic anemia. Blood. 101(4):1236–42. https://doi.org/10.1182/blood-2002-04-1134 PMID:12393680

Friedman GD, Oestreicher N, Chan J, Quesenberry CP Jr, Udaltsova N, Habel LA (2006). Antibiotics and risk of breast cancer: up to 9 years of follow-up of 2.1 million women. Cancer Epidemiol Biomarkers Prev. 15(11):2102–6. https://doi.org/10.1158/1055-9965.EPI-06-0401 PMID:17119034

Friesen MC, Costello S, Eisen EA (2009). Quantitative exposure to metalworking fluids and bladder cancer incidence in a cohort of autoworkers. Am J Epidemiol. 169(12):1471–8. https://doi.org/10.1093/aje/kwp073https://doi.org/10.1093/aje/kwp073 PMID:19414495

Friesen MC, Costello S, Thurston SW, Eisen EA (2011). Distinguishing the common components of oil- and water-based metalworking fluids for assessment of cancer incidence risk in autoworkers. Am J Ind Med. 54(6):450–60. https://doi.org/10.1002/ajim.20932 PMID:21328414

Friis S, Nielsen GL, Mellemkjaer L, McLaughlin JK, Thulstrup AM, Blot WJ, et al. (2002). Cancer risk in persons receiving prescriptions for paracetamol: a Danish cohort study. Int J Cancer. 97(1):96–101. https://doi.org/10.1002/ijc.1581 PMID:11774249

Fritschi L (2000). Cancer in veterinarians. Occup Environ Med. 57(5):289–97. https://doi.org/10.1136/oem.57.5.289 PMID:10769295

Fritz H, Seely D, McGowan J, Skidmore B, Fernandes R, Kennedy DA, et al. (2014). Black cohosh and breast cancer: a systematic review. Integr Cancer Ther. 13(1):12–29. https://doi.org/10.1177/1534735413477191https://doi.org/10.1177/1534735413477191 PMID:23439657

Frizzell C, Ndossi D, Verhaegen S, Dahl E, Eriksen G, Sørlie M, et al. (2011). Endocrine disrupting effects of zearalenone, alpha- and beta-zearalenol at the level of nuclear receptor binding and steroidogenesis. Toxicol Lett. 206(2):210–7. https://doi.org/10.1016/j.toxlet.2011.07.015 PMID:21803136

Fu J, Jiao J, Weng K, Yu D, Li R (2017a). Zebrafish methanol exposure causes patterning defects and suppressive cell proliferation in retina. Am J Transl Res. 9(6):2975–83. PMID:28670385

Fu JP, Zhao B, Li YQ, Liu SS, Yin WH, Huang JQ, et al. (2018). [Discussion of emissions and health risk of polycyclic aromatic hydrocarbons (PAHs) from the retreading process of waste tires]. Huan Jing Ke Xue. 39(6):2963–70. PMID:29965656 [Chinese]

Fu PP (2017). Pyrrolizidine alkaloids: metabolic activation pathways leading to liver tumor initiation. Chem Res Toxicol. 30(1):81–93. https://doi.org/10.1021/acs.chemrestox.6b00297 PMID:28092947

Fu Z, Zhao F, Chen K, Xu J, Li P, Xia D, et al. (2017b). Association between urinary phthalate metabolites and risk of

breast cancer and uterine leiomyoma. Reprod Toxicol. 74:134–42. https://doi.org/10.1016/j.reprotox.2017.09.009 PMID:28951174

Fuhrimann S, Mol HGJ, Dias J, Dalvie MA, Röösli M, Degrendele C, et al. (2022). Quantitative assessment of multiple pesticides in silicone wristbands of children/guardian pairs living in agricultural areas in South Africa. Sci Total Environ. 812:152330. https://doi.org/10.1016/j.scitotenv.2021.152330 PMID:34906574

Fujino C, Tamura Y, Tange S, Nakajima H, Sanoh S, Watanabe Y, et al. (2016). Metabolism of methiocarb and carbaryl by rat and human livers and plasma, and effect on their PXR, CAR and PPARα activities. J Toxicol Sci. 41(5):677–91. https://doi.org/10.2131/jts.41.677 PMID:27665777

Fujioka N, Ainslie-Waldman CE, Upadhyaya P, Carmella SG, Fritz VA, Rohwer C, et al. (2014). Urinary 3,3′-diindolylmethane: a biomarker of glucobrassicin exposure and indole-3-carbinol uptake in humans. Cancer Epidemiol Biomarkers Prev. 23(2):282–7. https://doi.org/10.1158/1055-9965.EPI-13-0645 PMID:24357105

Fujita K, Matsushita M, De Velasco MA, Hatano K, Minami T, Nonomura N, et al. (2023). The gut-prostate axis: a new perspective of prostate cancer biology through the gut microbiome. Cancers (Basel). 15(5):1375. https://doi.org/10.3390/cancers15051375 PMID:36900168

Fukuma K, Fukushima T, Matsuo I, Mimori H, Maeyama M (1983). A graduated regimen of clomiphene citrate: its correlation to glycogen content of the endometrium and serum levels of estradiol and progesterone in infertile patients at the midluteal phase. Fertil Steril. 39(6):780–4. https://doi.org/10.1016/S0015-0282(16)47117-7 PMID:6852278

Fukushima S, Kasai T, Umeda Y, Ohnishi M, Sasaki T, Matsumoto M (2018). Carcinogenicity of multi-walled carbon nanotubes: challenging issue on hazard assessment. J Occup Health. 60(1):10–30. https://doi.org/10.1539/joh.17-0102-RA PMID:29046510

Fung C, Fossa SD, Milano MT, Oldenburg J, Travis LB (2013). Solid tumors after chemotherapy or surgery for testicular nonseminoma: a population-based study. J Clin Oncol. 31(30):3807–14. https://doi.org/10.1200/JCO.2013.50.3409 PMID:24043737

Furlong BB, Weaver RP, Goldstein JA (1987). Covalent binding to DNA and mutagenicity of 2,4-diaminotoluene metabolites produced by isolated hepatocytes and 9000 g supernatant from Fischer 344 rats. Carcinogenesis. 8(2):247–51. https://doi.org/10.1093/carcin/8.2.247 PMID:3802408

Furnes B, Schlenk D (2005). Extrahepatic metabolism of carbamate and organophosphate thioether compounds by the flavin-containing monooxygenase and cytochrome P450 systems. Drug Metab Dispos. 33(2):214–8. https://doi.org/10.1124/dmd.104.000984 PMID:15547051

Furst A, Schlauder M, Sasmore DP (1976). Tumorigenic activity of lead chromate. Cancer Res. 36(5):1779–83. PMID:1268834

Furst A, Schlauder MC (1971). The hamster as a model for metal carcinogenesis. Proc West Pharmacol Soc. 14:68–71.

Gabbianelli R, Nasuti C, Falcioni G, Cantalamessa F (2004). Lymphocyte DNA damage in rats exposed to pyrethroids: effect of supplementation with vitamins E and C. Toxicology. 203(1–3):17–26. https://doi.org/10.1016/j.tox.2004.05.012 PMID:15363578

Gabet S, Lemarchand C, Guénel P, Slama R (2021). Breast cancer risk in association with atmospheric pollution exposure: a meta-analysis of effect estimates followed by a health impact assessment. Environ Health Perspect. 129(5):57012. https://doi.org/10.1289/EHP8419 PMID:34038220

Gad MF, Mossa AH, Refaie AA, Ibrahim NE, Mohafrash SMM (2022). Benchmark dose and the adverse effects of exposure to pendimethalin at low dose in female rats. Basic Clin Pharmacol Toxicol. 130(2):301–19. https://doi.org/10.1111/bcpt.13683 PMID:34738321

Gade A, Vasile GF, Rubenstein R (2023). Intense Pulsed Light (IPL) Therapy [Updated 2023 Apr 10]. StatPearls [Internet]. Treasure Island (FL), USA: StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK580525/

Gadhia SR, Calabro AR, Barile FA (2012). Trace metals alter DNA repair and histone modification pathways concurrently in mouse embryonic stem cells. Toxicol Lett. 212(2):169–79. https://doi.org/10.1016/j.toxlet.2012.05.013 PMID:22641096

Gadupudi GS, Chung KT (2011). Comparative genotoxicity of 3-hydroxyanthranilic acid and anthranilic acid in the presence of a metal cofactor Cu (II) in vitro. Mutat Res. 726(2):200–8. https://doi.org/10.1016/j.mrgentox.2011.09.012 PMID:22015263

Gaine ME, Chatterjee S, Abel T (2018). Sleep deprivation and the epigenome. Front Neural Circuits. 12:14. https://doi.org/10.3389/fncir.2018.00014 PMID:29535611

Galeano Niño JL, Wu H, LaCourse KD, Kempchinsky AG, Baryiames A, Barber B, et al. (2022). Effect of the intratumoral microbiota on spatial and cellular heterogeneity in cancer. Nature. 611(7937):810–7. https://doi.org/10.1038/s41586-022-05435-0 PMID:36385528

Galiotte MP, Kohler P, Mussi G, Gattás GJ (2008). Assessment of occupational genotoxic risk among Brazilian hairdressers. Ann Occup Hyg. 52(7):645–51. PMID:18596021

Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C, et al. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. Environ Mol Mutagen. 10 Suppl 10:1–175. https://doi.org/10.1002/em.2850100502https://doi.org/10.1002/em.2850100502 PMID:3319609

Galvan-Ramirez ML, Troyo R, Roman S, Calvillo-Sanchez C, Bernal-Redondo R (2012). A systematic review and meta-analysis of *Toxoplasma gondii* infection among the Mexican population. Parasit Vectors. 5(1):271. https://doi.org/10.1186/1756-3305-5-271 PMID:23181616

Gandarilla-Esparza DD, Calleros-Rincón EY, Macias HM, González-Delgado MF, Vargas GG, Sustaita JD, et al. (2021). FOXE1 polymorphisms and chronic exposure to nitrates in drinking water cause metabolic dysfunction, thyroid abnormalities, and genotoxic damage in women. Genet Mol Biol. 44(3):e20210020. https://doi.org/10.1590/1678-4685-gmb-2021-0020https://doi.org/10.1590/1678-4685-gmb-2021-0020 PMID:34617949

Gao F, Jiang LP, Chen M, Geng CY, Yang G, Ji F, et al. (2013). Genotoxic effects induced by zearalenone in a human embryonic kidney cell line. Mutat Res. 755(1):6–10. https://doi.org/10.1016/j.mrgentox.2013.04.009 PMID:23643527

Garcia E, Bradshaw PT, Eisen EA (2018b). Breast cancer incidence and exposure to metalworking fluid in a cohort of female autoworkers. Am J Epidemiol. 187(3):539–47. https://doi.org/10.1093/aje/kwx264 PMID:29020170

Garcia E, Hurley S, Nelson DO, Hertz A, Reynolds P (2015). Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. Environ Health. 14(1):14. https://doi.org/10.1186/1476-069X-14-14 PMID:25636809

García-Núñez A, Jiménez-Gómez G, Hidalgo-Molina A, Córdoba-Doña JA, León-Jiménez A, Campos-Caro A (2022). Inflammatory indices obtained from routine blood tests show an inflammatory state associated with disease progression in engineered stone silicosis patients. Sci Rep. 12(1):8211. https://doi.org/10.1038/s41598-022-11926-x PMID:35581230

García-Quiroz J, Vázquez-Almazán B, García-Becerra R, Díaz L, Avila E (2022). The interaction of human papillomavirus infection and prostaglandin E2 signalling in carcinogenesis: a focus on cervical cancer therapeutics. Cells. 11(16):2528. https://doi.org/10.3390/cells11162528 PMID:36010605

Garcia-Saenz A, de Miguel AS, Espinosa A, Costas L, Aragonés N, Tonne C, et al. (2020). Association between outdoor light-at-night exposure and colorectal cancer in Spain. Epidemiology. 31(5):718–27. https://doi.org/10.1097/EDE.0000000000001226 PMID:32639250

Garcia-Saenz A, Sánchez de Miguel A, Espinosa A, Valentin A, Aragonés N, Llorca J, et al. (2018). Evaluating the association between artificial light-at-night exposure and breast and prostate cancer risk in Spain (MCC-Spain Study). Environ Health Perspect. 126(4):047011. https://doi.org/10.1289/EHP1837 PMID:29687979

Gargouri B, Boukholda K, Kumar A, Benazzouz A, Fetoui H, Fiebich BL, et al. (2020). Bifenthrin insecticide promotes oxidative stress and increases inflammatory mediators in human neuroblastoma cells through NF-kappaB pathway. Toxicol In Vitro. 65:104792. https://doi.org/10.1016/j.tiv.2020.104792 PMID:32061760

h-throughput H295R homogenous time resolved fluorescence assay for androgen and estrogen steroidogenesis screening. Toxicol In Vitro. 92:105659. https://doi.org/10.1016/j.tiv.2023.105659 PMID:37557933

Garrett NE, Stack HF, Waters MD (1986). Evaluation of the genetic activity profiles of 65 pesticides. Mutat Res. 168(3):301–25. https://doi.org/10.1016/0165-1110(86)90024-2https://doi.org/10.1016/0165-1110(86)90024-2 PMID:3796654

Garritson J, Krynski L, Haverbeck L, Haughian JM, Pullen NA, Hayward R (2020). Physical activity delays accumulation of immunosuppressive myeloid-derived suppressor cells. PLoS One. 15(6):e0234548. https://doi.org/10.1371/journal.pone.0234548 PMID:32542046

Gascoigne DA, Minhaj MM, Aksenov DP (2022). Neonatal anesthesia and oxidative stress. Antioxidants. 11(4):787. https://doi.org/10.3390/antiox11040787https://doi.org/10.3390/antiox11040787 PMID:35453473

Gassas A, Courtney S, Armstrong C, Kapllani E, Muise AM, Schechter T (2015). Unrelated donor hematopoietic stem cell transplantation for infantile enteropathy due to IL-10/IL-10 receptor defect. Pediatr Transplant. 19(4):E101–3. https://doi.org/10.1111/petr.12452 PMID:25761563

Gaston KJ, Duffy JP, Bennie J (2015). Quantifying the erosion of natural darkness in the global protected area system. Conserv Biol. 29(4):1132–41. https://doi.org/10.1111/cobi.12462 PMID:25693660

Gatehouse D (1980). Mutagenicity of 1,2 ring-fused acenaphthenes against *S. typhimurium* TA1537 and TA1538: structure-activity relationship. Mutat Res. 78(2):121–35. https://doi.org/10.1016/0165-1218(80)90091-9 PMID:6993940

Gaudet MM, Carter BD, Brinton LA, Falk RT, Gram IT, Luo J, et al. (2017). Pooled analysis of active cigarette smoking and invasive breast cancer risk in 14 cohort studies. Int J Epidemiol. 46(3):881–93. PMID:28031315

Ge J, Wang X, Meng Q, Tang M, Jiang W, Jiang J, et al. (2023). Maternal cerium nitrate exposure induces developmental immunotoxicity in BALB/c mouse offspring. Toxicol Lett. 374(3374):57–67. https://doi.org/10.1016/j.toxlet.2022.12.008 PMID:36549429

Gea M, Zhang C, Tota R, Gilardi G, Di Nardo G, Schilirò T (2022). Assessment of five pesticides as endocrine-disrupting chemicals: effects on estrogen receptors and aromatase. Int J Environ Res Public Health. 19(4):1959. https://doi.org/10.3390/ijerph19041959 PMID:35206146

Gebbink WA, van Leeuwen SPJ (2020). Environmental contamination and human exposure to PFASs near a fluorochemical production plant: review of historic and current PFOA and GenX contamination in the Netherlands. Environ Int. 137:105583. https://doi.org/10.1016/j.envint.2020.105583 PMID:32106048

Gebel T (2012). Small difference in carcinogenic potency between GBP nanomaterials and GBP micromaterials. Arch Toxicol. 86(7):995–1007. https://doi.org/10.1007/s00204-012-0835-1 PMID:22418597

Geczik AM, Falk RT, Xu X, Wiafe-Addai B, Yarney J, Awuah B, et al. (2023). Relation of circulating estrogens with hair relaxer and skin lightener use among postmenopausal women in Ghana. J Expo Sci Environ Epidemiol. 33(2):301–10. https://doi.org/10.1038/s41370-021-00407-4 PMID:34992224

Geier DA, Geier MR (2023). Urine glyphosate exposure and serum sex hormone disruption within the 2013–2014 National Health and Nutrition Examination survey (NHANES). Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 316:137796. https://doi.org/10.1016/j.chemosphere.2023.137796 PMID:36632954

Genchi G, Carocci A, Lauria G, Sinicropi MS, Catalano A (2020). Nickel: human health and environmental toxicology. Int J Environ Res Public Health. 17(3):679. https://doi.org/10.3390/ijerph17030679 PMID:31973020

Geng CX, Tanamal P, Arvisais-Anhalt S, Tomasino M, Gheit T, Bishop JA, et al. (2022). Clinical and biologic characteristics and outcomes in young and middle-aged patients with laryngeal cancer: a retrospective cohort analysis. Otolaryngol Head Neck Surg. 167(4):688–98. https://doi.org/10.1177/01945998211073707 PMID:35077266

Gentile JM, Gentile GJ, Bultman J, Sechriest R, Wagner ED, Plewa MJ (1982). An evaluation of the genotoxic properties of insecticides following plant and animal activation. Mutat Res. 101(1):19–29. https://doi.org/10.1016/0165-1218(82)90161-6 PMID:7043246

George J, Prasad S, Mahmood Z, Shukla Y (2010). Studies on glyphosate-induced carcinogenicity in mouse skin: a proteomic approach. J Proteomics. 73(5):951–64. https://doi.org/10.1016/j.jprot.2009.12.008 PMID:20045496

George VC, Rupasinghe HPV (2018). DNA damaging and apoptotic potentials of bisphenol A and bisphenol S in human bronchial epithelial cells. Environ Toxicol Pharmacol. 60:52–7. https://doi.org/10.1016/j.etap.2018.04.009

PMID:29660610

Gera R, Mokbel R, Igor I, Mokbel K (2018). Does the use of hair dyes increase the risk of developing breast cancer? A meta-analysis and review of the literature. Anticancer Res. 38(2):707–16. PMID:29374694

Gerl A, Schierl R (2000). Urinary excretion of platinum in chemotherapy-treated long-term survivors of testicular cancer. Acta Oncol. 39(4):519–22. https://doi.org/10.1080/028418600750013447 PMID:11041115

Gethings-Behncke C, Coleman HG, Jordao HWT, Longley DB, Crawford N, Murray LJ, et al. (2020). *Fusobacterium nucleatum* in the colorectum and its association with cancer risk and survival: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 29(3):539–48. https://doi.org/10.1158/1055-9965.EPI-18-1295 PMID:31915144

Ghasemiesfe M, Barrow B, Leonard S, Keyhani S, Korenstein D (2019). Association between marijuana use and risk of cancer: a systematic review and meta-analysis. JAMA Netw Open. 2(11):e1916318. https://doi.org/10.1001/jamanetworkopen.2019.16318 PMID:31774524

Gherardi RK, Aouizerate J, Cadusseau J, Yara S, Authier FJ (2016). Aluminum adjuvants of vaccines injected into the muscle: normal fate, pathology and associated disease. Morphologie. 100(329):85–94. https://doi.org/10.1016/j.morpho.2016.01.002 PMID:26948677

Ghosh M, Chakraborty A, Bandyopadhyay M, Mukherjee A (2011). Multi-walled carbon nanotubes (MWCNT): induction of DNA damage in plant and mammalian cells. J Hazard Mater. 197:327–36. https://doi.org/10.1016/j.jhazmat.2011.09.090 PMID:21999988

Ghosh S (2019). Cisplatin: the first metal based anticancer drug. Bioorg Chem. 88:102925. https://doi.org/10.1016/j.bioorg.2019.102925 PMID:31003078

Gi M, Fujioka M, Kakehashi A, Okuno T, Masumura K, Nohmi T, et al. (2018). In vivo positive mutagenicity of 1,4-dioxane and quantitative analysis of its mutagenicity and carcinogenicity in rats. Arch Toxicol. 92(10):3207–21. https://doi.org/10.1007/s00204-018-2282-0 PMID:30155721

Giersch K, Allweiss L, Volz T, Helbig M, Bierwolf J, Lohse AW, et al. (2015). Hepatitis delta co-infection in humanized mice leads to pronounced induction of innate immune responses in comparison to HBV mono-infection. J Hepatol. 63(2):346–53. https://doi.org/10.1016/j.jhep.2015.03.011 PMID:25795587

Giersig C (2008). Progestin and breast cancer. The missing pieces of a puzzle. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 51(7):782–6. https://doi.org/10.1007/s00103-008-0586-6 PMID:18592338

Gilboa D, Koren G, Barer Y, Katz R, Rotem R, Lunenfeld E, et al. (2019). Assisted reproductive technology and the risk of pediatric cancer: a population-based study and a systematic review and meta analysis. Cancer Epidemiol. 63:101613. https://doi.org/10.1016/j.canep.2019.101613 PMID:31606679

Giorgi G, Del Re B (2021). Epigenetic dysregulation in various types of cells exposed to extremely low-frequency magnetic fields. Cell Tissue Res. 386(1):1–15. https://doi.org/10.1007/s00441-021-03489-6 PMID:34287715

Giorio C, Safer A, Sánchez-Bayo F, Tapparo A, Lentola A, Girolami V, et al. (2021). An update of the Worldwide Integrated Assessment (WIA) on systemic insecticides. Part 1: new molecules, metabolism, fate, and transport. Environ Sci Pollut Res Int. 28(10):11716–48. https://doi.org/10.1007/s11356-017-0394-3 PMID:29105037

Giovannelli L, Pitozzi V, Moretti S, Boddi V, Dolara P (2006). Seasonal variations of DNA damage in human lymphocytes: correlation with different environmental variables. Mutat Res. 593(1–2):143–52. https://doi.org/10.1016/j.mrfmmm.2005.07.002 PMID:16095632

Girtman KL, Baylin A, O'Brien LM, Jansen EC (2022). Later sleep timing and social jetlag are related to increased inflammation in a population with a high proportion of OSA: findings from the Cleveland Family Study. J Clin Sleep Med. 18(9):2179–87. https://doi.org/10.5664/jcsm.10078 PMID:35686375

Giulivo M, Lopez de Alda M, Capri E, Barceló D (2016). Human exposure to endocrine disrupting compounds: their role in reproductive systems, metabolic syndrome and breast cancer. A review. Environ Res. 151:251–64. https://doi.org/10.1016/j.envres.2016.07.011 PMID:27504873

Gleave K, Lissenden N, Richardson M, Ranson H (2017). Piperonyl butoxide (PBO) combined with pyrethroids in long-lasting insecticidal nets (LLINs) to prevent malaria in Africa. Cochrane Libr. 1–97.

https://doi.org/10.1002/14651858.CD012776https://doi.org/10.1002/14651858.CD012776

Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schäffer AA, Noyan F, et al. (2009). Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. N Engl J Med. 361(21):2033–45. https://doi.org/10.1056/NEJMoa0907206 PMID:19890111

Gminski R, Tang T, Mersch-Sundermann V (2010). Cytotoxicity and genotoxicity in human lung epithelial A549 cells caused by airborne volatile organic compounds emitted from pine wood and oriented strand boards. Toxicol Lett. 196(1):33–41. https://doi.org/10.1016/j.toxlet.2010.03.015https://doi.org/10.1016/j.toxlet.2010.03.015 PMID:20362040

Go V, Garey J, Wolff MS, Pogo BG (1999). Estrogenic potential of certain pyrethroid compounds in the MCF-7 human breast carcinoma cell line. Environ Health Perspect. 107(3):173–7. https://doi.org/10.1289/ehp.99107173 PMID:10064545

Godri Pollitt KJ, Kim JH, Peccia J, Elimelech M, Zhang Y, Charkoftaki G, et al. (2019). 1,4-Dioxane as an emerging water contaminant: state of the science and evaluation of research needs. Sci Total Environ. 690:853–66. https://doi.org/10.1016/j.scitotenv.2019.06.443 PMID:31302550

Göen T, Schaller B, Jäger T, Bräu-Dümler Ch, Schaller KH, Drexler H (2015). Biological monitoring of exposure and effects in workers employed in a selenium-processing plant. Int Arch Occup Environ Health. 88(5):623–30. https://doi.org/10.1007/s00420-014-0989-7 PMID:25280955

Goffe B, Papp K, Gratton D, Krueger GG, Darif M, Lee S, et al. (2005). An integrated analysis of thirteen trials summarizing the long-term safety of alefacept in psoriasis patients who have received up to nine courses of therapy. Clin Ther. 27(12):1912–21. https://doi.org/10.1016/j.clinthera.2005.12.007 PMID:16507377

Gold LS, De Roos AJ, Waters M, Stewart P (2008). Systematic literature review of uses and levels of occupational exposure to tetrachloroethylene. J Occup Environ Hyg. 5(12):807–39. https://doi.org/10.1080/15459620802510866 PMID:18949603

Goldberg MS, Villeneuve PJ, Crouse D, To T, Weichenthal SA, Wall C, et al. (2019). Associations between incident breast cancer and ambient concentrations of nitrogen dioxide from a national land use regression model in the Canadian National Breast Screening Study. Environ Int. 133 Pt B:105182. https://doi.org/10.1016/j.envint.2019.105182 PMID:31648153

Goldner WS, Sandler DP, Yu F, Shostrom V, Hoppin JA, Kamel F, et al. (2013). Hypothyroidism and pesticide use among male private pesticide applicators in the agricultural health study. J Occup Environ Med. 55(10):1171–8. https://doi.org/10.1097/JOM.0b013e31829b290b PMID:24064777

Goldoni A, Klauck CR, Da Silva ST, Da Silva MD, Ardenghi PG, Da Silva LB (2014). DNA damage in Wistar rats exposed to dithiocarbamate pesticide mancozeb. Folia Biol (Praha). 60(4):202–4. https://doi.org/10.14712/fb2014060040202

Golka K, Kopps S, Myslak ZW (2004). Carcinogenicity of azo colorants: influence of solubility and bioavailability. Toxicol Lett. 151(1):203–10. https://doi.org/10.1016/j.toxlet.2003.11.016 PMID:15177655

Gollapudi BB, Williams AL, Bus JS (2021). A review of the genotoxicity of the industrial chemical cumene. Mutat Res Rev Mutat Res. 787:108364. https://doi.org/10.1016/j.mrrev.2021.108364 PMID:34083043

Gomes-Carneiro MR, Viana ME, Felzenszwalb I, Paumgartten FJ (2005). Evaluation of β-myrcene, α-terpinene and (+)- and (−)-α-pinene in the Salmonella/microsome assay. Food Chem Toxicol. 43(2):247–52. https://doi.org/10.1016/j.fct.2004.09.011https://doi.org/10.1016/j.fct.2004.09.011 PMID:15621337

Gómez-Martín A, Altakroni B, Lozano-Paniagua D, Margison GP, de Vocht F, Povey AC, et al. (2015). Increased N7-methyldeoxyguanosine DNA adducts after occupational exposure to pesticides and influence of genetic polymorphisms of paraoxonase-1 and glutathione S-transferase M1 and T1. Environ Mol Mutagen. 56(5):437–45. https://doi.org/10.1002/em.21929 PMID:25427726

Goncalves MD, Lu C, Tutnauer J, Hartman TE, Hwang SK, Murphy CJ, et al. (2019). High-fructose corn syrup enhances intestinal tumor growth in mice. Science. 363(6433):1345–9. https://doi.org/10.1126/science.aat8515 PMID:30898933

Gong Y, Dong F, Geng Y, Zhuang H, Ma Z, Zhou Z, et al. (2019). Selenium concentration, dietary intake and risk of

hepatocellular carcinoma – a systematic review with meta-analysis. Nutr Hosp. 36(6):1430–7. PMID:31718210

Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, et al. (2014). Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob Control. 23(2):133–9. https://doi.org/10.1136/tobaccocontrol-2012-050859 PMID:23467656

Gooch JW (2011). Cumene hydroperoxide. In: Encyclopedic Dictionary of Polymers. 2nd ed. p.186. New York (NY), USA: Springer Publishing. Available from:

Goodman JE, Becich MJ, Bernstein DM, Case BW, Mandel JH, Nel AE, et al. (2023). Non-asbestiform elongate mineral particles and mesothelioma risk: human and experimental evidence. Environ Res. 230:114578. https://doi.org/10.1016/j.envres.2022.114578 PMID:36965797

Goodrich JM, Basu N, Franzblau A, Dolinoy DC (2013). Mercury biomarkers and DNA methylation among Michigan dental professionals. Environ Mol Mutagen. 54(3):195–203. https://doi.org/10.1002/em.21763 PMID:23444121

Gorelick NJ, Hutchins DA, Tannenbaum SR, Wogan GN (1989). Formation of DNA and hemoglobin adducts of fluoranthene after single and multiple exposures. Carcinogenesis. 10(9):1579–87. https://doi.org/10.1093/carcin/10.9.1579 PMID:2670302

Gorelick NJ, Wogan GN (1989). Fluoranthene-DNA adducts: identification and quantification by an HPLC-32P-postlabeling method. Carcinogenesis. 10(9):1567–77. https://doi.org/10.1093/carcin/10.9.1567 PMID:2670301

Gosens I, Mathijssen LE, Bokkers BG, Muijser H, Cassee FR (2014). Comparative hazard identification of nano- and micro-sized cerium oxide particles based on 28-day inhalation studies in rats. Nanotoxicology. 8(6):643–53. https://doi.org/10.3109/17435390.2013.815814 PMID:23768316

Goto S, Asada S, Fushiwaki Y, Mori Y, Tanaka N, Umeda M, et al. (2004). Tumor-promoting activity and mutagenicity of 5 termiticide compounds. J UOEH. 26(4):423–30. https://doi.org/10.7888/juoeh.26.423 PMID:15624354

Götz ME, Eisenreich A, Frenzel J, Sachse B, Schäfer B (2023). Occurrence of alkenylbenzenes in plants: flavours and possibly toxic plant metabolites. Plants. 12(11):2075. https://doi.org/10.3390/plants12112075 PMID:37299054

Gouda MA, Subbiah V (2023a). Expanding the benefit: dabrafenib/trametinib as tissue-agnostic therapy for *BRAF*^{V600E}-positive adult and pediatric solid tumors. Am Soc Clin Oncol Educ Book. 43(43):e404770. https://doi.org/10.1200/EDBK_404770 PMID:37159870

Gouda MA, Subbiah V (2023b). Precision oncology for BRAF-mutant cancers with BRAF and MEK inhibitors: from melanoma to tissue-agnostic therapy. ESMO Open. 8(2):100788. https://doi.org/10.1016/j.esmoop.2023.100788 PMID:36842301

Gouveia MJ, Pakharukova MY, Laha T, Sripa B, Maksimova GA, Rinaldi G, et al. (2017). Infection with *Opisthorchis felineus* induces intraepithelial neoplasia of the biliary tract in a rodent model. Carcinogenesis. 38(9):929–37. https://doi.org/10.1093/carcin/bgx042 PMID:28910999

Govender Y, Avenant C, Verhoog NJ, Ray RM, Grantham NJ, Africander D, et al. (2014). The injectable-only contraceptive medroxyprogesterone acetate, unlike norethisterone acetate and progesterone, regulates inflammatory genes in endocervical cells via the glucocorticoid receptor. PLoS One. 9(5):e96497. https://doi.org/10.1371/journal.pone.0096497 PMID:24840644

Government of Canada (2017). Canadian cannabis survey – 2017. Summary. Ottawa (ON), Canada: Government of Canada. Available from: https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/canadian-cannabis-survey-2017-summary.html, accessed September 2024.

Government of Canada (2024) Toxic substances list: chlorinated alkanes. Ottawa (ON), Canada: Government of Canada. Available from: https://www.canada.ca/en/environment-climate-change/services/management-toxic-substances/list-canadian-environmental-protection-act/chlorinated-alkanes.html, accessed June 2024.

Gozal D, Ham SA, Mokhlesi B (2016). Sleep apnea and cancer: analysis of a nationwide population sample. Sleep. 39(8):1493–500. https://doi.org/10.5665/sleep.6004 PMID:27166241

Graber JM, Stayner LT, Cohen RA, Conroy LM, Attfield MD (2014). Respiratory disease mortality among US coal miners; results after 37 years of follow-up. Occup Environ Med. 71(1):30–9. https://doi.org/10.1136/oemed-2013-101597 PMID:24186945

Grabowski Ł, Pierzynowska K, Kosznik-Kwaśnicka K, Stasiłojć M, Jerzemowska G, Węgrzyn A, et al. (2023). Sex-dependent differences in behavioral and immunological responses to antibiotic and bacteriophage administration in mice. Front Immunol. 14:1133358. https://doi.org/10.3389/fimmu.2023.1133358 PMID:37304279

Gram IT, Park SY, Kolonel LN, Maskarinec G, Wilkens LR, Henderson BE, et al. (2015). Smoking and risk of breast cancer in a racially/ethnically diverse population of mainly women who do not drink alcohol: the MEC study. Am J Epidemiol. 182(11):917–25. https://doi.org/10.1093/aje/kwv092 PMID:26493265

Gram IT, Wiik AB, Lund E, Licaj I, Braaten T (2022). Never-smokers and the fraction of breast cancer attributable to second-hand smoke from parents during childhood: the Norwegian Women and Cancer Study 1991–2018. Int J Epidemiol. 50(6):1927–35. https://doi.org/10.1093/ije/dyab153 PMID:34999865

Granvogl M, Koehler P, Latzer L, Schieberle P (2008). Development of a stable isotope dilution assay for the quantitation of glycidamide and its application to foods and model systems. J Agric Food Chem. 56(15):6087–92. https://doi.org/10.1021/jf800280b PMID:18624425

Green T, Toghill A, Lee R, Waechter F, Weber E, Noakes J (2005a). Thiamethoxam induced mouse liver tumors and their relevance to humans. Part 1: mode of action studies in the mouse. Toxicol Sci. 86(1):36–47. https://doi.org/10.1093/toxsci/kfi124 PMID:15716477

Green T, Toghill A, Lee R, Waechter F, Weber E, Peffer R, et al. (2005b). Thiamethoxam induced mouse liver tumors and their relevance to humans. Part 2: species differences in response. Toxicol Sci. 86(1):48–55. https://doi.org/10.1093/toxsci/kfi125 PMID:15716476

Grevelding CG (1995). The female-specific W1 sequence of the Puerto Rican strain of *Schistosoma mansoni* occurs in both genders of a Liberian strain. Mol Biochem Parasitol. 71(2):269–72. https://doi.org/10.1016/0166-6851(94)00058-U PMID:7477111

Griffiths P, Reeves M (2021). Pathogenesis of human cytomegalovirus in the immunocompromised host. Nat Rev Microbiol. 19(12):759–73. https://doi.org/10.1038/s41579-021-00582-z

Grigore F, Yang H, Hanson ND, VanBrocklin MW, Sarver AL, Robinson JP (2020). BRAF inhibition in melanoma is associated with the dysregulation of histone methylation and histone methyltransferases. Neoplasia. 22(9):376–89. https://doi.org/10.1016/j.neo.2020.06.006 PMID:32629178

Grimsrud TK, Berge SR, Haldorsen T, Andersen A (2002). Exposure to different forms of nickel and risk of lung cancer. Am J Epidemiol. 156(12):1123–32. https://doi.org/10.1093/aje/kwf165 PMID:12480657

Grivennikov SI (2013). Inflammation and colorectal cancer: colitis-associated neoplasia. Semin Immunopathol. 35(2):229–44. https://doi.org/10.1007/s00281-012-0352-6 PMID:23161445

Groot HJ, Lubberts S, de Wit R, Witjes JA, Kerst JM, de Jong IJ, et al. (2018). Risk of solid cancer after treatment of testicular germ cell cancer in the platinum era. J Clin Oncol. 36(24):2504–13. https://doi.org/10.1200/JCO.2017.77.4174 PMID:29989856

Gruebele A, Zawaski K, Kaplan D, Novak RF (1996). Cytochrome P4502E1- and cytochrome P4502B1/2B2-catalyzed carbon tetrachloride metabolism: effects on signal transduction as demonstrated by altered immediate-early (c-Fos and c-Jun) gene expression and nuclear AP-1 and NF-kappa B transcription factor levels. Drug Metab Dispos. 24:15–22. https://dmd.aspetjournals.org/content/24/1/15.long PMID:8825185

Gu J, He F, Clifford GM, Li M, Fan Z, Li X, et al. (2023). A systematic review and meta-analysis on the relative and attributable risk of *Helicobacter pylori* infection and cardia and non-cardia gastric cancer. Expert Rev Mol Diagn. 23(12):1251–61. https://doi.org/10.1080/14737159.2023.2277377 PMID:37905778

Gu W, Zhang J, Ren C, Gao Y, Zhang T, Long Y, et al. (2022). The association between biomarkers of acrylamide and cancer mortality in U.S. adult population: evidence from NHANES 2003–2014. Front Oncol. 12:970021. https://doi.org/10.3389/fonc.2022.970021 PMID:36249016

Guarino M, Kumar P, Felser A, Terracciano LM, Guixé-Muntet S, Humar B, et al. (2020). Exercise attenuates the transition from fatty liver to steatohepatitis and reduces tumor formation in mice. Cancers (Basel). 12(6):1407. https://doi.org/10.3390/cancers12061407https://doi.org/10.3390/cancers12061407 PMID:32486073

Guedes Pinto T, de Moraes Malinverni AC, Renno ACM, Ribeiro DA (2023). Do hairdressers comprise a high risk group for genotoxicity? A systematic review. Int Arch Occup Environ Health. 96(8):1077–86.

https://doi.org/10.1007/s00420-023-01999-0 PMID:37486377

Guérard M, Zeller A, Festag M, Schubert C, Singer T, Müller L (2014). Genotoxicity testing of peptides: folate deprivation as a marker of exaggerated pharmacology. Toxicol Appl Pharmacol. 279(3):419–27. https://doi.org/10.1016/j.taap.2014.06.022https://doi.org/10.1016/j.taap.2014.06.022 PMID:24997324

Guerrero-Vargas NN, Navarro-Espíndola R, Guzmán-Ruíz MA, Basualdo MDC, Espitia-Bautista E, López-Bago A, et al. (2017). Circadian disruption promotes tumor growth by anabolic host metabolism; experimental evidence in a rat model. BMC Cancer. 17(1):625. https://doi.org/10.1186/s12885-017-3636-3 PMID:28874144

Guidolin V, Carlson ES, Carrà A, Villalta PW, Maertens LA, Hecht SS, et al. (2021). Identification of new markers of alcohol-derived DNA damage in humans. Biomolecules. 11(3):366. https://doi.org/10.3390/biom11030366 PMID:33673538

Guiñazú N, Rena V, Genti-Raimondi S, Rivero V, Magnarelli G (2012). Effects of the organophosphate insecticides phosmet and chlorpyrifos on trophoblast JEG-3 cell death, proliferation and inflammatory molecule production. Toxicol In Vitro. 26(3):406–13. https://doi.org/10.1016/j.tiv.2012.01.003 PMID:22265773

Gulati S, Kosik P, Durdik M, Skorvaga M, Jakl L, Markova E, et al. (2020). Effects of different mobile phone UMTS signals on DNA, apoptosis and oxidative stress in human lymphocytes. Environ Pollut. 267:115632. https://doi.org/10.1016/j.envpol.2020.115632 PMID:33254645

Guler ZR, Yilmaz U, Uzunosmanoglu K, Ozturk B, Abudayyak M, Ozden S (2023). Assessment of global DNA methylation in SH-SY5Y cells exposed to the neonicotinoid insecticides imidacloprid and thiamethoxam. Int J Toxicol. 42(4):345–51. https://doi.org/10.1177/10915818231154470 PMID:36723994

Gunn JS, Marshall JM, Baker S, Dongol S, Charles RC, Ryan ET (2014). *Salmonella* chronic carriage: epidemiology, diagnosis, and gallbladder persistence. Trends Microbiol. 22(11):648–55. https://doi.org/10.1016/j.tim.2014.06.007 PMID:25065707

Guo LC, Liu T, Yang Y, Yu S, Gao Y, Huang W, et al. (2020). Changes in thyroid hormone related proteins and gene expression induced by polychlorinated biphenyls and halogen flame retardants exposure of children in a Chinese e-waste recycling area. Sci Total Environ. 742:140597. https://doi.org/10.1016/j.scitotenv.2020.140597 PMID:32629271

Guo NL, Zhang JX, Wu JP, Xu YH (2017). Isoflurane promotes glucose metabolism through up-regulation of *miR-21* and suppresses mitochondrial oxidative phosphorylation in ovarian cancer cells. Biosci Rep. 37(6):BSR20170818. https://doi.org/10.1042/BSR20170818https://doi.org/10.1042/BSR20170818 PMID:28951521

Gupta I, Pedersen S, Vranic S, Al Moustafa AE (2022a). Implications of gut microbiota in epithelial–mesenchymal transition and cancer progression: a concise review. Cancers (Basel). 14(12):2964. https://doi.org/10.3390/cancers14122964 PMID:35740629

Gupta N, Sekhri S (2014). Impact of laundry detergents on environment – a review. Journal of Asian Regional Association for Home Economics. 21(4):149.

Gupta P, Hodgman CF, Alvarez-Florez C, Schadler KL, Markofski MM, O'Connor DP, et al. (2022b). Comparison of three exercise interventions with and without gemcitabine treatment on pancreatic tumor growth in mice: no impact on tumor infiltrating lymphocytes. Front Physiol. 13:1039988. https://doi.org/10.3389/fphys.2022.1039988https://doi.org/10.3389/fphys.2022.1039988 PMID:36479351

Gürler M, Bayram B (2023). Estimation of ethanol and methanol exposure through jarred fruit purees. Ann Ist Super Sanita. 59(4):260–6. https://www.iss.it/documents/20126/0/ANN_23_04_04.pdf PMID:38088392

Guseva Canu I, Batsungnoen K, Maynard A, Hopf NB (2020a). State of knowledge on the occupational exposure to carbon nanotubes. Int J Hyg Environ Health. 225:113472. https://doi.org/10.1016/j.ijheh.2020.113472 PMID:32035287

Guseva Canu I, Gaillen-Guedy A, Antilla A, Charles S, Fraize-Frontier S, Luce D, et al. (2022). Lung cancer mortality in the European cohort of titanium dioxide workers: a reanalysis of the exposure–response relationship. Occup Environ Med. 79(9):oemed-2021–108030. https://doi.org/10.1136/oemed-2021-108030 PMID:35501125

Guseva Canu I, Gaillen-Guedy A, Wild P, Straif K, Luce D (2020b). Lung cancer mortality in the French cohort of titanium dioxide workers: some aetiological insights. Occup Environ Med. 77(11):795–7.

https://doi.org/10.1136/oemed-2020-106522 PMID:32737152

Gustavsson P, Andersson T, Gustavsson A, Reuterwall C (2017). Cancer incidence in female laboratory employees: extended follow-up of a Swedish cohort study. Occup Environ Med. 74(11):823–6. https://doi.org/10.1136/oemed-2016-104184 PMID:28526715

Gustavsson P, Bigert C, Andersson T, Kader M, Härmä M, Selander J, et al. (2023). Night work and breast cancer risk in a cohort of female healthcare employees in Stockholm, Sweden. Occup Environ Med. 80(7):372–6. https://doi.org/10.1136/oemed-2022-108673

Gustavsson P, Reuterwall C, Sadigh J, Söderholm M (1999). Mortality and cancer incidence among laboratory technicians in medical research and routine laboratories (Sweden). Cancer Causes Control. 10(1):59–64. https://doi.org/10.1023/A:1008892830922 PMID:10334643

Guth S, Baum M, Cartus AT, Diel P, Engel KH, Engeli B, et al. (2023). Evaluation of the genotoxic potential of acrylamide: arguments for the derivation of a tolerable daily intake (TDI value). Food Chem Toxicol. 173(173):113632. https://doi.org/10.1016/j.fct.2023.113632 PMID:36708862

Guthold R, Stevens GA, Riley LM, Bull FC (2018). Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1·9 million participants. Lancet Glob Health. 6(10):e1077–86. https://doi.org/10.1016/S2214-109X(18)30357-7 PMID:30193830

Guzeloglu-Kayisli O, Basar M, Shapiro JP, Semerci N, Huang JS, Schatz F, et al. (2014). Long-acting progestin-only contraceptives enhance human endometrial stromal cell expressed neuronal pentraxin-1 and reactive oxygen species to promote endothelial cell apoptosis. J Clin Endocrinol Metab. 99(10):E1957–66. https://doi.org/10.1210/jc.2014-1770 PMID:25029423

Ha M, Huang X, Li L, Lu D, Liu C (2021). PKCα mediated by the PI3K/Akt–FOXA1 cascade facilitates cypermethrin-induced hyperthyroidism. Sci Total Environ. 757:143727. https://doi.org/10.1016/j.scitotenv.2020.143727 PMID:33250241

Håberg SE, Page CM, Lee Y, Nustad HE, Magnus MC, Haftorn KL, et al. (2022). DNA methylation in newborns conceived by assisted reproductive technology. Nat Commun. 13(1):1896. https://doi.org/10.1038/s41467-022-29540-w PMID:35393427

Hadkhale K, Martinsen JI, Weiderpass E, Kjaerheim K, Sparen P, Tryggvadottir L, et al. (2017). Occupational exposure to solvents and bladder cancer: a population-based case control study in Nordic countries. Int J Cancer. 140(8):1736–46. https://doi.org/10.1002/ijc.30593 PMID:28032642

Hager E, Chen J, Zhao L (2022). Minireview: parabens exposure and breast cancer. Int J Environ Res Public Health. 19(3):1873. https://doi.org/10.3390/ijerph19031873 PMID:35162895

Haggard DE, Karmaus AL, Martin MT, Judson RS, Setzer RW, Paul Friedman K (2018). High-throughput H295R steroidogenesis assay: utility as an alternative and a statistical approach to characterize effects on steroidogenesis. Toxicol Sci. 162(2):509–34. https://doi.org/10.1093/toxsci/kfx274https://doi.org/10.1093/toxsci/kfx274 PMID:29216406

Hagiwara A, Takesada Y, Tanaka H, Tamano S, Hirose M, Ito N, et al. (2001). Dose-dependent induction of glandular stomach preneoplastic and neoplastic lesions in male F344 rats treated with catechol chronically. Toxicol Pathol. 29(2):180–6. https://doi.org/10.1080/019262301317052459 PMID:11421485

Hagström K, Jacobsen G, Sigsgaard T, Schaumburg I, Erlandsen M, Schlunssen V (2012). Predictors of monoterpene exposure in the Danish furniture industry. Ann Occup Hyg. 56(3):253–63. https://doi.org/10.1093/annhyg/mer091 PMID:22025531

Haidar Z, Traboulsi H, Eidelman DH, Baglole CJ (2023). Differential inflammatory profile in the lungs of mice exposed to cannabis smoke with varying THC:CBD ratio. Arch Toxicol. 97(7):1963–78. https://doi.org/10.1007/s00204-023-03514-3 PMID:37179517

Hakura A, Koyama1 N, Seki Y, Sonoda J, Asakura S (2022). *o*-Aminoazotoluene, 7,12- dimethylbenz[*a*]anthracene, and *N*-ethyl-*N*-nitrosourea, which are mutagenic but not carcinogenic in the colon, rapidly induce colonic tumors in mice with dextran sulfate sodium-induced colitis. Genes Environ. 44(1):11. https://doi.org/10.1186/s41021-022-00240-7https://doi.org/10.1186/s41021-022-00240-7 PMID:35351212

Hall AL, Kromhout H, Schüz J, Peters S, Portengen L, Vermeulen R, et al. (2020). Laryngeal cancer risks in workers exposed to lung carcinogens: exposure–effect analyses using a quantitative job exposure matrix. Epidemiology. 31(1):145–54. https://doi.org/10.1097/EDE.0000000000001120 PMID:31577634

Hall EC, Engels EA, Pfeiffer RM, Segev DL (2015). Association of antibody induction immunosuppression with cancer after kidney transplantation. Transplantation. 99(5):1051–7. https://doi.org/10.1097/TP.0000000000000449 PMID:25340595

Hallinger DR, Murr AS, Buckalew AR, Simmons SO, Stoker TE, Laws SC (2017). Development of a screening approach to detect thyroid disrupting chemicals that inhibit the human sodium iodide symporter (NIS). Toxicol In Vitro. 40:66–78. https://doi.org/10.1016/j.tiv.2016.12.006https://doi.org/10.1016/j.tiv.2016.12.006 PMID:27979590

Hamill PV, Steinberger E, Levine RJ, Rodriguez-Rigau LJ, Lemeshow S, Avrunin JS (1982). The epidemiologic assessment of male reproductive hazard from occupational exposure to TDA and DNT. J Occup Med. 24(12):985–93.https://journals.lww.com/joem/abstract/1982/12000/the_epidemiologic_assessment_of_male_reproductive.12.aspx PMID:6818333

Hammond MG, Talbert LM (1982). Clomiphene citrate therapy of infertile women with low luteal phase progesterone levels. Obstet Gynecol. 59(3):275–9. https://journals.lww.com/greenjournal/abstract/1982/03000/clomiphene_citrate_therapy_of_infertile_women_with.2.aspx PMID:7078874

Hamouda MM, El-Saied AS, Zaher A, Khalil AF, ElBlihy AA, Nabih N, et al. (2024). *Toxoplasma gondii*: seroprevalence and association with childhood brain tumors in Egypt. Acta Trop. 251:107123. https://doi.org/10.1016/j.actatropica.2024.107123 PMID:38242223

Hamra GB, Laden F, Cohen AJ, Raaschou-Nielsen O, Brauer M, Loomis D (2015). Lung cancer and exposure to nitrogen dioxide and traffic: a systematic review and meta-analysis. Environ Health Perspect. 123(11):1107–12. https://doi.org/10.1289/ehp.1408882 PMID:25870974

Han G, Tan Z, Jing H, Ning J, Li Z, Gao S, et al. (2021). Comet assay evaluation of lanthanum nitrate DNA damage in C57-ras transgenic mice. Biol Trace Elem Res. 199(10):3728–36. https://doi.org/10.1007/s12011-020-02500-5 PMID:33403576

Han M, Guo Z, Li G, Sang N (2013). Nitrogen dioxide inhalation induces genotoxicity in rats. Chemosphere. 90(11):2737–42. https://doi.org/10.1016/j.chemosphere.2012.11.057 PMID:23332788

Han YW (2015). *Fusobacterium nucleatum*: a commensal-turned pathogen. Curr Opin Microbiol. 23:141–7. https://doi.org/10.1016/j.mib.2014.11.013 PMID:25576662

Hanana H, Kleinert C, Gagné F (2021a). Toxicity of representative mixture of five rare earth elements in juvenile rainbow trout (*Oncorhynchus mykiss*) juveniles. Environ Sci Pollut Res Int. 28(22):28263–74. https://doi.org/10.1007/s11356-020-12218-5 PMID:33534100

Hanana H, Taranu ZE, Turcotte P, Gagnon C, Kowalczyk J, Gagné F (2021b). Evaluation of general stress, detoxification pathways, and genotoxicity in rainbow trout exposed to rare earth elements dysprosium and lutetium. Environ Sci Pollut Res Int. 208:111588.

Handa O, Kokura S, Adachi S, Takagi T, Naito Y, Tanigawa T, et al. (2006). Methylparaben potentiates UV-induced damage of skin keratinocytes. Toxicology. 227(1–2):62–72. https://doi.org/10.1016/j.tox.2006.07.018 PMID:16938376

Hang D, Wang L, Fang Z, Du M, Wang K, He X, et al. (2023). Ultra-processed food consumption and risk of colorectal cancer precursors: results from 3 prospective cohorts. J Natl Cancer Inst. 115(2):155–64. https://doi.org/10.1093/jnci/djac221 PMID:36477589

Hanna E, Rémuzat C, Auquier P, Toumi M (2017). Gene therapies development: slow progress and promising prospect. J Mark Access Health Policy. 5(1):1265293. https://doi.org/10.1080/20016689.2017.1265293 PMID:28265348

Hao Y, Zhang Y, Ni H, Gao J, Yang Y, Xu W, et al. (2019). Evaluation of the cytotoxic effects of glyphosate herbicides in human liver, lung, and nerve. J Environ Sci Health B. 54(9):737–44. https://doi.org/10.1080/03601234.2019.1633215 PMID:31232652

Hapgood JP, Ray RM, Govender Y, Avenant C, Tomasicchio M (2014). Differential glucocorticoid receptor-mediated effects on immunomodulatory gene expression by progestin contraceptives: implications for HIV-1 pathogenesis. Am J Reprod Immunol. 71(6):505–12. https://doi.org/10.1111/aji.12214 PMID:24547700

Hardell E, Kärrman A, van Bavel B, Bao J, Carlberg M, Hardell L (2014). Case–control study on perfluorinated alkyl acids (PFAAs) and the risk of prostate cancer. Environ Int. 63:35–9. https://doi.org/10.1016/j.envint.2013.10.005 PMID:24246240

Hardell L (1977). Maligna mesenkymala tumörer och exposition för fenoxisyror – en klinisk observation [Malignant mesenchymal tumors and exposure to phenoxy acids – a clinical observation]. Lakartidningen. 74(33):2753–4. PMID:895290 [Swedish]

Hardell L, Carlberg M, Nordström M, Eriksson M (2023). Exposure to phenoxyacetic acids and glyphosate as risk factors for non-Hodgkin lymphoma – pooled analysis of three Swedish case–control studies including the sub-type hairy cell leukemia. Leuk Lymphoma. 64(5):997–1004. https://doi.org/10.1080/10428194.2023.2190434 PMID:36938909

Hardell L, Carlberg M, Söderqvist F, Mild KH (2013). Pooled analysis of case–control studies on acoustic neuroma diagnosed 1997–2003 and 2007–2009 and use of mobile and cordless phones. Int J Oncol. 43(4):1036–44. https://doi.org/10.3892/ijo.2013.2025 PMID:23877578

Hardell L, Sandström A (1979). Case–control study: soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. Br J Cancer. 39(6):711–7. https://doi.org/10.1038/bjc.1979.125 PMID:444410

Harding BN, Castaño-Vinyals G, Palomar-Cros A, Papantoniou K, Espinosa A, Skene DJ, et al. (2022b). Changes in melatonin and sex steroid hormone production among men as a result of rotating night shift work – the HORMONIT study. Scand J Work Environ Health. 48(1):41–51. https://doi.org/10.5271/sjweh.3991 PMID:34623452

Harding BN, Skene DJ, Espinosa A, Middleton B, Castaño-Vinyals G, Papantoniou K, et al. (2022a). Metabolic profiling of night shift work – the HORMONIT study. Chronobiol Int. 39(11):1508–16. https://doi.org/10.1080/07420528.2022.2131562 PMID:36210507

Hargreave M, Mørch LS, Andersen KK, Winther JF, Schmiegelow K, Kjaer SK (2018). Maternal use of hormonal contraception and risk of childhood leukaemia: a nationwide, population-based cohort study. Lancet Oncol. 19(10):1307–14. https://doi.org/10.1016/S1470-2045(18)30479-0 PMID:30197174

Hargreave M, Mørch LS, Winther JF, Schmiegelow K, Kjaer SK (2022). Association between maternal hormonal contraception use and central nervous system tumors in children. JAMA. 327(1):59–66. https://doi.org/10.1001/jama.2021.22482 PMID:34982120

Harja M, Buema G, Bucur D (2022). Recent advances in removal of Congo Red dye by adsorption using an industrial waste. Sci Rep. 12(1):6087. https://doi.org/10.1038/s41598-022-10093-3 PMID:35414682

Harkness JH, Hitzemann RJ, Edmunds S, Phillips TJ (2013). Effects of sodium butyrate on methamphetamine-sensitized locomotor activity. Behav Brain Res. 239:139–47. https://doi.org/10.1016/j.bbr.2012.10.046 PMID:23137698

Harland EC, Cardeilhac PT (1975). Excretion of carbon-14-labeled aflatoxin B1 via bile, urine, and intestinal contents of the chicken. Am J Vet Res. 36(7):909–12. PMID:1147354

Härle L, von Bülow V, Knedla L, Stettler F, Müller H, Zahner D, et al. (2023). Hepatocyte integrity depends on c-Jun-controlled proliferation in *Schistosoma mansoni* infected mice. Sci Rep. 13(1):20390. https://doi.org/10.1038/s41598-023-47646-z PMID:37990129

Harper-Harrison G, Shanahan MM (2024). Hormone Replacement Therapy. StatPearls [Internet]. Treasure Island (FL), USA: StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493191/

Harris BHL, Macaulay VM, Harris DA, Klenerman P, Karpe F, Lord SR, et al. (2022). Obesity: a perfect storm for carcinogenesis. Cancer Metastasis Rev. 41(3):491–515. https://doi.org/10.1007/s10555-022-10046-2 PMID:36038791

Harris KL, Myers JN, Ramesh A (2013). Benzo(a)pyrene modulates fluoranthene-induced cellular responses in HT-29 colon cells in a dual exposure system. Environ Toxicol Pharmacol. 36(2):358–67.

https://doi.org/10.1016/j.etap.2013.04.017 PMID:23732482

Hart JE, Bertrand KA, DuPre N, James P, Vieira VM, VoPham T, et al. (2018). Exposure to hazardous air pollutants and risk of incident breast cancer in the nurses' health study II. Environ Health. 17(1):28. https://doi.org/10.1186/s12940-018-0372-3 PMID:29587753

Hartman C, Legoff L, Capriati M, Lecuyer G, Kernanec PY, Tevosian S, et al. (2021). Epigenetic effects promoted by neonicotinoid thiacloprid exposure. Front Cell Dev Biol. 9:691060. https://doi.org/10.3389/fcell.2021.691060 PMID:34295895

Hasegawa R, Cabral R, Hoshiya T, Hakoi K, Ogiso T, Boonyaphiphat P, et al. (1993). Carcinogenic potential of some pesticides in a medium-term multi-organ bioassay in rats. Int J Cancer. 54(3):489–93. https://doi.org/10.1002/ijc.2910540322 PMID:8509224

Hasegawa R, Furukawa F, Toyoda K, Jang JJ, Yamashita K, Sato S, et al. (1988a). Study for tumor-initiating effect of acetaminophen in two-stage liver carcinogenesis of male F344 rats. Carcinogenesis. 9(5):755–9. https://doi.org/10.1093/carcin/9.5.755 PMID:3365836

Hasegawa R, Ito N (1992). Liver medium-term bioassay in rats for screening of carcinogens and modifying factors in hepatocarcinogenesis. Food Chem Toxicol. 30(11):979–92. https://doi.org/10.1016/0278-6915(92)90184-M PMID:1473791

Hasegawa R, Takahashi M, Furukawa F, Toyoda K, Sato H, Jang JJ, et al. (1988b). Carcinogenicity study of tetramethylthiuram disulfide (thiram) in F344 rats. Toxicology. 51(2–3):155–65. https://doi.org/10.1016/0300-483X(88)90146-1 PMID:3176026

Haseman JK, Hailey JR (1997). An update of the National Toxicology Program database on nasal carcinogens. Mutat Res. 380(1–2):3–11. https://doi.org/10.1016/S0027-5107(97)00121-8 PMID:9385384

Hassan MM, Zaghloul AS, El-Serag HB, Soliman O, Patt YZ, Chappell CL, et al. (2001). The role of hepatitis C in hepatocellular carcinoma: a case control study among Egyptian patients. J Clin Gastroenterol. 33(2):123–6. https://doi.org/10.1097/00004836-200108000-00006 PMID:11468438

Hassen W, Ayed-Boussema I, Oscoz AA, Lopez AC, Bacha H (2007). The role of oxidative stress in zearalenone-mediated toxicity in Hep G2 cells: oxidative DNA damage, gluthatione depletion and stress proteins induction. Toxicology. 232(3):294–302. https://doi.org/10.1016/j.tox.2007.01.015 PMID:17339071

Hatem E, El Banna N, Huang ME (2017). Multifaceted roles of glutathione and glutathione-based systems in carcinogenesis and anticancer drug resistance. Antioxid Redox Signal. 27(15):1217–34. https://doi.org/10.1089/ars.2017.7134https://doi.org/10.1089/ars.2017.7134

Hattori K, Sobue T, Zha L, Kitamura T, Shimomura Y, Iwasaki M, et al. (2022). Association between working hours and cancer risk in Japan: the Japan public health center-based prospective study. J Occup Health. 64(1):e12375. https://doi.org/10.1002/1348-9585.12375 PMID:36502469

Hauri D, Spycher B, Huss A, Zimmermann F, Grotzer M, von der Weid N, et al.; Swiss National Cohort; Swiss Paediatric Oncology Group (SPOG) (2013). Domestic radon exposure and risk of childhood cancer: a prospective census-based cohort study. Environ Health Perspect. 121(10):1239–44. https://doi.org/10.1289/ehp.1306500 PMID:23942326

Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. (2012). Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 380(9839):358–65. https://doi.org/10.1016/S0140-6736(12)60868-X PMID:22735384

Haworth S, Lawlor T, Mortelmans K, Speck W, Zeiger E (1983). *Salmonella* mutagenicity test results for 250 chemicals. Environ Mutagen. 5 S1:1–142. https://doi.org/10.1002/em.2860050703 PMID:6365529

Hayakawa J, Ohmichi M, Kurachi H, Kanda Y, Hisamoto K, Nishio Y, et al. (2000). Inhibition of BAD phosphorylation either at serine 112 via extracellular signal-regulated protein kinase cascade or at serine 136 via Akt cascade sensitizes human ovarian cancer cells to cisplatin. Cancer Res. 60(21):5988–94. https://aacrjournals.org/cancerres/article/60/21/5988/506806/Inhibition-of-BAD-Phosphorylation-Either-at-Serine PMID:11085518

Hayashi M, Ikenaga N, Nakata K, Luo H, Zhong P, Date S, et al. (2023). Intratumor *fusobacterium nucleatum* promotes

the progression of pancreatic cancer via the CXCL1–CXCR2 axis. Cancer Sci. 114(9):3666–78. https://doi.org/10.1111/cas.15901 PMID:37438965

He B, Wang X, Wei L, Kong B, Jin Y, Xie X, et al. (2018a). β-Cypermethrin and its metabolite 3-phenoxybenzoic acid induce cytotoxicity and block granulocytic cell differentiation in HL-60 cells. Acta Biochim Biophys Sin (Shanghai). 50(8):740–7. https://doi.org/10.1093/abbs/gmy068 PMID:29945211

He JL, Wu HB, Hu WL, Liu JJ, Zhang Q, Xiao W, et al. (2022b). Exposure to multiple trace elements and thyroid cancer risk in Chinese adults: a case–control study. Int J Hyg Environ Health. 246:114049. https://doi.org/10.1016/j.ijheh.2022.114049 PMID:36279789

He L, Michailidou F, Gahlon HL, Zeng W (2022c). Hair dye ingredients and potential health risks from exposure to hair dyeing. Chem Res Toxicol. 35(6):901–15. https://doi.org/10.1021/acs.chemrestox.1c00427 PMID:35666914

He X, Barnett LM, Jeon J, Zhang Q, Alqahtani S, Black M, et al. (2024). Real-time exposure to 3D-printing emissions elicits metabolic and pro-inflammatory responses in human airway epithelial cells. Toxics. 12(1):67. https://doi.org/10.3390/toxics12010067 PMID:38251022

He X, Jiang J, Zhang XX (2022d). Environmental exposure to low-dose perfluorohexanesulfonate promotes obesity and non-alcoholic fatty liver disease in mice fed a high-fat diet. Environ Sci Pollut Res Int. 29(32):49279–90. https://doi.org/10.1007/s11356-022-19369-7 PMID:35217953

He X, Xia Q, Woodling K, Lin G, Fu PP (2017). Pyrrolizidine alkaloid-derived DNA adducts are common toxicological biomarkers of pyrrolizidine alkaloid N-oxides. Yao Wu Shi Pin Fen Xi. 25(4):984–91. PMID:28987376

He Y, de Araújo Júnior RF, Cavalcante RS, Yu Z, Schomann T, Gu Z, et al. (2023). Effective breast cancer therapy based on palmitic acid-loaded PLGA nanoparticles. Biomater Adv. 145:213270. https://doi.org/10.1016/j.bioadv.2022.213270https://doi.org/10.1016/j.bioadv.2022.213270 PMID:36603405

He Y, Peng L, Zhang W, Liu C, Yang Q, Zheng S, et al. (2018b). Adipose tissue levels of polybrominated diphenyl ethers and breast cancer risk in Chinese women: a case–control study. Environ Res. 167:160–8. https://doi.org/10.1016/j.envres.2018.07.009 PMID:30014897

He Y, Shi M, Wu X, Ma J, Ng KT, Xia Q, et al. (2021). Mutational signature analysis reveals widespread contribution of pyrrolizidine alkaloid exposure to human liver cancer. Hepatology. 74(1):264–80. https://doi.org/10.1002/hep.31723https://doi.org/10.1002/hep.31723 PMID:33462832

He Y, Si Y, Li X, Hong J, Yu C, He N (2022a). The relationship between tobacco and breast cancer incidence: a systematic review and meta-analysis of observational studies. Front Oncol. 12:961970. https://doi.org/10.3389/fonc.2022.961970 PMID:36185316

Health Canada (2016). Screening assessment internationally classified substance grouping cresol (phenol, methyl-) substances. Ottawa (ON), Canada: Environment and Climate Change Canada, Health Canada. Available from: https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/screening-assessment10.html, accessed June 2024.

Health Canada (2018). Guidelines for Canadian drinking water quality guideline technical document. Bromate. Ottawa (ON), Canada: Health Canada. Available from: https://www.canada.ca/content/dam/hc-sc/documents/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-bromate/bromate-2018-final-eng.pdf, accessed September 2020.

Heath JC, Daniel MR (1964). The production of malignant tumours by nickel in the rat. Br J Cancer. 18(2):261–4. https://doi.org/10.1038/bjc.1964.30 PMID:14189681

Heck JE, Park AS, Qiu J, Cockburn M, Ritz B (2013). An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring. Environ Res. 127:1–6. https://doi.org/10.1016/j.envres.2013.09.002 PMID:24139061

Heck JE, Park AS, Qiu J, Cockburn M, Ritz B (2015). Retinoblastoma and ambient exposure to air toxics in the perinatal period. J Expo Sci Environ Epidemiol. 25(2):182–6. https://doi.org/10.1038/jes.2013.84 PMID:24280682

Hedelund L, Lerche C, Wulf HC, Haedersdal M (2006). Carcinogenesis related to intense pulsed light and UV exposure: an experimental animal study. Lasers Med Sci. 21(4):198–201. https://doi.org/10.1007/s10103-006-0395-9 PMID:16964439

Heikkila K, Nyberg ST, Madsen IE, de Vroome E, Alfredsson L, Bjorner JJ, et al.; IPD-Work Consortium (2016). Long working hours and cancer risk: a multi-cohort study. Br J Cancer. 114(7):813–8. https://doi.org/10.1038/bjc.2016.9 PMID:26889978

Heindel JJ, Belcher S, Flaws JA, Prins GS, Ho SM, Mao J, et al. (2020). Data integration, analysis, and interpretation of eight academic CLARITY-BPA studies. Reprod Toxicol. 98:29–60. https://doi.org/10.1016/j.reprotox.2020.05.014https://doi.org/10.1016/j.reprotox.2020.05.014 PMID:32682780

Helaskoski E, Suojalehto H, Virtanen H, Airaksinen L, Kuuliala O, Aalto-Korte K, et al. (2014). Occupational asthma, rhinitis, and contact urticaria caused by oxidative hair dyes in hairdressers. Ann Allergy Asthma Immunol. 112(1):46–52. https://doi.org/10.1016/j.anai.2013.10.002 PMID:24331393

Hellesnes R, Kvammen Ø, Myklebust TÅ, Bremnes RM, Karlsdottir Á, Negaard HFS, et al. (2020). Continuing increased risk of second cancer in long-term testicular cancer survivors after treatment in the cisplatin era. Int J Cancer. 147(1):21–32. https://doi.org/10.1002/ijc.32704 PMID:31597192

Helyes Z, Kemény Á, Csekő K, Szőke É, Elekes K, Mester M, et al. (2017). Marijuana smoke induces severe pulmonary hyperresponsiveness, inflammation, and emphysema in a predictive mouse model not via CB1 receptor activation. Am J Physiol Lung Cell Mol Physiol. 313(2):L267–77. https://doi.org/10.1152/ajplung.00354.2016 PMID:28495855

Hemgesberg M, Stegmüller S, Cartus A, Hemmer S, Püttmann M, Stockis JP, et al. (2021). Acrylamide-derived DNA adducts in human peripheral blood mononuclear cell DNA: correlation with body mass. Food Chem Toxicol. 157:112575. https://doi.org/10.1016/j.fct.2021.112575 PMID:34560178

Henderson CJ, Cameron AR, Chatham L, Stanley LA, Wolf CR (2015). Evidence that the capacity of nongenotoxic carcinogens to induce oxidative stress is subject to marked variability. Toxicol Sci. 145(1):138–48. https://doi.org/10.1093/toxsci/kfv039 PMID:25690736

Henderson TO, Oeffinger KC, Whitton J, Leisenring W, Neglia J, Meadows A, et al. (2012a). Secondary gastrointestinal cancer in childhood cancer survivors: a cohort study. Ann Intern Med. 156(11):757–66, W-260. https://doi.org/10.7326/0003-4819-156-11-201206050-00002 PMID:22665813

Henderson TO, Rajaraman P, Stovall M, Constine LS, Olive A, Smith SA, et al. (2012b). Risk factors associated with secondary sarcomas in childhood cancer survivors: a report from the childhood cancer survivor study. Int J Radiat Oncol Biol Phys. 84(1):224–30. https://doi.org/10.1016/j.ijrobp.2011.11.022 PMID:22795729

Hengge UR, Baumann M, Maleba R, Brockmeyer NH, Goos M (1996). Oxymetholone promotes weight gain in patients with advanced human immunodeficiency virus (HIV-1) infection. Br J Nutr. 75(1):129–38. https://doi.org/10.1079/BJN19960116 PMID:8785183

Henneicke-von Zepelin HH, Meden H, Kostev K, Schröder-Bernhardi D, Stammwitz U, Becher H (2007). Isopropanolic black cohosh extract and recurrence-free survival after breast cancer. Int J Clin Pharmacol Ther. 45(3):143–54. https://doi.org/10.5414/CPP45143 PMID:17416109

Henschenmacher B, Bitsch A, de Las Heras Gala T, Forman HJ, Fragoulis A, Ghezzi P, et al. (2022). The effect of radiofrequency electromagnetic fields (RF-EMF) on biomarkers of oxidative stress in vivo and in vitro: a protocol for a systematic review. Environ Int. 158:106932. https://doi.org/10.1016/j.envint.2021.106932 PMID:34662800

Hercog K, Maisanaba S, Filipič M, Sollner-Dolenc M, Kač L, Žegura B (2019). Genotoxic activity of bisphenol A and its analogues bisphenol S, bisphenol F and bisphenol AF and their mixtures in human hepatocellular carcinoma (HepG2) cells. Sci Total Environ. 687:267–76. https://doi.org/10.1016/j.scitotenv.2019.05.486 PMID:31207516

Heredia-García G, Gómez-Oliván LM, Orozco-Hernández JM, Luja-Mondragón M, Islas-Flores H, SanJuan-Reyes N, et al. (2019). Alterations to DNA, apoptosis and oxidative damage induced by sucralose in blood cells of *Cyprinus carpio*. Sci Total Environ. 692:411–21. https://doi.org/10.1016/j.scitotenv.2019.07.165 PMID:31351285

Hermelink R, Leitzmann MF, Markozannes G, Tsilidis K, Pukrop T, Berger F, et al. (2022). Sedentary behavior and cancer – an umbrella review and meta-analysis. Eur J Epidemiol. 37(5):447–60. https://doi.org/10.1007/s10654-022-00873-6https://doi.org/10.1007/s10654-022-00873-6 PMID:35612669

Hermes GL, Delgado B, Tretiakova M, Cavigelli SA, Krausz T, Conzen SD, et al. (2009). Social isolation dysregulates endocrine and behavioral stress while increasing malignant burden of spontaneous mammary tumors. Proc Natl Acad Sci USA. 106(52):22393–8. https://doi.org/10.1073/pnas.0910753106 PMID:20018726

Hernández AF, Casado I, Pena G, Gil F, Villanueva E, Pla A (2008). Low level of exposure to pesticides leads to lung dysfunction in occupationally exposed subjects. Inhal Toxicol. 20(9):839–49. https://doi.org/10.1080/08958370801905524 PMID:18645724

Hess JA, Khasawneh MK (2015). Cancer metabolism and oxidative stress: insights into carcinogenesis and chemotherapy via the non-dihydrofolate reductase effects of methotrexate. BBA Clin. 3:152–61. https://doi.org/10.1016/j.bbacli.2015.01.006 PMID:26674389

Hessel PA, Kalmes R, Smith TJ, Lau E, Mink PJ, Mandel J (2004). A nested case–control study of prostate cancer and atrazine exposure. J Occup Environ Med. 46(4):379–85. https://doi.org/10.1097/01.jom.0000121128.73921.a1 PMID:15076656

Hiasa Y, Ohshima M, Kitahori Y, Konishi N, Shimoyama T, Sakaguchi Y, et al. (1988). The promoting effects of food dyes, erythrosine (Red 3) and rose bengal B (Red 105), on thyroid tumors in partially thyroidectomized N-bis(2-hydroxypropyl)-nitrosamine-treated rats. Jpn J Cancer Res. 79(3):314–9. https://doi.org/10.1111/j.1349-7006.1988.tb01593.x PMID:2836348

Hickey M, Krikun G, Kodaman P, Schatz F, Carati C, Lockwood CJ (2006). Long-term progestin-only contraceptives result in reduced endometrial blood flow and oxidative stress. J Clin Endocrinol Metab. 91(9):3633–8. https://doi.org/10.1210/jc.2006-0724 PMID:16757524

Hidalgo MA, Carretta MD, Burgos RA (2021). Long chain fatty acids as modulators of immune cells function: contribution of FFA1 and FFA4 receptors. Front Physiol. 12:668330. https://doi.org/10.3389/fphys.2021.668330https://doi.org/10.3389/fphys.2021.668330 PMID:34276398

Hilakivi-Clarke L, Cho E, Onojafe I, Raygada M, Clarke R (1999). Maternal exposure to genistein during pregnancy increases carcinogen-induced mammary tumorigenesis in female rat offspring. Oncol Rep. 6(5):1089–95. https://doi.org/10.3892/or.6.5.1089 PMID:10425307

Hilding AC, Hilding DA, Larson DM, Aufderheide AC (1981). Biological effects of ingested amosite asbestos, taconite tailings, diatomaceous earth and Lake Superior water in rats. Arch Environ Health. 36(6):298–303. https://doi.org/10.1080/00039896.1981.10667641 PMID:7316567

Hilgert Jacobsen-Pereira C, Dos Santos CR, Troina Maraslis F, Pimentel L, Feijó AJL, Iomara Silva C, et al. (2018). Markers of genotoxicity and oxidative stress in farmers exposed to pesticides. Ecotoxicol Environ Saf. 148:177–83. https://doi.org/10.1016/j.ecoenv.2017.10.004 PMID:29055201

Hines EP, Mendola P, von Ehrenstein OS, Ye X, Calafat AM, Fenton SE (2015). Concentrations of environmental phenols and parabens in milk, urine and serum of lactating North Carolina women. Reprod Toxicol. 54:120–8. https://doi.org/10.1016/j.reprotox.2014.11.006 PMID:25463527

Hiraga K, Fujii T (1985). Carcinogenicity testing of acetaminophen in F344 rats. Jpn J Cancer Res. 76(2):79–85. PMID:3920105

Hirata N, Shim YH, Pravdic D, Lohr NL, Pratt PF Jr, Weihrauch D, et al. (2011). Isoflurane differentially modulates mitochondrial reactive oxygen species production via forward versus reverse electron transport flow: implications for preconditioning. Anesthesiology. 115(3):531–40. https://doi.org/10.1097/ALN.0b013e31822a2316https://doi.org/10.1097/ALN.0b013e31822a2316 PMID:21862887

Hirono I, Haga M, Fujii M, Matsuura S, Matsubara N, Nakayama M, et al. (1979). Induction of hepatic tumors in rats by senkirkine and symphytine. J Natl Cancer Inst. 63(2):469–72. PMID:287835

Hirose M, Hakoi K, Takahashi S, Hoshiya T, Akagi K, Lin C, et al. (1999). Sequential morphological and biological changes in the glandular stomach induced by oral administration of catechol to male F344 rats. Toxicol Pathol. 27(4):448–55. https://doi.org/10.1177/019262339902700409 PMID:10485826

Hobbs CA, Chhabra RS, Recio L, Streicker M, Witt KL (2012). Genotoxicity of styrene–acrylonitrile trimer in brain, liver, and blood cells of weanling F344 rats. Environ Mol Mutagen. 53(3):227–38. https://doi.org/10.1002/em.21680 PMID:22351108

Hodak E, David M (2004). Alefacept: a review of the literature and practical guidelines for management. Dermatol Ther. 17(5):383–92. https://doi.org/10.1111/j.1396-0296.2004.04041.x PMID:15379773

Hoerauf KH, Schrögendorfer KF, Wiesner G, Gruber M, Spacek A, Kress HG, et al. (1999). Sister chromatid exchange in human lymphocytes exposed to isoflurane and nitrous oxide in vitro. Br J Anaesth. 82(2):268–70. https://doi.org/10.1093/bja/82.2.268https://doi.org/10.1093/bja/82.2.268 PMID:10365006

Hofer S, Stonig M, Wally V, Hartmann A, Fuchs D, Hermann M, et al. (2018). Contradictory effects of chemical filters in UV/ROS-stressed human keratinocyte and fibroblast cells. Altern Anim Exp. 36(2):231–44. https://doi.org/10.14573/altex.1808201 PMID:30488083

Hoffman H-R, Matusch R, Baniahmad A (2013). Isolation of atraric acid, synthesis of atraric acid derivatives, and use of atraric acid and the derivatives thereof for the treatment of benign prostatic hyperplasia, prostate carcinoma and spinobulbar muscular atrophy. United States Patent US8481519B2. https://patents.google.com/patent/US8481519B2/en.

Hoffman K, Lorenzo A, Butt CM, Hammel SC, Henderson BB, Roman SA, et al. (2017). Exposure to flame retardant chemicals and occurrence and severity of papillary thyroid cancer: a case–control study. Environ Int. 107:235–42. https://doi.org/10.1016/j.envint.2017.06.021 PMID:28772138

Hofmann J, Guardado J, Keifer M, Wesseling C (2006). Mortality among a cohort of banana plantation workers in Costa Rica. Int J Occup Environ Health. 12(4):321–8. https://doi.org/10.1179/oeh.2006.12.4.321 PMID:17168219

Hofmann JN, Beane Freeman LE, Murata K, Andreotti G, Shearer JJ, Thoren K, et al. (2021). Lifetime pesticide use and monoclonal gammopathy of undetermined significance in a prospective cohort of male farmers. Environ Health Perspect. 129(1):17003. https://doi.org/10.1289/EHP6960 PMID:33404262

Hogervorst JG, Schouten LJ, Konings EJ, Goldbohm RA, van den Brandt PA (2007). A prospective study of dietary acrylamide intake and the risk of endometrial, ovarian, and breast cancer. Cancer Epidemiol Biomarkers Prev. 16(11):2304–13. https://doi.org/10.1158/1055-9965.EPI-07-0581 PMID:18006919

Hogervorst JGF, van den Brandt PA, Godschalk RWL, van Schooten FJ, Schouten LJ (2017). Interactions between dietary acrylamide intake and genes for ovarian cancer risk. Eur J Epidemiol. 32(5):431–41. https://doi.org/10.1007/s10654-017-0244-0 PMID:28391539

Høgsberg T, Jacobsen NR, Clausen PA, Serup J (2013). Black tattoo inks induce reactive oxygen species production correlating with aggregation of pigment nanoparticles and product brand but not with the polycyclic aromatic hydrocarbon content. Exp Dermatol. 22(7):464–9. https://doi.org/10.1111/exd.12178 PMID:23800057

Hoisnard L, Lebrun-Vignes B, Maury S, Mahevas M, El Karoui K, Roy L, et al. (2022). Adverse events associated with JAK inhibitors in 126,815 reports from the WHO pharmacovigilance database. Sci Rep. 12(1):7140. https://doi.org/10.1038/s41598-022-10777-w PMID:35504889

Hojo M, Maeno A, Sakamoto Y, Ohnuki A, Tada Y, Yamamoto Y, et al. (2022). Two-year intermittent exposure of a multiwalled carbon nanotube by intratracheal instillation induces lung tumors and pleural mesotheliomas in F344 rats. Part Fibre Toxicol. 19(1):38. https://doi.org/10.1186/s12989-022-00478-7 PMID:35590372

Holden HE, Stoll RE, Blanchard KT (1999). Oxymetholone: II. Evaluation in the Tg-AC transgenic mouse model for detection of carcinogens. Toxicol Pathol. 27(5):507–12. https://doi.org/10.1177/019262339902700502 PMID:10528629

Holland N, Davé V, Venkat S, Wong H, Donde A, Balmes JR, et al. (2015). Ozone inhalation leads to a dose-dependent increase of cytogenetic damage in human lymphocytes. Environ Mol Mutagen. 56(4):378–87. https://doi.org/10.1002/em.21921 PMID:25451016

Holly EA, Lele C (1997). Non-Hodgkin's lymphoma in HIV-positive and HIV-negative homosexual men in the San Francisco Bay Area: allergies, prior medication use, and sexual practices. J Acquir Immune Defic Syndr Hum Retrovirol. 15(3):211–22. https://doi.org/10.1097/00042560-199707010-00005 PMID:9257656

Holmes AL, Wise SS, Sandwick SJ, Lingle WL, Negron VC, Thompson WD, et al. (2006). Chronic exposure to lead chromate causes centrosome abnormalities and aneuploidy in human lung cells. Cancer Res. 66(8):4041–8. https://doi.org/10.1158/0008-5472.CAN-05-3312 PMID:16618723

Hong H-HL, Ton T-VT, Kim Y, Wakamatsu N, Clayton NP, Chan PC, et al. (2008). Genetic alterations in K-ras and p53 cancer genes in lung neoplasms from $B6C3F_1$ mice exposed to cumene. Toxicol Pathol. 36(5):720–6. https://doi.org/10.1177/0192623308320280 PMID:18648094

Hong HL, Devereux TR, Melnick RL, Eldridge SR, Greenwell A, Haseman J, et al. (1997). Both K-ras and H-ras protooncogene mutations are associated with Harderian gland tumorigenesis in $B6C3F_1$ mice exposed to isoprene for 26 weeks. Carcinogenesis. 18(4):783–9. https://doi.org/10.1093/carcin/18.4.783 PMID:9111215

Hong J, Yu X, Pan X, Zhao X, Sheng L, Sang X, et al. (2014). Pulmonary toxicity in mice following exposure to cerium chloride. Biol Trace Elem Res. 159(1–3):269–77. https://doi.org/10.1007/s12011-014-9953-3 PMID:24736977

Horibata K, Takasawa H, Hojo M, Taquahashi Y, Shigano M, Yokota S, et al. (2022). In vivo genotoxicity assessment of a multiwalled carbon nanotube in a mouse ex vivo culture. Genes Environ. 44(1):24. https://doi.org/10.1186/s41021-022-00253-2 PMID:36258253

Hoseiny Asl Nazarlu Z, Matini M, Bahmanzadeh M, Foroughi-Parvar F (2020). *Toxoplasma gondii*: a possible inducer of oxidative stress in reproductive system of male rats. Iran J Parasitol. 15(4):521–9. https://doi.org/10.18502/ijpa.v15i4.4857 PMID:33884009

Hosoda M, Nugraha ED, Akata N, Yamada R, Tamakuma Y, Sasaki M, et al. (2021). A unique high natural background radiation area – dose assessment and perspectives. Sci Total Environ. 750:142346. https://doi.org/10.1016/j.scitotenv.2020.142346 PMID:33182182

Hostiuc S, Ionescu IV, Drima E (2021). Mouthwash use and the risk of oral, pharyngeal, and laryngeal cancer. a meta-analysis. Int J Environ Res Public Health. 18(15):8215. https://doi.org/10.3390/ijerph18158215 PMID:34360508

Hou J, Yu J, Qin Z, Liu X, Zhao X, Hu X, et al. (2021). Guadipyr, a new insecticide, induces microbiota dysbiosis and immune disorders in the midgut of silkworms (*Bombyx mori*). Environ Pollut. 286:117531. https://doi.org/10.1016/j.envpol.2021.117531 PMID:34126519

Hou J, Zhang Y, Zhu Y, Zhou B, Ren C, Liang S, et al. (2019). α-Pinene induces apoptotic cell death via caspase activation in human ovarian cancer cells. Med Sci Monit. 25:6631–8. https://doi.org/10.12659/MSM.916419https://doi.org/10.12659/MSM.916419 PMID:31482864

Hou L, Lee WJ, Rusiecki J, Hoppin JA, Blair A, Bonner MR, et al. (2006). Pendimethalin exposure and cancer incidence among pesticide applicators. Epidemiology. 17(3):302–7. https://doi.org/10.1097/01.ede.0000201398.82658.50 PMID:16452832

Howell SK, Haidle CW, Wang YM (1986). Daunorubicin-induced DNA lesions in isolated rat hepatocytes and mammary epithelial cells. Biochim Biophys Acta. 868(4):254–61. https://doi.org/10.1016/0167-4781(86)90062-X PMID:3790570

Howell SK, Stephens LC, Wang YM (1989). Daunorubicin-induced mammary tumors in the rat. Eur J Cancer Clin Oncol. 25(11):1549–54. https://doi.org/10.1016/0277-5379(89)90296-4 PMID:2591446

Howley PM, Pfister HJ (2015). Beta genus papillomaviruses and skin cancer. Virology. 479–480:290–6. https://doi.org/10.1016/j.virol.2015.02.004 PMID:25724416

Hoy RF, Dimitriadis C, Abramson M, Glass DC, Gwini S, Hore-Lacy F, et al. (2023). Prevalence and risk factors for silicosis among a large cohort of stone benchtop industry workers. Occup Environ Med. 80(8):439–46. https://doi.org/10.1136/oemed-2023-108892 PMID:37328266

Hrelia P, Fimognari C, Maffei F, Vigagni F, Mesirca R, Pozzetti L, et al. (1996). The genetic and non-genetic toxicity of the fungicide vinclozolin. Mutagenesis. 11(5):445–53. https://doi.org/10.1093/mutage/11.5.445 PMID:8921505

Hrncir T (2022). Gut microbiota dysbiosis: triggers, consequences, diagnostic and therapeutic options. Microorganisms. 10(3):578. https://doi.org/10.3390/microorganisms10030578 PMID:35336153

HSDB (2009). Hazardous Substances Data Bank; now PubChem. Bethesda (MD), USA: National Center for Biotechnology Information. Now available from: https://pubchem.ncbi.nlm.nih.gov/, accessed September 2024.

Hsiao P-K, Lin Y-C, Shih T-S, Chiung Y-M (2009). Effects of occupational exposure to 1,4-dichlorobenzene on hematologic, kidney, and liver functions. Int Arch Occup Environ Health. 82(9):1077–85. https://doi.org/10.1007/s00420-009-0398-5 PMID:19247685

Hsu SS, Lin YS, Chen HC, Liang WZ (2023). Involvement of oxidative stress-related apoptosis in chlorpyrifos-induced cytotoxicity and the ameliorating potential of the antioxidant vitamin E in human glioblastoma cells. Environ Toxicol. 38(9):2143–54. https://doi.org/10.1002/tox.23850 PMID:37283489

Hsu YH, Huang HP, Chang HR (2019). The uremic toxin p-cresol promotes the invasion and migration on carcinoma cells via Ras and mTOR signalling. Toxicol In Vitro. 58:126–31. https://doi.org/10.1016/j.tiv.2019.03.029https://doi.org/10.1016/j.tiv.2019.03.029 PMID:30910523

Hu H, Shklovskaya E, Deva A, Xu H, Fan K, Brosamer K, et al. (2023). Diagnosis of breast implant associated anaplastic large cell lymphoma by analysis of cytokines in peri-implant seromas. Am J Hematol. 98(11):E312–4. https://doi.org/10.1002/ajh.27055 PMID:37646570

Hu J, Ramshesh VK, McGill MR, Jaeschke H, Lemasters JJ (2016a). Low dose acetaminophen induces reversible mitochondrial dysfunction associated with transient c-Jun N-terminal kinase activation in mouse liver. Toxicol Sci. 150(1):204–15. https://doi.org/10.1093/toxsci/kfv319 PMID:26721299

Hu K, Tian Y, Du Y, Huang L, Chen J, Li N, et al. (2016b). Atrazine promotes RM1 prostate cancer cell proliferation by activating STAT3 signalling. Int J Oncol. 48(5):2166–74. https://doi.org/10.3892/ijo.2016.3433 PMID:26984284

Hu L, Luo D, Zhou T, Tao Y, Feng J, Mei S (2017). The association between non-Hodgkin lymphoma and organophosphate pesticides exposure: a meta-analysis. Environ Pollut. 231(Pt 1):319–28. https://doi.org/10.1016/j.envpol.2017.08.028 PMID:28810201

Hu X, Fatima S, Chen M, Xu K, Huang C, Gong RH, et al. (2021b). Toll-like receptor 4 is a master regulator for colorectal cancer growth under high-fat diet by programming cancer metabolism. Cell Death Dis. 12(8):791. https://doi.org/10.1038/s41419-021-04076-xhttps://doi.org/10.1038/s41419-021-04076-x PMID:34385421

Hu Y, Li D, Ma X, Liu R, Qi Y, Yuan C, et al. (2021a). Effects of 2,4-dichlorophenol exposure on zebrafish: implications for the sex hormone synthesis. Aquat Toxicol. 236:105868. https://doi.org/10.1016/j.aquatox.2021.105868 PMID:34051627

Huang BH, Duncan MJ, Cistulli PA, Nassar N, Hamer M, Stamatakis E (2022b). Sleep and physical activity in relation to all-cause, cardiovascular disease and cancer mortality risk. Br J Sports Med. 56(13):718–24. https://doi.org/10.1136/bjsports-2021-104046 PMID:34187783

Huang D, Zhang X, Zhang C, Li H, Li D, Hu Y, et al. (2018a). 2,4-Dichlorophenol induces DNA damage through ROS accumulation and GSH depletion in goldfish *Carassius auratus.* Environ Mol Mutagen. 59(9):798–804. https://doi.org/10.1002/em.22209 PMID:30091148

Huang F, Chen Z, Chen H, Lu W, Xie S, Meng QH, et al. (2018b). Cypermethrin promotes lung cancer metastasis via modulation of macrophage polarization by targeting microRNA-155/Bcl6. Toxicol Sci. 163(2):454–65. https://doi.org/10.1093/toxsci/kfy039 PMID:29471534

Huang H, Liang J, Tang P, Yu C, Fan H, Liao Q, et al. (2022c). Associations of bisphenol exposure with thyroid hormones in pregnant women: a prospective birth cohort study in China. Environ Sci Pollut Res Int. 29(58):87170–83. https://doi.org/10.1007/s11356-022-21817-3 PMID:35802331

Huang J, Ding J, Wang X, Gu C, He Y, Li Y, et al. (2022d). Transfer of neuron-derived α-synuclein to astrocytes induces neuroinflammation and blood–brain barrier damage after methamphetamine exposure: Involving the regulation of nuclear receptor-associated protein 1. Brain Behav Immun. 106:247–61. https://doi.org/10.1016/j.bbi.2022.09.002 PMID:36089218

Huang J, Duan Z, Wang Y, Redmon PB, Eriksen MP (2020a). Use of electronic nicotine delivery systems (ENDS) in China: evidence from citywide representative surveys from five Chinese cities in 2018. Int J Environ Res Public Health. 17(7):2541. https://doi.org/10.3390/ijerph17072541 PMID:32276336

Huang JK, Huang CJ, Chen WC, Liu SI, Hsu SS, Chang HT, et al. (2005). Independent [Ca2+]i increases and cell proliferation induced by the carcinogen safrole in human oral cancer cells. Naunyn Schmiedebergs Arch Pharmacol. 372(1):88–94. https://doi.org/10.1007/s00210-005-1086-y PMID:16080004

Huang JW, Bai YY, Zeeshan M, Liu RQ, Dong GH (2023c). Effects of exposure to chlorinated paraffins on human health: a scoping review. Sci Total Environ. 886(2023):163953. https://doi.org/10.1016/j.scitotenv.2023.163953 PMID:37164081

Huang M, Dong J, Yang S, Xiao M, Guo H, Zhang J, et al. (2023b). Ecotoxicological effects of common fungicides on the eastern honeybee *Apis cerana cerana* (Hymenoptera). Sci Total Environ. 868:161637. https://doi.org/10.1016/j.scitotenv.2023.161637 PMID:36649770

Huang P, Duda DG, Jain RK, Fukumura D (2008). Histopathologic findings and establishment of novel tumor lines from spontaneous tumors in FVB/N mice. Comp Med. 58(3):253–63. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2693079/ PMID:18589867

Huang P, Yang J, Song Q (2014). Atrazine affects phosphoprotein and protein expression in MCF-10A human breast epithelial cells. Int J Mol Sci. 15(10):17806–26. https://doi.org/10.3390/ijms151017806 PMID:25275270

Huang PC, Waits A, Chen HC, Chang WT, Jaakkola JJK, Huang HB (2020b). Mediating role of oxidative/nitrosative stress biomarkers in the associations between phthalate exposure and thyroid function in Taiwanese adults. Environ Int. 140:105751. https://doi.org/10.1016/j.envint.2020.105751https://doi.org/10.1016/j.envint.2020.105751 PMID:32353668

Huang W, Zhao C, Zhong H, Zhang S, Xia Y, Cai Z (2019). Bisphenol S induced epigenetic and transcriptional changes in human breast cancer cell line MCF-7. Environ Pollut. 246:697–703. https://doi.org/10.1016/j.envpol.2018.12.084 PMID:30616060

Huang X, Yan P, Ding W, Zhou C, Xu Q, Li M, et al. (2022a). α-Pinene inhibits the growth of cervical cancer cells through its proapoptotic activity by regulating the miR-34a-5p/Bcl-2 signalling axis. Drug Dev Res. 83(8):1766–76. https://doi.org/10.1002/ddr.21994https://doi.org/10.1002/ddr.21994 PMID:36074793

Huang Y, Huang Y, Chang A, Wang J, Zeng X, Wu J (2016). Is *Toxoplasma gondii* infection a risk factor for leukemia? An evidence-based meta-analysis. Med Sci Monit. 22:1547–52. https://doi.org/10.12659/MSM.897155 PMID:27155015

Huang Z, Chen B, Ren B, Tu D, Wang Z, Wang C, et al. (2023a). Smart mechanoluminescent phosphors: a review of strontium-aluminate-based materials, properties, and their advanced application technologies. Adv Sci (Weinh). 10(3):e2204925. https://doi.org/10.1002/advs.202204925 PMID:36372543

Huen K, Gunn L, Duramad P, Jeng M, Scalf R, Holland N (2006). Application of a geographic information system to explore associations between air pollution and micronucleus frequencies in African American children and adults. Environ Mol Mutagen. 47(4):236–46. https://doi.org/10.1002/em.20193 PMID:16416421

Hueper WC (1952). Experimental studies in metal cancerigenesis. I. Nickel cancers in rats. Tex Rep Biol Med. 10(1):167–86. PMID:14922272

Hueper WC (1955). Experimental studies in metal carcinogenesis. IV: Cancer produced by parenterally introduced metallic nickel. J Natl Cancer Inst. 16(1):55–67. PMID:13243113

Hung A, Nelson H, Koehle MS (2022). The acute effects of exercising in air pollution: a systematic review of randomized controlled trials. Sports Med. 52(1):139–64. https://doi.org/10.1007/s40279-021-01544-4 PMID:34499337

Hung PH, Savidge M, De M, Kang JC, Healy SM, Valerio LG Jr (2020). In vitro and in silico genetic toxicity screening of flavor compounds and other ingredients in tobacco products with emphasis on ENDS. J Appl Toxicol. 40(11):1566–87. https://doi.org/10.1002/jat.4020 PMID:32662109

Huo Z, Ge F, Li C, Cheng H, Lu Y, Wang R, et al. (2021). Genetically predicted insomnia and lung cancer risk: a Mendelian randomization study. Sleep Med. 87:183–90. https://doi.org/10.1016/j.sleep.2021.06.044 PMID:34627121

Hurley PM (1998). Mode of carcinogenic action of pesticides inducing thyroid follicular cell tumors in rodents. Environ Health Perspect. 106(8):437–45. https://doi.org/10.1289/ehp.98106437 PMID:9681970

Hurley S, Goldberg D, Nelson D, Hertz A, Horn-Ross PL, Bernstein L, et al. (2014). Light at night and breast cancer risk among California teachers. Epidemiology. 25(5):697–706. https://doi.org/10.1097/EDE.0000000000000137 PMID:25061924

Hurley S, Goldberg D, Park JS, Petreas M, Bernstein L, Anton-Culver H, et al. (2019). A breast cancer case–control study of polybrominated diphenyl ether (PBDE) serum levels among California women. Environ Int. 127:412–9. https://doi.org/10.1016/j.envint.2019.03.043 PMID:30954728

Hursting SD, Perkins SN, Lavigne JA, Beltran L, Haines DC, Hill HL, et al. (2009). Urothelial overexpression of insulin-like growth factor-1 increases susceptibility to *p*-cresidine-induced bladder carcinogenesis in transgenic mice. Mol Carcinog. 48(8):671–7. https://doi.org/10.1002/mc.20548https://doi.org/10.1002/mc.20548

PMID:19415693

Hurwitz LM, Beane Freeman LE, Andreotti G, Hofmann JN, Parks CG, Sandler DP, et al. (2023). Joint associations between established genetic susceptibility loci, pesticide exposures, and risk of prostate cancer. Environ Res. 237(Pt 2):117063. https://doi.org/10.1016/j.envres.2023.117063 PMID:37659638

Hüser S, Guth S, Joost HG, Soukup ST, Köhrle J, Kreienbrock L, et al. (2018). Effects of isoflavones on breast tissue and the thyroid hormone system in humans: a comprehensive safety evaluation. Arch Toxicol. 92(9):2703–48. https://doi.org/10.1007/s00204-018-2279-8 PMID:30132047

Huss A, Spoerri A, Egger M, Kromhout H, Vermeulen R; Swiss National Cohort (2018). Occupational extremely low frequency magnetic fields (ELF-MF) exposure and hematolymphopoietic cancers – Swiss National Cohort analysis and updated meta-analysis. Environ Res. 164:467–74. https://doi.org/10.1016/j.envres.2018.03.022 PMID:29587222

Hvidtfeldt UA, Chen J, Andersen ZJ, Atkinson R, Bauwelinck M, Bellander T, et al. (2021b). Long-term exposure to fine particle elemental components and lung cancer incidence in the ELAPSE pooled cohort. Environ Res. 193:110568. https://doi.org/10.1016/j.envres.2020.110568 PMID:33278469

Hvidtfeldt UA, Chen J, Rodopoulou S, Strak M, de Hoogh K, Andersen ZJ, et al. (2023). Long-term air pollution exposure and malignant intracranial tumours of the central nervous system: a pooled analysis of six European cohorts. Br J Cancer. 129(4):656–64. https://doi.org/10.1038/s41416-023-02348-1 PMID:37420001

Hvidtfeldt UA, Severi G, Andersen ZJ, Atkinson R, Bauwelinck M, Bellander T, et al. (2021a). Long-term low-level ambient air pollution exposure and risk of lung cancer – a pooled analysis of 7 European cohorts. Environ Int. 146:106249. https://doi.org/10.1016/j.envint.2020.106249 PMID:33197787

Hwang J, Ramachandran G, Raynor PC, Alexander BH, Mandel JH (2013). Comprehensive assessment of exposures to elongate mineral particles in the taconite mining industry. Ann Occup Hyg. 57(8):966–78. PMID:23792972

Hyland C, Bradman A, Gerona R, Patton S, Zakharevich I, Gunier RB, et al. (2019). Organic diet intervention significantly reduces urinary pesticide levels in US children and adults. Environ Res. 171:568–75. https://doi.org/10.1016/j.envres.2019.01.024 PMID:30765100

Hyland C, Hernandez A, Gaudreau É, Larose J, Bienvenu JF, Meierotto L, et al. (2024). Examination of urinary pesticide concentrations, protective behaviors, and risk perceptions among Latino and Latina farmworkers in Southwestern Idaho. Int J Hyg Environ Health. 255:114275. https://doi.org/10.1016/j.ijheh.2023.114275 PMID:37866282

Hytönen S, Alfheim I, Sorsa M (1983). Effect of emissions from residential wood stoves on SCE induction in CHO cells. Mutat Res. 118(1–2):69–75. https://doi.org/10.1016/0165-1218(83)90117-9 PMID:6346087

IARC (1972). Some inorganic substances, chlorinated hydrocarbons, aromatic amines, *N*-nitroso compounds and natural products. IARC Monogr Eval Carcinog Risk Chem Man. 1:1–184. Available from: https://publications.iarc.fr/19

IARC (1973). Some inorganic and organometallic compounds. IARC Monogr Eval Carcinog Risk Chem Man. 2:1–181. Available from: https://publications.iarc.who.int/20

IARC (1975). Some aromatic azo compounds. IARC Monogr Eval Carcinog Risk Chem Man. 8:1–357. Available from: https://publications.iarc.who.int/26

IARC (1976a). Some carbamates, thiocarbamates and carbazides. IARC Monogr Eval Carcinog Risk Chem Man. 12:1–282. Available from: https://publications.iarc.who.int/30 PMID:188751

IARC (1976b). Some naturally occurring substances. IARC Monogr Eval Carcinog Risk Chem Man. 10:1–353. Available from: https://publications.iarc.who.int/28 PMID:992652

IARC (1977). Asbestos. IARC Monogr Eval Carcinog Risk Chem Man. 14:1–106. Available from: https://publications.iarc.who.int/32 PMID:863456

IARC (1978). Some aromatic amines and related nitro compounds – hair dyes, colouring agents and miscellaneous industrial chemicals. IARC Monogr Eval Carcinog Risk Chem Man. 16:1–400. Available from: https://publications.iarc.who.int/34

IARC (1979a). Sex hormones (II). IARC Monogr Eval Carcinog Risk Chem Hum. 21:1–583. Available from: https://publications.iarc.who.int/39

IARC (1979b). Some halogenated hydrocarbons. IARC Monogr Eval Carcinog Risk Chem Hum. 20:1–609. Available from: https://publications.iarc.who.int/38 PMID:296120

IARC (1979c). Some monomers, plastics and synthetic elastomers, and acrolein. IARC Monogr Eval Carcinog Risk Chem Hum. 19:1–513. Available from: https://publications.iarc.who.int/37 PMID:285915

IARC (1982). Some industrial chemicals and dyestuffs. IARC Monogr Eval Carcinog Risk Chem Hum. 29:1–416. Available from: https://publications.iarc.who.int/47 PMID:6957379

IARC (1983). Polynuclear aromatic compounds, Part 1, chemical, environmental and experimental data. IARC Monogr Eval Carcinog Risk Chem Hum. 32:1–477. Available from: https://publications.iarc.who.int/50 PMID:6586639

IARC (1985). Allyl compounds, aldehydes, epoxides and peroxides. IARC Monogr Eval Carcinog Risk Chem Hum. 36:1–369. Available from: https://publications.iarc.who.int/54 PMID:3864739

IARC (1986). Some naturally occurring and synthetic food components, furocoumarins and ultraviolet radiation. IARC Monogr Eval Carcinog Risk Chem Hum. 40:1–444. Available from: https://publications.iarc.who.int/58 PMID:3472998

IARC (1987a). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. IARC Monogr Eval Carcinog Risks Hum Suppl. 7:1–440. Available from: https://publications.iarc.who.int/139 PMID:3482203

IARC (1987b). Genetic and related effects: an updating of selected IARC monographs from Volumes 1 to 42. IARC Monogr Eval Carcinog Risks Hum Suppl. 6:1–729. Available from: https://publications.iarc.who.int/138 PMID:3504843

IARC (1990a). Chromium, nickel and welding. IARC Monogr Eval Carcinog Risks Hum. 49:1–677. Available from: https://publications.iarc.who.int/67 PMID:2232124

IARC (1990b). Some flame retardants and textile chemicals, and exposures in the textile manufacturing industry. IARC Monogr Eval Carcinog Risks Hum. 48:1–345. Available from: https://publications.iarc.who.int/66 PMID:2374288

IARC (1991). Occupational exposures in insecticide application, and some pesticides. IARC Monogr Eval Carcinog Risks Hum. 53:5–612. Available from: https://publications.iarc.who.int/71 PMID:1688189

IARC (1993a). Some naturally occurring substances: food items and constituents, heterocyclic aromatic amines and mycotoxins. IARC Monogr Eval Carcinog Risks Hum. 56:1–599. Available from: https://publications.iarc.who.int/74

IARC (1993b). Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. IARC Monogr Eval Carcinog Risks Hum. 58:1–444. Available from: https://publications.iarc.who.int/76 PMID:8022054

IARC (1994a). Hepatitis viruses. IARC Monogr Eval Carcinog Risks Hum. 59:1–286. Available from: https://publications.iarc.who.int/77 PMID:7933461

IARC (1994b). Schistosomes, liver flukes and *Helicobacter pylori*. IARC Monogr Eval Carcinog Risks Hum. 61:1–270. Available from: https://publications.iarc.who.int/79 PMID:7715068

IARC (1994c). Some industrial chemicals. IARC Monogr Eval Carcinog Risks Hum. 60:1–560. Available from: https://publications.iarc.who.int/78 PMID:7869568

IARC (1995). Dry cleaning, some chlorinated solvents and other industrial chemicals. IARC Monogr Eval Carcinog Risks Hum. 63:1–551. Available from: https://publications.iarc.who.int/81 PMID:9139128

IARC (1996). Printing processes and printing inks, carbon black and some nitro compounds. IARC Monogr Eval Carcinog Risks Hum. 65:1–578. Available from: https://publications.iarc.fr/83 PMID:9148039

IARC (1997). Silica, some silicates, coal dust and *para*-aramid fibrils. IARC Monogr Eval Carcinog Risks Hum. 68:1–506. Available from: https://publications.iarc.fr/86 PMID:9303953

IARC (1999a). Surgical implants and other foreign bodies. IARC Monogr Eval Carcinog Risks Hum. 74:1–409. Available from: https://publications.iarc.who.int/92 PMID:10804970

IARC (1999b). Some chemicals that cause tumours of the kidney or urinary bladder in rodents and some other substances. IARC Monogr Eval Carcinog Risks Hum. 73:1–674. Available from: https://publications.iarc.who.int/91

IARC (1999c). Hormonal contraception and post-menopausal hormonal therapy. IARC Monogr Eval Carcinog Risks Hum. 72:1–660. Available from: https://publications.iarc.who.int/90

IARC (1999d). Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide (Part 1, Part 2, Part 3). IARC Monogr Eval Carcinog Risks Hum. 71:1–1586. Available from: https://publications.iarc.fr/89 PMID:10507919

IARC (2000). Some industrial chemicals. IARC Monogr Eval Carcinog Risks Hum. 77:1–563. Available from: https://publications.iarc.who.int/95 PMID:11236796

IARC (2001). Some thyrotropic agents. IARC Monogr Eval Carcinog Risks Hum. 79:1–763. Available from: https://publications.iarc.who.int/97

IARC (2002a). Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. IARC Monogr Eval Carcinog Risks Hum. 82:1–590. Available from: https://publications.iarc.who.int/100 PMID:12687954

IARC (2002b). Non-ionizing radiation, Part 1: static and extremely low-frequency (ELF) electric and magnetic fields. IARC Monogr Eval Carcinog Risks Hum. 80:1–429. Available from: https://publications.iarc.who.int/98 PMID:12071196

IARC (2006a). Formaldehyde, 2-butoxyethanol and 1-*tert*-butoxypropan-2-ol. IARC Monogr Eval Carcinog Risks Hum. 88:1–478. Available from: https://publications.iarc.who.int/106 PMID:17366697

IARC (2006b). Inorganic and organic lead compounds. IARC Monogr Eval Carcinog Risks Hum. 87:1–506. Available from: https://publications.iarc.who.int/105 PMID:17191367

IARC (2007). Human papillomaviruses. IARC Monogr Eval Carcinog Risks Hum. 90:1–670. Available from: https://publications.iarc.who.int/108 PMID:18354839

IARC (2010a). Some aromatic amines, organic dyes, and related exposures. IARC Monogr Eval Carcinog Risks Hum. 99:1–692. Available from: https://publications.iarc.who.int/117 PMID:21528837

IARC (2010b). Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. IARC Monogr Eval Carcinog Risks Hum. 92:1–853. Available from: https://publications.iarc.who.int/110 PMID:21141735

IARC (2010c). Ingested nitrate and nitrite, and cyanobacterial peptide toxins. IARC Monogr Eval Carcinog Risks Hum. 94:1–450. Available from: https://publications.iarc.who.int/112 PMID:21141240

IARC (2010d). Painting, firefighting, and shiftwork. IARC Monogr Eval Carcinog Risks Hum. 98:1–804. Available from: https://publications.iarc.who.int/116 PMID:21381544

IARC (2010e). Household use of solid fuels and high-temperature frying. IARC Monogr Eval Carcinog Risks Hum. 95:1–430. Available from: https://publications.iarc.who.int/113 PMID:20701241

IARC (2010f). Carbon black, titanium dioxide, and talc. IARC Monogr Eval Carcinog Risks Hum. 93:1–452. Available from: https://publications.iarc.fr/111 PMID:21449489

IARC (2012a). Biological agents. IARC Monogr Eval Carcinog Risks Hum. 100B:1–475. Available from: https://publications.iarc.who.int/119 PMID:23189750

IARC (2012b). Chemical agents and related occupations. IARC Monogr Eval Carcinog Risks Hum. 100F:1–599. Available from: https://publications.iarc.fr/123 PMID:23189753

IARC (2012c). Arsenic, metals, fibres, and dusts. IARC Monogr Eval Carcinog Risks Hum. 100C:1–501. Available from: https://publications.iarc.who.in/120 PMID:23189751

IARC (2012d). Pharmaceuticals. IARC Monogr Eval Carcinog Risks Hum. 100A:1–435. Available from: https://publications.iarc.who.int/118 PMID:23189749

IARC (2012e). Radiation. IARC Monogr Eval Carcinog Risks Hum. 100D:1–341. Available from: https://publications.iarc.who.int/121 PMID:23189752

IARC (2012f). Personal habits and indoor combustions. IARC Monogr Eval Carcinog Risks Hum. 100E:1–575. Available from: https://publications.iarc.who.int/122 PMID:23193840

IARC (2013a). Non-ionizing radiation, Part 2: Radiofrequency electromagnetic fields. IARC Monogr Eval Carcinog Risks Hum. 102:1–462. Available from: https://publications.iarc.fr/126 PMID:24772662

IARC (2013b). Bitumens and bitumen emissions, and some *N*- and *S*-heterocyclic polycyclic aromatic hydrocarbons. IARC Monogr Eval Carcinog Risks Hum. 103:1–342. Available from: https://publications.iarc.who.int/127 PMID:24791350

IARC (2013c). Some chemicals present in industrial and consumer products, food and drinking-water. IARC Monogr Eval Carcinog Risks Hum. 101:1–553. Available from: https://publications.iarc.who.int/125 PMID:24772663

IARC (2014a). Malaria and some polyomaviruses (SV40, BK, JC, and Merkel cell viruses). IARC Monogr Eval Carcinog Risks Hum. 104:1–353. Available from: https://publications.iarc.fr/128 PMID:26173303

IARC (2014b). Trichloroethylene, tetrachloroethylene, and some other chlorinated agents. IARC Monogr Eval Carcinog Risks Hum. 106:1–514. Available from: https://publications.iarc.who.int/130 PMID:26214861

IARC (2015). Outdoor air pollution. IARC Monogr Eval Carcinog Risks Hum. 109:1–448. Available from: https://publications.iarc.who.int/538 PMID:29905447

IARC (2016). Q&A on glyphosate. Lyon, France: International Agency for Research on Cancer. Available from: https://www.iarc.who.int/wp-content/uploads/2018/11/QA_Glyphosate.pdf, accessed March 2024.

IARC (2017a). Some organophosphate insecticides and herbicides. IARC Monogr Eval Carcinog Risks Hum. 112:1–452. Available from: https://publications.iarc.who.int/549 PMID:31829533

IARC (2017b). Some chemicals used as solvents and in polymer manufacture. IARC Monogr Eval Carcinog Risks Hum. 110:1–276. Available from https://publications.iarc.fr/547 PMID:31829531

IARC (2017c). Some nanomaterials and some fibres. IARC Monogr Eval Carcinog Risks Hum. 111:1–316. Available from: https://publications.iarc.who.int/552 PMID:31829532

IARC (2018a). Drinking coffee, mate, and very hot beverages. IARC Monogr Eval Carcinog Risks Hum. 116:1–499. Available from: https://publications.iarc.who.int/566 PMID:31310458

IARC (2018b). Red meat and processed meat. IARC Monogr Eval Carcinog Risks Hum. 114:1–506. Available from: https://publications.iarc.who.int/564 PMID:29949327

IARC (2018c). Absence of excess body fatness. IARC Handb Cancer Prev. 16:1–645. Available from: https://publications.iarc.who.int/570 PMID:37200467

IARC (2019a). IARC Monographs on the identification of carcinogenic hazards to humans. Report of the advisory group to recommend priorities for the *IARC Monographs* during 2020–2024. Lyon, France: International Agency for Research on Cancer. Available from: https://monographs.iarc.who.int/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf, accessed September 2020.

IARC (2019b). Preamble to the *IARC Monographs* (amended January 2019). Lyon, France: International Agency for Research on Cancer. Available from: https://monographs.iarc.who.int/iarc-monographs-preamble-preamble-to-the-iarc-monographs/, accessed September 2020.

IARC (2020). Night shift work. IARC Monogr Identif Carcinog Hazard Hum. 124:1–371. Available from: https://publications.iarc.who.int/593 PMID:33656825

IARC (2021). Some aromatic amines and related compounds. IARC Monogr Identif Carcinog Hazard Hum. 127:1–267. Available from: https://publications.iarc.who.int/599 PMID:35044736

IARC (2023a). Occupational exposure as a firefighter. IARC Monogr Identif Carcinog Hazard Hum. 132:1–728. Available from: https://publications.iarc.who.int/615 PMID:37963216

IARC (2023b). Cobalt, antimony compounds, and weapons-grade tungsten alloy. IARC Monogr Identif Carcinog Hazards Hum. 131:1–594. Available from: https://publications.iarc.who.int/618 PMID:38109325

IARC (2024a). Aspartame, methyleugenol, and isoeugenol. IARC Monogr Identif Carcinog Hazard Hum. 134:1–686. Available from: https://publications.iarc.who.int/627

IARC (2024b). Perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS). IARC Monogr Identif Carcinog Hazard Hum. 135:1–728. Available from: https://publications.iarc.who.int/636

IARC (2024c). Research on potential long-term health effects of tattooing. Lyon, France: International Agency for Research on Cancer. Available from: https://tattoo.iarc.who.int/projects, accessed October 2024

Ibrahim MA, Hazhirkarzar B, Dubin AB (2023). Gadolinium magnetic resonance imaging. Treasure Island (FL): StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482487/.

Ichikawa S, Goshima S (2024). Gadoxetic acid-enhanced liver MRI: everything you need to know. Invest Radiol. 59(1):53–68. https://doi.org/10.1097/RLI.0000000000000990 PMID:37227150

Ide V, Vanderschueren D, Antonio L (2020). Treatment of men with central hypogonadism: alternatives for testosterone replacement therapy. Int J Mol Sci. 22(1):21. https://doi.org/10.3390/ijms22010021 PMID:33375030

IFA (2024). GESTIS – International limit values for chemical agents. Sankt Augustin, Germany: Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung. Available from: https://www.dguv.de/ifa/gestis/gestis-internationale-grenzwerte-fuer-chemische-substanzen-limit-values-for-chemical-agents/index-2.jsp, accessed September 2024.

IFRA (2009). Safrole, isosafrole, dihydrosafrole. IFRA Standard. Geneva, Switzerland: International Fragrance Association. Available from: https://ifrafragrance.org/standards/IFRA_STD48_0129.pdf, accessed September 2024.

Igarashi A, Ohtsu S, Muroi M, Tanamoto K (2006). Effects of possible endocrine disrupting chemicals on bacterial component-induced activation of NF-kappaB. Biol Pharm Bull. 29(10):2120–2. https://doi.org/10.1248/bpb.29.2120 PMID:17015962

IHS Chemical (2016). Methanol. Presenter: Marc Alvarado, February 2016. Available from: https://www.methanol.org/wp-content/uploads/2016/07/Marc-Alvarado-Global-Methanol-February-2016-IMPCA-for-upload-to-website.pdf, accessed March 2024.

Ijaz S, Ullah A, Shaheen G, Jahan S (2020). Exposure of BPA and its alternatives like BPB, BPF, and BPS impair subsequent reproductive potentials in adult female Sprague Dawley rats. Toxicol Mech Methods. 30(1):60–72. https://doi.org/10.1080/15376516.2019.1652873 PMID:31424294

Ila HB, Topaktas M, Rencuzogullari E, Kayraldiz A, Donbak L, Daglioglu YK (2008). Genotoxic potential of cyfluthrin. Mutat Res. 656(1–2):49–54. https://doi.org/10.1016/j.mrgentox.2008.07.005 PMID:18692594

Illinois EPA (2021). Health advisory for perfluorohexanesulfonic acid (PFHxS). Chemical abstract services registry number (CASRN) 355-46-4. Springfield (IL), USA: Office of Toxicity Assessment, Illinois Environmental Protection Agency. Available from: https://epa.illinois.gov/content/dam/soi/en/web/epa/topics/water-quality/pfas/documents/ha-pfhxs.pdf, accessed March 2024.

ILO (1919). C001- Hours of Work (Industry) Convention, 1919 (No. 1). Washington, USA: International Labor Organization. Available from: https://normlex.ilo.org/dyn/normlex/en/f?p=NORMLEXPUB:12100:0::NO::P12100_ILO_CODE:C001, accessed October 2024.

ILO (2012a). Analytical chemist: international hazard datasheets on occupation. Geneva, Switzerland: International Labor Organization. Available from: https://www.ilo.org/safework/cis/WCMS_184643/lang--en/index.htm, accessed September 2024.

ILO (2012b). Chemist, physical: international hazard datasheets on occupation. Geneva, Switzerland: International Labor Organization. Available from: https://www.ilo.org/safework/cis/WCMS_192260/lang--en/index.htm, accessed September 2024.

ILO (2012c). Worker, laboratory: international hazard datasheets on occupations (HDO). Geneva, Switzerland: International Labor Organization. Available from: https://www.ilo.org/global/topics/safety-and-health-at-work/resources-library/publications/WCMS_113135/lang--en/index.htm, accessed September 2024.

ILO & WHO (2006). Biphenyl. International chemical safety card (ICSC) 0106. Geneva, Switzerland: International Labour Organization and World Health Organization. Available from:

https://www.ilo.org/dyn/icsc/showcard.display?p_lang=en&p_card_id=0106&p_version=2, accessed December 2023.

Ilyushina N, Egorova O, Rakitskii V (2019). Limitations of pesticide genotoxicity testing using the bacterial in vitro method. Toxicol In Vitro. 57:110–6. https://doi.org/10.1016/j.tiv.2019.02.018 PMID:30807808

Imai S, Morimoto J, Sekigawa S (1983) [Additive toxicity test of thiabendazole and diphenyl in mice]. Nara Igaku Zasshi. 30(5):512–22. https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/782628 [Japanese]

Imaida K, Ishihara Y, Nishio O, Nakanishi K, Ito N (1983). Carcinogenicity and toxicity tests on *p*-phenylenediamine in F344 rats. Toxicol Lett. 16(3–4):259–69. PMID:6857722

Imran I, Ansari A, Saleem S, Azhar A, Zehra S (2022). Insights of OPs and PYR cytotoxic potential in vitro and genotoxic impact on PON1 genetic variant among exposed workers in Pakistan. Sci Rep. 12(1):9498. https://doi.org/10.1038/s41598-022-13454-0 PMID:35680920

In SJ, Kim SH, Go RE, Hwang KA, Choi KC (2015). 2,4-dihydroxybenzophenone and nonylphenol stimulated MCF-7 breast cancer growth by regulating cell cycle and metastasis-related genes via an estrogen receptor α-dependent pathway. J Toxicol Environ Health A. 78(8):492–505. https://doi.org/10.1080/15287394.2015.1010464https://doi.org/10.1080/15287394.2015.1010464 PMID:25849766

INCHEM (1992). Bifenthrin (Pesticide residues in food: 1992 evaluations Part II Toxicology). Geneva, Switzerland: International Programme on Chemical Safety, World Health Organization. Available from: https://www.inchem.org/documents/jmpr/jmpmono/v92pr04.htm, accessed September 2024.

INCHEM (1994). Environmental health criteria 162. Brominated diphenyl ethers. Geneva, Switzerland: International Programme on Chemical Safety, World Health Organization. Available from: http://www.inchem.org/documents/jmpr/jmpmono/v96pr02.htm, accessed March 2024

INCHEM (1996). Evaluation for carbaryl. Geneva, Switzerland: International Programme on Chemical Safety, World Health Organization. Available from: http://www.inchem.org/documents/jmpr/jmpmono/v96pr02.htm, accessed March 2024.

INCHEM (2003). Carbadox. International Chemical Safety Cards, ICSC: 1510. Inter-Organization Programme for the Sound Management of Chemicals. Geneva, Switzerland: International Programme on Chemical Safety, World Health Organization. Available from: https://www.inchem.org/documents/icsc/icsc/eics1510.htm, accessed January 2024.

Industry Data Analytics (2020). Mancozeb market – growth, trends and forecast (2021–2026) by types, by application, by regions and by key players: UPL, Coromandel International, Indofil, DowDuPont. Pune, India: Industry Data Analytics. Available from: https://www.industrydataanalytics.com/reports/global-Mancozeb-market, accessed January 2024.

Innes JR, Ulland BM, Valerio MG, Petrucelli L, Fishbein L, Hart ER, et al. (1969). Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. J Natl Cancer Inst. 42(6):1101–14. PMID:5793189

Inokawa H, Umemura Y, Shimba A, Kawakami E, Koike N, Tsuchiya Y, et al. (2020). Chronic circadian misalignment accelerates immune senescence and abbreviates lifespan in mice. Sci Rep. 10(1):2569. https://doi.org/10.1038/s41598-020-59541-y PMID:32054990

Inoue-Choi M, Jones RR, Anderson KE, Cantor KP, Cerhan JR, Krasner S, et al. (2015). Nitrate and nitrite ingestion and risk of ovarian cancer among postmenopausal women in Iowa. Int J Cancer. 137(1):173–82. https://doi.org/10.1002/ijc.29365https://doi.org/10.1002/ijc.29365 PMID:25430487

Inoue-Choi M, Ward MH, Cerhan JR, Weyer PJ, Anderson KE, Robien K (2012). Interaction of nitrate and folate on the risk of breast cancer among postmenopausal women. Nutr Cancer. 64(5):685–94. https://doi.org/10.1080/01635581.2012.687427https://doi.org/10.1080/01635581.2012.687427 PMID:22642949

Inoue-Choi M, Weyer PJ, Jones RR, Booth BJ, Cantor KP, Robien K, et al. (2016). Atrazine in public water supplies and risk of ovarian cancer among postmenopausal women in the Iowa Women's Health Study. Occup Environ Med. 73(9):582–7. https://doi.org/10.1136/oemed-2016-103575 PMID:27371663

INSERM Collective Expertise Centre (2022). Effects of pesticides on health: new data. Montrouge, France: Édition Diffusion Presse Sciences. https://www.ncbi.nlm.nih.gov/books/NBK581472/ PMID:35759550.

Inskip PD, Robison LL, Stovall M, Smith SA, Hammond S, Mertens AC, et al. (2009). Radiation dose and breast cancer risk in the childhood cancer survivor study. J Clin Oncol. 27(24):3901–7. https://doi.org/10.1200/JCO.2008.20.7738 PMID:19620485

Institute of Medicine (2000). Institute of medicine, food and nutrition board. dietary reference intakes: Vitamin C, Vitamin E, selenium, and carotenoids. Washington (DC), USA: National Academy Press.

International Telecommunications Union (2022). Mobile phone ownership. Facts and Figures 2022. Geneva, Switzerland: International Telecommunications Union. Available from: https://www.itu.int/itu-d/reports/statistics/2022/11/24/ff22-mobile-phone-ownership/, accessed January 2024.

IPCS (1988). Poisons Information Monograph 335: Methanol. Geneva, Switzerland: International Programme on Chemical Safety, World Health Organization. Available from: https://www.inchem.org/documents/pims/chemical/pim335.htm, accessed March 2024.

Iqbal J, Kahane A, Park AL, Huang T, Meschino WS, Ray JG (2019). Hormone levels in pregnancy and subsequent risk of maternal breast and ovarian cancer: a systematic review. J Obstet Gynaecol Can. 41(2):217–22. https://doi.org/10.1016/j.jogc.2018.03.133 PMID:30528445

Iribarne-Durán LM, Serrano L, Peinado FM, Peña-Caballero M, Hurtado JA, Vela-Soria F, et al. (2022). Biomonitoring bisphenols, parabens, and benzophenones in breast milk from a human milk bank in Southern Spain. Sci Total Environ. 830:154737. https://doi.org/10.1016/j.scitotenv.2022.154737 PMID:35337871

Isaksen IM, Dankel SN (2023). Ultra-processed food consumption and cancer risk: a systematic review and meta-analysis. Clin Nutr. 42(6):919–28. https://doi.org/10.1016/j.clnu.2023.03.018 PMID:37087831

ISAPS (2022). International Survey on Aesthetic/Cosmetic Procedures performed in 2022. Mount Royal (NJ), USA: International Society of Aesthetic Plastic Surgery. Available at: https://www.isaps.org/discover/about-isaps/global-statistics/reports-and-press-releases/global-survey-2022-full-report-and-press-releases/, accessed September 2024.

Ishiguro H, Kawahara T, Zheng Y, Netto GJ, Miyamoto H (2014). Reduced glucocorticoid receptor expression predicts bladder tumor recurrence and progression. Am J Clin Pathol. 142(2):157–64. https://doi.org/10.1309/AJCPU8UCEZYG4WTV PMID:25015855

Ishii A, Matsuoka H, Aji T, Hayatsu H, Wataya Y, Arimoto S, et al. (1989). Evaluation of the mutagenicity and the tumor-promoting activity of parasite extracts: *Schistosoma japonicum* and *Clonorchis sinensis.* Mutat Res. 224(2):229–33. https://doi.org/10.1016/0165-1218(89)90160-2 PMID:2552310

Ishii Y, Kuroda K, Matsushita K, Yokoo Y, Takasu S, Kijima A, et al. (2017). Phosphorylation of protein phosphatase 2A facilitated an early stage of chemical carcinogenesis. Toxicol Appl Pharmacol. 336:75–83. https://doi.org/10.1016/j.taap.2017.10.009 PMID:29054680

Ishii Y, Okamura T, Inoue T, Tasaki M, Umemura T, Nishikawa A (2009). Dietary catechol causes increased oxidative DNA damage in the livers of mice treated with acetaminophen. Toxicology. 263(2–3):93–9. https://doi.org/10.1016/j.tox.2009.06.022 PMID:19576946

Ishii Y, Umemura T, Kanki K, Kuroiwa Y, Nishikawa A, Ito R, et al. (2006). Possible involvement of NO-mediated oxidative stress in induction of rat forestomach damage and cell proliferation by combined treatment with catechol and sodium nitrite. Arch Biochem Biophys. 447(2):127–35. https://doi.org/10.1016/j.abb.2006.01.017 PMID:16530157

Ishikawa M, Tanaka S, Arai M, Genda Y, Sakamoto A (2012). Differences in microRNA changes of healthy rat liver between sevoflurane and propofol anesthesia. Anesthesiology. 117(6):1245–52. https://doi.org/10.1097/ALN.0b013e3182746676https://doi.org/10.1097/ALN.0b013e3182746676 PMID:23090150

Islam JY, Hoppin J, Mora AM, Soto-Martinez ME, Gamboa LC, Castañeda JEP, et al. (2023). Respiratory and allergic outcomes among 5-year-old children exposed to pesticides. Thorax. 78(1):41–9. https://doi.org/10.1136/thoraxjnl-2021-218068https://doi.org/10.1136/thoraxjnl-2021-218068 PMID:35210357

Islami F, Poustchi H, Pourshams A, Khoshnia M, Gharavi A, Kamangar F, et al. (2020). A prospective study of tea drinking temperature and risk of esophageal squamous cell carcinoma. Int J Cancer. 146(1):18–25. https://doi.org/10.1002/ijc.32220 PMID:30891750

Isomura K, Chikahira M, Teranishi K, Hamada K (1984). Induction of mutations and chromosome aberrations in lung cells following in vivo exposure of rats to nitrogen oxides. Mutat Res. 136(2):119–25. https://doi.org/10.1016/0165-1218(84)90153-8 PMID:6717477

Issah I, Arko-Mensah J, Agyekum TP, Dwomoh D, Fobil JN (2021). Electronic waste exposure and DNA damage: a systematic review and meta-analysis. Rev Environ Health. 38(1):15–31. https://doi.org/10.1515/reveh-2021-0074 PMID:34727591

Ito N, Hasegawa R, Imaida K, Takahashi S, Shirai T (1994). Medium-term rat liver bioassay for rapid detection of carcinogens and modifiers of hepatocarcinogenesis. Drug Metab Rev. 26(1–2):431–42. https://doi.org/10.3109/03602539409029807 PMID:8082578

Iturburu FG, Simoniello MF, Medici S, Panzeri AM, Menone ML (2018). Imidacloprid causes DNA damage in fish: clastogenesis as a mechanism of genotoxicity. Bull Environ Contam Toxicol. 100(6):760–4. https://doi.org/10.1007/s00128-018-2338-0 PMID:29663041

Ivantsova E, Lopez-Scarim V, Sultan A, English C, Biju A, Souders CL 2nd, et al. (2023). Evidence for neurotoxicity and oxidative stress in zebrafish embryos/larvae treated with HFPO-DA ammonium salt (GenX). Environ Toxicol Pharmacol. 104:104315. https://doi.org/10.1016/j.etap.2023.104315 PMID:37984673

Iversen L, Fielding S, Lidegaard Ø, Hannaford PC (2020). Contemporary hormonal contraception and risk of endometrial cancer in women younger than age 50: a retrospective cohort study of Danish women. Contraception. 102(3):152–8. https://doi.org/10.1016/j.contraception.2020.06.008 PMID:32592798

Iwamoto A, Kawai M, Furuse M, Yasuo S (2014). Effects of chronic jet lag on the central and peripheral circadian clocks in CBA/N mice. Chronobiol Int. 31(2):189–98. https://doi.org/10.3109/07420528.2013.837478 PMID:24147659

Iwasaki M, Itoh H, Sawada N, Tsugane S (2023). Exposure to environmental chemicals and cancer risk: epidemiological evidence from Japanese studies. Genes Environ. 45(1):10. https://doi.org/10.1186/s41021-023-00268-3 PMID:36949525

Iyad N, S Ahmad M, Alkhatib SG, Hjouj M (2023). Gadolinium contrast agents – challenges and opportunities of a multidisciplinary approach: literature review. Eur J Radiol Open. 11:100503. https://doi.org/10.1016/j.ejro.2023.100503 PMID:37456927

Izano MA, Sofrygin OA, Picciotto S, Bradshaw PT, Eisen EA (2019). Metalworking fluids and colon cancer risk: longitudinal targeted minimum loss-based estimation. Environ Epidemiol. 3(1):e035. https://doi.org/10.1097/EE9.0000000000000035 PMID:33778333

Jablonická A, Poláková H, Karelová J, Vargová M (1989). Analysis of chromosome aberrations and sister-chromatid exchanges in peripheral blood lymphocytes of workers with occupational exposure to the mancozeb-containing fungicide Novozir Mn80. Mutat Res. 224(2):143–6. https://doi.org/10.1016/0165-1218(89)90148-1https://doi.org/10.1016/0165-1218(89)90148-1 PMID:2797033

Jablonowski ND, Schäffer A, Burauel P (2011). Still present after all these years: persistence plus potential toxicity raise questions about the use of atrazine. Environ Sci Pollut Res Int. 18(2):328–31. https://doi.org/10.1007/s11356-010-0431-y PMID:21191660

Jabłońska-Trypuć A, Wydro U, Wołejko E, Makuła M, Krętowski R, Naumowicz M, et al. (2023). Selected fungicides as potential EDC estrogenic micropollutants in the environment. Molecules. 28(21):7437. https://doi.org/10.3390/molecules28217437 PMID:37959855

Jackson AL, Loeb LA (2001). The contribution of endogenous sources of DNA damage to the multiple mutations in cancer. Mutat Res. 477(1-2):7–21. https://doi.org/10.1016/S0027-5107(01)00091-4 PMID:11376682

Jackson P, Hougaard KS, Boisen AM, Jacobsen NR, Jensen KA, Møller P, et al. (2012a). Pulmonary exposure to carbon black by inhalation or instillation in pregnant mice: effects on liver DNA strand breaks in dams and offspring. Nanotoxicology. 6(5):486–500. https://doi.org/10.3109/17435390.2011.587902 PMID:21649560

Jackson P, Hougaard KS, Vogel U, Wu D, Casavant L, Williams A, et al. (2012b). Exposure of pregnant mice to carbon black by intratracheal instillation: toxicogenomic effects in dams and offspring. Mutat Res. 745(1–2):73–83. https://doi.org/10.1016/j.mrgentox.2011.09.018 PMID:22001195

Jacob SE, Brod BA (2011). Paraphenylenediamine in black henna tattoos: sensitization of toddlers indicates a clear need for legislative action. J Clin Aesthet Dermatol. 4(12):46–7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3244359/ PMID:22191009

Jacobsen NR, Møller P, Jensen KA, Vogel U, Ladefoged O, Loft S, et al. (2009). Lung inflammation and genotoxicity following pulmonary exposure to nanoparticles in ApoE−/− mice. Part Fibre Toxicol. 6(1):2. https://doi.org/10.1186/1743-8977-6-2 PMID:19138394

Jacobstein R, Polis CB (2014). Progestin-only contraception: injectables and implants. Best Pract Res Clin Obstet Gynaecol. 28(6):795–806. https://doi.org/10.1016/j.bpobgyn.2014.05.003 PMID:24996766

Jahan F, Chinni SV, Samuggam S, Reddy LV, Solayappan M, Su Yin L (2022). The complex mechanism of the *Salmonella typhi* biofilm formation that facilitates pathogenicity: a review. Int J Mol Sci. 23(12):6462. https://doi.org/10.3390/ijms23126462 PMID:35742906

Jahankhani K, Ahangari F, Adcock IM, Mortaz E (2023). Possible cancer-causing capacity of COVID-19: is SARS-CoV-2 an oncogenic agent? Biochimie. 213:130–8. https://doi.org/10.1016/j.biochi.2023.05.014 PMID:37230238

Jahanshahifard S, Ahmadpour-Kacho M, Pasha YZ (2012). Effects of phototherapy on cytokines' levels and white blood cells in term neonate with hyperbilirubinemia. J Clin Neonatol. 1(3):139–42. https://doi.org/10.4103/2249-4847.101696 PMID:24027710

Jain M, Singh M (2023). Assisted reproductive technology (ART) techniques. In: StatPearls [Internet]. Treasure Island (FL), USA: StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK576409/ PMID:35015434

Jalalabadi F, Doval AF, Neese V, Andrews E, Spiegel AJ (2021). Breast implant utilization trends in USA versus Europe and the impact of BIA-ALCL publications. Plast Reconstr Surg Glob Open. 9(3):e3449. https://doi.org/10.1097/GOX.0000000000003449 PMID:33968547

Jalles C, Lepelley M, Mouret S, Charles J, Leccia MT, Trabelsi S (2022). Skin cancers under janus kinase inhibitors: a World Health Organization drug safety database analysis. Therapie. 77(6):649–56. https://doi.org/10.1016/j.therap.2022.04.005 PMID:35710462

James P, Bertrand KA, Hart JE, Schernhammer ES, Tamimi RM, Laden F (2017). Outdoor light at night and breast cancer incidence in the Nurses' Health Study II. Environ Health Perspect. 125(8):087010. https://doi.org/10.1289/EHP935 PMID:28886600

James SJ, Pogribna M, Miller BJ, Bolon B, Muskhelishvili L (1997). Characterization of cellular response to silicone implants in rats: implications for foreign-body carcinogenesis. Biomaterials. 18(9):667–75. https://doi.org/10.1016/S0142-9612(96)00189-5 PMID:9151998

Jandova J, Wondrak GT (2022). Vemurafenib drives epithelial-to-mesenchymal transition gene expression in BRAF inhibitor–resistant $BRAF^{V600E}$/$NRAS^{Q61K}$ melanoma enhancing tumor growth and metastasis in a bioluminescent murine model. J Invest Dermatol. 142(5):1456–1465.e1. https://doi.org/10.1016/j.jid.2021.10.007 PMID:34687745

Jang Y, Choi YJ, Lim YH, Lee KS, Kim BN, Shin CH, et al. (2021). Associations between thyroid hormone levels and urinary concentrations of bisphenol A, F, and S in 6-year-old children in Korea. J Prev Med Public Health. 54(1):37–45. https://doi.org/10.3961/jpmph.20.310 PMID:33618498

Jang YC, Leung CY, Huang HL (2023). Association of menopausal hormone therapy with risk of pancreatic cancer: a systematic review and meta-analysis of cohort studies. Cancer Epidemiol Biomarkers Prev. 32(1):114–22. https://doi.org/10.1158/1055-9965.EPI-22-0518 PMID:36306390

Janik E, Niemcewicz M, Ceremuga M, Stela M, Saluk-Bijak J, Siadkowski A, et al. (2020). Molecular aspects of mycotoxins – a serious problem for human health. Int J Mol Sci. 21(21):8187. https://doi.org/10.3390/ijms21218187 PMID:33142955

Jarosiewicz M, Krokosz A, Marczak A, Bukowska B (2019). Changes in the activities of antioxidant enzymes and reduced glutathione level in human erythrocytes exposed to selected brominated flame retardants. Chemosphere.

227:93–9. https://doi.org/10.1016/j.chemosphere.2019.04.008 PMID:30986606

Jayaweera M, Perera H, Gunawardana B, Manatunge J (2020). Transmission of COVID-19 virus by droplets and aerosols: a critical review on the unresolved dichotomy. Environ Res. 188:109819. https://doi.org/10.1016/j.envres.2020.109819 PMID:32569870

JBRC (1998). Subchronic inhalation toxicity and carcinogenicity studies of carbon tetra-chloride in F344 rats and BDF1 mice (studies nos. 0020, 0021, 0043, and 0044) (unpublished report to the Ministry of Labor). Kanagawa, Japan: Japan Bioassay Research Center.

JBRC (2019). [Report nitrogen dioxide in the inhalation of p53 KO mice in the 26-week carcinogenicity study. Test number 0904.] Report for Ministry of Health, Labour and Welfare. Kanagawa, Japan: Japan Bioassay Research Center. Available from: https://www.mhlw.go.jp/content/11201000/000638309.pdf, accessed January 2024. [Japanese]

JBRC (2019a). [Report of medium-term carcinogenicity study of nitrogen dioxide by inhalation in p53 KO mice. Test number 0904.] Kanagawa, Japan: Japan Bioassay Research Center. Available from: https://anzeninfo.mhlw.go.jp/user/anzen/kag/ankgc10.html, accessed January 2024. [Japanese]

JBRC (2019b). [Report of medium-term carcinogenicity study of nitrogen dioxide by inhalation in ras H2 mice. Test number 0905.] Kanagawa, Japan: Japan Bioassay Research Center. Available from: https://anzeninfo.mhlw.go.jp/user/anzen/kag/ankgc10.html, accessed January 2024. [Japanese]

JBRC (2020a). [Report of 2-year carcinogenicity study of anatase-type nano-TiO_2 by inhalation in F344 rats. Test number 0883.] Kanagawa, Japan: Japan Bioassay Research Center. Available from: https://www.mhlw.go.jp/content/11201000/000678843.pdf, accessed January 2024. [Japanese]

JBRC (2020b). [Report of 2-year carcinogenicity study of anatase-type nano-TiO2 by inhalation in F344 rats. Test number 0883.] Tables. Kanagawa, Japan: Japan Bioassay Research Center. Available from: https://anzeninfo.mhlw.go.jp/user/anzen/kag/pdf/gan/0883TABLE.pdf, accessed January 2024. [Japanese]

JBRC (2022a). [Report on the carcinogenicity of butyraldehyde by inhalation in rat.] Kanagawa, Japan: Japan Bioassay Research Center. Available from: https://anzeninfo.mhlw.go.jp/user/anzen/kag/pdf/gan/0914MAIN.pdf, accessed January 2024. [Japanese]

JBRC (2022b). Report on the carcinogenicity of butyraldehyde by inhalation in rat. Tables. Kanagawa, Japan: Japan Bioassay Research Center. Available from: https://anzeninfo.mhlw.go.jp/user/anzen/kag/pdf/gan/0914TABLE.pdf, accessed January 2024.

JBRC (2022c). [Allyl alcohol in rats. Inhalation carcinogenicity study report. Test number 0918. Tables.] Kanagawa, Japan: Japan Bioassay Research Center. Available from: https://anzeninfo.mhlw.go.jp/user/anzen/kag/pdf/gan/0918TABLE.pdf, accessed December 2023. [Japanese]

Jenkins S, Wang J, Eltoum I, Desmond R, Lamartiniere CA (2011). Chronic oral exposure to bisphenol A results in a nonmonotonic dose response in mammary carcinogenesis and metastasis in MMTV-erbB2 mice. Environ Health Perspect. 119(11):1604–9. https://doi.org/10.1289/ehp.1103850 PMID:21988766

Jennerwein M, Andrews PA (1995). Effect of intracellular chloride on the cellular pharmacodynamics of cis-diamminedichloroplatinum(II). Drug Metab Dispos. 23(2):178–84. https://dmd.aspetjournals.org/content/23/2/178.long PMID:7736908

Jennings AS, Schwartz SL, Balter NJ, Gardner D, Witorsch RJ (1990). Effects of oral erythrosine (2′,4′,5′,7′-tetraiodofluorescein) on the pituitary-thyroid axis in rats. Toxicol Appl Pharmacol. 103(3):549–56. https://doi.org/10.1016/0041-008X(90)90327-Q PMID:2160137

Jensen NB, Justesen SD, Larsen A, Ernst E, Pedersen LH (2021). A systematic overview of the spermatotoxic and genotoxic effects of methotrexate, ganciclovir and mycophenolate mofetil. Acta Obstet Gynecol Scand. 100(9):1557–80. https://doi.org/10.1111/aogs.14151 PMID:33755191

Jeschke P, Nauen R, Schindler M, Elbert A (2011). Overview of the status and global strategy for neonicotinoids. J Agric Food Chem. 59(7):2897–908. https://doi.org/10.1021/jf101303g PMID:20565065

Jeurissen SM, Punt A, Boersma MG, Bogaards JJP, Fiamegos YC, Schilter B, et al. (2007). Human cytochrome p450 enzyme specificity for the bioactivation of estragole and related alkenylbenzenes. Chem Res Toxicol. 20(5):798–

806. https://doi.org/10.1021/tx700012d PMID:17407329

Jha AM, Singh AC (1994). Clastogenicity of lanthanides–induction of micronuclei in root tips of *Vicia faba.* Mutat Res. 322(3):169–72. https://doi.org/10.1016/0165-1218(94)90003-5 PMID:7521516

Jha AM, Singh AC (1995). Clastogenicity of lanthanides: induction of chromosomal aberration in bone marrow cells of mice in vivo. Mutat Res. 341(3):193–7. https://doi.org/10.1016/0165-1218(95)90009-8 PMID:7529360

Ji L, Zhong B, Jiang X, Mao F, Liu G, Song B, et al. (2017). Actein induces autophagy and apoptosis in human bladder cancer by potentiating ROS/JNK and inhibiting AKT pathways. Oncotarget. 8(68):112498–515. https://doi.org/10.18632/oncotarget.22274https://doi.org/10.18632/oncotarget.22274 PMID:29348843

Jiang B, Kauffman AE, Li L, McFee W, Cai B, Weinstein J, et al. (2020b). Health impacts of environmental contamination of micro- and nanoplastics: a review. Environ Health Prev Med. 25(1):29. https://doi.org/10.1186/s12199-020-00870-9 PMID:32664857

Jiang B, Kronenberg F, Nuntanakorn P, Qiu MH, Kennelly EJ (2006). Evaluation of the botanical authenticity and phytochemical profile of black cohosh products by high-performance liquid chromatography with selected ion monitoring liquid chromatography–mass spectrometry. J Agric Food Chem. 54(9):3242–53. https://doi.org/10.1021/jf0606149https://doi.org/10.1021/jf0606149 PMID:16637680

Jiang F, Teng M, Zhu YX, Li YJ (2020a). No association between dietary acrylamide and renal cell carcinoma: an updated meta-analysis. J Sci Food Agric. 100(7):3071–7. https://doi.org/10.1002/jsfa.10339 PMID:32077494

Jiménez-Garza O, Ghosh M, Barrow TM, Godderis L (2023). Toxicomethylomics revisited: a state-of-the-science review about DNA methylation modifications in blood cells from workers exposed to toxic agents. Front Public Health. 11:1073658. https://doi.org/10.3389/fpubh.2023.1073658 PMID:36891347

Jin D, Wu S, Zhang YG, Lu R, Xia Y, Dong H, et al. (2015). Lack of vitamin D receptor causes dysbiosis and changes the functions of the murine intestinal microbiome. Clin Ther. 37(5):996–1009.e7. https://doi.org/10.1016/j.clinthera.2015.04.004 PMID:26046242

Jin R, McConnell R, Catherine C, Xu S, Walker DI, Stratakis N, et al. (2020). Perfluoroalkyl substances and severity of nonalcoholic fatty liver in children: an untargeted metabolomics approach. Environ Int. 134:105220. https://doi.org/10.1016/j.envint.2019.105220https://doi.org/10.1016/j.envint.2019.105220 PMID:31744629

Jin Y, Pan X, Fu Z (2014). Exposure to bifenthrin causes immunotoxicity and oxidative stress in male mice. Environ Toxicol. 29(9):991–9. https://doi.org/10.1002/tox.21829 PMID:23172818

Jin Y, Wang J, Sun X, Ye Y, Xu M, Wang J, et al. (2013). Exposure of maternal mice to cis-bifenthrin enantioselectively disrupts the transcription of genes related to testosterone synthesis in male offspring. Reprod Toxicol. 42:156–63. https://doi.org/10.1016/j.reprotox.2013.08.006 PMID:23994515

Jirau-Colón H, González-Parrilla L, Martinez-Jiménez J, Adam W, Jiménez-Velez B (2019). Rethinking the dental amalgam dilemma: an integrated toxicological approach. Int J Environ Res Public Health. 16(6):1036. https://doi.org/10.3390/ijerph16061036 PMID:30909378

JMPR (1995). Vinclozolin. Report: FAO Plant production and protection paper, 133, 1996 – Pesticide residues in food – 1995. Geneva, Switzerland: Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO Toxicological and Environmental Core Assessment. Available from https://apps.who.int/pesticide-residues-jmpr-database/pesticide?name=VINCLOZOLIN, accessed January 2024.

JMPR (2006) Pesticide residues in food 2006. Joint FAO/WHO Meeting on Pesticide Residues. Mo 187. Rome, Italy: Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues. Available from: https://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/report2006jmpr.pdf, accessed January 2024.

Jo H, Cha B, Kim H, Brito S, Kwak BM, Kim ST, et al. (2021). α-Pinene enhances the anticancer activity of natural killer cells via ERK/AKT pathway. Int J Mol Sci. 22(2):656. https://doi.org/10.3390/ijms22020656https://doi.org/10.3390/ijms22020656 PMID:33440866

Joe E, Ringman JM (2019). Cognitive symptoms of Alzheimer's disease: clinical management and prevention. BMJ. 367:l6217. https://doi.org/10.1136/bmj.l6217 PMID:31810978

Joechle W (1964). Trends in photophysiologic concepts. Ann N Y Acad Sci. 117(1):88–104. https://doi.org/10.1111/j.1749-6632.1964.tb48164.x PMID:14196671

Johns LE, Jones ME, Schoemaker MJ, McFadden E, Ashworth A, Swerdlow AJ (2018). Domestic light at night and breast cancer risk: a prospective analysis of 105 000 UK women in the Generations Study. Br J Cancer. 118(4):600–6. https://doi.org/10.1038/bjc.2017.359 PMID:29360812

Johnson M, Luukinen B, Gervais J, Buhl K, Stone D (2010). Bifenthrin. General fact sheet. Corvallis (OR), USA: National Pesticide Information Center, Oregon State University Extension Services. Available from http://npic.orst.edu/factsheets/bifgen.html, accessed September 2024.

Johnson-Arbor K, Dubey R (2023). Doxorubicin In: StatPearls [Internet]. Treasure Island (FL), USA: StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK459232/ PMID:29083582

Johnston HJ, Hutchison GR, Christensen FM, Peters S, Hankin S, Stone V (2009). Identification of the mechanisms that drive the toxicity of TiO_2 particulates: the contribution of physicochemical characteristics. Part Fibre Toxicol. 6(1):33. https://doi.org/10.1186/1743-8977-6-33 PMID:20017923

Jomini S, Labille J, Bauda P, Pagnout C (2012). Modifications of the bacterial reverse mutation test reveals mutagenicity of TiO_2 nanoparticles and byproducts from a sunscreen TiO_2-based nanocomposite. Toxicol Lett. 215(1):54–61. https://doi.org/10.1016/j.toxlet.2012.09.012 PMID:23026263

Jones CR, Sabbioni G (2003). Identification of DNA adducts using HPLC/MS/MS following in vitro and in vivo experiments with arylamines and nitroarenes. J Environ Sci (China). 16(10):1251–63. https://doi.org/10.1021/tx020064iPMID:14565767

Jones CR, Sepai O, Liu YY, Yan H, Sabbioni G (2005). Urinary metabolites of workers exposed to nitrotoluenes. Biomarkers. 10(1):10–28. https://doi.org/10.1080/13547500500079670 PMID:16097390

Jones DJL, Singh R, Emms V, Farmer PB, Grant D, Quinn P, et al. (2022b). Determination of N7-glycidamide guanine adducts in human blood DNA following exposure to dietary acrylamide using liquid chromatography/tandem mass spectrometry. Rapid Commun Mass Spectrom. 36(6):e9245. https://doi.org/10.1002/rcm.9245 PMID:34939243

Jones EV, Dickman MJ, Whitmarsh AJ (2007). Regulation of p73-mediated apoptosis by c-Jun N-terminal kinase. Biochem J. 405(3):617–23. https://doi.org/10.1042/BJ20061778 PMID:17521288

Jones GS, Graubard BI, Ramirez Y, Liao LM, Huang WY, Alvarez CS, et al. (2022a). Sweetened beverage consumption and risk of liver cancer by diabetes status: a pooled analysis. Cancer Epidemiol. 79:102201. https://doi.org/10.1016/j.canep.2022.102201 PMID:35728406

Jones ME, Schoemaker MJ, Wright LB, Ashworth A, Swerdlow AJ (2017a). Smoking and risk of breast cancer in the Generations Study cohort. Breast Cancer Res. 19(1):118. https://doi.org/10.1186/s13058-017-0908-4 PMID:29162146

Jones RR, DellaValle CT, Weyer PJ, Robien K, Cantor KP, Krasner S, et al. (2019). Ingested nitrate, disinfection by-products, and risk of colon and rectal cancers in the Iowa Women's Health Study cohort. Environ Int. 126:242–51. https://doi.org/10.1016/j.envint.2019.02.010 PMID:30822653

Jones RR, Fisher JA, Hasheminassab S, Kaufman JD, Freedman ND, Ward MH, et al. (2023a). Outdoor ultrafine particulate matter and risk of lung cancer in Southern California. Am J Respir Crit Care Med. 209(3):307–15. https://doi.org/10.1164/rccm.202305-0902OC PMID:37856832

Jones RR, Fisher JA, Medgyesi DN, Buller ID, Liao LM, Gierach G, et al. (2023b). Ethylene oxide emissions and incident breast cancer and non-Hodgkin lymphoma in a US cohort. J Natl Cancer Inst. 115(4):405–12. https://doi.org/10.1093/jnci/djad004 PMID:36633307

Jones RR, Madrigal JM, Troisi R, Surcel HM, Öhman H, Kivelä J, et al. (2024). Maternal serum concentrations of per- and polyfluoroalkyl substances and childhood acute lymphoblastic leukemia. J Natl Cancer Inst. 116(5):728–36. https://doi.org/10.1093/jnci/djad261 PMID:38092046

Jones RR, Weyer PJ, DellaValle CT, Inoue-Choi M, Anderson KE, Cantor KP, et al. (2016). Nitrate from drinking water and diet and bladder cancer among postmenopausal women in Iowa. Environ Health Perspect. 124(11):1751–8. https://doi.org/10.1289/EHP191 PMID:27258851

Jones RR, Weyer PJ, DellaValle CT, Robien K, Cantor KP, Krasner S, et al. (2017b). Ingested nitrate, disinfection by-

products, and kidney cancer risk in older women. Epidemiology. 28(5):703–11. https://doi.org/10.1097/EDE.0000000000000647https://doi.org/10.1097/EDE.0000000000000647 PMID:28252454

Jönsson H, Mattsson S (1998). Thyroid burdens of 125I in hospital laboratory workers during a 20-y period. Health Phys. 75(5):475–8. https://doi.org/10.1097/00004032-199811000-00002 PMID:9790555

Jordan VC, Jeng MH, Catherino WH, Parker CJ (1993). The estrogenic activity of synthetic progestins used in oral contraceptives. Cancer. 71 4 Suppl:1501–5. https://doi.org/10.1002/cncr.2820710415 PMID:8431886

Jørgensen JT, Johansen MS, Ravnskjær L, Andersen KK, Bräuner EV, Loft S, et al. (2016). Long-term exposure to ambient air pollution and incidence of brain tumours: The Danish Nurse Cohort. Neurotoxicology. 55:122–30. https://doi.org/10.1016/j.neuro.2016.06.003 PMID:27265017

Jorsaraei SG, Maliji G, Azadmehr A, Moghadamnia AA, Faraji AA (2014). Immunotoxicity effects of carbaryl in vivo and in vitro. Environ Toxicol Pharmacol. 38(3):838–44. https://doi.org/10.1016/j.etap.2014.09.004 PMID:25461543

Jose CC, Wang Z, Tanwar VS, Zhang X, Zang C, Cuddapah S (2019). Nickel-induced transcriptional changes persist post exposure through epigenetic reprogramming. Epigenetics Chromatin. 12(1):75. https://doi.org/10.1186/s13072-019-0324-3 PMID:31856895

Joustra V, Li Yim AYF, van Gennep S, Hageman I, de Waard T, Levin E, et al. (2024). Peripheral blood DNA methylation signatures and response to tofacitinib in moderate-to-severe ulcerative colitis. J Crohns Colitis. 18(8):1179–89(8):1179–89. https://doi.org/10.1093/ecco-jcc/jjad129 PMID:37526299

Juarez Facio AT, Yon J, Corbière C, Rogez-Florent T, Castilla C, Lavanant H, et al. (2022). Toxicological impact of organic ultrafine particles (UFPs) in human bronchial epithelial BEAS-2B cells at air-liquid interface. Toxicol In Vitro. 78:105258. https://doi.org/10.1016/j.tiv.2021.105258 PMID:34653646

Judde JG, Breillout F, Clemenceau C, Poupon MF, Jasmin C (1987). Inhibition of rat natural killer cell function by carcinogenic nickel compounds: preventive action of manganese. J Natl Cancer Inst. 78(6):1185–90. PMID:2438444

Judson RS, Magpantay FM, Chickarmane V, Haskell C, Tania N, Taylor J, et al. (2015). Integrated model of chemical perturbations of a biological pathway using 18 in vitro high-throughput screening assays for the estrogen receptor. Toxicol Sci. 148(1):137–54. https://doi.org/10.1093/toxsci/kfv168https://doi.org/10.1093/toxsci/kfv168 PMID:26272952

Jung D, Choe Y, Shin J, Kim E, Min G, Kim D, et al. (2022). Risk assessment of indoor air quality and its association with subjective symptoms among office workers in Korea. Int J Environ Res Public Health. 19(4):2446. https://doi.org/10.3390/ijerph19042446 PMID:35206634

Jung HN, Zerin T, Podder B, Song HY, Kim YS (2014). Cytotoxicity and gene expression profiling of polyhexamethylene guanidine hydrochloride in human alveolar A549 cells. Toxicol In Vitro. 28(4):684–92. https://doi.org/10.1016/j.tiv.2014.02.004 PMID:24583197

Jyoti J, Basu S, Pratap Singh B, Dhakate SR (2015). Superior mechanical and electrical properties of multiwall carbon nanotube reinforced acrylonitrile butadiene styrene high performance composites. Compos, Part B Eng. 83(1):58–65. https://doi.org/10.1016/j.compositesb.2015.08.055

Kaae J, Boyd HA, Hansen AV, Wulf HC, Wohlfahrt J, Melbye M (2010). Photosensitizing medication use and risk of skin cancer. Cancer Epidemiol Biomarkers Prev. 19(11):2942–9. https://doi.org/10.1158/1055-9965.EPI-10-0652 PMID:20861398

Kabátková M, Svobodová J, Pěnčíková K, Mohatad DS, Šmerdová L, Kozubík A, et al. (2015). Interactive effects of inflammatory cytokine and abundant low-molecular-weight PAHs on inhibition of gap junctional intercellular communication, disruption of cell proliferation control, and the AhR-dependent transcription. Toxicol Lett. 232(1):113–21. https://doi.org/10.1016/j.toxlet.2014.09.023 PMID:25268939

Kabi A, Nickerson KP, Homer CR, McDonald C (2012). Digesting the genetics of inflammatory bowel disease: insights from studies of autophagy risk genes. Inflamm Bowel Dis. 18(4):782–92. https://doi.org/10.1002/ibd.21868 PMID:21936032

Kachuri L, Beane Freeman LE, Spinelli JJ, Blair A, Pahwa M, Koutros S, et al. (2020). Insecticide use and risk of non-Hodgkin lymphoma subtypes: a subset meta-analysis of the North American Pooled Project. Int J Cancer. 147(12):3370–83. https://doi.org/10.1002/ijc.33164 PMID:32574374

Kadawathagedara M, Botton J, de Lauzon-Guillain B, Meltzer HM, Alexander J, Brantsaeter AL, et al. (2018). Dietary acrylamide intake during pregnancy and postnatal growth and obesity: results from the Norwegian Mother and Child Cohort Study (MoBa). Environ Int. 113:325–34. https://doi.org/10.1016/j.envint.2018.01.004 PMID:29398013

Kaden DA, Hites RA, Thilly WG (1979). Mutagenicity of soot and associated polycyclic aromatic hydrocarbons to *Salmonella typhimurium*. Cancer Res. 39(10):4152–9. PMID:383281

Kadin ME, Adams WP Jr, Inghirami G, Di Napoli A (2020). Does breast implant-associated ALCL begin as a lymphoproliferative disorder? Plast Reconstr Surg. 145(1):30e–8e. https://doi.org/10.1097/PRS.0000000000006390 PMID:31577659

Kahveci H, Dogan H, Karaman A, Caner I, Tastekin A, Ikbal M (2013). Phototherapy causes a transient DNA damage in jaundiced newborns. Drug Chem Toxicol. 36(1):88–92. https://doi.org/10.3109/01480545.2011.653491 PMID:22360583

Kaidar M, Mitler A, Greenberg M, Cohen-Adam D, Abu-Ata M, Borovitz Y (2021). [Hair straightening – not straightforward]. Harefuah. 160(12):810–3. PMID:34957717 [Hebrew]

Kakadia S, Yarlagadda N, Awad R, Kundranda M, Niu J, Naraev B, et al. (2018). Mechanisms of resistance to BRAF and MEK inhibitors and clinical update of US Food and Drug Administration-approved targeted therapy in advanced melanoma. OncoTargets Ther. 11:7095–107. https://doi.org/10.2147/OTT.S182721 PMID:30410366

Kakaei K, Padervand M, Akinay Y, Dawi E, Ashames A, Saleem L, et al. (2023). A critical mini-review on challenge of gaseous O_3 toward removal of viral bioaerosols from indoor air based on collision theory. Environ Sci Pollut Res Int. 30(36):84918–32. https://doi.org/10.1007/s11356-023-28402-2 PMID:37380862

Kalantari N, Gorgani-Firouzjaee T, Hassani S, Chehrazi M, Ghaffari S (2020). Association between *Toxoplasma gondii* exposure and hematological malignancies: a systematic review and meta-analysis. Microb Pathog. 148:104440. https://doi.org/10.1016/j.micpath.2020.104440 PMID:32822769

Kalayasiri R, Dadwat K, Thika S, Sirivichayakul S, Maes M (2023). Methamphetamine (MA) use and MA-induced psychosis are associated with increasing aberrations in the compensatory immunoregulatory system, interleukin-1α, and CCL5 levels. Transl Psychiatry. 13(1):361. https://doi.org/10.1038/s41398-023-02645-6 PMID:37996407

Kaledin VI, Glazko TT, Krass PM, Chesnokova VM (1978). [Mechanisms of the immunodepression caused by *ortho*-aminoazotoluene and its noncarcinogenic analog in mice]. Vopr Onkol. 24(9):46–52. PMID:706294 [Russian]

Kaminski TFA, Dalla Lana DF, Quintana LD, Schmitt EG, Kaminski TA, Paula FR, et al. (2020). Fumonisin B_1 induces toxicity in human leukocytes at low concentrations: are computational studies effective to determine biosafety? Toxicon. 182:7–12. https://doi.org/10.1016/j.toxicon.2020.04.100 PMID:32376361

Kanaya N, Bernal L, Chang G, Yamamoto T, Nguyen D, Wang Y-Z, et al. (2019). Molecular mechanisms of polybrominated diphenyl ethers (BDE-47, BDE-100, and BDE-153) in human breast cancer cells and patient-derived xenografts. Toxicol Sci. 169(2):380–98. https://doi.org/10.1093/toxsci/kfz054 PMID:30796839

Kandyala R, Raghavendra SP, Rajasekharan ST (2010). Xylene: an overview of its health hazards and preventive measures. J Oral Maxillofac Pathol. 14(1):1–5. https://doi.org/10.4103/0973-029X.64299 PMID:21180450

Kaneko N, Sugioka T, Sakurai H (2007). Aluminum compounds enhance lipid peroxidation in liposomes: insight into cellular damage caused by oxidative stress. J Inorg Biochem. 101(6):967–75. https://doi.org/10.1016/j.jinorgbio.2007.03.005 PMID:17467804

Kang H, Lee JP, Choi K (2021b). Exposure to phthalates and environmental phenols in association with chronic kidney disease (CKD) among the general US population participating in multi-cycle NHANES (2005–2016). Sci Total Environ. 791:148343. https://doi.org/10.1016/j.scitotenv.2021.148343 PMID:34126474

Kang HG, Jeong SH, Cho JH, Kim DG, Park JM, Cho MH (2004). Chlropyrifos-methyl shows anti-androgenic activity without estrogenic activity in rats. Toxicology. 199(2-3):219–30. https://doi.org/10.1016/j.tox.2004.02.025 PMID:15147795

Kang M, Na HY, Ahn S, Kim JW, Lee S, Ahn S, et al. (2022b). Gallbladder adenocarcinomas undergo subclonal diversification and selection from precancerous lesions to metastatic tumors. eLife. 11:e78636. https://doi.org/10.7554/eLife.78636 PMID:36476508

Kang MS, Kim SH, Yang MJ, Kim HY, Kim IH, Kang JW, et al. (2022a). Polyhexamethylene guanidine phosphate-induced necrosis may be linked to pulmonary fibrosis. Toxicol Lett. 362:1–16. https://doi.org/10.1016/j.toxlet.2022.03.009 PMID:35430302

Kang MY, Jung J, Koo JW, Kim I, Kim HR, Myong JP (2021a). Increased risk of gastric cancer in workers with occupational dust exposure. Korean J Intern Med (Korean Assoc Intern Med). 36 Suppl 1:S18–26. https://doi.org/10.3904/kjim.2019.421 PMID:32375207

Kania N, Setiawan B, Widjadjanto E, Nurdiana N, Widodo MA, Kusuma HM (2014). Subchronic inhalation of coal dust particulate matter 10 induces bronchoalveolar hyperplasia and decreases MUC5AC expression in male Wistar rats. Exp Toxicol Pathol. 66(8):383–9. https://doi.org/10.1016/j.etp.2014.06.001 PMID:24975055

Kano H, Umeda Y, Kasai T, Sasaki T, Matsumoto M, Yamazaki K, et al. (2009). Carcinogenicity studies of 1,4-dioxane administered in drinking-water to rats and mice for 2 years. Food Chem Toxicol. 47(11):2776–84. https://doi.org/10.1016/j.fct.2009.08.012 PMID:19703511

Kanter J, Thompson AA, Pierciey FJ Jr, Hsieh M, Uchida N, Leboulch P, et al. (2023). Lovo-cel gene therapy for sickle cell disease: treatment process evolution and outcomes in the initial groups of the HGB-206 study. Am J Hematol. 98(1):11–22. https://doi.org/10.1002/ajh.26741 PMID:36161320

Karadag A, Yesilyurt A, Unal S, Keskin I, Demirin H, Uras N, et al. (2009). A chromosomal-effect study of intensive phototherapy versus conventional phototherapy in newborns with jaundice. Mutat Res. 676(1–2):17–20. https://doi.org/10.1016/j.mrgentox.2009.03.008 PMID:19376266

Karagas MR, Cushing GL Jr, Greenberg ER, Mott LA, Spencer SK, Nierenberg DW (2001). Non-melanoma skin cancers and glucocorticoid therapy. Br J Cancer. 85(5):683–6. https://doi.org/10.1054/bjoc.2001.1931 PMID:11531252

Karakoçak BB, Patel S, Ravi N, Biswas P (2019). Investigating the effects of stove emissions on ocular and cancer cells. Sci Rep. 9(1):1870. https://doi.org/10.1038/s41598-019-38803-4 PMID:30755694

Karaman EF, Zeybel M, Ozden S (2020). Evaluation of the epigenetic alterations and gene expression levels of HepG2 cells exposed to zearalenone and α-zearalenol. Toxicol Lett. 326:52–60. https://doi.org/10.1016/j.toxlet.2020.02.015 PMID:32119988

Karami S, Daughtery SE, Schwartz K, Davis FG, Ruterbusch JJ, Wacholder S, et al. (2016). Analgesic use and risk of renal cell carcinoma: a case–control, cohort and meta-analytic assessment. Int J Cancer. 139(3):584–92. https://doi.org/10.1002/ijc.30108 PMID:27009534

Karimi A, Mohebbi E, Mckay-Chopin S, Rashidian H, Hadji M, Peyghambari V, et al. (2022). Human papillomavirus and risk of head and neck squamous cell carcinoma in Iran. Microbiol Spectr. 10(4):e0011722. https://doi.org/10.1128/spectrum.00117-22 PMID:35708339

Karimi-Maleh H, Liu Y, Li Z, Darabi R, Orooji Y, Karaman C, et al. (2023). Calf thymus ds-DNA intercalation with pendimethalin herbicide at the surface of ZIF-8/Co/rGO/C_3N_4/ds-DNA/SPCE; A bio-sensing approach for pendimethalin quantification confirmed by molecular docking study. Chemosphere. 332:138815. https://doi.org/10.1016/j.chemosphere.2023.138815 PMID:37146774

Karlsson HL, Ljungman AG, Lindbom J, Möller L (2006). Comparison of genotoxic and inflammatory effects of particles generated by wood combustion, a road simulator and collected from street and subway. Toxicol Lett. 165(3):203–11. https://doi.org/10.1016/j.toxlet.2006.04.003 PMID:16716543

Karmaus AL, Toole CM, Filer DL, Lewis KC, Martin MT (2016). High-throughput screening of chemical effects on steroidogenesis using H295R human adrenocortical carcinoma cells. Toxicol Sci. 150(2):323–32. https://doi.org/10.1093/toxsci/kfw002 PMID:26781511

Karregat JJJP, Rustemeyer T, van der Bent SAS, Spiekstra SW, Thon M, Fernandez Rivas D, et al. (2021). Assessment of cytotoxicity and sensitization potential of intradermally injected tattoo inks in reconstructed human skin. Contact Dermatitis. 85(3):324–39. https://doi.org/10.1111/cod.13908 PMID:34029376

Karthikeyan R, Kanimozhi G, Prasad NR, Agilan B, Ganesan M, Srithar G (2018). Alpha pinene modulates UVA-induced oxidative stress, DNA damage and apoptosis in human skin epidermal keratinocytes. Life Sci. 212:150–8. https://doi.org/10.1016/j.lfs.2018.10.004https://doi.org/10.1016/j.lfs.2018.10.004 PMID:30292828

Kasai T, Kano H, Umeda Y, Sasaki T, Ikawa N, Nishizawa T, et al. (2009). Two-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male rats. Inhal Toxicol. 21(11):889–97. https://doi.org/10.1080/08958370802629610 PMID:19681729

Kasai T, Umeda Y, Ohnishi M, Mine T, Kondo H, Takeuchi T, et al. (2016). Lung carcinogenicity of inhaled multi-walled carbon nanotube in rats. Part Fibre Toxicol. 13(1):53. https://doi.org/10.1186/s12989-016-0164-2 PMID:27737701

Kasi RA, Moi CS, Kien YW, Yian KR, Chin NW, Yen NK, et al. (2015). *para*-Phenylenediamine-induces apoptosis via a pathway dependent on PTK-Ras-Raf-JNK activation but independent of the PI3K/Akt pathway in NRK-52E cells. Mol Med Rep. 11(3):2262–8. https://doi.org/10.3892/mmr.2014.2979 PMID:25411820

Kasprzak KS, Diwan BA, Konishi N, Misra M, Rice JM (1990). Initiation by nickel acetate and promotion by sodium barbital of renal cortical epithelial tumors in male F344 rats. Carcinogenesis. 11(4):647–52. https://doi.org/10.1093/carcin/11.4.647 PMID:2323003

Katabaro JM, Yan Y, Hu T, Yu Q, Cheng X (2022). A review of the effects of artificial light at night in urban areas on the ecosystem level and the remedial measures. Front Public Health. 10:969945. https://doi.org/10.3389/fpubh.2022.969945 PMID:36299764

Kato M, Yamaguchi M, Ooka A, Takahashi R, Suzuki T, Onoda K, et al. (2023). Non-target GC–MS analyses of fecal VOCs in NASH-hepatocellular carcinoma model STAM mice. Sci Rep. 13(1):8924. https://doi.org/10.1038/s41598-023-36091-7https://doi.org/10.1038/s41598-023-36091-7 PMID:37264108

Kato T, Totsuka Y, Ishino K, Matsumoto Y, Tada Y, Nakae D, et al. (2013). Genotoxicity of multi-walled carbon nanotubes in both in vitro and in vivo assay systems. Nanotoxicology. 7(4):452–61. https://doi.org/10.3109/17435390.2012.674571 PMID:22397533

Katsidzira L, Gangaidzo IT, Makunike-Mutasa R, Manyanga T, Matsena-Zingoni Z, Thomson S, et al. (2019). A case–control study of risk factors for colorectal cancer in an African population. Eur J Cancer Prev. 28(3):145–50. https://doi.org/10.1097/CEJ.0000000000000439 PMID:29649072

Kaur K, Kaur R (2018). Occupational pesticide exposure, impaired DNA repair, and diseases. Indian J Occup Environ Med. 22(2):74–81. https://doi.org/10.4103/ijoem.IJOEM_45_18 PMID:30319227

Kawai M, Saegusa Y, Dewa Y, Nishimura J, Kemmochi S, Harada T, et al. (2010b). Elevation of cell proliferation via generation of reactive oxygen species by piperonyl butoxide contributes to its liver tumor-promoting effects in mice. Arch Toxicol. 84(2):155–64. https://doi.org/10.1007/s00204-009-0498-8 PMID:20101389

Kawai M, Saegusa Y, Jin M, Dewa Y, Nishimura J, Harada T, et al. (2009). Mechanistic study on hepatocarcinogenesis of piperonyl butoxide in mice. Toxicol Pathol. 37(6):761–9. https://doi.org/10.1177/0192623309344087https://doi.org/10.1177/0192623309344087 PMID:19690152

Kawai M, Saegusa Y, Kemmochi S, Harada T, Shimamoto K, Shibutani M, et al. (2010a). Cytokeratin 8/18 is a useful immunohistochemical marker for hepatocellular proliferative lesions in mice. J Vet Med Sci. 72(3):263–9. https://doi.org/10.1292/jvms.09-0329https://doi.org/10.1292/jvms.09-0329 PMID:20035116

Kawai T, Yasugi T, Mizunuma K, Horiguchi S, Morioka I, Miyashita K, et al. (1992). Monitoring of workers exposed to a mixture of toluene, styrene and methanol vapours by means of diffusive air sampling, blood analysis and urinalysis. Int Arch Occup Environ Health. 63(6):429–35. https://doi.org/10.1007/BF00386940 PMID:1544693

Kawanishi S, Hiraku Y, Pinlaor S, Ma N (2006). Oxidative and nitrative DNA damage in animals and patients with inflammatory diseases in relation to inflammation-related carcinogenesis. Biol Chem. 387(4):365–72. https://doi.org/10.1515/BC.2006.049 PMID:16606333

Kay JE, Brody JG, Schwarzman M, Rudel RA (2024). Application of the key characteristics framework to identify potential breast carcinogens using publicly available *in vivo*, *in vitro*, and *in silico* data. Environ Health Perspect. 132(1):17002. https://doi.org/10.1289/EHP13233 PMID:38197648

Kaya FF, Topaktaş M (2007). Genotoxic effects of potassium bromate on human peripheral lymphocytes in vitro. Mutat

Res. 626(1–2):48–52. https://doi.org/10.1016/j.mrgentox.2006.08.006 PMID:17118698

Kayser EB, Suthammarak W, Morgan PG, Sedensky MM (2011). Isoflurane selectively inhibits distal mitochondrial complex I in *Caenorhabditis elegans*. Anesth Analg. 112(6):1321–9. https://doi.org/10.1213/ANE.0b013e3182121d37https://doi.org/10.1213/ANE.0b013e3182121d37 PMID:21467554

Keerthisinghe TP, Wang F, Wang M, Yang Q, Li J, Yang J, et al. (2020). Long-term exposure to TET increases body weight of juvenile zebrafish as indicated in host metabolism and gut microbiome. Environ Int. 139:105705. https://doi.org/10.1016/j.envint.2020.105705 PMID:32283355

Kegel P, Letzel S, Rossbach B (2014). Biomonitoring in wearers of permethrin impregnated battle dress uniforms in Afghanistan and Germany. Occup Environ Med. 71(2):112–7. https://doi.org/10.1136/oemed-2012-101279 PMID:24343973

Kelly FL, Sun J, Fischer BM, Voynow JA, Kummarapurugu AB, Zhang HL, et al. (2014). Diacetyl induces amphiregulin shedding in pulmonary epithelial cells and in experimental bronchiolitis obliterans. Am J Respir Cell Mol Biol. 51(4):568–74. https://doi.org/10.1165/rcmb.2013-0339OChttps://doi.org/10.1165/rcmb.2013-0339OC PMID:24816162

Kelly FL, Weinberg KE, Nagler AE, Nixon AB, Star MD, Todd JL, et al. (2019). EGFR-dependent IL8 production by airway epithelial cells after exposure to the food flavoring chemical 2,3-butanedione. Toxicol Sci. 169(2):534–42. https://doi.org/10.1093/toxsci/kfz066 PMID:30851105

Kennedy L, Sandhu JK, Harper ME, Cuperlovic-Culf M (2020). Role of glutathione in cancer: from mechanisms to therapies. Biomolecules. 10(10):1–27. https://doi.org/10.3390/biom10101429https://doi.org/10.3390/biom10101429 PMID:33050144

Keshet-Sitton A, Or-Chen K, Yitzhak S, Tzabary I, Haim A (2017). Light and the city: breast cancer risk factors differ between urban and rural women in Israel. Integr Cancer Ther. 16(2):176–87. https://doi.org/10.1177/1534735416660194 PMID:27440788

Kettel LM, Roseff SJ, Berga SL, Mortola JF, Yen SS (1993). Hypothalamic–pituitary–ovarian response to clomiphene citrate in women with polycystic ovary syndrome. Fertil Steril. 59(3):532–8. https://doi.org/10.1016/S0015-0282(16)55795-1 PMID:8458453

Kettner NM, Voicu H, Finegold MJ, Coarfa C, Sreekumar A, Putluri N, et al. (2016). Circadian homeostasis of liver metabolism suppresses hepatocarcinogenesis. Cancer Cell. 30(6):909–24. https://doi.org/10.1016/j.ccell.2016.10.007 PMID:27889186

Khairy MA, Lohmann R (2019). Organophosphate flame retardants in the indoor and outdoor dust and gas-phase of Alexandria, Egypt. Chemosphere. 220:275–85. https://doi.org/10.1016/j.chemosphere.2018.12.140 PMID:30590294

Khalil AM, Abu Khadra KM, Aljaberi AM, Gagaa MH, Issa HS (2014). Assessment of oxidant/antioxidant status in saliva of cell phone users. Electromagn Biol Med. 33(2):92–7. https://doi.org/10.3109/15368378.2013.783855 PMID:23781989

Khan MW, Juutilainen J, Auvinen A, Naarala J, Pukkala E, Roivainen P (2021). A cohort study on adult hematological malignancies and brain tumors in relation to magnetic fields from indoor transformer stations. Int J Hyg Environ Health. 233:113712. https://doi.org/10.1016/j.ijheh.2021.113712 PMID:33601135

Khan N, Sultana S (2004). Induction of renal oxidative stress and cell proliferation response by ferric nitrilotriacetate (Fe-NTA): diminution by soy isoflavones. Chem Biol Interact. 149(1):23–35. https://doi.org/10.1016/j.cbi.2004.06.003 PMID:15294441

Khan RB, Phulukdaree A, Chuturgoon AA (2018). Concentration-dependent effect of fumonisin B_1 on apoptosis in oesophageal cancer cells. Hum Exp Toxicol. 37(7):762–71. https://doi.org/10.1177/0960327117735570 PMID:29027485

Khan SA, Chatterton RT, Michel N, Bryk M, Lee O, Ivancic D, et al. (2012). Soy isoflavone supplementation for breast cancer risk reduction: a randomized phase II trial. Cancer Prev Res (Phila). 5(2):309–19. https://doi.org/10.1158/1940-6207.CAPR-11-0251 PMID:22307566

Kheifets L, Crespi CM, Hooper C, Cockburn M, Amoon AT, Vergara XP (2017). Residential magnetic fields exposure and childhood leukemia: a population-based case–control study in California. Cancer Causes Control. 28(10):1117–23. https://doi.org/10.1007/s10552-017-0951-6 PMID:28900736

Kieliszek M (2019). Selenium-fascinating microelement, properties and sources in food. Molecules. 24(7):1298. https://doi.org/10.3390/molecules24071298 PMID:30987088

Kielsen K, Oostenbrink LVE, von Asmuth EGJ, Jansen-Hoogendijk AM, van Ostaijen-Ten Dam MM, Ifversen M, et al. (2021). IL-7 and IL-15 levels reflect the degree of T cell depletion during lymphopenia and are associated with an expansion of effector memory T cells after pediatric hematopoietic stem cell transplantation. J Immunol. 206(12):2828–38. https://doi.org/10.4049/jimmunol.2001077 PMID:34108260

Kim A, Cohen MS (2016). The discovery of vemurafenib for the treatment of BRAF-mutated metastatic melanoma. Expert Opin Drug Discov. 11(9):907–16. https://doi.org/10.1080/17460441.2016.1201057 PMID:27327499

Kim AS, Ko HJ, Kwon JH, Lee JM (2018b). Exposure to secondhand smoke and risk of cancer in never smokers: a meta-analysis of epidemiologic studies. Int J Environ Res Public Health. 15(9):1981. https://doi.org/10.3390/ijerph15091981 PMID:30208628

Kim B, Shin JH, Kim HP, Jo MS, Kim HS, Lee JS, et al. (2022c). Assessment and mitigation of exposure of 3-D printer emissions. Front Toxicol. 3:817454. https://doi.org/10.3389/ftox.2021.817454 PMID:35295129

Kim C, Jeong SH, Kim J, Kang JY, Nam YJ, Togloom A, et al. (2021b). Evaluation of the long-term effect of polyhexamethylene guanidine phosphate in a rat lung model using conventional chest computed tomography with histopathologic analysis. PLoS One. 16(9):e0256756. https://doi.org/10.1371/journal.pone.0256756 PMID:34492061

Kim C, Jeong SH, Kim J, Lee KY, Cha J, Lee CH, et al. (2021a). Evaluation of polyhexamethylene guanidine-induced lung injuries by chest CT, pathologic examination, and RNA sequencing in a rat model. Sci Rep. 11(1):6318. https://doi.org/10.1038/s41598-021-85662-z PMID:33737587

Kim IY, Shin JH, Kim HS, Lee SJ, Kang IH, Kim TS, et al. (2004). Assessing estrogenic activity of pyrethroid insecticides using in vitro combination assays. J Reprod Dev. 50(2):245–55. https://doi.org/10.1262/jrd.50.245 PMID:15118252

Kim JE, Lee S, Lee AY, Seo HW, Chae C, Cho MH (2015a). Intratracheal exposure to multi-walled carbon nanotubes induces a nonalcoholic steatohepatitis-like phenotype in C57BL/6J mice. Nanotoxicology. 9(5):613–23. https://doi.org/10.3109/17435390.2014.963186 PMID:25265201

Kim JY, Yi BR, Go RE, Hwang KA, Nam KH, Choi KC (2014b). Methoxychlor and triclosan stimulates ovarian cancer growth by regulating cell cycle- and apoptosis-related genes via an estrogen receptor-dependent pathway. Environ Toxicol Pharmacol. 37(3):1264–74. https://doi.org/10.1016/j.etap.2014.04.013 PMID:24835555

Kim K, Sung HK, Jang J, Kang CM, Lee K, Park SK (2022a). Biological assessment of potential exposure to occupational substances in current semiconductor workers with at least 5 years of employment. Int J Environ Res Public Health. 19(14):8737. https://doi.org/10.3390/ijerph19148737 PMID:35886589

Kim K, Sung HK, Lee K, Park SK (2022b). Semiconductor work, leukemia, and cancer risk: a systematic review and meta-analysis. Int J Environ Res Public Health. 19(22):14733. https://doi.org/10.3390/ijerph192214733 PMID:36429453

Kim KH, Kabir E, Jahan SA (2016). Review of electronic cigarettes as tobacco cigarette substitutes: their potential human health impact. J Environ Sci Health Part C Environ Carcinog Ecotoxicol Rev. 34(4):262–75. https://doi.org/10.1080/10590501.2016.1236604 PMID:27635466

Kim M, Park J, An G, Lim W, Song G (2023). Pendimethalin exposure disrupts mitochondrial function and impairs processes related to implantation. Reproduction. 165(5):491–505. https://doi.org/10.1530/REP-22-0397 PMID:36847425

Kim MH, Kim H, Paek D (2014a). The health impacts of semiconductor production: an epidemiologic review. Int J Occup Environ Health. 20(2):95–114. https://doi.org/10.1179/2049396713Y.0000000050 PMID:24999845

Kim S, Yang X, Yin A, Zha J, Beharry Z, Bai A, et al. (2019). Dietary palmitate cooperates with Src kinase to promote prostate tumor progression. Prostate. 79(8):896–908. https://doi.org/10.1002/pros.23796 PMID:30900312

Kim S, Yoon C, Ham S, Park J, Kwon O, Park D, et al. (2018c). Chemical use in the semiconductor manufacturing industry. Int J Occup Environ Health. 24(3–4):109–18. https://doi.org/10.1080/10773525.2018.1519957 PMID:30281405

Kim SH, Hwang KA, Shim SM, Choi KC (2015b). Growth and migration of LNCaP prostate cancer cells are promoted by triclosan and benzophenone-1 via an androgen receptor signalling pathway. Environ Toxicol Pharmacol. 39(2):568–76. https://doi.org/10.1016/j.etap.2015.01.003 PMID:25682003

Kim SH, Singh MP, Sharma C, Kang SC (2018a). Fumonisin B1 actuates oxidative stress-associated colonic damage via apoptosis and autophagy activation in murine model. J Biochem Mol Toxicol. 22(7):e22161. https://doi.org/10.1002/jbt.22161 PMID:29785744

Kimura M, Fujii Y, Yamamoto R, Yafune A, Hayashi SM, Suzuki K, et al. (2013). Involvement of multiple cell cycle aberrations in early preneoplastic liver cell lesions by tumor promotion with thioacetamide in a two-stage rat hepatocarcinogenesis model. Exp Toxicol Pathol. 65(7–8):979–88. https://doi.org/10.1016/j.etp.2013.01.012 PMID:23474136

Kimura M, Mizukami S, Watanabe Y, Hasegawa-Baba Y, Onda N, Yoshida T, et al. (2015). Disruption of spindle checkpoint function ahead of facilitation of cell proliferation by repeated administration of hepatocarcinogens in rats. J Toxicol Sci. 40(6):855–71. https://doi.org/10.2131/jts.40.855https://doi.org/10.2131/jts.40.855 PMID:26558467

Kimura M, Mizukami S, Watanabe Y, Onda N, Yoshida T, Shibutani M (2016). Aberrant cell cycle regulation in rat liver cells induced by post-initiation treatment with hepatocarcinogens/hepatocarcinogenic tumor promoters. Exp Toxicol Pathol. 68(7):399–408. https://doi.org/10.1016/j.etp.2016.06.002https://doi.org/10.1016/j.etp.2016.06.002 PMID:27402199

King TO (1976). Target organ toxicity of GS-6244 (carbadox) and CP-17,056 (desoxycarbadox) with chronic administration in rats. Unpublished. Submitted to WHO by Pfizer Central Research, Groton, CT, USA.

Kinslow CJ, DeStephano DM, Rohde CH, Kachnic LA, Cheng SK, Neugut AI, et al. (2022a). Risk of anaplastic large cell lymphoma following postmastectomy implant reconstruction in women with breast cancer and ductal carcinoma in situ. JAMA Netw Open. 5(11):e2243396. https://doi.org/10.1001/jamanetworkopen.2022.43396 PMID:36413370

Kinslow CJ, Kim A, Sanchez GI, Cheng SK, Kachnic LA, Neugut AI, et al. (2022b). Incidence of anaplastic large-cell lymphoma of the breast in the US, 2000 to 2018. JAMA Oncol. 8(9):1354–6. https://doi.org/10.1001/jamaoncol.2022.2624 PMID:35862042

Kirkland D, Aardema MJ, Battersby RV, Beevers C, Burnett K, Burzlaff A, et al. (2022). A weight of evidence review of the genotoxicity of titanium dioxide (TiO_2). Regul Toxicol Pharmacol. 136:105263. https://doi.org/10.1016/j.yrtph.2022.105263 PMID:36228836

Kirkland D, Kovochich M, More SL, Murray FJ, Monnot AD, Miller JV, et al. (2021). A comprehensive weight of evidence assessment of published acetaminophen genotoxicity data: implications for its carcinogenic hazard potential. Regul Toxicol Pharmacol. 122:104892. https://doi.org/10.1016/j.yrtph.2021.104892 PMID:33592196

Kisby GE, Muniz JF, Scherer J, Lasarev MR, Koshy M, Kow YW, et al. (2009). Oxidative stress and DNA damage in agricultural workers. J Agromedicine. 14(2):206–14. https://doi.org/10.1080/10599240902824042 PMID:19437279

Kiselev VI, Ashrafyan LA, Muyzhnek EL, Gerfanova EV, Antonova IB, Aleshikova OI, et al. (2018). A new promising way of maintenance therapy in advanced ovarian cancer: a comparative clinical study. BMC Cancer. 18(1):904. https://doi.org/10.1186/s12885-018-4792-9 PMID:30236079

Kiss I, Kuhn M, Hrusak K, Buchler B, Boublikova L, Buchler T (2022). Insomnia in patients treated with checkpoint inhibitors for cancer: a meta-analysis. Front Oncol. 12:946307. https://doi.org/10.3389/fonc.2022.946307 PMID:35982959

Kjaerstad MB, Taxvig C, Andersen HR, Nellemann C (2010). Mixture effects of endocrine disrupting compounds in vitro. Int J Androl. 33(2):425–33. https://doi.org/10.1111/j.1365-2605.2009.01034.x PMID:20132345

Klaunig JE, Babich MA, Baetcke KP, Cook JC, Corton JC, David RM, et al. (2003). PPARalpha agonist-induced rodent tumors: modes of action and human relevance. Crit Rev Toxicol. 33(6):655–780.

https://doi.org/10.1080/713608372 PMID:14727734

Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. (2011). Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 306(14):1549–56. https://doi.org/10.1001/jama.2011.1437 PMID:21990298

Kleinjans JC, Albering HJ, Marx A, van Maanen JM, van Agen B, ten Hoor F, et al. (1991). Nitrate contamination of drinking water: evaluation of genotoxic risk in human populations. Environ Health Perspect. 94:189–93. PMID:1954930

Kliemann N, Rauber F, Bertazzi Levy R, Viallon V, Vamos EP, Cordova R, et al. (2023). Food processing and cancer risk in Europe: results from the prospective EPIC cohort study. Lancet Planet Health. 7(3):e219–32. https://doi.org/10.1016/S2542-5196(23)00021-9 PMID:36889863

Klingelhöfer D, Braun M, Brüggmann D, Groneberg DA (2022). Neonicotinoids: a critical assessment of the global research landscape of the most extensively used insecticide. Environ Res. 213:113727. https://doi.org/10.1016/j.envres.2022.113727 PMID:35732199

Klotz DM, Arnold SF, McLachlan JA (1997). Inhibition of 17 beta-estradiol and progesterone activity in human breast and endometrial cancer cells by carbamate insecticides. Life Sci. 60(17):1467–75. https://doi.org/10.1016/S0024-3205(97)00098-2 PMID:9126867

Klufah F, Mobaraki G, Chteinberg E, Alharbi RA, Winnepenninckx V, Speel EJM, et al. (2020). High prevalence of human polyomavirus 7 in cholangiocarcinomas and adjacent peritumoral hepatocytes: preliminary findings. Microorganisms. 8(8):1125. https://doi.org/10.3390/microorganisms8081125 PMID:32726909

Klufah F, Mobaraki G, Liu D, Alharbi RA, Kurz AK, Speel EJM, et al. (2021). Emerging role of human polyomaviruses 6 and 7 in human cancers. Infect Agent Cancer. 16(1):35. https://doi.org/10.1186/s13027-021-00374-3 PMID:34001216

Kluger N, Seité S, Taieb C (2019). The prevalence of tattooing and motivations in five major countries over the world. J Eur Acad Dermatol Venereol. 33(12):e484–6. https://doi.org/10.1111/jdv.15808 PMID:31310367

Knipe H (2023). Gadoxetate disodium. Cotham (VIC), Australia: Radiopaedia. Available from: https://radiopaedia.org/articles/gadoxetate-disodium, accessed September 2024.

Knuckles ME, Inyang F, Ramesh A (2004). Acute and subchronic oral toxicity of fluoranthene in F-344 rats. Ecotoxicol Environ Saf. 59(1):102–8. https://doi.org/10.1016/S0147-6513(03)00110-6 PMID:15261730

Knutsen HK, Barregård L, Bignami M, Brüschweiler B, Ceccatelli S, Cottrill B, et al.; EFSA Panel on Contaminants in the Food Chain (CONTAM) (2018). Appropriateness to set a group health-based guidance value for fumonisins and their modified forms. EFSA J. 16(2):e05172. PMID:32625807

Kobayashi H, Ming ZW, Watanabe H, Ohnishi Y (1987). A quantitative study on the distribution of asbestos bodies in extrapulmonary organs. Acta Pathol Jpn. 37(3):375–83. https://doi.org/10.1111/j.1440-1827.1987.tb00372.x PMID:3618215

Kobayashi K, Inada K, Furihata C, Tsukamoto T, Ikehara Y, Yamamoto M, et al. (1999). Effects of low dose catechol on glandular stomach carcinogenesis in BALB/c mice initiated with *N*-methyl-*N*-nitrosourea. Cancer Lett. 139(2):167–72. https://doi.org/10.1016/S0304-3835(99)00037-3 PMID:10395174

Kobayashi K, Shimizu N, Tsukamoto T, Inada K, Nakanishi H, Goto K, et al. (1997). Dose-dependent promoting effects of catechol on glandular stomach carcinogenesis in BALB/c mice initiated with *N*-methyl-*N*-nitrosourea. Jpn J Cancer Res. 88(12):1143–8. https://doi.org/10.1111/j.1349-7006.1997.tb00342.x PMID:9473731

Koch C, Sures B (2018). Environmental concentrations and toxicology of 2,4,6-tribromophenol (TBP). Environ Pollut. 233:706–13. https://doi.org/10.1016/j.envpol.2017.10.127 PMID:29126092

Koehler C, Ginzkey C, Friehs G, Hackenberg S, Froelich K, Scherzed A, et al. (2010). Aspects of nitrogen dioxide toxicity in environmental urban concentrations in human nasal epithelium. Toxicol Appl Pharmacol. 245(2):219–25. https://doi.org/10.1016/j.taap.2010.03.003 PMID:20214917

Koehler C, Ginzkey C, Friehs G, Hackenberg S, Froelich K, Scherzed A, et al. (2011). Ex vivo toxicity of nitrogen dioxide in human nasal epithelium at the WHO defined 1-h limit value. Toxicol Lett. 207(1):89–95. https://doi.org/10.1016/j.toxlet.2011.08.004 PMID:21864657

Koehler C, Thielen S, Ginzkey C, Hackenberg S, Scherzed A, Burghartz M, et al. (2013). Nitrogen dioxide is genotoxic in urban concentrations. Inhal Toxicol. 25(6):341–7. https://doi.org/10.3109/08958378.2013.788104 PMID:23701639

Koeman T, van den Brandt PA, Slottje P, Schouten LJ, Goldbohm RA, Kromhout H, et al. (2014). Occupational extremely low-frequency magnetic field exposure and selected cancer outcomes in a prospective Dutch cohort. Cancer Causes Control. 25(2):203–14. https://doi.org/10.1007/s10552-013-0322-x PMID:24241907

Kohara A, Suzuki T, Honma M, Hirano N, Ohsawa K, Ohwada T, et al. (2001). Mutation spectrum of o-aminoazotoluene in the cII gene of lambda/lacZ transgenic mice (MutaMouse). Mutat Res. 491(1–2):211–20. https://doi.org/10.1016/S1383-5718(01)00143-7https://doi.org/10.1016/S1383-5718(01)00143-7 PMID:11287313

Kohn DB, Sadelain M, Glorioso JC (2003). Occurrence of leukaemia following gene therapy of X-linked SCID [published correction appears in Nat Rev Cancer. (2003) 3(11):883]. Nat Rev Cancer. 3(7):477–88. https://doi.org/10.1038/nrc1122 PMID:12835668

Kokova D, Verhoeven A, Perina EA, Ivanov VV, Heijink M, Yazdanbakhsh M, et al. (2021). Metabolic homeostasis in chronic helminth infection is sustained by organ-specific metabolic rewiring. ACS Infect Dis. 7(4):906–16. https://doi.org/10.1021/acsinfecdis.1c00026 PMID:33764039

Kokova D, Verhoeven A, Perina EA, Ivanov VV, Knyazeva EM, Saltykova IV, et al. (2020). Plasma metabolomics of the time resolved response to *Opisthorchis felineus* infection in an animal model (golden hamster, *Mesocricetus auratus*). PLoS Negl Trop Dis. 14(1):e0008015. https://doi.org/10.1371/journal.pntd.0008015 PMID:31978047

Koller LD, Kerkvliet NI, Exon JH (1985). Neoplasia induced in male rats fed lead acetate, ethyl urea, and sodium nitrite. Toxicol Pathol. 13(1):50–7. https://doi.org/10.1177/019262338501300107 PMID:4035262

Kolling A, Ernst H, Rittinghausen S, Heinrich U (2011). Relationship of pulmonary toxicity and carcinogenicity of fine and ultrafine granular dusts in a rat bioassay. Inhal Toxicol. 23(9):544–54. https://doi.org/10.3109/08958378.2011.594458 PMID:21819261

Kollmann Z, Schneider S, Fux M, Bersinger NA, von Wolff M (2017). Gonadotrophin stimulation in IVF alters the immune cell profile in follicular fluid and the cytokine concentrations in follicular fluid and serum. Hum Reprod. 32(4):820–31. https://doi.org/10.1093/humrep/dex005 PMID:28201504

Komakech R, Kang Y, Lee JH, Omujal F (2017). A review of the potential of phytochemicals from *Prunus africana* (Hook f.) kalkman stem bark for chemoprevention and chemotherapy of prostate cancer. Evid Based Complement Alternat Med. 2017(1):3014019. https://doi.org/10.1155/2017/3014019https://doi.org/10.1155/2017/3014019 PMID:28286531

Könen-Adıgüzel S, Ergene S (2018). In vitro evaluation of the genotoxicity of CeO_2 nanoparticles in human peripheral blood lymphocytes using cytokinesis–block micronucleus test, comet assay, and gamma H2AX. Toxicol Ind Health. 34(5):293–300. https://doi.org/10.1177/0748233717753780 PMID:29554819

Kong DL, Kong FY, Liu XY, Yan C, Cui J, Tang RX, et al. (2019). Soluble egg antigen of *Schistosoma japonicum* induces pyroptosis in hepatic stellate cells by modulating ROS production. Parasit Vectors. 12(1):475. https://doi.org/10.1186/s13071-019-3729-8 PMID:31610797

Kongtip P, Nankongnab N, Pundee R, Kallayanatham N, Pengpumkiat S, Chungcharoen J, et al. (2021). Acute changes in thyroid hormone levels among Thai pesticide sprayers. Toxics. 9(1):16. https://doi.org/10.3390/toxics9010016 PMID:33477987

Kongtip P, Sasrisuk S, Preklang S, Yoosook W, Sujirarat D (2013). Assessment of occupational exposure to malathion and bifenthrin in mosquito control sprayers through dermal contact. J Med Assoc Thai. 96(Suppl 5):S82–91. https://www.thaiscience.info/journals/Article/JMAT/10905979.pdf PMID:24851577

Kose O, Rachidi W, Beal D, Erkekoglu P, Fayyad-Kazan H, Kocer Gumusel B (2020). The effects of different bisphenol derivatives on oxidative stress, DNA damage and DNA repair in RWPE-1 cells: a comparative study. J Appl Toxicol. 40(5):643–54. https://doi.org/10.1002/jat.3934 PMID:31875995

Koshiol J, Gao YT, Dean M, Egner P, Nepal C, Jones K, et al. (2017). Association of aflatoxin and gallbladder cancer. Gastroenterology. 153(2):488–494.e1. https://doi.org/10.1053/j.gastro.2017.04.005 PMID:28428144

Koshiol J, Wozniak A, Cook P, Adaniel C, Acevedo J, Azócar L, et al.; Gallbladder Cancer Chile Working Group (2016). *Salmonella enterica* serovar Typhi and gallbladder cancer: a case–control study and meta-analysis. Cancer Med. 5(11):3310–3235. https://doi.org/10.1002/cam4.915 PMID:27726295

Koshiol J, Zhu B, Wang R, Hildesheim A, Gao YT, Egner PA, et al. (2024). Association of aflatoxin with gallbladder cancer in a case–control study nested within a Chinese cohort. Int J Cancer. 154(5):801–6. https://doi.org/10.1002/ijc.34755 PMID:37840351

Koshlukova SE, Reed NR (2014). Carbaryl. In: Encyclopedia of toxicology. Third Edition. pp. 668–672. Amsterdam, Netherlands: Elsevier. Available from:

Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, et al. (2013). *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe. 14(2):207–15. https://doi.org/10.1016/j.chom.2013.07.007 PMID:23954159

Kotepui KU, Kotepui M (2021). Malaria infection and risk for endemic Burkitt lymphoma: a systematic review and meta-analysis. Int J Environ Res Public Health. 18(11):5886. https://doi.org/10.3390/ijerph18115886 PMID:34070881

Kotin P, Falk HL (1963). Organic peroxides, hydrogen peroxide, epoxides, and neoplasia. Radiat Res. Suppl 3:193–211. PMID:14035075

Kotseva K (2001). Occupational exposure to low concentrations of carbon disulfide as a risk factor for hypercholesterolaemia. Int Arch Occup Environ Health. 74(1):38–42. https://doi.org/10.1007/s004200000186 PMID:11196079

Koutros S, Beane Freeman LE, Berndt SI, Andreotti G, Lubin JH, Sandler DP, et al. (2010). Pesticide use modifies the association between genetic variants on chromosome 8q24 and prostate cancer. Cancer Res. 70(22):9224–33. https://doi.org/10.1158/0008-5472.CAN-10-1078 PMID:20978189

Koutros S, Beane Freeman LE, Lubin JH, Heltshe SL, Andreotti G, Barry KH, et al. (2013). Risk of total and aggressive prostate cancer and pesticide use in the Agricultural Health Study. Am J Epidemiol. 177(1):59–74. https://doi.org/10.1093/aje/kws225 PMID:23171882

Koutros S, Harris SA, Spinelli JJ, Blair A, McLaughlin JR, Zahm SH, et al. (2019). Non-Hodgkin lymphoma risk and organophosphate and carbamate insecticide use in the north American pooled project. Environ Int. 127:199–205. https://doi.org/10.1016/j.envint.2019.03.018 PMID:30928843

Kovshirina YV, Fedorova OS, Vtorushin SV, Kovshirina AE, Ivanov SD, Chizhikov AV, et al. (2019). Case report: two cases of cholangiocarcinoma in patients with *Opisthorchis felineus* infection in Western Siberia, Russian Federation. Am J Trop Med Hyg. 100(3):599–603. https://doi.org/10.4269/ajtmh.18-0652 PMID:30594265

Kowalska K, Habrowska-Górczyńska DE, Domińska K, Urbanek KA, Piastowska-Ciesielska AW (2020). ERβ and NFκB-modulators of zearalenone-induced oxidative stress in human prostate cancer cells. Toxins (Basel). 12(3):199. https://doi.org/10.3390/toxins12030199 PMID:32235729

Kowalska K, Habrowska-Górczyńska DE, Urbanek KA, Domińska K, Piastowska-Ciesielska AW (2018). Estrogen receptor α is crucial in zearalenone-induced invasion and migration of prostate cancer cells. Toxins (Basel). 10(3):98. https://doi.org/10.3390/toxins10030098 PMID:29495557

Kraav SL, Lehto SM, Kauhanen J, Hantunen S, Tolmunen T (2021). Loneliness and social isolation increase cancer incidence in a cohort of Finnish middle-aged men. A longitudinal study. Psychiatry Res. 299:113868. https://doi.org/10.1016/j.psychres.2021.113868https://doi.org/10.1016/j.psychres.2021.113868 PMID:33774371

Krasner SW, Kostopoulou M, Toledano MB, Wright J, Patelarou E, Kogevinas M, et al. (2016a). Occurrence of DBPs in drinking water of European regions for epidemiology studies. J Am Water Works Assoc. 108(10):E501E512. https://doi.org/10.5942/jawwa.2016.108.0152

Kreiss K, Cox-Ganser J (1997). Metalworking fluid-associated hypersensitivity pneumonitis: a workshop summary. Am J Ind Med. 32(4):423–32. https://doi.org/10.1002/(SICI)1097-0274(199710)32:4<423::AID-AJIM16>3.0.CO;2-5 PMID:9258399

Kreuzer M, Walsh L, Schnelzer M, Tschense A, Grosche B (2008). Radon and risk of extrapulmonary cancers: results of the German uranium miners' cohort study, 1960–2003. Br J Cancer. 99(11):1946–53.

https://doi.org/10.1038/sj.bjc.6604776 PMID:19002172

Kricker A, Weber MF, Brenner N, Banks E, Pawlita M, Sitas F, et al. (2020). High ambient solar UV correlates with greater beta HPV seropositivity in New South Wales, Australia. Cancer Epidemiol Biomarkers Prev. 29(1):49–56. https://doi.org/10.1158/1055-9965.EPI-19-0400 PMID:31597664

Kricker A, Weber MF, Pawlita M, Sitas F, Hodgkinson VS, Rahman B, et al. (2022). Cutaneous β HPVs, sun exposure, and risk of squamous and basal cell skin cancers in Australia. Cancer Epidemiol Biomarkers Prev. 31(3):614–24. https://doi.org/10.1158/1055-9965.EPI-21-1000 PMID:34933956

Krikun G, Sakkas D, Schatz F, Buchwalder L, Hylton D, Tang C, et al. (2004). Endometrial angiopoietin expression and modulation by thrombin and steroid hormones: a mechanism for abnormal angiogenesis following long-term progestin-only contraception. Am J Pathol. 164(6):2101–7. https://doi.org/10.1016/S0002-9440(10)63768-6 PMID:15161644

Krishnamachari KA, Bhat RV, Nagarajan V, Tilak TB (1975). Hepatitis due to aflatoxicosis. An outbreak in Western India. Lancet. 1(7915):1061–3. https://doi.org/10.1016/S0140-6736(75)91829-2 PMID:48730

Kroenke CH, Kubzansky LD, Schernhammer ES, Holmes MD, Kawachi I (2006). Social networks, social support, and survival after breast cancer diagnosis. J Clin Oncol. 24(7):1105–11. https://doi.org/10.1200/JCO.2005.04.2846https://doi.org/10.1200/JCO.2005.04.2846 PMID:16505430

Krsak M, Wada NI, Plankey MW, Kinney GL, Epeldegui M, Okafor CN, et al. (2021). Self-reported cannabis use and markers of inflammation in men who have sex with men with and without HIV. Cannabis Cannabinoid Res. 6(2):165–73. https://doi.org/10.1089/can.2019.0083 PMID:33912681

Krüger CT, Lachenmeier DW, Kratz E, Mildau G (2013). Rapid colorimetric analysis of para-phenylenediamine in henna-based, non-permanent tattoo color mixtures. Cosmetics and Toiletries magazine. 126(7):496–501. https://www.cosmeticsandtoiletries.com/testing/method-process/article/21837039/rapid-colorimetric-analysis-of-para-phenylenediamine-in-henna-based-non-permanent-tattoo-color-mixtures

Ksheerasagar RL, Kaliwal BB (2003). Temporal effects of mancozeb on testes, accessory reproductive organs and biochemical constituents in albino mice. Environ Toxicol Pharmacol. 15(1):9–17. https://doi.org/10.1016/j.etap.2003.08.006https://doi.org/10.1016/j.etap.2003.08.006 PMID:21782674.

Kugathas S, Audouze K, Ermler S, Orton F, Rosivatz E, Scholze M, et al. (2016). Effects of common pesticides on prostaglandin D2 (PGD2) inhibition in SC5 mouse Sertoli cells, evidence of binding at the COX-2 active site, and implications for endocrine disruption. Environ Health Perspect. 124(4):452–9. https://doi.org/10.1289/ehp.1409544 PMID:26359731

Kuijpers E, Bekker C, Fransman W, Brouwer D, Tromp P, Vlaanderen J, et al. (2016). Occupational exposure to multi-walled carbon nanotubes during commercial production synthesis and handling. Ann Occup Hyg. 60(3):305–17. https://doi.org/10.1093/annhyg/mev082 PMID:26613611

Kumah EA, Fopa RD, Harati S, Boadu P, Zohoori FV, Pak T (2023). Human and environmental impacts of nanoparticles: a scoping review of the current literature. BMC Public Health. 23(1):1059. https://doi.org/10.1186/s12889-023-15958-4 PMID:37268899

Kumar A, Lubet RA, Fox JT, Nelson WG, Seifried H, Grubbs CJ, et al. (2021). Effects of high-fructose diet *vs*. Teklad diet in the MNU-induced rat mammary cancer model: altered tumorigenesis, metabolomics and tumor RNA expression. J Obes Chronic Dis. 5(1):67–78. https://doi.org/10.17756/jocd.2021-041 PMID:33834161

Kumar S, Khodoun M, Kettleson EM, McKnight C, Reponen T, Grinshpun SA, et al. (2014). Glyphosate-rich air samples induce IL-33, TSLP and generate IL-13 dependent airway inflammation. Toxicology. 325:42–51. https://doi.org/10.1016/j.tox.2014.08.008 PMID:25172162

Kumar S, Xie H, Shi H, Gao J, Juhlin CC, Björnhagen V, et al. (2020). Merkel cell polyomavirus oncoproteins induce microRNAs that suppress multiple autophagy genes. Int J Cancer. 146(6):1652–66. https://doi.org/10.1002/ijc.32503 PMID:31180579

Kumarasamy C, Pisaniello D, Gaskin S, Hall T (2022). What do safety data sheets for artificial stone products tell us about composition? A comparative analysis with physicochemical data. Ann Work Expo Health. 66(7):937–45. https://doi.org/10.1093/annweh/wxac020 PMID:35411922

Kumari M, Kumari SI, Grover P (2014b). Genotoxicity analysis of cerium oxide micro and nanoparticles in Wistar rats after 28 days of repeated oral administration. Mutagenesis. 29(6):467–79. https://doi.org/10.1093/mutage/geu038 PMID:25209125

Kumari M, Kumari SI, Kamal SS, Grover P (2014a). Genotoxicity assessment of cerium oxide nanoparticles in female Wistar rats after acute oral exposure. Mutat Res Genet Toxicol Environ Mutagen. 775–776:7–19. https://doi.org/10.1016/j.mrgentox.2014.09.009 PMID:25435351

Kumle M, Weiderpass E, Braaten T, Persson I, Adami HO, Lund E (2002). Use of oral contraceptives and breast cancer risk: The Norwegian-Swedish Women's Lifestyle and Health Cohort Study. Cancer Epidemiol Biomarkers Prev. 11(11):1375–81. https://aacrjournals.org/cebp/article/11/11/1375/166628/Use-of-Oral-Contraceptives-and-Breast-Cancer PMID:12433714

Kundu N, Domingues CC, Patel J, Aljishi M, Ahmadi N, Fakhri M, et al. (2020). Sucralose promotes accumulation of reactive oxygen species (ROS) and adipogenesis in mesenchymal stromal cells. Stem Cell Res Ther. 11(1):250. https://doi.org/10.1186/s13287-020-01753-0 PMID:32586409

Kurl RN, Morris ID (1978). Differential depletion of cytoplasmic high affinity oestrogen receptors after the in vivo administration of the antioestrogens, clomiphene, MER-25 and tamoxifen. Br J Pharmacol. 62(4):487–93. https://doi.org/10.1111/j.1476-5381.1978.tb07752.x PMID:656695

Kuroda K, Terao K, Akao M (1987). Inhibitory effect of fumaric acid on hepatocarcinogenesis by thioacetamide in rats. J Natl Cancer Inst. 79(5):1047–51. PMID:3479633

Kurt A, Aygun AD, Kurt AN, Godekmerdan A, Akarsu S, Yilmaz E (2009). Use of phototherapy for neonatal hyperbilirubinemia affects cytokine production and lymphocyte subsets. Neonatology. 95(3):262–6. https://doi.org/10.1159/000171216 PMID:19005263

Kurttio P, Savolainen K (1990). Ethylenethiourea in air and in urine as an indicator of exposure to ethylenebisdithiocarbamate fungicides. Scand J Work Environ Health. 16(3):203–7. https://doi.org/10.5271/sjweh.1793 PMID:2382123

Kurttio P, Savolainen K, Tuominen R, Kosma VM, Naukkarinen A, Männistö P, et al. (1986). Ethylenethiourea and nabam induced alterations of function and morphology of thyroid gland in rats. Arch Toxicol Suppl. 9:339–44. https://doi.org/10.1007/978-3-642-71248-7_61 PMID:3468914

Kwak K, Paek D, Zoh KE (2019). Exposure to asbestos and the risk of colorectal cancer mortality: a systematic review and meta-analysis. Occup Environ Med. 76(11):861–71. https://doi.org/10.1136/oemed-2019-105735 PMID:31594840

Kwapniewski R, Kozaczka S, Hauser R, Silva MJ, Calafat AM, Duty SM (2008). Occupational exposure to dibutyl phthalate among manicurists. J Occup Environ Med. 50(6):705–11. https://doi.org/10.1097/JOM.0b013e3181651571 PMID:18545098

Kwiatkowska M, Reszka E, Woźniak K, Jabłońska E, Michałowicz J, Bukowska B (2017). DNA damage and methylation induced by glyphosate in human peripheral blood mononuclear cells (in vitro study). Food Chem Toxicol. 105:93–8. https://doi.org/10.1016/j.fct.2017.03.051 PMID:28351773

Kyba CCM, Altıntaş YÖ, Walker CE, Newhouse M (2023). Citizen scientists report global rapid reductions in the visibility of stars from 2011 to 2022. Science. 379(6629):265–8. https://doi.org/10.1126/science.abq7781 PMID:36656932

Kyba CCM, Kuester T, Sánchez de Miguel A, Baugh K, Jechow A, Hölker F, et al. (2017). Artificially lit surface of Earth at night increasing in radiance and extent. Sci Adv. 3(11):e1701528. https://doi.org/10.1126/sciadv.1701528 PMID:29181445

Kyjovska ZO, Jacobsen NR, Saber AT, Bengtson S, Jackson P, Wallin H, et al. (2015). DNA damage following pulmonary exposure by instillation to low doses of carbon black (Printex 90) nanoparticles in mice. Environ Mol Mutagen. 56(1):41–9. https://doi.org/10.1002/em.21888 PMID:25042074

Kyte SL, Gewirtz DA (2018). The influence of nicotine on lung tumor growth, cancer chemotherapy, and chemotherapy-induced peripheral neuropathy. J Pharmacol Exp Ther. 366(2):303–13. https://doi.org/10.1124/jpet.118.249359 PMID:29866790

La DK, Froines JR (1994). Formation and removal of DNA adducts in Fischer-344 rats exposed to 2,4-diaminotoluene. Arch Toxicol. 69(1):8–13. https://doi.org/10.1007/s002040050129 PMID:7717858

Labrèche F, Goldberg MS, Valois MF, Nadon L (2010). Postmenopausal breast cancer and occupational exposures. Occup Environ Med. 67(4):263–9. https://doi.org/10.1136/oem.2009.049817 PMID:20360196

Lachenmeier DW, Neufeld M, Rehm J (2021). The impact of unrecorded alcohol use on health: what do we know in 2020? J Stud Alcohol Drugs. 82(1):28–41. https://doi.org/10.15288/jsad.2021.82.28 PMID:33573720

Ladd-Acosta C, Feinberg JI, Brown SC, Lurmann FW, Croen LA, Hertz-Picciotto I, et al. (2019). Epigenetic marks of prenatal air pollution exposure found in multiple tissues relevant for child health. Environ Int. 126:363–76. https://doi.org/10.1016/j.envint.2019.02.028 PMID:30826615

LaDou J, Harrison RJ, editors (2013). Current Diagnosis & Treatment: Occupational & Environmental Medicine. 5th Edition. New York (NY), USA: McGraw–Hill Education. Available from: https://accessmedicine.mhmedical.com/content.aspx?bookid=1186&sectionid=66477163

Lafranconi M, Anderson J, Budinsky R, Corey L, Forsberg N, Klapacz J, et al. (2023). An integrated assessment of the 1,4-dioxane cancer mode of action and threshold response in rodents. Regul Toxicol Pharmacol. 142:105428. https://doi.org/10.1016/j.yrtph.2023.105428 PMID:37277058

Lagorio S, Blettner M, Baaken D, Feychting M, Karipidis K, Loney T, et al. (2021). The effect of exposure to radiofrequency fields on cancer risk in the general and working population: a protocol for a systematic review of human observational studies. Environ Int. 157:106828. https://doi.org/10.1016/j.envint.2021.106828 PMID:34433115

Lai KC, Chen WC, Tsai FJ, Li SY, Chou MC, Jeng LB (2005). Glutathione *S*-transferase M1 gene null genotype and gastric cancer risk in Taiwan. Hepatogastroenterology. 52(66):1916–9. PMID:16334806

Lai KY, Sarkar C, Ni MY, Cheung LWT, Gallacher J, Webster C (2021). Exposure to light at night (LAN) and risk of breast cancer: a systematic review and meta-analysis. Sci Total Environ. 762:143159. https://doi.org/10.1016/j.scitotenv.2020.143159 PMID:33131852

Lakdawalla AA, Netrawali MS (1988). Mutagenicity, comutagenicity, and antimutagenicity of erythrosine (FD and C red 3), a food dye, in the Ames/*Salmonella* assay. Mutat Res. 204(2):131–9. https://doi.org/10.1016/0165-1218(88)90083-3 PMID:2830505

Lake BG, Price RJ, Scott MP, Chatham LR, Vardy A, Osimitz TG (2020). Piperonyl butoxide: mode of action analysis for mouse liver tumour formation and human relevance. Toxicology. 439:152465. https://doi.org/10.1016/j.tox.2020.152465https://doi.org/10.1016/j.tox.2020.152465 PMID:32320717

Laliberté J, Carruthers VB (2008). Host cell manipulation by the human pathogen *Toxoplasma gondii.* Cell Mol Life Sci. 65(12):1900–15. https://doi.org/10.1007/s00018-008-7556-x PMID:18327664

Lallas K, Anagnostis P, Theocharis P, Boureka E, Kyrgidis A, Klonos E, et al. (2023). The effect of menopausal hormone therapy on the risk of melanoma and keratinocyte skin cancer: a systematic review and meta-analysis of observational studies. Maturitas. 168:20–8. https://doi.org/10.1016/j.maturitas.2022.10.010 PMID:36372010

Lamartiniere CA, Jenkins S, Betancourt AM, Wang J, Russo J (2011). Exposure to the endocrine disruptor bisphenol A alters susceptibility for mammary cancer. Horm Mol Biol Clin Investig. 5(2):45–52. https://doi.org/10.1515/HMBCI.2010.075https://doi.org/10.1515/HMBCI.2010.075 PMID:21687816

Lambert B, Sten M, Söderhäll S, Ringborg U, Lewensohn R (1983). DNA repair replication, DNA breaks and sister-chromatid exchange in human cells treated with adriamycin in vitro. Mutat Res. 111(2):171–84. https://doi.org/10.1016/0027-5107(83)90061-1 PMID:6633548

Lambert CS, Alexander BH, Ramachandran G, MacLehose RF, Nelson HH, Ryan AD, et al. (2016). A case–control study of mesothelioma in Minnesota iron ore (taconite) miners. Occup Environ Med. 73(2):103–9. https://doi.org/10.1136/oemed-2015-103105 PMID:26655961

Lamkin DM, Bradshaw KP, Chang J, Epstein M, Gomberg J, Prajapati KP, et al. (2021). Physical activity modulates mononuclear phagocytes in mammary tissue and inhibits tumor growth in mice. PeerJ. 9:e10725. https://doi.org/10.7717/peerj.10725 PMID:33552733

Lamsal LN, Martin RV, Parrish DD, Krotkov NA (2013). Scaling relationship for NO_2 pollution and urban population

size: a satellite perspective. Environ Sci Technol. 47(14):7855–61. https://doi.org/10.1021/es400744g PMID:23763377

Landim BC, de Jesus MM, Bosque BP, Zanon RG, da Silva CV, Góes RM, et al. (2018). Stimulating effect of palmitate and insulin on cell migration and proliferation in PNT1A and PC3 prostate cells: counteracting role of metformin. Prostate. 78(10):731–42. https://doi.org/10.1002/pros.23517 PMID:29635803

Landmesser A, Scherer M, Scherer G, Sarkar M, Edmiston JS, Niessner R, et al. (2021). Assessment of the potential vaping-related exposure to carbonyls and epoxides using stable isotope-labeled precursors in the e-liquid. Arch Toxicol. 95(8):2667–76. https://doi.org/10.1007/s00204-021-03097-x PMID:34159432

Lanfranchi G, Paglialunga S, Levis AG (1988). Mammalian cell transformation induced by chromium(VI) compounds in the presence of nitrilotriacetic acid. J Toxicol Environ Health. 24(2):251–60. https://doi.org/10.1080/15287398809531158 PMID:3385800

Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, et al. (2014). Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 371(20):1867–76. https://doi.org/10.1056/NEJMoa1408868 PMID:25265494

Larramendy ML, Dulout FN, Bianchi NO, Olivero OA (1980). In vivo dose–response relationship in bone-marrow cells of mice treated with adriamycin. Mutat Res. 79(2):133–40. https://doi.org/10.1016/0165-1218(80)90081-6 PMID:7432371

Larsen R, Ryder LP, Svejgaard A, Gniadecki R (2007). Changes in circulating lymphocyte subpopulations following administration of the leucocyte function-associated antigen-3 (LFA-3)/IgG1 fusion protein alefacept. Clin Exp Immunol. 149(1):23–30. https://doi.org/10.1111/j.1365-2249.2007.03380.x PMID:17403057

Latifovic L, Freeman LEB, Spinelli JJ, Pahwa M, Kachuri L, Blair A, et al. (2020). Pesticide use and risk of Hodgkin lymphoma: results from the North American Pooled Project (NAPP). Cancer Causes Control. 31(6):583–99. https://doi.org/10.1007/s10552-020-01301-4 PMID:32314107

Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K; International Agency for Research on Cancer Handbook Working Group (2016). Body fatness and cancer – viewpoint of the IARC Working Group. N Engl J Med. 375(8):794–8. https://doi.org/10.1056/NEJMsr1606602 PMID:27557308

Laurent C, Nicolae A, Laurent C, Le Bras F, Haioun C, Fataccioli V, et al. (2020). Gene alterations in epigenetic modifiers and JAK-STAT signalling are frequent in breast implant-associated ALCL. Blood. 135(5):360–70. PMID:31774495

Lavigne E, Lima I, Hatzopoulou M, Van Ryswyk K, van Donkelaar A, Martin RV, et al. (2020). Ambient ultrafine particle concentrations and incidence of childhood cancers. Environ Int. 145:106135. https://doi.org/10.1016/j.envint.2020.106135 PMID:32979813

LaVoie EJ, Cai ZW, Meschter CL, Weyand EH (1994). Tumorigenic activity of fluoranthene, 2-methylfluoranthene and 3-methylfluoranthene in newborn CD-1 mice. Carcinogenesis. 15(10):2131–5. https://doi.org/10.1093/carcin/15.10.2131 PMID:7955044

LaVoie EJ, Hecht SS, Bedenko V, Hoffmann D (1982). Identification of the mutagenic metabolites of fluoranthene, 2-methylfluoranthene, and 3-methylfluoranthene. Carcinogenesis. 3(8):841–6. https://doi.org/10.1093/carcin/3.8.841 PMID:7127666

Law BF, Pearce T, Siegel PD (2007). Case study: safety and chemical exposure evaluation at a small biodiesel production facility. J Occup Environ Hyg. PMID:21667372

Lazennec G, Jorgensen C (2008). Concise review: adult multipotent stromal cells and cancer: risk or benefit? Stem Cells. 26(6):1387–94. https://doi.org/10.1634/stemcells.2007-1006 PMID:18388305

Le Y, Li X, Chen S, Ning KG, Guo X, Wu CG, et al. (2022a). Actein contributes to black cohosh extract-induced genotoxicity in human TK6 cells. J Appl Toxicol. 42(9):1491–502. https://doi.org/10.1002/jat.4313https://doi.org/10.1002/jat.4313 PMID:35261072

Le YT, Youn JS, Cho H, Jeon K, Lim J, Jeon KJ (2022b). α-Fe_2O_3 nanoparticles and hazardous air pollutants release during cooking using cast iron wok in a commercial Chinese restaurant. Environ Pollut. 307:119578. https://doi.org/10.1016/j.envpol.2022.119578 PMID:35688388

Le Deley MC, Suzan F, Cutuli B, Delaloge S, Shamsaldin A, Linassier C, et al. (2007). Anthracyclines, mitoxantrone, radiotherapy, and granulocyte colony-stimulating factor: risk factors for leukemia and myelodysplastic syndrome after breast cancer. J Clin Oncol. 25(3):292–300. https://doi.org/10.1200/JCO.2006.05.9048 PMID:17159192

Le Guennec D, Goepp M, Farges MC, Rougé S, Vasson MP, Caldefie-Chezet F, et al. (2021). Spontaneous physical activity in obese condition favours antitumour immunity leading to decreased tumour growth in a syngeneic mouse model of carcinogenesis. Cancers (Basel). 14(1):59. https://doi.org/10.3390/cancers14010059 PMID:35008220

Leal Filho W, May J, May M, Nagy GJ (2023). Climate change and malaria: some recent trends of malaria incidence rates and average annual temperature in selected sub-Saharan African countries from 2000 to 2018. Malar J. 22(1):248. https://doi.org/10.1186/s12936-023-04682-4 PMID:37641080

LeBaron MJ, Geter DR, Rasoulpour RJ, Gollapudi BB, Thomas J, Murray J, et al. (2013). An integrated approach for prospectively investigating a mode-of-action for rodent liver effects. Toxicol Appl Pharmacol. 270(2):164–73. https://doi.org/10.1016/j.taap.2013.04.009 PMID:23607986

LeBaron MJ, Gollapudi BB, Terry C, Billington R, Rasoulpour RJ (2014). Human relevance framework for rodent liver tumors induced by the insecticide sulfoxaflor. Crit Rev Toxicol. 44(sup2) Suppl 2:15–24. https://doi.org/10.3109/10408444.2014.910751 PMID:24832551

LeBoeuf RA, Laishes BA, Hoekstra WG (1985). Effects of dietary selenium concentration on the development of enzyme-altered liver foci and hepatocellular carcinoma induced by diethylnitrosamine or N-acetylaminofluorene in rats. Cancer Res. 45(11 Pt 1):5489–95. PMID:2865004

Lechasseur A, Mouchiroud M, Tremblay F, Bouffard G, Milad N, Pineault M, et al. (2022). Glycerol contained in vaping liquids affects the liver and aspects of energy homeostasis in a sex-dependent manner. Physiol Rep. 10(2):e15146. https://doi.org/10.14814/phy2.15146 PMID:35075822

Ledda C, Cannizzaro E, Cinà D, Filetti V, Vitale E, Paravizzini G, et al. (2021). Oxidative stress and DNA damage in agricultural workers after exposure to pesticides. J Occup Med Toxicol. 16(1):1. https://doi.org/10.1186/s12995-020-00290-z PMID:33413467

Lee DB, An SY, Pyo SS, Kim J, Kim SW, Yoon DW (2023a). Sleep fragmentation accelerates carcinogenesis in a chemical-induced colon cancer model. Int J Mol Sci. 24(5):4547. https://doi.org/10.3390/ijms24054547 PMID:36901981

Lee DW, Cho S, Shin A (2023b). Lymphohematopoietic cancer mortality among Korean semiconductor manufacturing workers. BMC Public Health. 23(1):1473. https://doi.org/10.1186/s12889-023-16325-z PMID:37533044

Lee H, Jeong SH, Lee H, Kim C, Nam YJ, Kang JY, et al. (2022b). Analysis of lung cancer-related genetic changes in long-term and low-dose polyhexamethylene guanidine phosphate (PHMG-p) treated human pulmonary alveolar epithelial cells. BMC Pharmacol Toxicol. 23(1):19. https://doi.org/10.1186/s40360-022-00559-5 PMID:35354498

Lee HR, Hwang KA, Nam KH, Kim HC, Choi KC (2014). Progression of breast cancer cells was enhanced by endocrine-disrupting chemicals, triclosan and octylphenol, via an estrogen receptor-dependent signalling pathway in cellular and mouse xenograft models. Chem Res Toxicol. 27(5):834–42. https://doi.org/10.1021/tx5000156 PMID:24684733

Lee HS, Amarakoon D, Tamia G, Park Y, Smolensky D, Lee SH (2022a). Pendimethalin induces apoptotic cell death through activating ER stress-mediated mitochondrial dysfunction in human umbilical vein endothelial cells. Food Chem Toxicol. 168:113370. https://doi.org/10.1016/j.fct.2022.113370 PMID:35985363

Lee HW, Park SH, Weng MW, Wang HT, Huang WC, Lepor H, et al. (2018). E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells. Proc Natl Acad Sci USA. 115(7):E1560–9. https://doi.org/10.1073/pnas.1718185115 PMID:29378943

Lee JD, Lee JY, Kwack SJ, Shin CY, Jang HJ, Kim HY, et al. (2019). Risk assessment of triclosan, a cosmetic preservative. Toxicol Res. 35(2):137–54. https://doi.org/10.5487/TR.2019.35.2.137 PMID:31015896

Lee JM, Liu TY, Wu DC, Tang HC, Leh J, Wu MT, et al. (2005). Safrole–DNA adducts in tissues from esophageal cancer patients: clues to areca-related esophageal carcinogenesis. Mutat Res. 565(2):121–8. https://doi.org/10.1016/j.mrgentox.2004.10.007 PMID:15661610

Lee JW, Oh H, You JY, Lee ES, Lee JH, Song SE, et al. (2023c). Therapy-related myeloid neoplasm in early breast

cancer patients treated with adjuvant chemotherapy. Eur J Cancer. 191:112952. https://doi.org/10.1016/j.ejca.2023.112952 PMID:37473463

Lee KA, Ma W, Sikavi DR, Drew DA, Nguyen LH, Bowyer RCE, et al.; COPE consortium (2021a). Cancer and risk of COVID-19 through a general community survey. Oncologist. 26(1):e182–5. https://doi.org/10.1634/theoncologist.2020-0572 PMID:32845538

Lee KH, Jeong D (2012). Bimodal actions of selenium essential for antioxidant and toxic pro-oxidant activities: the selenium paradox. Mol Med Rep. 5(2):299–304. PMID:22051937

Lee M, Leskova W, Eshaq RS, Harris NR (2021c). Retinal hypoxia and angiogenesis with methamphetamine. Exp Eye Res. 206:108540. https://doi.org/10.1016/j.exer.2021.108540 PMID:33736986

Lee S, Jeong W, Kannan K, Moon HB (2016b). Occurrence and exposure assessment of organophosphate flame retardants (OPFRs) through the consumption of drinking water in Korea. Water Res. 103:182–8. https://doi.org/10.1016/j.watres.2016.07.034 PMID:27450356

Lee W, Ahn YS, Lee S, Song BM, Hong S, Yoon JH (2016a). Occupational exposure to crystalline silica and gastric cancer: a systematic review and meta-analysis. Occup Environ Med. 73(11):794–801. https://doi.org/10.1136/oemed-2016-103552 PMID:27621410

Lee W, Kang SK, Choi WJ (2021b). Effect of long work hours and shift work on high-sensitivity C-reactive protein levels among Korean workers. Scand J Work Environ Health. 47(3):200–7. https://doi.org/10.5271/sjweh.3933 PMID:33201246

Lee WJ, Blair A, Hoppin JA, Lubin JH, Rusiecki JA, Sandler DP, et al. (2004). Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. J Natl Cancer Inst. 96(23):1781–9. https://doi.org/10.1093/jnci/djh324 PMID:15572760

Lee WJ, Cantor KP, Berzofsky JA, Zahm SH, Blair A (2004b). Non-Hodgkin's lymphoma among asthmatics exposed to pesticides. Int J Cancer. 111(2):298–302. https://doi.org/10.1002/ijc.20273 PMID:15197786

Lee WJ, Hoppin JA, Blair A, Lubin JH, Dosemeci M, Sandler DP, et al. (2004a). Cancer incidence among pesticide applicators exposed to alachlor in the Agricultural Health Study. Am J Epidemiol. 159(4):373–80. https://doi.org/10.1093/aje/kwh040 PMID:14769641

Lee YM, Song BC, Yeum KJ (2015). Impact of volatile anesthetics on oxidative stress and inflammation. BioMed Res Int. 2015:242709. https://doi.org/10.1155/2015/242709 PMID:26101769

Legeay S, Billat PA, Clere N, Nesslany F, Bristeau S, Faure S, et al. (2018). Two dechlorinated chlordecone derivatives formed by in situ chemical reduction are devoid of genotoxicity and mutagenicity and have lower proangiogenic properties compared to the parent compound. Environ Sci Pollut Res Int. 25(15):14313–23. https://doi.org/10.1007/s11356-017-8592-6 PMID:28210952

Legoff L, D'Cruz SC, Bouchekhchoukha K, Monfort C, Jaulin C, Multigner L, et al. (2021a). In utero exposure to chlordecone affects histone modifications and activates LINE-1 in cord blood. Life Sci Alliance. 4(6):e202000944. https://doi.org/10.26508/lsa.202000944 PMID:33837044

Legoff L, D'Cruz SC, Lebosq M, Gely-Pernot A, Bouchekhchoukha K, Monfort C, et al. (2021b). Developmental exposure to chlordecone induces transgenerational effects in somatic prostate tissue which are associated with epigenetic histone trimethylation changes. Environ Int. 152:106472. https://doi.org/10.1016/j.envint.2021.106472 PMID:33711761

Legoff L, Dali O, D'Cruz SC, Suglia A, Gely-Pernot A, Hémery C, et al. (2019). Ovarian dysfunction following prenatal exposure to an insecticide, chlordecone, associates with altered epigenetic features. Epigenetics Chromatin. 12(1):29. https://doi.org/10.1186/s13072-019-0276-7 PMID:31084621

Leija-Montoya AG, González-Ramírez J, Martínez-Coronilla G, Mejía-León ME, Isiordia-Espinoza M, Sánchez-Muñoz F, et al. (2022). Roles of microRNAs and long non-coding RNAs encoded by parasitic helminths in human carcinogenesis. Int J Mol Sci. 23(15):8173. https://doi.org/10.3390/ijms23158173 PMID:35897749

Leikauf GD, Kim S-H, Jang A-S (2020). Mechanisms of ultrafine particle-induced respiratory health effects. Exp Mol Med. 52(3):329–37. https://doi.org/10.1038/s12276-020-0394-0 PMID:32203100

Lemaire G, Mnif W, Mauvais P, Balaguer P, Rahmani R (2006). Activation of alpha- and beta-estrogen receptors by

persistent pesticides in reporter cell lines. Life Sci. 79(12):1160–9. https://doi.org/10.1016/j.lfs.2006.03.023 PMID:16626760

Leon ME, Beane Freeman LE, Douwes J, Hoppin JA, Kromhout H, Lebailly P, et al. (2011). AGRICOH: a consortium of agricultural cohorts. Int J Environ Res Public Health. 8(5):1341–57. https://doi.org/10.3390/ijerph8051341 PMID:21655123

Leon ME, Schinasi LH, Lebailly P, Beane Freeman LE, Nordby KC, Ferro G, et al. (2019). Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway and the USA: a pooled analysis from the AGRICOH consortium. Int J Epidemiol. 48(5):1519–35. https://doi.org/10.1093/ije/dyz017 PMID:30880337

León-Jiménez A, Hidalgo-Molina A, Conde-Sánchez MÁ, Pérez-Alonso A, Morales-Morales JM, García-Gámez EM, et al. (2020). Artificial stone silicosis: rapid progression following exposure cessation. Chest. 158(3):1060–8. https://doi.org/10.1016/j.chest.2020.03.026 PMID:32563682

Leonard RC, Kreckmann KH, Sakr CJ, Symons JM (2008). Retrospective cohort mortality study of workers in a polymer production plant including a reference population of regional workers. Ann Epidemiol. 18(1):15–22. https://doi.org/10.1016/j.annepidem.2007.06.011 PMID:17900928

Leonard SS, Wang S, Shi X, Jordan BS, Castranova V, Dubick MA (2000). Wood smoke particles generate free radicals and cause lipid peroxidation, DNA damage, NFkappaB activation and TNF-alpha release in macrophages. Toxicology. 150(1–3):147–57. https://doi.org/10.1016/S0300-483X(00)00256-0 PMID:10996671

Leonetti CP, Butt CM, Stapleton HM (2018). Disruption of thyroid hormone sulfotransferase activity by brominated flame retardant chemicals in the human choriocarcinoma placenta cell line, BeWo. Chemosphere. 197:81–8. https://doi.org/10.1016/j.chemosphere.2017.12.172 PMID:29331935

Lerche CM, Heerfordt IM, Serup J, Poulsen T, Wulf HC (2017). Red tattoos, ultraviolet radiation and skin cancer in mice. Exp Dermatol. 26(11):1091–6. https://doi.org/10.1111/exd.13383 PMID:28500679

Lerche CM, Sepehri M, Serup J, Poulsen T, Wulf HC (2015). Black tattoos protect against UVR-induced skin cancer in mice. Photodermatol Photoimmunol Photomed. 31(5):261–8. https://doi.org/10.1111/phpp.12181 PMID:26018407

Leroyer A, Gomajee H, Leroy R, Mazzuca M, Leleu B, Nisse C (2022). Cancer mortality and chemical exposure in a retrospective zinc and lead smelter cohort: a 48-year follow-up. Int J Hyg Environ Health. 242:113955. https://doi.org/10.1016/j.ijheh.2022.113955 PMID:35385816

Lerro CC, Andreotti G, Koutros S, Lee WJ, Hofmann JN, Sandler DP, et al. (2018b). Alachlor use and cancer incidence in the Agricultural Health Study: an updated analysis. J Natl Cancer Inst. 110(9):950–8. https://doi.org/10.1093/jnci/djy005 PMID:29471327

Lerro CC, Beane Freeman LE, DellaValle CT, Andreotti G, Hofmann JN, Koutros S, et al. (2021). Pesticide exposure and incident thyroid cancer among male pesticide applicators in agricultural health study. Environ Int. 146:106187. https://doi.org/10.1016/j.envint.2020.106187 PMID:33126065

Lerro CC, Beane Freeman LE, DellaValle CT, Kibriya MG, Aschebrook-Kilfoy B, Jasmine F, et al. (2018a). Occupational pesticide exposure and subclinical hypothyroidism among male pesticide applicators. Occup Environ Med. 75(2):79–89. https://doi.org/10.1136/oemed-2017-104431 PMID:28775130

Lerro CC, Koutros S, Andreotti G, Friesen MC, Alavanja MC, Blair A, et al. (2015). Organophosphate insecticide use and cancer incidence among spouses of pesticide applicators in the Agricultural Health Study. Occup Environ Med. 72(10):736–44. https://doi.org/10.1136/oemed-2014-102798 PMID:26150671

Lesseur C, Pirrotte P, Pathak KV, Manservisi F, Mandrioli D, Belpoggi F, et al. (2021). Maternal urinary levels of glyphosate during pregnancy and anogenital distance in newborns in a US multicenter pregnancy cohort. Environ Pollut. 280:117002. https://doi.org/10.1016/j.envpol.2021.117002 PMID:33812205

Letavayová L, Vlcková V, Brozmanová J (2006). Selenium: from cancer prevention to DNA damage. Toxicology. 227(1–2):1–14. https://doi.org/10.1016/j.tox.2006.07.017 PMID:16935405

Leung HKM, Lo EKK, Chen C, Zhang F, Felicianna, Ismaiah MJ, et al. (2023). Zearalenone attenuates colitis associated colorectal tumorigenesis through Ras/Raf/ERK pathway suppression and SCFA-producing bacteria promotion.

Biomed Pharmacother. 164:114973. https://doi.org/10.1016/j.biopha.2023.114973 PMID:37269808

Levin R, Villanueva CM, Beene D, Cradock AL, Donat-Vargas C, Lewis J, et al. (2023). US drinking water quality: exposure risk profiles for seven legacy and emerging contaminants. J Expo Sci Environ Epidemiol. 34(1):3–22. https://doi.org/10.1038/s41370-023-00597-zPMID:37739995

Levine MM, Black RE, Lanata C (1982). Precise estimation of the numbers of chronic carriers of *Salmonella typhi* in Santiago, Chile, an endemic area. J Infect Dis. 146(6):724–6. https://doi.org/10.1093/infdis/146.6.724 PMID:7142746

Levine RJ, Turner MJ, Crume YS, Dale ME, Starr TB, Rickert DE (1985). Assessing exposure to dinitrotoluene using a biological monitor. J Occup Med. 27(9):627–38. PMID:4045574

Levy D, Christin-Maitre S, Leroy I, Bergeron C, Garcia E, Freitas S, et al. (1997). The endometrial approach in contraception. Ann N Y Acad Sci. 828(1):59–83. https://doi.org/10.1111/j.1749-6632.1997.tb48524.x PMID:9329824

Lewis KA, Tzilivakis J, Warner D, Green A (2016). An international databasefor pesticide risk assessments and management. Hum Ecol Risk Assess. 22(4):1050–64. https://doi.org/10.1080/10807039.2015.1133242

Li A, Zhang Y, Ma Y, Xu R, Song L, Cao W, et al. (2022b). The effects of coal dust exposure on DNA damage and repair of human bronchial epithelial cells. Toxicol Ind Health. 38(7):389–98. https://doi.org/10.1177/07482337221100483 PMID:35624533

Li B, Tang SP, Wang KZ (2016b). Esophagus cancer and occupational exposure to asbestos: results from a meta-analysis of epidemiology studies. Dis Esophagus. 29(5):421–8. https://doi.org/10.1111/dote.12341 PMID:25758922

Li H, Hammarstrand S, Midberg B, Xu Y, Li Y, Olsson DS, et al. (2022c). Cancer incidence in a Swedish cohort with high exposure to perfluoroalkyl substances in drinking water. Environ Res. 204(Pt C):112217. https://doi.org/10.1016/j.envres.2021.112217 PMID:34662573

Li H, Wang M, Kang W, Lin Z, Gan F, Huang K (2021c). Non-cytotoxic dosage of fumonisin B1 aggravates ochratoxin A-induced nephrocytotoxicity and apoptosis via ROS-dependent JNK/MAPK signalling pathway. Toxicology. 457:152802. https://doi.org/10.1016/j.tox.2021.152802 PMID:33905761

Li H, Yin J, Li L, Deng J, Feng C, Zuo Z (2013b). Isoflurane postconditioning reduces ischemia-induced nuclear factor-κB activation and interleukin 1β production to provide neuroprotection in rats and mice. Neurobiol Dis. 54:216–24. https://doi.org/10.1016/j.nbd.2012.12.014 PMID:23313315

Li J, Bai H, Qiao H, Du C, Yao P, Zhang Y, et al. (2023a). Causal effects of COVID-19 on cancer risk: a Mendelian randomization study. J Med Virol. 95(4):e28722. https://doi.org/10.1002/jmv.28722 PMID:37185860

Li J, Butcher J, Mack D, Stintzi A (2015a). Functional impacts of the intestinal microbiome in the pathogenesis of inflammatory bowel disease. Inflamm Bowel Dis. 21(1):139–53. https://doi.org/10.1097/MIB.0000000000000215 PMID:25248007

Li J, Jiang S, Huang C, Yang X (2022e). Atraric acid ameliorates hyperpigmentation through the downregulation of the PKA/CREB/MITF signalling pathway. Int J Mol Sci. 23(24):15952. https://doi.org/10.3390/ijms232415952https://doi.org/10.3390/ijms232415952 PMID:36555593

Li J, Zeng T, Tang S, Zhong M, Huang Q, Li X, et al. (2021d). Medical ozone induces proliferation and migration inhibition through ROS accumulation and PI3K/AKT/NF-κB suppression in human liver cancer cells in vitro. Clin Transl Oncol. 23(9):1847–56. https://doi.org/10.1007/s12094-021-02594-w PMID:33821368

Li JH, Hu HC, Chen WB, Lin SK (2003). Genetic toxicity of methamphetamine in vitro and in human abusers. Environ Mol Mutagen. 42(4):233–42. https://doi.org/10.1002/em.10198 PMID:14673868

Li L, Jiang M, Li X, Zhou B (2021e). Association between coalmine dust and mortality risk of lung cancer: a meta-analysis. BioMed Res Int. 2021:6624799. https://doi.org/10.1155/2021/6624799 PMID:33763477

Li N, Georas S, Alexis N, Fritz P, Xia T, Williams MA, et al. (2016a). A work group report on ultrafine particles (American Academy of Allergy, Asthma & Immunology): why ambient ultrafine and engineered nanoparticles should receive special attention for possible adverse health outcomes in human subjects. J Allergy Clin Immunol. 138(2):386–96. https://doi.org/10.1016/j.jaci.2016.02.023 PMID:27130856

Li N, Xu N, Lin Y, Lei L, Ju LS, Morey TE, et al. (2020b). Roles of testosterone and estradiol in mediation of acute neuroendocrine and electroencephalographic effects of sevoflurane during the sensitive period in rats. Front Endocrinol (Lausanne). 11:545973. https://doi.org/10.3389/fendo.2020.545973 PMID:33101193

Li P, Zhang H, Lu J, Li G (2023b). Low concentration sulfolane-based electrolyte for high voltage lithium metal batteries. Angew Chem Int Ed Engl. 62(10):e202216312. https://doi.org/10.1002/anie.202216312 PMID:36640438

Li Q, Kobayashi M, Kawada T (2014a). Carbamate pesticide-induced apoptosis and necrosis in human natural killer cells. J Biol Regul Homeost Agents. 28(1):23–32. PMID:24750788

Li Q, Kobayashi M, Kawada T (2015b). Carbamate pesticide-induced apoptosis in human T lymphocytes. Int J Environ Res Public Health. 12(4):3633–45. https://doi.org/10.3390/ijerph120403633 PMID:25837344

Li Q, Zheng T, Holford TR, Boyle P, Zhang Y, Dai M (2010). Light at night and breast cancer risk: results from a population-based case–control study in Connecticut, USA. Cancer Causes Control. 21(12):2281–5. https://doi.org/10.1007/s10552-010-9653-z PMID:20927578

Li S, Liu J, Zheng X, Ren L, Yang Y, Li W, et al. (2021b). Tumorigenic bacteria in colorectal cancer: mechanisms and treatments. Cancer Biol Med. 19(2):147–62. https://doi.org/10.20892/j.issn.2095-3941.2020.0651 PMID:34586760

Li W, Ruan W, Cui X, Lu Z, Wang D (2022d). Blood volatile organic aromatic compounds concentrations across adulthood in relation to total and cause specific mortality: a prospective cohort study. Chemosphere. 286(Pt 1):131590. https://doi.org/10.1016/j.chemosphere.2021.131590 PMID:34293566

Li W, Xu J, Zhang R, Li Y, Wang J, Zhang X, et al. (2021a). Is periodontal disease a risk indicator for colorectal cancer? A systematic review and meta-analysis. J Clin Periodontol. 48(3):336–47. https://doi.org/10.1111/jcpe.13402 PMID:33179280

Li WQ, Drucker AM, Cho E, Laden F, VoPham T, Li S, et al. (2018). Tetracycline use and risk of incident skin cancer: a prospective study. Br J Cancer. 118(2):294–8. https://doi.org/10.1038/bjc.2017.378 PMID:29073637

Li X, Chen Z, Chen Z, Zhang Y (2013a). A human health risk assessment of rare earth elements in soil and vegetables from a mining area in Fujian Province, Southeast China. Chemosphere. 93(6):1240–6. https://doi.org/10.1016/j.chemosphere.2013.06.085 PMID:23891580

Li X, He S, Xiao H, He TT, Zhang JD, Luo ZR, et al. (2022f). Neonicotinoid insecticides promote breast cancer progression via G protein-coupled estrogen receptor: In vivo, in vitro and in silico studies. Environ Int. 170:107568. https://doi.org/10.1016/j.envint.2022.107568 PMID:36240625

Li X, He X, Chen S, Guo X, Bryant MS, Guo L, et al. (2020a). Evaluation of pyrrolizidine alkaloid-induced genotoxicity using metabolically competent TK6 cell lines. Food Chem Toxicol. 145:111662. https://doi.org/10.1016/j.fct.2020.111662 PMID:32798647

Li X, Liu Y, Wang Y, Li X, Liu X, Guo M, et al. (2020c). Sucralose promotes colitis-associated colorectal cancer risk in a murine model along with changes in microbiota. Front Oncol. 10:710. https://doi.org/10.3389/fonc.2020.00710 PMID:32582527

Li Y, Pelah A, An J, Yu YX, Zhang XY (2014b). Concentration- and time-dependent genotoxicity profiles of isoprene monoepoxides and diepoxide, and the cross-linking potential of isoprene diepoxide in cells. Toxicol Rep. 1:36–45. https://doi.org/10.1016/j.toxrep.2014.03.002 PMID:28962224

Li YS, Ren HC, Cao JH (2022a). Correlation of SARSCoV2 to cancer: carcinogenic or anticancer? Int J Oncol. 60(4):42. https://doi.org/10.3892/ijo.2022.5332 PMID:35234272

Li Z, Düllmann J, Schiedlmeier B, Schmidt M, von Kalle C, Meyer J, et al. (2002). Murine leukemia induced by retroviral gene marking. Science. 296(5567):497. https://doi.org/10.1126/science.1068893

Li Z, Hogan KA, Cai C, Rieth S (2016c). Human health effects of biphenyl: key findings and scientific issues. Environ Health Perspect. 124(6):703–12. https://doi.org/10.1289/ehp.1509730 PMID:26529796

Lian T, Zhang X, Wang X, Wang R, Gao H, Tai F, et al. (2020). Neonatal exposure to chlordecone alters female social behaviors and central estrogen alpha receptor expression in socially monogamous mandarin voles. Toxicol Res (Camb). 9(3):173–81. https://doi.org/10.1093/toxres/tfaa014 PMID:32670549

Liang CK, Quan NY, Cao SR, He XZ, Ma F (1988). Natural inhalation exposure to coal smoke and wood smoke induces lung cancer in mice and rats. Biomed Environ Sci. 1(1):42–50. PMID:3268107

Liang F, Huo X, Wang W, Li Y, Zhang J, Feng Y, et al. (2020). Association of bisphenol A or bisphenol S exposure with oxidative stress and immune disturbance among unexplained recurrent spontaneous abortion women. Chemosphere. 257:127035. https://doi.org/10.1016/j.chemosphere.2020.127035 PMID:32702804

Liang F, Yan B (2020). Oxidative damage in the liver and kidney induced by dermal exposure to diisononyl phthalate in Balb/c mice. Toxicol Ind Health. 36(1):30–40. https://doi.org/10.1177/0748233719900861 PMID:32096457

Liao HY, Chung YT, Lai CH, Wang SL, Chiang HC, Li LA, et al. (2014). Six-month follow-up study of health markers of nanomaterials among workers handling engineered nanomaterials. Nanotoxicology. 8 Suppl 1:100–10. https://doi.org/10.3109/17435390.2013.858793 PMID:24295335

Licá ICL, Frazão GCCG, Nogueira RA, Lira MGS, Dos Santos VAF, Rodrigues JGM, et al. (2023). Immunological mechanisms involved in macrophage activation and polarization in schistosomiasis. Parasitology. 150(5):401–15. https://doi.org/10.1017/S0031182023000021 PMID:36601859

Lichtenauer M, Mildner M, Werba G, Beer L, Hoetzenecker K, Baumgartner A, et al. (2012). Anti-thymocyte globulin induces neoangiogenesis and preserves cardiac function after experimental myocardial infarction. PLoS One. 7(12):e52101. https://doi.org/10.1371/journal.pone.0052101 PMID:23284885

Lightfoot NE, Berriault CJ, Seilkop SK, Conard BR (2017). Nonrespiratory mortality and cancer incidence in a cohort of Canadian nickel workers. Arch Environ Occup Health. 72(4):187–203. https://doi.org/10.1080/19338244.2016.1197879 PMID:27268254

Lijinsky W, Reuber MD (1987). Chronic carcinogenesis studies of acrolein and related compounds. Toxicol Ind Health. 3(3):337–45. https://doi.org/10.1177/074823378700300306 PMID:3686537

Lillo MA, Nichols C, Perry C, Runke S, Krutilina R, Seagroves TN, et al. (2017). Methylparaben stimulates tumor initiating cells in ER+ breast cancer models. J Appl Toxicol. 37(4):417–25. https://doi.org/10.1002/jat.3374https://doi.org/10.1002/jat.3374 PMID:27581495

Lim JE, Huang J, Männistö S, Weinstein SJ, Albanes D (2022). Hair dye use and prostate cancer risk: a prospective analysis in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort. Cancer. 128(6):1260–6. https://doi.org/10.1002/cncr.34035 PMID:34797564

Lim JE, Huang J, Weinstein SJ, Parisi D, Männistö S, Albanes D (2023b). Serum metabolomic profile of hair dye use. Sci Rep. 13(1):3776. https://doi.org/10.1038/s41598-023-30590-3 PMID:36882504

Lim KPK, Lee AJL, Jiang X, Teng TZJ, Shelat VG (2023a). The link between *Helicobacter pylori* infection and gallbladder and biliary tract diseases: a review. Ann Hepatobiliary Pancreat Surg. 27(3):241–50. https://doi.org/10.14701/ahbps.22-056 PMID:37357161

Lin D, Song Q, Liu J, Chen F, Zhang Y, Wu Z, et al. (2022). Potential gut microbiota features for non-invasive detection of schistosomiasis. Front Immunol. 13:941530. https://doi.org/10.3389/fimmu.2022.941530 PMID:35911697

Lin L, Ding Y, Wang Y, Wang Z, Yin X, Yan G, et al. (2017). Functional lipidomics: palmitic acid impairs hepatocellular carcinoma development by modulating membrane fluidity and glucose metabolism. Hepatology. 66(2):432–48. https://doi.org/10.1002/hep.29033https://doi.org/10.1002/hep.29033 PMID:28073184

Lin RT, Chien LC, Jimba M, Furuya S, Takahashi K (2019). Implementation of national policies for a total asbestos ban: a global comparison. Lancet Planet Health. 3(8):e341–8. https://doi.org/10.1016/S2542-5196(19)30109-3 PMID:31439315

Lin S, Xu G, Chen Z, Liu X, Li J, Ma L, et al. (2020). Tea drinking and the risk of esophageal cancer: focus on tea type and drinking temperature. Eur J Cancer Prev. 29(5):382–7. https://doi.org/10.1097/CEJ.0000000000000568 PMID:32740163

Lin Y, Lagergren J, Lu Y (2011). Dietary acrylamide intake and risk of esophageal cancer in a population-based case–control study in Sweden. Int J Cancer. 128(3):676–81. https://doi.org/10.1002/ijc.25608 PMID:20715108

Lind P, Dalene M, Skarping G, Hagmar L (1996). Toxicokinetics of 2,4- and 2,6-toluenediamine in hydrolysed urine and plasma after occupational exposure to 2,4- and 2,6- toluene diisocyanate. Occup Environ Med. 53(2):94–9. https://doi.org/10.1136/oem.53.2.94 PMID:8777457

Lindberg HK, Falck GC, Singh R, Suhonen S, Järventaus H, Vanhala E, et al. (2013). Genotoxicity of short single-wall and multi-wall carbon nanotubes in human bronchial epithelial and mesothelial cells in vitro. Toxicology. 313(1):24–37. https://doi.org/10.1016/j.tox.2012.12.008 PMID:23266321

Linden A, Gülden M, Martin HJ, Maser E, Seibert H (2008). Peroxide-induced cell death and lipid peroxidation in C6 glioma cells. Toxicol In Vitro. 22(5):1371–6. https://doi.org/10.1016/j.tiv.2008.02.003 PMID:18346863

Linders AN, Dias IB, López Fernández T, Tocchetti CG, Bomer N, Van der Meer P (2024). A review of the pathophysiological mechanisms of doxorubicin-induced cardiotoxicity and aging. NPJ Aging. 10(1):9. https://doi.org/10.1038/s41514-024-00135-7 PMID:38263284

Linillos-Pradillo B, Paredes SD, Ortiz-Cabello M, Schlumpf M, Lichtensteiger W, Vara E, et al. (2023a). Activation of NLRP3 inflammasome in liver of Long Evans lactating rats and its perinatal effects in the offspring after bisphenol F exposure. Int J Mol Sci. 24(18):14129. https://doi.org/10.3390/ijms241814129 PMID:37762434

Linillos-Pradillo B, Rancan L, Murias JG, Schlumpf M, Lichtensteiger W, Tresguerres JAF, et al. (2023b). Oxidative stress increases in liver of lactating rats after BPF-low-dose exposure: perinatal effects in the offspring. Sci Rep. 13(1):11229. https://doi.org/10.1038/s41598-023-38434-w PMID:37433837

Lioi MB, Scarfì MR, Santoro A, Barbieri R, Zeni O, Di Berardino D, et al. (1998a). Genotoxicity and oxidative stress induced by pesticide exposure in bovine lymphocyte cultures in vitro. Mutat Res. 403(1–2):13–20. https://doi.org/10.1016/S0027-5107(98)00010-4 PMID:9726001

Lioi MB, Scarfi MR, Santoro A, Barbieri R, Zeni O, Salvemini F, et al. (1998b). Cytogenetic damage and induction of pro-oxidant state in human lymphocytes exposed in vitro to gliphosate, vinclozolin, atrazine, and DPX-E9636. Environ Mol Mutagen. 32(1):39–46. https://doi.org/10.1002/(SICI)1098-2280(1998)32:1<39::AID-EM5>3.0.CO;2-6 PMID:9707097

Lipsky MM, Hinton DE, Klaunig JE, Trump BF (1981). Biology of hepatocellular neoplasia in the mouse. I. Histogenesis of safrole-induced hepatocellular carcinoma. J Natl Cancer Inst. 67(2):365–76. PMID:6943375

Lisieska-Żołnierczyk S, Gajęcka M, Dąbrowski M, Zielonka Ł, Gajęcki MT (2023). A cohort study investigating zearalenone concentrations and selected steroid levels in patients with sigmoid colorectal cancer or colorectal cancer. Toxins (Basel). 16(1):15. https://doi.org/10.3390/toxins16010015 PMID:38251232

Little A, Tangney M, Tunney MM, Buckley NE (2023). *Fusobacterium nucleatum*: a novel immune modulator in breast cancer? Expert Rev Mol Med. 25:e15. https://doi.org/10.1017/erm.2023.9 PMID:37009688

Liu B, Jung KH, Horton MK, Camann DE, Liu X, Reardon AM, et al. (2012). Prenatal exposure to pesticide ingredient piperonyl butoxide and childhood cough in an urban cohort. Environ Int. 48(1):156–61. https://doi.org/10.1016/j.envint.2012.07.009https://doi.org/10.1016/j.envint.2012.07.009 PMID:22935766

Liu C, Deng YL, Zheng TZ, Yang P, Jiang XQ, Liu EN, et al. (2020). Urinary biomarkers of phthalates exposure and risks of thyroid cancer and benign nodule. J Hazard Mater. 383:121189. https://doi.org/10.1016/j.jhazmat.2019.121189 PMID:31541958

Liu C, Liu Z, Fang Y, Liao Z, Zhang Z, Yuan X, et al. (2023c). Exposure to dithiocarbamate fungicide maneb in vitro and in vivo: neuronal apoptosis and underlying mechanisms. Environ Int. 171:107696. https://doi.org/10.1016/j.envint.2022.107696 PMID:36563597

Liu CT, Yang CC, Chien WC, Chung CH, Tsai CS, Tsai YT, et al. (2022d). Association between long-term usage of acetylcholinesterase inhibitors and lung cancer in the elderly: a nationwide cohort study. Sci Rep. 12(1):3531. https://doi.org/10.1038/s41598-022-06377-3 PMID:35241672

Liu D, Lu L, Wang M, Hussain B, Tian S, Luo W, et al. (2019). Tetracycline uptake by pak choi grown on contaminated soils and its toxicity in human liver cell line HL-7702. Environ Pollut. 253:312–21. https://doi.org/10.1016/j.envpol.2019.06.086 PMID:31323614

Liu G, Cai W, Liu H, Jiang H, Bi Y, Wang H (2021b). The association of bisphenol A and phthalates with risk of breast cancer: a meta-analysis. Int J Environ Res Public Health. 18(5):2375. https://doi.org/10.3390/ijerph18052375 PMID:33804363

Liu H, Huang Y, Huang M, Wang M, Ming Y, Chen W, et al. (2023a). From nitrate to NO: potential effects of nitrate-reducing bacteria on systemic health and disease. Eur J Med Res. 28(1):425. https://doi.org/10.1186/s40001-023-01413-y PMID:37821966

Liu J, Wang L, Li S, Lin Z, Yang G, Miao Z (2024). Association of urine glyphosate levels with renal injury biomarkers in children living close to major vegetable-producing regions in China. Sci Total Environ. 912:168677. https://doi.org/10.1016/j.scitotenv.2023.168677 PMID:38007119

Liu J, Yang Y, Zhuang S, Yang Y, Li F, Liu W (2011). Enantioselective endocrine-disrupting effects of bifenthrin on hormone synthesis in rat ovarian cells. Toxicology. 290(1):42–9. https://doi.org/10.1016/j.tox.2011.08.016 PMID:21871944

Liu JA, Walton JC, Bumgarner JR, Walker WH 2nd, Meléndez-Fernández OH, DeVries AC, et al. (2022b). Chronic exposure to dim light at night disrupts cell-mediated immune response and decreases longevity in aged female mice. Chronobiol Int. 39(12):1674–83. https://doi.org/10.1080/07420528.2022.2135442 PMID:36268694

Liu K, Cao H, Li B, Guo C, Zhao W, Han X, et al. (2022c). Long-term exposure to ambient nitrogen dioxide and ozone modifies systematic low-grade inflammation: The CHCN-BTH study. Int J Hyg Environ Health. 239:113875. https://doi.org/10.1016/j.ijheh.2021.113875 PMID:34757279

Liu KH, Kim CS, Kim JH (2003). Human exposure assessment to mancozeb during treatment of mandarin fields. Bull Environ Contam Toxicol. 70(2):336–42. https://doi.org/10.1007/s00128-002-0196-1 PMID:12545368

Liu KH, Liao LM, Ro LS, Wu YL, Yeh TS (2008). Thalidomide attenuates tumor growth and preserves fast-twitch skeletal muscle fibers in cholangiocarcinoma rats. Surgery. 143(3):375–83. https://doi.org/10.1016/j.surg.2007.09.035 PMID:18291259

Liu Q, Zhang J, Luo X, Ihsan A, Liu X, Dai M, et al. (2016b). Further investigations into the genotoxicity of quinoxaline-di-N-oxides and their primary metabolites. Food Chem Toxicol. 93:145–57. https://doi.org/10.1016/j.fct.2016.04.029 PMID:27170491

Liu T, Gao R, Li L, Wu B, Wu F (2023b). Analysis of the association between janus kinase inhibitors and malignant skin tumors using the Food and Drug Administration Adverse Event Reporting System. Int J Clin Pharm. 45(6):1483–91. https://doi.org/10.1007/s11096-023-01634-5 PMID:37606843

Liu TY, Chen CC, Chen CL, Chi CW (1999). Safrole-induced oxidative damage in the liver of Sprague-Dawley rats. Food Chem Toxicol. 37(7):697–702. https://doi.org/10.1016/S0278-6915(99)00055-1 PMID:10496370

Liu TY, Chung YT, Wang PF, Chi CW, Hsieh LL (2004). Safrole-DNA adducts in human peripheral blood – an association with areca quid chewing and CYP2E1 polymorphisms. Mutat Res. 559(1–2):59–66. https://doi.org/10.1016/j.mrgentox.2003.12.013 PMID:15066574

Liu W, Yang R, Payne AS, Schowalter RM, Spurgeon ME, Lambert PF, et al. (2016a). Identifying the target cells and mechanisms of Merkel cell polyomavirus infection. Cell Host Microbe. 19(6):775–87. https://doi.org/10.1016/j.chom.2016.04.024 PMID:27212661

Liu W, You J (2020). Molecular mechanisms of Merkel cell polyomavirus transformation and replication. Cell Host Microbe. 7(1):289–307. https://doi.org/10.1146/annurev-virology-011720-121757PMID:32603631

Liu X, Zhan T, Gao Y, Cui S, Liu W, Zhang C, et al. (2022g). 2,4-dihydroxybenzophenone induced aberrant proliferation and metastasis of ovarian cancer cells via activated ERα and Wnt/β-catenin signalling pathways. Environ Pollut. 292 Pt B:118370. https://doi.org/10.1016/j.envpol.2021.118370 PMID:34656677

Liu XM, Shao JZ, Xiang LX, Chen XY (2006). Cytotoxic effects and apoptosis induction of atrazine in a grass carp (*Ctenopharyngodon idellus*) cell line. Environ Toxicol. 21(1):80–9. https://doi.org/10.1002/tox.20159 PMID:16463256

Liu Y, Tang W, Ao J, Zhang J, Feng L (2022f). Transcriptomics integrated with metabolomics reveals the effect of bisphenol F (BPF) exposure on intestinal inflammation. Sci Total Environ. 816:151644. https://doi.org/10.1016/j.scitotenv.2021.151644 PMID:34774955

Liu Z, Guo C, Tai P, Sun L, Chen Z (2021a). The exposure of gadolinium at environmental relevant levels induced genotoxic effects in *Arabidopsis thaliana* (L.). Ecotoxicol Environ Saf. 215:112138. https://doi.org/10.1016/j.ecoenv.2021.112138 PMID:33740487

Liu Z, Zhang L, Liang Y, Lu L (2022a). Pathology and molecular mechanisms of *Schistosoma japonicum*-associated liver fibrosis. Front Cell Infect Microbiol. 12:1035765. https://doi.org/10.3389/fcimb.2022.1035765 PMID:36389166

Liu ZZ, Duan XX, Yuan MC, Yu J, Hu X, Han X, et al. (2022e). Glucagon-like peptide-1 receptor activation by liraglutide promotes breast cancer through NOX4/ROS/VEGF pathway. Life Sci. 294:120370. https://doi.org/10.1016/j.lfs.2022.120370https://doi.org/10.1016/j.lfs.2022.120370 PMID:35124000

LiverTox (2021). LiverTox: clinical and research information on drug-induced liver injury. Alefacept. Bethesda (MD), USA: National Institute of Diabetes and Digestive and Kidney Diseases. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548345/, accessed September 2024.

Lizunkova P, Enuwosa E, Chichger H (2019). Activation of the sweet taste receptor T1R3 by sucralose attenuates VEGF-induced vasculogenesis in a cell model of the retinal microvascular endothelium. Graefes Arch Clin Exp Ophthalmol. 257(1):71–81. https://doi.org/10.1007/s00417-018-4157-8 PMID:30353220

Llewellyn GC, McCay JA, Brown RD, Musgrove DL, Butterworth LF, Munson AE, et al. (1998). Immunological evaluation of the mycotoxin patulin in female $B6C3F_1$ mice. Food Chem Toxicol. 36(12):1107–15. https://doi.org/10.1016/S0278-6915(98)00084-2 PMID:9862653

Llorca M, Farré M (2021). Current insights into potential effects of micro-nanoplastics on human health by *in-vitro* tests. Front Toxicol. 3:752140. https://doi.org/10.3389/ftox.2021.752140 PMID:35295102

Lo CH, Blot WJ, Teras LR, Visvanathan K, Le Marchand L, Haiman CA, et al. (2021a). Prediagnostic antibody responses to *Fusobacterium nucleatum* proteins are not associated with risk of colorectal cancer in a large US consortium. Cancer Epidemiol Biomarkers Prev. 30(6):1279–82. https://doi.org/10.1158/1055-9965.EPI-20-1471 PMID:33737297

Lo EKK, Lee JC, Turner PC, El-Nezami H (2021b). Low dose of zearalenone elevated colon cancer cell growth through G protein-coupled estrogenic receptor. Sci Rep. 11(1):7403. https://doi.org/10.1038/s41598-021-86788-w PMID:33795755

Lockwood CJ, Kumar P, Krikun G, Kadner S, Dubon P, Critchley H, et al. (2004). Effects of thrombin, hypoxia, and steroids on interleukin-8 expression in decidualized human endometrial stromal cells: implications for long-term progestin-only contraceptive-induced bleeding. J Clin Endocrinol Metab. 89(3):1467–75. https://doi.org/10.1210/jc.2003-030141 PMID:15001649

Logrieco A, Moretti A, Ritieni A, Bottalico A, Corda P (1995). Occurrence and toxigenicity of *Fusarium proliferatum* from preharvest maize ear rot, and associated mycotoxins, in Italy. Plant Dis. 79(7):727–31. https://doi.org/10.1094/PD-79-0727

Long J, Li J, Yuan X, Tang Y, Deng Z, Xu S, et al. (2019). Potential association between rosacea and cancer: a study in a medical center in southern China. J Dermatol. 46(7):570–6. https://doi.org/10.1111/1346-8138.14918 PMID:31120152

Long Q, Huang Y, Shang J, Liu Y, Chen C (2020). Black carbon induces cytotoxicity and NLRP3 inflammasome activation in human corneal epithelial cells. Curr Eye Res. 45(6):680–5. https://doi.org/10.1080/02713683.2019.1698051 PMID:31765230

Lopez M, Clarkson MR, Albin M, Sayegh MH, Najafian N (2006). A novel mechanism of action for anti-thymocyte globulin: induction of CD4+CD25+Foxp3+ regulatory T cells. J Am Soc Nephrol. 17(10):2844–53. https://doi.org/10.1681/ASN.2006050422 PMID:16914538

Lopez P, van Sisseren M, De Marco S, Jekel A, de Nijs M, Mol HG (2015). A straightforward method to determine flavouring substances in food by GC–MS. Food Chem. 174:407–16. https://doi.org/10.1016/j.foodchem.2014.11.011 PMID:25529699

Lori G, Tassinari R, Narciso L, Udroiu I, Sgura A, Maranghi F, et al. (2021). Toxicological comparison of mancozeb and zoxamide fungicides at environmentally relevant concentrations by an in vitro approach. Int J Environ Res Public Health. 18(16):8591. https://doi.org/10.3390/ijerph18168591 PMID:34444340

Louisse J, Rijkers D, Stoopen G, Holleboom WJ, Delagrange M, Molthof E, et al. (2019). Determination of genotoxic potencies of pyrrolizidine alkaloids in HepaRG cells using the γH2AX assay. Food Chem Toxicol. 131:110532. https://doi.org/10.1016/j.fct.2019.05.040 PMID:31154085

Lovell D (2010). Is tetrachloroethylene genotoxic or not? Mutagenesis. 25(5):443–6. https://doi.org/10.1093/mutage/geq036 PMID:20634266

Lovell MM, Coco R (1984). Chromosomal damage induced in human lymphocytes by medroxyprogesterone acetate treatment for precocious puberty. Medicina (B Aires). 44(2):163–6. PMID:6242250

Lowry LK, Tolos WP, Boeniger MF, Nony CR, Bowman MC (1980). Chemical monitoring of urine from workers potentially exposed to benzidine-derived azo dyes. Toxicol Lett. 7(1):29–36. https://doi.org/10.1016/0378-4274(80)90081-8https://doi.org/10.1016/0378-4274(80)90081-8 PMID:7292513

Lozano-Lorca M, Olmedo-Requena R, Vega-Galindo MV, Vázquez-Alonso F, Jiménez-Pacheco A, Salcedo-Bellido I, et al. (2020). Night shift work, chronotype, sleep duration, and prostate cancer risk: CAPLIFE study. Int J Environ Res Public Health. 17(17):6300. https://doi.org/10.3390/ijerph17176300 PMID:32872503

Lu H, Shi X, Costa M, Huang C (2005). Carcinogenic effect of nickel compounds. Mol Cell Biochem. 279(1–2):45–67. https://doi.org/10.1007/s11010-005-8215-2 PMID:16283514

Lu L, Hu J, Chao T, Chen Z, Liu Z, Luo X, et al. (2020a). Loss of natural resistance to schistosome in T cell deficient rat. PLoS Negl Trop Dis. 14(12):e0008909. https://doi.org/10.1371/journal.pntd.0008909 PMID:33347431

Lu QJ, Bo YC, Zhao Y, Zhao EJ, Sapa WB, Yao MJ, et al. (2016). Glutathione *S*-transferase M1 polymorphism and esophageal cancer risk: an updated meta-analysis based on 37 studies. World J Gastroenterol. 22(5):1911–8. https://doi.org/10.3748/wjg.v22.i5.1911https://doi.org/10.3748/wjg.v22.i5.1911 PMID:26855551

Lu S, Long F, Lu P, Lei B, Jiang Z, Liu G, et al. (2018). Benzophenone-UV filters in personal care products and urine of schoolchildren from Shenzhen, China: exposure assessment and possible source. Sci Total Environ. 640–641:1214–20. https://doi.org/10.1016/j.scitotenv.2018.06.015 PMID:30021286

Lu X, Fraszczyk E, van der Meer TP, van Faassen M, Bloks VW, Kema IP, et al.; BIOS Consortium (2020c). An epigenome-wide association study identifies multiple DNA methylation markers of exposure to endocrine disruptors. Environ Int. 144:106016. https://doi.org/10.1016/j.envint.2020.106016 PMID:32916427

Lu Y, Liu L, Chen Q, Wei J, Cao G, Zhang J (2020b). Domestic radon exposure and risk of childhood leukemia: a meta-analysis. J BUON. 25(2):1035–41. https://www.jbuon.com/archive/25-2-1035.pdf PMID:32521903

Luce D, Dugas J, Vaidie A, Michineau L, El-Yamani M, Multigner L (2020). A cohort study of banana plantation workers in the French West Indies: first mortality analysis (2000–2015). Environ Sci Pollut Res Int. 27(33):41014–22. https://doi.org/10.1007/s11356-019-06481-4 PMID:31621027

Luce D, Gérin M, Morcet JF, Leclerc A (1997). Sinonasal cancer and occupational exposure to textile dust. Am J Ind Med. 32(3):205–10. https://doi.org/10.1002/(SICI)1097-0274(199709)32:3<205::AID-AJIM4>3.0.CO;2-W PMID:9219648

Lucia RM, Liao X, Huang WL, Forman D, Kim A, Ziogas A, et al. (2023). Association of glyphosate exposure with blood DNA methylation in a cross-sectional study of postmenopausal women. Environ Health Perspect. 130(4):47001. https://doi.org/10.1289/EHP10174 PMID:35377194

Lucio FT, Almeida IV, Buzo MG, Vicentini VEP (2023). Genetic instability in farmers using pesticides: A study in Brazil with analysis combining alkaline comet and micronucleus assays. Mutat Res Genet Toxicol Environ Mutagen. 886:503587. https://doi.org/10.1016/j.mrgentox.2023.503587 PMID:36868698

Luckert C, Hessel S, Lenze D, Lampen A (2015). Disturbance of gene expression in primary human hepatocytes by hepatotoxic pyrrolizidine alkaloids: a whole genome transcriptome analysis. Toxicol In Vitro. 29(7):1669–82. https://doi.org/10.1016/j.tiv.2015.06.021 PMID:26100227

Lüder CG, Gross U (2005). Apoptosis and its modulation during infection with *Toxoplasma gondii*: molecular mechanisms and role in pathogenesis. Curr Top Microbiol Immunol. 289:219–37. https://doi.org/10.1007/3-540-27320-4_10 PMID:15791958

Luft P, Oostingh GJ, Gruijthuijsen Y, Horejs-Hoeck J, Lehmann I, Duschl A (2008). Patulin influences the expression of Th1/Th2 cytokines by activated peripheral blood mononuclear cells and T cells through depletion of intracellular glutathione. Environ Toxicol. 23(1):84–95. https://doi.org/10.1002/tox.20309 PMID:18214930

Luke B, Brown MB, Wantman E, Schymura MJ, Browne ML, Fisher SC, et al. (2022). The risks of birth defects and childhood cancer with conception by assisted reproductive technology. Hum Reprod. 37(11):2672–89. https://doi.org/10.1093/humrep/deac196 PMID:36112004

Lunderberg DM, Misztal PK, Liu Y, Arata C, Tian Y, Kristensen K, et al. (2021). High-resolution exposure assessment for volatile organic compounds in two California residences. Environ Sci Technol. 55(10):6740–51. https://doi.org/10.1021/acs.est.0c08304 PMID:33945266

Lundy SK, Lukacs NW (2013). Chronic schistosome infection leads to modulation of granuloma formation and systemic immune suppression. Front Immunol. 4:39. https://doi.org/10.3389/fimmu.2013.00039 PMID:23429492

Luo H, Ge H (2022). Hot tea consumption and esophageal cancer risk: a meta-analysis of observational studies. Front Nutr. 9:831567. https://doi.org/10.3389/fnut.2022.831567 PMID:35479756

Luo J, Sands M, Wactawski-Wende J, Song Y, Margolis KL (2013). Sleep disturbance and incidence of thyroid cancer in postmenopausal women the Women's Health Initiative. Am J Epidemiol. 177(1):42–9. https://doi.org/10.1093/aje/kws193 PMID:23221728

Luu HM, Hutter JC, Bushar HF (1998). A physiologically based pharmacokinetic model for 2,4-toluenediamine leached from polyurethane foam-covered breast implants. Environ Health Perspect. 106(7):393–400. https://doi.org/10.1289/ehp.98106393 PMID:9637796

Lv Q, Liang X, Nong K, Gong Z, Qin T, Qin X, et al. (2021a). Advances in research on the toxicological effects of selenium. Bull Environ Contam Toxicol. 106(5):715–26. https://doi.org/10.1007/s00128-020-03094-3 PMID:33420800

Lv Y, Chen S, Zhu B, Xu H, Xu S, Liu W, et al. (2021b). Exposure to 50 Hz extremely-low-frequency magnetic fields induces no DNA damage in cells by gamma H2AX technology. BioMed Res Int. 2021:8510315. https://doi.org/10.1155/2021/8510315 PMID:33628815

Lvova MN, Ponomarev DV, Tarasenko AA, Kovner AV, Minkova GA, Tsyganov MA, et al. (2023). Curcumin and its supramolecular complex with disodium glycyrrhizinate as potential drugs for the liver fluke infection caused by *Opisthorchis felineus.* Pathogens. 12(6):819. https://doi.org/10.3390/pathogens12060819 PMID:37375509

Lynge E (1985). A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. Br J Cancer. 52(2):259–70. https://doi.org/10.1038/bjc.1985.186 PMID:4027168

Lynn RK, Donielson DW, Ilias AM, Kennish JM, Wong K, Matthews HB (1980). Metabolism of bisazobiphenyl dyes derived from benzidine, 3,3′-dimethylbenzidine or 3,3′-dimethoxybenzidine to carcinogenic aromatic amines in the dog and rat. Toxicol Appl Pharmacol. 56(2):248–58. https://doi.org/10.1016/0041-008X(80)90296-3https://doi.org/10.1016/0041-008X(80)90296-3 PMID:7466824

Lyu YL, Kerrigan JE, Lin CP, Azarova AM, Tsai YC, Ban Y, et al. (2007). Topoisomerase IIbeta mediated DNA double-strand breaks: implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. Cancer Res. 67(18):8839–46. https://doi.org/10.1158/0008-5472.CAN-07-1649 PMID:17875725

Ma G, Wang Q, Ma K, Chen Y, Lu J, Zhang J, et al. (2023). Enantioselective metabolism of novel chiral insecticide paichongding by human cytochrome P450 3A4: a computational insight. Environ Pollut. 333:122088. https://doi.org/10.1016/j.envpol.2023.122088 PMID:37348694

Ma L, Bai Y, Pu H, Gou F, Dai M, Wang H, et al. (2015). Histone methylation in nickel-smelting industrial workers. PLoS One. 10(10):e0140339. https://doi.org/10.1371/journal.pone.0140339 PMID:26474320

Ma P, Yan B, Zeng Q, Liu X, Wu Y, Jiao M, et al. (2014). Oral exposure of Kunming mice to diisononyl phthalate induces hepatic and renal tissue injury through the accumulation of ROS. Protective effect of melatonin. Food Chem Toxicol. 68:247–56. https://doi.org/10.1016/j.fct.2014.03.027 PMID:24685826

Ma P, Yao Y, Sun W, Dai S, Zhou C (2017). Daily sedentary time and its association with risk for colorectal cancer in adults: a dose–response meta-analysis of prospective cohort studies. Medicine (Baltimore). 96(22):e7049. https://doi.org/10.1097/MD.0000000000007049https://doi.org/10.1097/MD.0000000000007049 PMID:28562564

Ma Y, Han J, Guo Y, Lam PK, Wu RS, Giesy JP, et al. (2012). Disruption of endocrine function in in vitro H295R cell-based and in in vivo assay in zebrafish by 2,4-dichlorophenol. Aquat Toxicol. 106–107:173–81. https://doi.org/10.1016/j.aquatox.2011.11.006 PMID:22155427

Ma-Hock L, Treumann S, Strauss V, Brill S, Luizi F, Mertler M, et al. (2009). Inhalation toxicity of multiwall carbon nanotubes in rats exposed for 3 months. Toxicol Sci. 112(2):468–81. https://doi.org/10.1093/toxsci/kfp146 PMID:19584127

Macedo PA, Schleier JJ 3rd, Reed M, Kelley K, Goodman GW, Brown DA, et al. (2010). Evaluation of efficacy and human health risk of aerial ultra-low volume applications of pyrethrins and piperonyl butoxide for adult mosquito management in response to West Nile virus activity in Sacramento County, California. J Am Mosq Control Assoc. 26(1):57–66. https://doi.org/10.2987/09-5961.1https://doi.org/10.2987/09-5961.1 PMID:20402352

MacGregor SR, McManus DP, Sivakumaran H, Egwang TG, Adriko M, Cai P, et al. (2023). Development of CRISPR/Cas13a-based assays for the diagnosis of *Schistosomiasis*. EBioMedicine. 94:104730. https://doi.org/10.1016/j.ebiom.2023.104730 PMID:37487416

Mackevica A, Revilla P, Brinch A, Hansen SF (2016). Current uses of nanomaterials in biocidal products and treated articles in the EU. Environ Sci Nano. 3(5):1195–205. https://doi.org/10.1039/C6EN00212A

MacLennan PA, Delzell E, Sathiakumar N, Myers SL (2003). Mortality among triazine herbicide manufacturing workers. J Toxicol Environ Health A. 66(6):501–17. https://doi.org/10.1080/15287390306356 PMID:12712593

Maddalon A, Cari L, Iulini M, Alhosseini MN, Galbiati V, Marinovich M, et al. (2023). Impact of endocrine disruptors on peripheral blood mononuclear cells in vitro: role of gender. Arch Toxicol. 97(12):3129–50. https://doi.org/10.1007/s00204-023-03592-3 PMID:37676302

Maddalon A, Iulini M, Galbiati V, Colosio C, Mandić-Rajčević S, Corsini E (2022). Direct effects of glyphosate on *in vitro* T helper cell differentiation and cytokine production. Front Immunol. 13:854837. https://doi.org/10.3389/fimmu.2022.854837 PMID:35359959

Madden KS, Szpunar MJ, Brown EB (2013). Early impact of social isolation and breast tumor progression in mice. Brain Behav Immun. 30 Suppl:S135–41. https://doi.org/10.1016/j.bbi.2012.05.003https://doi.org/10.1016/j.bbi.2012.05.003 PMID:22610067

Madrigal JM, Gunier RB, Jones RR, Flory A, Metayer C, Nuckols JR, et al. (2023). Contributions of nearby agricultural insecticide applications to indoor residential exposures. Environ Int. 171:107657. https://doi.org/10.1016/j.envint.2022.107657 PMID:36493610

Madrigal JM, Jones RR, Gunier RB, Whitehead TP, Reynolds P, Metayer C, et al. (2021). Residential exposure to carbamate, organophosphate, and pyrethroid insecticides in house dust and risk of childhood acute lymphoblastic leukemia. Environ Res. 201:111501. https://doi.org/10.1016/j.envres.2021.111501 PMID:34139223

Madrigal JM, Troisi R, Surcel HM, Öhman H, Kivelä J, Kiviranta H, et al. (2024). Prediagnostic serum concentrations of per- and polyfluoroalkyl substances and risk of papillary thyroid cancer in the Finnish Maternity Cohort. Int J Cancer. 154(6):979–91. https://doi.org/10.1002/ijc.34776 PMID:37902275

Madsen LW, Knauf JA, Gotfredsen C, Pilling A, Sjögren I, Andersen S, et al. (2012). GLP-1 receptor agonists and the thyroid: C-cell effects in mice are mediated via the GLP-1 receptor and not associated with RET activation. Endocrinology. 153(3):1538–47. https://doi.org/10.1210/en.2011-1864https://doi.org/10.1210/en.2011-1864 PMID:22234463

Maeng SH, Yu IJ (1997). Mutagenicity of 2-bromopropane. Ind Health. 35(1):87–95. https://doi.org/10.2486/indhealth.35.87 PMID:9009506

Maes A, Verschaeve L (2016). Genetic damage in humans exposed to extremely low-frequency electromagnetic fields. Arch Toxicol. 90(10):2337–48. https://doi.org/10.1007/s00204-016-1769-9 PMID:27334374

Magenis ML, Damiani AP, de Marcos PS, de Pieri E, de Souza E, Vilela TC, et al. (2020). Fructose consumption during pregnancy and lactation causes DNA damage and biochemical changes in female mice. Mutagenesis. 35(2):179–87. https://doi.org/10.1093/mutage/geaa001 PMID:31967303

Magenis ML, Damiani AP, de Oliveira Monteiro I, Dagostin LS, Dos Santos da Silva N, Scussel R, et al. (2023). Maternal exercise during pregnancy modulates genotoxicity caused by high fructose consumption in mice offspring. Mutagenesis. 39(2):119–40. https://doi.org/10.1093/mutage/gead035 PMID:38019677

Magnuson BA, Roberts A, Nestmann ER (2017). Critical review of the current literature on the safety of sucralose. Food Chem Toxicol. 106 Pt A:324–55. https://doi.org/10.1016/j.fct.2017.05.047 PMID:28558975

Magnusson M, Beath K, Cooter R, Locke M, Prince HM, Elder E, et al. (2019). The epidemiology of breast implant-associated anaplastic large cell lymphoma in Australia and New Zealand confirms the highest risk for grade 4 surface breast implants. Plast Reconstr Surg. 143(5):1285–92. https://doi.org/10.1097/PRS.0000000000005500 PMID:30789476

Mahaboonpeeti R, Kongtip P, Nankongnab N, Tipayamongkholgul M, Bunngamchairat A, Yoosook W, et al. (2018). Evaluation of dermal exposure to the herbicide alachlor among vegetable farmers in Thailand. Ann Work Expo Health. 62(9):1147–58. https://doi.org/10.1093/annweh/wxy081 PMID:30239593

Mahady GB, Fabricant D, Chadwick LR, Dietz B (2002). Black cohosh: an alternative therapy for menopause? Nutr Clin Care. 5(6):283–9. https://doi.org/10.1046/j.1523-5408.2002.05603.xhttps://doi.org/10.1046/j.1523-5408.2002.05603.x PMID:12557811

Mahai G, Wan Y, Wang A, Qian X, Li J, Li Y, et al. (2023). Exposure to multiple neonicotinoid insecticides, oxidative stress, and gestational diabetes mellitus: association and potential mediation analyses. Environ Int. 179:108173. https://doi.org/10.1016/j.envint.2023.108173 PMID:37651928

Mahajan R, Blair A, Coble J, Lynch CF, Hoppin JA, Sandler DP, et al. (2007). Carbaryl exposure and incident cancer in the Agricultural Health Study. Int J Cancer. 121(8):1799–805. https://doi.org/10.1002/ijc.22836 PMID:17534892

Mahajan R, Blair A, Lynch CF, Schroeder P, Hoppin JA, Sandler DP, et al. (2006). Fonofos exposure and cancer incidence in the agricultural health study. Environ Health Perspect. 114(12):1838–42. https://doi.org/10.1289/ehp.9301 PMID:17185272

Mahmood S, MacInnis RJ, English DR, Karahalios A, Lynch BM (2017). Domain-specific physical activity and sedentary behaviour in relation to colon and rectal cancer risk: a systematic review and meta-analysis. Int J Epidemiol. 46(6):1797–813. https://doi.org/10.1093/ije/dyx137https://doi.org/10.1093/ije/dyx137 PMID:29025130

Maisonneuve P, Lowenfels AB (2015). Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol. 44(1):186–98. https://doi.org/10.1093/ije/dyu240 PMID:25502106

Makris KC, Efthymiou N, Konstantinou C, Anastasi E, Schoeters G, Kolossa-Gehring M, et al. (2022). Oxidative stress of glyphosate, AMPA and metabolites of pyrethroids and chlorpyrifos pesticides among primary school children in Cyprus. Environ Res. 212 Pt B:113316. https://doi.org/10.1016/j.envres.2022.113316 PMID:35439459

Maksimova GA, Pakharukova MY, Kashina EV, Zhukova NA, Kovner AV, Lvova MN, et al. (2017). Effect of *Opisthorchis felineus* infection and dimethylnitrosamine administration on the induction of cholangiocarcinoma in Syrian hamsters. Parasitol Int. 66(4):458–63. https://doi.org/10.1016/j.parint.2015.10.002

Malagoli C, Malavolti M, Wise LA, Balboni E, Fabbi S, Teggi S, et al. (2023). Residential exposure to magnetic fields from high-voltage power lines and risk of childhood leukemia. Environ Res. 232:116320. https://doi.org/10.1016/j.envres.2023.116320 PMID:37271435

Malavolti M, Malagoli C, Wise LA, Poli M, Notari B, Taddei I, et al. (2023). Residential exposure to magnetic fields from transformer stations and risk of childhood leukemia. Environ Res. 245:118043. https://doi.org/10.1016/j.envres.2023.118043 PMID:38145739

Malekinejad F, Fink-Gremmels J, Malekinejad H (2023). Zearalenone and its metabolite exposure directs oestrogen metabolism towards potentially carcinogenic metabolites in human breast cancer MCF-7 cells. Mycotoxin Res. 39(1):45–56. https://doi.org/10.1007/s12550-022-00472-0 PMID:36517666

Malekzadeh Gonabadi N, Shamsara M, Kordi Tamandani DM, Shojaei S, Alavi SM (2023). Different effects of low-level laser therapy on the proliferation of HT29 cells in culture and xenograft models. J Lasers Med Sci. 14:e31. https://doi.org/10.34172/jlms.2023.31 PMID:37744016

Malicka I, Siewierska K, Olbromski M, Glatzel-Plucinska N, Podhorska-Okolow M, Dziegiel P, et al. (2022). The influence of physical training on the immune system of rats during *N*-methyl-*N*-nitrosourea-induced carcinogenesis. J Clin Med. 11(21):6371. https://doi.org/10.3390/jcm11216371 PMID:36362598

Malik P, Hashim T, Varma S, Diaz L, Chowdhary A, Bapat P, et al. (2022). BTEX (benzene, toluene, ethylbenzene, and xylene) and risk of cancer – a study from Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey. Am J Clin Pathol. 158(Suppl 1) Supplement_1:S102–3. https://doi.org/10.1093/ajcp/aqac126.216

Mallet V, Hamed K, Schwarzinger M (2017). Prognosis of patients with chronic hepatitis B in France (2008–2013): a nationwide, observational and hospital-based study. J Hepatol. 66(3):514–20. https://doi.org/10.1016/j.jhep.2016.10.031 PMID:27826056

Malloy EJ, Miller KL, Eisen EA (2007). Rectal cancer and exposure to metalworking fluids in the automobile manufacturing industry. Occup Environ Med. 64(4):244–9. https://doi.org/10.1136/oem.2006.027300 PMID:16912088

Maltseva A, Serra C, Kogevinas M (2016). Cancer risk among workers of a secondary aluminium smelter. Occup Med (Lond). 66(5):412–4. https://doi.org/10.1093/occmed/kqw054 PMID:27170736

Mancini FR, Cano-Sancho G, Gambaretti J, Marchand P, Boutron-Ruault MC, Severi G, et al. (2020b). Perfluorinated alkylated substances serum concentration and breast cancer risk: Evidence from a nested case–control study in the French E3N cohort. Int J Cancer. 146(4):917–28. https://doi.org/10.1002/ijc.32357https://doi.org/10.1002/ijc.32357 PMID:31008526

Mancini FR, Cano-Sancho G, Mohamed O, Cervenka I, Omichessan H, Marchand P, et al. (2020a). Plasma concentration of brominated flame retardants and postmenopausal breast cancer risk: a nested case–control study in the French E3N cohort. Environ Health. 19(1):54. https://doi.org/10.1186/s12940-020-00607-9 PMID:32434563

Mandon M, Huet S, Dubreil E, Fessard V, Le Hégarat L (2019). Three-dimensional HepaRG spheroids as a liver model to study human genotoxicity in vitro with the single cell gel electrophoresis assay. Sci Rep. 9(1):10548. https://doi.org/10.1038/s41598-019-47114-7 PMID:31332230

Mantovani A, Pierotti MA (2008). Cancer and inflammation: a complex relationship. Cancer Lett. 267(2):180–1. https://doi.org/10.1016/j.canlet.2008.05.003 PMID:18562089

Manibusan MK, Odin M, Eastmond DA (2007). Postulated carbon tetrachloride mode of action: a review. J Environ Sci Health Part C Environ Carcinog Ecotoxicol Rev. 25(3):185–209. https://doi.org/10.1080/10590500701569398 PMID:17763046

Manigrasso M, Protano C, Vitali M, Avino P (2019). Where do ultrafine particles and nano-sized particles come from? J Alzheimers Dis. 68(4):1371–90. https://doi.org/10.3233/JAD-181266 PMID:31006689

Mann SW, Yuschak MM, Amyes SJ, Aughton P, Finn JP (2000a). A carcinogenicity study of sucralose in the CD-1 mouse. Food Chem Toxicol. 38 Suppl 2:S91–7. https://doi.org/10.1016/S0278-6915(00)00030-2 PMID:10882820

Mann SW, Yuschak MM, Amyes SJ, Aughton P, Finn JP (2000b). A combined chronic toxicity/carcinogenicity study of sucralose in Sprague-Dawley rats. Food Chem Toxicol. 38 Suppl 2:S71–89. https://doi.org/10.1016/S0278-6915(00)00029-6 PMID:10882819

Mann WJ, Muttray A, Schaefer D, Klimek L, Faas M, Konietzko J (2002). Exposure to 200 ppm of methanol increases the concentrations of interleukin-1beta and interleukin-8 in nasal secretions of healthy volunteers. Ann Otol Rhinol Laryngol. 111(7 Pt 1):633–8. https://doi.org/10.1177/000348940211100711 PMID:12126020

Mannetje A (2006). Should dental amalgam fillings fill us with fear? Onkologie. 29(5):196–7. https://karger.com/onk/article-pdf/29/5/196/3315114/000092730.pdf PMID:16679779

Manske MK, Beltz LA, Dhanwada KR (2004). Low-level atrazine exposure decreases cell proliferation in human fibroblasts. Arch Environ Contam Toxicol. 46(4):438–44. https://doi.org/10.1007/s00244-003-3087-5 PMID:15253040

Mao H, Zhang L, Li J, Zhao Y, Wu Y, Ni S (2023a). [Associations of a mixture of eleven endocrine disruptors in human urine with the risk of papillary thyroid cancer]. Wei Sheng Yan Jiu. 52(6):986–92. PMID:38115664 [Chinese]

Mao JF, Li W, Ong CN, He Y, Jong M-C, Gin KY-H (2022). Assessment of human exposure to benzophenone-type UV filters: a review. Environ Int. 167:107405. https://doi.org/10.1016/j.envint.2022.107405 PMID:35843073

Mao W, Qu J, Zhong S, Wu X, Mao K, Liao K, et al. (2023b). Associations between urinary parabens and lung cancer. Environ Sci Pollut Res Int. 30(24):66186–94. https://doi.org/10.1007/s11356-023-26953-yhttps://doi.org/10.1007/s11356-023-26953-y PMID:37097579

Marabini L, Ozgen S, Turacchi S, Aminti S, Arnaboldi F, Lonati G, et al. (2017). Ultrafine particles (UFPs) from domestic wood stoves: genotoxicity in human lung carcinoma A549 cells. Mutat Res Genet Toxicol Environ Mutagen. 820:39–46. https://doi.org/10.1016/j.mrgentox.2017.06.001 PMID:28676265

Marasas WFO, Jaskiewicz K, Venter FS, Van Schalkwyk DJ (1988). *Fusarium moniliforme* contamination of maize in oesophageal cancer areas in Transkei. S Afr Med J. 74(3):110–4. https://journals.co.za/doi/pdf/10.10520/AJA20785135_8793 PMID:3399988

Marasas WFO, Kriek NPJ, Wiggins VM, Steyn PS, Towers DK, Hastie TJ (1979). Incidence, geographical distribution and toxigenicity of *Fusarium* species in South African corn. Phytopathology. 69:1181–5. https://doi.org/10.1094/Phyto-69-1181

Marasas WFO, Wehner FC, Van Rensburg SJ, Van Schalkwyk DJ (1981). Mycoflora of corn produced in human oesophageal cancer areas in Transkei, Southern Africa. Phytopathology. 71:792–6. https://doi.org/10.1094/Phyto-71-792

Marchetti S, Bengalli R, Floris P, Colombo A, Mantecca P (2021). Combustion-derived particles from biomass sources differently promote epithelial-to-mesenchymal transition on A549 cells. Arch Toxicol. 95(4):1379–90. https://doi.org/10.1007/s00204-021-02983-8 PMID:33481051

Marcuzzi GP, Hufbauer M, Kasper HU, Weißenborn SJ, Smola S, Pfister H (2009). Spontaneous tumour development in human papillomavirus type 8 E6 transgenic mice and rapid induction by UV-light exposure and wounding. J Gen Virol. 90(Pt 12):2855–64. https://doi.org/10.1099/vir.0.012872-0 PMID:19692543

Mardhiyah D, Komaruddin WN, Jalal FN, Wuryanti S, Bahri S, Qomariah Q, et al. (2021). Comparison of thyroid hormone levels between women farmers and non-farmers in Banten Indonesia. Int J Environ Res Public Health. 18(12):6618. https://doi.org/10.3390/ijerph18126618 PMID:34205433

Marengo E, Aceto M (2003). Statistical investigation of the differences in the distribution of metals in Nebbiolo-based wines. Food Chem. 81(4):621–30. https://doi.org/10.1016/S0308-8146(02)00564-2

Marin ML, Murtha J, Dong W, Pestka JJ (1996). Effects of mycotoxins on cytokine production and proliferation in EL-4 thymoma cells. J Toxicol Environ Health. 48(4):379–96. https://doi.org/10.1080/009841096161267 PMID:8691508

Marino M, Puppo F, Del Bo' C, Vinelli V, Riso P, Porrini M, et al. (2021). A systematic review of worldwide consumption of ultra-processed foods: findings and criticisms. Nutrients. 13(8):2778. https://doi.org/10.3390/nu13082778 PMID:34444936

Marotta V, Russo G, Gambardella C, Grasso M, La Sala D, Chiofalo MG, et al. (2019). Human exposure to bisphenol AF and diethylhexylphthalate increases susceptibility to develop differentiated thyroid cancer in patients with thyroid nodules. Chemosphere. 218:885–94. https://doi.org/10.1016/j.chemosphere.2018.11.084 PMID:30609493

Marpegan L, Leone MJ, Katz ME, Sobrero PM, Bekinstein TA, Golombek DA (2009). Diurnal variation in endotoxin-induced mortality in mice: correlation with proinflammatory factors. Chronobiol Int. 26(7):1430–42. https://doi.org/10.3109/07420520903408358 PMID:19916840

Marquardt H, Philips FS, Sternberg SS (1976). Tumorigenicity in vivo and induction of malignant transformation and mutagenesis in cell cultures by adriamycin and daunomycin. Cancer Res. 36(6):2065–9. PMID:1268859

Marques E, Pfohl M, Wei W, Tarantola G, Ford L, Amaeze O, et al. (2022). Replacement per- and polyfluoroalkyl substances (PFAS) are potent modulators of lipogenic and drug metabolizing gene expression signatures in primary human hepatocytes. Toxicol Appl Pharmacol. 442:115991. https://doi.org/10.1016/j.taap.2022.115991 PMID:35337807

Marsh GM, Keeton KA, Riordan AS, Best EA, Benson SM (2019). Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis. Int Arch Occup Environ Health. 92(7):919–39. https://doi.org/10.1007/s00420-019-01438-z PMID:31111206

Marshall NS, Wong KK, Cullen SR, Knuiman MW, Grunstein RR (2014). Sleep apnea and 20-year follow-up for all-cause mortality, stroke, and cancer incidence and mortality in the Busselton Health Study cohort. J Clin Sleep Med. 10(4):355–62. https://doi.org/10.5664/jcsm.3600 PMID:24733978

Martelli A, Robbiano L, Carrozzino R, Puglia CP, Mattioli F, Angiola M, et al. (2000). DNA damage induced by 3,3′-dimethoxybenzidine in liver and urinary bladder cells of rats and humans. Toxicol Sci. 53(1):71–6. https://doi.org/10.1093/toxsci/53.1.71https://doi.org/10.1093/toxsci/53.1.71 PMID:10653523

Martin JC, Daniel H, LeBouffant L (1975). Short- and long-term experimental study of the toxicity of coal-mine dust and of some of its constituents. Inhaled Part. 4(Pt 1):361–71. PMID:1236169

Martin TA, Jayanthi S, McCoy MT, Brannock C, Ladenheim B, Garrett T, et al. (2012). Methamphetamine causes differential alterations in gene expression and patterns of histone acetylation/hypoacetylation in the rat nucleus accumbens. PLoS One. 7(3):e34236. https://doi.org/10.1371/journal.pone.0034236 PMID:22470541

Martínez MA, Rodríguez JL, Lopez-Torres B, Martínez M, Martínez-Larrañaga MR, Anadón A, et al. (2019). Oxidative stress and related gene expression effects of cyfluthrin in human neuroblastoma SH-SY5Y cells: protective effect of melatonin. Environ Res. 177:108579. https://doi.org/10.1016/j.envres.2019.108579 PMID:31330490

Martínez-Paz P, Morales M, Martínez-Guitarte JL, Morcillo G (2013). Genotoxic effects of environmental endocrine disruptors on the aquatic insect *Chironomus riparius* evaluated using the comet assay. Mutat Res Genet Toxicol Environ Mutagen. 758(1–2):41–7. https://doi.org/10.1016/j.mrgentox.2013.09.005 PMID:24060506

Martínez-Varea A, Pellicer B, Serra V, Hervás-Marín D, Martínez-Romero A, Bellver J, et al. (2015). The maternal cytokine and chemokine profile of naturally conceived gestations is mainly preserved during in vitro fertilization and egg donation pregnancies. J Immunol Res. 2015:128616. https://doi.org/10.1155/2015/128616 PMID:26346343

Martins C, Cação R, Cole KJ, Phillips DH, Laires A, Rueff J, et al. (2012). Estragole: a weak direct-acting food-borne genotoxin and potential carcinogen. Mutat Res. 747(1):86–92. https://doi.org/10.1016/j.mrgentox.2012.04.009 PMID:22561883

Martins EM, Arbilla G, Gatti LV (2010). Volatile organic compounds in a residential and commercial urban area with a diesel, compressed natural gas and oxygenated gasoline vehicular fleet. Bull Environ Contam Toxicol. 84(2):175–9. https://doi.org/10.1007/s00128-009-9886-2https://doi.org/10.1007/s00128-009-9886-2 PMID:19787279

Martynhak BJ, Hogben AL, Zanos P, Georgiou P, Andreatini R, Kitchen I, et al. (2017). Transient anhedonia phenotype and altered circadian timing of behaviour during night-time dim light exposure in Per3$^{-/-}$ mice, but not wildtype mice. Sci Rep. 7(1):40399. https://doi.org/10.1038/srep40399 PMID:28071711

Mary SJ, Girish KL, Joseph TI, Sathyan P (2018). Genotoxic effects of silver amalgam and composite restorations: micronuclei-based cohort and case–control study in oral exfoliated cells. Contemp Clin Dent. 9(2):249–54. https://doi.org/10.4103/ccd.ccd_849_17 PMID:29875569

Masukume G, Mmbaga BT, Dzamalala CP, Mlombe YB, Finch P, Nyakunga-Maro G, et al. (2022). A very-hot food and beverage thermal exposure index and esophageal cancer risk in Malawi and Tanzania: findings from the ESCCAPE case–control studies. Br J Cancer. 127(6):1106–15. https://doi.org/10.1038/s41416-022-01890-8 PMID:35768549

Mathews JM, Watson SL, Snyder RW, Burgess JP, Morgan DL (2010). Reaction of the butter flavorant diacetyl (2,3-butanedione) with N-α-acetylarginine: a model for epitope formation with pulmonary proteins in the etiology of obliterative bronchiolitis. J Agric Food Chem. 58(24):12761–8. https://doi.org/10.1021/jf103251whttps://doi.org/10.1021/jf103251w PMID:21077678

Matos C, Peter K, Weich L, Peuker A, Schoenhammer G, Roider T, et al. (2022). Anti-thymocyte globulin treatment augments 1,25-dihydroxyvitamin D3 serum levels in patients undergoing hematopoietic stem cell transplantation. Front Immunol. 12:803726. https://doi.org/10.3389/fimmu.2021.803726 PMID:35058935

Matsuda T, Matsumoto A, Uchida M, Kanaly RA, Misaki K, Shibutani S, et al. (2007). Increased formation of hepatic N2-ethylidene-2′-deoxyguanosine DNA adducts in aldehyde dehydrogenase 2-knockout mice treated with ethanol. Carcinogenesis. 28(11):2363–6. https://doi.org/10.1093/carcin/bgm057 PMID:17361010

Matsushita M, Kuwamoto S, Iwasaki T, Higaki-Mori H, Yashima S, Kato M, et al. (2013). Detection of Merkel cell polyomavirus in the human tissues from 41 Japanese autopsy cases using polymerase chain reaction. Intervirology. 56(1):1–5. https://doi.org/10.1159/000338620 PMID:22986833

Mattioli F, Martelli A, Gosmar M, Garbero C, Manfredi V, Varaldo E, et al. (2006). DNA fragmentation and DNA repair synthesis induced in rat and human thyroid cells by chemicals carcinogenic to the rat thyroid. Mutat Res. 609(2):146–53. https://doi.org/10.1016/j.mrgentox.2006.06.028 PMID:16942904

Mattioli R, Ilari A, Colotti B, Mosca L, Fazi F, Colotti G (2023). Doxorubicin and other anthracyclines in cancers: activity, chemoresistance and its overcoming. Mol Aspects Med. 93:101205. https://doi.org/10.1016/j.mam.2023.101205 PMID:37515939

Mattiuzzo M, Fiore M, Ricordy R, Degrassi F (2006). Aneuploidy-inducing capacity of two widely used pesticides. Carcinogenesis. 27(12):2511–8. https://doi.org/10.1093/carcin/bgl102 PMID:16777991

Mayr SI, Hafizovic K, Waldfahrer F, Iro H, Kütting B (2010). Characterization of initial clinical symptoms and risk factors for sinonasal adenocarcinomas: results of a case–control study. Int Arch Occup Environ Health. 83(6):631–8. https://doi.org/10.1007/s00420-009-0479-5https://doi.org/10.1007/s00420-009-0479-5 PMID:19885670

Mazzei JL, Figueiredo EV, da Veiga LJ, Aiub CA, Guimarães PI, Felzenszwalb I (2010). Mutagenic risks induced by homemade hair straightening creams with high formaldehyde content. J Appl Toxicol. 30(1):8–14. https://doi.org/10.1002/jat.1464 PMID:19701882

Mbanefo EC, Agbo CT, Zhao Y, Lamanna OK, Thai KH, Karinshak SE, et al. (2020). IPSE, an abundant egg-secreted protein of the carcinogenic helminth *Schistosoma haematobium*, promotes proliferation of bladder cancer cells and angiogenesis. Infect Agent Cancer. 15(1):63. https://doi.org/10.1186/s13027-020-00331-6 PMID:33101456

McAlpine CS, Kiss MG, Zuraikat FM, Cheek D, Schiroli G, Amatullah H, et al. (2022). Sleep exerts lasting effects on hematopoietic stem cell function and diversity. J Exp Med. 219(11):e20220081. https://doi.org/10.1084/jem.20220081 PMID:36129517

McCallum GP, Siu M, Ondovcik SL, Sweeting JN, Wells PG (2011). Methanol exposure does not lead to accumulation of oxidative DNA damage in bone marrow and spleen of mice, rabbits or primates. Mol Carcinog. 50(3):163–72. https://doi.org/10.1002/mc.20701 PMID:21104990

McCredie M, Pommer W, McLaughlin JK, Stewart JH, Lindblad P, Mandel JS, et al. (1995). International renal-cell cancer study. II. Analgesics. Int J Cancer. 60(3):345–9. https://doi.org/10.1002/ijc.2910600312 PMID:7829242

McCullough ML, Hodge RA, Campbell PT, Guinter MA, Patel AV (2022). Sugar- and artificially-sweetened beverages and cancer mortality in a large US prospective cohort. Cancer Epidemiol Biomarkers Prev. 31(10):1907–18. https://doi.org/10.1158/1055-9965.EPI-22-0392 PMID:36107009

McDowell RD, Hughes C, Murchie P, Cardwell C (2021). A systematic assessment of the association between frequently prescribed medicines and the risk of common cancers: a series of nested case–control studies. BMC Med. 19(1):22. https://doi.org/10.1186/s12916-020-01891-5 PMID:33494748

McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, et al. (2001). Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev. 10(11):1155–63. https://aacrjournals.org/cebp/article/10/11/1155/164036/Non-Hodgkin-s-Lymphoma-and-Specific-Pesticide PMID:11700263

McElvenny DM, van Tongeren M, Turner MC, Benke G, Figuerola J, Fleming S, et al. (2018). The INTEROCC case–control study: risk of meningioma and occupational exposure to selected combustion products, dusts and other chemical agents. Occup Environ Med. 75(1):12–22. https://doi.org/10.1136/oemed-2016-104280 PMID:28947494

McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM, Yellon DM (2017). Anthracycline chemotherapy and cardiotoxicity. Cardiovasc Drugs Ther. 31(1):63–75. https://doi.org/10.1007/s10557-016-6711-0 PMID:28185035

McGregor D, Lang M (1996). Carbon tetrachloride: genetic effects and other modes of action. Mutat Res. 366(3):181–95. PMID:9033667

McMichael-Phillips DF, Harding C, Morton M, Roberts SA, Howell A, Potten CS, et al. (1998). Effects of soy-protein supplementation on epithelial proliferation in the histologically normal human breast. Am J Clin Nutr. 68(6) Suppl:1431S–5S. https://doi.org/10.1093/ajcn/68.6.1431S PMID:9848512

McNerney ME, Godley LA, Le Beau MM (2017). Therapy-related myeloid neoplasms: when genetics and environment collide. Nat Rev Cancer. 17(9):513–27. https://doi.org/10.1038/nrc.2017.60 PMID:28835720

Medda E, Santini F, De Angelis S, Franzellin F, Fiumalbi C, Perico A, et al. (2017). Iodine nutritional status and thyroid effects of exposure to ethylenebisdithiocarbamates. Environ Res. 154:152–9. https://doi.org/10.1016/j.envres.2016.12.019 PMID:28073049

Medgyesi DN, Trabert B, Fisher JA, Xiao Q, James P, White AJ, et al. (2023). Outdoor light at night and risk of endometrial cancer in the NIH-AARP diet and health study. Cancer Causes Control. 34(2):181–7. https://doi.org/10.1007/s10552-022-01632-4 PMID:36222982

Medgyesi DN, Trabert B, Sampson J, Weyer PJ, Prizment A, Fisher JA, et al. (2022). Drinking water disinfection byproducts, ingested nitrate, and risk of endometrial cancer in postmenopausal women. Environ Health Perspect. 130(5):57012. https://doi.org/10.1289/EHP10207https://doi.org/10.1289/EHP10207 PMID:35622390

Medicines and Healthcare Products Regulatory Agency (2021) First progestogen-only contraceptive pills to be available to purchase from pharmacies. Press Release. London, UK: Medicines and Healthcare Products Regulatory Agency, Government of the United Kingdom. Available from: https://www.gov.uk/government/news/first-progesterone-only-contraceptive-pills-to-be-available-to-purchase-from-pharmacies, accessed February 2024.

Medithi S, Kasa YD, Ajumeera R, Jee B, Kodali V, Jonnalagadda PR (2022b). Effect of organophosphorus pesticide exposure on the immune cell phenotypes among farm women and their children. Arch Environ Occup Health. 77(9):702–10. https://doi.org/10.1080/19338244.2021.2002795 PMID:34817298

Medithi S, Kasa YD, Jee B, Venkaiah K, Jonnalagadda PR (2022a). Alterations in reproductive hormone levels among farm women and their children occupationally exposed to organophosphate pesticides. Women Health. 62(5):454–64. https://doi.org/10.1080/03630242.2022.2085844 PMID:35676759

Mehrab N, Chorom M, Norouzi Masir M, Biswas JK, Fernandes de Souza M, Meers E (2023). Impact of soil treatment with *Nitrilo Triacetic Acid* (NTA) on Cd fractionation and microbial biomass in cultivated and uncultivated calcareous soil. J Environ Health Sci Eng. 21(2):319–32. https://doi.org/10.1007/s40201-023-00857-y PMID:37869606

Mehta SS, Elizabeth Hodgson M, Lunn RM, Ashley CE, Arroyave WD, Sandler DP, et al. (2023). Indoor wood-burning from stoves and fireplaces and incident lung cancer among Sister Study participants. Environ Int. 178:108128. https://doi.org/10.1016/j.envint.2023.108128 PMID:37542784

Meira LB, Bugni JM, Green SL, Lee CW, Pang B, Borenshtein D, et al. (2008). DNA damage induced by chronic inflammation contributes to colon carcinogenesis in mice. J Clin Invest. 118(7):2516–25. https://doi.org/10.1172/JCI35073 PMID:18521188

Mellemgaard A, Gaarslev K (1988). Risk of hepatobiliary cancer in carriers of *Salmonella typhi*. J Natl Cancer Inst. 80(4):288. https://doi.org/10.1093/jnci/80.4.288 PMID:3351964

Meloni F, Satta G, Padoan M, Montagna A, Pilia I, Argiolas A, et al. (2021). Occupational exposure to glyphosate and risk of lymphoma: results of an Italian multicenter case–control study. Environ Health. 20(1):49. https://doi.org/10.1186/s12940-021-00729-8 PMID:33910586

Meltz ML (2003). Radiofrequency exposure and mammalian cell toxicity, genotoxicity, and transformation. Bioelectromagnetics. 24 S6:S196–213. https://doi.org/10.1002/bem.10176 PMID:14628315

Mendaš G, Vuletić M, Galić N, Drevenkar V (2012). Urinary metabolites as biomarkers of human exposure to atrazine: atrazine mercapturate in agricultural workers. Toxicol Lett. 210(2):174–81. https://doi.org/10.1016/j.toxlet.2011.11.023 PMID:22155356

Mendoza MD, Santonja C, Gonzalez-Vela C, Concha A, Iglesias Pena N, Andrés-Esteban EM, et al. (2020). The presence of Merkel cell carcinoma polyomavirus is associated with a distinct phenotype in neoplastic Merkel cell carcinoma cells and their tissue microenvironment. PLoS One. 15(7):e0232517. https://doi.org/10.1371/journal.pone.0232517 PMID:32687503

Mendy A, Pinney SM (2022). Exposure to neonicotinoids and serum testosterone in men, women, and children. Environ Toxicol. 37(6):1521–8. https://doi.org/10.1002/tox.23503 PMID:35191592

Menegaux F, Baruchel A, Bertrand Y, Lescoeur B, Leverger G, Nelken B, et al. (2006). Household exposure to pesticides and risk of childhood acute leukaemia. Occup Environ Med. 63(2):131–4. https://doi.org/10.1136/oem.2005.023036 PMID:16421392

Mercado-Feliciano M, Cora MC, Witt KL, Granville CA, Hejtmancik MR, Fomby L, et al. (2012). An ethanolic extract of black cohosh causes hematological changes but not estrogenic effects in female rodents. Toxicol Appl Pharmacol. 263(2):138–47. https://doi.org/10.1016/j.taap.2012.05.022 PMID:22687605

Metayer C, Colt JS, Buffler PA, Reed HD, Selvin S, Crouse V, et al. (2013). Exposure to herbicides in house dust and risk of childhood acute lymphoblastic leukemia. J Expo Sci Environ Epidemiol. 23(4):363–70. https://doi.org/10.1038/jes.2012.115 PMID:23321862

Mevissen M, Ward JM, Kopp-Schneider A, McNamee JP, Wood AW, Rivero TM, et al. (2022). Effects of radiofrequency electromagnetic fields (RF EMF) on cancer in laboratory animal studies. Environ Int. 161:107106. https://doi.org/10.1016/j.envint.2022.107106 PMID:35091376

Meyers JM, Grace M, Uberoi A, Lambert PF, Munger K (2018). Inhibition of TGF-β and NOTCH signalling by cutaneous papillomaviruses. Front Microbiol. 9:389. https://doi.org/10.3389/fmicb.2018.00389 PMID:29568286

Meyers JM, Uberoi A, Grace M, Lambert PF, Munger K (2017). Cutaneous HPV8 and MmuPV1 E6 proteins target the NOTCH and TGF-β tumor suppressors to inhibit differentiation and sustain keratinocyte proliferation. PLoS Pathog. 13(1):e1006171. https://doi.org/10.1371/journal.ppat.1006171 PMID:28107544

Mhatre MC, Shah PN, Juneja HS (1984). Effect of varying photoperiods on mammary morphology, DNA synthesis, and hormone profile in female rats. J Natl Cancer Inst. 72(6):1411–6. PMID:6427503

Miao H, Liu X, Li J, Zhang L, Zhao Y, Liu S, et al. (2020). Associations of urinary phthalate metabolites with risk of papillary thyroid cancer. Chemosphere. 241:125093. https://doi.org/10.1016/j.chemosphere.2019.125093https://doi.org/10.1016/j.chemosphere.2019.125093 PMID:31629241

Michallet MC, Preville X, Flacher M, Fournel S, Genestier L, Revillard JP (2003). Functional antibodies to leukocyte adhesion molecules in antithymocyte globulins. Transplantation. 75(5):657–62. https://doi.org/10.1097/01.TP.0000053198.99206.E6 PMID:12640305

Michałowicz J, Włuka A, Bukowska B (2022). A review on environmental occurrence, toxic effects and transformation of man-made bromophenols. Sci Total Environ. 811:152289. https://doi.org/10.1016/j.scitotenv.2021.152289 PMID:34902422

Michaud DS, Gallo V, Schlehofer B, Tjønneland A, Olsen A, Overvad K, et al. (2010). Reproductive factors and exogenous hormone use in relation to risk of glioma and meningioma in a large European cohort study. Cancer Epidemiol Biomarkers Prev. 19(10):2562–9. https://doi.org/10.1158/1055-9965.EPI-10-0447 PMID:20802020

Michel A, Kopp-Schneider A, Zentgraf H, Gruber AD, de Villiers EM (2006). E6/E7 expression of human papillomavirus type 20 (HPV-20) and HPV-27 influences proliferation and differentiation of the skin in UV-irradiated SKH-hr1 transgenic mice. J Virol. 80(22):11153–64. https://doi.org/10.1128/JVI.00954-06 PMID:16971438

Mickus R, Jančiukė G, Raškevičius V, Mikalayeva V, Matulytė I, Marksa M, et al. (2021). The effect of nutmeg essential oil constituents on Novikoff hepatoma cell viability and communication through Cx43 gap junctions. Biomed Pharmacother. 135:111229. https://doi.org/10.1016/j.biopha.2021.111229https://doi.org/10.1016/j.biopha.2021.111229 PMID:33444950

Middleton DR, Menya D, Kigen N, Oduor M, Maina SK, Some F, et al. (2019b). Hot beverages and oesophageal cancer risk in western Kenya: findings from the ESCCAPE case–control study. Int J Cancer. 144(11):2669–76. https://doi.org/10.1002/ijc.32032 PMID:30496610

Middleton DRS, Xie SH, Bouaoun L, Byrnes G, Song GH, Schüz J, et al. (2019a). Esophageal thermal exposure to hot beverages: a comparison of metrics to discriminate distinct consumption habits. Cancer Epidemiol Biomarkers Prev. 28(12):2005–13. https://doi.org/10.1158/1055-9965.EPI-19-0856 PMID:31558508

Miguel Alfonso RA, Yael Yvette BH, Irma Martha MD, Cyndia Azucena GA, Briscia Socorro BV, José Francisco HM, et al. (2022). Genotoxic effects of the ochratoxin A (OTA), its main metabolite (OTα) per se and in combination with fumonisin B1 in HepG2 cells and human lymphocytes. Mutat Res Genet Toxicol Environ Mutagen. 878:503482. https://doi.org/10.1016/j.mrgentox.2022.503482 PMID:35649676

Mikoczy Z, Tinnerberg H, Björk J, Albin M (2011). Cancer incidence and mortality in Swedish sterilant workers exposed to ethylene oxide: updated cohort study findings 1972–2006. Int J Environ Res Public Health. 8(6):2009–19. https://doi.org/10.3390/ijerph8062009 PMID:21776215

Miligi L, Piro S, Airoldi C, Di Rico R, Ricci R, Paredes Alpaca RI, et al. (2023). Formaldehyde and acetaldehyde exposure in "non-traditional" occupational sectors: bakeries and pastry producers. Int J Environ Res Public Health. 20(3):1983. https://doi.org/10.3390/ijerph20031983 PMID:36767350

Miller CN, Dye JA, Schladweiler MC, Richards JH, Ledbetter AD, Stewart EJ, et al. (2018). Acute inhalation of ozone induces DNA methylation of apelin in lungs of Long-Evans rats. Inhal Toxicol. 30(4–5):178–86. https://doi.org/10.1080/08958378.2018.1483984 PMID:29947284

Mills PK, Yang R, Riordan D (2005). Lymphohematopoietic cancers in the United Farm Workers of America (UFW), 1988–2001. Cancer Causes Control. 16(7):823–30. https://doi.org/10.1007/s10552-005-2703-2https://doi.org/10.1007/s10552-005-2703-2 PMID:16132792

Mimaki S, Totsuka Y, Suzuki Y, Nakai C, Goto M, Kojima M, et al. (2016). Hypermutation and unique mutational signatures of occupational cholangiocarcinoma in printing workers exposed to haloalkanes. Carcinogenesis. 37(8):817–26. https://doi.org/10.1093/carcin/bgw066 PMID:27267998

Min YS, Choi H, Yoo CI, Ahn YS (2019). Cancer mortality in Korean workers occupationally exposed to methanol: a cohort study. Int Arch Occup Environ Health. 92(4):551–7. https://doi.org/10.1007/s00420-018-1389-1 PMID:30535884

Ming-Chai C, Chi-Yuan C, Pei-Yu C, Jen-Chun H (1980). Evolution of colorectal cancer in schistsosomiasis: transitional mucosal changes adjacent to large intestinal carcinoma in colectomy specimens. Cancer. 46(7):1661–75. https://doi.org/10.1002/1097-0142(19801001)46:7<1661::AID-CNCR2820460728>3.0.CO;2-O PMID:7417960

Mínguez-Alarcón L, Souter I, Chiu YH, Williams PL, Ford JB, Ye X, et al.; Earth Study Team (2016). Urinary concentrations of cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester, a metabolite of the non-phthalate plasticizer di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH), and markers of ovarian response among women attending a fertility center. Environ Res. 151:595–600. https://doi.org/10.1016/j.envres.2016.08.012 PMID:27591839

Minnesota Pollution Control Agency (2023). Perfluorohexane sulfonic acid: acquatic toxicity profile. St. Paul (MN), USA: Minnesota Pollution Control Agency. Available from: https://www.pca.state.mn.us/air-water-land-climate/perfluorohexane-sulfonic-acid-aquatic-toxicity-profile, accessed March 2024.

Minozzo R, Deimling LI, Gigante LP, Santos-Mello R (2004). Micronuclei in peripheral blood lymphocytes of workers exposed to lead. Mutat Res. 565(1):53–60. https://doi.org/10.1016/j.mrgentox.2004.09.003 PMID:15576239

Minskaia E, Galieva A, Egorov AD, Ivanov R, Karabelsky A (2023). Viral vectors in gene replacement therapy. Biochemistry (Mosc). 88(12):2157–78. https://doi.org/10.1134/S0006297923120179 PMID:38462459

Miranda RA, Silva BS, de Moura EG, Lisboa PC (2023). Pesticides as endocrine disruptors: programming for obesity and diabetes. Endocrine. 79(3):437–47. https://doi.org/10.1007/s12020-022-03229-y PMID:36301509

Miranda-Guevara A, Muñoz-Acevedo A, Fiorillo-Moreno O, Acosta-Hoyos A, Pacheco-Londoño L, Quintana-Sosa M, et al. (2023). The dangerous link between coal dust exposure and DNA damage: unraveling the role of some of the chemical agents and oxidative stress. Environ Geochem Health. 45(10):7081–97. https://doi.org/10.1007/s10653-023-01697-3 PMID:37542205

Miranda-Vilela AL, Botelho AJ, Muehlmann LA (2014). An overview of chemical straightening of human hair: technical aspects, potential risks to hair fibre and health and legal issues. Int J Cosmet Sci. 36(1):2–11. https://doi.org/10.1111/ics.12093 PMID:24102549

Mistry AR, Felix CA, Whitmarsh RJ, Mason A, Reiter A, Cassinat B, et al. (2005). DNA topoisomerase II in therapy-related acute promyelocytic leukemia. N Engl J Med. 352(15):1529–38. https://doi.org/10.1056/NEJMoa042715 PMID:15829534

Mitchell AD, Rudd CJ, Caspary WJ (1988). Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: intralaboratory results for sixty-three coded chemicals tested at SRI International. Environ Mol Mutagen. 12 Suppl 13:37–101. https://doi.org/10.1002/em.2860120504 PMID:3416841

Mitchell DF, Shankwalker GB, Shazer S (1960). Determining the tumorigenicity of dental materials. J Dent Res. 39(5):1023–8. https://doi.org/10.1177/00220345600390050401 PMID:13771327

Mizukami S, Ichimura R, Kemmochi S, Taniai E, Shimamoto K, Ohishi T, et al. (2010). Induction of GST-P-positive proliferative lesions facilitating lipid peroxidation with possible involvement of transferrin receptor up-regulation and ceruloplasmin down-regulation from the early stage of liver tumor promotion in rats. Arch Toxicol. 84(4):319–31. https://doi.org/10.1007/s00204-009-0496-x PMID:20091025

Moffit JS, Her LS, Mineo AM, Knight BL, Phillips JA, Thibodeau MS (2013). Assessment of inhibin B as a biomarker of testicular injury following administration of carbendazim, cetrorelix, or 1,2-dibromo-3-chloropropane in Wistar Han rats. Birth Defects Res B Dev Reprod Toxicol. 98(1):17–28. https://doi.org/10.1002/bdrb.21045 PMID:23364888

Mohr TKG, DiGuiseppi W, Hatton J, Anderson J (2020). Environmental investigation and remediation. 1,4-Dioxane and other solvent stabilizers. Second edition. Chapter 2; pp. 291–318. Abingdon, UK: Routledge. Available from: https://www.routledge.com/Environmental-Investigation-and-Remediation-14-Dioxane-and-other-Solvent-Stabilizers-Second-Edition/Mohr-DiGuiseppi-Hatton-Anderson/p/book/9781138393967?srsltid=AfmBOoqAlif7e_WF0UD-RGxmem782MrlRWZTwySsTyBO43zqGMT04sSt

Mohty M (2007). Mechanisms of action of antithymocyte globulin: T-cell depletion and beyond. Leukemia. 21(7):1387–94. https://doi.org/10.1038/sj.leu.2404683 PMID:17410187

Moir D, Rickert WS, Levasseur G, Larose Y, Maertens R, White P, et al. (2008). A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. Chem Res Toxicol. 21(2):494–502. https://doi.org/10.1021/tx700275p PMID:18062674

Moizhess TG, Vasiliev JM (1989). Early and late stages of foreign-body carcinogenesis can be induced by implants of different shapes. Int J Cancer. 44(3):449–53. https://doi.org/10.1002/ijc.2910440312https://doi.org/10.1002/ijc.2910440312 PMID:2777411

Mokra K, Kuźmińska-Surowaniec A, Woźniak K, Michałowicz J (2017). Evaluation of DNA-damaging potential of bisphenol A and its selected analogs in human peripheral blood mononuclear cells (in vitro study). Food Chem Toxicol. 100:62–9. https://doi.org/10.1016/j.fct.2016.12.003 PMID:27923681

Mokra K, Woźniak K, Bukowska B, Sicińska P, Michałowicz J (2018). Low-concentration exposure to BPA, BPF and BPAF induces oxidative DNA bases lesions in human peripheral blood mononuclear cells. Chemosphere. 201:119–26. https://doi.org/10.1016/j.chemosphere.2018.02.166 PMID:29518729

Mol JA, van Garderen E, Rutteman GR, Rijnberk A (1996). New insights in the molecular mechanism of progestin-induced proliferation of mammary epithelium: induction of the local biosynthesis of growth hormone (GH) in the mammary glands of dogs, cats and humans. J Steroid Biochem Mol Biol. 57(1–2):67–71. https://doi.org/10.1016/0960-0760(95)00251-0 PMID:8645618

Møller P, Muruzabal D, Bakuradze T, Richling E, Bankoglu EE, Stopper H, et al. (2020). Potassium bromate as positive assay control for the Fpg-modified comet assay. Mutagenesis. 35(4):341–8. https://doi.org/10.1093/mutage/geaa011 PMID:32319518

Momi N, Ponnusamy MP, Kaur S, Rachagani S, Kunigal SS, Chellappan S, et al. (2013). Nicotine/cigarette smoke promotes metastasis of pancreatic cancer through α7nAChR-mediated MUC4 upregulation. Oncogene. 32(11):1384–95. https://doi.org/10.1038/onc.2012.163 PMID:22614008

Monack DM (2012). *Salmonella* persistence and transmission strategies. Curr Opin Microbiol. 15(1):100–7. https://doi.org/10.1016/j.mib.2011.10.013 PMID:22137596

Mondal NK, Mukherjee B, Das D, Ray MR (2010). Micronucleus formation, DNA damage and repair in premenopausal women chronically exposed to high level of indoor air pollution from biomass fuel use in rural India. Mutat Res. 697(1–2):47–54. https://doi.org/10.1016/j.mrgentox.2010.02.006 PMID:20156583

Montalbano AM, Albano GD, Anzalone G, Moscato M, Gagliardo R, Di Sano C, et al. (2020). Cytotoxic and genotoxic effects of the flame retardants (PBDE-47, PBDE-99 and PBDE-209) in human bronchial epithelial cells. Chemosphere. 245:125600. https://doi.org/10.1016/j.chemosphere.2019.125600 PMID:31864052

Monteiro CA (2009). Nutrition and health. The issue is not food, nor nutrients, so much as processing. Public Health Nutr. 12(5):729–31. https://doi.org/10.1017/S1368980009005291 PMID:19366466

Monteiro CA, Cannon G, Lawrence M, Costa Louzada ML, Pereira Machado P (2019b). Ultra-processed foods, diet quality, and health using the NOVA classification system. Rome, Italy: Food and Agriculture Organization (FAO). Available from: https://openknowledge.fao.org/server/api/core/bitstreams/5277b379-0acb-4d97-a6a3-602774104629/content, accessed September 2024.

Monteiro CA, Cannon G, Levy RB, Moubarac JC, Louzada ML, Rauber F, et al. (2019a). Ultra-processed foods: what they are and how to identify them. Public Health Nutr. 22(5):936–41. https://doi.org/10.1017/S1368980018003762 PMID:30744710

Montes-Grajales D, Olivero-Verbel J (2020). Structure-based identification of endocrine disrupting pesticides targeting breast cancer proteins. Toxicology. 439:152459. https://doi.org/10.1016/j.tox.2020.152459 PMID:32278787

Montévil M, Acevedo N, Schaeberle CM, Bharadwaj M, Fenton SE, Soto AM (2020). A combined morphometric and statistical approach to assess nonmonotonicity in the developing mammary gland of rats in the CLARITY-BPA study. Environ Health Perspect. 128(5):57001. https://doi.org/10.1289/EHP6301 PMID:32438830

Moon CS (2017). Estimations of the lethal and exposure doses for representative methanol symptoms in humans. Ann Occup Environ Med. 29(1):44. https://doi.org/10.1186/s40557-017-0197-5 PMID:29026612

Moon J, Yoo H (2021). Residential radon exposure and leukemia: a meta-analysis and dose–response meta-analyses for ecological, case–control, and cohort studies. Environ Res. 202:111714. https://doi.org/10.1016/j.envres.2021.111714 PMID:34274332

Moorman WJ, Reutman SS, Shaw PB, Blade LM, Marlow D, Vesper H, et al. (2012). Occupational exposure to acrylamide in closed system production plants: air levels and biomonitoring. J Toxicol Environ Health A. 75(2):100–11. https://doi.org/10.1080/15287394.2011.615109 PMID:22129237

Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø (2017). Contemporary hormonal contraception and the risk of breast cancer. N Engl J Med. 377(23):2228–39. https://doi.org/10.1056/NEJMoa1700732 PMID:29211679

Morfeld P, McCunney RJ (2007). Carbon black and lung cancer: testing a new exposure metric in a German cohort. Am J Ind Med. 50(8):565–7. https://doi.org/10.1002/ajim.20491 PMID:17620319

Morfeld P, McCunney RJ (2009). Carbon black and lung cancer-testing a novel exposure metric by multi-model inference. Am J Ind Med. 52(11):890–9. https://doi.org/10.1002/ajim.20754 PMID:19753595

Morfeld P, McCunney RJ (2010). Bayesian bias adjustments of the lung cancer SMR in a cohort of German carbon black production workers. J Occup Med Toxicol. 5(1):23. https://doi.org/10.1186/1745-6673-5-23 PMID:20701747

Morgan DL, Dunnick JK, Goehl T, Jokinen MP, Matthews HB, Zeiger E, et al. (1994). Summary of the National Toxicology Program benzidine dye initiative. Environ Health Perspect. 102(Suppl 2) suppl 2:63–78. https://doi.org/10.1289/ehp.9410263https://doi.org/10.1289/ehp.9410263 PMID:7925189

Morgan MK (2020). Dietary pyrethroid exposures and intake doses for 188 duplicate-single solid food items consumed by North Carolina adults. Toxics. 8(1):6. https://doi.org/10.3390/toxics8010006 PMID:31978951

Morgan MK, MacMillan DK, Zehr D, Sobus JR (2018). Pyrethroid insecticides and their environmental degradates in repeated duplicate-diet solid food samples of 50 adults. J Expo Sci Environ Epidemiol. 28(1):40–5. https://doi.org/10.1038/jes.2016.69 PMID:27966670

Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, Zeiger E (1986). *Salmonella* mutagenicity tests: II. Results from the testing of 270 chemicals. Environ Mutagen. 8 Suppl 7:1–119. https://doi.org/10.1002/em.2860080802https://doi.org/10.1002/em.2860080802 PMID:3516675

Mortensen A, Aguilar F, Crebelli R, Di Domenico A, Dusemund B, Frutos MJ, et al.; EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) (2017). Re-evaluation of fatty acids (E 570) as a food additive. EFSA J. 15(5):e04785. PMID:32625490

Morton LM, Dores GM, Schonfeld SJ, Linet MS, Sigel BS, Lam CJK, et al. (2019). Association of chemotherapy for solid tumors with development of therapy-related myelodysplastic syndrome or acute myeloid leukemia in the modern era. JAMA Oncol. 5(3):318–25. https://doi.org/10.1001/jamaoncol.2018.5625 PMID:30570657

Mossanda K, Poncelet F, Fouassin A, Mercier M (1979). Detection of mutagenic polycyclic aromatic hydrocarbons in African smoked fish. Food Cosmet Toxicol. 17(2):141–3. https://doi.org/10.1016/0015-6264(79)90212-8 PMID:383588

Mounika P (2013). *Helicobacter pylori* infection and risk of lung cancer: a meta-analysis. Lung Cancer Int. 2013:131869. https://doi.org/10.1155/2013/131869 PMID:26316939

Moura-Corrêa MJ (2023). Leukemia mortality among benzene-exposed workers in Brazil (2006–2011). Int J Environ Res Public Health. 20(13):6314. https://doi.org/10.3390/ijerph20136314 PMID:37444161

Moutschen-Dahmen J, Moutschen-Dahmen M, Degraeve N, Houbrechts N, Colizzi A (1975). Proceedings: genetical hazards of aldehydes from mouse experiments. Mutat Res. 29(2):205. https://doi.org/10.1016/0027-5107(75)90130-X PMID:1186729

Moyano P, García J, García JM, Pelayo A, Muñoz-Calero P, Frejo MT, et al. (2020). Chlorpyrifos-induced cell proliferation in human breast cancer cell lines differentially mediated by estrogen and aryl hydrocarbon receptors and KIAA1363 enzyme after 24 h and 14 days exposure. Chemosphere. 251:126426. https://doi.org/10.1016/j.chemosphere.2020.126426 PMID:32171938

Moyano P, García JM, García J, Pelayo A, Muñoz-Calero P, Frejo MT, et al. (2021). Chlorpyrifos induces cell proliferation in MCF-7 and MDA-MB-231 cells, through cholinergic and Wnt/β-catenin signalling disruption, AChE-R upregulation and oxidative stress generation after single and repeated treatment. Food Chem Toxicol. 152:112241. https://doi.org/10.1016/j.fct.2021.112241 PMID:33930485

Mpountoukas P, Pantazaki A, Kostareli E, Christodoulou P, Kareli D, Poliliou S, et al. (2010). Cytogenetic evaluation and DNA interaction studies of the food colorants amaranth, erythrosine and tartrazine. Food Chem Toxicol. 48(10):2934–44. https://doi.org/10.1016/j.fct.2010.07.030 PMID:20667460

Msibi SS, Chen CY, Chang CP, Chen CJ, Chiang SY, Wu KY (2021). High pesticide inhalation exposure from multiple spraying sources amongst applicators in Eswatini, southern Africa. Pest Manag Sci. 77(10):4303–12. https://doi.org/10.1002/ps.6459 PMID:33942970

Msibi SS, Su LJ, Chen CY, Chang CP, Chen CJ, Wu KY, et al. (2023). Impacts of agricultural pesticide contamination: an integrated risk assessment of rural communities of Eswatini. Toxics. 11(9):770. https://doi.org/10.3390/toxics11090770 PMID:37755780

Mueller WH (2006). Dental amalgam fillings and cancer – consideration of long-term processes. Onkologie. 29(5):227–30. https://karger.com/onk/article-abstract/29/5/227/244561/Dental-Amalgam-Fillings-and-Cancer-Consideration?redirectedFrom=PDF PMID:16679785

Mughini-Gras L, Schaapveld M, Kramers J, Mooij S, Neefjes-Borst EA, Pelt WV, et al. (2018). Increased colon cancer risk after severe *Salmonella* infection. PLoS One. 13(1):e0189721. https://doi.org/10.1371/journal.pone.0189721 PMID:29342165

Muguruma M, Kawai M, Dewa Y, Nishimura J, Saegusa Y, Yasuno H, et al. (2009). Threshold dose of piperonyl butoxide that induces reactive oxygen species-mediated hepatocarcinogenesis in rats. Arch Toxicol. 83(2):183–93. https://doi.org/10.1007/s00204-008-0340-8https://doi.org/10.1007/s00204-008-0340-8 PMID:18648771

Muguruma M, Unami A, Kanki M, Kuroiwa Y, Nishimura J, Dewa Y, et al. (2007). Possible involvement of oxidative stress in piperonyl butoxide induced hepatocarcinogenesis in rats. Toxicology. 236(1–2):61–75. https://doi.org/10.1016/j.tox.2007.03.025 PMID:17498859

Muhammed F, Dogan D (2021). Toxicity and biochemical responses induced by phosmet in rainbow trout (*Oncorhynchus mykiss*). Toxicol Res (Camb). 10(5):983–91. https://doi.org/10.1093/toxres/tfab084 PMID:34733483

Mukherjee B, Dutta A, Roychoudhury S, Ray MR (2013). Chronic inhalation of biomass smoke is associated with DNA damage in airway cells: involvement of particulate pollutants and benzene. J Appl Toxicol. 33(4):281–9. https://doi.org/10.1002/jat.1748 PMID:22131134

Mukherjee D, Coffey M, Maisels MJ (2018). Frequency and duration of phototherapy in preterm infants <35 weeks gestation. J Perinatol. 38(9):1246–51. https://doi.org/10.1038/s41372-018-0153-4 PMID:29915375

Mulder FJ, Klufah F, Janssen FME, Farshadpour F, Willems SM, de Bree R, et al. (2021). Presence of human papillomavirus and Epstein–Barr virus, but absence of Merkel cell polyomavirus, in head and neck cancer of non-smokers and non-drinkers. Front Oncol. 10:560434. https://doi.org/10.3389/fonc.2020.560434 PMID:33552950

Mullee A, Romaguera D, Pearson-Stuttard J, Viallon V, Stepien M, Freisling H, et al. (2019). Association between soft drink consumption and mortality in 10 European countries. JAMA Intern Med. 179(11):1479–90. https://doi.org/10.1001/jamainternmed.2019.2478 PMID:31479109

Muller J, Delos M, Panin N, Rabolli V, Huaux F, Lison D (2009). Absence of carcinogenic response to multiwall carbon nanotubes in a 2-year bioassay in the peritoneal cavity of the rat. Toxicol Sci. 110(2):442–8. https://doi.org/10.1093/toxsci/kfp100 PMID:19429663

Müller P, Stock T, Bauer S, Wolff I (2002). Genotoxicological characterisation of complex mixtures. Genotoxic effects of a complex mixture of perhalogenated hydrocarbons. Mutat Res. 515(1–2):99–109. https://doi.org/10.1016/S1383-5718(02)00005-0 PMID:11909758

Mullington JM, Simpson NS, Meier-Ewert HK, Haack M (2010). Sleep loss and inflammation. Best Pract Res Clin Endocrinol Metab. 24(5):775–84. https://doi.org/10.1016/j.beem.2010.08.014 PMID:21112025

Multigner L, Ndong JR, Giusti A, Romana M, Delacroix-Maillard H, Cordier S, et al. (2010). Chlordecone exposure and risk of prostate cancer. J Clin Oncol. 28(21):3457–62. https://doi.org/10.1200/JCO.2009.27.2153 PMID:20566993

Mulvenon AR (2015). Occupational exposure to isoflurane anesthetic gas in the research environment. Dissertation. Omaha (NB), USA: University of Nebraska Medical Centre, Environmental Health, Occupational Health & Toxicology Graduate Program. Available from: https://digitalcommons.unmc.edu/cgi/viewcontent.cgi?article=1028&context=etd, accessed September 2024.

Mumford JL, Helmes CT, Lee XM, Seidenberg J, Nesnow S (1990). Mouse skin tumorigenicity studies of indoor coal and wood combustion emissions from homes of residents in Xuan Wei, China with high lung cancer mortality. Carcinogenesis. 11(3):397–403. https://doi.org/10.1093/carcin/11.3.397 PMID:2311182

Mumford JL, Lee X, Lewtas J, Young TL, Santella RM (1993). DNA adducts as biomarkers for assessing exposure to polycyclic aromatic hydrocarbons in tissues from Xuan Wei women with high exposure to coal combustion emissions and high lung cancer mortality. Environ Health Perspect. 99:83–7. https://doi.org/10.1289/ehp.939983 PMID:8319664

Munnia A, Bollati V, Russo V, Ferrari L, Ceppi M, Bruzzone M, et al. (2023). Traffic-related air pollution and ground-level ozone associated global DNA hypomethylation and bulky DNA adduct formation. Int J Mol Sci. 24(3):2041. https://doi.org/10.3390/ijms24032041 PMID:36768368

Muñoz-Quezada MT, Iglesias V, Lucero B, Steenland K, Barr DB, Levy K, et al. (2012). Predictors of exposure to organophosphate pesticides in schoolchildren in the province of Talca, Chile. Environ Int. 47:28–36. https://doi.org/10.1016/j.envint.2012.06.002 PMID:22732215

Murphy CC, Cirillo PM, Krigbaum NY, Singal AG, Jones DP, Zaki T, et al. (2023). In-utero exposure to antibiotics and risk of colorectal cancer in a prospective cohort of 18 000 adult offspring. Int J Epidemiol. 52(5):1448–58. https://doi.org/10.1093/ije/dyad004 PMID:36692207

Murray AR, Kisin ER, Kommineni C, Vallyathan V, Castranova V, Shvedova AA (2007b). Pro/antioxidant status and AP-1 transcription factor in murine skin following topical exposure to cumene hydroperoxide. Carcinogenesis. 28(7):1582–8. https://doi.org/10.1093/carcin/bgm001 PMID:17234724

Murray TJ, Maffini MV, Ucci AA, Sonnenschein C, Soto AM (2007a). Induction of mammary gland ductal hyperplasias and carcinoma in situ following fetal bisphenol A exposure. Reprod Toxicol. 23(3):383–90. https://doi.org/10.1016/j.reprotox.2006.10.002https://doi.org/10.1016/j.reprotox.2006.10.002 PMID:17123778

Musthapa MS, Lohani M, Tiwari S, Mathur N, Prasad R, Rahman Q (2004). Cytogenetic biomonitoring of Indian women cooking with biofuels: micronucleus and chromosomal aberration tests in peripheral blood lymphocytes. Environ Mol Mutagen. 43(4):243–9. https://doi.org/10.1002/em.20018 PMID:15141363

Mutlu E, Warren SH, Ebersviller SM, Kooter IM, Schmid JE, Dye JA, et al. (2016). Mutagenicity and pollutant emission factors of solid-fuel cookstoves: comparison with other combustion sources. Environ Health Perspect. 124(7):974–82. https://doi.org/10.1289/ehp.1509852 PMID:26895221

Mužinić V, Ramić S, Želježić D (2019). Chromosome missegregation and aneuploidy induction in human peripheral blood lymphocytes in vitro by low concentrations of chlorpyrifos, imidacloprid and α-cypermethrin. Environ Mol Mutagen. 60(1):72–84. https://doi.org/10.1002/em.22235 PMID:30264469

Myhr BC, Caspary WJ (1988). Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: intralaboratory results for sixty-three coded chemicals tested at Litton Bionetics, Inc. Environ Mol Mutagen. 12 Suppl 13:103–94. https://doi.org/10.1002/em.2860120505 PMID:3416838

Na J, Chen H, An H, Li N, Yan L, Ye R, et al. (2022). Association of rare earth elements with passive smoking among housewives in Shanxi Province, China. Int J Environ Res Public Health. 19(1):559. https://doi.org/10.3390/ijerph19010559 PMID:35010818

Nadarajah V, Cohen RE, Neiders ME, Aguirre A (1996). Cellular inflammatory responses to implanted dental materials. J Prosthet Dent. 75(5):552–61. https://doi.org/10.1016/S0022-3913(96)90462-X PMID:8709023

Nagai A, Kano Y, Funasaka R, Nakamuro K (2002). Mutagenic characteristics and contribution of polycyclic aromatic hydro-carbons to mutagenicity of concentrates from municipal riverwater by blue chitin column. J Health Sci. 48(3):232–41. https://doi.org/10.1248/jhs.48.232

Nagano K, Sasaki T, Umeda Y, Nishizawa T, Ikawa N, Ohbayashi H, et al. (2007). Inhalation carcinogenicity and chronic toxicity of carbon tetrachloride in rats and mice. Inhal Toxicol. 19(13):1089–103. https://doi.org/10.1080/08958370701628770 PMID:17957549

Nagaraja V, Eslick GD (2014). Systematic review with meta-analysis: the relationship between chronic *Salmonella typhi* carrier status and gall-bladder cancer. Aliment Pharmacol Ther. 39(8):745–50. https://doi.org/10.1111/apt.12655 PMID:24612190

Nagpal N, Bettiol SS, Isham A, Hoang H, Crocombe LA (2017). A review of mercury exposure and health of dental personnel. Saf Health Work. 8(1):1–10. https://doi.org/10.1016/j.shaw.2016.05.007 PMID:28344835

Nakamura H, Wang Y, Kurita T, Adomat H, Cunha GR, Wang Y (2011). Genistein increases epidermal growth factor receptor signalling and promotes tumor progression in advanced human prostate cancer. PLoS One. 6(5):e20034. https://doi.org/10.1371/journal.pone.0020034 PMID:21603581

Naldini L (2015). Gene therapy returns to centre stage. Nature. 526(7573):351–60. https://doi.org/10.1038/nature15818 PMID:26469046

Narizzano AM, Bohannon ME, East AG, Guigni BA, Quinn MJ Jr (2023). Reproductive and immune effects emerge at similar thresholds of PFHxS in deer mice. Reprod Toxicol. 120:108421. https://doi.org/10.1016/j.reprotox.2023.108421https://doi.org/10.1016/j.reprotox.2023.108421 PMID:37330177

Narula N, Wong ECL, Dehghan M, Mente A, Rangarajan S, Lanas F, et al. (2021). Association of ultra-processed food intake with risk of inflammatory bowel disease: prospective cohort study. BMJ. 374(1554):n1554. https://doi.org/10.1136/bmj.n1554 PMID:34261638

Narumi K, Ashizawa K, Takashima R, Takasawa H, Katayama S, Tsuzuki Y, et al. (2012). Development of a repeated-dose liver micronucleus assay using adult rats: an investigation of diethylnitrosamine and 2,4-diaminotoluene. Mutat Res. 747(2):234–9. https://doi.org/10.1016/j.mrgentox.2012.05.012 PMID:22677510

Nascimento-Gonçalves E, Seixas F, Palmeira C, Martins G, Fonseca C, Duarte JA, et al. (2024). Lifelong exercise training promotes the remodelling of the immune system and prostate signallome in a rat model of prostate carcinogenesis. Geroscience. 46(1):817–40. https://doi.org/10.1007/s11357-023-00806-5 PMID:37171559

Nashev LG, Schuster D, Laggner C, Sodha S, Langer T, Wolber G, et al. (2010). The UV-filter 2,4-dihydroxybenzophenone inhibits 17beta-hydroxysteroid dehydrogenase type 3: virtual screening as a strategy to identify potential endocrine disrupting chemicals. Biochem Pharmacol. 79(8):1189–99. https://doi.org/10.1016/j.bcp.2009.12.005 PMID:20005209

National Industrial Chemicals Notification and Assessment Scheme (1989). File No.: LTD/1021 Polyhexamethyleneguanidine phosphate. Chemicals Notification and Assessment. Surry Hills (NSW), Australia: National Industrial Chemicals Notification and Assessment Scheme. Available from: https://www.industrialchemicals.gov.au/sites/default/files/LTD1021 Public Report PDF.pdf, accessed September 2024.

Nauclér CS, Geisler J, Vetvik K (2019). The emerging role of human cytomegalovirus infection in human carcinogenesis: a review of current evidence and potential therapeutic implications. Oncotarget. 10(42):4333–47. https://doi.org/10.18632/oncotarget.27016 PMID:31303966

Navaneethan U, Parsi MA, Gutierrez NG, Bhatt A, Venkatesh PG, Lourdusamy D, et al. (2014). Volatile organic compounds in bile can diagnose malignant biliary strictures in the setting of pancreatic cancer: a preliminary observation. Gastrointest Endosc. 80(6):1038–45. https://doi.org/10.1016/j.gie.2014.04.016 PMID:24929484

Navaneethan U, Parsi MA, Lourdusamy V, Bhatt A, Gutierrez NG, Grove D, et al. (2015). Volatile organic compounds in bile for early diagnosis of cholangiocarcinoma in patients with primary sclerosing cholangitis: a pilot study. Gastrointest Endosc. 81(4):943–9.e1. https://doi.org/10.1016/j.gie.2014.09.041 PMID:25500329

Navarrete-Meneses MP, Salas-Labadía C, Sanabrais-Jiménez M, Santana-Hernández J, Serrano-Cuevas A, Juárez-Velázquez R, et al. (2017). Exposure to the insecticides permethrin and malathion induces leukemia and lymphoma-associated gene aberrations in vitro. Toxicol In Vitro. 44:17–26. https://doi.org/10.1016/j.tiv.2017.06.013 PMID:28624474

Navarro I, de la Torre A, Sanz P, Baldi I, Harkes P, Huerta-Lwanga E, et al. (2023b). Occurrence of pesticide residues in indoor dust of farmworker households across Europe and Argentina. Sci Total Environ. 905:167797. https://doi.org/10.1016/j.scitotenv.2023.167797 PMID:37838044

Navarro KM, Fent K, Mayer AC, Brueck SE, Toennis C, Law B, et al. (2023a). Characterization of inhalation exposures at a wildfire incident during the Wildland Firefighter Exposure and Health Effects (WFFEHE) Study. Ann Work Expo Health. 67(8):1011–7. https://doi.org/10.1093/annweh/wxad046 PMID:37597244

Navarro-Lafuente F, Adoamnei E, Arense-Gonzalo JJ, Prieto-Sánchez MT, Sánchez-Ferrer ML, Parrado A, et al.; NELA Study group (2022). Maternal urinary concentrations of bisphenol A during pregnancy are associated with global DNA methylation in cord blood of newborns in the "NELA" birth cohort. Sci Total Environ. 838(Pt 4):156540. https://doi.org/10.1016/j.scitotenv.2022.156540 PMID:35688234

NCBI (2020). Biphenyl. PubChem compound summary for CID 7095. Bethesda (MD), USA: National Center for Biotechnology Information, United States National Library of Medicine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Biphenyl, accessed December 2023.

NCBI (2024a). Ethyl anthranilate. PubChem compound summary for CID 6877. Bethesda (MD), USA: National Center for Biotechnology Information, United States National Library of Medicine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/6877, accessed January 2024.

NCBI (2024b). Menthyl anthranilate. PubChem compound summary for CID 8633. Bethesda (MD), USA: National Center for Biotechnology Information, United States National Library of Medicine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/8633, accessed January 2024.

NCBI (2024c). Methyl anthranilate. PubChem compound summary for CID 8635. Bethesda (MD), USA: National Center for Biotechnology Information, United States National Library of Medicine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/8635, accessed January 2024.

NCBI (2024d). *p*-Phenylenediamine. PubChem compound summary. Bethesda (MD), USA: National Center for Biotechnology Information, United States National Library of Medicine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/p-Phenylenediamine, accessed January 2024.

NCBI (2024e). Allyl alcohol. PubChem compound summary for CID 7858. Bethesda (MD), USA: National Center for Biotechnology Information, United States National Library of Medicine. Available from https://pubchem.ncbi.nlm.nih.gov/compound/Allyl-alcohol, accessed December 2023.

NCBI (2024f). *p*-Cresol. PubChem compound summary for CID 6877. Bethesda (MD), USA: National Center for Biotechnology Information, United States National Library of Medicine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/2879, accessed January 2024.

NCBI (2024g). Butyraldehyde. PubChem compound summary for CID 261. Bethesda (MD), USA: National Center for Biotechnology Information, United States National Library of Medicine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/261, accessed January 2024.

NCBI (2024h). 2-Benzyl-4-chlorophenol (compound). PubChem compound summary. Bethesda (MD), USA: National Center for Biotechnology Information, United States National Library of Medicine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/2-Benzyl-4-chlorophenol#section=Probable-Routes-of-Human-Exposure, accessed June 2024.

NCI (1979a). Bioassay of sodium diethyldithiocarbamate for possible carcinogenicity. Bethesda (MD), USA: National Cancer Institute, U.S. Department of Health, Education, and Welfare. Technical Report Series No. 172. Available at: https://ntp.niehs.nih.gov/publications/reports/tr/100s/tr172, accessed September 2024.

NCI (1979b). Bioassay of piperonyl butoxide for possible carcinogenicity. Carcinogenesis. NCI-CG-TR-120 Technical Report Series NO. 120. Bethesda (MD), USA: National Cancer Institute, U.S. Department of Health, Education, and Welfare. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr120.pdf, accessed September 2024.

NCI (1979c). Bioassay of *p*-cresidine for possible carcinogenicity (CAS no. 120-71-8). NCI-CG-TR-142. Technical report series No. 142. Bethesda (MD), USA: National Cancer Institute, U.S. Department of Health and Human Services. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr142.pdf, accessed September 2024.

NCI (1980) Bioassay of cinnamyl anthranilate for possible carcinogenicity (Tech. Rep. Ser. No. 196; DHEW Publ. No. (NIH) 80–1752, No. (NTP) 80–10). Washington (DC), USA: Government Printing Office.

NCI (2014). The "accidental" cure – platinum-based treatment for cancer: the discovery of cisplatin. Bethesda (MD), USA: National Cancer Institute, U.S. Department of Health, Education, and Welfare. Available from: https://www.cancer.gov/research/progress/discovery/cisplatin, accessed January 2024.

NCI (2017). Acrylamide and cancer risk. Bethesda (MD), USA: National Cancer Institute, U.S. Department of Health, Education, and Welfare. Available from: https://www.cancer.gov/about-cancer/causes-prevention/risk/diet/acrylamide-fact-sheet, accessed January 2024.

NCI (2022). Virtual Pooled Registry – Cancer Linkage System (VPR–CLS) Project. Bethesda (MD), USA: National Cancer Institute, U.S. Department of Health, Education, and Welfare. Available from: https://surveillance.cancer.gov/research/vpr-cls.html, accessed December 2023.

Neagu N, Dianzani C, Venuti A, Bonin S, Voidăzan S, Zalaudek I, et al. (2023). The role of HPV in keratinocyte skin cancer development: a systematic review. J Eur Acad Dermatol Venereol. 37(1):40–6. https://doi.org/10.1111/jdv.18548 PMID:36000380

Neale PA, Stalter D, Tang JYM, Escher BI (2015). Bioanalytical evidence that chemicals in tattoo ink can induce adaptive stress responses. J Hazard Mater. 296:192–200. https://doi.org/10.1016/j.jhazmat.2015.04.051 PMID:25929673

NEDO (1985a). 24-month inhalation carcinogenicity study on methanol in Fischer rats (test no.: 5A–268). Volumes 1–10. Tokyo, Japan: Mitsubishi Kasei Institute for Toxicological and Environmental Sciences. Available from: https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/196316

NEDO (1985b). 18-month inhalation carcinogenicity study of methanol in B6C3F_1 mice (test no.: 4A–223). Volumes 1–9. Tokyo, Japan: Mitsubishi Kasei Institute for Toxicological and Environmental Sciences.

Negi S, Shukla S, Patel SK, Vikram A, Gaur P, Kamar MD, et al. (2023). Benzo(ghi)perylene (BgP) a black tattoo ingredient induced skin toxicity via direct and indirect mode of DNA damage under UVA irradiation. Chem Biol Interact. 379:110508. https://doi.org/10.1016/j.cbi.2023.110508 PMID:37150498

Negro F, Lok AS, Hepatitis D (2023). Hepatitis D: a review. JAMA. 330(24):2376–87. https://doi.org/10.1001/jama.2023.23242 PMID:37943548

Nehlig A, Cunha RA (2020). The coffee–acrylamide apparent paradox: an example of why the health impact of a specific compound in a complex mixture should not be evaluated in isolation. Nutrients. 12(10):3141. https://doi.org/10.3390/nu12103141 PMID:33066651

Nelson GB, Ross JA (1998). DNA adduct formation by the pesticide alachlor and its metabolite 2-chloro-N-(2,6-diethylphenyl)acetamide (CDEPA). Bull Environ Contam Toxicol. 60(3):387–94. https://doi.org/10.1007/s001289900638 PMID:9528697

Nelson JS, Burchfiel CM, Fekedulegn D, Andrew ME (2012). Potential risk factors for incident glioblastoma multiforme: the Honolulu Heart Program and Honolulu–Asia Aging Study. J Neurooncol. 109(2):315–21. https://doi.org/10.1007/s11060-012-0895-3 PMID:22588335

Nemmar A, Yuvaraju P, Beegam S, Fahim MA, Ali BH (2017). Cerium oxide nanoparticles in lung acutely induce oxidative stress, inflammation, and DNA damage in various organs of mice. Oxid Med Cell Longev. 2017(1):9639035. https://doi.org/10.1155/2017/9639035 PMID:28392888

Nepal C, Zhu B, O'Rourke CJ, Bhatt DK, Lee D, Song L, et al.; CGR Exome Studies Group (2021). Integrative molecular characterisation of gallbladder cancer reveals micro-environment-associated subtypes. J Hepatol. 74(5):1132–44. https://doi.org/10.1016/j.jhep.2020.11.033 PMID:33276026

Nesić D, Hsu Y, Stebbins CE (2004). Assembly and function of a bacterial genotoxin. Nature. 429(6990):429–33. https://doi.org/10.1038/nature02532 PMID:15164065

Nesslany F, Simar-Meintières S, Watzinger M, Talahari I, Marzin D (2008). Characterization of the genotoxicity of nitrilotriacetic acid. Environ Mol Mutagen. 49(6):439–52. https://doi.org/10.1002/em.20403 PMID:18449932

Neta G, Stewart PA, Rajaraman P, Hein MJ, Waters MA, Purdue MP, et al. (2012). Occupational exposure to chlorinated solvents and risks of glioma and meningioma in adults. Occup Environ Med. 69(11):793–801. https://doi.org/10.1136/oemed-2012-100742 PMID:22864249

Neves MB, Silva Junior UND, Gonçalves AF, Fagundes LS, Abreu AC, Takita LC, et al. (2023). The effect of aerobic and resistance exercise on the progression of colorectal cancer in an animal model. Acta Cir Bras. 38:e384923. https://doi.org/10.1590/acb384923 PMID:37878986

Nevstad NP (1978). Sister chromatid exchanges and chromosomal aberrations induced in human lymphocytes by the cytostatic drug adriamycin in vivo and in vitro. Mutat Res. 57(2):253–8. https://doi.org/10.1016/0027-5107(78)90275-0 PMID:661843

New Jersey Department of Health (2017) Allyl alcohol. Right to know. Hazardous substances fact sheet. Trenton (NJ), USA: New Jersey Health. Available from: https://www.nj.gov/health/eoh/rtkweb/documents/fs/0036.pdf, accessed December 2023.

Newhook R, Meek ME, Caldbick D (2002). Carbon disulfide. Concise international chemical assessment document 46. Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety; Available from https://apps.who.int/iris/handle/10665/42554

Newman TB, Wickremasinghe AC, Walsh EM, Grimes BA, McCulloch CE, Kuzniewicz MW (2016). Retrospective cohort study of phototherapy and childhood cancer in northern California. Pediatrics. 137(6):e20151354. https://doi.org/10.1542/peds.2015-1354 PMID:27217477

Ngoc LTN, Park D, Lee YC (2022). Human health impacts of residential radon exposure: updated systematic review and meta-analysis of case–control studies. Int J Environ Res Public Health. 20(1):97. https://doi.org/10.3390/ijerph20010097 PMID:36612419

Nguyen A, Crespi CM, Vergara X, Kheifets L (2023). Pesticides as a potential independent childhood leukemia risk factor and as a potential confounder for electromagnetic fields exposure. Environ Res. 238(Pt 1):116899. https://doi.org/10.1016/j.envres.2023.116899 PMID:37598846

Nguyen HT, Kawahara M, Vuong CK, Fukushige M, Yamashita T, Ohneda O (2022). SARS-CoV-2 M protein facilitates malignant transformation of breast cancer cells. Front Oncol. 12:923467. https://doi.org/10.3389/fonc.2022.923467 PMID:35747796

NHS England (2018). Breast and Cosmetic Implant Registry – October 2016 to June 2018, management information. London, UK: NHS England. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/mi-breast-and-cosmetic-implant-registry/oct16-jun18, accessed January 2024.

NHS UK (2022). Guidance. Carbon tetrachloride: general information. London, UK: UK Health Security Agency Radiation, Chemicals and Environment Directorate. Available from: https://www.gov.uk/government/publications/carbon-tetrachloride-properties-incident-management-and-toxicology/carbon-tetrachloride-general-information, accessed March 2024.

Ni C, Li C, Dong Y, Guo X, Zhang Y, Xie Z (2017). Anesthetic isoflurane induces DNA damage through oxidative stress and p53 pathway. Mol Neurobiol. 54(5):3591–605. https://doi.org/10.1007/s12035-016-9937-8 PMID:27194299

NICNAS (2014). 1,2-Benzenediol: human health tier II assessment. IMAP single assessment report. Southbank (VIC), Australia: National Industrial Chemicals Notification and Assessment Scheme. Available from: https://cdnservices.industrialchemicals.gov.au/statements/IMAP_2%20-%20IMAP%20Assessment%20-%2004%20July%202014.pdf, accessed September 2024.

Nielsen C, Andréasson K, Olsson H, Engfeldt M, Jöud A (2023). Cohort profile: the Swedish Tattoo and Body Modifications Cohort (TABOO). BMJ Open. 13(5):e069664. https://doi.org/10.1136/bmjopen-2022-069664 PMID:37142309

Nielsen NR, Stahlberg C, Strandberg-Larsen K, Kristensen TS, Zhang ZF, Hundrup YA, et al. (2008). Are work-related stressors associated with diagnosis of more advanced stages of incident breast cancers? Cancer Causes Control. 19(3):297–303. https://doi.org/10.1007/s10552-007-9092-7 PMID:18027093

Nieto FJ, Peppard PE, Young T, Finn L, Hla KM, Farré R (2012). Sleep-disordered breathing and cancer mortality: results from the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med. 186(2):190–4. https://doi.org/10.1164/rccm.201201-0130OC PMID:22610391

NIH (2024a). Daunorubicin. Molecular targets platform. Bethesda (MD), USA: National Cancer Institute, National Institute of Health, US Department of Health and Human Services. Available from: https://moleculartargets.ccdi.cancer.gov/drug/CHEMBL178, accessed January 2024.

NIH (2024b). *p*-Nitrotoluene. E88IMG14EX. Inxight Drugs [online database]. Rockville (MD), USA: National Centre for Advancing Translational Sciences, National Institute of Health. Available from: https://drugs.ncats.io/substance/E88IMG14EX, accessed January 2024.

Nikaido Y, Yoshizawa K, Pei RJ, Yuri T, Danbara N, Hatano T, et al. (2003). Prepubertal zearalenone exposure suppresses *N*-methyl-*N*-nitrosourea-induced mammary tumorigenesis but causes severe endocrine disruption in female Sprague-Dawley rats. Nutr Cancer. 47(2):164–70. https://doi.org/10.1207/s15327914nc4702_9 PMID:15087269

Nikkilä A, Arvela H, Mehtonen J, Raitanen J, Heinäniemi M, Lohi O, et al. (2020). Predicting residential radon concentrations in Finland: model development, validation, and application to childhood leukemia. Scand J Work Environ Health. 46(3):278–92. https://doi.org/10.5271/sjweh.3867 PMID:31763683

Nikula KJ, Avila KJ, Griffith WC, Mauderly JL (1997). Lung tissue responses and sites of particle retention differ between rats and cynomolgus monkeys exposed chronically to diesel exhaust and coal dust. Fundam Appl Toxicol. 37(1):37–53. https://doi.org/10.1006/faat.1997.2297 PMID:9193921

Nilsson E, King SE, McBirney M, Kubsad D, Pappalardo M, Beck D, et al. (2018). Vinclozolin induced epigenetic transgenerational inheritance of pathologies and sperm epimutation biomarkers for specific diseases. PLoS One. 13(8):e0202662. https://doi.org/10.1371/journal.pone.0202662 PMID:30157260

NIOSH (1983). Glycerol. National Occupational Exposure Survey (1981–1983). Estimated numbers of employees potentially exposed to specific agents by 2-digit Standard Industrial Classification (SIC). Washington (DC), USA: National Institute for Occupational Safety and Health. Available from: https://web.archive.org/web/20111026171131/http://www.cdc.gov/noes/noes1/35085sic.html, accessed September 2024.

NIOSH (1990a). C.I. Solvent Yellow 3. National Occupational Exposure Survey (1981–1983). Washington (DC), USA: National Institute for Occupational Safety and Health. Available from:

https://web.archive.org/web/20060327114426/http://www.cdc.gov/noes/noes1/m1409sic.html, accessed July 2024.

NIOSH (1990b). Thioacetamide. National Occupational Exposure Survey (1981–1983). Washington (DC), USA: National Institute for Occupational Safety and Health. Available from: https://web.archive.org/web/20041228151321/http://www.cdc.gov/noes/noes1/83086sic.html, accessed July 2024.

NIOSH (2011). Health hazard evaluation report: formaldehyde exposures during Brazilian Blowout hair smoothing treatment at a hair salon – Ohio. By Durgam S, Page E. Cincinnati (OH), USA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. Available from: https://www.cdc.gov/niosh/hhe/reports/pdfs/2011-0014-3147.pdf

NIOSH (2013). Current intelligence bulletin 65: occupational exposure to carbon nanotubes and nanofibers. By: Zumwalde R; Kuempel E; Birch E; Trout D; Castranova. Cincinnati (OH), USA: US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2013–145. Available from: https://www.cdc.gov/niosh/docs/2013-145/, accessed September 2024.

NIOSH (2016a). Criteria for a recommended standard: occupational exposure to diacetyl and 2,3-pentanedione. By McKernan LT, Niemeier RT, Kreiss K, Hubbs A, Park R, Dankovic D, et al. Cincinnati (OH), USA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2016–111. Available from: https://www.cdc.gov/niosh/docs/2016-111/default.html, accessed September 2024.

NIOSH (2016b). NIOSH list of antineoplastic and other hazardous drugs in healthcare settings. By Connor TH, MacKenzie BA, DeBord DG, Trout DB, O'Callaghan JP. Cincinnati (OH), USA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. Available from: https://www.cdc.gov/niosh/docs/2016-161/default.html, accessed March 2024.

NIOSH (2024). Adult blood lead epidemiology and surveillance (ABLES) program. Available from: https://www.cdc.gov/niosh/lead/programs/index.html, accessed March 2024.

Nitiss JL (2009). Targeting DNA topoisomerase II in cancer chemotherapy. Nat Rev Cancer. 9(5):338–50. https://doi.org/10.1038/nrc2607 PMID:19377506

Niu Y, Chen R, Xia Y, Cai J, Lin Z, Liu C, et al. (2018). Personal ozone exposure and respiratory inflammatory response: the role of DNA methylation in the arginase–nitric oxide synthase pathway. Environ Sci Technol. 52(15):8785–91. https://doi.org/10.1021/acs.est.8b01295 PMID:29985591

Njumbe Ediage E, Diana Di Mavungu J, Song S, Sioen I, De Saeger S (2013). Multimycotoxin analysis in urines to assess infant exposure: a case study in Cameroon. Environ Int. 57–58:50–9. https://doi.org/10.1016/j.envint.2013.04.002 PMID:23669720

Nocturne G, Pascaud J, Ly B, Tahmasebi F, Mariette X (2020). JAK inhibitors alter NK cell functions and may impair immunosurveillance against lymphomagenesis. Cell Mol Immunol. 17(5):552–3. https://doi.org/10.1038/s41423-019-0320-3 PMID:31664224

Noël A, Ghosh A (2022). Carbonyl profiles of electronic nicotine delivery system (ENDS) aerosols reflect both the chemical composition and the numbers of E-liquid ingredients-focus on the *in vitro* toxicity of strawberry and vanilla flavors. Int J Environ Res Public Health. 19(24):16774. https://doi.org/10.3390/ijerph192416774 PMID:36554655

Nogueira E (1987). Rat renal carcinogenesis after chronic simultaneous exposure to lead acetate and N-nitrosodiethylamine. Virchows Arch B Cell Pathol Incl Mol Pathol. 53(6):365–74. https://doi.org/10.1007/BF02890265 PMID:2891221

Nogueira L, Foerster C, Groopman J, Egner P, Koshiol J, Ferreccio C; Gallbladder Cancer Chile Working Group (2015). Association of aflatoxin with gallbladder cancer in Chile. JAMA. 313(20):2075–7. https://doi.org/10.1001/jama.2015.4559 PMID:26010638

Nomura H, Hamada R, Wada K, Saito I, Nishihara N, Kitahara Y, et al. (2022). Temporal trend and cross-sectional characterization of urinary concentrations of glyphosate in Japanese children from 2006 to 2015. Int J Hyg Environ Health. 242:113963. https://doi.org/10.1016/j.ijheh.2022.113963

Norén E, Lindh C, Rylander L, Glynn A, Axelsson J, Littorin M, et al. (2020). Concentrations and temporal trends in pesticide biomarkers in urine of Swedish adolescents, 2000–2017. J Expo Sci Environ Epidemiol. 30(4):756–67. https://doi.org/10.1038/s41370-020-0212-8

Norppa H, Sorsa M, Vainio H, Gröhn P, Heinonen E, Holsti L, et al. (1980). Increased sister chromatid exchange frequencies in lymphocytes of nurses handling cytostatic drugs. Scand J Work Environ Health. 6(4):299–301. https://doi.org/10.5271/sjweh.2605

Notani PN, Shah P, Jayant K, Balakrishnan V (1993). Occupation and cancers of the lung and bladder: a case–control study in Bombay. Int J Epidemiol. 22(2):185–91. https://doi.org/10.1093/ije/22.2.185

Nováková K, Bláha L, Babica P (2012). Tumor promoting effects of cyanobacterial extracts are potentiated by anthropogenic contaminants – evidence from in vitro study. Chemosphere. 89(1):30–7. https://doi.org/10.1016/j.chemosphere.2012.04.008

Novoselov SV, Calvisi DF, Labunskyy VM, Factor VM, Carlson BA, Fomenko DE, et al. (2005). Selenoprotein deficiency and high levels of selenium compounds can effectively inhibit hepatocarcinogenesis in transgenic mice. Oncogene. 24(54):8003–11. https://doi.org/10.1038/sj.onc.1208940

NTIS (1968). Evaluation of carcinogenic, teratogenic and mutagenic activities of selected pesticides and industrial chemicals. Volume I. Carcinogenic study. Report no. NCI-DCCP-CG-1973–1-1. Springfield (VA), USA: National Technical Information Service, U.S. Department of Commerce. Available from: https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=PB223159, accessed March 2024.

NTP (1977). Bioassays of nitrilotriacetic acid (NTA) and nitrilotriacetic acid, trisodium salt, monohydrate (Na_3-NTA-H_2O) for possible carcinogenicity. Natl Cancer Inst Carcinog Tech Rep Ser. 6:1–203. Available from https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr006.pdf

NTP (1978). Bioassay of 5-nitro-o-toluidine for possible carcinogenicity (CAS no. 99-55-8). Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/publications/reports/tr/100s/tr107, accessed September 2024.

NTP (1979). Bioassay of 2,4-diaminotoluene for possible carcinogenicity. Natl Cancer Inst Carcinog Tech Rep Ser. 162:1–139. https://ntp.niehs.nih.gov/publications/reports/tr/100s/tr162

NTP (1980). Bioassay of selenium sulfide (dermal study) for possible carcinogenicity. CAS no. 7446-34-6. NCI-CG-TR-197. NTP-80-18. Bethesda (MD), USA: National Cancer Institute, U.S. Department of Health and Human Services. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr197.pdf, accessed September 2024.

NTP (1982a). NTP Technical report series no. 235. Carcinogenesis bioassay of zearalenone (CAS no. 17924-92-4) in F344/N rats and B6C3F_1 mice (feed study). Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr235.pdf, accessed September 2024.

NTP (1982b). Carcinogenesis bioassay of butyl benzyl phthalate in F344/N rats and B6C3F_1 mice (feed study). Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/publications/reports/tr/200s/tr213, accessed September 2024

NTP (1986a) Ethyl anthranilate (87–25–2). Chemical effects in biological systems (CEBS). Research Triangle Park, NC (USA): National Toxicology Program, National Institutes of Health. Available from: https://cebs.niehs.nih.gov/cebs/test_article/87-25-2, accessed September 2024.

NTP (1986b). NTP toxicology and carcinogenesis studies of chlorinated paraffins (C23, 43% chlorine) (CAS no. 108171-27-3) in F344/N rats and B6C3F_1 mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 305:1–202. https://ntp.niehs.nih.gov/publications/reports/tr/300s/tr305 PMID:12748724

NTP (1986c). Toxicology and carcinogenesis studies of xylenes (mixed) (60% m-xylene, 14% p-xylene, 9% o-xylene, and 17% ethylbenzene) (CAS no. 1330-20-7) in F3441N rats and B6C3Fi mice (gavage studies). TOX 327.

Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr327.pdf, accessed September 2024.

NTP (1987). NTP toxicology and carcinogenesis studies of 1,4-dichlorobenzene (CAS no. 106-46-7) in F344/N rats and $B6C3F_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 319:1–198. https://ntp.niehs.nih.gov/publications/reports/tr/300s/tr319

NTP (1989a). NTP toxicology and carcinogenesis studies of tetracycline hydrochloride (CAS no. 64-75-5) in F344/N rats and $B6C3F_1$ mice (feed studies). Natl Toxicol Program Tech Rep Ser. 344:1–172. https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr344.pdf

NTP (1989b). NTP toxicology and carcinogenesis studies of 2,4-dichlorophenol (CAS no. 120-83-2) in F344/N rats and $B6C3F_1$ mice (feed studies). Natl Toxicol Program Tech Rep Ser. 353:1–182. https://ntp.niehs.nih.gov/publications/reports/tr/300s/tr353

NTP (1990). NTP toxicology and carcinogenesis studies of 3,3′-dimethoxybenzidine dihydrochloride (CAS no. 20325-40-0) in F344/N rats (drinking water studies). Natl Toxicol Program Tech Rep Ser. 372:1–201. https://ntp.niehs.nih.gov/publications/reports/tr/300s/tr372

NTP (1991). Toxicology and carcinogenesis studies of 3,3'-dimethylbenzidine dihydrochloride in F344/N rats. Drinking-water studies. Technical report series. No. 390. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr390.pdf, accessed March 2024.

NTP (1992a). NTP toxicology and carcinogenesis studies of ethylene thiourea (CAS: 96-45-7) in F344 Rats and $B6C3F_1$ mice (feed studies). Natl Toxicol Program Tech Rep Ser. 388:1–256. https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr388.pdf

NTP (1992b). NTP report on the toxicity studies of cresols (CAS nos. 95-48-7, 108-39-4, and 106-44-5) in F344/N rats and $B6C3F_1$ mice (feed studies). Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/st_rpts/tox009.pdf, accessed September 2024.

NTP (1993). Toxicology and carcinogenesis studies of acetaminophen (CAS no. 103-90-2) in F344/N rats and $B6C3F_1$ mice (feed studies). National Toxicology Program Technical Report Series No. 394. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr394.pdf, accessed January 2024.

NTP (1994b). NTP toxicology and carcinogenesis studies of ozone (CAS no. 10028-15-6) and ozone/NNK (CAS no. 10028-15-6/ 64091-91-4) in F344/N rats and $B6C3F_1$ mice (inhalation studies). Natl Toxicol Program Tech Rep Ser. 440:1–314. https://ntp.niehs.nih.gov/publications/reports/tr/400s/tr440

NTP (1994a). NTP toxicology and carcinogenesis studies of o-benzyl-p-chlorophenol (CAS no. 120-32-1) in F344/N rats and $B6C3F_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 424:1–304. https://ntp.niehs.nih.gov/publications/reports/tr/400s/tr424

NTP (1995a). NTP toxicology and carcinogenesis studies of t-butyl alcohol (CAS no. 75-65-0) in F344/N rats and $B6C3F_1$ mice (drinking water studies). Natl Toxicol Program Tech Rep Ser. 436:1–305. https://ntp.niehs.nih.gov/publications/reports/tr/400s/tr436

NTP (1995b). NTP initiation/promotion study of *o*-benzyl-*p*-chlorophenol (CAS no. 120-32-1) in Swiss (CD-1®) mice (mouse skin study). Natl Toxicol Program Tech Rep Ser. 444:1–136. https://ntp.niehs.nih.gov/publications/reports/tr/400s/tr444

NTP (1997a). Tumor incidence for selected control animal groups. Historical controls database. Rats: Fischer F344. 1984–1997 (feed). Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available at: https://ntp.niehs.nih.gov/sites/default/files/ntp/historical_controls/nih-07_1997/r_hcrpt_rte19971112.rpt, accessed September 2024.

NTP (1997b). Toxicology and carcinogenesis studies of butyl benzyl phthalate in F344/N rats (feed studies). Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/publications/reports/tr/400s/tr458, accessed September 2024

NTP (1999). NTP toxicology and carcinogenesis studies of glutaraldehyde (CAS no. 111-30-8) in F344/N rats and B6C3F$_1$ mice (inhalation studies). Natl Toxicol Program Tech Rep Ser. 490:1–234. https://ntp.niehs.nih.gov/publications/reports/tr/400s/tr490

NTP (1999a). NTP toxicology and carcinogenesis studies of oxymetholone (CAS no. 434-07-1) in F344/N rats and toxicology studies of oxymetholone in B6C3F$_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 485:1–233. https://ntp.niehs.nih.gov/publications/reports/tr/400s/tr485

NTP (2001). Toxicology and carcinogenesis studies of indium phosphide (CAS no. 22398-90-7) in F344/N rats and B6C3F$_1$ mice (inhalation studies). Natl Toxicol Program Tech Rep Ser. 499(499):7–340. https://ntp.niehs.nih.gov/publications/reports/tr/400s/tr499

NTP (2002). Toxicology and carcinogenesis studies of *p*-nitrotoluene (CAS no. 99-99-0) in F344/N rats and B6C3F(1) mice (feed studies). Natl Toxicol Program Tech Rep Ser. 498:1–277. https://ntp.niehs.nih.gov/publications/reports/tr/400s/tr498

NTP (2006). NTP technical report on the comparative toxicity studies of allyl acetate, allyl alcohol, and acrolein (CAS nos. 591-87-7, 107-18-6, and 107-02-8) administered by gavage to F344/N rats and B6C3F$_1$ mice. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/st_rpts/tox048.pdf, accessed December 2023.

NTP (2007a). Toxicology and carcinogenesis study of genistein in Sprague-Dawley rats (feed study). Natl Toxicol Program Tech Rep Ser. 545:1–240. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr545.pdf

NTP (2007b). Toxicology and carcinogenesis studies of alpha-methylstyrene (CAS no. 98-83-9) in F344/N rats and B6C3F$_1$ mice (inhalation studies). Natl Toxicol Program Tech Rep Ser. 543:1–210. https://ntp.niehs.nih.gov/publications/reports/tr/500s/tr543

NTP (2008). NTP technical report on the toxicology and carcinogenesis studies of cresols (CAS no. 1319-77-3) in male F344/N rats and female B6C3F$_1$ mice (feed studies). Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr550.pdf, accessed September 2024.

NTP (2009). TR-542. Toxicology and carcinogenesis studies of cumene (CASRN 98-82-8) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC (USA): National Toxicology Program, National Institutes of Health. Available from: https://cebs.niehs.nih.gov/cebs/publication/TR-542, accessed September 2024.

NTP (2010). Toxicology and carcinogenesis studies of androstenedione (CAS no. 63-05-8) in F344/N rats and B6C3F$_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 560:1, 7–31, 33–171 passim. https://ntp.niehs.nih.gov/publications/reports/tr/500s/tr560

NTP (2011). Nitrilotriacetic acid. CAS no. 139-13-9. Report on carcinogens, fifteenth edition. Research Triangle Park, NC (USA): National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/content/profiles/nitrilotriaceticacid.pdf, accessed March 2024.

NTP (2012a). Final report on the cumene (CASRN 98-82-8) genotoxicity studies. [Studies were conducted under NTP Contract N01-ES-34415 at ILS, Inc.]. Research Triangle Park, NC (USA): National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/thirteenth/genotoxstudies/cumenegtox_508.pdf, accessed September 2024.

NTP (2012b). NTP toxicology and carcinogenesis study of styrene–acrylonitrile trimer in F344/N rats (perinatal and postnatal feed studies). Natl Toxicol Program Tech Rep Ser. 573:1–156. https://ntp.niehs.nih.gov/publications/reports/tr/500s/tr573

NTP (2013). Report on carcinogens monograph on cumene: RoC Monograph 02. Rep Carcinog Monogr. 02(02):1–166. https://doi.org/10.22427/ROC-MGRAPH-02 PMID:24810860

NTP (2014). NTP toxicology and carcinogenesis studies of glycidamide (CAS no. 5694-00-8) in F344/N Nctr rats and B6C3F$_1$/Nctr mice (drinking water studies). Natl Toxicol Program Tech Rep Ser. 588:1–276. https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr588_508.pdf

NTP (2015). Technical report on the toxicology studies of CIMSTAR 3800 in F344/NTac rats and B6C3F$_1$/N mice and toxicology and carcinogenesis studies of CIMSTAR 3800 in Wistar Han [Crl:WI(Han)] rats and B6C3F$_1$/N mice

(inhalation studies): NTP technical report 586. Research Triangle Park, NC (USA): National Toxicology Program, National Institutes of Health. https://www.ncbi.nlm.nih.gov/books/NBK561062/

NTP (2016a). Pentabromodiphenyl ether (32534–81–9). Chemical effects in biological systems (CEBS). Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://cebs.niehs.nih.gov/cebs/test_article/32534-81-9, accessed September 2024.

NTP (2016b). NTP technical report on the toxicology studies of a pentabromodiphenyl ether mixture [DE-71 (technical grade)] (CASRN 32534-81-9) in F344/N rats and B6C3F$_1$/N mice and toxicology and carcinogenesis studies of a pentabromodiphenyl ether mixture [DE-71 (technical grade)] in Wistar Han [Crl:WI(Han)] rats and B6C3F1/N mice (gavage studies). Technical Report 589. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr589_508.pdf, accessed September 2024.

NTP (2016c). Report on carcinogens monograph on Merkel cell polyomavirus: report on carcinogens Monograph 11. Research Triangle Park (NC): National Toxicology Program, National Institutes of Health. Available from: https://www.ncbi.nlm.nih.gov/books/NBK580505/, accessed September 2024.

NTP (2016d). NTP technical report on the toxicity studies of α-pinene (CAS no. 80-56-8) administered by inhalation to F344/N rats and B6C3F$_1$/N mice. Toxicity report 81. Research Triangle Park, NC (USA): National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/st_rpts/tox081_508.pdf, accessed September 2024.

NTP (2016e). NTP technical report on the toxicology and carcinogenesis studies of TRIM® VX in Wistar Han [Crl:WI (Han)] rats and B6C3F$_1$/N mice (inhalation studies). NTP TR 591. Research Triangle Park, NC (USA): National Toxicology Program, National Institutes of Health. Available from https://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2016/february/tr591_peerdraft.pdf, accessed September 2024.

NTP (2016f). Toxicity studies of sodium thioglycolate administered dermally to F344/N rats and B6C3F$_1$/N mice. Natl Toxicol Program Tech Rep Ser. 80:1. https://ntp.niehs.nih.gov/publications/reports/tox/000s/tox080

NTP (2017). NTP research report on biological activity of bisphenol A (BPA) structural analogues and functional alternatives. NTP RR 4. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/results/pubs/rr/reports/rr04_508.pdf, accessed September 2024.

NTP (2018a). Toxicology and carcinogenesis studies in B6C3F$_1$/N mice exposed to whole-body radio frequency radiation at a frequency (1900 MHz) and modulations (GSM and CDMA) used by cell phones. Natl Toxicol Program Tech Rep Ser. 596. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr596_508.pdf, accessed September 2024.

NTP (2018b). Toxicology and carcinogenesis studies in Hsd:Sprague Dawley SD rats exposed to whole-body radiofrequency radiation at a frequency (900 MHz) and modulations (GSM and CDMA) used by cellphones. Natl Toxicol Program Tech Rep Ser. 595:NTP-TR-595. https://www.niehs.nih.gov/ntp-temp/tr595_508.pdf

NTP (2018c). Monograph on haloacetic acids found as water disinfection by-products. Report on carcinogens. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/ntp/roc/monographs/haafinal_508.pdf, accessed March 2019.

NTP (2018d). NTP toxicology and carcinogenesis studies of 2,3-butanedione in Wistar Han [Crl:WI (Han)] rats and B6C3F$_1$/N mice (inhalation studies). Natl Toxicol Program Tech Rep Ser. 593:1–198. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr593_508.pdf

NTP (2019a). NTP Technical report on the toxicity studies of 1020 long multiwalled carbon nanotubes administered by inhalation to Sprague Dawley (Hsd:Sprague Dawley® SD®) rats and B6C3F$_1$/N mice: toxicity report 94. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551597/, accessed September 2024.

NTP (2019b) Genetic toxicity evaluation of carbaryl (63–25–2) in DNA damage study G10952 in Sprague-Dawley Rats. National Toxicology Program, National Institutes of Health. Available from: https://cebs.niehs.nih.gov/cebs/test_article/63-25-2, accessed September 2024.

NTP (2020a). NTP research report on the scoping review of prenatal exposure to progestogens and adverse health outcomes: Research report 17 [Internet]. Research Triangle Park (NC): National Toxicology Program, National Institutes of Health. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564160/, accessed September 2024.

NTP (2020b). Toxicology and carcinogenesis studies of 2-hydroxy-4-methoxybenzophenone administered in feed to Sprague Dawley (Hsd:Sprague Dawley SD) rats and B6C3F$_1$/N mice. Natl Toxicol Program Tech Rep Ser. 597:NTP-TR-597.

NTP (2021a). 15th report on carcinogens. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://www.ncbi.nlm.nih.gov/books/NBK590769/, accessed February 2024.

NTP (2021b). NTP Cancer hazard assessment report on night shift work and light at night. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://www.ncbi.nlm.nih.gov/books/NBK571598/ PMID:34197056

NTP (2021c). NTP technical report on the toxicology and carcinogenesis studies of di(2-ethylhexyl) phthalate (CASRN 117-81-7) administered in feed to Sprague Dawley (Hsd:Sprague Dawley SD) rats. Technical Report 601. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://doi.org/10.22427/NTP-TR-601, accessed September 2024.

NTP (2021f). Nickel compounds and metallic nickel. Report on carcinogens. 15th ed. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. https://www.ncbi.nlm.nih.gov/books/NBK590828/

NTP (2021d). NTP technical report on the toxicology and carcinogenesis studies of di-n-butyl phthalate (CASRN 84-74-2) administered in feed to Sprague Dawley (Hsd:Sprague Dawley SD) rats and B6C3F$_1$/N mice. Technical Report 600. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. , accessed September 2024.

NTP (2021e). Oxymetholone. Report on carcinogens. 15th ed. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/ntp/roc/content/profiles/tetrachlorodibenzodioxin.pdf, accessed September 2024.

NTP (2022). NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) Rats (revised). Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/st_rpts/tox096_508.pdf, accessed September 2024.

NTP (2023a). NTP technical report on the toxicology and carcinogenesis studies of an isomeric mixture of tris(chloropropyl) phosphate administered in feed to Sprague Dawley (Hsd:Sprague Dawley SD) rats and B6C3F$_1$/N mice. Technical Report 602. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://ntp.niehs.nih.gov/sites/default/files/2023-06/tr602_508.pdf, accessed December 2023.

NTP (2023b). Tris(2-chloro-1-methylethyl) phosphate. CASRN 13674-84-5. Integrated chemical environment (ICE) version 4.0.1. Available from: https://ice.ntp.niehs.nih.gov/Search, accessed December 2023.

NTP (2023c). Toxicology and carcinogenesis studies of black cohosh root extract (CASRN 84776-26-1) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats and female B6C3F$_1$/N mice. NTP Technical Report 603. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://www.ncbi.nlm.nih.gov/books/NBK598365/

NTP (2023d). Integrated Chemical Environment (ICE) version 4.0.1. Search by CASRN 85-68-7. Available from: https://ice.ntp.niehs.nih.gov/Search, accessed October 2024.

NTP (2023e). Integrated Chemical Environment (ICE) version 4.0.1. Search by CASRN 28553-12-0. Available from: https://ice.ntp.niehs.nih.gov/Search, accessed October 2024.

NTP (2023f). 2,4-Dimethylphenol (105–67–9). Chemical effects in biological systems. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://cebs.niehs.nih.gov/cebs/test_article/105-67-9, accessed September 2024.

NTP (2023g). Butyraldehyde (123–72–8). Chemical effects in biological systems. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://cebs.niehs.nih.gov/cebs/test_article/123-72-8, accessed February 2024.

NTP (2023h). 5-Nitro-*o*-toluidine (99–55–8). Chemical effects in biological systems. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://cebs.niehs.nih.gov/cebs/test_article/99-55-8, accessed February 2024.

NTP (2024a). Safrole (94–59–7). Chemical effects in biological systems. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: , accessed September 2024.

NTP (2024b). Dibutyl phthalate (84–74–2). Chemical effects in biological systems. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. Available from: https://cebs.niehs.nih.gov/cebs/test_article/84-74-2, accessed September 2024.

NTP (2024c). Methyl anthranilate (134-20-3). Chemical effects in biological systems. Research Triangle Park (NC), USA: National Toxicology Program, National Institutes of Health. , accessed July 2024.

NTP (2024d). Sulfolane. Research overview. Research Triangle Park (NC), USA: National Toxicology Program. Available from: https://ntp.niehs.nih.gov/whatwestudy/topics/sulfolane, accessed October 2024

Numachi Y, Shen H, Yoshida S, Fujiyama K, Toda S, Matsuoka H, et al. (2007). Methamphetamine alters expression of DNA methyltransferase 1 mRNA in rat brain. Neurosci Lett. 414(3):213–7. https://doi.org/10.1016/j.neulet.2006.12.052

Numachi Y, Yoshida S, Yamashita M, Fujiyama K, Naka M, Matsuoka H, et al. (2004). Psychostimulant alters expression of DNA methyltransferase mRNA in the rat brain. Ann N Y Acad Sci. 1025(1):102–9. https://doi.org/10.1196/annals.1316.013

Nunes EM, López RVM, Sudenga SL, Gheit T, Tommasino M, Baggio ML, et al.; HIM Study group (2017). Concordance of beta-papillomavirus across anogenital and oral anatomic sites of men: The HIM Study. Virology. 510:55–9. https://doi.org/10.1016/j.virol.2017.07.006

Nurminen M, Hernberg S (1984). Cancer mortality among carbon disulfide-exposed workers. J Occup Med. 26(5):341. https://doi.org/10.1097/00043764-198405000-00003

Nyakutsikwa B, Britton J, Bogdanovica I, Boobis A, Langley T (2021). Characterising vaping products in the United Kingdom: an analysis of Tobacco Products Directive notification data. Addiction. 116(9):2521–8. https://doi.org/10.1111/add.15463

Nyirenda MH, Nijjar JS, Frleta-Gilchrist M, Gilchrist DS, Porter D, Siebert S, et al. (2023). JAK inhibitors disrupt T cell-induced proinflammatory macrophage activation. RMD Open. 9(1):e002671. https://doi.org/10.1136/rmdopen-2022-002671

O'Grady TJ, Rinaldi S, Michels KA, Adami HO, Buring JE, Chen Y, et al. (2024). Association of hormonal and reproductive factors with differentiated thyroid cancer risk in women: a pooled prospective cohort analysis. Int J Epidemiol. 53(1):dyad172. https://doi.org/10.1093/ije/dyad172

O'Leary ES, Schoenfeld ER, Stevens RG, Kabat GC, Henderson K, Grimson R, et al.; Electromagnetic Fields and Breast Cancer on Long Island Study Group (2006). Shift work, light at night, and breast cancer on Long Island, New York. Am J Epidemiol. 164(4):358–66. https://doi.org/10.1093/aje/kwj211

Oberdörster G, Oberdörster E, Oberdörster J (2005). Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect. 113(7):823–39. https://doi.org/10.1289/ehp.7339

Oberholzer PA, Kee D, Dziunycz P, Sucker A, Kamsukom N, Jones R, et al. (2012). RAS mutations are associated with the development of cutaneous squamous cell tumors in patients treated with RAF inhibitors. J Clin Oncol. 30(3):316–21. https://doi.org/10.1200/JCO.2011.36.7680

Obi N, Chang-Claude J, Berger J, Braendle W, Slanger T, Schmidt M, et al. (2009). The use of herbal preparations to alleviate climacteric disorders and risk of postmenopausal breast cancer in a German case–control study. Cancer Epidemiol Biomarkers Prev. 18(8):2207–13. https://doi.org/10.1158/1055-9965.EPI-09-0298

Obón-Santacana M, Freisling H, Peeters PH, Lujan-Barroso L, Ferrari P, Boutron-Ruault MC, et al. (2016). Acrylamide and glycidamide hemoglobin adduct levels and endometrial cancer risk: a nested case–control study in nonsmoking postmenopausal women from the EPIC cohort. Int J Cancer. 138(5):1129–38. https://doi.org/10.1002/ijc.29853

Oda Y, Zhang Y, Buchinger S, Reifferscheid G, Yang M (2012). Roles of human sulfotransferases in genotoxicity of carcinogens using genetically engineered umu test strains. Environ Mol Mutagen. 53(2):152–64. https://doi.org/10.1002/em.20696

OECD (2004). SIDS initial assessment report for tetrahydrothiophene-1,1-dioxide. Paris, France: Organisation for Economic Co-operation and Development. Available from: https://hpvchemicals.oecd.org/ui/handler.axd?id=cbde8e42-6a4f-4112-acf2-09ffcbcf210b, accessed September 2024.

OECD (2005). OECD SIDS Isoprene. CAS no 78-79-5. UNEP Publications. Paris, France: Organisation for Economic Co-operation and Development. Available from: https://hpvchemicals.oecd.org/UI/handler.axd?id=2d19a70d-10ec-4ff9-9b9a-0978d0db8798, accessed September 2024.

OECD (2007). OECD Existing chemicals database. High production volume chemicals. Paris, France: Organisation for Economic Co-operation and Development. Available from: https://hpvchemicals.oecd.org/UI/Search.aspx, accessed April 2024.

OECD (2009a). *n*-Butyraldehyde. CAS no: 123-72-8. OECD existing chemicals database. Paris, France: Organisation for Economic Co-operation and Development. Available from: https://hpvchemicals.oecd.org/UI/SIDS_Details.aspx?key=0d3dd31d-f06f-4cd3-b972-2997c70a1365&idx=0, accessed December 2023.

OECD (2009b). The 2007 OECD list of high production volume. OECD environment, health and safety publications series on testing and assessment No. 112. Paris, France: Organisation for Economic Co-operation and Development. Available from: https://one.oecd.org/document/env/jm/mono(2009)40/en/pdf, accessed January 2024.

OECD (2014). Test No. 474: mammalian erythrocyte micronucleus test, OECD guidelines for the testing of chemicals. Paris, France: OECD Publishing. Available from:

OEHHA (2013a). Evidence on the carcinogenicity of butyl benzyl phthalate (BBP). Oakland (CA), USA: Office of Environmental Health Hazard Assessment. Available from: https://oehha.ca.gov/media/downloads/proposition-65/chemicals/bbphid10042013.pdf, accessed September 2024.

OEHHA (2013b). Evidence on the carcinogenicity of diisononyl phthalate (DINP). Oakland (CA), USA: Office of Environmental Health Hazard Assessment. Available from: https://oehha.ca.gov/media/downloads/proposition-65/chemicals/dinphid100413.pdf, accessed December 2023.

OEHHA (2022a). Proposition 65. Evidence on the carcinogenicity of bisphenol A (BPA). Reproductive and cancer hazard assessment. Oakland (CA), USA: Office of Environmental Health Hazard Assessment. Available from: https://oehha.ca.gov/media/downloads/proposition-65/chemicals/bpahid093022.pdf, accessed February 2024.

OEHHA (2022b). Notification level recommendation for perfluorohexane sulfonic acid (PFHxS) in drinking water. Oakland (CA), USA: Office of Environmental Health Hazard Assessment. Available from: https://oehha.ca.gov/media/pfhxsnl031722.pdf, accessed September 2024.

<eref>OECD (2023), Test 456: H295R Steroidogenesis Assay, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris. Available from: https://read.oecd.org/10.1787/9789264122642-en?format=pdf, accessed October 2024.</eref>

OEHHA (2024) 3,3′-Dimethoxybenzidine (*o*-Dianisidine). Chemicals considered or listed under proposition 45. Oakland (CA), USA: Office of Environmental Health Hazard Assessment. Available from: https://oehha.ca.gov/proposition-65/chemicals/33-dimethoxybenzidine-o-dianisidine, accessed February 2024.

Oh TK, Song IA (2020). Long-term glucocorticoid use and cancer risk: a population-based cohort study in South Korea. Cancer Prev Res (Phila). 13(12):1017–26. https://doi.org/10.1158/1940-6207.CAPR-20-0161

Ohlwein S, Kappeler R, Kutlar Joss M, Künzli N, Hoffmann B (2019). Health effects of ultrafine particles: a systematic literature review update of epidemiological evidence. Int J Public Health. 64(4):547–59. https://doi.org/10.1007/s00038-019-01202-7

Ohno Y, Miyajima A, Sunouchi M (1998). Alternative methods for mechanistic studies in toxicology. Screening of hepatotoxicity of pesticides using freshly isolated and primary cultured hepatocytes and non-liver-derived cells, SIRC cells. Toxicol Lett. 102–103:569–73. https://doi.org/10.1016/S0378-4274(98)00250-1

Ohsawa K, Hirano N, Sugiura M, Nakagawa S, Kimura M (2000). Genotoxicity of *o*-aminoazotoluene (AAT) determined by the Ames test, the in vitro chromosomal aberration test, and the transgenic mouse gene mutation assay. Mutat Res. 471(1–2):113–26. https://doi.org/10.1016/S1383-5718(00)00120-0

Oikawa S, Hirosawa I, Hirakawa K, Kawanishi S (2001). Site specificity and mechanism of oxidative DNA damage induced by carcinogenic catechol. Carcinogenesis. 22(8):1239–45. https://doi.org/10.1093/carcin/22.8.1239

Oishi S (2002). Effects of butyl paraben on the male reproductive system in mice. Arch Toxicol. 76(7):423–9. https://doi.org/10.1007/s00204-002-0360-8https://doi.org/10.1007/s00204-002-0360-8 PMID:12111007

Ojha A, Srivastava N (2014). In vitro studies on organophosphate pesticides induced oxidative DNA damage in rat lymphocytes. Mutat Res Genet Toxicol Environ Mutagen. 761:10–7. https://doi.org/10.1016/j.mrgentox.2014.01.007

Ojo AF, Peng C, Ng JC (2022). Genotoxicity assessment of per- and polyfluoroalkyl substances mixtures in human liver cells (HepG2). Toxicology. 482:153359. https://doi.org/10.1016/j.tox.2022.153359https://doi.org/10.1016/j.tox.2022.153359 PMID:36341878

Ojo AF, Xia Q, Peng C, Ng JC (2021). Evaluation of the individual and combined toxicity of perfluoroalkyl substances to human liver cells using biomarkers of oxidative stress. Chemosphere. 281:130808. https://doi.org/10.1016/j.chemosphere.2021.130808https://doi.org/10.1016/j.chemosphere.2021.130808 PMID:34022600

Okamiya H, Mitsumori K, Onodera H, Ito S, Imazawa T, Yasuhara K, et al. (1998). Mechanistic study on liver tumor promoting effects of piperonyl butoxide in rats. Arch Toxicol. 72(11):744–50. https://doi.org/10.1007/s002040050569https://doi.org/10.1007/s002040050569 PMID:9879813

Olazarán J, Carnero-Pardo C, Fortea J, Sánchez-Juan P, García-Ribas G, Viñuela F, et al. (2023). Prevalence of treated patients with Alzheimer's disease: current trends and COVID-19 impact. Alzheimers Res Ther. 15(1):130. https://doi.org/10.1186/s13195-023-01271-0

Oliveira-Brett AM, da Silva LA (2002). A DNA-electrochemical biosensor for screening environmental damage caused by s-triazine derivatives. Anal Bioanal Chem. 373(8):717–23. https://doi.org/10.1007/s00216-002-1259-1

Olivera PA, Lasa JS, Bonovas S, Danese S, Peyrin-Biroulet L (2020). Safety of janus kinase inhibitors in patients with inflammatory bowel diseases or other immune-mediated diseases: a systematic review and meta-analysis. Gastroenterology. 158(6):1554–1573.e12. https://doi.org/10.1053/j.gastro.2020.01.001

Oller AR, Kirkpatrick DT, Radovsky A, Bates HK (2008). Inhalation carcinogenicity study with nickel metal powder in Wistar rats. Toxicol Appl Pharmacol. 233(2):262–75. https://doi.org/10.1016/j.taap.2008.08.017

Olsen CM, Meussen-Elholm ET, Holme JA, Hongslo JK (2002). Brominated phenols: characterization of estrogen-like activity in the human breast cancer cell-line MCF-7. Toxicol Lett. 129(1-2):55–63. https://doi.org/10.1016/S0378-4274(01)00469-6

Olsen GW, Lanham JM, Bodner KM, Hylton DB, Bond GG (1990). Determinants of spermatogenesis recovery among workers exposed to 1,2-dibromo-3-chloropropane. J Occup Med. 32(10):979–84.

Olstørn HB, Paulsen JE, Alexander J (2007). Effects of perinatal exposure to acrylamide and glycidamide on intestinal tumorigenesis in Min/+ mice and their wild-type litter mates. Anticancer Res. 27 6B:3855–64. https://ar.iiarjournals.org/content/27/6B/3855.long

Olszak T, An D, Zeissig S, Vera MP, Richter J, Franke A, et al. (2012). Microbial exposure during early life has persistent effects on natural killer T cell function. Science. 336(6080):489–93. https://doi.org/10.1126/science.1219328

Omaiye EE, Luo W, McWhirter KJ, Pankow JF, Talbot P (2020). Electronic cigarette refill fluids sold worldwide: flavor chemical composition, toxicity, and hazard analysis. Chem Res Toxicol. 33(12):2972–87. https://doi.org/10.1021/acs.chemrestox.0c00266

Omura K, Uehara T, Morikawa Y, Hayashi H, Mitsumori K, Minami K, et al. (2014). Detection of initiating potential of non-genotoxic carcinogens in a two-stage hepatocarcinogenesis study in rats. J Toxicol Sci. 39(5):785–94. https://doi.org/10.2131/jts.39.785

Onaran I, Güven G, Ozaydin A, Ulutin T (2001). The influence of GSTM1 null genotype on susceptibility to in vitro oxidative stress. Toxicology. 157(3):195–205. https://doi.org/10.1016/S0300-483X(00)00358-9

Onda M, Ghoreschi K, Steward-Tharp S, Thomas C, O'Shea JJ, Pastan IH, et al. (2014). Tofacitinib suppresses antibody responses to protein therapeutics in murine hosts. J Immunol. 193(1):48–55. https://doi.org/10.4049/jimmunol.1400063

Onoda A, Takeda K, Umezawa M (2017). Dose-dependent induction of astrocyte activation and reactive astrogliosis in mouse brain following maternal exposure to carbon black nanoparticle. Part Fibre Toxicol. 14(1):4. https://doi.org/10.1186/s12989-017-0184-6

Onyije FM, Olsson A, Baaken D, Erdmann F, Stanulla M, Wollschläger D, et al. (2022). Environmental risk factors for childhood acute lymphoblastic leukemia: an umbrella review. Breast Cancer Res. 14(2):382. https://doi.org/10.3390/cancers14020382

Ooi JH, Li Y, Rogers CJ, Cantorna MT (2013). Vitamin D regulates the gut microbiome and protects mice from dextran sodium sulfate-induced colitis. J Nutr. 143(10):1679–86. https://doi.org/10.3945/jn.113.180794

Opelz G, Döhler B (2004). Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant. 4(2):222–30. https://doi.org/10.1046/j.1600-6143.2003.00325.x

Osada Y, Horie Y, Nakae S, Sudo K, Kanazawa T (2019). STAT6 and IL-10 are required for the anti-arthritic effects of *Schistosoma mansoni* via different mechanisms. Clin Exp Immunol. 195(1):109–20. https://doi.org/10.1111/cei.13214

Osgood RS, Upham BL, Bushel PR, Velmurugan K, Xiong KN, Bauer AK (2017). Secondhand smoke-prevalent polycyclic aromatic hydrocarbon binary mixture-induced specific mitogenic and pro-inflammatory cell signalling events in lung epithelial cells. Toxicol Sci. 157(1):156–71. https://doi.org/10.1093/toxsci/kfx027

OSHA (2011). Hazard alert update: hair straightening products that could release formaldehyde. Washington (DC), USA: Occupational Safety and Health Administration. Available from: https://www.osha.gov/sites/default/files/publications/hazard_alert.pdf, accessed March 2024.

Osimitz TG, Sommers N, Kingston R (2009). Human exposure to insecticide products containing pyrethrins and piperonyl butoxide (2001–2003). Food Chem Toxicol. 47(7):1406–15. https://doi.org/10.1016/j.fct.2009.03.015https://doi.org/10.1016/j.fct.2009.03.015 PMID:19306908

Ospina M, Schütze A, Morales-Agudelo P, Vidal M, Wong LY, Calafat AM (2022). Exposure to glyphosate in the United States: data from the 2013–2014 National Health and Nutrition Examination Survey. Environ Int. 170:107620. https://doi.org/10.1016/j.envint.2022.107620

Osswald H, Frank HK, Komitowski D, Winter H (1978). Long-term testing of patulin administered orally to Sprague-Dawley rats and Swiss mice. Food Cosmet Toxicol. 16(3):243–7. https://doi.org/10.1016/S0015-6264(76)80520-2

Ostenfeld EB, Erichsen R, Thorlacius-Ussing O, Riis AH, Sørensen HT (2013). Use of systemic glucocorticoids and the risk of colorectal cancer. Aliment Pharmacol Ther. 37(1):146–52. https://doi.org/10.1111/apt.12115

Othmène YB, Salem IB, Hamdi H, Annabi E, Abid-Essefi S (2021). Tebuconazole induced cytotoxic and genotoxic effects in HCT116 cells through ROS generation. Pestic Biochem Physiol. 174:104797. https://doi.org/10.1016/j.pestbp.2021.104797

Ottenbros I, Lebret E, Huber C, Lommen A, Antignac JP, Čupr P, et al. (2023). Assessment of exposure to pesticide mixtures in five European countries by a harmonized urinary suspect screening approach. Int J Hyg Environ Health. 248:114105. https://doi.org/10.1016/j.ijheh.2022.114105

Otto C, Rohde-Schulz B, Schwarz G, Fuchs I, Klewer M, Altmann H, et al. (2007). In vivo characterization of progestins with reduced non-genomic activity in vitro. Ernst Schering Found Symp Proc. 1(1):151–70. https://link.springer.com/chapter/10.1007/2789_2008_077

Ou S, He H, Qu L, Wu W, Gan L, Liu J (2017). Renal pathology in patients with occupational exposure to carbon disulphide: a case series. Nephrology (Carlton). 22(10):755–60. https://doi.org/10.1111/nep.12853

Ou Z, Gao Y, Jiang D, Cui J, Ren Y, Tang S, et al. (2022). Global trends in death, years of life lost, and years lived with disability caused by breast cancer attributable to secondhand smoke from 1990 to 2019. Front Oncol. 12:853038. https://doi.org/10.3389/fonc.2022.853038

Ouanes Z, Ayed-Boussema I, Baati T, Creppy EE, Bacha H (2005). Zearalenone induces chromosome aberrations in mouse bone marrow: preventive effect of 17beta-estradiol, progesterone and vitamin E. Mutat Res. 565(2):139–49. https://doi.org/10.1016/j.mrgentox.2004.10.005

Ouellet-Hellstrom R, Rench JD (1996). Bladder cancer incidence in arylamine workers. J Occup Environ Med. 38(12):1239–47. https://doi.org/10.1097/00043764-199612000-00009https://doi.org/10.1097/00043764-199612000-00009 PMID:8978515

Outzen M, Tjønneland A, Hughes DJ, Jenab M, Frederiksen K, Schomburg L, et al. (2021). Toenail selenium, plasma selenoprotein P and risk of advanced prostate cancer: a nested case–control study. Int J Cancer. 148(4):876–83. https://doi.org/10.1002/ijc.33267

Ovchinnikova LP, Bogdanova LA, Kaledin VI (2013). Mutagenic activation reduces carcinogenic activity of ortho-aminoazotoluene for mouse liver. Bull Exp Biol Med. 154(5):664–8. https://doi.org/10.1007/s10517-013-2025-4https://doi.org/10.1007/s10517-013-2025-4 PMID:23658894

Pacifici GM, Vannucci L, Bencini C, Tusini G, Mosca F (1991). Sulphation of hydroxybiphenyls in human tissues. Xenobiotica. 21(9):1113–8. https://doi.org/10.3109/00498259109039551

Padda IS, Bhatt R, Parmar M (2023). Tofacitinib. In: StatPearls [Internet]. Treasure Island (FL), USA: StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK572148/ PMID:34283514

Pagano G, Guida M, Siciliano A, Oral R, Koçbaş F, Palumbo A, et al. (2016). Comparative toxicities of selected rare earth elements: sea urchin embryogenesis and fertilization damage with redox and cytogenetic effects. Environ Res. 147:453–60. https://doi.org/10.1016/j.envres.2016.02.031

Paget-Bailly S, Cyr D, Luce D (2012). Occupational exposures and cancer of the larynx – systematic review and meta-analysis. J Occup Environ Med. 54(1):71–84. https://doi.org/10.1097/JOM.0b013e31823c1343

Pahwa M, Beane Freeman LE, Spinelli JJ, Blair A, McLaughlin JR, Zahm SH, et al. (2019). Glyphosate use and associations with non-Hodgkin lymphoma major histological sub-types: findings from the North American Pooled Project. Scand J Work Environ Health. 45(6):600–9. https://doi.org/10.5271/sjweh.3830

Paini A, Punt A, Scholz G, Gremaud E, Spenkelink B, Alink G, et al. (2012). In vivo validation of DNA adduct formation by estragole in rats predicted by physiologically based biodynamic modelling. Mutagenesis. 27(6):653–63. https://doi.org/10.1093/mutage/ges031

Pakharukova MY, Mordvinov VA (2022). Similarities and differences among the Opisthorchiidae liver flukes: insights from *Opisthorchis felineus.* Parasitology. 149(10):1306–18. https://doi.org/10.1017/S0031182022000397

Pakharukova MY, Zaparina OG, Kapushchak YK, Baginskaya NV, Mordvinov VA (2019a). *Opisthorchis felineus* infection provokes time-dependent accumulation of oxidative hepatobiliary lesions in the injured hamster liver. PLoS One. 14(5):e0216757. https://doi.org/10.1371/journal.pone.0216757https://doi.org/10.1371/journal.pone.0216757

Pakharukova MY, Zaparina OG, Kovner AV, Mordvinov VA (2019b). Inhibition of *Opisthorchis felineus* glutathione-dependent prostaglandin synthase by resveratrol correlates with attenuation of cholangiocyte neoplasia in a hamster model of *Opisthorchiasis.* Int J Parasitol. 49(12):963–73. https://doi.org/10.1016/j.ijpara.2019.07.002https://doi.org/10.1016/j.ijpara.2019.07.002

Pala V, Krogh V, Muti P, Chajès V, Riboli E, Micheli A, et al. (2001). Erythrocyte membrane fatty acids and subsequent breast cancer: a prospective Italian study. J Natl Cancer Inst. 93(14):1088–95. https://doi.org/10.1093/jnci/93.14.1088

Palli D, Sera F, Giovannelli L, Masala G, Grechi D, Bendinelli B, et al. (2009). Environmental ozone exposure and oxidative DNA damage in adult residents of Florence, Italy. Environ Pollut. 157(5):1521–5. https://doi.org/10.1016/j.envpol.2008.09.011

Palus J, Rydzynski K, Dziubaltowska E, Wyszynska K, Natarajan AT, Nilsson R (2003). Genotoxic effects of occupational exposure to lead and cadmium. Mutat Res. 540(1):19–28. https://doi.org/10.1016/S1383-5718(03)00167-0

Pan Y, Qin H, Zheng L, Guo Y, Liu W (2022). Disturbance in transcriptomic profile, proliferation and multipotency in human mesenchymal stem cells caused by hexafluoropropylene oxides. Environ Pollut. 292 Pt B:118483. https://doi.org/10.1016/j.envpol.2021.118483

Pandey H, Tang DWT, Wong SH, Lal D (2023). Gut microbiota in colorectal cancer: biological role and therapeutic opportunities. Cancers (Basel). 15(3):866. https://doi.org/10.3390/cancers15030866

Panella TJ, Huang AT (1990). Effect of thimerosal in leukemia, in leukemic cell lines, and on normal hematopoiesis. Cancer Res. 50(14):4429–35.

Panganiban L, Cortes-Maramba N, Dioquino C, Suplido ML, Ho H, Francisco-Rivera A, et al. (2004). Correlation between blood ethylenethiourea and thyroid gland disorders among banana plantation workers in the Philippines. Environ Health Perspect. 112(1):42–5. https://doi.org/10.1289/ehp.6499

Pankowska MM, Lu H, Wheaton AG, Liu Y, Lee B, Greenlund KJ, et al. (2023). Prevalence and geographic patterns of self-reported short sleep duration among US adults, 2020. Prev Chronic Dis. 20:E53. https://doi.org/10.5888/pcd20.220400

Panthangi V, Cyril Kurupp AR, Raju A, Luthra G, Shahbaz M, Almatooq H, et al. (2022). Association between *Helicobacter pylori* infection and the risk of pancreatic cancer: a systematic review based on observational studies. Cureus. 14(8):e28543. https://doi.org/10.7759/cureus.28543

Panyala A, Chinde S, Kumari SI, Rahman MF, Mahboob M, Kumar JM, et al. (2019). Comparative study of toxicological assessment of yttrium oxide nano- and microparticles in Wistar rats after 28 days of repeated oral administration. Mutagenesis. 34(2):181–201. https://doi.org/10.1093/mutage/gey044

Papaioannou M, Schleich S, Prade I, Degen S, Roell D, Schubert U, et al. (2009). The natural compound atraric acid is an antagonist of the human androgen receptor inhibiting cellular invasiveness and prostate cancer cell growth. J Cell Mol Med. 13(8b) 8B:2210–23. https://doi.org/10.1111/j.1582-4934.2008.00426.x

Papantoniou K, Castaño-Vinyals G, Espinosa A, Turner MC, Martín-Sánchez V, Casabonne D, et al. (2021). Sleep duration and napping in relation to colorectal and gastric cancer in the MCC-Spain study. Sci Rep. 11(1):11822. https://doi.org/10.1038/s41598-021-91275-3

Papantoniou K, Konrad P, Haghayegh S, Strohmaier S, Eliassen AH, Schernhammer E (2023). Rotating night shift work, sleep, and thyroid cancer risk in the Nurses' Health Study 2. Cancers (Basel). 15(23):5673. https://doi.org/10.3390/cancers15235673

Pappuswamy M, Chaudhary A, Meyyazhagan A, Alagamuthu KK, Balasubramanian B, Arumugam VA, et al. (2023). DNA damage on buccal epithelial cells, personal working in the rubber industry occupationally exposed to carbon disulfide (CS2). Asian Pac J Cancer Prev. 24(2):357–61. https://doi.org/10.31557/APJCP.2023.24.2.357

Parada H Jr, Gammon MD, Ettore HL, Chen J, Calafat AM, Neugut AI, et al. (2019). Urinary concentrations of environmental phenols and their associations with breast cancer incidence and mortality following breast cancer. Environ Int. 130:104890. https://doi.org/10.1016/j.envint.2019.05.084https://doi.org/10.1016/j.envint.2019.05.084 PMID:31228785

Parhi L, Alon-Maimon T, Sol A, Nejman D, Shhadeh A, Fainsod-Levi T, et al. (2020). Breast cancer colonization by *Fusobacterium nucleatum* accelerates tumor growth and metastatic progression. Nat Commun. 11(1):3259. https://doi.org/10.1038/s41467-020-16967-2

Park AS, Ritz B, Yu F, Cockburn M, Heck JE (2020). Prenatal pesticide exposure and childhood leukemia – a California statewide case–control study. Int J Hyg Environ Health. 226:113486. https://doi.org/10.1016/j.ijheh.2020.113486

Park CJ, Nah WH, Lee JE, Oh YS, Gye MC (2012). Butyl paraben-induced changes in DNA methylation in rat epididymal spermatozoa. Andrologia. 44 Suppl 1:187–93. https://doi.org/10.1111/j.1439-0272.2011.01162.xhttps://doi.org/10.1111/j.1439-0272.2011.01162.x PMID:21592178

Park CY, Oh SH, Kang SM, Lim YS, Hwang SB (2009a). Hepatitis delta virus large antigen sensitizes to TNF-alpha-induced NF-kappaB signalling. Mol Cells. 28(1):49–55. https://doi.org/10.1007/s10059-009-0100-5https://doi.org/10.1007/s10059-009-0100-5 PMID:19711042

Park D (2018b). Review for retrospective exposure assessment methods used in epidemiologic cancer risk studies of semiconductor workers: limitations and recommendations. Saf Health Work. 9(3):249–56. https://doi.org/10.1016/j.shaw.2018.05.005

Park D-U (2023). Review on the association between exposure to extremely low frequency-magnetic fields (ELF-MF) and childhood leukaemia. Korean J Environ Health. 49(2):57–65. https://doi.org/10.5668/JEHS.2023.49.2.57

Park EJ, Cho WS, Jeong J, Yi J, Choi K, Park K (2009b). Pro-inflammatory and potential allergic responses resulting from B cell activation in mice treated with multi-walled carbon nanotubes by intratracheal instillation. Toxicology. 259(3):113–21. https://doi.org/10.1016/j.tox.2009.02.009

Park H, Jang JK, Shin JA (2011). Quantitative exposure assessment of various chemical substances in a wafer fabrication industry facility. Saf Health Work. 2(1):39–51. https://doi.org/10.5491/SHAW.2011.2.1.39

Park JH, Seo YH, Jang JH, Jeong CH, Lee S, Park B (2017). Asiatic acid attenuates methamphetamine-induced neuroinflammation and neurotoxicity through blocking of NF-kB/STAT3/ERK and mitochondria-mediated apoptosis pathway. J Neuroinflammation. 14(1):240. https://doi.org/10.1186/s12974-017-1009-0

Park JS, Park YJ, Kim HR, Chung KH (2019). Polyhexamethylene guanidine phosphate-induced ROS-mediated DNA damage caused cell cycle arrest and apoptosis in lung epithelial cells. J Toxicol Sci. 44(6):415–24. https://doi.org/10.2131/jts.44.415

Park M, Baker W, Cambow D, Gogerty D, Leda AR, Herlihy B, et al. (2021). Methamphetamine enhances HIV-induced aberrant proliferation of neural progenitor cells via the FOXO3-mediated mechanism. Mol Neurobiol. 58(11):5421–36. https://doi.org/10.1007/s12035-021-02407-9

Park MA, Hwang KA, Lee HR, Yi BR, Jeung EB, Choi KC (2013). 2,4-dihydroxybenzophenone stimulated the growth of BG-1 ovarian cancer cells by cell cycle regulation via an estrogen receptor alpha-mediated signalling pathway in cellular and xenograft mouse models. Toxicology. 305:41–8. https://doi.org/10.1016/j.tox.2012.12.021https://doi.org/10.1016/j.tox.2012.12.021 PMID:23328252

Park RM (2018a). Risk assessment for metalworking fluids and cancer outcomes. Am J Ind Med. 61(3):198–203. https://doi.org/10.1002/ajim.22809https://doi.org/10.1002/ajim.22809 PMID:2932S7473

Park RM (2020). Associations between exposure to ethylene oxide, job termination, and cause-specific mortality risk. Am J Ind Med. 63(7):577–88. https://doi.org/10.1002/ajim.23115

Park S, Zhunis A, Constantinides M, Aiello LM, Quercia D, Cha M (2023). Social dimensions impact individual sleep quantity and quality. Sci Rep. 13(1):9681. https://doi.org/10.1038/s41598-023-36762-5

Park TJ, Kim HS, Byun KH, Jang JJ, Lee YS, Lim IK (2001). Sequential changes in hepatocarcinogenesis induced by diethylnitrosamine plus thioacetamide in Fischer 344 rats: induction of gankyrin expression in liver fibrosis, pRB degradation in cirrhosis, and methylation of p16(INK4A) exon 1 in hepatocellular carcinoma. Mol Carcinog. 30(3):138–50. https://doi.org/10.1002/mc.1022

Park Y, Ramirez Y, Xiao Q, Liao LM, Jones GS, McGlynn KA (2022). Outdoor light at night and risk of liver cancer in the NIH-AARP diet and health study. Cancer Causes Control. 33(9):1215–8. https://doi.org/10.1007/s10552-022-01602-w

Parks CG, Hofmann JN, Beane Freeman LE, Sandler DP (2021). Agricultural pesticides and shingles risk in a prospective cohort of licensed pesticide applicators. Environ Health Perspect. 129(7):77005. https://doi.org/10.1289/EHP7797

Parks CG, Hoppin JA, De Roos AJ, Costenbader KH, Alavanja MC, Sandler DP (2016). Rheumatoid arthritis in Agricultural Health Study spouses: associations with pesticides and other farm exposures. Environ Health Perspect. 124(11):1728–34. https://doi.org/10.1289/EHP129https://doi.org/10.1289/EHP129 PMID:27285288

Parks M, Rosebraugh C (2010). Weighing risks and benefits of liraglutide – the FDA's review of a new antidiabetic therapy. N Engl J Med. 362(9):774–7. https://doi.org/10.1056/NEJMp1001578https://doi.org/10.1056/NEJMp1001578 PMID:20164475

Parny M, Coste A, Aubouy A, Rahabi M, Prat M, Pipy B, et al. (2022). Differential immunomodulatory effects of six pesticides of different chemical classes on human monocyte-derived macrophage functions. Food Chem Toxicol. 163:112992. https://doi.org/10.1016/j.fct.2022.112992

Parry TL, Tichy L, Brantley JT (2022). Cardioprotective effects of preconditioning exercise in the female tumor bearing mouse. Front Cell Dev Biol. 10:950479. https://doi.org/10.3389/fcell.2022.950479https://doi.org/10.3389/fcell.2022.950479 PMID:36531941

Parthasarathy NJ, Kumar RS, Manikandan S, Narayanan GS, Kumar RV, Devi RS (2006). Effect of methanol-induced oxidative stress on the neuroimmune system of experimental rats. Chem Biol Interact. 161(1):14–25. https://doi.org/10.1016/j.cbi.2006.02.005

Parvez SM, Jahan F, Brune MN, Gorman JF, Rahman MJ, Carpenter D, et al. (2021). Health consequences of exposure to e-waste: an updated systematic review. Lancet Planet Health. 5(12):e905–20. https://doi.org/10.1016/S2542-5196(21)00263-1

Parween F, Sarker A, Gupta RD (2022). Chlorpyrifos and parathion regulate oxidative stress differentially through the expression of paraoxonase 2 in human neuroblastoma cell. Neurotoxicology. 93:60–70. https://doi.org/10.1016/j.neuro.2022.08.016

Pascual G, Avgustinova A, Mejetta S, Martín M, Castellanos A, Attolini CS-O, et al. (2017). Targeting metastasis-initiating cells through the fatty acid receptor CD36. Nature. 541(7635):41–5. https://doi.org/10.1038/nature20791https://doi.org/10.1038/nature20791 PMID:27974793

Pasha Shaik A, Sankar S, Reddy SC, Das PG, Jamil K (2006). Lead-induced genotoxicity in lymphocytes from peripheral blood samples of humans: in vitro studies. Drug Chem Toxicol. 29(1):111–24. https://doi.org/10.1080/01480540500408739

Paskaleva EE, Arra M, Liu Y, Guo H, Swartz G, Kennedy JS, et al. (2014). Evaluation of potential genotoxicity of HIV entry inhibitors derived from natural sources. PLoS One. 9(3):e93108. https://doi.org/10.1371/journal.pone.0093108

Pasqualini JR, Ebert C, Chetrite GS (2001). Biological effects of progestins in breast cancer. Gynecol Endocrinol. 15(sup6) Suppl 6):44–52. https://doi.org/10.1080/gye.15.s6.44.52

Pasqualli T, Chaves PEE, da Veiga Pereira L, Serpa ÉA, Flávio Souza de Oliveira L, Mansur Machado M (2020b). The use of fructose as a sweetener. Is it a safe alternative for our immune system? J Food Biochem. 44(11):e13496. https://doi.org/10.1111/jfbc.13496

Pasqualli T, E Chaves PE, da Veiga Pereira L, Adílio Serpa É, de Oliveira LFS, Machado MM (2020a). Sucralose causes non-selective CD4 and CD8 lymphotoxicity via probable regulation of the MAPK8/APTX/EID1 genes: an in vitro/in silico study. Clin Exp Pharmacol Physiol. 47(10):1751–7. https://doi.org/10.1111/1440-1681.13362

Pasquer F, Ochsner U, Zarn J, Keller B (2006). Common and distinct gene expression patterns induced by the herbicides 2,4-dichlorophenoxyacetic acid, cinidon-ethyl and tribenuron-methyl in wheat. Pest Manag Sci. 62(12):1155–67. https://doi.org/10.1002/ps.1291

Pastoor T, Rose P, Lloyd S, Peffer R, Green T (2005). Case study: weight of evidence evaluation of the human health relevance of thiamethoxam-related mouse liver tumors. Toxicol Sci. 86(1):56–60. https://doi.org/10.1093/toxsci/kfi126

Pattison MJ, Mackenzie KF, Arthur JSC (2012). Inhibition of JAKs in macrophages increases lipopolysaccharide-induced cytokine production by blocking IL-10-mediated feedback. J Immunol. 189(6):2784–92. https://doi.org/10.4049/jimmunol.1200310

Paul KB, Thompson JT, Simmons SO, Vanden Heuvel JP, Crofton KM (2013). Evidence for triclosan-induced activation of human and rodent xenobiotic nuclear receptors. Toxicol In Vitro. 27(7):2049–60. https://doi.org/10.1016/j.tiv.2013.07.008

Paulson KG, Carter JJ, Johnson LG, Cahill KW, Iyer JG, Schrama D, et al. (2010). Antibodies to Merkel cell polyomavirus T antigen oncoproteins reflect tumor burden in merkel cell carcinoma patients. Cancer Res. 70(21):8388–97. https://doi.org/10.1158/0008-5472.CAN-10-2128

Pauluhn J (2010). Subchronic 13-week inhalation exposure of rats to multiwalled carbon nanotubes: toxic effects are determined by density of agglomerate structures, not fibrillar structures. Toxicol Sci. 113(1):226–42. https://doi.org/10.1093/toxsci/kfp247

Pavlatos AM, Fultz O, Monberg MJ, Vootkur A, PharmD AV (2001). Review of oxymetholone: a 17α-alkylated anabolic-androgenic steroid. Clin Ther. 23(6):789–801, discussion 771. https://doi.org/10.1016/S0149-2918(01)80070-9

Pawar G, Abdallah MA, de Sáa EV, Harrad S (2017). Dermal bioaccessibility of flame retardants from indoor dust and the influence of topically applied cosmetics. J Expo Sci Environ Epidemiol. 27(1):100–5. https://doi.org/10.1038/jes.2015.84

Paz-Trejo C, Gómez-Arroyo S (2017). Genotoxic evaluation of common commercial pesticides in human peripheral blood lymphocytes. Toxicol Ind Health. 33(12):938–45. https://doi.org/10.1177/0748233717736121https://doi.org/10.1177/0748233717736121 PMID:29137571

Peacock A, Leung J, Larney S, Colledge S, Hickman M, Rehm J, et al. (2018). Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addiction. 113(10):1905–26. https://doi.org/10.1111/add.14234

Pedersen C, Bräuner EV, Rod NH, Albieri V, Andersen CE, Ulbak K, et al. (2014). Distance to high-voltage power lines and risk of childhood leukemia – an analysis of confounding by and interaction with other potential risk factors. PLoS One. 9(9):e107096. https://doi.org/10.1371/journal.pone.0107096

Pedersen C, Johansen C, Schüz J, Olsen JH, Raaschou-Nielsen O (2015). Residential exposure to extremely low-frequency magnetic fields and risk of childhood leukaemia, CNS tumour and lymphoma in Denmark. Br J Cancer. 113(9):1370–4. https://doi.org/10.1038/bjc.2015.365

Pedersen M, Stafoggia M, Weinmayr G, Andersen ZJ, Galassi C, Sommar J, et al. (2018). Is there an association between ambient air pollution and bladder cancer incidence? Analysis of 15 European cohorts. Eur Urol Focus. 4(1):113–20. https://doi.org/10.1016/j.euf.2016.11.008

Pederson HJ, Faubion SS, Pruthi S, Goldfarb S (2023). RE: Systemic or vaginal hormone therapy after early breast cancer: a Danish observational cohort study. J Natl Cancer Inst. 115(2):220–1. https://doi.org/10.1093/jnci/djac211

Pega F, Náfrádi B, Momen NC, Ujita Y, Streicher KN, Prüss-Üstün AM, et al.; Technical Advisory Group (2021). Global, regional, and national burdens of ischemic heart disease and stroke attributable to exposure to long working hours for 194 countries, 2000–2016: a systematic analysis from the WHO/ILO Joint Estimates of the Work-related Burden of Disease and Injury. Environ Int. 154:106595. https://doi.org/10.1016/j.envint.2021.106595

Pegram RA, Andersen ME, Warren SH, Ross TM, Claxton LD (1997). Glutathione S-transferase-mediated mutagenicity of trihalomethanes in *Salmonella typhimurium*: contrasting results with bromodichloromethane off chloroform. Toxicol Appl Pharmacol. 144(1):183–8. https://doi.org/10.1006/taap.1997.8123

Peinado FM, Iribarne-Durán LM, Artacho-Cordón F (2023). Human exposure to bisphenols, parabens, and benzophenones, and its relationship with the inflammatory response: a systematic review. Int J Mol Sci. 24(8):7325. https://doi.org/10.3390/ijms24087325https://doi.org/10.3390/ijms24087325 PMID:37108488

Pelucchi C, Bosetti C, Galeone C, La Vecchia C (2015). Dietary acrylamide and cancer risk: an updated meta-analysis. Int J Cancer. 136(12):2912–22. https://doi.org/10.1002/ijc.29339

Peng C, Jie-Xin L (2021). The incidence and risk of cutaneous toxicities associated with dabrafenib in melanoma patients: a systematic review and meta-analysis. Eur J Hosp Pharm Sci Pract. 28(4):182–9. https://doi.org/10.1136/ejhpharm-2020-002347

Peng J, Wang T, Zhu H, Guo J, Li K, Yao Q, et al. (2014). Multiplex PCR/mass spectrometry screening of biological carcinogenic agents in human mammary tumors. J Clin Virol. 61(2):255–9. https://doi.org/10.1016/j.jcv.2014.07.010

Peng Y, Fang W, Yan L, Wang Z, Wang P, Yu J, et al. (2020). Early life stage bioactivity assessment of short-chain chlorinated paraffins at environmentally relevant concentrations by concentration-dependent transcriptomic analysis of zebrafish embryos. Environ Sci Technol. 54(2):996–1004. https://doi.org/10.1021/acs.est.9b04879

Pepłońska B, Sobala W, Szeszenia-Dabrowska N (2001). Mortality pattern in the cohort of workers exposed to carbon disulfide. Int J Occup Med Environ Health. 14(3):267–74.

Pepłońska B, Szeszenia-Dabrowska N, Sobala W, Wilczyńska U (1996). A mortality study of workers with reported chronic occupational carbon disulfide poisoning. Int J Occup Med Environ Health. 9(4):291–9. http://oldwww.imp.lodz.pl/upload/oficyna/artykuly/pdf/full/Pep10-03-01.pdf

Peprah S, Ogwang MD, Kerchan P, Reynolds SJ, Tenge CN, Were PA, et al. (2020). Risk factors for Burkitt lymphoma in East African children and minors: a case–control study in malaria-endemic regions in Uganda, Tanzania and Kenya. Int J Cancer. 146(4):953–69. https://doi.org/10.1002/ijc.32390

Perchellet JP, Abney NL, Thomas RM, Guislain YL, Perchellet EM (1987). Effects of combined treatments with selenium, glutathione, and vitamin E on glutathione peroxidase activity, ornithine decarboxylase induction, and complete and multistage carcinogenesis in mouse skin. Cancer Res. 47(2):477–85.

Pereira LC, de Souza AO, Meireles G, Franco-Bernardes MF, Tasso MJ, Bruno V, et al. (2016). Comparative study of genotoxicity induced by six different PBDEs. Basic Clin Pharmacol Toxicol. 119(4):396–404. https://doi.org/10.1111/bcpt.12595

Perissinotto CM, Covinsky KE (2014). Living alone, socially isolated or lonely – what are we measuring? J Gen Intern Med. 29(11):1429–31. https://doi.org/10.1007/s11606-014-2977-8https://doi.org/10.1007/s11606-014-2977-8 PMID:25092012

Perlman D, Mandel JH, Odo N, Ryan A, Lambert C, MacLehose RF, et al. (2018). Pleural abnormalities and exposure to elongate mineral particles in Minnesota iron ore (taconite) workers. Am J Ind Med. 61(5):391–9. https://doi.org/10.1002/ajim.22828

Perocco P, Santucci MA, Gasperi Campani A, Forti GC (1989). Toxic and DNA-damaging activities of the fungicides mancozeb and thiram (TMTD) on human lymphocytes in vitro. Teratog Carcinog Mutagen. 9(2):75–81. https://doi.org/10.1002/tcm.1770090203

Perrone G, Ferrara M, Medina A, Pascale M, Magan N (2020). Toxigenic fungi and mycotoxins in a climate change scenario: ecology, genomics, distribution, prediction and prevention of the risk. Microorganisms. 8(10):1496. https://doi.org/10.3390/microorganisms8101496

Peteffi GP, Antunes MV, Carrer C, Valandro ET, Santos S, Glaeser J, et al. (2016). Environmental and biological monitoring of occupational formaldehyde exposure resulting from the use of products for hair straightening. Environ Sci Pollut Res Int. 23(1):908–17. https://doi.org/10.1007/s11356-015-5343-4

Petitjean K, Verres Y, Bristeau S, Ribault C, Aninat C, Olivier C, et al. (2024). Low concentrations of ethylene bisdithiocarbamate pesticides maneb and mancozeb impair manganese and zinc homeostasis to induce oxidative stress and caspase-dependent apoptosis in human hepatocytes. Chemosphere. 346:140535. https://doi.org/10.1016/j.chemosphere.2023.140535

Petnicki-Ocwieja T, Hrncir T, Liu YJ, Biswas A, Hudcovic T, Tlaskalova-Hogenova H, et al. (2009). Nod2 is required for the regulation of commensal microbiota in the intestine. Proc Natl Acad Sci USA. 106(37):15813–8. https://doi.org/10.1073/pnas.0907722106

Petrick JL, Joslin CE, Johnson CE, Camacho TF, Peres LC, Bandera EV, et al. (2023). Menopausal hormone therapy use and risk of ovarian cancer by race: the ovarian cancer in women of African ancestry consortium. Br J Cancer. 129(12):1956–67. https://doi.org/10.1038/s41416-023-02407-7

Petruska JM, Frank DW, Freeman GB, Evans EW, MacDonald JS (2002). Toxicity and carcinogenicity studies of chlorpromazine hydrochloride and *p*-cresidine in the p53 heterozygous mouse model. Toxicol Pathol. 30(6):696–704. https://doi.org/10.1080/01926230290166788

Peyre L, Zucchini-Pascal N, Rahmani R (2014). Atrazine represses S100A4 gene expression and TPA-induced motility in HepG2 cells. Toxicol In Vitro. 28(2):156–63. https://doi.org/10.1016/j.tiv.2013.10.019

Pfohl-Leszkowicz A, Chekir-Ghedira L, Bacha H (1995). Genotoxicity of zearalenone, an estrogenic mycotoxin: DNA adduct formation in female mouse tissues. Carcinogenesis. 16(10):2315–20. https://doi.org/10.1093/carcin/16.10.2315

Phelps DW, Palekar AI, Conley HE, Ferrero G, Driggers JH, Linder KE, et al. (2023). Legacy and emerging per- and polyfluoroalkyl substances suppress the neutrophil respiratory burst. J Immunotoxicol. 20(1):2176953. https://doi.org/10.1080/1547691X.2023.2176953

Phelps NH, Singleton RK, Zhou B, Heap RA, Mishra A, Bennett JE, et al.; NCD Risk Factor Collaboration (NCD-RisC) (2024). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. Lancet. 403(10431):1027–50. https://doi.org/10.1016/S0140-6736(23)02750-2

Phillips B, Veljkovic E, Peck MJ, Buettner A, Elamin A, Guedj E, et al. (2015). A 7-month cigarette smoke inhalation study in C57BL/6 mice demonstrates reduced lung inflammation and emphysema following smoking cessation or aerosol exposure from a prototypic modified risk tobacco product. Food Chem Toxicol. 80:328–45. https://doi.org/10.1016/j.fct.2015.03.009

Phillips DH, Reddy MV, Randerath K (1984). 32P-post-labelling analysis of DNA adducts formed in the livers of animals treated with safrole, estragole and other naturally-occurring alkenylbenzenes. II. Newborn male B6C3F1 mice. Mutagenesis. 5(12):1623–8. https://doi.org/10.1093/carcin/5.12.1623

Phillips JC, Price RJ, Cunninghame ME, Osimitz TG, Cockburn A, Gabriel KL, et al. (1997). Effect of piperonyl butoxide on cell replication and xenobiotic metabolism in the livers of CD-1 mice and F344 rats. Fundam Appl Toxicol. 38(1):64–74. https://doi.org/10.1006/faat.1997.2326https://doi.org/10.1006/faat.1997.2326 PMID:9268606

Phillips ML, Johnson DL, Johnson AC (2013). Determinants of respirable silica exposure in stone countertop fabrication: a preliminary study. J Occup Environ Hyg. 10(7):368–73. https://doi.org/10.1080/15459624.2013.789706

Phung MT, Lee AW, Wu AH, Berchuck A, Cho KR, Cramer DW, et al.; Ovarian Cancer Association Consortium; Australian Ovarian Cancer Study Group and the Ovarian Cancer Association Consortium; Ovarian Cancer Association Consortium (2021). Depot-medroxyprogesterone acetate use is associated with decreased risk of ovarian cancer: the mounting evidence of a protective role of progestins. Cancer Epidemiol Biomarkers Prev. 30(5):927–35. https://doi.org/10.1158/1055-9965.EPI-20-1355

Phung MT, Muthukumar A, Trabert B, Webb PM, Jordan SJ, Terry KL, et al. (2022b). Effects of risk factors for ovarian cancer in women with and without endometriosis. Fertil Steril. 118(5):960–9. https://doi.org/10.1016/j.fertnstert.2022.07.019

Phung VLH, Uttajug A, Ueda K, Yulianti N, Latif MT, Naito D (2022a). A scoping review on the health effects of smoke haze from vegetation and peatland fires in Southeast Asia: issues with study approaches and interpretation. PLoS One. 17(9):e0274433. https://doi.org/10.1371/journal.pone.0274433

Pi N, Chia SE, Ong CN, Kelly BC (2016). Associations of serum organohalogen levels and prostate cancer risk: results from a case–control study in Singapore. Chemosphere. 144:1505–12. https://doi.org/10.1016/j.chemosphere.2015.10.020

Piccoli C, Cremonese C, Koifman RJ, Koifman S, Freire C (2016). Pesticide exposure and thyroid function in an agricultural population in Brazil. Environ Res. 151:389–98. https://doi.org/10.1016/j.envres.2016.08.011

Picetti R, Deeney M, Pastorino S, Miller MR, Shah A, Leon DA, et al. (2022). Nitrate and nitrite contamination in drinking water and cancer risk: a systematic review with meta-analysis. Environ Res. 210:112988. https://doi.org/10.1016/j.envres.2022.112988

Pich O, Cortes-Bullich A, Muiños F, Pratcorona M, Gonzalez-Perez A, Lopez-Bigas N (2021). The evolution of hematopoietic cells under cancer therapy. Nat Commun. 12(1):4803. https://doi.org/10.1038/s41467-021-24858-3

Piel C, Pouchieu C, Carles C, Béziat B, Boulanger M, Bureau M, et al.; AGRICAN group (2019b). Agricultural exposures to carbamate herbicides and fungicides and central nervous system tumour incidence in the cohort AGRICAN. Environ Int. 130:104876. https://doi.org/10.1016/j.envint.2019.05.070

Piel C, Pouchieu C, Migault L, Béziat B, Boulanger M, Bureau M, et al.; AGRICAN group (2019a). Increased risk of central nervous system tumours with carbamate insecticide use in the prospective cohort AGRICAN. Int J Epidemiol. 48(2):512–26. https://doi.org/10.1093/ije/dyy246

Pierozan P, Cattani D, Karlsson O (2022). Tumorigenic activity of alternative per- and polyfluoroalkyl substances (PFAS): mechanistic in vitro studies. Sci Total Environ. 808:151945. https://doi.org/10.1016/j.scitotenv.2021.151945

Pietroiusti A, Stockmann-Juvala H, Lucaroni F, Savolainen K (2018). Nanomaterial exposure, toxicity, and impact on human health. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 10(5):e1513. https://doi.org/10.1002/wnan.1513

Pietryk EW, Clement K, Elnagheeb M, Kuster R, Kilpatrick K, Love MI, et al. (2018). Intergenerational response to the endocrine disruptor vinclozolin is influenced by maternal genotype and crossing scheme. Reprod Toxicol. 78:9–19. https://doi.org/10.1016/j.reprotox.2018.03.005

Pijpe A, Slottje P, van Pelt C, Stehmann F, Kromhout H, van Leeuwen FE, et al. (2014). The Nightingale study: rationale, study design and baseline characteristics of a prospective cohort study on shift work and breast cancer risk among nurses. BMC Cancer. 14(1):47. https://doi.org/10.1186/1471-2407-14-47 PMID:24475944

Pillay D, Chuturgoon AA, Nevines E, Manickum T, Deppe W, Dutton MF (2002). The quantitative analysis of zearalenone and its derivatives in plasma of patients with breast and cervical cancer. Clin Chem Lab Med. 40(9):946–51. https://doi.org/10.1515/CCLM.2002.166

Pineton de Chambrun G, Body-Malapel M, Frey-Wagner I, Djouina M, Deknuydt F, Atrott K, et al. (2014). Aluminum enhances inflammation and decreases mucosal healing in experimental colitis in mice. Mucosal Immunol. 7(3):589–601. https://doi.org/10.1038/mi.2013.78

Pinho RA, Bonatto F, Andrades M, Frota ML Jr, Ritter C, Klamt F, et al. (2004). Lung oxidative response after acute coal dust exposure. Environ Res. 96(3):290–7. https://doi.org/10.1016/j.envres.2003.10.006

Pinto IS, Neto IF, Soares HM (2014). Biodegradable chelating agents for industrial, domestic, and agricultural applications – a review. Environ Sci Pollut Res Int. 21(20):11893–906. https://doi.org/10.1007/s11356-014-2592-6

Pintova S, Dharmupari S, Moshier E, Zubizarreta N, Ang C, Holcombe RF (2019). Genistein combined with FOLFOX or FOLFOX-Bevacizumab for the treatment of metastatic colorectal cancer: phase I/II pilot study. Cancer Chemother Pharmacol. 84(3):591–8. https://doi.org/10.1007/s00280-019-03886-3

Pirbudak Cocelli L, Ugur MG, Karadasli H (2012). Comparison of effects of low-flow sevoflurane and desflurane anesthesia on neutrophil and T-cell populations. Curr Ther Res Clin Exp. 73(1–2):41–51. https://doi.org/10.1016/j.curtheres.2012.02.005https://doi.org/10.1016/j.curtheres.2012.02.005 PMID:24653511

Piscianz E, Valencic E, Cuzzoni E, De Iudicibus S, De Lorenzo E, Decorti G, et al. (2014). Fate of lymphocytes after withdrawal of tofacitinib treatment. PLoS One. 9(1):e85463. https://doi.org/10.1371/journal.pone.0085463

Pisinger C (2015). A systematic review of health effects of electronic cigarettes. Geneva, Switzerland: World Health Organization. Available from https://www.who.int/docs/default-source/tobacco-hq/regulating-tobacco-products/backgroundpapersends3-4november-.pdf

Pisinger C, Døssing M (2014). A systematic review of health effects of electronic cigarettes. Prev Med. 69:248–60. https://doi.org/10.1016/j.ypmed.2014.10.009

Pittet B, Montandon D, Pittet D (2005). Infection in breast implants. Lancet Infect Dis. 5(2):94–106. https://doi.org/10.1016/S1473-3099(05)70084-0

Piwowar A, Żurawska-Płaksej E, Bizoń A, Sawicka E, Płaczkowska S, Prescha A (2023). The impact of dietary nitrates and acrylamide intake on systemic redox status in healthy young adults. Int J Occup Med Environ Health. 36(6):773–87. https://doi.org/10.13075/ijomeh.1896.02246

Pizzorno J (2014). Glutathione! Integr Med (Encinitas). 13(1):8–12. https://doi.org/10.1007/3-540-36723-3_1 PMID:26770075

Pletzer B, Winkler-Crepaz K, Maria Hillerer K (2023). Progesterone and contraceptive progestin actions on the brain: a systematic review of animal studies and comparison to human neuroimaging studies. Front Neuroendocrinol. 69:101060. https://doi.org/10.1016/j.yfrne.2023.101060

Płoska A, Wozniak M, Hedhli J, Konopka CJ, Skondras A, Matatov S, et al. (2023). In vitro and in vivo imaging-based evaluation of doxorubicin anticancer treatment in combination with the herbal medicine black cohosh. Int J Mol Sci. 24(24):17506. https://doi.org/10.3390/ijms242417506https://doi.org/10.3390/ijms242417506 PMID:38139334

Poirier LA, Theiss JC, Arnold LJ, Shimkin MB (1984). Inhibition by magnesium and calcium acetates of lead subacetate- and nickel acetate-induced lung tumors in strain A mice. Cancer Res. 44(4):1520–2.

Poirier MC, Reed E, Litterst CL, Katz D, Gupta-Burt S (1992). Persistence of platinum–ammine–DNA adducts in gonads and kidneys of rats and multiple tissues from cancer patients. Cancer Res. 52(1):149–53.

Pokhrel LR, Grady KD (2021). Risk assessment of occupational exposure to anesthesia isoflurane in the hospital and veterinary settings. Sci Total Environ. 783:146894. https://doi.org/10.1016/j.scitotenv.2021.146894

Polesie S, Gillstedt M, Paoli J, Osmancevic A (2020). Methotrexate treatment for patients with psoriasis and risk of cutaneous melanoma: a nested case–control study. Br J Dermatol. 183(4):684–91. https://doi.org/10.1111/bjd.18887

Polesie S, Gillstedt M, Schmidt SAJ, Egeberg A, Pottegård A, Kristensen K (2023). Use of methotrexate and risk of skin cancer: a nationwide case–control study. Br J Cancer. 128(7):1311–9. https://doi.org/10.1038/s41416-023-02172-7

Polesie S, Gillstedt M, Sönnergren HH, Osmancevic A, Paoli J (2017). Methotrexate treatment and risk for cutaneous malignant melanoma: a retrospective comparative registry-based cohort study. Br J Dermatol. 176(6):1492–9. https://doi.org/10.1111/bjd.15170

Policard M, Jain S, Rego S, Dakshanamurthy S (2021). Immune characterization and profiles of SARS-CoV-2 infected patients reveals potential host therapeutic targets and SARS-CoV-2 oncogenesis mechanism. Virus Res. 301:198464. https://doi.org/10.1016/j.virusres.2021.198464

Polychronakis I, Dounias G, Makropoulos V, Riza E, Linos A (2013). Work-related leukemia: a systematic review. J Occup Med Toxicol. 8(1):14. https://doi.org/10.1186/1745-6673-8-14

Polyzos SA, Zeglinas C, Artemaki F, Doulberis M, Kazakos E, Katsinelos P, et al. (2018). *Helicobacter pylori* infection and esophageal adenocarcinoma: a review and a personal view. Ann Gastroenterol. 31(1):8–13.

Pommier Y, Leo E, Zhang H, Marchand C (2010). DNA topoisomerases and their poisoning by anticancer and antibacterial drugs. Chem Biol. 17(5):421–33. https://doi.org/10.1016/j.chembiol.2010.04.012

Pond ZA, Saha PK, Coleman CJ, Presto AA, Robinson AL, Arden Pope Iii C (2022). Mortality risk and long-term exposure to ultrafine particles and primary fine particle components in a national US cohort. Environ Int. 167:107439. https://doi.org/10.1016/j.envint.2022.107439

Porras SP, Hartonen M, Koponen J, Ylinen K, Louhelainen K, Tornaeus J, et al. (2020). Occupational exposure of plastics workers to diisononyl phthalate (DiNP) and di(2-propylheptyl) phthalate (DPHP) in Finland. Int J Environ Res Public Health. 17(6):2035. https://doi.org/10.3390/ijerph17062035

Portnov BA, Stevens RG, Samociuk H, Wakefield D, Gregorio DI (2016). Light at night and breast cancer incidence in Connecticut: an ecological study of age group effects. Sci Total Environ. 572:1020–4. https://doi.org/10.1016/j.scitotenv.2016.08.006

Poschner S, Wackerlig J, Dobusch D, Pachmann B, Banh SJ, Thalhammer T, et al. (2020). Actaea racemosa L. extract inhibits steroid sulfation in human breast cancer cells: effects on androgen formation. Phytomedicine. 79:153357. https://doi.org/10.1016/j.phymed.2020.153357https://doi.org/10.1016/j.phymed.2020.153357 PMID:33011631

Poteser M, Laguzzi F, Schettgen T, Vogel N, Weber T, Murawski A, et al. (2022). Trends of exposure to acrylamide as measured by urinary biomarkers levels within the HBM4EU biomonitoring aligned studies (2000–2021). Toxics. 10(8):443. https://doi.org/10.3390/toxics10080443

Pott F, Blome H, Bruch J, Friedberg KD, Coll ET (1990). Einstufungsvorschlag fur anorganische und organische Fasern. Arbeitsmed Sozialmed Praventivmed. 25(10):463–6. [German]

Pott F, Roller M (2005). Carcinogenicity study with nineteen granular dusts in rats. Eur J Oncol. 10(4):249–81. https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/157790

Pott F, Ziem U, Reiffer FJ, Huth F, Ernst H, Mohr U (1987). Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. Exp Pathol. 32(3):129–52. https://doi.org/10.1016/S0232-1513(87)80044-0

Potula R, Haldar B, Cenna JM, Sriram U, Fan S (2018). Methamphetamine alters T cell cycle entry and progression: role in immune dysfunction. Cell Death Discov. 4(1):44. https://doi.org/10.1038/s41420-018-0045-6

Potula R, Hawkins BJ, Cenna JM, Fan S, Dykstra H, Ramirez SH, et al. (2010). Methamphetamine causes mitrochondrial oxidative damage in human T lymphocytes leading to functional impairment. J Immunol. 185(5):2867–76. https://doi.org/10.4049/jimmunol.0903691

Powis G, Moore DJ, Wilke TJ, Santone KS (1987). A high-performance liquid chromatography assay for measuring integrated biphenyl metabolism by intact cells: its use with rat liver and human liver and kidney. Anal Biochem. 167(1):191–8. https://doi.org/10.1016/0003-2697(87)90151-5

Praga C, Bergh J, Bliss J, Bonneterre J, Cesana B, Coombes RC, et al. (2005). Risk of acute myeloid leukemia and myelodysplastic syndrome in trials of adjuvant epirubicin for early breast cancer: correlation with doses of epirubicin and cyclophosphamide. J Clin Oncol. 23(18):4179–91. https://doi.org/10.1200/JCO.2005.05.029

Prajapati N, Cordina-Duverger E, Boileau A, Faure E, Guénel P (2023). Exposure to outdoor artificial light at night and breast cancer risk: a population-based case–control study in two French departments (the CECILE study). Frontiers in Environmental Health. 2:1268828. https://doi.org/10.3389/fenvh.2023.1268828

Prasetyo A, Adi Rahardja A, Tsuroya Azzahro D, Pawitra Miranti I, Saraswati I, Nur Kholis F (2019). *Nephrolepis exaltata* herbal mask increases nasal IgA levels and pulmonary function in textile factory workers. Adv Prev Med. 2019:5687135. https://doi.org/10.1155/2019/5687135

Preston RJ, Skare JA, Aardema MJ (2010). A review of biomonitoring studies measuring genotoxicity in humans exposed to hair dyes. Mutagenesis. 25(1):17–23. https://doi.org/10.1093/mutage/gep044

Presutti R, Harris SA, Kachuri L, Spinelli JJ, Pahwa M, Blair A, et al. (2016). Pesticide exposures and the risk of multiple myeloma in men: an analysis of the North American Pooled Project. Int J Cancer. 139(8):1703–14. https://doi.org/10.1002/ijc.30218

Préville X, Flacher M, LeMauff B, Beauchard S, Davelu P, Tiollier J, et al. (2001). Mechanisms involved in antithymocyte globulin immunosuppressive activity in a nonhuman primate model. Transplantation. 71(3):460–8. https://doi.org/10.1097/00007890-200102150-00021

Price RJ, Burch R, Chatham LR, Higgins LG, Currie RA, Lake BG (2020). An assay for screening xenobiotics for inhibition of rat thyroid gland peroxidase activity. Xenobiotica. 50(3):318–22. https://doi.org/10.1080/00498254.2019.1629044https://doi.org/10.1080/00498254.2019.1629044 PMID:31180273

Pridgen GW, Zhu J, Wei Y (2023). Exposure to p-dichlorobenzene and prevalent endocrine-related reproductive cancers among US women. Environ Sci Pollut Res Int. 30(32):78324–31. https://doi.org/10.1007/s11356-023-27876-4

Prins GS, Hu WY, Xie L, Shi GB, Hu DP, Birch L, et al. (2018). Evaluation of bisphenol A (BPA) exposures on prostate stem cell homeostasis and prostate cancer risk in the NCTR-Sprague-Dawley rat: An NIEHS/FDA CLARITY-BPA consortium study. Environ Health Perspect. 126(11):117001. https://doi.org/10.1289/EHP3953https://doi.org/10.1289/EHP3953 PMID:30387366

Prins GS, Patisaul HB, Belcher SM, Vandenberg LN (2019). CLARITY-BPA academic laboratory studies identify consistent low-dose Bisphenol A effects on multiple organ systems. Basic Clin Pharmacol Toxicol. 125(Suppl 3) Suppl 3:14–31. https://doi.org/10.1111/bcpt.13125https://doi.org/10.1111/bcpt.13125 PMID:30207065

Pritchett N, Spangler EC, Gray GM, Livinski AA, Sampson JN, Dawsey SM, et al. (2022). Exposure to outdoor particulate matter air pollution and risk of gastrointestinal cancers in adults: a systematic review and meta-analysis of epidemiologic evidence. Environ Health Perspect. 130(3):36001. https://doi.org/10.1289/EHP9620

Procianoy RS, Silveira RC, Fonseca LT, Heidemann LA, Neto EC (2010). The influence of phototherapy on serum cytokine concentrations in newborn infants. Am J Perinatol. 27(5):375–9. https://doi.org/10.1055/s-0029-1243311

PubChem (2009). 2,4-dichlorophenol. Compound summary. Bethesda (MD), USA: National Center for Biotechnology Information. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/8449, accessed September 2024.

PubChem (2023). Carbadox. Compound summary. Bethesda (MD), USA: National Center for Biotechnology Information. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Mecadox, accessed January 2024.

PubChem (2024a). Doxorubicin. Compound summary. Bethesda (MD), USA: National Center for Biotechnology Information. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/doxorubicin, accessed March 2024.

PubChem (2024b). Ametryn. Compound summary. Bethesda (MD), USA: National Center for Biotechnology Information. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/13263, accessed January 2024.

PubChem (2024c). 2-Methylbiphenyl-3-ylmethyl (Z)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate. Compound summary. Bethesda (MD), USA: National Center for Biotechnology Information. Available from https://pubchem.ncbi.nlm.nih.gov/compound/5281872, accessed January 2024.

PubChem (2024d). Cyfluthrin. Compound summary. Bethesda (MD), USA: National Center for Biotechnology Information. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/104926, accessed January 2024.

PubChem (2024e). Hexythiazox. Compound summary. Bethesda (MD), USA: National Center for Biotechnology Information. Available from https://pubchem.ncbi.nlm.nih.gov/compound/13218777, accessed January 2024.

PubChem (2024f). Metyltetraprole. Compound summary. Bethesda (MD), USA: National Center for Biotechnology Information. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/89881183, accessed January 2024.

PubChem (2024g). Proquinazid. Compound summary. Bethesda (MD), USA: National Center for Biotechnology Information. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/11057771, accessed January 2024.

PubChem (2024h) Erythrosin B. Compound summary. Bethesda (MD), USA: National Center for Biotechnology Information. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Erythrosin-B#section=Use-Classification, accessed January 2024.

PubChem (2024i). Fluoroanthene. Compound summary. Bethesda (MD), USA: National Center for Biotechnology Information. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/9154#section=Uses, accessed January 2024.

Public Health England (2016). Methanol. General Information. Compendium of Chemical Hazards. PHE publications gateway number: 2014790. London, UK: Public Health England. Available from: https://assets.publishing.service.gov.uk/media/5a81a58be5274a2e8ab551b9/methanol_general_information.pdf, accessed December 2023.

Puel O, Galtier P, Oswald IP (2010). Biosynthesis and toxicological effects of patulin. Toxins (Basel). 2(4):613–31. https://doi.org/10.3390/toxins2040613

Puigvehí M, Moctezuma-Velázquez C, Villanueva A, Llovet JM (2019). The oncogenic role of hepatitis delta virus in hepatocellular carcinoma. JHEP Rep Innov Hepatol. 1(2):120–30. https://doi.org/10.1016/j.jhepr.2019.05.001https://doi.org/10.1016/j.jhepr.2019.05.001 PMID:32039360

Pukkala E, Martinsen JI, Lynge E, Gunnarsdottir HK, Sparén P, Tryggvadottir L, et al. (2009). Occupation and cancer – follow-up of 15 million people in five Nordic countries. Acta Oncol. 48(5):646–790. https://doi.org/10.1080/02841860902913546

Pulat S, Subedi L, Pandey P, Bhosle SR, Hur JS, Shim JH, et al. (2023). Topical delivery of atraric acid derived from *Stereocaulon japonicum* with enhanced skin permeation and hair regrowth activity for androgenic alopecia. Pharmaceutics. 15(2):340. https://doi.org/10.3390/pharmaceutics15020340

Purdue MP (2003). Glucocorticoid use and skin cancers. Br J Cancer. 89(5):951–2, author reply 952–3. https://doi.org/10.1038/sj.bjc.6601221

Purdue MP, Rhee J, Denic-Roberts H, McGlynn KA, Byrne C, Sampson J, et al. (2023). A nested case control study of serum per- and polyfluoroalkyl substances and testicular germ cell tumors among US Air Force servicemen. Environ Health Perspect. 131(7):77007. https://doi.org/10.1289/EHP12603https://doi.org/10.1289/EHP12603 PMID:37458713

Purnomo HD, Kusuma RA, Sianturi E, Haroen RF, Solichin MR, Nissa C, et al. (2023). The effects of hepatogomax enteral formula on systemic inflammation, caecum short-chain fatty acid levels, and liver histopathology in thioacetamide-induced rats. J Nutr Metab. 2023:2313503. https://doi.org/10.1155/2023/2313503 https://onlinelibrary.wiley.com/doi/10.1155/2023/2313503

Pylak-Piwko O, Nieradko-Iwanicka B (2021). Subacute poisoning with bifenthrin increases the level of interleukin 1β in mice kidneys and livers. BMC Pharmacol Toxicol. 22(1):21. https://doi.org/10.1186/s40360-021-00490-1

Qi G, Zuo X, Zhou L, Aoki E, Okamula A, Watanebe M, et al. (2015). Effects of extremely low-frequency electromagnetic fields (ELF-EMF) exposure on B6C3F$_1$ mice. Environ Health Prev Med. 20(4):287–93. https://doi.org/10.1007/s12199-015-0463-5

Qin L, Deng HY, Chen SJ, Wei W (2019). A meta-analysis on the relationship between hair dye and the incidence of non-Hodgkin's lymphoma. Med Princ Pract. 28(3):222–30. https://doi.org/10.1159/000496447

Qiu DC, Hubbard AE, Zhong B, Zhang Y, Spear RC (2005). A matched, case–control study of the association between *Schistosoma japonicum* and liver and colon cancers, in rural China. Ann Trop Med Parasitol. 99(1):47–52. https://doi.org/10.1179/136485905X19883

Qiu W, Hu J, Magnuson JT, Greer J, Yang M, Chen Q, et al. (2020). Evidence linking exposure of fish primary macrophages to antibiotics activates the NF-kB pathway. Environ Int. 138:105624. https://doi.org/10.1016/j.envint.2020.105624

Qu J, Mao W, Liao K, Zhang Y, Jin H (2022). Association between urinary bisphenol analogue concentrations and lung cancer in adults: a case–control study. Environ Pollut. 315:120323. https://doi.org/10.1016/j.envpol.2022.120323

Quds R, Iqbal Z, Arif A, Mahmood R (2023). Mancozeb-induced cytotoxicity in human erythrocytes: enhanced generation of reactive species, hemoglobin oxidation, diminished antioxidant power, membrane damage and morphological changes. Pestic Biochem Physiol. 193:105453. https://doi.org/10.1016/j.pestbp.2023.105453https://doi.org/10.1016/j.pestbp.2023.105453 PMID:37248021

Queen J, Domingue JC, White JR, Stevens C, Udayasuryan B, Nguyen TTD, et al. (2021). Comparative analysis of colon cancer-derived *Fusobacterium nucleatum* subspecies: inflammation and colon tumorigenesis in murine models. MBio. 13(1):e0299121. https://doi.org/10.1128/mbio.02991-21

Quetglas-Llabrés MM, Monserrat-Mesquida M, Bouzas C, Mateos D, Ugarriza L, Gómez C, et al. (2023). Oxidative stress and inflammatory biomarkers are related to high intake of ultra-processed food in old adults with metabolic syndrome. Antioxidants. 12(8):1532. https://doi.org/10.3390/antiox12081532

Quist AJL, Inoue-Choi M, Weyer PJ, Anderson KE, Cantor KP, Krasner S, et al. (2018). Ingested nitrate and nitrite, disinfection by-products, and pancreatic cancer risk in postmenopausal women. Int J Cancer. 142(2):251–61. https://doi.org/10.1002/ijc.31055https://doi.org/10.1002/ijc.31055 PMID:28921575

Rababa'h AM, Hussein SA, Khabour OF, Alzoubi KH (2020). The protective effect of cilostazol in genotoxicity induced by methotrexate in human cultured lymphocytes. Curr Mol Pharmacol. 13(2):137–43. https://doi.org/10.2174/1874467212666191023120118

Radi Z, Bartholomew P, Elwell M, Vogel WM (2013). Comparative pathophysiology, toxicology, and human cancer risk assessment of pharmaceutical-induced hibernoma. Toxicol Appl Pharmacol. 273(3):456–63. https://doi.org/10.1016/j.taap.2013.10.011

Rádiková Z, Tajtáková M, Kocan A, Trnovec T, Seböková E, Klimes I, et al. (2008). Possible effects of environmental nitrates and toxic organochlorines on human thyroid in highly polluted areas in Slovakia. Thyroid. 18(3):353–62. https://doi.org/10.1089/thy.2007.0182https://doi.org/10.1089/thy.2007.0182 PMID:18298316

Rafaniello C, Ferrajolo C, Gaio M, Zinzi A, Scavone C, Sullo MG, et al. (2020). Tisagenlecleucel in children and young adults: reverse translational research by using real-world safety data. Pharmaceuticals (Basel). 13(9):258. https://doi.org/10.3390/ph13090258

Raffo A, D'Aloise A, Magrì AL, Leclercq C (2013). Quantitation of tr-cinnamaldehyde, safrole and myristicin in cola-flavoured soft drinks to improve the assessment of their dietary exposure. Food Chem Toxicol. 59:626–35. https://doi.org/10.1016/j.fct.2013.06.058

Rage E, Richardson DB, Demers PA, Do M, Fenske N, Kreuzer M, et al. (2020). PUMA – pooled uranium miners analysis: cohort profile. Occup Environ Med. 77(3):194–200. https://doi.org/10.1136/oemed-2019-105981

Ragnoli B, Pochetti P, Pignatti P, Barbieri M, Mondini L, Ruggero L, et al. (2022). Sleep deprivation, immune suppression and SARS-CoV-2 infection. Int J Environ Res Public Health. 19(2):904. https://doi.org/10.3390/ijerph19020904

Rahiman F, Pool EJ (2014). The in vitro effects of artificial and natural sweeteners on the immune system using whole blood culture assays. J Immunoassay Immunochem. 35(1):26–36. https://doi.org/10.1080/15321819.2013.784197

Rahman MF, Mahboob M, Danadevi K, Saleha Banu B, Grover P (2002). Assessment of genotoxic effects of chloropyriphos and acephate by the comet assay in mice leucocytes. Mutat Res. 516(1-2):139–47. https://doi.org/10.1016/S1383-5718(02)00033-5

Rahmouni F, Badraoui R, Amri N, Elleuch A, El-Feki A, Rebai T, et al. (2019). Hepatotoxicity and nephrotoxicity in rats induced by carbon tetrachloride and the protective effects of *Teucrium polium* and vitamin C. Toxicol Mech Methods. 29(5):313–21. https://doi.org/10.1080/15376516.2018.1519864

Rahmouni F, Saoudi M, Amri N, El-Feki A, Rebai T, Badraoui R (2018). Protective effect of *Teucrium polium* on carbon tetrachloride induced genotoxicity and oxidative stress in rats. Arch Physiol Biochem. 124(1):1–9. https://doi.org/10.1080/13813455.2017.1347795

Rajaraman P, Stewart PA, Samet JM, Schwartz BS, Linet MS, Zahm SH, et al. (2006). Lead, genetic susceptibility, and risk of adult brain tumors. Cancer Epidemiol Biomarkers Prev. 15(12):2514–20. https://doi.org/10.1158/1055-9965.EPI-06-0482

Ramez AM, Elmahallawy EK, Elshopakey GE, Saleh AA, Moustafa SM, Al-Brakati A, et al. (2021). Hepatosplenic protective actions of *Spirulina platensis* and matcha green tea against *Schistosoma mansoni* infection in mice via antioxidative and anti-inflammatory mechanisms. Front Vet Sci. 8:650531. https://doi.org/10.3389/fvets.2021.650531

Ramezani M, Baharzadeh F, Almasi A, Sadeghi M (2020). A systematic review and meta-analysis: evaluation of the β-human papillomavirus in immunosuppressed individuals with cutaneous squamous cell carcinoma. Biomedicine (Taipei). 10(4):1–10. https://doi.org/10.37796/2211-8039.1110

Ramhøj L, Hass U, Gilbert ME, Wood C, Svingen T, Usai D, et al. (2020). Evaluating thyroid hormone disruption: investigations of long-term neurodevelopmental effects in rats after perinatal exposure to perfluorohexane sulfonate (PFHxS). Sci Rep. 10(1):2672. https://doi.org/10.1038/s41598-020-59354-z

Ramirez SH, Potula R, Fan S, Eidem T, Papugani A, Reichenbach N, et al. (2009). Methamphetamine disrupts blood–brain barrier function by induction of oxidative stress in brain endothelial cells. J Cereb Blood Flow Metab. 29(12):1933–45. https://doi.org/10.1038/jcbfm.2009.112

Ramkissoon C, Song Y, Yen S, Southam K, Page S, Pisaniello D, et al. (2023). Understanding the pathogenesis of engineered stone-associated silicosis: the effect of particle chemistry on the lung cell response. Respirology. 29(3):217–27. https://doi.org/10.1111/resp.14625

Ramos JSA, Pedroso TMA, Godoy FR, Batista RE, de Almeida FB, Francelin C, et al. (2021). Multi-biomarker responses to pesticides in an agricultural population from central Brazil. Sci Total Environ. 754:141893. https://doi.org/10.1016/j.scitotenv.2020.141893

Ramprasad C, Willis Gwenzi W, Chaukura N, Wan Azelee NI, Rajapaksha AU, Naushad M, et al. (2022). Strategies and options for the sustainable recovery of rare earth elements from electrical and electronic waste. Chem Eng J. 442(1):135992. https://doi.org/10.1016/j.cej.2022.135992

Rana I, Rieswijk L, Steinmaus C, Zhang L (2021). Formaldehyde and brain disorders: a meta-analysis and bioinformatics approach. Neurotox Res. 39(3):924–48. https://doi.org/10.1007/s12640-020-00320-y

Randerath K, Haglund RE, Phillips DH, Reddy MV (1984). 32P-post-labelling analysis of DNA adducts formed in the livers of animals treated with safrole, estragole and other naturally-occurring alkenylbenzenes. I. Adult female CD-1 mice. Carcinogenesis. 5(12):1613–22. https://doi.org/10.1093/carcin/5.12.1613

Rashmi B, Chinna SK, Rodrigues C, Anjaly D, Bankur PK, Kannaiyan K (2020). Occurrence of micronuclei in exfoliated buccal mucosal cells in mobile phone users: a case–control study. Indian J Dent Res. 31(5):734–7. https://doi.org/10.4103/ijdr.IJDR_634_18

Raso G, Li Y, Zhao Z, Balen J, Williams GM, McManus DP (2009). Spatial distribution of human *Schistosoma japonicum* infections in the Dongting Lake Region, China. PLoS One. 4(9):e6947. https://doi.org/10.1371/journal.pone.0006947

Raszewski G, Lemieszek MK, Łukawski K (2016). Cytotoxicity induced by cypermethrin in human neuroblastoma cell line SH-SY5Y. Ann Agric Environ Med. 23(1):106–10. https://doi.org/10.5604/12321966.1196863

Raucy JL, Kraner JC, Lasker JM (1993). Bioactivation of halogenated hydrocarbons by cytochrome P4502E1. Crit Rev Toxicol. 23(1):1–20. https://doi.org/10.3109/10408449309104072

Ravula AR, Yenugu S (2021). Pyrethroid based pesticides – chemical and biological aspects. Crit Rev Toxicol. 51(2):117–40. https://doi.org/10.1080/10408444.2021.1879007

Ray D, Kidane D (2016). Gut microbiota imbalance and base excision repair dynamics in colon cancer. J Cancer. 7(11):1421–30. https://doi.org/10.7150/jca.15480

Rebbeck TR, Troxel AB, Norman S, Bunin GR, DeMichele A, Baumgarten M, et al. (2007). A retrospective case–control study of the use of hormone-related supplements and association with breast cancer. Int J Cancer. 120(7):1523–8. https://doi.org/10.1002/ijc.22485https://doi.org/10.1002/ijc.22485 PMID:17205521

Rebouillat P, Vidal R, Cravedi JP, Taupier-Letage B, Debrauwer L, Gamet-Payrastre L, et al. (2021). Prospective association between dietary pesticide exposure profiles and postmenopausal breast cancer risk in the NutriNet-Santé cohort. Int J Epidemiol. 50(4):1184–98. https://doi.org/10.1093/ije/dyab015

Reboussin BA, Wagoner KG, Ross JC, Suerken CK, Sutfin EL (2021). Tobacco and marijuana co-use in a cohort of young adults: patterns, correlates and reasons for co-use. Drug Alcohol Depend. 227:109000. https://doi.org/10.1016/j.drugalcdep.2021.109000

Reddy A, Conde C, Peterson C, Nugent K (2022). Residential radon exposure and cancer. Oncol Rev. 16(1):558. https://doi.org/10.4081/oncol.2022.558

Redmond LS, Ogwang MD, Kerchan P, Reynolds SJ, Tenge CN, Were PA, et al. (2020). Endemic Burkitt lymphoma: a complication of asymptomatic malaria in sub-Saharan Africa based on published literature and primary data from Uganda, Tanzania, and Kenya. Malar J. 19(1):239. https://doi.org/10.1186/s12936-020-03312-7

Reece AS, Hulse GK (2022). Cannabinoid and substance relationships of European congenital anomaly patterns: a space-time panel regression and causal inferential study. Environ Epigenet. 8(1):dvab015. https://doi.org/10.1093/eep/dvab015

Reeves KW, Díaz Santana M, Manson JE, Hankinson SE, Zoeller RT, Bigelow C, et al. (2019). Urinary phthalate biomarker concentrations and postmenopausal breast cancer risk. J Natl Cancer Inst. 111(10):1059–67. https://doi.org/10.1093/jnci/djz002

Rehfuess E, Mehta S, Prüss-Ustün A (2006). Assessing household solid fuel use: multiple implications for the Millennium Development Goals. Environ Health Perspect. 114(3):373–8. https://doi.org/10.1289/ehp.8603

Reid TM, Morton KC, Wang CY, King CM (1983). Conversion of Congo red and 2-azoxyfluorene to mutagens following in vitro reduction by whole-cell rat cecal bacteria. Mutat Res. 117(1–2):105–12. https://doi.org/10.1016/0165-1218(83)90157-X

Reigstad MM, Storeng R, Myklebust TÅ, Oldereid NB, Omland AK, Robsahm TE, et al. (2017). Cancer risk in women treated with fertility drugs according to parity status – a registry-based cohort study. Cancer Epidemiol Biomarkers Prev. 26(6):953–62. https://doi.org/10.1158/1055-9965.EPI-16-0809

Reisfeld B, de Conti A, El Ghissassi F, Benbrahim-Tallaa L, Gwinn W, Grosse Y, et al. (2022). KC-hits: a tool to aid in the evaluation and classification of chemical carcinogens. Bioinformatics. 38(10):2961–2. https://doi.org/10.1093/bioinformatics/btac189 PMID:35561175

Reitano E, de'Angelis N, Gavriilidis P, Gaiani F, Memeo R, Inchingolo R, et al. (2021). Oral bacterial microbiota in digestive cancer patients: a systematic review. Microorganisms. 9(12):2585. https://doi.org/10.3390/microorganisms9122585

Remigio RV, Andreotti G, Sandler DP, Erickson PA, Koutros S, Albert PS, et al. (2024). An updated evaluation of atrazine–cancer incidence associations among pesticide applicators in the Agricultural Health Study Cohort. Environ Health Perspect. 132(2):27010. https://doi.org/10.1289/EHP13684

Ren J, Zhuo Y, He F, Lv L, Xing M, Guo Y, et al. (2023). Longitudinal immune profiling highlights CD4+ T cell exhaustion correlated with liver fibrosis in *Schistosoma japonicum* infection. J Immunol. 210(1):82–95. https://doi.org/10.4049/jimmunol.2200301

Renthal W, Carle TL, Maze I, Covington HE 3rd, Truong HT, Alibhai I, et al. (2008). Delta FosB mediates epigenetic desensitization of the c-fos gene after chronic amphetamine exposure. J Neurosci. 28(29):7344–9. https://doi.org/10.1523/JNEUROSCI.1043-08.2008

Renwick LC, Brown D, Clouter A, Donaldson K (2004). Increased inflammation and altered macrophage chemotactic responses caused by two ultrafine particle types. Occup Environ Med. 61(5):442–7. https://doi.org/10.1136/oem.2003.008227

Renzelli V, Gallo M, Morviducci L, Marino G, Ragni A, Tuveri E, et al. (2023). Polybrominated diphenyl ethers (PBDEs) and human health: effects on metabolism, diabetes and cancer. Cancers (Basel). 15(17):4237. https://doi.org/10.3390/cancers15174237

Reulen RC, Kellen E, Buntinx F, Zeegers MP (2007). Bladder cancer and occupation: a report from the Belgian case–control study on bladder cancer risk. Am J Ind Med. 50(6):449–54. https://doi.org/10.1002/ajim.20469

Reus AA, Reisinger K, Downs TR, Carr GJ, Zeller A, Corvi R, et al. (2013). Comet assay in reconstructed 3D human epidermal skin models–investigation of intra- and inter-laboratory reproducibility with coded chemicals. Mutagenesis. 28(6):709–20. https://doi.org/10.1093/mutage/get051

Revanth MP, Aparna S, Madankumar PD (2020). Effects of mobile phone radiation on buccal mucosal cells: a systematic review. Electromagn Biol Med. 39(4):273–81. https://doi.org/10.1080/15368378.2020.1793168

Reza MA, Reza MH, Mahdiyeh L, Mehdi F, Hamid ZN (2015). Evaluation frequency of Merkel cell polyoma, Epstein–Barr and mouse mammary tumor viruses in patients with breast cancer in Kerman, southeast of Iran. Asian Pac J Cancer Prev. 16(16):7351–7. https://doi.org/10.7314/APJCP.2015.16.16.7351

Rhee J, Graubard BI, Purdue MP (2021). Blood lead levels and lung cancer mortality: an updated analysis of NHANES II and III. Cancer Med. 10(12):4066–74. https://doi.org/10.1002/cam4.3943

Rheeder JP, Marasas WFO, Thiel PG, Sydenham EW, Shephard GS, Van Schalkwyk DJ (1992). *Fusarium moniliforme* and fumonisins in corn in relation to human esophageal cancer in Transkei. Phytopathology. 82(3):353–7. https://doi.org/10.1094/Phyto-82-353

Ribas G, Surrallés J, Carbonell E, Xamena N, Creus A, Marcos R (1996). Genotoxicity of the herbicides alachlor and maleic hydrazide in cultured human lymphocytes. Mutagenesis. 11(3):221–7. https://doi.org/10.1093/mutage/11.3.221

Ribeiro DA, Pereira PC, Machado JM, Silva SB, Pessoa AW, Salvadori DM (2004). Does toxoplasmosis cause DNA damage? An evaluation in isogenic mice under normal diet or dietary restriction. Mutat Res. 559(1–2):169–76. https://doi.org/10.1016/j.mrgentox.2004.01.007

Ribeiro E, Ladeira C, Viegas S (2017). Occupational exposure to bisphenol A (BPA): a reality that still needs to be unveiled. Toxics. 5(3):22. https://doi.org/10.3390/toxics5030022

Riboli E, Beland FA, Lachenmeier DW, Marques MM, Phillips DH, Schernhammer E, et al. (2023). Carcinogenicity of aspartame, methyleugenol, and isoeugenol. Mol Nutr Food Res. 24(8):848–80. https://doi.org/10.1016/S1470-2045(23)00341-8

Ricci F, Fania L, Antonelli F, Ricci F, Perino F, Di Lella G, et al. (2022). Melanoma on tattoos: a case study and review of the literature. Eur J Dermatol. 32(6):703–8. https://doi.org/10.1684/ejd.2022.4353

Richardson AK, Walker LC, Cox B, Rollag H, Robinson BA, Morrin H, et al. (2020). Breast cancer and cytomegalovirus. Clin Transl Oncol. 22(4):585–602. https://doi.org/10.1007/s12094-019-02164-1

Richardson DB, Rage E, Demers PA, Do MT, DeBono N, Fenske N, et al. (2021). Mortality among uranium miners in North America and Europe: the Pooled Uranium Miners Analysis (PUMA). Int J Epidemiol. 50(2):633–43. https://doi.org/10.1093/ije/dyaa195

Richardson GM, Wilson R, Allard D, Purtill C, Douma S, Gravière J (2011). Mercury exposure and risks from dental amalgam in the US population, post-2000. Sci Total Environ. 409(20):4257–68. https://doi.org/10.1016/j.scitotenv.2011.06.035

Richfield-Fratz N, Baczynskyj WM, Miller GC, Bailey JE Jr (1989). Isolation, characterization and determination of trace organic impurities in FD&C red no. 40. J Chromatogr A. 467(1):167–76. https://doi.org/10.1016/S0021-9673(01)93961-5https://doi.org/10.1016/S0021-9673(01)93961-5 PMID:2753932

Richmond RC, Anderson EL, Dashti HS, Jones SE, Lane JM, Strand LB, et al. (2019). Investigating causal relations between sleep traits and risk of breast cancer in women: Mendelian randomisation study. BMJ. 365:12327. https://doi.org/10.1136/bmj.l2327

Richter HG, Mendez N, Halabi D, Torres-Farfan C, Spichiger C (2022). New integrative approaches to discovery of pathophysiological mechanisms triggered by night shift work. Chronobiol Int. 39(2):269–84. https://doi.org/10.1080/07420528.2021.1994984

Ricker K, Cheng V, Hsieh CJ, Tsai FC, Osborne G, Li K, et al. (2024). Application of the key characteristics of carcinogens to bisphenol A. Int J Toxicol. 43(3):253–90. https://doi.org/10.1177/10915818231225161

Rider CV, Chan P, Herbert RA, Kissling GE, Fomby LM, Hejtmancik MR, et al. (2016). Dermal exposure to cumene hydroperoxide. Toxicol Pathol. 44(5):749–62. https://doi.org/10.1177/0192623316636712

Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, et al.; CIRT Investigators (2019). Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med. 380(8):752–62. https://doi.org/10.1056/NEJMoa1809798

Rietjens IMCM, Michael A, Bolt HM, Siméon B, Andrea H, Nils H, et al. (2022). The role of endogenous versus exogenous sources in the exposome of putative genotoxins and consequences for risk assessment. Arch Toxicol. 96(5):1297–352. https://doi.org/10.1007/s00204-022-03242-0

Riley RT, Merrill AH Jr (2019). Ceramide synthase inhibition by fumonisins: a perfect storm of perturbed sphingolipid metabolism, signalling, and disease. J Lipid Res. 60(7):1183–9. https://doi.org/10.1194/jlr.S093815

Riley RT, Torres O, Matute J, Gregory SG, Ashley-Koch AE, Showker JL, et al. (2015). Evidence for fumonisin inhibition of ceramide synthase in humans consuming maize-based foods and living in high exposure communities in Guatemala. Mol Nutr Food Res. 59(11):2209–24. https://doi.org/10.1002/mnfr.201500499

Ritonja J, McIsaac MA, Sanders E, Kyba CCM, Grundy A, Cordina-Duverger E, et al. (2020). Outdoor light at night at residences and breast cancer risk in Canada. Eur J Epidemiol. 35(6):579–89. https://doi.org/10.1007/s10654-020-00610-x

Rittinghausen S, Bellmann B, Creutzenberg O, Ernst H, Kolling A, Mangelsdorf I, et al. (2013). Evaluation of immunohistochemical markers to detect the genotoxic mode of action of fine and ultrafine dusts in rat lungs. Toxicology. 303:177–86. https://doi.org/10.1016/j.tox.2012.11.007

RIVM (2023). NANoREG Results Repository. Bilthoven, The Netherlands: National Institute for Public Health and the Environment (RIVM), Available from: https://www.rivm.nl/en/international-projects/nanoreg, accessed October 2024.

Rizzetto M, Canese MG, Aricò S, Crivelli O, Trepo C, Bonino F, et al. (1977). Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. Gut. 18(12):997–1003. https://doi.org/10.1136/gut.18.12.997https://doi.org/10.1136/gut.18.12.997 PMID:75123

Rjiba-Touati K, Amara I, Bousabbeh M, Salem IB, Azzebi A, Guedri Y, et al. (2018). Recombinant human erythropoietin prevents etoposide- and methotrexate-induced toxicity in kidney and liver tissues via the regulation of oxidative damage and genotoxicity in Wistar rats. Hum Exp Toxicol. 37(8):848–58. https://doi.org/10.1177/0960327117733553

Robarts DR, Venneman KK, Gunewardena S, Apte U (2022). GenX induces fibroinflammatory gene expression in primary human hepatocytes. Toxicology. 477:153259. https://doi.org/10.1016/j.tox.2022.153259

Robbiano L, Carrozzino R, Bacigalupo M, Corbu C, Brambilla G (2002). Correlation between induction of DNA fragmentation in urinary bladder cells from rats and humans and tissue-specific carcinogenic activity. Toxicology. 179(1–2):115–28. https://doi.org/10.1016/S0300-483X(02)00354-2

Robbiano L, Carrozzino R, Puglia CP, Corbu C, Brambilla G (1999). Correlation between induction of DNA fragmentation and micronuclei formation in kidney cells from rats and humans and tissue-specific carcinogenic activity. Toxicol Appl Pharmacol. 161(2):153–9. https://doi.org/10.1006/taap.1999.8796

Robens JF, Dill GS, Ward JM, Joiner JR, Griesemer RA, Douglas JF (1980). Thirteen-week subchronic toxicity studies of Direct Blue 6, Direct Black 38, and Direct Brown 95 dyes. Toxicol Appl Pharmacol. 54(3):431–42. https://doi.org/10.1016/0041-008X(80)90170-2

Robertson SE, Yasukawa M, Marchion DC, Xiong Y, Naqvi SMH, Gheit T, et al. (2023). Prevalence of viral DNA in high-grade serous epithelial ovarian cancer and correlation with clinical outcomes. PLoS One. 18(12):e0294448. https://doi.org/10.1371/journal.pone.0294448

Robinson SN, Zens MS, Perry AE, Spencer SK, Duell EJ, Karagas MR (2013). Photosensitizing agents and the risk of non-melanoma skin cancer: a population-based case–control study. J Invest Dermatol. 133(8):1950–5. https://doi.org/10.1038/jid.2013.33

Rochester JR, Bolden AL (2015). Bisphenol S and F: a systematic review and comparison of the hormonal activity of bisphenol A substitutes. Environ Health Perspect. 123(7):643–50. https://doi.org/10.1289/ehp.1408989

Roderfeld M, Padem S, Lichtenberger J, Quack T, Weiskirchen R, Longerich T, et al. (2020). *Schistosoma mansoni* egg-secreted antigens activate hepatocellular carcinoma-associated transcription factors c-Jun and STAT3 in hamster and human hepatocytes. Hepatology. 72(2):626–41. https://doi.org/10.1002/hep.30192

Rodricks JV, Swenberg JA, Borzelleca JF, Maronpot RR, Shipp AM (2010). Triclosan: a critical review of the experimental data and development of margins of safety for consumer products. Crit Rev Toxicol. 40(5):422–84. https://doi.org/10.3109/10408441003667514

Rodrigues EG, Herrick RF, Stewart J, Palacios H, Laden F, Clark W, et al. (2020). Case–control study of brain and other central nervous system cancer among workers at semiconductor and storage device manufacturing facilities. Occup Environ Med. 77(4):238–48. https://doi.org/10.1136/oemed-2019-106120

Rodrigues EG, Stewart J, Herrick R, Palacios H, Laden F, Clark W, et al. (2019). Retrospective exposure assessment for semiconductor and storage device manufacturing facilities. J Occup Environ Med. 61(4):e132–8. https://doi.org/10.1097/JOM.0000000000001544

Rodríguez-Cano AM, González-Ludlow I, Suárez-Rico BV, Montoya-Estrada A, Piña-Ramírez O, Parra-Hernández SB, et al. (2022). Ultra-processed food consumption during pregnancy and its association with maternal oxidative stress markers. Antioxidants. 11(7):1415. https://doi.org/10.3390/antiox11071415

Roe FJC, Boyland E, Dukes CE, Mitchley BCV (1965). Failure of testosterone or xanthopterin to influence the induction of renal neoplasms by lead in rats. Br J Cancer. 19(4):860–6. https://doi.org/10.1038/bjc.1965.99

Rohr P, Kvitko K, da Silva FR, Menezes AP, Porto C, Sarmento M, et al. (2013). Genetic and oxidative damage of peripheral blood lymphocytes in workers with occupational exposure to coal. Mutat Res Genet Toxicol Environ Mutagen. 758(1–2):23–8. https://doi.org/10.1016/j.mrgentox.2013.08.006

Rojanapo W, Kupradinun P, Tepsuwan A, Chutimataewin S, Tanyakaset M (1986). Carcinogenicity of an oxidation product of *p*-phenylenediamine. Carcinogenesis. 7(12):1997–2002. https://doi.org/10.1093/carcin/7.12.1997https://doi.org/10.1093/carcin/7.12.1997 PMID:3779896

Rollerova E, Tulinska J, Liskova A, Kuricova M, Kovriznych J, Mlynarcikova A, et al. (2015). Titanium dioxide nanoparticles: some aspects of toxicity/focus on the development. Endocr Regul. 49(2):97–112. https://doi.org/10.4149/endo_2015_02_97

Rollison DE, Amorrortu RP, Zhao Y, Messina JL, Schell MJ, Fenske NA, et al. (2021). Cutaneous human papillomaviruses and the risk of keratinocyte carcinomas. Cancer Res. 81(17):4628–38. https://doi.org/10.1158/0008-5472.CAN-21-0805

Roma GC, de Oliveira PR, Araujo AM, Bechara GH, Mathias MI (2012a). Genotoxic and mutagenic effects of permethrin in mice: micronuclei analysis in peripheral blood erythrocytes. Microsc Res Tech. 75(12):1732–6. https://doi.org/10.1002/jemt.22124

Roma GC, De Oliveira PR, Bechara GH, Camargo Mathias MI (2012b). Cytotoxic effects of permethrin on mouse liver and spleen cells. Microsc Res Tech. 75(2):229–38. https://doi.org/10.1002/jemt.21047

Romeo S, Zeni O, Sannino A, Lagorio S, Biffoni M, Scarfì MR (2021). Genotoxicity of radiofrequency electromagnetic fields: protocol for a systematic review of in vitro studies. Environ Int. 148:106386. https://doi.org/10.1016/j.envint.2021.106386

Rooney MR, Lutsey PL, Bhatti P, Prizment A (2019). Urinary 2,5-dicholorophenol and 2,4-dichlorophenol concentrations and prevalent disease among adults in the National Health and Nutrition Examination Survey (NHANES). Occup Environ Med. 76(3):181–8. https://doi.org/10.1136/oemed-2018-105278

Röösli M, Lagorio S, Schoemaker MJ, Schüz J, Feychting M (2019). Brain and salivary gland tumors and mobile phone use: evaluating the evidence from various epidemiological study designs. Annu Rev Public Health. 40(1):221–38. https://doi.org/10.1146/annurev-publhealth-040218-044037

Ropejko K, Twarużek M (2021). Zearalenone and its metabolites – general overview, occurrence, and toxicity. Toxins (Basel). 13(1):35. https://doi.org/10.3390/toxins13010035

Ropek N, Al-Serori H, Mišík M, Nersesyan A, Sitte HH, Collins AR, et al. (2019). Methamphetamine ("crystal meth") causes induction of DNA damage and chromosomal aberrations in human derived cells. Food Chem Toxicol. 128:1–7. https://doi.org/10.1016/j.fct.2019.03.035

Rosa MJ, Armendáriz-Arnez C, Gudayol-Ferré E, Prehn M, Fuhrimann S, Eskenazi B, et al. (2024). Association of pesticide exposure with neurobehavioral outcomes among avocado farmworkers in Mexico. Int J Hyg Environ Health. 256:114322. https://doi.org/10.1016/j.ijheh.2024.114322

Rosales-Gómez CA, Martínez-Carrillo BE, Reséndiz-Albor AA, Ramírez-Durán N, Valdés-Ramos R, Mondragón-Velásquez T, et al. (2018). Chronic consumption of sweeteners and its effect on glycaemia, cytokines, hormones, and lymphocytes of GALT in CD1 mice. BioMed Res Int. 2018:1345282. https://doi.org/10.1155/2018/1345282

Rosenmai AK, Ahrens L, le Godec T, Lundqvist J, Oskarsson A (2018). Relationship between peroxisome proliferator-activated receptor alpha activity and cellular concentration of 14 perfluoroalkyl substances in HepG2 cells. J Appl Toxicol. 38(2):219–26. https://doi.org/10.1002/jat.3515

Rosenmai AK, Dybdahl M, Pedersen M, Alice van Vugt-Lussenburg BM, Wedebye EB, Taxvig C, et al. (2014). Are structural analogues to bisphenol a safe alternatives? Toxicol Sci. 139(1):35–47. https://doi.org/10.1093/toxsci/kfu030

Rosman LB, Beylin VG, Gaddamidi V, Hooberman BH, Sinsheimer JE (1986). Mutagenicity of para-substituted α-methylstyrene oxide derivatives with *Salmonella*. Mutat Res. 171(2–3):63–70. https://doi.org/10.1016/0165-1218(86)90036-4https://doi.org/10.1016/0165-1218(86)90036-4 PMID:3528837

Ross AG, Yuesheng L, Sleigh AS, Yi L, Williams GM, Wu WZ, et al. (1997). Epidemiologic features of *Schistosoma japonicum* among fishermen and other occupational groups in the Dongting Lake region (Hunan Province) of China. Am J Trop Med Hyg. 57(3):302–8. https://doi.org/10.4269/ajtmh.1997.57.302

Rostami A, Riahi SM, Gamble HR, Fakhri Y, Nourollahpour Shiadeh M, Danesh M, et al. (2020). Global prevalence of latent toxoplasmosis in pregnant women: a systematic review and meta-analysis. Clin Microbiol Infect. 26(6):673–83. https://doi.org/10.1016/j.cmi.2020.01.008

Rothe M, Schambach A, Biasco L (2014). Safety of gene therapy: new insights to a puzzling case. Curr Gene Ther. 14(6):429–36. https://doi.org/10.2174/1566523214666140918110905

Rotterdam Convention (2011a). Decision guidance document: alachlor. In Annex 3: Operation of the prior informed consent procedure for banned or severely restricted chemicals. Châtelaine, Switzerland: Secretariat of the Rotterdam Convention. Available from: https://www.pic.int/TheConvention/Chemicals/AnnexIIIChemicals/tabid/1132/language/en-US/Default.aspx, accessed September 2024.

Roxby AC, Fredricks DN, Odem-Davis K, Ásbjörnsdóttir K, Masese L, Fiedler TL, et al. (2016). Changes in vaginal microbiota and immune mediators in HIV-1-seronegative Kenyan women initiating depot medroxyprogesterone acetate. J Acquir Immune Defic Syndr. 71(4):359–66. https://doi.org/10.1097/QAI.0000000000000866

Roy SS, Begum M, Ghosh S (2018). Exploration of teratogenic and genotoxic effects of fruit ripening retardant Alar (daminozide) on model organism *Drosophila melanogaster*. Interdiscip Toxicol. 11(1):27–37. https://doi.org/10.2478/intox-2018-0004

Royal Society (2008). Ground-level ozone in the 21st century: future trends, impacts and policy implications. Science policy report 15/08. London, UK: The Royal Society. Available from: https:// royalsociety.org/topics-policy/publications/2008/ground-level-ozone/, accessed September 2024

Royal Society of Canada (2022). Understanding immune responses to SARS-COV-2. Voices of the SRC. Ottawa (ON), USA: The Royal Society of Canada. Available from: https://rsc-src.ca/en/voices/understanding-immune-responses-to-sars-cov-2, accessed January 2024.

Ruan H, Wu J, Zhang F, Jin Z, Tian J, Xia J, et al. (2023). Zearalenone exposure disrupts STAT-ISG15 in rat colon: a potential linkage between zearalenone and inflammatory bowel disease. Toxins (Basel). 15(6):392. https://doi.org/10.3390/toxins15060392

Ruan V, Czer LS, Awad M, Kittleson M, Patel J, Arabia F, et al. (2017). Use of anti-thymocyte globulin for induction therapy in cardiac transplantation: a review. Transplant Proc. 49(2):253–9. https://doi.org/10.1016/j.transproceed.2016.11.034

Ruanpeng D, Thongprayoon C, Cheungpasitporn W, Harindhanavudhi T (2017). Sugar and artificially sweetened beverages linked to obesity: a systematic review and meta-analysis. QJM. 110(8):513–20. https://doi.org/10.1093/qjmed/hcx068

Ruberto S, Santovito A, Simula ER, Noli M, Manca MA, Sechi LA (2022). Bisphenols induce human genomic damage and modulate HERVs/env expression. Environ Mol Mutagen. 63(6):275–85. https://doi.org/10.1002/em.22499

Rubinstein MR, Wang X, Liu W, Hao Y, Cai G, Han YW (2013). *Fusobacterium nucleatum* promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin. Cell Host Microbe. 14(2):195–206. https://doi.org/10.1016/j.chom.2013.07.012

Rubio L, Marcos R, Hernández A (2020). Potential adverse health effects of ingested micro- and nanoplastics on humans. Lessons learned from *in vivo* and *in vitro* mammalian models. J Toxicol Environ Health B Crit Rev. 23(2):51–68. https://doi.org/10.1080/10937404.2019.1700598

Rudel RA, Ackerman JM, Attfield KR, Brody JG (2014). New exposure biomarkers as tools for breast cancer epidemiology, biomonitoring, and prevention: a systematic approach based on animal evidence. Environ Health Perspect. 122(9):881–95. https://doi.org/10.1289/ehp.1307455https://doi.org/10.1289/ehp.1307455 PMID:24818537

Ruder AM, Yiin JH, Waters MA, Carreón T, Hein MJ, Butler MA, et al.; Brain Cancer Collaborative Study Group (2013). The Upper Midwest Health Study: gliomas and occupational exposure to chlorinated solvents. Occup Environ Med. 70(2):73–80. https://doi.org/10.1136/oemed-2011-100588

Rudiansyah M, Jasim SA, Mohammad Pour ZG, Athar SS, Jeda AS, Doewes RI, et al. (2022). Coronavirus disease 2019 (COVID-19) update: from metabolic reprogramming to immunometabolism. J Med Virol. 94(10):4611–27. https://doi.org/10.1002/jmv.27929

Ruiz-Casado A, Martín-Ruiz A, Pérez LM, Provencio M, Fiuza-Luces C, Lucia A (2017). Exercise and the hallmarks of cancer. Trends Cancer. 3(6):423–41. https://doi.org/10.1016/j.trecan.2017.04.007

Ruocco E, Gambardella A, Langella GG, Lo Schiavo A, Ruocco V (2015). Cutaneous sarcoidosis: an intriguing model of immune dysregulation. Int J Dermatol. 54(1):1–12. https://doi.org/10.1111/ijd.12566

Rusiecki JA, Patel R, Koutros S, Beane-Freeman L, Landgren O, Bonner MR, et al. (2009). Cancer incidence among pesticide applicators exposed to permethrin in the Agricultural Health Study. Environ Health Perspect. 117(4):581–6. https://doi.org/10.1289/ehp.11318

Russell MD, Stovin C, Alveyn E, Adeyemi O, Chan CKD, Patel V, et al. (2023). JAK inhibitors and the risk of malignancy: a meta-analysis across disease indications. Ann Rheum Dis. 82(8):1059–67. https://doi.org/10.1136/ard-2023-224049

Russell WR, Gratz SW, Duncan SH, Holtrop G, Ince J, Scobbie L, et al. (2011). High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. Am J Clin Nutr. 93(5):1062–72. https://doi.org/10.3945/ajcn.110.002188

Ryan KR, Cesta MF, Herbert R, Brix A, Cora M, Witt K, et al. (2017). Comparative pulmonary toxicity of inhaled metalworking fluids in rats and mice. Toxicol Ind Health. 33(5):385–405. https://doi.org/10.1177/0748233716653912https://doi.org/10.1177/0748233716653912 PMID:27343050

Saad SY, Najjar TA, Alashari M (2004). Role of non-selective adenosine receptor blockade and phosphodiesterase inhibition in cisplatin-induced nephrogonadal toxicity in rats. Clin Exp Pharmacol Physiol. 31(12):862–7. https://doi.org/10.1111/j.1440-1681.2004.04127.x

Saadat N, Zhang L, Hyer S, Padmanabhan V, Woo J, Engeland CG, et al. (2022). Psychosocial and behavioral factors affecting inflammation among pregnant African American women. Brain Behav Immun Health. 22:100452. https://doi.org/10.1016/j.bbih.2022.100452

Saadatian-Elahi M, Norat T, Goudable J, Riboli E (2004). Biomarkers of dietary fatty acid intake and the risk of breast cancer: a meta-analysis. Int J Cancer. 111(4):584–91. https://doi.org/10.1002/ijc.20284

Sabatino DE, Bushman FD, Chandler RJ, Crystal RG, Davidson BL, Dolmetsch R, et al.; American Society of Gene and Cell Therapy (ASGCT) Working Group on AAV Integration (2022). Evaluating the state of the science for adeno-associated virus integration: an integrated perspective. Mol Ther. 30(8):2646–63. https://doi.org/10.1016/j.ymthe.2022.06.004https://doi.org/10.1016/j.ymthe.2022.06.004

Sabbioni G, Castaño A, Esteban López M, Göen T, Mol H, Riou M, et al. (2022). Literature review and evaluation of biomarkers, matrices and analytical methods for chemicals selected in the research program Human Biomonitoring for the European Union (HBM4EU). Environ Int. 169(2022):107458. https://doi.org/10.1016/j.envint.2022.107458

Saber TM, Abo-Elmaaty AMA, Abdel-Ghany HM (2019). Curcumin mitigates mancozeb-induced hepatotoxicity and genotoxicity in rats. Ecotoxicol Environ Saf. 183:109467. https://doi.org/10.1016/j.ecoenv.2019.109467

Sabol I, Smahelova J, Klozar J, Mravak-Stipetic M, Gheit T, Tommasino M, et al. (2016). Beta-HPV types in patients with head and neck pathology and in healthy subjects. J Clin Virol. 82:159–65. https://doi.org/10.1016/j.jcv.2016.07.019

Sabry AH, El-Aal AA, Mahmoud NS, Nabil Y, Aziz IZ (2015). An initial indication of predisposing risk of *Schistosoma mansoni* infection for hepatocellular carcinoma. J Egypt Soc Parasitol. 45(2):233–40. https://doi.org/10.12816/0017568

Sacdalan DB, Lucero JA (2021). The association between inflammation and immunosuppression: implications for ICI biomarker development. OncoTargets Ther. 14:2053–64. https://doi.org/10.2147/OTT.S278089

Sadef Y, Shakil S, Majeed D, Zahra N, Ben Abdallah F, Ben Ali M (2023). Evaluating aflatoxins and Sudan dyes contamination in red chili and turmeric and its health impacts on consumer safety of Lahore, Pakistan. Food Chem Toxicol. 182:114116. https://doi.org/10.1016/j.fct.2023.114116

Sadovska L, Auders J, Keiša L, Romanchikova N, Silamiķele L, Kreišmane M, et al. (2022). Exercise-induced extracellular vesicles delay the progression of prostate cancer. Front Mol Biosci. 8:784080. https://doi.org/10.3389/fmolb.2021.784080

Sadowski MC, Pouwer RH, Gunter JH, Lubik AA, Quinn RJ, Nelson CC (2014). The fatty acid synthase inhibitor triclosan: repurposing an anti-microbial agent for targeting prostate cancer. Oncotarget. 5(19):9362–81. https://doi.org/10.18632/oncotarget.2433

Safe Work Australia (2023). Engineered stone ban. Canberra (ACT), Australia: Safe Work Australia. Available from: https://www.safeworkaustralia.gov.au/safety-topic/hazards/crystalline-silica-and-silicosis/prohibition-use-engineered-stone, accessed September 2024.

Said Salem NI, Noshy MM, Said AA (2017). Modulatory effect of curcumin against genotoxicity and oxidative stress induced by cisplatin and methotrexate in male mice. Food Chem Toxicol. 105:370–6. https://doi.org/10.1016/j.fct.2017.04.007

Saieva C, Aprea C, Tumino R, Masala G, Salvini S, Frasca G, et al. (2004). Twenty-four-hour urinary excretion of ten pesticide metabolites in healthy adults in two different areas of Italy (Florence and Ragusa). Sci Total Environ. 332(1-3):71–80. https://doi.org/10.1016/j.scitotenv.2004.02.026

Sakamoto Y, Inoue K, Takahashi M, Taketa Y, Kodama Y, Nemoto K, et al. (2013). Different pathways of constitutive androstane receptor-mediated liver hypertrophy and hepatocarcinogenesis in mice treated with piperonyl butoxide or decabromodiphenyl ether. Toxicol Pathol. 41(8):1078–92. https://doi.org/10.1177/0192623313482055https://doi.org/10.1177/0192623313482055 PMID:23531792

Sakazaki H, Ueno H, Umetani K, Utsumi H, Nakamuro K (2001). Immunotoxicological evaluation of environmental chemicals utilizing mouse lymphocyte mitogenesis test. J Health Sci. 47(3):258–71. https://doi.org/10.1248/jhs.47.258

Saláková M, Košlabová E, Vojtěchová Z, Tachezy R, Šroller V (2016). Detection of human polyomaviruses MCPyV, HPyV6, and HPyV7 in malignant and non-malignant tonsillar tissues. J Med Virol. 88(4):695–702. https://doi.org/10.1002/jmv.24385

Salama M, Mohammed DM, Fahmy K, Al-Senosy NK, Ebeed NM, Farouk A (2023). Evaluation of the cytotoxicity and genotoxicity potential of synthetic diacetyl food flavoring in silico, in vivo, and in vitro. Food Chem Toxicol. 178:113923. https://doi.org/10.1016/j.fct.2023.113923https://doi.org/10.1016/j.fct.2023.113923 PMID:37399938

Salamanca-Fernández E, Rodríguez-Barranco M, Amiano P, Delfrade J, Chirlaque MD, Colorado S, et al. (2021). Bisphenol-A exposure and risk of breast and prostate cancer in the Spanish European Prospective Investigation into Cancer and Nutrition study. Environ Health. 20(1):88. https://doi.org/10.1186/s12940-021-00779-yhttps://doi.org/10.1186/s12940-021-00779-y PMID:34399780

Salari S, Amiri MS, Ramezani M, Moghadam AT, Elyasi S, Sahebkar A, et al. (2021). Ethnobotany, phytochemistry, traditional and modern uses of *Actaea racemosa* L. (black cohosh): a review. Adv Exp Med Biol. 1308:403–49. https://doi.org/10.1007/978-3-030-64872-5_24https://doi.org/10.1007/978-3-030-64872-5_24 PMID:33861455

Saleem T, Kasi A (2023). Daunorubicin. In: StatPearls [Internet]. Treasure Island (FL), USA: StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559073 PMID:32644499

Saleh DM, Alexander WT, Numano T, Ahmed OHM, Gunasekaran S, Alexander DB, et al. (2020). Comparative carcinogenicity study of a thick, straight-type and a thin, tangled-type multi-walled carbon nanotube administered by intra-tracheal instillation in the rat. Part Fibre Toxicol. 17(1):48. https://doi.org/10.1186/s12989-020-00382-y

Saleh DM, Luo S, Ahmed OHM, Alexander DB, Alexander WT, Gunasekaran S, et al. (2022). Assessment of the toxicity and carcinogenicity of double-walled carbon nanotubes in the rat lung after intratracheal instillation: a two-year study. Part Fibre Toxicol. 19(1):30. https://doi.org/10.1186/s12989-022-00469-8

Salfate G, Sánchez J (2022). Rare earth elements uptake by synthetic polymeric and cellulose-based materials: a review. Polymers (Basel). 14(21):4786. https://doi.org/10.3390/polym14214786

Salimiaghdam N, Singh L, Schneider K, Chwa M, Atilano SR, Nalbandian A, et al. (2022). Effects of fluoroquinolones and tetracyclines on mitochondria of human retinal MIO-M1 cells. Exp Eye Res. 214:108857. https://doi.org/10.1016/j.exer.2021.108857

Salomaa S, Sorsa M, Alfheim I, Lepannen A (1985). Genotoxic effects of smoke emissions in mammalian cells. Environ Int. 11(2–4):311–6. https://doi.org/10.1016/0160-4120(85)90023-6

Salvan A, Ranucci A, Lagorio S, Magnani C; SETIL Research Group (2015). Childhood leukemia and 50 Hz magnetic fields: findings from the Italian SETIL case–control study. Int J Environ Res Public Health. 12(2):2184–204. https://doi.org/10.3390/ijerph120202184

Samoto H, Fukui Y, Ukai H, Okamoto S, Takada S, Ohashi F, et al. (2006). Field survey on types of organic solvents used in enterprises of various sizes. Int Arch Occup Environ Health. 79(7):558–67. https://doi.org/10.1007/s00420-005-0082-3

Sánchez OF, Lin L, Bryan CJ, Xie J, Freeman JL, Yuan C (2020). Profiling epigenetic changes in human cell line induced by atrazine exposure. Environ Pollut. 258:113712. https://doi.org/10.1016/j.envpol.2019.113712

Sánchez de Miguel A, Bennie J, Rosenfeld E, Dzurjak S, Gaston KJ (2022). Environmental risks from artificial nighttime lighting widespread and increasing across Europe. Sci Adv. 8(37):eabl6891. https://doi.org/10.1126/sciadv.abl6891

Sánchez de Miguel A, Kyba CCM, Zamorano J, Gallego J, Gaston KJ (2020). The nature of the diffuse light near cities detected in nighttime satellite imagery. Sci Rep. 10(1):7829. https://doi.org/10.1038/s41598-020-64673-2

Sanders JM, Bucher JR, Peckham JC, Kissling GE, Hejtmancik MR, Chhabra RS (2009). Carcinogenesis studies of cresols in rats and mice. Toxicology. 257(1–2):33–9. https://doi.org/10.1016/j.tox.2008.12.005https://doi.org/10.1016/j.tox.2008.12.005 PMID:19114085

Sanderson JT, Letcher RJ, Heneweer M, Giesy JP, van den Berg M (2001). Effects of chloro-s-triazine herbicides and metabolites on aromatase activity in various human cell lines and on vitellogenin production in male carp hepatocytes. Environ Health Perspect. 109(10):1027–31. https://doi.org/10.1289/ehp.011091027

Sandhu MA, Saeed AA, Khilji MS, Ahmed A, Latif MS, Khalid N (2013). Genotoxicity evaluation of chlorpyrifos: a gender related approach in regular toxicity testing. J Toxicol Sci. 38(2):237–44. https://doi.org/10.2131/jts.38.237

Sangkham S, Faikhaw O, Munkong N, Sakunkoo P, Arunlertaree C, Chavali M, et al. (2022). A review on microplastics and nanoplastics in the environment: their occurrence, exposure routes, toxic studies, and potential effects on human health. Mar Pollut Bull. 181:113832. https://doi.org/10.1016/j.marpolbul.2022.113832

Santana JS, Sartorelli P, Guadagnin RC, Matsuo AL, Figueiredo CR, Soares MG, et al. (2012). Essential oils from *Schinus terebinthifolius* leaves – chemical composition and in vitro cytotoxicity evaluation. Pharm Biol. 50(10):1248–53. https://doi.org/10.3109/13880209.2012.666880

Santos DB, Schiar VP, Ribeiro MC, Schwab RS, Meinerz DF, Allebrandt J, et al. (2009). Genotoxicity of organoselenium compounds in human leukocytes in vitro. Mutat Res. 676(1–2):21–6. https://doi.org/10.1016/j.mrgentox.2009.03.006

Santos T, Cancian G, Neodini DN, Mano DR, Capucho C, Predes FS, et al. (2015). Toxicological evaluation of ametryn effects in Wistar rats. Exp Toxicol Pathol. 67(10):525–32. https://doi.org/10.1016/j.etp.2015.08.001

Santovito A, Ruberto S, Gendusa C, Cervella P (2018). In vitro evaluation of genomic damage induced by glyphosate on human lymphocytes. Environ Sci Pollut Res Int. 25(34):34693–700. https://doi.org/10.1007/s11356-018-3417-9

Sapbamrer R, Thongtip S, Khacha-Ananda S, Sittitoon N, Wunnapuk K (2020). Changes in lung function and respiratory symptoms during pesticide spraying season among male sprayers. Arch Environ Occup Health. 75(2):88–97. https://doi.org/10.1080/19338244.2019.1577208

Saquib Q, Siddiqui MA, Ansari SM, Alwathnani HA, Musarrat J, Al-Khedhairy AA (2021). Cytotoxicity and genotoxicity of methomyl, carbaryl, metalaxyl, and pendimethalin in human umbilical vein endothelial cells. J Appl Toxicol. 41(5):832–46. https://doi.org/10.1002/jat.4139

Sargisian N, Lannering B, Petzold M, Opdahl S, Gissler M, Pinborg A, et al. (2022). Cancer in children born after frozen-thawed embryo transfer: a cohort study. PLoS Med. 19(9):e1004078. https://doi.org/10.1371/journal.pmed.1004078

Sarink D, Franke AA, White KK, Wu AH, Cheng I, Quon B, et al. (2021). BPA, parabens, and phthalates in relation to endometrial cancer risk: a case–control study nested in the multiethnic cohort. Environ Health Perspect. 129(5):57702. https://doi.org/10.1289/EHP8998

Sarma SN, Kim YJ, Song M, Ryu JC (2011). Induction of apoptosis in human leukemia cells through the production of reactive oxygen species and activation of HMOX1 and Noxa by benzene, toluene, and o-xylene. Toxicology. 280(3):109–17. https://doi.org/10.1016/j.tox.2010.11.017

Saruta N, Yamaguchi S, Nakatomi Y (1958). Sarcoma produced by subdermal administration of paraphenylenediamine. Kyushu J Med Sci. 9:94–101.

Sasaki YF, Izumiyama F, Nishidate E, Matsusaka N, Tsuda S (1997b). Detection of rodent liver carcinogen genotoxicity by the alkaline single-cell gel electrophoresis (Comet) assay in multiple mouse organs (liver, lung, spleen, kidney, and bone marrow). Mutat Res. 391(3):201–14. https://doi.org/10.1016/S1383-5718(97)00072-7

Sasaki YF, Kawaguchi S, Kamaya A, Ohshita M, Kabasawa K, Iwama K, et al. (2002). The comet assay with 8 mouse organs: results with 39 currently used food additives. Mutat Res. 519(1–2):103–19. https://doi.org/10.1016/S1383-5718(02)00128-6

Sasaki YF, Nishidate E, Su YQ, Matsusaka N, Tsuda S, Susa N, et al. (1998). Organ-specific genotoxicity of the potent rodent bladder carcinogens *o*-anisidine and *p*-cresidine. Mutat Res. 412(2):155–60. https://doi.org/10.1016/S1383-5718(97)00183-6https://doi.org/10.1016/S1383-5718(97)00183-6 PMID:9539969

Sasaki YF, Saga A, Akasaka M, Yoshida K, Nishidate E, Su YQ, et al. (1997a). In vivo genotoxicity of ortho-phenylphenol, biphenyl, and thiabendazole detected in multiple mouse organs by the alkaline single cell gel electrophoresis assay. Mutat Res. 395(2–3):189–98. https://doi.org/10.1016/S1383-5718(97)00168-X

Sathiakumar N, MacLennan PA, Mandel J, Delzell E (2011). A review of epidemiologic studies of triazine herbicides and cancer. Crit Rev Toxicol. 41 Suppl 1:1–34. https://doi.org/10.3109/10408444.2011.554793

Satoh M, Kondo Y, Mita M, Nakagawa I, Naganuma A, Imura N (1993). Prevention of carcinogenicity of anticancer drugs by metallothionein induction. Cancer Res. 53(20):4767–8.

Sauvain JJ, Suarez G, Hopf NB, Batsungnoen K, Charriere N, Andre F, et al. (2021). Oxidative potential of aerosolized metalworking fluids in occupational settings. Int J Hyg Environ Health. 235:113775. https://doi.org/10.1016/j.ijheh.2021.113775

Savva GM, Pachnio A, Kaul B, Morgan K, Huppert FA, Brayne C, et al.; Medical Research Council Cognitive Function and Ageing Study (2013). Cytomegalovirus infection is associated with increased mortality in the older population. Aging Cell. 12(3):381–7. https://doi.org/10.1111/acel.12059

Sawyer DB, Fukazawa R, Arstall MA, Kelly RA (1999). Daunorubicin-induced apoptosis in rat cardiac myocytes is inhibited by dexrazoxane. Circ Res. 84(3):257–65. https://doi.org/10.1161/01.RES.84.3.257

Saxena N, Ansari KM, Kumar R, Chaudhari BP, Dwivedi PD, Das M (2011). Role of mitogen activated protein kinases in skin tumorigenicity of patulin. Toxicol Appl Pharmacol. 257(2):264–71. https://doi.org/10.1016/j.taap.2011.09.012

Scala M, Bosetti C, Bagnardi V, Possenti I, Specchia C, Gallus S, et al. (2023). Dose–response relationships between cigarette smoking and breast cancer risk: a systematic review and meta-analysis. J Epidemiol. 33(12):640–8. https://doi.org/10.2188/jea.JE20220206

Scalia Carneiro AP, Algranti E, Chérot-Kornobis N, Silva Bezerra F, Tibiriça Bon AM, Felicidade Tomaz Braz N, et al. (2020). Inflammatory and oxidative stress biomarkers induced by silica exposure in crystal craftsmen. Am J Ind Med. 63(4):337–47. https://doi.org/10.1002/ajim.23088

Scanu T, Spaapen RM, Bakker JM, Pratap CB, Wu LE, Hofland I, et al. (2015). *Salmonella* manipulation of host signaling pathways provokes cellular transformation associated with gallbladder carcinoma. Cell Host Microbe. 17(6):763–74. https://doi.org/10.1016/j.chom.2015.05.002

SCCS (2021). Opinion on propylparaben. Brussels, Belgium: Scientific Committee on Consumer Safety, European Commission. Available from: https://health.ec.europa.eu/system/files/2022-08/sccs_o_243.pdf, accessed February 2024.

SCCS (2022). SCCS Scientific advice on the safety of triclocarban and triclosan as substances with potential endocrine disrupting properties in cosmetic products. SCCS/1643/22. Final scientific advice. Brussels, Belgium: Scientific Committee on Consumer Safety, European Commission. Available from: https://health.ec.europa.eu/document/download/b43f36b5-6a19-4b76-88f5-6c1bf8fd8ade_en?filename=sccs_o_265.pdf, accessed February 2024.

SCF (2001). Opinion of the Scientific Committee on Food on estragole (1-allyl-4-methoxybenzene). Brussels, Belgium: Scientific Committee on Food, European Commission. Available from: https://ec.europa.eu/food/fs/sc/scf/out104_en.pdf, accessed September 2024.

Schaffert A, Arnold J, Karkossa I, Blüher M, von Bergen M, Schubert K (2021). The emerging plasticizer alternative DINCH and its metabolite MINCH induce oxidative stress and enhance inflammatory responses in human THP-1 macrophages. Cells. 10(9):2367. https://doi.org/10.3390/cells10092367

Scheepers PTJ, Duca RC, Galea KS, Godderis L, Hardy E, Knudsen LE, et al.; Hbm Eu E-Waste Study Team (2021). HBM4EU occupational biomonitoring study on e-waste-study protocol. Int J Environ Res Public Health. 18(24):12987. https://doi.org/10.3390/ijerph182412987

Schernhammer E, Bogl L, Hublin C, Strohmaier S, Zebrowska M, Erber A, et al. (2023). The association between night shift work and breast cancer risk in the Finnish twins cohort. Eur J Epidemiol. 38(5):533–43. https://doi.org/10.1007/s10654-023-00983-9

Schettgen T, Heudorf U, Drexler H, Angerer J (2002). Pyrethroid exposure of the general population – is this due to diet. Toxicol Lett. 134(1-3):141–5. https://doi.org/10.1016/S0378-4274(02)00183-2

Schettgen T, Rossbach B, Kütting B, Letzel S, Drexler H, Angerer J (2004). Determination of haemoglobin adducts of acrylamide and glycidamide in smoking and non-smoking persons of the general population. Int J Hyg Environ Health. 207(6):531–9. https://doi.org/10.1078/1438-4639-00324

Schiano C, Grimaldi V, Franzese M, Fiorito C, De Nigris F, Donatelli F, et al. (2020). Non-nutritional sweeteners effects on endothelial vascular function. Toxicol In Vitro. 62:104694. https://doi.org/10.1016/j.tiv.2019.104694

Schiffman SS, Scholl EH, Furey TS, Nagle HT (2023). Toxicological and pharmacokinetic properties of sucralose-6-acetate and its parent sucralose: *in vitro* screening assays. J Toxicol Environ Health B Crit Rev. 26(6):307–41. https://doi.org/10.1080/10937404.2023.2213903

Schirinzi GF, Pérez-Pomeda I, Sanchís J, Rossini C, Farré M, Barceló D (2017). Cytotoxic effects of commonly used nanomaterials and microplastics on cerebral and epithelial human cells. Environ Res. 159:579–87. https://doi.org/10.1016/j.envres.2017.08.043

Schleich S, Papaioannou M, Baniahmad A, Matusch R (2006). Activity-guided isolation of an antiandrogenic compound of *Pygeum africanum.* Planta Med. 72(6):547–51. https://doi.org/10.1055/s-2006-941472https://doi.org/10.1055/s-2006-941472 PMID:16773539

Schmid D, Leitzmann MF (2014). Television viewing and time spent sedentary in relation to cancer risk: a meta-analysis. J Natl Cancer Inst. 106(7):dju098. https://doi.org/10.1093/jnci/dju098

Schock H, Surcel HM, Zeleniuch-Jacquotte A, Grankvist K, Lakso HÅ, Fortner RT, et al. (2014). Early pregnancy sex steroids and maternal risk of epithelial ovarian cancer. Endocr Relat Cancer. 21(6):831–44. https://doi.org/10.1530/ERC-14-0282

Schoental R, Head MA, Peacock PR (1954). Senecio alkaloids; primary liver tumours in rats as a result of treatment with (1) a mixture of alkaloids from S. jacobaea Lin.; (2) retrorsine; (3) isatidine. Br J Cancer. 8(3):458–65. https://doi.org/10.1038/bjc.1954.49

Schoeny RS, Smith CC, Loper JC (1979). Non-mutagenicity for Salmonella of the chlorinated hydrocarbons aroclor 1254, 1,2,4-trichlorobenzene, mirex and kepone. Mutat Res. 68(2):125–32. https://doi.org/10.1016/0165-1218(79)90140-X

Schraufnagel DE (2020). The health effects of ultrafine particles. Exp Mol Med. 52(3):311–7. https://doi.org/10.1038/s12276-020-0403-3

Schrenk D, Bignami M, Bodin L, Chipman JK, Del Mazo J, Grasl-Kraupp B, et al.; EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) (2020b). Risk to human health related to the presence of perfluoroalkyl substances in food. EFSA J. 18(9):e06223. PMID:32994824

Schrenk D, Gao L, Lin G, Mahony C, Mulder PPJ, Peijnenburg A, et al. (2020a). Pyrrolizidine alkaloids in food and phytomedicine: occurrence, exposure, toxicity, mechanisms, and risk assessment – a review. Food Chem Toxicol. 136:111107. https://doi.org/10.1016/j.fct.2019.111107https://doi.org/10.1016/j.fct.2019.111107 PMID:31904473

Schrock JM, McDade TW, D'Aquila RT, Mustanski B (2022). Does body mass index explain the apparent anti-inflammatory effects of cannabis use? Results from a cohort study of sexual and gender minority youth. Drug Alcohol Depend. 233:109344. https://doi.org/10.1016/j.drugalcdep.2022.109344

Schroeder JC, Olshan AF, Baric R, Dent GA, Weinberg CR, Yount B, et al. (2001). Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. Epidemiology. 12(6):701–9. https://doi.org/10.1097/00001648-200111000-00020

Schubauer-Berigan MK, Dahm MM, Toennis CA, Sammons DL, Eye T, Kodali V, et al. (2020). Association of occupational exposures with *ex vivo* functional immune response in workers handling carbon nanotubes and nanofibers. Nanotoxicology. 14(3):404–19. https://doi.org/10.1080/17435390.2020.1717007

Schuermann D, Mevissen M (2021). Manmade electromagnetic fields and oxidative stress – biological effects and consequences for health. Int J Mol Sci. 22(7):3772. https://doi.org/10.3390/ijms22073772

Schuermann D, Ziemann C, Barekati Z, Capstick M, Oertel A, Focke F, et al. (2020). Assessment of genotoxicity in human cells exposed to modulated electromagnetic fields of wireless communication devices. Genes (Basel). 11(4):347. https://doi.org/10.3390/genes11040347

Schullehner J, Hansen B, Thygesen M, Pedersen CB, Sigsgaard T (2018). Nitrate in drinking water and colorectal cancer risk: a nationwide population-based cohort study. Int J Cancer. 143(1):73–9. https://doi.org/10.1002/ijc.31306

Schulte A, Pandeya N, Fawcett J, Fritschi L, Risch HA, Webb PM, et al. (2015). Association between *Helicobacter pylori* and pancreatic cancer risk: a meta-analysis. Cancer Causes Control. 26(7):1027–35. https://doi.org/10.1007/s10552-015-0595-3

Schulz MD, Atay C, Heringer J, Romrig FK, Schwitalla S, Aydin B, et al. (2014). High-fat diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity. Nature. 514(7523):508–12. https://doi.org/10.1038/nature13398

Schüz J, Jacobsen R, Olsen JH, Boice JD Jr, McLaughlin JK, Johansen C (2006). Cellular telephone use and cancer risk: update of a nationwide Danish cohort. J Natl Cancer Inst. 98(23):1707–13. https://doi.org/10.1093/jnci/djj464

Schüz J, Kovalevskiy E, Olsson A, Moissonnier M, Ostroumova E, Ferro G, et al. (2024). Cancer mortality in chrysotile miners and millers, Russian Federation: main results (Asbest Chrysotile Cohort Study). J Natl Cancer Inst. 116(6):866–75.

Schüz J, Pirie K, Reeves GK, Floud S, Beral V; Million Women Study Collaborators (2022). Cellular telephone use and the risk of brain tumors: update of the UK Million Women Study. J Natl Cancer Inst. 114(5):704–11. https://doi.org/10.1093/jnci/djac042

Schwabe RF, Jobin C (2013). The microbiome and cancer. Nat Rev Cancer. 13(11):800–12. https://doi.org/10.1038/nrc3610 PMID:24132111

Schwabl P, Köppel S, Königshofer P, Bucsics T, Trauner M, Reiberger T, et al. (2019). Detection of various microplastics in human stool: a prospective case series. Ann Intern Med. 171(7):453–7. https://doi.org/10.7326/M19-0618

Schwimmer H, Metzer A, Pilosof Y, Szyf M, Machnes ZM, Fares F, et al. (2014). Light at night and melatonin have opposite effects on breast cancer tumors in mice assessed by growth rates and global DNA methylation. Chronobiol Int. 31(1):144–50. https://doi.org/10.3109/07420528.2013.842925

Schwotzer D, Ernst H, Schaudien D, Kock H, Pohlmann G, Dasenbrock C, et al. (2017). Effects from a 90-day inhalation toxicity study with cerium oxide and barium sulfate nanoparticles in rats. Part Fibre Toxicol. 14(1):23. https://doi.org/10.1186/s12989-017-0204-6

Schwotzer D, Niehof M, Schaudien D, Kock H, Hansen T, Dasenbrock C, et al. (2018). Cerium oxide and barium sulfate nanoparticle inhalation affects gene expression in alveolar epithelial cells type II. J Nanobiotechnology. 16(1):16. https://doi.org/10.1186/s12951-018-0343-4

Secher T, Gaillot O, Ryffel B, Chamaillard M (2010). Remote control of intestinal tumorigenesis by innate immunity. Cancer Res. 70(5):1749–52. https://doi.org/10.1158/0008-5472.CAN-09-3401

Secretariat of the Stockholm Convention (2009). Governments unite to step-up reduction on global DDT reliance and add nine new chemicals under international treaty. Press release, Geneva, 9 May 2009. Châtelaine, Switzerland: Secretariat of the Stockholm Convention. Available from: https://chm.pops.int/Convention/Pressrelease/COP4Geneva8May2009/tabid/542/, accessed March 2024.

Segovia-Mendoza M, Palacios-Arreola MI, Monroy-Escamilla LM, Soto-Piña AE, Nava-Castro KE, Becerril-Alarcón Y, et al. (2022). Association of serum levels of plasticizers compounds, phthalates and bisphenols, in patients and survivors of breast cancer: a real connection? Int J Environ Res Public Health. 19(13):8040. https://doi.org/10.3390/ijerph19138040

Seidlová-Wuttke D, Thelen P, Wuttke W (2006). Inhibitory effects of a black cohosh (*Cimicifuga racemosa*) extract on prostate cancer. Planta Med. 72(6):521–6. https://doi.org/10.1055/s-2006-931538https://doi.org/10.1055/s-2006-931538 PMID:16773536

Seilkop SK, Lightfoot NE, Berriault CJ, Conard BR (2017). Respiratory cancer mortality and incidence in an updated cohort of Canadian nickel production workers. Arch Environ Occup Health. 72(4):204–19. https://doi.org/10.1080/19338244.2016.1199532

Sekeroğlu ZA, Sekeroğlu V (2012). Effects of *Viscum album* L. extract and quercetin on methotrexate-induced cyto-genotoxicity in mouse bone marrow cells. Mutat Res. 746(1):56–9. https://doi.org/10.1016/j.mrgentox.2012.02.012

Sellappa S, Prathyumnan S, Joseph S, Keyan KS, Balachandar V (2010). Genotoxic effects of textile printing dye exposed workers in India detected by micronucleus assay. Asian Pac J Cancer Prev. 11(4):919–22. https://journal.waocp.org/article_25306_6b03fb44f3f5526ac892caecf3b82f89.pdf PMID:21133601

Semenov DE, Zhukova NA, Tolstikova TG, Sorokina IV, Lushnikova EL (2016). Specific features of progression of the parasitic invasion, caused by *Opisthorchis felineus*, in golden hamsters. Bull Exp Biol Med. 161(4):481–6. https://doi.org/10.1007/s10517-016-3443-xhttps://doi.org/10.1007/s10517-016-3443-x

Senft V, Losan F, Tucek M (1992). Cytogenetic analysis of chromosomal aberrations of peripheral lymphocytes in workers occupationally exposed to nickel. Mutat Res. 279(3):171–9. https://doi.org/10.1016/0165-1218(92)90064-7

Senior M (2022). Fresh from the biotech pipeline: too much, too fast? Nat Biotechnol. 40(2):155–62. https://doi.org/10.1038/s41587-022-01208-2

Seo JE, Guo X, Petibone DM, Shelton SD, Chen Y, Li X, et al. (2021). Mechanistic evaluation of black cohosh extract-induced genotoxicity in human cells. Toxicol Sci. 182(1):96–106. https://doi.org/10.1093/toxsci/kfab044https://doi.org/10.1093/toxsci/kfab044 PMID:33856461

Seomun G, Lee J, Park J (2021). Exposure to extremely low-frequency magnetic fields and childhood cancer: a systematic review and meta-analysis. PLoS One. 16(5):e0251628. https://doi.org/10.1371/journal.pone.0251628

Sepehri M, Lerche CM, Hutton Carlsen K, Serup J (2017). Search for internal cancers in mice tattooed with inks of high contents of potential carcinogens: a one-year autopsy study of red and black tattoo inks banned in the market. Dermatology. 233(1):94–9. https://doi.org/10.1159/000468150

Sereda B, Bouwman H, Kylin H (2009). Comparing water, bovine milk, and indoor residual spraying as possible sources of DDT and pyrethroid residues in breast milk. J Toxicol Environ Health A. 72(13):842–51. https://doi.org/10.1080/15287390902800447

Sergi CM (2019). Malathion: an insecticide. In: Encyclopedia of environmental health, 2nd edition. Volume 4, pp.190–3. Available from: https://doi.org/10.1016/B978-0-12-409548-9.11317-X

Serra C, Bonfill X, Sunyer J, Urrutia G, Turuguet D, Bastús R, et al.; Working Group on the Study of Bladder Cancer in the County of Vallès Occidental (2000). Bladder cancer in the textile industry. Scand J Work Environ Health. 26(6):476–81. https://doi.org/10.5271/sjweh.571

Serra C, Kogevinas M, Silverman DT, Turuguet D, Tardon A, Garcia-Closas R, et al. (2008). Work in the textile industry in Spain and bladder cancer. Occup Environ Med. 65(8):552–9. https://doi.org/10.1136/oem.2007.035667

Setayesh T, Nersesyan A, Mišík M, Ferk F, Langie S, Andrade VM, et al. (2018). Impact of obesity and overweight on DNA stability: few facts and many hypotheses. Mutat Res Rev Mutat Res. 777:64–91. https://doi.org/10.1016/j.mrrev.2018.07.001

Seto EY, Lee YJ, Liang S, Zhong B (2007). Individual and village-level study of water contact patterns and *Schistosoma japonicum* infection in mountainous rural China. Trop Med Int Health. 12(10):1199–209. https://doi.org/10.1111/j.1365-3156.2007.01903.x

Séverin I, Jondeau A, Dahbi L, Chagnon MC (2005). 2,4-Diaminotoluene (2,4-DAT)-induced DNA damage, DNA repair and micronucleus formation in the human hepatoma cell line HepG2. Toxicology. 213(1–2):138–46. https://doi.org/10.1016/j.tox.2005.05.021

Shabad LM, Kolesnichenko TS, Golub NI (1975). The effect produced by some carcinogenic nitrosocompounds on organ cultures from human embryonic lung and kidney tissues. Int J Cancer. 16(5):768–78. https://doi.org/10.1002/ijc.2910160509

Shah R, Shah VK, Emin M, Gao S, Sampogna RV, Aggarwal B, et al. (2023). Mild sleep restriction increases endothelial oxidative stress in female persons. Sci Rep. 13(1):15360. https://doi.org/10.1038/s41598-023-42758-y

Shahin MM, Chopy C, Lequesne N (1985). Comparisons of mutation induction by six monocyclic aromatic amines in *Salmonella typhimurium* tester strains TA97, TA1537, and TA1538. Environ Mutagen. 7(4):535–46. https://doi.org/10.1002/em.2860070412

Shakeel M, Jabeen F, Shabbir S, Asghar MS, Khan MS, Chaudhry AS (2016). Toxicity of nano-titanium dioxide (TiO2-NP) through various routes of exposure: a review. Biol Trace Elem Res. 172(1):1–36. https://doi.org/10.1007/s12011-015-0550-x

Shang JZ, Li SR, Li XQ, Zhou YT, Ma X, Liu L, et al. (2022). Simazine perturbs the maturational competency of mouse oocyte through inducing oxidative stress and DNA damage. Ecotoxicol Environ Saf. 230:113105. https://doi.org/10.1016/j.ecoenv.2021.113105

Sharma A, Panwar S, Singh AK, Jakhar KK (2007). Studies on the genotoxic effects of sucralose in laboratory mice. Indian J Anim Res. 41(1):1–8.

Shauly O, Gould DJ, Siddiqi I, Patel KM, Carey J (2019). The first reported case of gluteal implant-associated anaplastic large cell lymphoma (ALCL). Aesthet Surg J. 39(7):NP253–8. https://doi.org/10.1093/asj/sjz044

Shaw MH, Kamada N, Warner N, Kim YG, Nuñez G (2011). The ever-expanding function of NOD2: autophagy, viral recognition, and T cell activation. Trends Immunol. 32(2):73–9. https://doi.org/10.1016/j.it.2010.12.007

Shearer JJ, Callahan CL, Calafat AM, Huang W, Jones RR, Sabbisetti VS, et al. (2020). Serum concentrations of per- and polyfluoroalkyl substances and risk of renal cell carcinoma. J Natl Cancer Inst. 113(5):580–7. https://doi.org/10.1093/jnci/djaa143

Shearer JJ, Sandler DP, Andreotti G, Murata K, Shrestha S, Parks CG, et al. (2021). Pesticide use and kidney function among farmers in the Biomarkers of Exposure and Effect in Agriculture study. Environ Res. 199:111276. https://doi.org/10.1016/j.envres.2021.111276

Sheinin M, Jeong B, Paidi RK, Pahan K (2022). Regression of lung cancer in mice by intranasal administration of SARS-CoV-2 spike S1. Cancers (Basel). 14(22):5648. https://doi.org/10.3390/cancers14225648

Shen D, Mao W, Liu T, Lin Q, Lu X, Wang Q, et al. (2014). Sedentary behavior and incident cancer: a meta-analysis of prospective studies. PLoS One. 9(8):e105709. https://doi.org/10.1371/journal.pone.0105709https://doi.org/10.1371/journal.pone.0105709 PMID:25153314

Shen DW, Pouliot LM, Hall MD, Gottesman MM (2012). Cisplatin resistance: a cellular self-defense mechanism resulting from multiple epigenetic and genetic changes. Pharmacol Rev. 64(3):706–21. https://doi.org/10.1124/pr.111.005637

Shen LT, Ge MW, Hu FH, Jia YJ, Tang W, Zhang WQ, et al. (2023). The connection between six common air pollution particles and adult brain tumors: a meta-analysis of 26,217,930 individuals. Environ Sci Pollut Res Int. 30(50):108525–37. https://doi.org/10.1007/s11356-023-29955-y

Shen X, Dong Y, Xu Z, Wang H, Miao C, Soriano SG, et al. (2013). Selective anesthesia-induced neuroinflammation in developing mouse brain and cognitive impairment. Anesthesiology. 118(3):502–15. https://doi.org/10.1097/ALN.0b013e3182834d77

Sherif M, Makame KR, Östlundh L, Paulo MS, Nemmar A, Ali BR, et al. (2023). Genotoxicity of occupational pesticide exposures among agricultural workers in Arab countries: a systematic review and meta-analysis. Toxics. 11(8):663. https://doi.org/10.3390/toxics11080663

Sheweita SA, Alsamghan AS (2020). Molecular mechanisms contributing bacterial infections to the incidence of various types of cancer. Mediators Inflamm. 2020:4070419. https://doi.org/10.1155/2020/4070419

Shi J, Han S, Zhang J, Liu Y, Chen Z, Jia G (2022). Advances in genotoxicity of titanium dioxide nanoparticles in vivo and in vitro. NanoImpact. 25:100377. https://doi.org/10.1016/j.impact.2021.100377

Shi Y, Liu L, Hamada T, Nowak JA, Giannakis M, Ma Y, et al. (2020). Night-shift work duration and risk of colorectal cancer according to IRS1 and IRS2 expression. Cancer Epidemiol Biomarkers Prev. 29(1):133–40. https://doi.org/10.1158/1055-9965.EPI-19-0325

Shi YE, Johansen MV, Li FR, Willingham AL, Bøgh HO, Liao LG, et al. (2001). An epidemiological investigation of congenital *Schistosoma japonicum* transmission in Hubei Province, PR China. Southeast Asian J Trop Med Public Health. 32(2):323–5.

Shil A, Olusanya O, Ghufoor Z, Forson B, Marks J, Chichger H (2020). Artificial sweeteners disrupt tight junctions and barrier function in the intestinal epithelium through activation of the sweet taste receptor, T1R3. Nutrients. 12(6):1862. https://doi.org/10.3390/nu12061862

Shimizu R, Ibaragi S, Eguchi T, Kuwajima D, Kodama S, Nishioka T, et al. (2019). Nicotine promotes lymph node metastasis and cetuximab resistance in head and neck squamous cell carcinoma. Int J Oncol. 54(1):283–94.

Shin S, Go RE, Kim CW, Hwang KA, Nam KH, Choi KC (2016). Effect of 2,4-dihydroxybenzophenone and octylphenol on the regulation of epithelial-mesenchymal transition via an estrogen receptor-dependent pathway in estrogen receptor expressing ovarian cancer cells. Food Chem Toxicol. 93:58–65. https://doi.org/10.1016/j.fct.2016.04.026

Shiraiwa K, Takita M, Tsutsumi M, Kinugasa T, Denda A, Takahashi S, et al. (1989). Diphenyl induces urolithiasis but does not possess the ability to promote carcinogenesis by *N*-ethyl-*N*-hydroxyethylnitrosame in kidneys of rats. J Toxicol Pathol. 2(1):41–8. https://doi.org/10.1293/tox.2.41

Shirley M (2018). Encorafenib and binimetinib: first global approvals. Drugs. 78(12):1277–84. https://doi.org/10.1007/s40265-018-0963-x

Shrestha A, Ritz B, Wilhelm M, Qiu J, Cockburn M, Heck JE (2014). Prenatal exposure to air toxics and risk of Wilms' tumor in 0- to 5-year-old children. J Occup Environ Med. 56(6):573–8. https://doi.org/10.1097/JOM.0000000000000167

Shrestha D, Liu S, Hammond SK, LaValley MP, Weiner DE, Eisen EA, et al. (2016). Risk of renal cell carcinoma following exposure to metalworking fluids among autoworkers. Occup Environ Med. 73(10):656–62. https://doi.org/10.1136/oemed-2016-103769

Shrestha S, Parks CG, Goldner WS, Kamel F, Umbach DM, Ward MH, et al. (2018a). Pesticide use and incident hypothyroidism in pesticide applicators in the Agricultural Health Study. Environ Health Perspect. 126(9):97008. https://doi.org/10.1289/EHP3194

Shrestha S, Parks CG, Goldner WS, Kamel F, Umbach DM, Ward MH, et al. (2018b). Incident thyroid disease in female spouses of private pesticide applicators. Environ Int. 118:282–92. https://doi.org/10.1016/j.envint.2018.05.041https://doi.org/10.1016/j.envint.2018.05.041 PMID:29908479

Shrestha S, Parks CG, Umbach DM, Hofmann JN, Beane Freeman LE, Blair A, et al. (2022). Use of permethrin and other pyrethroids and mortality in the Agricultural Health Study. Occup Environ Med. 79(10):664–72. https://doi.org/10.1136/oemed-2021-108156

Shuda M, Guastafierro A, Geng X, Shuda Y, Ostrowski SM, Lukianov S, et al. (2015). Merkel cell polyomavirus small T antigen induces cancer and embryonic Merkel cell proliferation in a transgenic mouse model. PLoS One. 10(11):e0142329. https://doi.org/10.1371/journal.pone.0142329

Shuda M, Kwun HJ, Feng H, Chang Y, Moore PS (2011). Human Merkel cell polyomavirus small T antigen is an oncoprotein targeting the 4E–BP1 translation regulator. J Clin Invest. 121(9):3623–34. https://doi.org/10.1172/JCI46323

Shukla Y, Antony M, Kumar S, Mehrotra NK (1990). Carcinogenic activity of a carbamate fungicide, mancozeb on mouse skin. Cancer Lett. 53(2–3):191–5. https://doi.org/10.1016/0304-3835(90)90213-Hhttps://doi.org/10.1016/0304-3835(90)90213-H PMID:2208079

Shukla Y, Arora A (2001). Transplacental carcinogenic potential of the carbamate fungicide mancozeb. J Environ Pathol Toxicol Oncol. 20(2):127–31. https://doi.org/10.1615/JEnvironPatholToxicolOncol.v20.i2.70https://doi.org/10.1615/JEnvironPatholToxicolOncol.v20.i2.70 PMID:11394711

Shukla Y, Yadav A, Arora A (2002). Carcinogenic and cocarcinogenic potential of cypermethrin on mouse skin. Cancer Lett. 182(1):33–41. https://doi.org/10.1016/S0304-3835(02)00077-0

Shutter MC, Akhondi H (2023). Tetracycline. In: StatPearls [Internet]. Treasure Island (FL), USA: StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549905/ PMID:31751095.

Shvedova AA, Kisin ER, Murray A, Kommineni C, Vallyathan V, Castranova V (2004). Pro/antioxidant status in murine skin following topical exposure to cumene hydroperoxide throughout the ontogeny of skin cancer. Biochemistry (Mosc). 69(1):23–31. https://doi.org/10.1023/B:BIRY.0000016347.35373.39

Si Z, Yang G, Wang X, Yu Z, Pang Q, Zhang S, et al. (2023). An unconventional cancer-promoting function of methamphetamine in hepatocellular carcinoma. Life Sci Alliance. 6(3):e202201660. https://doi.org/10.26508/lsa.202201660

Sichero L, Rollison DE, Amorrortu RP, Tommasino M (2019). Beta human papillomavirus and associated diseases. Acta Cytol. 63(2):100–8. https://doi.org/10.1159/000492659

Siciliano A, Guida M, Pagano G, Trifuoggi M, Tommasi F, Lofrano G, et al. (2021). Cerium, gadolinium, lanthanum, and neodymium effects in simplified acid mine discharges to *Raphidocelis subcapitata*, *Lepidium sativum*, and *Vicia faba.* Sci Total Environ. 787:147527. https://doi.org/10.1016/j.scitotenv.2021.147527

Sicińska P, Mokra K, Wozniak K, Michałowicz J, Bukowska B (2021). Genotoxic risk assessment and mechanism of DNA damage induced by phthalates and their metabolites in human peripheral blood mononuclear cells. Sci Rep. 11(1):1658. https://doi.org/10.1038/s41598-020-79932-5

Siddique YH, Ara G, Beg T, Afzal M (2006). Genotoxic potential of medroxyprogesterone acetate in cultured human peripheral blood lymphocytes. Life Sci. 80(3):212–8. https://doi.org/10.1016/j.lfs.2006.09.005

Siddiqui S, Cox J, Herzig R, Palaniyandi S, Hildebrandt GC, Munker R (2019). Anti-thymocyte globulin in haematology: recent developments. Indian J Med Res. 150(3):221–7. https://doi.org/10.4103/ijmr.IJMR_752_19

Siddiqui SI, Allehyani ES, Al-Harbi SA, Hasan Z, Abomuti MA, Rajor HK, et al. (2023). Investigation of congo red toxicity towards different living organisms: a review. Processes (Basel). 11(3):807. https://doi.org/10.3390/pr11030807

Sidthilaw S, Sapbamrer R, Pothirat C, Wunnapuk K, Khacha-Ananda S (2022). Effects of exposure to glyphosate on oxidative stress, inflammation, and lung function in maize farmers, northern Thailand. BMC Public Health. 22(1):1343. https://doi.org/10.1186/s12889-022-13696-7

Siew EL, Mansor M, Choon Ooi T, Sharif R, Jamhari AA, Rajab NF (2023). In vitro mutagenicity evaluation of PM_1 and $PM_{0.1}$ air particulates in the urban area of Malaysia. Malays J Med Health Sci. 19 (Suppl 11): 36–44.

Siew VK, Duh CY, Wang SK (2009). Human cytomegalovirus UL76 induces chromosome aberrations. J Biomed Sci. 16(1):107. https://doi.org/10.1186/1423-0127-16-107

Silling S, Kreuter A, Gambichler T, Meyer T, Stockfleth E, Wieland U (2022). Epidemiology of Merkel cell polyomavirus infection and Merkel cell carcinoma. Cancers (Basel). 14(24):6176. https://doi.org/10.3390/cancers14246176

Sills RC, Hong HL, Boorman GA, Devereux TR, Melnick RL (2001). Point mutations of K-ras and H-ras genes in forestomach neoplasms from control $B6C3F_1$ mice and following exposure to 1,3-butadiene, isoprene or chloroprene for up to 2 years. Chem Biol Interact. 135–136:373–86. https://doi.org/10.1016/S0009-2797(01)00179-X

Silva IS, Wark PA, McCormack VA, Mayer D, Overton C, Little V, et al. (2009). Ovulation-stimulation drugs and cancer risks: a long-term follow-up of a British cohort. Br J Cancer. 100(11):1824–31. https://doi.org/10.1038/sj.bjc.6605086

Silver SR, Pinkerton LE, Fleming DA, Jones JH, Allee S, Luo L, et al. (2014). Retrospective cohort study of a microelectronics and business machine facility. Am J Ind Med. 57(4):412–24. https://doi.org/10.1002/ajim.22288

Silverii GA, Monami M, Gallo M, Ragni A, Prattichizzo F, Renzelli V, et al. (2024). Glucagon-like peptide-1 receptor agonists and risk of thyroid cancer: a systematic review and meta-analysis of randomized controlled trials. Diabetes Obes Metab. 26(3):891–900. https://doi.org/10.1111/dom.15382https://doi.org/10.1111/dom.15382 PMID:38018310

Simba H, Kuivaniemi H, Abnet CC, Tromp G, Sewram V (2023). Environmental and life-style risk factors for esophageal squamous cell carcinoma in Africa: a systematic review and meta-analysis. BMC Public Health. 23(1):1782. https://doi.org/10.1186/s12889-023-16629-0

Simin J, Tamimi RM, Engstrand L, Callens S, Brusselaers N (2020). Antibiotic use and the risk of breast cancer: a systematic review and dose–response meta-analysis. Pharmacol Res. 160:105072. https://doi.org/10.1016/j.phrs.2020.105072

Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S (2015). Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther. 17(1):212. https://doi.org/10.1186/s13075-015-0728-9

Simula TP, Glancey MJ, Söderlund EJ, Dybing E, Wolf CR (1993). Increased mutagenicity of 1,2-dibromo-3-chloropropane and tris(2,3-dibromopropyl)phosphate in *Salmonella* TA100 expressing human glutathione S-transferases. Carcinogenesis. 14(11):2303–7. https://doi.org/10.1093/carcin/14.11.2303

Sinclair J, Sissons P (2006). Latency and reactivation of human cytomegalovirus. J Gen Virol. 87(Pt 7):1763–79. https://doi.org/10.1099/vir.0.81891-0

Singh KV, Gautam R, Meena R, Nirala JP, Jha SK, Rajamani P (2020). Effect of mobile phone radiation on oxidative stress, inflammatory response, and contextual fear memory in Wistar rat. Environ Sci Pollut Res Int. 27(16):19340–51. https://doi.org/10.1007/s11356-020-07916-z

Singh M, Kaur P, Sandhir R, Kiran R (2008). Protective effects of vitamin E against atrazine-induced genotoxicity in rats. Mutat Res. 654(2):145–9. https://doi.org/10.1016/j.mrgentox.2008.05.010

Singh VK, Pal R, Srivastava P, Misra G, Shukla Y, Sharma PK (2021). Exposure of androgen mimicking environmental chemicals enhances proliferation of prostate cancer (LNCaP) cells by inducing AR expression and epigenetic modifications. Environ Pollut. 272:116397. https://doi.org/10.1016/j.envpol.2020.116397

Singh Z, Chadha P (2015). Human health hazard posed by textile dyes: a genotoxic perspective. J Hum Health. 1:42–5. Full text

Singh Z, Chadha P (2016). Textile industry and occupational cancer. J Occup Med Toxicol. 11(1):39. https://doi.org/10.1186/s12995-016-0128-3

Sinicropi MS, Iacopetta D, Ceramella J, Catalano A, Mariconda A, Pellegrino M, et al. (2022). Triclosan: a small molecule with controversial roles. Antibiotics (Basel). 11(6):735. https://doi.org/10.3390/antibiotics11060735

Sinitsky MY, Minina VI, Gafarov NI, Asanov MA, Larionov AV, Ponasenko AV, et al. (2016). Assessment of DNA damage in underground coal miners using the cytokinesis-block micronucleus assay in peripheral blood lymphocytes. Mutagenesis. 31(6):669–75. https://doi.org/10.1093/mutage/gew038

Sinués B, Pérez J, Bernal ML, Sáenz MA, Lanuza J, Bartolomé M (1992). Urinary mutagenicity and N-acetylation phenotype in textile industry workers exposed to arylamines. Cancer Res. 52(18):4885–9.

Sirota L, Straussberg R, Gurary N, Aloni D, Bessler H (1999). Phototherapy for neonatal hyperbilirubinemia affects cytokine production by peripheral blood mononuclear cells. Eur J Pediatr. 158(11):910–3. https://doi.org/10.1007/s004310051240

Sisler JD, Li R, McKinney W, Mercer RR, Ji Z, Xia T, et al. (2016). Differential pulmonary effects of CoO and La2O3 metal oxide nanoparticle responses during aerosolized inhalation in mice. Part Fibre Toxicol. 13(1):42. https://doi.org/10.1186/s12989-016-0155-3

Sivulka DJ (2005). Assessment of respiratory carcinogenicity associated with exposure to metallic nickel: a review. Regul Toxicol Pharmacol. 43(2):117–33. https://doi.org/10.1016/j.yrtph.2005.06.014

Sivulka DJ, Seilkop SK, Lascelles K, Conard BR, Jones SF, Collinson EC (2014). Reconstruction of historical exposures at a Welsh nickel refinery (1953–2000). Ann Occup Hyg. 58(6):739–60.

Skalny A, Aschner M, Paoliello M, Santamaria A, Nikitina N, Rejniuk V, et al. (2021). Endocrine-disrupting activity of mancozeb. Arh Farm (Belgr). 71(6):491–507. https://doi.org/10.5937/arhfarm71-34359

Skinner MK (2016). Endocrine disruptors in 2015: epigenetic transgenerational inheritance. Nat Rev Endocrinol. 12(2):68–70. https://doi.org/10.1038/nrendo.2015.206

Skinner MK, Anway MD (2007). Epigenetic transgenerational actions of vinclozolin on the development of disease and cancer. Crit Rev Oncog. 13(1):75–82. https://doi.org/10.1615/CritRevOncog.v13.i1.30

Slamenová D, Dusinská M, Gábelová A, Bohusová T, Ruppová K (1992). Decemtione (Imidan)-induced single-strand breaks to human DNA, mutations at the hgprt locus of V79 cells, and morphological transformations of embryo cells. Environ Mol Mutagen. 20(1):73–8. https://doi.org/10.1002/em.2850200111

Smedby KE, Baecklund E, Askling J (2006). Malignant lymphomas in autoimmunity and inflammation: a review of risks, risk factors, and lymphoma characteristics. Cancer Epidemiol Biomarkers Prev. 15(11):2069–77. https://doi.org/10.1158/1055-9965.EPI-06-0300

Smith ER, Quinn MM (1992). Uterotropic action in rats of amsonic acid and three of its synthetic precursors. J Environ Sci (China). 36(1):13–25. https://doi.org/10.1080/15287399209531620

Smith RL, Adams TB, Doull J, Feron VJ, Goodman JI, Marnett LJ, et al. (2002). Safety assessment of allylalkoxybenzene derivatives used as flavouring substances – methyl eugenol and estragole. Food Chem Toxicol. 40(7):851–70. https://doi.org/10.1016/S0278-6915(02)00012-1

Smith-Roe SL, Swartz CD, Shepard KG, Bryce SM, Dertinger SD, Waidyanatha S, et al. (2018). Black cohosh extracts and powders induce micronuclei, a biomarker of genetic damage, in human cells. Environ Mol Mutagen. 59(5):416–26. https://doi.org/10.1002/em.22182https://doi.org/10.1002/em.22182 PMID:29668046

Smyser BP, Hodgson E (1985). Metabolism of phosphorus-containing compounds by pig liver microsomal FAD-containing monooxygenase. Biochem Pharmacol. 34(8):1145–50. https://doi.org/10.1016/0006-2952(85)90487-3

Snegin E, Gusev A, Snegina E, Barkhatov A, Vasyukova I, Artemchuk O (2020). Genotoxicity evaluation of multiwalled carbon nanotubes: in vivo studies in mice. IOP Conf Ser Earth Environ Sci. 433(1):012010. https://doi.org/10.1088/1755-1315/433/1/012010

So R, Chen J, Stafoggia M, de Hoogh K, Katsouyanni K, Vienneau D, et al. (2023). Long-term exposure to elemental components of fine particulate matter and all-natural and cause-specific mortality in a Danish nationwide administrative cohort study. Environ Res. 224:115552. https://doi.org/10.1016/j.envres.2023.115552

Socas L, Zumbado M, Pérez-Luzardo O, Ramos A, Pérez C, Hernández JR, et al. (2005). Hepatocellular adenomas associated with anabolic androgenic steroid abuse in bodybuilders: a report of two cases and a review of the literature. Br J Sports Med. 39(5):e27–27. https://doi.org/10.1136/bjsm.2004.013599

Socié G, Henry-Amar M, Bacigalupo A, Hows J, Tichelli A, Ljungman P, et al.; European Bone Marrow Transplantation – Severe Aplastic Anaemia Working Party (1993). Malignant tumors occurring after treatment of aplastic anemia. N Engl J Med. 329(16):1152–7. https://doi.org/10.1056/NEJM199310143291603

Søderlund EJ, Meyer DJ, Ketterer B, Nelson SD, Dybing E, Holme JA (1995). Metabolism of 1,2-dibromo-3-chloropropane by glutathione S-transferases. Chem Biol Interact. 97(3):257–72. https://doi.org/10.1016/0009-2797(95)03621-R

Söderqvist G (1998). Effects of sex steroids on proliferation in normal mammary tissue. Ann Med. 30(6):511–24. https://doi.org/10.3109/07853899809002598

Soffritti M, Belpoggi F, Cevolani D, Guarino M, Padovani M, Maltoni C (2002a). Results of long-term experimental studies on the carcinogenicity of methyl alcohol and ethyl alcohol in rats. Ann N Y Acad Sci. 982(1):46–69. https://doi.org/10.1111/j.1749-6632.2002.tb04924.x

Soffritti M, Belpoggi F, Lambertin L, Lauriola M, Padovani M, Maltoni C (2002b). Results of long-term experimental studies on the carcinogenicity of formaldehyde and acetaldehyde in rats. Ann N Y Acad Sci. 982(1):87–105. https://doi.org/10.1111/j.1749-6632.2002.tb04926.x

Soffritti M, Padovani M, Tibaldi E, Falcioni L, Manservisi F, Lauriola M, et al. (2016). Sucralose administered in feed, beginning prenatally through lifespan, induces hematopoietic neoplasias in male Swiss mice. Int J Occup Environ Health. 22(1):7–17. https://doi.org/10.1080/10773525.2015.1106075

Soffritti M, Tibaldi E, Padovani M, Hoel DG, Giuliani L, Bua L, et al. (2016a). Synergism between sinusoidal-50 Hz magnetic field and formaldehyde in triggering carcinogenic effects in male Sprague-Dawley rats. Am J Ind Med. 59(7):509–21. https://doi.org/10.1002/ajim.22598

Soffritti M, Tibaldi E, Padovani M, Hoel DG, Giuliani L, Bua L, et al. (2016b). Life-span exposure to sinusoidal-50 Hz magnetic field and acute low-dose γ radiation induce carcinogenic effects in Sprague-Dawley rats. Int J Radiat Biol. 92(4):202–14. https://doi.org/10.3109/09553002.2016.1144942

Solan ME, Senthilkumar S, Aquino GV, Bruce ED, Lavado R (2022). Comparative cytotoxicity of seven per- and polyfluoroalkyl substances (PFAS) in six human cell lines. Toxicology. 477:153281. https://doi.org/10.1016/j.tox.2022.153281

Solcia E, Ballerini L, Bellini O, Sala L, Bertazzoli C (1978). Mammary tumors induced in rats by adriamycin and daunomycin. Cancer Res. 38(5):1444–6. https://aacrjournals.org/cancerres/article/38/5/1444/483063/Mammary-Tumors-Induced-in-Rats-by-Adriamycin-and

Somani SM, Khalique A (1982). Distribution and metabolism of 2,4-dichlorophenol in rats. J Toxicol Environ Health. 9(5–6):889–97. https://doi.org/10.1080/15287398209530211

Song E, Xia X, Su C, Dong W, Xian Y, Wang W, et al. (2014a). Hepatotoxicity and genotoxicity of patulin in mice, and its modulation by green tea polyphenols administration. Food Chem Toxicol. 71:122–7. https://doi.org/10.1016/j.fct.2014.06.009

Song JA, Park HJ, Yang MJ, Jung KJ, Yang HS, Song CW, et al. (2014b). Polyhexamethyleneguanidine phosphate induces severe lung inflammation, fibrosis, and thymic atrophy. Food Chem Toxicol. 69:267–75. https://doi.org/10.1016/j.fct.2014.04.027

Song JH, Ahn J, Park MY, Park J, Lee YM, Myong JP, et al. (2022b). Health effects associated with humidifier disinfectant use: a systematic review for exploration. J Korean Med Sci. 37(33):e257. https://doi.org/10.3346/jkms.2022.37.e257

Song M, Jayasekara H, Pelucchi C, Rabkin CS, Johnson KC, Hu J, et al. (2023b). Reproductive factors, hormonal interventions, and gastric cancer risk in the Stomach Cancer Pooling (StoP) Project. Cancer Causes Control. 35(4):727–37. https://doi.org/10.1007/s10552-023-01829-1

Song MK, Lee HS, Ryu JC (2015). Integrated analysis of microRNA and mRNA expression profiles highlights aldehyde-induced inflammatory responses in cells relevant for lung toxicity. Toxicology. 334:111–21. https://doi.org/10.1016/j.tox.2015.06.007https://doi.org/10.1016/j.tox.2015.06.007 PMID:26079696

Song P, Sekhon HS, Jia Y, Keller JA, Blusztajn JK, Mark GP, et al. (2003). Acetylcholine is synthesized by and acts as an autocrine growth factor for small cell lung carcinoma. Cancer Res. 63(1):214–21. https://aacrjournals.org/cancerres/article/63/1/214/509886/Acetylcholine-Is-Synthesized-by-and-Acts-as-an

Song S, Kim S, Kim D, Yoon C (2022a). Occupational exposure to refractory ceramic fibers in the semiconductor scrubber manufacturing industry. Saf Health Work. 13(3):357–63. https://doi.org/10.1016/j.shaw.2022.04.005

Song S, Lei L, Zhang R, Liu H, Du J, Li N, et al. (2023a). Circadian disruption and breast cancer risk: evidence from a case–control study in China. Cancers (Basel). 15(2):419. https://doi.org/10.3390/cancers15020419

Sorahan T, Harrington JMA (2007). A "lugged" analysis of lung cancer risks in UK carbon black production workers, 1951–2004. Am J Ind Med. 50(8):555–64. https://doi.org/10.1002/ajim.20481

Sorg O, Janer V, Antille C, Carraux P, Leemans E, Masgrau E, et al. (2007). Effect of intense pulsed-light exposure on lipid peroxides and thymine dimers in human skin in vivo. Arch Dermatol. 143(3):363–6. https://doi.org/10.1001/archderm.143.3.363

Sorrentino G, Ruggeri N, Zannini A, Ingallina E, Bertolio R, Marotta C, et al. (2017). Glucocorticoid receptor signalling activates YAP in breast cancer. Nat Commun. 8(1):14073. https://doi.org/10.1038/ncomms14073

Souza AD, Devi R (2014). Cytokinesis blocked micronucleus assay of peripheral lymphocytes revealing the genotoxic effect of formaldehyde exposure. Clin Anat. 27(3):308–12. https://doi.org/10.1002/ca.22291 https://onlinelibrary.wiley.com/doi/10.1002/ca.22291

Souza DV, Claudio SR, Da Silva CLF, Marangoni KP, Peres RC, Ribeiro DA (2020). Genomic instability in peripheral blood and buccal mucosal cells of marijuana smokers: the impact of tobacco smoke. Asian Pac J Cancer Prev. 21(5):1235–9. https://doi.org/10.31557/APJCP.2020.21.5.1235

Souza Cruz EM, Bitencourt de Morais JM, Dalto da Rosa CV, da Silva Simões M, Comar JF, de Almeida Chuffa LG, et al. (2020). Long-term sucrose solution consumption causes metabolic alterations and affects hepatic oxidative stress in Wistar rats. Biol Open. 9(3):bio047282. https://doi.org/10.1242/bio.047282

Sozer Karadagli S, Kaftan G, Cansever I, Armagan G, Sogut O (2024). Tattoo inks: evaluation of cellular responses and analysis of some trace metals. Biometals. 37(2):495–505. https://doi.org/10.1007/s10534-023-00564-z

Sozeri B, Gulez N, Aksu G, Kutukculer N, Akalın T, Kandiloglu G (2012). Pesticide-induced scleroderma and early intensive immunosuppressive treatment. Arch Environ Occup Health. 67(1):43–7. https://doi.org/10.1080/19338244.2011.564231

Spaan M, van den Belt-Dusebout AW, Lambalk CB, van Boven HH, Schats R, Kortman M, et al. (2021). Long-term risk of ovarian cancer and borderline tumors after assisted reproductive technology. J Natl Cancer Inst. 113(6):699–709. https://doi.org/10.1093/jnci/djaa163

Spagnuolo C, Russo GL, Orhan IE, Habtemariam S, Daglia M, Sureda A, et al. (2015). Genistein and cancer: current status, challenges, and future directions. Adv Nutr. 6(4):408–19. https://doi.org/10.3945/an.114.008052

Spalding JW, French JE, Tice RR, Furedi-Machacek M, Haseman JK, Tennant RW (1999). Development of a transgenic mouse model for carcinogenesis bioassays: evaluation of chemically induced skin tumors in Tg.AC mice. Toxicol Sci. 49(2):241–54. https://doi.org/10.1093/toxsci/49.2.241

Spanoghe P, Ryckaert B, Van Gheluwe C, Van Labeke MC (2010). Fate of vinclozolin, thiabendazole and dimethomorph during storage, handling and forcing of chicory. Pest Manag Sci. 66(2):126–31. https://doi.org/10.1002/ps.1838

Spanu D, Pretta A, Lai E, Persano M, Donisi C, Mariani S, et al. (2022). Hepatocellular carcinoma and microbiota: implications for clinical management and treatment. World J Hepatol. 14(7):1319–32. https://doi.org/10.4254/wjh.v14.i7.1319

Spassova MA, Miller DJ, Eastmond DA, Nikolova NS, Vulimiri SV, Caldwell J, et al. (2013). Dose–response analysis of bromate-induced DNA damage and mutagenicity is consistent with low-dose linear, nonthreshold processes. Environ Mol Mutagen. 54(1):19–35. https://doi.org/10.1002/em.21737

Spencer Chapman M, Cull AH, Ciuculescu MF, Esrick EB, Mitchell E, Jung H, et al. (2023). Clonal selection of hematopoietic stem cells after gene therapy for sickle cell disease. Nat Med. 29(12):3175–83. https://doi.org/10.1038/s41591-023-02636-6https://doi.org/10.1038/s41591-023-02636-6

Spurgeon ME (2022). Small DNA tumor viruses and human cancer: preclinical models of virus infection and disease. Tumour Virus Res. 14:200239. https://doi.org/10.1016/j.tvr.2022.200239

Spyridopoulou K, Tiptiri-Kourpeti A, Lampri E, Fitsiou E, Vasileiadis S, Vamvakias M, et al. (2017). Dietary mastic oil extracted from *Pistacia lentiscus* var. chia suppresses tumor growth in experimental colon cancer models. Sci Rep. 7(1):3782. https://doi.org/10.1038/s41598-017-03971-8https://doi.org/10.1038/s41598-017-03971-8 PMID:28630399

Srinivasan MP, Bhopale KK, Caracheo AA, Kaphalia L, Loganathan G, Balamurugan AN, et al. (2021). Differential cytotoxicity, ER/oxidative stress, dysregulated AMPKα signalling, and mitochondrial stress by ethanol and its metabolites in human pancreatic acinar cells. Alcohol Clin Exp Res. 45(5):961–78. https://doi.org/10.1111/acer.14595

Srivastav AK, Dubey D, Chopra D, Singh J, Negi S, Mujtaba SF, et al. (2020). Oxidative stress-mediated photoactivation of carbazole inhibits human skin cell physiology. J Cell Biochem. 121(2):1273–82. https://doi.org/10.1002/jcb.29360

Ssemugabo C, Bradman A, Ssempebwa JC, Sillé F, Guwatudde D (2022). Pesticide residues in fresh fruit and vegetables from farm to fork in the Kampala metropolitan area, Uganda. Environ Health Insights. 16:11786302221111866. https://doi.org/10.1177/11786302221111866

Stafoggia M, Oftedal B, Chen J, Rodopoulou S, Renzi M, Atkinson RW, et al. (2022). Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project. Lancet Planet Health. 6(1):e9–18. https://doi.org/10.1016/S2542-5196(21)00277-1

Stanczyk FZ (2003). All progestins are not created equal. Steroids. 68(10–13):879–90. https://doi.org/10.1016/j.steroids.2003.08.003

Stanczyk FZ, Hapgood JP, Winer S, Mishell DR Jr (2013). Progestogens used in postmenopausal hormone therapy: differences in their pharmacological properties, intracellular actions, and clinical effects. Endocr Rev. 34(2):171–208. https://doi.org/10.1210/er.2012-1008

Stanfill SB, Ashley DL (1999). Solid phase microextraction of alkenylbenzenes and other flavor-related compounds from tobacco for analysis by selected ion monitoring gas chromatography–mass spectrometry. J Chromatogr A. 858(1):79–89. https://doi.org/10.1016/S0021-9673(99)00796-7

Stanfill SB, Brown CR, Yan XJ, Watson CH, Ashley DL (2006). Quantification of flavor-related compounds in the unburned contents of bidi and clove cigarettes. J Agric Food Chem. 54(22):8580–8. https://doi.org/10.1021/jf060733o

Stanfill SB, Calafat AM, Brown CR, Polzin GM, Chiang JM, Watson CH, et al. (2003). Concentrations of nine alkenylbenzenes, coumarin, piperonal and pulegone in Indian bidi cigarette tobacco. Food Chem Toxicol. 41(2):303–17. https://doi.org/10.1016/S0278-6915(02)00230-2

Stanfill SB, Hecht SS, Joerger AC, González PJ, Maia LB, Rivas MG, et al. (2023). From cultivation to cancer: formation of *N*-nitrosamines and other carcinogens in smokeless tobacco and their mutagenic implications. Crit Rev Toxicol. 53(10):658–701. https://doi.org/10.1080/10408444.2023.2264327

Stanic B, Petrovic J, Basica B, Kaisarevic S, Schirmer K, Andric N (2021). Characterization of the ERK1/2 phosphorylation profile in human and fish liver cells upon exposure to chemicals of environmental concern. Environ Toxicol Pharmacol. 88:103749. https://doi.org/10.1016/j.etap.2021.103749https://doi.org/10.1016/j.etap.2021.103749 PMID:34547448

Stanulla M, Wang J, Chervinsky DS, Aplan PD (1997). Topoisomerase II inhibitors induce DNA double-strand breaks at a specific site within the AML1 locus. Leukemia. 11(4):490–6. https://doi.org/10.1038/sj.leu.2400632

Stapleton PA (2021). Micro- and nanoplastic transfer, accumulation, and toxicity in humans. Curr Opin Toxicol. 28:62–9. https://doi.org/10.1016/j.cotox.2021.10.001

Starr JM, Graham SE, Li W, Gemma AA, Morgan MK (2018). Variability of pyrethroid concentrations on hard surface kitchen flooring in occupied housing. Indoor Air. 28(5):665–75. https://doi.org/10.1111/ina.12471

Starrett GJ, Marcelus C, Cantalupo PG, Katz JP, Cheng J, Akagi K, et al. (2017). Merkel cell polyomavirus exhibits dominant control of the tumor genome and transcriptome in virus-associated Merkel cell carcinoma. MBio. 8(1):e02079–16. https://doi.org/10.1128/mBio.02079-16

Statista (2024). Distribution of rare earths production worldwide as of 2022, by country. New York (NY), USA: Statista Inc. Available from: https://www.statista.com/statistics/270277/mining-of-rare-earths-by-country/, accessed February 2024.

Staurengo-Ferrari L, Sanfelice RADS, de Souza JB, Assolini JP, Dos Santos DP, Cataneo AHD, et al. (2021). Impact of *Toxoplasma gondii* infection on TM3 Leydig cells: alterations in testosterone and cytokines levels. Acta Trop. 220:105938. https://doi.org/10.1016/j.actatropica.2021.105938

Stayner LT, Schullehner J, Semark BD, Jensen AS, Trabjerg BB, Pedersen M, et al. (2021). Exposure to nitrate from drinking water and the risk of childhood cancer in Denmark. Environ Int. 155:106613. https://doi.org/10.1016/j.envint.2021.106613

Stebbins RB, Coleman GL (1967). A twenty-six month chronic toxicity study of GS-6244 in rats – dose levels of 100, 50 10, 5, or 0 mg/kg. Unpublished. Submitted to WHO. Groton (CT), USA: Pfizer Central Research.

Steenland K, Barry V, Anttila A, Sallmén M, McElvenny D, Todd AC, et al. (2017). A cohort mortality study of lead-exposed workers in the USA, Finland and the UK. Occup Environ Med. 74(11):785–91. https://doi.org/10.1136/oemed-2017-104311

Steenland K, Barry V, Anttila A, Sallmen M, Mueller W, Ritchie P, et al. (2019). Cancer incidence among workers with blood lead measurements in two countries. Occup Environ Med. 76(9):603–10. https://doi.org/10.1136/oemed-2019-105786

Steenland K, Cedillo L, Tucker J, Hines C, Sorensen K, Deddens J, et al. (1997). Thyroid hormones and cytogenetic outcomes in backpack sprayers using ethylenebis(dithiocarbamate) (EBDC) fungicides in Mexico. Environ Health Perspect. 105(10):1126–30. https://doi.org/10.1289/ehp.971051126https://doi.org/10.1289/ehp.971051126 PMID:9349837

Steenland K, Stayner L, Deddens J (2004). Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. Occup Environ Med. 61(1):2–7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1757803/pdf/v061p00002.pdf

Steenland K, Whelan E, Deddens J, Stayner L, Ward E (2003). Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). Cancer Causes Control. 14(6):531–9. https://doi.org/10.1023/A:1024891529592

Steenland K, Winquist A (2021). PFAS and cancer, a scoping review of the epidemiologic evidence. Environ Res. 194:110690. https://doi.org/10.1016/j.envres.2020.110690https://doi.org/10.1016/j.envres.2020.110690 PMID:33385391

Stefaniak AB, Du Preez S, Du Plessis JL (2021). Additive manufacturing for occupational hygiene: a comprehensive review of processes, emissions, & exposures. J Toxicol Environ Health B Crit Rev. 17(5):173–222. https://doi.org/10.1080/10937404.2021.1936319

Stefaniak AB, LeBouf RF, Yi J, Ham J, Nurkewicz T, Schwegler-Berry DE, et al. (2017). Characterization of chemical contaminants generated by a desktop fused deposition modeling 3-dimensional printer. J Occup Environ Hyg. 14(7):540–50. https://doi.org/10.1080/15459624.2017.1302589

Stefanou DT, Souliotis VL, Zakopoulou R, Liontos M, Bamias A (2021). DNA damage repair: predictor of platinum efficacy in ovarian cancer? Biomedicines. 10(1):82. https://doi.org/10.3390/biomedicines10010082

Stefanova ME, Ing-Simmons E, Stefanov S, Flyamer I, Dorado Garcia H, Schöpflin R, et al. (2023). Doxorubicin changes the spatial organization of the genome around active promoters. Cells. 12(15):2001. https://doi.org/10.3390/cells12152001

Steffensen IL, Dirven H, Couderq S, David A, D'Cruz SC, Fernández MF, et al. (2020). Bisphenols and oxidative stress biomarkers – associations found in human studies, evaluation of methods used, and strengths and weaknesses of the biomarkers. Int J Environ Res Public Health. 17(10):3609. https://doi.org/10.3390/ijerph17103609

Stein MJ, Applebaum SA, Harrast JJ, Lipa JE, Matarasso A, Gosain AK (2023). Practice patterns in primary breast augmentation: a 16-year review of continuous certification tracer data from the American Board of Plastic Surgery. Plast Reconstr Surg. 152(6):1011e–21e. https://doi.org/10.1097/PRS.0000000000010497 PMID:37014959

Steinle P (2016). Characterization of emissions from a desktop 3D printer and indoor air measurements in office settings. J Occup Environ Hyg. 13(2):121–32. https://doi.org/10.1080/15459624.2015.1091957

Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J (2006). *Schistosomiasis* and water resources development: systematic review, meta-analysis, and estimates of people at risk. Lancet Infect Dis. 6(7):411–25. https://doi.org/10.1016/S1473-3099(06)70521-7

Steinmetz-Beck A, Szahidewicz-Krupska E, Beck B, Poreba R, Andrzejak R (2005). [Genotoxicity effect of chronic lead exposure assessed using the comet assay]. Med Pr. 56(4):295–302. [Polish]

Stephens B, Azimi P, El Orch Z, Ramos T (2013). Ultrafine particle emissions from desktop 3D printers. Atmos Environ. 79:334–9. https://doi.org/10.1016/j.atmosenv.2013.06.050

Stepien M, Duarte-Salles T, Fedirko V, Trichopoulou A, Lagiou P, Bamia C, et al. (2016). Consumption of soft drinks and juices and risk of liver and biliary tract cancers in a European cohort. Eur J Nutr. 55(1):7–20. https://doi.org/10.1007/s00394-014-0818-5

Stevens RG, Davis S (1996). The melatonin hypothesis: electric power and breast cancer. Environ Health Perspect. 104(Suppl 1) suppl 1:135–40. https://doi.org/10.1289/ehp.96104s1135

Stevens VL, Carter BD, Jacobs EJ, McCullough ML, Teras LR, Wang Y (2023). A prospective case–cohort analysis of plasma metabolites and breast cancer risk. Breast Cancer Res. 25(1):5. https://doi.org/10.1186/s13058-023-01602-x

Stewart PA, Fears T, Kross B, Ogilvie L, Blair A (1999). Exposure of farmers to phosmet, a swine insecticide. Scand J Work Environ Health. 25(1):33–8. https://doi.org/10.5271/sjweh.380

Stillwater BJ, Bull AC, Romagnolo DF, Neumayer LA, Donovan MG, Selmin OI (2020). Bisphenols and risk of breast cancer: a narrative review of the impact of diet and bioactive food components. Front Nutr. 7:581388. https://doi.org/10.3389/fnut.2020.581388

Stockdale AJ, Kreuels B, Henrion MYR, Giorgi E, Kyomuhangi I, de Martel C, et al. (2020). The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. J Hepatol. 73(3):523–32. https://doi.org/10.1016/j.jhep.2020.04.008

Stockmann-Juvala H, Alenius H, Savolainen K (2008). Effects of fumonisin B(1) on the expression of cytokines and chemokines in human dendritic cells. Food Chem Toxicol. 46(5):1444–51. https://doi.org/10.1016/j.fct.2007.12.004

Stoll RE, Holden HE, Barthel CH, Blanchard KT (1999). Oxymetholone: III. Evaluation in the p53+/− transgenic mouse model. Toxicol Pathol. 27(5):513–8. https://doi.org/10.1177/019262339902700503

Stollings LM, Jia LJ, Tang P, Dou H, Lu B, Xu Y (2016). Immune modulation by volatile anesthetics. Anesthesiology. 125(2):399–411.
https://doi.org/10.1097/ALN.0000000000001195https://doi.org/10.1097/ALN.0000000000001195
PMID:27286478

Stolzenberg-Solomon RZ, Blaser MJ, Limburg PJ, Perez-Perez G, Taylor PR, Virtamo J, et al.; ATBC Study (2001). *Helicobacter pylori* seropositivity as a risk factor for pancreatic cancer. J Natl Cancer Inst. 93(12):937–41. https://doi.org/10.1093/jnci/93.12.937

Stoner GD, Shimkin MB, Kniazeff AJ, Weisburger JH, Weisburger EK, Gori GB (1973). Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice. Cancer Res. 33(12):3069–85. https://aacrjournals.org/cancerres/article/33/12/3069/479316/Test-for-Carcinogenicity-of-Food-Additives-and

Stoner GD, Shimkin MB, Troxell MC, Thompson TL, Terry LS (1976). Test for carcinogenicity of metallic compounds by the pulmonary tumor response in strain A mice. Cancer Res. 36(5):1744–7.

Stout PR, Horn CK, Klette KL, Given J (2006). Occupational exposure to methamphetamine in workers preparing training AIDS for drug detection dogs. J Anal Toxicol. 30(8):551–3. https://doi.org/10.1093/jat/30.8.551

Stouten H, Bessems JG (1998). Toxicological profile for o-benzyl-p-chlorophenol. J Appl Toxicol. 18(4):271–9. https://doi.org/10.1002/(SICI)1099-1263(199807/08)18:4<271::AID-JAT504>3.0.CO;2-B

Studstill CJ, Mac M, Moody CA (2023). Interplay between the DNA damage response and the life cycle of DNA tumor viruses. Tumour Virus Res. 16:200272. https://doi.org/10.1016/j.tvr.2023.200272

Sturgeon SR, Potischman N, Malone KE, Dorgan JF, Daling J, Schairer C, et al. (2004). Serum levels of sex hormones and breast cancer risk in premenopausal women: a case–control study (USA). Cancer Causes Control. 15(1):45–53. https://doi.org/10.1023/B:CACO.0000016574.79728.11

Su F, Viros A, Milagre C, Trunzer K, Bollag G, Spleiss O, et al. (2012). RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. N Engl J Med. 366(3):207–15. https://doi.org/10.1056/NEJMoa1105358

Su Y, Santucci-Pereira J, Dang NM, Kanefsky J, Rahulkannan V, Hillegass M, et al. (2022). Effects of pubertal exposure to butyl benzyl phthalate, perfluorooctanoic acid, and zeranol on mammary gland development and tumorigenesis in rats. Int J Mol Sci. 23(3):1398. https://doi.org/10.3390/ijms23031398

Su YP, Tang JM, Tang Y, Gao HY (2005). Histological and ultrastructural changes induced by selenium in early experimental gastric carcinogenesis. World J Gastroenterol. 11(29):4457–60. https://doi.org/10.3748/wjg.v11.i29.4457

Suárez-Larios K, Salazar-Martínez AM, Montero-Montoya R (2017). Screening of pesticides with the potential of inducing DSB and successive recombinational repair. J Toxicol. 2017:3574840. https://doi.org/10.1155/2017/3574840

Suarez-Torres JD, Orozco CA, Ciangherotti CE (2021). The numerical probability of carcinogenicity to humans of some antimicrobials: nitro-monoaromatics (including 5-nitrofurans and 5-nitroimidazoles), quinoxaline-1,4-dioxides (including carbadox), and chloramphenicol. Toxicol In Vitro. 75:105172. https://doi.org/10.1016/j.tiv.2021.105172

Suarez Uribe ND, Pezzini MF, Dall'Agnol J, Marroni N, Benitez S, Benedetti D, et al. (2023). Study of liver toxicity and DNA damage due to exposure to the pesticide Mancozeb in an experimental animal model – a pilot model. Eur Rev Med Pharmacol Sci. 27(13):6374–83.

Suh KS, Chon S, Choi EM (2017). Actein protects against methylglyoxal-induced oxidative damage in osteoblastic MC3T3–E1 cells. J Sci Food Agric. 97(1):207–14. https://doi.org/10.1002/jsfa.7713https://doi.org/10.1002/jsfa.7713 PMID:26991449

Suhua W, Rongzhu L, Changqing Y, Guangwei X, Fangan H, Junjie J, et al. (2010). Lipid peroxidation and changes of trace elements in mice treated with paradichlorobenzene. Biol Trace Elem Res. 136(3):320–36. https://doi.org/10.1007/s12011-009-8552-1

SAMHSA (2022). Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2021 National Survey on Drug Use and Health (HHS Publication No. PEP22-07-01-005, NSDUH Series H-57). Rockville (MD), USA: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Available from: https://www.samhsa.gov/data/report/2021-nsduh-annual-national-report. Accessed October, 2024.

Sedentary Behaviour Research Network (2012). Letter to the editor: standardized use of the terms "sedentary" and "sedentary behaviours". Appl Physiol Nutr Metab. 37(3):540–2. https://doi.org/10.1139/h2012-024 PMID:22540258

Su Mun L, Wye Lum S, Kong Yuiin Sze G, Hock Yoong C, Ching Yung K, Kah Lok L, et al. (2021). Association of microbiome with oral squamous cell carcinoma: a systematic review of the metagenomic studies. Int J Environ Res Public Health. 18(14):7224. https://doi.org/10.3390/ijerph18147224 PMID:34299675

Sui H, Matsumoto H, Wako Y, Kawasako K (2015). Evaluation of in vivo genotoxicity by thioacetamide in a 28-day repeated-dose liver micronucleus assay using male young adult rats. Mutat Res Genet Toxicol Environ Mutagen. 780–781:81–4. https://doi.org/10.1016/j.mrgentox.2014.10.001 https://www.sciencedirect.com/science/article/abs/pii/S1383571814002617?via%3Dihub PMID:25892627

Sullivan PA, Eisen EA, Woskie SR, Kriebel D, Wegman DH, Hallock MF, et al. (1998). Mortality studies of metalworking fluid exposure in the automobile industry: VI. A case-control study of esophageal cancer. Am J Ind Med. 34(1):36–48. https://doi.org/10.1002/(SICI)1097-0274(199807)34:1<36::AID-AJIM6>3.0.CO;2-O PMID:9617386

Sultana S, Khan N, Sharma S, Alam A (2003). Modulation of biochemical parameters by Hemidesmus indicus in cumene hydroperoxide-induced murine skin: possible role in protection against free radicals-induced cutaneous oxidative stress and tumor promotion. J Ethnopharmacol. 85(1):33–41. https://doi.org/10.1016/S0378-8741(02)00360-4 PMID:12576200

Sun G, Wang S, Hu X, Su J, Huang T, Yu J, et al. (2007). Fumonisin B1 contamination of home-grown corn in high-risk areas for esophageal and liver cancer in China. Food Addit Contam. 24(2):181–5. https://doi.org/10.1080/02652030601013471 PMID:17364919

Sun L, Zhang Y, Wen S, Li Q, Chen R, Lai X, et al. (2022b). Extract of *Jasminum grandiflorum* L. alleviates CCl_4-induced liver injury by decreasing inflammation, oxidative stress and hepatic CYP2E1 expression in mice. Biomed Pharmacother. 152:113255. https://doi.org/10.1016/j.biopha.2022.113255 PMID:35689859

Sun Y, Huang K, Long M, Yang S, Zhang Y (2022a). An update on immunotoxicity and mechanisms of action of six environmental mycotoxins. Food Chem Toxicol. 163:112895. https://doi.org/10.1016/j.fct.2022.112895 PMID:35219766

Sundell M, Brynhildsen J, Spetz Holm AC, Fredrikson M, Hoffmann M (2023). Trends in the incidence, prevalence and sales volume of menopausal hormone therapy in Sweden from 2000 to 2021. Maturitas. 175:107787. https://doi.org/10.1016/j.maturitas.2023.107787 PMID:37354643

Sundell M, Ginstman C, Månsson A, Forslund I, Brynhildsen J (2019). Patterns of prescription and discontinuation of contraceptives for Swedish women with obesity and normal-weight women. Eur J Contracept Reprod Health Care. 24(3):192–7. https://doi.org/10.1080/13625187.2019.1610873 PMID:31112059

Sunderam S, Kissin DM, Crawford S, Folger SG, Jamieson DJ, Barfield WD; Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, CDC (2014). Assisted reproductive technology surveillance – United States, 2011. MMWR Surveill Summ. 63(11):1–28. https://doi.org/10.15585/mmwr.ss6411a1 PMID:25426741

Sunderman FW Jr (1984). Carcinogenicity of nickel compounds in animals. IARC Sci Publ. 53(53):127–42. PMID:6532978

Sundkvist AM, Olofsson U, Haglund P (2010). Organophosphorus flame retardants and plasticizers in marine and fresh water biota and in human milk. J Environ Monit. 12(4):943–51. https://doi.org/10.1039/b921910b PMID:20383376

Surasi K, Ballen B, Weinberg JL, Materna BL, Harrison R, Cummings KJ, et al. (2022). Elevated exposures to respirable crystalline silica among engineered stone fabrication workers in California, January 2019–February 2020. Am J Ind Med. 65(9):701–7. https://doi.org/10.1002/ajim.23416 PMID:35899403

Sutcliffe AG, Purkayastha M, Brison DR, Nelson SM, Roberts SA, Lawlor DA (2023). General health in a cohort of children conceived after assisted reproductive technology in the United Kingdom: a population-based record-linkage study. Am J Obstet Gynecol. 228(1):82.e1–17. https://doi.org/10.1016/j.ajog.2022.07.032 PMID:35934120

Suzui M, Futakuchi M, Fukamachi K, Numano T, Abdelgied M, Takahashi S, et al. (2016). Multiwalled carbon nanotubes intratracheally instilled into the rat lung induce development of pleural malignant mesothelioma and lung tumors. Cancer Sci. 107(7):924–35. https://doi.org/10.1111/cas.12954 PMID:27098557

Suzuki S, Cohen SM, Arnold LL, Kato H, Fuji S, Pennington KL, et al. (2018). Orally administered nicotine effects on rat urinary bladder proliferation and carcinogenesis. Toxicology. 398–399:31–40. https://doi.org/10.1016/j.tox.2018.02.008 PMID:29501575

Suzuki Y, Umemura T, Hibi D, Inoue T, Jin M, Ishii Y, et al. (2012b). Possible involvement of genotoxic mechanisms in estragole-induced hepatocarcinogenesis in rats. Arch Toxicol. 86(10):1593–601. https://doi.org/10.1007/s00204-012-0865-8 PMID:22576464

Suzuki Y, Umemura T, Ishii Y, Hibi D, Inoue T, Jin M, et al. (2012a). Possible involvement of sulfotransferase 1A1 in estragole-induced DNA modification and carcinogenesis in the livers of female mice. Mutat Res. 749(1–2):23–8. https://doi.org/10.1016/j.mrgentox.2012.07.002 PMID:22885592

Swartz SJ, Morimoto LM, Whitehead TP, DeRouen MC, Ma X, Wang R, et al. (2022). Proximity to endocrine-disrupting pesticides and risk of testicular germ cell tumors (TGCT) among adolescents: a population-based case–control study in California. Int J Hyg Environ Health. 239:113881. https://doi.org/10.1016/j.ijheh.2021.113881 PMID:34839102

Sweeney MR, Nichols HB, Jones RR, Olshan AF, Keil AP, Engel LS, et al. (2022). Light at night and the risk of breast cancer: findings from the Sister study. Environ Int. 169:107495. https://doi.org/10.1016/j.envint.2022.107495 PMID:36084405

Sweeney MR, Sandler DP, Niehoff NM, White AJ (2020). Shift work and working at night in relation to breast cancer incidence. Cancer Epidemiol Biomarkers Prev. 29(3):687–9. https://doi.org/10.1158/1055-9965.EPI-19-1314 PMID:31915142

Swern D, Wieder R, McDonough M, Meranze DR, Shimkin MB (1970). Investigation of fatty acids and derivatives for carcinogenic activity. Cancer Res. 30(4):1037–46. PMID:5504346

Sykora L, Vortel V (1986). Post-natal study of the carcinogenicity of cyadox and carbadox. Biol Vet Praha. 22:53–62.

Szychowski KA, Skóra B, Bar M, Piechowiak T (2022). Triclosan (TCS) affects the level of DNA methylation in the human oral squamous cell carcinoma (SCC-15) cell line in a nontoxic concentration. Biomed Pharmacother. 149:112815. https://doi.org/10.1016/j.biopha.2022.112815 PMID:35286965

Tabibian SS, Sharifzadeh M (2023). Statistical and analytical investigation of methanol applications, production technologies, value-chain and economy with a special focus on renewable methanol. Renew Sustain Energy Rev. 179:113281. https://doi.org/10.1016/j.rser.2023.113281

Tabish AM, Poels K, Hoet P, Godderis L (2012). Epigenetic factors in cancer risk: effect of chemical carcinogens on global DNA methylation pattern in human TK6 cells. PLoS One. 7(4):e34674. https://doi.org/10.1371/journal.pone.0034674 PMID:22509344

Taeger D, Pesch B, Kendzia B, Behrens T, Jöckel KH, Dahmann D, et al. (2015). Lung cancer among coal miners, ore miners and quarrymen: smoking-adjusted risk estimates from the synergy pooled analysis of case–control studies. Scand J Work Environ Health. 41(5):467–77. https://doi.org/10.5271/sjweh.3513 PMID:26153779

Tai WP, Nie GJ, Chen MJ, Yaz TY, Guli A, Wuxur A, et al. (2017). Hot food and beverage consumption and the risk of esophageal squamous cell carcinoma: a case-control study in a northwest area in China. Medicine (Baltimore). 96(50):e9325. https://doi.org/10.1097/MD.0000000000009325 PMID:29390400

Tainio M, Jovanovic Andersen Z, Nieuwenhuijsen MJ, Hu L, de Nazelle A, An R, et al. (2021). Air pollution, physical activity and health: a mapping review of the evidence. Environ Int. 147:105954. https://doi.org/10.1016/j.envint.2020.105954 PMID:33352412

Tait S, Lori G, Tassinari R, La Rocca C, Maranghi F (2022). In vitro assessment and toxicological prioritization of pesticide mixtures at concentrations derived from real exposure in occupational scenarios. Int J Environ Res Public Health. 19(9):5202. https://doi.org/10.3390/ijerph19095202 PMID:35564597

Tajtáková M, Semanová Z, Tomková Z, Szökeová E, Majoros J, Rádiková Z, et al. (2006). Increased thyroid volume and frequency of thyroid disorders signs in schoolchildren from nitrate polluted area. Chemosphere. 62(4):559–64. https://doi.org/10.1016/j.chemosphere.2005.06.030https://doi.org/10.1016/j.chemosphere.2005.06.030 PMID:16095667

Takagi A, Hirose A, Futakuchi M, Tsuda H, Kanno J (2012). Dose-dependent mesothelioma induction by intraperitoneal administration of multi-wall carbon nanotubes in p53 heterozygous mice. Cancer Sci. 103(8):1440–4. https://doi.org/10.1111/j.1349-7006.2012.02318.x PMID:22537085

Takahashi O, Ohashi N, Nakae D, Ogata A (2011). Parenteral paradichlorobenzene exposure reduces sperm production, alters sperm morphology and exhibits an androgenic effect in rats and mice. Food Chem Toxicol. 49(1):49–56. https://doi.org/10.1016/j.fct.2010.09.029 PMID:20932873

Takahashi O, Oishi S, Fujitani T, Tanaka T, Yoneyama M (1994a). Piperonyl butoxide induces hepatocellular carcinoma in male CD-1 mice. Arch Toxicol. 68(7):467–9. https://doi.org/10.1007/s002040050098https://doi.org/10.1007/s002040050098 PMID:7979964

Takahashi O, Oishi S, Fujitani T, Tanaka T, Yoneyama M (1994b). Chronic toxicity studies of piperonyl butoxide in F344 rats: induction of hepatocellular carcinoma. Fundam Appl Toxicol. 22(2):293–303. https://doi.org/10.1006/faat.1994.1033https://doi.org/10.1006/faat.1994.1033 PMID:7911767

Takahashi O, Oishi S, Fujitani T, Tanaka T, Yoneyama M (1997). Chronic toxicity studies of piperonyl butoxide in CD-1 mice: induction of hepatocellular carcinoma. Toxicology. 124(2):95–103. https://doi.org/10.1016/S0300-483X(97)00136-4 PMID:9457999

Takahashi O, Oishi S, Yoneyama M, Ogata A, Kamimura H (2007). Antiestrogenic effect of paradichlorobenzene in immature mice and rats. Arch Toxicol. 81(7):505–17. https://doi.org/10.1007/s00204-007-0179-4 PMID:17593412

Takaki KK, Roca FJ, Schramm G, Wilbers RHP, Ittiprasert W, Brindley PJ, et al. (2021). Tumor necrosis factor and *Schistosoma mansoni* egg antigen omega-1 shape distinct aspects of the early egg-induced granulomatous response. PLoS Negl Trop Dis. 15(1):e0008814. https://doi.org/10.1371/journal.pntd.0008814 PMID:33465071

Takanashi S, Hara K, Aoki K, Usui Y, Shimizu M, Haniu H, et al. (2012). Carcinogenicity evaluation for the application of carbon nanotubes as biomaterials in rasH2 mice. Sci Rep. 2(1):498. https://doi.org/10.1038/srep00498 PMID:22787556

Takemura Y, Kikuchi S, Inaba Y (1998). Epidemiologic study of the relationship between schistosomiasis due to *Schistosoma japonicum* and liver cancer/cirrhosis. Am J Trop Med Hyg. 59(4):551–6. https://doi.org/10.4269/ajtmh.1998.59.551 PMID:9790429

Takemura Y, Tanifuji T, Okazaki S, Shinko Y, Otsuka I, Horai T, et al. (2022). Epigenetic clock analysis in methamphetamine dependence. Psychiatry Res. 317:114901. https://doi.org/10.1016/j.psychres.2022.114901 PMID:36244160

Takeuchi Y, Ichihara G, Kamijima M (1997). A review on toxicity of 2-bromopropane: mainly on its reproductive toxicity. J Occup Health. 39(3):179–91. https://doi.org/10.1539/joh.39.179

Talibov M, Olsson A, Bailey H, Erdmann F, Metayer C, Magnani C, et al. (2019). Parental occupational exposure to low-frequency magnetic fields and risk of leukaemia in the offspring: findings from the Childhood Leukaemia International Consortium (CLIC). Occup Environ Med. 76(10):746–53. https://doi.org/10.1136/oemed-2019-105706 PMID:31358566

Tallman MS, Gray R, Bennett JM, Variakojis D, Robert N, Wood WC, et al. (1995). Leukemogenic potential of adjuvant chemotherapy for early-stage breast cancer: the Eastern Cooperative Oncology Group experience. J Clin Oncol. 13(7):1557–63. https://doi.org/10.1200/JCO.1995.13.7.1557 PMID:7602344

Tamijani SMS, Valian N, Heravi M, Ahmadiani A, Beirami E, Dargahi L (2022). Implication of thyroid hormone receptors in methamphetamine neurocognitive effects. Neurotoxicology. 90:130–5. https://doi.org/10.1016/j.neuro.2022.03.003 PMID:35301009

Tamura M, Ito H, Matsui H, Hyodo I (2014). Acetaldehyde is an oxidative stressor for gastric epithelial cells. J Clin Biochem Nutr. 55(1):26–31. https://doi.org/10.3164/jcbn.14-12 PMID:25120276

Tang MS, Wu XR, Lee HW, Xia Y, Deng FM, Moreira AL, et al. (2019). Electronic-cigarette smoke induces lung adenocarcinoma and bladder urothelial hyperplasia in mice. Proc Natl Acad Sci USA. 116(43):21727–31. https://doi.org/10.1073/pnas.1911321116 PMID:31591243

Tange S, Fujimoto N, Uramaru N, Wong FF, Sugihara K, Ohta S, et al. (2016). In vitro metabolism of methiocarb and carbaryl in rats, and its effect on their estrogenic and antiandrogenic activities. Environ Toxicol Pharmacol. 41:289–97. https://doi.org/10.1016/j.etap.2015.08.014 PMID:26774076

Taniai E, Kawai M, Dewa Y, Nishimura J, Harada T, Saegusa Y, et al. (2009). Crosstalk between PTEN/Akt2 and TGFbeta signalling involving EGF receptor down-regulation during the tumor promotion process from the early stage in a rat two-stage hepatocarcinogenesis model. Cancer Sci. 100(5):813–20. https://doi.org/10.1111/j.1349-7006.2009.01120.x PMID:19309364

Taniai E, Yafune A, Kimura M, Morita R, Nakane F, Suzuki K, et al. (2012). Fluctuations in cell proliferation, apoptosis, and cell cycle regulation at the early stage of tumor promotion in rat two-stage carcinogenesis models. Breast Cancer Res. 37(6):1113–26. https://doi.org/10.2131/jts.37.1113 PMID:23208427

Tao Y, Phung D, Dong F, Xu J, Liu X, Wu X, et al. (2019). Urinary monitoring of neonicotinoid imidacloprid exposure to pesticide applicators. Sci Total Environ. 669:721–8. https://doi.org/10.1016/j.scitotenv.2019.03.040 PMID:30893627

Tareke E, Golding BT, Small RD, Törnqvist M (1998). Haemoglobin adducts from isoprene and isoprene monoepoxides. Xenobiotica. 28(7):663–72. https://doi.org/10.1080/004982598239245 PMID:9711810

Tasaki M, Kuroiwa Y, Inoue T, Hibi D, Matsushita K, Ishii Y, et al. (2013). Oxidative DNA damage and in vivo mutagenicity caused by reactive oxygen species generated in the livers of p53-proficient or -deficient gpt delta mice treated with non-genotoxic hepatocarcinogens. J Appl Toxicol. 33(12):1433–41. https://doi.org/10.1002/jat.2807 PMID:22972318

Taxvig C, Hass U, Axelstad M, Dalgaard M, Boberg J, Andeasen HR, et al. (2007). Endocrine-disrupting activities in vivo of the fungicides tebuconazole and epoxiconazole. Toxicol Sci. 100(2):464–73. https://doi.org/10.1093/toxsci/kfm227 PMID:17785682

Taylor SR, Ramsamooj S, Liang RJ, Katti A, Pozovskiy R, Vasan N, et al. (2021). Dietary fructose improves intestinal cell survival and nutrient absorption. Nature. 597(7875):263–7. https://doi.org/10.1038/s41586-021-03827-2 PMID:34408323

Tayour C, Ritz B, Langholz B, Mills PK, Wu A, Wilson JP, et al. (2019). A case–control study of breast cancer risk and ambient exposure to pesticides. Environ Epidemiol. 3(5):e070. https://doi.org/10.1097/EE9.0000000000000070 PMID:32166211

Tazi N, Semlali A, Loubaki L, Alamri A, Rouabhia M (2022). Cannabis smoke condensate induces human gingival epithelial cell damage through apoptosis, autophagy, and oxidative stress. Arch Oral Biol. 141:105498. https://doi.org/10.1016/j.archoralbio.2022.105498 PMID:35810494

Teepen JC, van Leeuwen FE, Tissing WJ, van Dulmen-den Broeder E, van den Heuvel-Eibrink MM, van der Pal HJ, et al.; DCOG LATER Study Group (2017). Long-term risk of subsequent malignant neoplasms after treatment of

childhood cancer in the DCOG LATER study cohort: role of chemotherapy. J Clin Oncol. 35(20):2288–98. https://doi.org/10.1200/JCO.2016.71.6902 PMID:28530852

Tegethoff K, Herbold BA, Bomhard EM (2000). Investigations on the mutagenicity of 1,4-dichlorobenzene and its main metabolite 2,5-dichlorophenol in vivo and in vitro. Mutat Res. 470(2):161–7. https://doi.org/10.1016/S1383-5718(00)00100-5 PMID:11027971

Tenter AM, Heckeroth AR, Weiss LM (2000). *Toxoplasma gondii*: from animals to humans. Int J Parasitol. 30(12–13):1217–58. https://doi.org/10.1016/S0020-7519(00)00124-7 PMID:11113252

Teo TLL, Coleman HM, Khan SJ (2016). Presence and select determinants of organophosphate flame retardants in public swimming pools. Sci Total Environ. 569-570:469–75. https://doi.org/10.1016/j.scitotenv.2016.06.085 PMID:27355519

Teschke K, Morgan MS, Checkoway H, Franklin G, Spinelli JJ, van Belle G, et al. (1997). Surveillance of nasal and bladder cancer to locate sources of exposure to occupational carcinogens. Occup Environ Med. 54(6):443–51. https://doi.org/10.1136/oem.54.6.443 PMID:9245952

Tharp AP, Maffini MV, Hunt PA, VandeVoort CA, Sonnenschein C, Soto AM (2012). Bisphenol A alters the development of the rhesus monkey mammary gland. Proc Natl Acad Sci USA. 109(21):8190–5. https://doi.org/10.1073/pnas.1120488109https://doi.org/10.1073/pnas.1120488109 PMID:22566636

Theorell-Haglöw J, Zhou X, Wittert G, Adams R, Appleton S, Reynolds A, et al. (2023). Does obstructive sleep apnea increase the risk of cancer and cancer mortality in combined community-based cohorts? J Sleep Res. 33(4):e14089. PMID:37990480

Thompson CM, Gaylor DW, Tachovsky JA, Perry C, Carakostas MC, Haws LC (2013). Development of a chronic noncancer oral reference dose and drinking water screening level for sulfolane using benchmark dose modeling. J Appl Toxicol. 33(12):1395–406. https://doi.org/10.1002/jat.2799 PMID:22936336

Thompson D, Kriebel D, Quinn MM, Wegman DH, Eisen EA (2005). Occupational exposure to metalworking fluids and risk of breast cancer among female autoworkers. Am J Ind Med. 47(2):153–60. https://doi.org/10.1002/ajim.20132 PMID:15662639

Thompson DA, Lehmler HJ, Kolpin DW, Hladik ML, Vargo JD, Schilling KE, et al. (2020). A critical review on the potential impacts of neonicotinoid insecticide use: current knowledge of environmental fate, toxicity, and implications for human health. Environ Sci Process Impacts. 22(6):1315–46. https://doi.org/10.1039/C9EM00586B PMID:32267911

Thomsen C, Lundanes E, Becher G (2001). Brominated flame retardants in plasma samples from three different occupational groups in Norway. J Environ Monit. 3(4):366–70. https://doi.org/10.1039/b104304h PMID:11523435

Thomson CA, Chow HHS, Wertheim BC, Roe DJ, Stopeck A, Maskarinec G, et al. (2017). A randomized, placebo-controlled trial of diindolylmethane for breast cancer biomarker modulation in patients taking tamoxifen. Breast Cancer Res Treat. 165(1):97–107. https://doi.org/10.1007/s10549-017-4292-7 PMID:28560655

Thysen B, Bloch E, Varma SK (1985a). Reproductive toxicity of 2,4-toluenediamine in the rat. 2. Spermatogenic and hormonal effects. J Toxicol Environ Health. 16(6):763–9. https://doi.org/10.1080/15287398509530787 PMID:3937900

Thysen B, Varma SK, Bloch E (1985b). Reproductive toxicity of 2,4-toluenediamine in the rat. 1. Effect on male fertility. J Toxicol Environ Health. 16(6):753–61. https://doi.org/10.1080/15287398509530786 PMID:4093994

Tian L, Mi N, Wang L, Huang C, Fu W, Bai M, et al. (2024). Regular use of paracetamol and risk of liver cancer: a prospective cohort study. BMC Cancer. 24(1):33. https://doi.org/10.1186/s12885-023-11767-5 PMID:38178090

Tirado-Ballestas IP, Alvarez-Ortega N, Maldonado-Rojas W, Olivero-Verbel J, Caballero-Gallardo K (2022). Oxidative stress and alterations in the expression of genes related to inflammation, DNA damage, and metal exposure in lung cells exposed to a hydroethanolic coal dust extract. Mol Biol Rep. 49(6):4861–71. https://doi.org/10.1007/s11033-022-07341-0 PMID:35334019

Tocharus J, Khonthun C, Chongthammakun S, Govitrapong P (2010). Melatonin attenuates methamphetamine-induced overexpression of pro-inflammatory cytokines in microglial cell lines. J Pineal Res. 48(4):347–52. https://doi.org/10.1111/j.1600-079X.2010.00761.x PMID:20374443

Tomasec P, Braud VM, Rickards C, Powell MB, McSharry BP, Gadola S, et al. (2000). Surface expression of HLA-E, an inhibitor of natural killer cells, enhanced by human cytomegalovirus gpUL40. Science. 287(5455):1031–3. https://doi.org/10.1126/science.287.5455.1031 PMID:10669413

Tomášek L, Kubik A (2006). Temporal and histological patterns of lung cancer risk from radon and smoking. Lung Cancer. 52:S29.

Tomásek L, Zárská H (2004). Lung cancer risk among Czech tin and uranium miners – comparison of lifetime detriment. Neoplasma. 51(4):255–60. Full text PMID:15254655

Tomášková H, Šplíchalová A, Šlachtová H, Urban P, Hajduková Z, Landecká I, et al. (2017). Mortality in miners with coal-workers' pneumoconiosis in the Czech Republic in the period 1992–2013. Int J Environ Res Public Health. 14(3):269. https://doi.org/10.3390/ijerph14030269 PMID:28272360

Tommasino M (2017). The biology of beta human papillomaviruses. Virus Res. 231:128–38. https://doi.org/10.1016/j.virusres.2016.11.013 PMID:27856220

Tompa A, Biró A, Jakab M (2016). Genotoxic monitoring of nurses handling cytotoxic drugs. Asia Pac J Oncol Nurs. 3(4):365–9. https://doi.org/10.4103/2347-5625.196484 PMID:28083554

Tong JH, Elmore S, Huang SS, Tachachartvanich P, Manz K, Pennell K, et al. (2023). Chronic exposure to low levels of parabens increases mammary cancer growth and metastasis in mice. Endocrinology. 164(3):bqad007. https://doi.org/10.1210/endocr/bqad007 PMID:36683225

Tönz O (1957). [Changes in the kidney of rats after chronic experimental exposure to lead.] Z Ges Exp Med. 128:361–77. [in German]

Toraason M, Butler MA, Ruder A, Forrester C, Taylor L, Ashley DL, et al. (2003). Effect of perchloroethylene, smoking, and race on oxidative DNA damage in female dry cleaners. Mutat Res. 539(1–2):9–18. https://doi.org/10.1016/S1383-5718(03)00130-X PMID:12948810

Torres O, Matute J, Gelineau-van Waes J, Maddox JR, Gregory SG, Ashley-Koch AE, et al. (2015). Human health implications from co-exposure to aflatoxins and fumonisins in maize-based foods in Latin America: Guatemala as a case study. World Mycotoxin J. 8(2):143–59. https://doi.org/10.3920/WMJ2014.1736

Tothill P, Klys HS, Matheson LM, McKay K, Smyth JF (1992). The long-term retention of platinum in human tissues following the administration of cisplatin or carboplatin for cancer chemotherapy. Eur J Cancer. 28A(8–9):1358–61. https://doi.org/10.1016/0959-8049(92)90519-8 PMID:1515251

Totsuka Y, Maesako Y, Ono H, Nagai M, Kato M, Gi M, et al. (2020). Comprehensive analysis of DNA adducts (DNA adductome analysis) in the liver of rats treated with 1,4-dioxane. Proc Jpn Acad, Ser B, Phys Biol Sci. 96(5):180–7. https://doi.org/10.2183/pjab.96.015 PMID:32389918

Tovalin H, Valverde M, Morandi MT, Blanco S, Whitehead L, Rojas E (2006). DNA damage in outdoor workers occupationally exposed to environmental air pollutants. Occup Environ Med. 63(4):230–6. https://doi.org/10.1136/oem.2005.019802 PMID:16556741

Towle KM, Grespin ME, Monnot AD (2017). Personal use of hair dyes and risk of leukemia: a systematic literature review and meta-analysis. Cancer Med. 6(10):2471–86. https://doi.org/10.1002/cam4.1162 PMID:28925101

Toyoda T, Kobayashi T, Miyoshi N, Matsushita K, Akane H, Morikawa T, et al. (2023). Mucosal damage and γ-H2AX formation in the rat urinary bladder induced by aromatic amines with structures similar to o-toluidine and o-anisidine. Arch Toxicol. 97(12):3197–207. https://doi.org/10.1007/s00204-023-03606-0 PMID:37773275

Toyoda-Hokaiwado N, Inoue T, Masumura K, Hayashi H, Kawamura Y, Kurata Y, et al. (2010). Integration of in vivo genotoxicity and short-term carcinogenicity assays using F344 gpt delta transgenic rats: in vivo mutagenicity of 2,4-diaminotoluene and 2,6-diaminotoluene structural isomers. Toxicol Sci. 114(1):71–8. https://doi.org/10.1093/toxsci/kfp306 PMID:20026473

Trafford AM, Parisi R, Kontopantelis E, Griffiths CEM, Ashcroft DM (2019). Association of psoriasis with the risk of developing or dying of cancer: a systematic review and meta-analysis. JAMA Dermatol. 155(12):1390–403. https://doi.org/10.1001/jamadermatol.2019.3056 PMID:31617868

Tran KB, Lang JJ, Compton K, Xu R, Acheson AR, Henrikson HJ, et al.; GBD 2019 Cancer Risk Factors Collaborators (2022). The global burden of cancer attributable to risk factors, 2010–19: a systematic analysis for the Global

Burden of Disease Study 2019. Lancet. 400(10352):563–91. https://doi.org/10.1016/S0140-6736(22)01438-6 PMID:35988567

Travinsky-Shmul T, Beresh O, Zaretsky J, Griess-Fishheimer S, Rozner R, Kalev-Altman R, et al. (2021). Ultra-processed food impairs bone quality, increases marrow adiposity and alters gut microbiome in mice. Foods. 10(12):3107. https://doi.org/10.3390/foods10123107 PMID:34945658

Travis LB, Andersson M, Gospodarowicz M, van Leeuwen FE, Bergfeldt K, Lynch CF, et al. (2000). Treatment-associated leukemia following testicular cancer. J Natl Cancer Inst. 92(14):1165–71. https://doi.org/10.1093/jnci/92.14.1165 PMID:10904090

Travis LB, Holowaty EJ, Bergfeldt K, Lynch CF, Kohler BA, Wiklund T, et al. (1999). Risk of leukemia after platinum-based chemotherapy for ovarian cancer. N Engl J Med. 340(5):351–7. https://doi.org/10.1056/NEJM199902043400504 PMID:9929525

TRI (2009). TRI Explorer Chemical Report. Washington (DC), USA: US Environmental Protection Agency. Available from: https://enviro.epa.gov/triexplorer/tri_release.chemical (select Safrole), accessed September 2024.

Tristan Asensi M, Napoletano A, Sofi F, Dinu M (2023). Low-grade inflammation and ultra-processed foods consumption: a review. Nutrients. 15(6):1546. https://doi.org/10.3390/nu15061546 PMID:36986276

Trock BJ, Hilakivi-Clarke L, Clarke R (2006). Meta-analysis of soy intake and breast cancer risk. J Natl Cancer Inst. 98(7):459–71. https://doi.org/10.1093/jnci/djj102 PMID:16595782

Trush MA, Kensler TW (1991). An overview of the relationship between oxidative stress and chemical carcinogenesis. Free Radic Biol Med. 10(3–4):201–9. https://doi.org/10.1016/0891-5849(91)90077-G PMID:1864525

Trutina Gavran M, Željezić D, Vranić L, Negovetić Vranić D, Grabarević L, Jurić-Kaćunarić D, et al. (2023). Assessment of cytotoxic and genotoxic effect of modern dental materials *in vivo*. Acta Stomatol Croat. 57(3):216–28. https://doi.org/10.15644/asc57/3/2 PMID:37808410

Tryphonas H, Bondy G, Miller JD, Lacroix F, Hodgen M, Mcguire P, et al. (1997). Effects of fumonisin B1 on the immune system of Sprague-Dawley rats following a 14-day oral (gavage) exposure. Fundam Appl Toxicol. 39(1):53–9. https://doi.org/10.1006/faat.1997.2348 PMID:9325027

Tsai MS, Chang SH, Kuo WH, Kuo CH, Li SY, Wang MY, et al. (2020). A case–control study of perfluoroalkyl substances and the risk of breast cancer in Taiwanese women. Environ Int. 142:105850. https://doi.org/10.1016/j.envint.2020.105850 PMID:32580117

Tsao YC, Gu PW, Liu SH, Tzeng IS, Chen JY, Luo JJ (2017). Nickel exposure and plasma levels of biomarkers for assessing oxidative stress in nickel electroplating workers. Biomarkers. 22(5):455–60. https://doi.org/10.1080/1354750X.2016.1252964 PMID:27775433

Tsatsakis A, Docea AO, Constantin C, Calina D, Zlatian O, Nikolouzakis TK, et al. (2019). Genotoxic, cytotoxic, and cytopathological effects in rats exposed for 18 months to a mixture of 13 chemicals in doses below NOAEL levels. Toxicol Lett. 316:154–70. https://doi.org/10.1016/j.toxlet.2019.09.004 PMID:31521832

Tse LA, Lee PMY, Ho WM, Lam AT, Lee MK, Ng SSM, et al. (2017). Bisphenol A and other environmental risk factors for prostate cancer in Hong Kong. Environ Int. 107:1–7. https://doi.org/10.1016/j.envint.2017.06.012https://doi.org/10.1016/j.envint.2017.06.012 PMID:28644961

Tsermpini EE, Plemenitaš Ilješ A, Dolžan V (2022). Alcohol-induced oxidative stress and the role of antioxidants in alcohol use disorder: a systematic review. Antioxidants. 11(7):1374. https://doi.org/10.3390/antiox11071374 PMID:35883865

Tsezou A, Kitsiou-Tzeli S, Galla A, Gourgiotis D, Papageorgiou J, Mitrou S, et al. (1996). High nitrate content in drinking water: cytogenetic effects in exposed children. Arch Environ Health. 51(6):458–61. https://doi.org/10.1080/00039896.1996.9936046 PMID:9012325

Tsuji PA, Santesmasses D, Lee BJ, Gladyshev VN, Hatfield DL (2021). Historical roles of selenium and selenoproteins in health and development: the good, the bad and the ugly. Int J Mol Sci. 23(1):5. https://doi.org/10.3390/ijms23010005 PMID:35008430

Tsuji T, Asanuma M, Miyazaki I, Miyoshi K, Ogawa N (2009). Reduction of nuclear peroxisome proliferator-activated receptor gamma expression in methamphetamine-induced neurotoxicity and neuroprotective effects of ibuprofen. Neurochem Res. 34(4):764–74. https://doi.org/10.1007/s11064-008-9863-x PMID:18946735

Tsukahara T, Haniu H (2011). Cellular cytotoxic response induced by highly purified multi-wall carbon nanotube in human lung cells. Mol Cell Biochem. 352(1–2):57–63. https://doi.org/10.1007/s11010-011-0739-z PMID:21298324

Tuček M, Bušová M, Čejchanová M, Schlenker A, Kapitán M (2020). Exposure to mercury from dental amalgam: actual contribution for risk assessment. Cent Eur J Public Health. 28(1):40–3. https://doi.org/10.21101/cejph.a5965 PMID:32228815

Tucker JD, Sorensen KJ, Ruder AM, McKernan LT, Forrester CL, Butler MA (2011). Cytogenetic analysis of an exposed-referent study: perchloroethylene-exposed dry cleaners compared to unexposed laundry workers. Environ Health. 10(1):16. https://doi.org/10.1186/1476-069X-10-16 PMID:21392400

Tucker JD, Wyrobek AJ, Ashworth LK, Christensen ML, Burton GV, Carrano AV, et al. (1990). Induction, accumulation, and persistence of sister chromatid exchanges in women with breast cancer receiving cyclophosphamide, adriamycin, and 5-fluorouracil chemotherapy. Cancer Res. 50(16):4951–6. https://aacrjournals.org/cancerres/article/50/16/4951/495358/Induction-Accumulation-and-Persistence-of-Sister PMID:2379160

Tuli HS, Tuorkey MJ, Thakral F, Sak K, Kumar M, Sharma AK, et al. (2019). Molecular mechanisms of action of genistein in cancer: recent advances. Front Pharmacol. 10:1336. https://doi.org/10.3389/fphar.2019.01336 PMID:31866857

Türkez H, Aydın E (2016). In vitro assessment of cytogenetic and oxidative effects of α-pinene. Toxicol Ind Health. 32(1):168–76. https://doi.org/10.1177/0748233713498456https://doi.org/10.1177/0748233713498456 PMID:24081629

Türkoğlu ŞA, Yaman K, Orallar H, Camsari C, Karabörk Ş, Ayaz E (2018). Acute toxoplasmosis and antioxidant levels in the liver, kidney and brain of rats. Ann Parasitol. 64(3):241–7. PMID:30316221

Turner MC, Cogliano V, Guyton K, Madia F, Straif K, Ward EM, et al. (2023). Research recommendations for selected IARC-classified agents: impact and lessons learned. Environ Health Perspect. 131(10):105001. https://doi.org/10.1289/EHP12547 PMID:37902675

Turner MC, Gracia-Lavedan E, Papantoniou K, Aragonés N, Castaño-Vinyals G, Dierssen-Sotos T, et al. (2022). Sleep and breast and prostate cancer risk in the MCC-Spain study. Sci Rep. 12(1):21807. https://doi.org/10.1038/s41598-022-25789-9 PMID:36526666

Tyagi S, George J, Singh R, Bhui K, Shukla Y (2011). Neoplastic alterations induced in mammalian skin following mancozeb exposure using in vivo and in vitro models. OMICS. 15(3):155–67. https://doi.org/10.1089/omi.2010.0076https://doi.org/10.1089/omi.2010.0076 PMID:21375462

Uberoi A, Lambert PF (2017). Rodent papillomaviruses. Viruses. 9(12):362. https://doi.org/10.3390/v9120362 PMID:29186900

Uberoi A, Yoshida S, Frazer IH, Pitot HC, Lambert PF (2016). Role of ultraviolet radiation in papillomavirus-induced disease. PLoS Pathog. 12(5):e1005664. https://doi.org/10.1371/journal.ppat.1005664 PMID:27244228

Uğuz AC, Naziroğlu M, Espino J, Bejarano I, González D, Rodríguez AB, et al. (2009). Selenium modulates oxidative stress-induced cell apoptosis in human myeloid HL-60 cells through regulation of calcium release and caspase-3 and 9 activities. J Membr Biol. 232(1–3):15–23. https://doi.org/10.1007/s00232-009-9212-2 PMID:19898892

Ulhaq ZS, Tse WKF (2023). Perfluorohexanesulfonic acid (PFHxS) induces oxidative stress and causes developmental toxicities in zebrafish embryos. J Hazard Mater. 457:131722. https://doi.org/10.1016/j.jhazmat.2023.131722https://doi.org/10.1016/j.jhazmat.2023.131722 PMID:37263022

Ulhaq ZS, Tse WKF (2024). PFHxS exposure and the risk of non-alcoholic fatty liver disease. Genes (Basel). 15(1):93. https://doi.org/10.3390/genes15010093https://doi.org/10.3390/genes15010093 PMID:38254982

Umeda Y, Aiso S, Yamazaki K, Ohnishi M, Arito H, Nagano K, et al. (2005). Carcinogenicity of biphenyl in mice by two years feeding. J Vet Med Sci. 67(4):417–24. https://doi.org/10.1292/jvms.67.417 PMID:15876793

Umeda Y, Arito H, Kano H, Ohnishi M, Matsumoto M, Nagano K, et al. (2002). Two-year study of carcinogenicity and chronic toxicity of biphenyl in rats. J Occup Health. 44(3):176–83. https://doi.org/10.1539/joh.44.176

UNEP (2023). Our planet is choking on plastic. Nairobi, Kenya: United Nations Environment Programme. Available from: https://www.unep.org/interactives/beat-plastic-pollution/?gad_source=1&gclid=EAIaIQobChMIsJHngOaIhAMVlgytBh0AjgMaEAAYASAAEgLLj_D_BwE, accessed September 2024

UNODC (2023). World Drug Report 2023. Vienna, Austria: United Nations Office of Drugs and Crime. Available from: https://www.unodc.org/unodc/en/data-and-analysis/world-drug-report-2023.html, accessed January 2024.

Unsal V, Cicek M, Sabancilar İ (2020). Toxicity of carbon tetrachloride, free radicals and role of antioxidants. Rev Environ Health. 36(2):279–95. https://doi.org/10.1515/reveh-2020-0048 PMID:32970608

UNSCEAR (2019). Sources, effects and risks of ionizing radiation. Report to the General Assembly with scientific annexes. Vienna, Austria: United Nations Scientific Committee on the Effects of Atomic Radiation. Available from: https://www.unscear.org/unscear/en/publications/2019.html, accessed September 2024.

Upham BL, Masten SJ, Lockwood BR, Trosko JE (1994). Nongenotoxic effects of polycyclic aromatic hydrocarbons and their oxygenation by-products on the intercellular communication of rat liver epithelial cells. Fundam Appl Toxicol. 23(3):470–5. https://doi.org/10.1006/faat.1994.1129 PMID:7835547

Urbano T, Vinceti M, Wise LA, Filippini T (2021). Light at night and risk of breast cancer: a systematic review and dose-response meta-analysis. Int J Health Geogr. 20(1):44. https://doi.org/10.1186/s12942-021-00297-7 PMID:34656111

US EPA (1985a). Glyphosate; EPA Reg.#: 524–308; Mouse oncogenicity study. Document No. 004370. Washington (DC), USA: Office of Pesticides and Toxic Substances, United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/103601/103601-183.pdf, accessed January 2024.

US EPA (1985b). EPA Reg.#: 524–308; Roundup; glyphosate; pathology report on additional kidney sections. Document No. 004855. Washington (DC), USA: Office of Pesticides and Toxic Substances, United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/103601/103601-207.pdf, accessed January 2024.

US EPA (1986a) Glyphosate; EPA Registration No. 524–308; Roundup; additional histopathological evaluations of kidneys in the chronic feeding study of glyphosate in mice. Document No. 005590. Washington (DC), USA: Office of Pesticides and Toxic Substances, United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/103601/103601-183.pdf, accessed September 2024.

US EPA (1986b). Carbon disulfide; CASRN 75-15-0. Integrated Risk Information System (IRIS) Chemical Assessment Summary (1986). Washington (DC), USA: Office of Pesticides and Toxic Substances, United States Environmental Protection Agency. Available from: https://iris.epa.gov/static/pdfs/0217_summary.pdf, accessed February 2024.

US EPA (1988). Furmecyclox; CASRN 60568-05-0. Integrated Risk Information System (IRIS). Chemical Assessment Summary. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0362_summary.pdf, accessed September 2024.

US EPA (1991). Dyfonate: Review of chronic/oncogenicity feeding study in rats. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-041701_7-Nov-91_050.pdf, accessed March 2024.

US EPA (1992). Carcinogenicity peer review of pendimethalin. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/108501/108501-178.pdf, accessed January 2024.

US EPA (1993a) Carcinogenicity peer review of tebuconazole. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/128997/128997-055.pdf, accessed January 2024.

US EPA (1993b). Carbaryl: Review of mouse carcinogenicity. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/056801/056801-104.pdf, accessed January 2024

US EPA (1996a). Fonofos. Draft toxicology chapter for reregistration eligibility. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-041701_3-Sep-96_a.pdf, accessed March 2024.

US EPA (1996b). Reregistration eligibility decision document (RED) for pendimethalin. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-108501_15-Mar-96_a.pdf, accessed January 2024.

US EPA (1997). Reregistration eligibility decision (RED). Pendimethalin. USEPA. Prevention, pesticides, and toxic Substances (7508W). EPA 738-R-97–007. Washington (DC), USA: United States Environmental Protection Agency. https://archive.epa.gov/pesticides/reregistration/web/pdf/0187red.pdf, accessed September 2024.

US EPA (1998). Alachlor. Reregistration Eligibility Decision (RED). EPA 738-R-98–020. Prevention, pesticides and toxic substances (7508C). Washington (DC), USA: United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/reregistration/web/pdf/0063.pdf, accessed February 2024.

US EPA (1999). O-Ethyl S-phenyl ethylphosphonodithioate (Fonofos). R.E.D. Facts. EPA 738-F-99–019. Prevention, pesticides and toxic substances. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/reregistration/web/pdf/0105fact.pdf, accessed September 2024.

US EPA (2000a). *p*-Phenylenediamine. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/sites/default/files/2016-09/documents/p-phenylenediamine.pdf, accessed January 2024.

US EPA (2000b). Catechol (Pyrocatechol). Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/sites/default/files/2016-09/documents/catechol-pyrocatechol.pdf, accessed January 2024.

US EPA (2001). Data evaluation record supplement to DER for MRID No. 44459301: cyfluthrin [chronic/oncogenicity study in rats]. (Scientific data reviews). Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-128831_16-Feb-01_c.pdf, accessed January 2024.

US EPA (2005). Ametryn. Reregistration Eligibility Decision (RED). EPA 738-R-05–006. Prevention, pesticides and toxic substances (7508C). Washington (DC), USA: United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/reregistration/web/pdf/ametryn_red.pdf, accessed February 2024.

US EPA (2006a). Reregistration eligibility decision (RED) for permethrin. Prevention, pesticides and toxic substances (7508C). EPA 738-R-06-017. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/reregistration/web/pdf/permethrin_red.pdf, accessed January 2024.

US EPA (2006b). Reregistration eligibility decision for chlorpyrifos. Washington (DC), USA: United States Environmental Protection Agency.

US EPA (2006c). Reregistration eligibility decision for terbufos. Washington (DC), USA: United States Environmental Protection Agency.

US EPA (2007). Provisional peer reviewed toxicity values for 2,4-dimethylphenol (CASRN 105-67-9). EPA/690/R-07/015F Final. Cincinnati (OH), USA: Superfund Health Risk Technical Support Center, National Center for Environmental Assessment, United States Environmental Protection Agency. Available from: https://cfpub.epa.gov/ncea/pprtv/documents/Dimethylphenol24.pdf, accessed February 2024.

US EPA (2008a). Health effects support document for fonofos. EPA document number: 822-R-08–009. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/sites/default/files/2014-09/documents/health_effects_support_document_for_fonofos.pdf, accessed January 2024.

US EPA (2008b). Health effects support document for *S*-ethyl dipropylthiocarbamate (EPTC). EPA document number: 822-R-08–006. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/sites/production/files/2014-09/documents/health_effects_support_document_for_eptc.pdf, accessed September 2024.

US EPA (2009a). Permethrin facts. EPA 738-F-09–001. Prevention, pesticides and toxic substances (7508P). Washington (DC), USA: United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/reregistration/web/pdf/permethrin-facts-2009.pdf, accessed February 2022.

US EPA (2009b). Short-chain chlorinated paraffins (SCCPs) and other chlorinated paraffins action plan. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/sites/default/files/2015-09/documents/sccps_ap_2009_1230_final.pdf, accessed January 2024.

US EPA (2009c). Provisional peer-reviewed toxicity values for allyl alcohol (CASRN 107-18-6). Cincinatti (OH), USA: Superfund Health Risk Technical Support Center, National Center for Environmental Assessment, United States Environmental Protection Agency. Available from: https://cfpub.epa.gov/ncea/pprtv/documents/AllylAlcohol.pdf, accessed December 2023.

US EPA (2011a). Chlorpyrifos: preliminary human health risk assessment for registration review. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://downloads.regulations.gov/EPA-HQ-OPP-2008-0850-0025/content.pdf, accessed March 2024.

US EPA (2011b). EPTC: Human health risk assessment for proposed uses on grass grown for seed. PC Code: 041401. DP Barcode: D371022. Washington (DC), USA: United States Environmental Protection Agency.

US EPA (2012a). Provisional peer-reviewed toxicity values for sulfolane (CASRN 126-33-0). Cincinnati (OH), USA: Superfund Health Risk Technical Support Center, National Center for Environmental Assessment, United States Environmental Protection Agency. Available from: https://cfpub.epa.gov/ncea/pprtv/documents/Sulfolane.pdf, accessed December 2023.

US EPA (2012b). Provisional peer-reviewed toxicity values for fluoranthene (CASRN 206-44-0). Cincinnati (OH), USA: Superfund Health Risk Technical Support Center, National Center for Environmental Assessment, United States Environmental Protection Agency. Available from: https://cfpub.epa.gov/ncea/pprtv/documents/Fluoranthene.pdf, accessed February 2024.

US EPA (2013a). Integrated science assessment for ozone and related photochemical oxidants. Report no.: EPA 600/R-10/076F. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=247492, accessed March 2024.

US EPA (2013b). Toxicological review of biphenyl. (CAS No. 92-52-4). In support of summary information on the integrated risk information system (IRIS). EPA/635/R-11/005F. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0013tr.pdf, accessed February 2024.

US EPA (2014). Priority pollutant list. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/sites/default/files/2015-09/documents/priority-pollutant-list-epa.pdf, accessed March 2024.

US EPA (2015). Terbufos. Occupational and residential exposure assessment for the registration review risk assessment. D420977. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://downloads.regulations.gov/EPA-HQ-OPP-2008-0119-0021/content.pdf, accessed March 2024.

US EPA (2016). Reregistration eligibility decision for phosmet. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/reregistration/web/pdf/phosmet_red.pdf, accessed March 2024.

US EPA (2017a). Ametryn – preliminary human health risk assessment for registration review. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://downloads.regulations.gov/EPA-HQ-OPP-2013-0249-0022/content.pdf, accessed March 2024.

US EPA (2017b). Pesticides industry sales and usage. 2008–2012 Market estimates. Washington (DC), USA: Biological and Economic Analysis Division, Office of Pesticide Programs, Office of Chemical Safety and Pollution Prevention, United States Environmental Protection Agency. Available from: https://www.epa.gov/sites/default/files/2017-01/documents/pesticides-industry-sales-usage-2016_0.pdf, accessed February 2024.

US EPA (2018a). Chemicals evaluated for carcinogenic potential. Annual cancer report 2018. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://apublica.org/wp-content/uploads/2020/05/chemicals-evaluated.pdf, accessed March 2024.

US EPA (2018b). Atrazine. Draft human health risk assessment for registration review. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.regulations.gov/document/EPA-HQ-OPP-2013-0266-1159, accessed February 2024.

US EPA (2018c). Registration review draft risk assessment for triclosan. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.regulations.gov/document/EPA-HQ-OPP-2012-0811-0020, accessed March 2024.

US EPA (2019). 4-Androstene-3,17-dione. 63-05-8. DTXSID8024523. Chemical details. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/chemical/details/DTXSID8024523, accessed September 2024.

US EPA (2020a). Hexythiazox. Human health risk assessment for amended tolerances on caneberry subgroup 13-07A and dates, dried fruit and establishment of a tolerance without U.S. registration for residues in tea. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://downloads.regulations.gov/EPA-HQ-OPP-2017-0155-0016/content.pdf, accessed March 2024.

US EPA (2020b). Final risk evaluation for 1,4-dioxane. CASRN: 123-91-1. EPA Document #EPA-740–R1-8007. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/sites/default/files/2020-12/documents/1._risk_evaluation_for_14-dioxane_casrn_123-91-1.pdf, accessed March 2024.

US EPA (2021). Revised carbaryl human health risk assessment. Washington (DC), USA: US Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention.

US EPA (2022). Drinking water health advisory: hexafluoropropylene oxide (HFPO) dimer acid (CASRN 13252-13-6) and HFPO dimer acid ammonium salt (CASRN 62037-80-3), also known as "GenX chemicals". EPA/822/R-22/005. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/system/files/documents/2022-06/drinking-water-genx-2022.pdf, accessed September 2024.

US EPA (2023a). Cypermethrin; pesticide tolerances. A rule by the Environmental Protection Agency. Published document: 2023-21821 (88 FR 68475). Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.federalregister.gov/documents/2023/10/04/2023-21821/cypermethrin-pesticide-tolerances, accessed March 2024.

US EPA (2023b). Phosmet Gowan Meeting Summary April 25, 2023. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.regulations.gov/document/EPA-HQ-OPP-2009-0316-0057, accessed September 2024.

US EPA (2024a). Chemview [online database]. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://chemview.epa.gov/chemview, accessed February 2024.

US EPA (2024b). Integrated science assessment (ISA) for lead (final report). EPA/600/R-23/375. Washington (DC), USA: United States Environmental Protection Agency. https://www.epa.gov/isa/integrated-science-assessment-isa-lead, accessed September 2024.

US EPA (2024c). C.I. Azoic Diazo Component 12. 99-55-8 | DTXSID4020959. CompTox chemicals dashboard. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/comptox-tools/comptox-chemicals-dashboard, accessed September 2024.

US EPA (2024d). Menthyl anthranilate. 134-09-8 | DTXSID3047895. CompTox chemicals dashboard. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/chemical/details/DTXSID3047895, accessed April 2024.

US EPA (2024e). Perfluorohexanesulfonic acid (PFHxS). CASRN 355-46-4. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=355410, accessed March 2024.

US EPA (2024f). Hazardous air pollutants: ethylene oxide (EtO). Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide, accessed February 2024.

US EPA (2024g). [Boscalid. Bioactivity – TOXCAST summary.] CompTox Chemicals Dashboard. Research Triangle Park (NC), USA: United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/chemical/details/DTXSID6034392, accessed September 2024.

US EPA (2024h). Carbaryl. Bioactivity – TOXCAST summary. CompTox Chemicals Dashboard. Research Triangle Park (NC), USA: United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/chemical/invitrodb/DTXSID9020247, accessed September 2024.

US EPA (2024i). [Phosmet. Bioactivity – TOXCAST summary.] CompTox Chemicals Dashboard. Research Triangle Park (NC), USA: United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/chemical/invitrodb/DTXSID5024261, accessed September 2024.

US EPA (2024j). [Pendimethalin. Bioactivity – TOXCAST summary.] CompTox Chemicals Dashboard. Research Triangle Park (NC), USA: United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/chemical/invitrodb/DTXSID7024245, accessed September 2024.

US EPA (2024k). [Vinclozolin. Bioactivity – TOXCAST summary.] CompTox Chemicals Dashboard. Research Triangle Park (NC), USA: United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/chemical/bioactivity-toxcast-models/DTXSID4022361

US EPA (2024l). [*ortho*-Benzyl-*para*-chlorophenol. Bioactivity – TOXCAST summary.] CompTox Chemicals Dashboard. Research Triangle Park (NC), USA: United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/chemical/invitrodb/DTXSID5020154

US FDA (2000). Sec. 73.2995 Luminescent zinc sulfide. Code of federal regulations. Title 21, Volume 1. 21CFR73.2995. 65 FR 48377, Aug. 8, 2000. Subchapter a – general. Part 73 – listing of color additives exempt from certification. Subpart C – cosmetics. Silver Spring (MD), USA: United States Food and Drug Administration. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=73.2995, accessed September 2024.

US FDA (2008). Ablavar (gadofosveset trisodium) injection for intravenous use. Initial US Approval: 2008. Highlights for prescribing information. Revised 12/2010. Reference ID: 2880323. Silver Spring (MD), USA: United States Food and Drug Administration.

US FDA (2017). FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss. FDA News Release, 18 December 2017. Silver Spring (MD), USA: United States Food and Drug Administration. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss, accessed May 2024.

US FDA (2018). What is Gene Therapy? Silver Spring (MD), USA: United States Food and Drug Administration. Available from: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy#:~:text=Gene%20therapy%20is%20a%20technique%20that%20modifies%20a,a%20disease-causing%20gene%20that%20is%20not%20functioning%20properly, accessed May 2024.

US FDA (2020). Long term follow-up after administration of human gene therapy products. Guidance for industry. Silver Spring (MD): Center for Biologics Evaluation and Research, United States Food and Drug Administration. Available from: https://www.fda.gov/media/113768/download, accessed September 2024.

US FDA. (2021). Dental amalgam fillings. Silver Spring (MD), USA: United States Food and Drug Administration. Available from: https://www.fda.gov/medical-devices/dental-devices/dental-amalgam-fillings, accessed January 2024.

US FDA (2022). Memorandum. Regulatory status and review of available information pertaining to 4-androstenedione: lack of general recognition of safety for its use in foods. Silver Spring (MD), USA: United States Food and Drug Administration. Available from: https://www.fda.gov/media/169491/download, accessed June 2024.

US FDA (2023a). Medical device reports of breast implant-associated anaplastic large cell lymphoma. Silver Spring (MD), USA: United States Food and Drug Administration. Available from: https://www.fda.gov/medical-devices/breast-implants/medical-device-reports-breast-implant-associated-anaplastic-large-cell-lymphoma, accessed September 2024.

US FDA (2023b). Questions and answers regarding carbadox. Silver Spring (MD), USA: United States Food and Drug Administration. Available from: https://www.fda.gov/animal-veterinary/product-safety-information/questions-and-answers-regarding-carbadox, accessed January 2024.

US FDA (2023c). FDA approves first nonprescription daily oral contraceptive. FDA news release. Silver Spring (MD), USA: United States Food and Drug Administration Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-nonprescription-daily-oral-contraceptive, accessed June 2024.

US FDA (2023d). Aspartame and other sweeteners in food. FDA response to external safety reviews of aspartame. Silver Spring (MD), USA: United States Food and Drug Administration. Available from: https://www.fda.gov/food/food-additives-petitions/aspartame-and-other-sweeteners-food#:~:text=Sucralose%20is%20a%20general%2Dpurpose,sugar%20substitute%20in%20baked%20goods, accessed March 2024.

US Federal Register (2024). Request for public comment on NIOSH initial recommendations to change the status of liraglutide and pertuzumab on the NIOSH list of antineoplastic and other hazardous drugs in healthcare settings. Washington (DC), USA: Office of the Federal Register. Available from: https://www.federalregister.gov/documents/2024/01/16/2024-00693/request-for-public-comment-on-niosh-initial-recommendations-to-change-the-status-of-liraglutide-and#:~:text=The%20manufacturer%27s%20request%20to%20reevaluate%20the%20inclusion%20of,and%20therefore%20adverse%20health%20effects%20from%20that%20exposure, accessed March 2024.

Usman MB, Priya K, Pandit S, Gupta PK (2022). Cancer risk and nullity of glutathione-S-transferase mu and theta 1 in occupational pesticide workers. Curr Pharm Biotechnol. 23(7):932–45. https://doi.org/10.2174/1389201022666210810092342 PMID:34375184

Usmani KA, Cho TM, Rose RL, Hodgson E (2006). Inhibition of the human liver microsomal and human cytochrome P450 1A2 and 3A4 metabolism of estradiol by deployment-related and other chemicals. Drug Metab Dispos. 34(9):1606–14. https://doi.org/10.1124/dmd.106.010439 PMID:16790556

Usmani KA, Rose RL, Hodgson E (2003). Inhibition and activation of the human liver microsomal and human cytochrome P450 3A4 metabolism of testosterone by deployment-related chemicals. Drug Metab Dispos. 31(4):384–91. https://doi.org/10.1124/dmd.31.4.384 PMID:12642463

Vagefi MR, Dragan L, Hughes SM, Klippenstein KA, Seiff SR, Woog JJ (2006). Adverse reactions to permanent eyeliner tattoo. Ophthalmic Plast Reconstr Surg. 22(1):48–51. https://doi.org/10.1097/01.iop.0000196713.94608.29 PMID:16418666

Vahle JL, Finch GL, Heidel SM, Hovland DN Jr, Ivens I, Parker S, et al. (2010). Carcinogenicity assessments of biotechnology-derived pharmaceuticals: a review of approved molecules and best practice recommendations. Toxicol Pathol. 38(4):522–53. https://doi.org/10.1177/0192623310368984 PMID:20472697

Valdiglesias V, Costa C, Sharma V, Kiliç G, Pásaro E, Teixeira JP, et al. (2013). Comparative study on effects of two different types of titanium dioxide nanoparticles on human neuronal cells. Food Chem Toxicol. 57:352–61. https://doi.org/10.1016/j.fct.2013.04.010 PMID:23597443

Valdiglesias V, Pásaro E, Méndez J, Laffon B (2010). In vitro evaluation of selenium genotoxic, cytotoxic, and protective effects: a review. Arch Toxicol. 84(5):337–51. https://doi.org/10.1007/s00204-009-0505-0 PMID:20033805

Valencia R, Mason JM, Woodruff RC, Zimmering S (1985). Chemical mutagenesis testing in *Drosophila*. III. Results of 48 coded compounds tested for the National Toxicology Program. Environ Mutagen. 7(3):325–48. https://doi.org/10.1002/em.2860070309https://doi.org/10.1002/em.2860070309 PMID:3930234

Valverde M, Fortoul TI, Díaz-Barriga F, Mejía J, del Castillo ER (2002). Genotoxicity induced in CD-1 mice by inhaled lead: differential organ response. Mutagenesis. 17(1):55–61. https://doi.org/10.1093/mutage/17.1.55 PMID:11752234

Valverde M, Trejo C, Rojas E (2001). Is the capacity of lead acetate and cadmium chloride to induce genotoxic damage due to direct DNA-metal interaction? Mutagenesis. 16(3):265–70. https://doi.org/10.1093/mutage/16.3.265 PMID:11320153

Van Belle AB, Cochez PM, de Heusch M, Pointner L, Opsomer R, Raynaud P, et al. (2019). IL-24 contributes to skin inflammation in *para*-phenylenediamine-induced contact hypersensitivity. Sci Rep. 9(1):1852. https://doi.org/10.1038/s41598-018-38156-4https://doi.org/10.1038/s41598-018-38156-4 PMID:30755657

van Bemmel DM, Visvanathan K, Beane Freeman LE, Coble J, Hoppin JA, Alavanja MC (2008). *S*-ethyl-*N*,*N*-dipropylthiocarbamate exposure and cancer incidence among male pesticide applicators in the agricultural health study: a prospective cohort. Environ Health Perspect. 116(11):1541–6. https://doi.org/10.1289/ehp.11371 PMID:19057708

van der Bent SAS, Rauwerdink D, Oyen EMM, Maijer KI, Rustemeyer T, Wolkerstorfer A (2021). Complications of tattoos and permanent makeup: overview and analysis of 308 cases. J Cosmet Dermatol. 20(11):3630–41. https://doi.org/10.1111/jocd.14498 PMID:34605159

van der Hem JGK, de Wreede LC, Brand A, Veelken H, Falkenburg JHF, Halkes CJM (2017). Long-term risk of cancer development in adult patients with idiopathic aplastic anemia after treatment with anti-thymocyte globulin. Haematologica. 102(10):e382–3. https://doi.org/10.3324/haematol.2017.171215 PMID:28705902

van der Zanden SY, Qiao X, Neefjes J (2021). New insights into the activities and toxicities of the old anticancer drug doxorubicin. FEBS J. 288(21):6095–111. https://doi.org/10.1111/febs.15583 PMID:33022843

Van Duuren BL, Goldschmidt BM (1976). Cocarcinogenic and tumor-promoting agents in tobacco carcinogenesis. J Natl Cancer Inst. 56(6):1237–42. https://doi.org/10.1093/jnci/56.6.1237 PMID:994224

Van Duuren BL, Langseth L, Orris L, Baden M, Kuschner M (1967). Carcinogenicity of epoxides, lactones, and peroxy compounds. V. Subcutaneous injection in rats. J Natl Cancer Inst. 39(6):1213–6. https://academic.oup.com/jnci/article-abstract/39/6/1213/1032771?redirectedFrom=fulltext PMID:6079866

Van Duuren BL, Langseth L, Orris L, Teebor G, Nelson N, Kuschner M (1966). Carcinogenicity of epoxides, lactones, and peroxy compounds. IV. Tumor response in epithelial and connective tissue in mice and rats. J Natl Cancer Inst. 37(6):825–38. https://academic.oup.com/jnci/article-abstract/37/6/825/894756 PMID:5955045

Van Duuren BL, Orris L, Nelson N (1965). Carcinogenicity of epoxides, lactones, and peroxy compounds. II. J Natl Cancer Inst. 35(4):707–17. https://academic.oup.com/jnci/article-abstract/35/4/707/870523?redirectedFrom=PDF PMID:5841060

Van Esch GJ, Kroes R (1969). The induction of renal tumours by feeding basic lead acetate to mice and hamsters. Br J Cancer. 23(4):765–71. https://doi.org/10.1038/bjc.1969.95 PMID:5367336

van Gerwen M, Colicino E, Guan H, Dolios G, Nadkarni GN, Vermeulen RCH, et al. (2023). Per- and polyfluoroalkyl substances (PFAS) exposure and thyroid cancer risk. EBioMedicine. 97:104831. https://doi.org/10.1016/j.ebiom.2023.104831https://doi.org/10.1016/j.ebiom.2023.104831 PMID:37884429

Van Hemelrijck M, Sollie S, Nelson WG, Yager JD, Kanarek NF, Dobs A, et al. (2019). Selenium and sex steroid hormones in a U.S. nationally representative sample of men: a role for the link between selenium and estradiol in prostate carcinogenesis? Cancer Epidemiol Biomarkers Prev. 28(3):578–83. https://doi.org/10.1158/1055-9965.EPI-18-0520 PMID:30482876

van Maanen JM, van Dijk A, Mulder K, de Baets MH, Menheere PC, van der Heide D, et al. (1994). Consumption of drinking water with high nitrate levels causes hypertrophy of the thyroid. Toxicol Lett. 72(1–3):365–74. https://doi.org/10.1016/0378-4274(94)90050-7 PMID:8202954

van Meeuwen JA, van Son O, Piersma AH, de Jong PC, van den Berg M (2008). Aromatase inhibiting and combined estrogenic effects of parabens and estrogenic effects of other additives in cosmetics. Toxicol Appl Pharmacol. 230(3):372–82. https://doi.org/10.1016/j.taap.2008.03.002 PMID:18486175

van Wel L, Liorni I, Huss A, Thielens A, Wiart J, Joseph W, et al. (2021). Radio-frequency electromagnetic field exposure and contribution of sources in the general population: an organ-specific integrative exposure assessment. J Expo Sci Environ Epidemiol. 31(6):999–1007. https://doi.org/10.1038/s41370-021-00287-8 PMID:33654268

van Wendel de Joode B, Mora AM, Córdoba L, Cano JC, Quesada R, Faniband M, et al. (2014). Aerial application of mancozeb and urinary ethylene thiourea (ETU) concentrations among pregnant women in Costa Rica: the Infants' Environmental Health Study (ISA). Environ Health Perspect. 122(12):1321–8. https://doi.org/10.1289/ehp.1307679 PMID:25198283

van Wijngaarden E, Dosemeci M (2006). Brain cancer mortality and potential occupational exposure to lead: findings from the National Longitudinal Mortality Study, 1979–1989. Int J Cancer. 119(5):1136–44. https://doi.org/10.1002/ijc.21947 PMID:16570286

Vanarsdall AL, Johnson DC (2012). Human cytomegalovirus entry into cells. Curr Opin Virol. 2(1):37–42. https://doi.org/10.1016/j.coviro.2012.01.001 PMID:22440964

Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR Jr, Lee DH, et al. (2012). Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr Rev. 33(3):378–455. https://doi.org/10.1210/er.2011-1050 PMID:22419778

Vanoirbeek JA, De Vooght V, Synhaeve N, Nemery B, Hoet PH (2009). Is toluene diamine a sensitizer and is there cross-reactivity between toluene diamine and toluene diisocyanate? Toxicol Sci. 109(2):256–64. https://doi.org/10.1093/toxsci/kfp065 PMID:19332649

Vardavas AI, Stivaktakis PD, Tzatzarakis MN, Fragkiadaki P, Vasilaki F, Tzardi M, et al. (2016). Long-term exposure to cypermethrin and piperonyl butoxide cause liver and kidney inflammation and induce genotoxicity in New Zealand white male rabbits. Food Chem Toxicol. 94:250–9. https://doi.org/10.1016/j.fct.2016.06.016 PMID:27321377

Varela-Moreiras G, Alonso-Aperte E, Rubio M, Gassó M, Deulofeu R, Alvarez L, et al. (1995). Carbon tetrachloride-induced hepatic injury is associated with global DNA hypomethylation and homocysteinemia: effect of S-adenosylmethionine treatment. Hepatology. 22(4 Pt 1):1310–5. https://doi.org/10.1002/hep.1840220442 PMID:7557886

Varona-Uribe ME, Torres-Rey CH, Díaz-Criollo S, Palma-Parra RM, Narváez DM, Carmona SP, et al. (2016). Exposure to pesticide mixtures and DNA damage among rice field workers. Arch Environ Occup Health. 71(1):3–9. https://doi.org/10.1080/19338244.2014.910489 PMID:24972111

Vasconcelos AL, Silva MJ, Louro H (2019). In vitro exposure to the next-generation plasticizer diisononyl cyclohexane-1,2-dicarboxylate (DINCH): cytotoxicity and genotoxicity assessment in human cells. J Toxicol Environ Health A. 82(9):526–36. https://doi.org/10.1080/15287394.2019.1634376 PMID:31242819

Vasuri F, Deserti M, Corradini AG, Tavolari S, Relli V, Palloni A, et al. (2023). Asbestos exposure as an additional risk factor for small duct intrahepatic cholangiocarcinoma: a pilot study. Sci Rep. 13(1):2580. https://doi.org/10.1038/s41598-023-27791-1 PMID:36781903

Veiga LH, Curtis RE, Morton LM, Withrow DR, Howell RM, Smith SA, et al. (2019). Association of breast cancer risk after childhood cancer with radiation dose to the breast and anthracycline use: a report from the Childhood Cancer Survivor Study. JAMA Pediatr. 173(12):1171–9. https://doi.org/10.1001/jamapediatrics.2019.3807 PMID:31657853

Veiga LHS, Vo JB, Curtis RE, Mille MM, Lee C, Ramin C, et al. (2022). Treatment-related thoracic soft tissue sarcomas in US breast cancer survivors: a retrospective cohort study. Lancet Oncol. 23(11):1451–64. https://doi.org/10.1016/S1470-2045(22)00561-7 PMID:36240805

Velazquez-Kronen R, MacDonald LA, Akinyemiju TF, Cushman M, Howard VJ (2023). Shiftwork, long working hours and markers of inflammation in a national US population-based sample of employed black and white men and women aged ≥ 45 years. Occup Environ Med. 80(11):635–43. https://doi.org/10.1136/oemed-2023-108902 PMID:37813482

Velicer CM, Heckbert SR, Lampe JW, Potter JD, Robertson CA, Taplin SH (2004). Antibiotic use in relation to the risk of breast cancer. JAMA. 291(7):827–35. https://doi.org/10.1001/jama.291.7.827 PMID:14970061

Venkatesh P, Kasi A (2023). Anthracyclines. In: StatPearls [Internet]. Treasure Island (FL), USA: StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538187/ PMID:30844214

Venuti A, Lohse S, Tommasino M, Smola S (2019). Cross-talk of cutaneous beta human papillomaviruses and the immune system: determinants of disease penetrance. Philos Trans R Soc Lond B Biol Sci. 374(1773):20180287. https://doi.org/10.1098/rstb.2018.0287

Verbanck M, Canouil M, Leloire A, Dhennin V, Coumoul X, Yengo L, et al. (2017). Low-dose exposure to bisphenols A, F and S of human primary adipocyte impacts coding and non-coding RNA profiles. PLoS One. 12(6):e0179583. https://doi.org/10.1371/journal.pone.0179583 PMID:28628672

Vermeulen R, Jönsson BA, Lindh CH, Kromhout H (2005). Biological monitoring of carbon disulphide and phthalate exposure in the contemporary rubber industry. Int Arch Occup Environ Health. 78(8):663–9. https://doi.org/10.1007/s00420-005-0017-z PMID:16041606

Verstraelen S, Remy S, Casals E, De Boever P, Witters H, Gatti A, et al. (2014). Gene expression profiles reveal distinct immunological responses of cobalt and cerium dioxide nanoparticles in two in vitro lung epithelial cell models. Toxicol Lett. 228(3):157–69. https://doi.org/10.1016/j.toxlet.2014.05.006 PMID:24821434

Verza FA, Valente VB, Oliveira LK, Kayahara GM, Crivelini MM, Furuse C, et al. (2021). Social isolation stress facilitates chemically induced oral carcinogenesis. PLoS One. 16(1):e0245190. https://doi.org/10.1371/journal.pone.0245190 PMID:33411841

Veschsanit N, Yang JL, Ngampramuan S, Viwatpinyo K, Pinyomahakul J, Lwin T, et al. (2021). Melatonin reverts methamphetamine-induced learning and memory impairments and hippocampal alterations in mice. Life Sci. 265:118844. https://doi.org/10.1016/j.lfs.2020.118844 PMID:33278389

Vescovo T, Pagni B, Piacentini M, Fimia GM, Antonioli M (2020). Regulation of autophagy in cells infected with oncogenic human viruses and its impact on cancer development. Front Cell Dev Biol. 8:47. https://doi.org/10.3389/fcell.2020.00047 PMID:32181249

Vesselinovitch SD (1983). Perinatal hepatocarcinogenesis. Biol Res Pregnancy Perinatol. 4(1):22–5. PMID:6303459

Vesselinovitch SD, Rao KV, Mihailovich N (1979a). Transplacental and lactational carcinogenesis by safrole. Cancer Res. 39(11):4378–80. https://aacrjournals.org/cancerres/article/39/11/4378/483261/Transplacental-and-Lactational-Carcinogenesis-by PMID:498070

Vesselinovitch SD, Rao KV, Mihailovich N (1979b). Neoplastic response of mouse tissues during perinatal age periods and its significance in chemical carcinogenesis. Natl Cancer Inst Monogr. 51(51):239–50. PMID:384263

Viarisio D, Gissmann L, Tommasino M (2017). Human papillomaviruses and carcinogenesis: well-established and novel models. Curr Opin Virol. 26:56–62. https://doi.org/10.1016/j.coviro.2017.07.014 PMID:28778034

Viarisio D, Mueller-Decker K, Kloz U, Aengeneyndt B, Kopp-Schneider A, Gröne HJ, et al. (2011). E6 and E7 from beta HPV38 cooperate with ultraviolet light in the development of actinic keratosis-like lesions and squamous cell carcinoma in mice. PLoS Pathog. 7(7):e1002125. https://doi.org/10.1371/journal.ppat.1002125 PMID:21779166

Viarisio D, Müller-Decker K, Accardi R, Robitaille A, Dürst M, Beer K, et al. (2018). Beta HPV38 oncoproteins act with a hit-and-run mechanism in ultraviolet radiation-induced skin carcinogenesis in mice. PLoS Pathog. 14(1):e1006783. https://doi.org/10.1371/journal.ppat.1006783 PMID:29324843

Victor H, Ganda V, Kiranadi B, Pinontoan R (2020). Metabolite identification from biodegradation of Congo red by *Pichia* sp. KnE Life Sciences. 5(2): https://doi.org/10.18502/kls.v5i2.6443

Victorin K (1994). Review of the genotoxicity of nitrogen oxides. Mutat Res. 317(1):43–55. https://doi.org/10.1016/0165-1110(94)90011-6 PMID:7507572

Vidal I, Fernández-Florido E, Marrero AD, Castilla L, R Quesada A, Martínez-Poveda B, et al. (2022). The immunomodulator dimethyl itaconate inhibits several key steps of angiogenesis in cultured endothelial cells. Int J Mol Sci. 23(24):15972. https://doi.org/10.3390/ijms232415972 PMID:36555614

Videnros C, Selander J, Wiebert P, Albin M, Plato N, Borgquist S, et al. (2020). Investigating the risk of breast cancer among women exposed to chemicals: a nested case–control study using improved exposure estimates. Int Arch Occup Environ Health. 93(2):261–9. https://doi.org/10.1007/s00420-019-01479-4 PMID:31650237

Viebahn-Haensler R, León Fernández OS (2021). Ozone in medicine. The low-dose ozone concept and its basic biochemical mechanisms of action in chronic inflammatory diseases. Int J Mol Sci. 22(15):7890. https://doi.org/10.3390/ijms22157890 PMID:34360655

Viegas S, Viegas C, Oppliger A (2018). Occupational exposure to mycotoxins: current knowledge and prospects. Ann Work Expo Health. 62(8):923–41. https://doi.org/10.1093/annweh/wxy070 PMID:30099513

Vig BK (1971). Chromosome aberrations induced in human leukocytes by the antileukemic antibiotic adriamycin. Cancer Res. 31(1):32–7. https://aacrjournals.org/cancerres/article/31/1/32/478119/Chromosome-Aberrations-Induced-in-Human-Leukocytes PMID:5099799

Vigo FM, Fraietta R, Rodrigues F, Carvalho CV, Bonetti TCS, Motta ELA (2021). Cumulus cell microRNA expression when LH is added to the ovarian stimulation protocol: a pilot study. Reprod Biomed Online. 43(6):1070–7. https://doi.org/10.1016/j.rbmo.2021.07.014 PMID:34674939

Vila J, Bowman JD, Richardson L, Kincl L, Conover DL, McLean D, et al.; INTEROCC Study Group (2016). A source-based measurement database for occupational exposure assessment of electromagnetic fields in the INTEROCC study: a literature review approach. Ann Occup Hyg. 60(2):184–204. PMID:26493616

Villafuerte G, Miguel-Puga A, Rodríguez EM, Machado S, Manjarrez E, Arias-Carrión O (2015). Sleep deprivation and oxidative stress in animal models: a systematic review. Oxid Med Cell Longev. 2015:234952. https://doi.org/10.1155/2015/234952 PMID:25945148

Villanueva CM, Cantor KP, Cordier S, Jaakkola JJ, King WD, Lynch CF, et al. (2004). Disinfection byproducts and bladder cancer: a pooled analysis. Epidemiology. 15(3):357–67. https://doi.org/10.1097/01.ede.0000121380.02594.fc PMID:15097021

Villanueva CM, Evlampidou I, Ibrahim F, Donat-Vargas C, Valentin A, Tugulea AM, et al. (2023). Global assessment of chemical quality of drinking water: the case of trihalomethanes. Water Res. 230:119568. https://doi.org/10.1016/j.watres.2023.119568 PMID:36621278

Villanueva CM, Grau-Pujol B, Evlampidou I, Escola V, Goñi-Irigoyen F, Kuckelkorn J, et al. (2021). Chemical and in vitro bioanalytical assessment of drinking water quality in Manhiça, Mozambique. J Expo Sci Environ Epidemiol. 31(2):276–88. https://doi.org/10.1038/s41370-020-00282-5 PMID:33414480

Villanueva F, Lara S, Notario A, Amo-Salas M, Cabañas B (2022). Formaldehyde, acrolein and other carbonyls in dwellings of university students. Levels and source characterization. Chemosphere. 288(Pt 1):132429. https://doi.org/10.1016/j.chemosphere.2021.132429 PMID:34606894

Villeneuve DL, Blackwell BR, Cavallin JE, Collins J, Hoang JX, Hofer RN, et al. (2023). Verification of in vivo estrogenic activity for four per- and polyfluoroalkyl substances (PFAS) identified as estrogen receptor agonists via new approach methodologies. Environ Sci Technol. 57(9):3794–803. https://doi.org/10.1021/acs.est.2c09315 PMID:36800546

Vindas R, Ortiz F, Ramírez V, Cuenca P (2004). [Genotoxicity of three pesticides used in Costa Rican banana plantations]. Rev Biol Trop. 52(3):601–9. https://revistas.ucr.ac.cr/index.php/rbt/article/view/15343 PMID:17361554 [Spanish]

Viscidi RP, Rollison DE, Sondak VK, Silver B, Messina JL, Giuliano AR, et al. (2011). Age-specific seroprevalence of Merkel cell polyomavirus, BK virus, and JC virus. Clin Vaccine Immunol. 18(10):1737–43. https://doi.org/10.1128/CVI.05175-11 PMID:21880855

Viswalingam A, Caldwell J (1997). Cinnamyl anthranilate causes coinduction of hepatic microsomal and peroxisomal enzymes in mouse but not rat. Toxicol Appl Pharmacol. 142(2):338–47. https://doi.org/10.1006/taap.1996.8043 PMID:9070357

Viitanen AK, Uuksulainen S, Koivisto AJ, Hämeri K, Kauppinen T (2017). Workplace measurements of ultrafine particles-a literature review. Ann Work Expo Health. 61(7):749–58. https://doi.org/10.1093/annweh/wxx049 PMID:28810681

Vlaanderen J, Pronk A, Rothman N, Hildesheim A, Silverman D, Hosgood HD, et al. (2017). A cross-sectional study of changes in markers of immunological effects and lung health due to exposure to multi-walled carbon nanotubes. Nanotoxicology. 11(3):395–404. https://doi.org/10.1080/17435390.2017.1308031 PMID:28301273

Vogel N, Frederiksen H, Lange R, Jørgensen N, Koch HM, Weber T, et al. (2023a). Urinary excretion of phthalates and the substitutes DINCH and DEHTP in Danish young men and German young adults between 2000 and 2017 – a time trend analysis. Int J Hyg Environ Health. 248:114080. https://doi.org/10.1016/j.ijheh.2022.114080 PMID:36657282

Vogel N, Schmidt P, Lange R, Gerofke A, Sakhi AK, Haug LS, et al. (2023b). Current exposure to phthalates and DINCH in European children and adolescents – results from the HBM4EU aligned studies 2014 to 2021. Int J Hyg Environ Health. 249:114101. https://doi.org/10.1016/j.ijheh.2022.114101 PMID:36805185

Von Behren J, Goldberg D, Hurley S, Clague DeHart J, Wang SS, Reynolds P (2023). Prospective analysis of sleep characteristics, chronotype, and risk of breast cancer in the California teachers study. Cancer Causes Control. 35(4):597–604. https://doi.org/10.1007/s10552-023-01817-5 PMID:37940783

von Bülow V, Gindner S, Baier A, Hehr L, Buss N, Russ L, et al. (2022). Metabolic reprogramming of hepatocytes by *Schistosoma mansoni* eggs. JHEP Rep Innov Hepatol. 5(2):100625. https://doi.org/10.1016/j.jhepr.2022.100625 PMID:36590323

von Bülow V, Schneider M, Dreizler D, Russ L, Baier A, Buss N, et al. (2024). *Schistosoma mansoni*-induced oxidative stress triggers hepatocellular proliferation. Cell Mol Gastroenterol Hepatol. 17(1):107–17. https://doi.org/10.1016/j.jcmgh.2023.08.014 PMID:37696392

von Ehrenstein OS, Heck JE, Park AS, Cockburn M, Escobedo L, Ritz B (2016). In utero and early-life exposure to ambient air toxics and childhood brain tumors: a population-based case–control study in California, USA. Environ Health Perspect. 124(7):1093–9. https://doi.org/10.1289/ehp.1408582 PMID:26505805

Von Tungeln LS, Doerge DR, Gamboa da Costa G, Matilde Marques M, Witt WM, Koturbash I, et al. (2012). Tumorigenicity of acrylamide and its metabolite glycidamide in the neonatal mouse bioassay. Int J Cancer. 131(9):2008–15. https://doi.org/10.1002/ijc.27493 PMID:22336951

Voss KA, Riley RT (2013). Fumonisin toxicity and mechanism of action: overview and current perspectives. Food Saf (Tokyo). 1(1):2013006. https://doi.org/10.14252/foodsafetyfscj.2013006

Voss KA, Riley RT, Norred WP, Bacon CW, Meredith FI, Howard PC, et al. (2001). An overview of rodent toxicities: liver and kidney effects of fumonisins and *Fusarium moniliforme.* Environ Health Perspect. 109(Suppl 2) suppl 2:259–66. https://doi.org/10.1289/ehp.01109s2259 PMID:11359694

Vrijheid M, Armstrong BK, Bédard D, Brown J, Deltour I, Iavarone I, et al. (2009b). Recall bias in the assessment of exposure to mobile phones. J Expo Sci Environ Epidemiol. 19(4):369–81. https://doi.org/10.1038/jes.2008.27 PMID:18493271

Vrijheid M, Richardson L, Armstrong BK, Auvinen A, Berg G, Carroll M, et al. (2009a). Quantifying the impact of selection bias caused by nonparticipation in a case–control study of mobile phone use. Ann Epidemiol. 19(1):33–41. https://doi.org/10.1016/j.annepidem.2008.10.006 PMID:19064187

Waalkes MP, Liu J, Kasprzak KS, Diwan BA (2006). Hypersusceptibility to cisplatin carcinogenicity in metallothionein-I/II double knockout mice: production of hepatocellular carcinoma at clinically relevant doses. Int J Cancer. 119(1):28–32. https://doi.org/10.1002/ijc.21245 PMID:16432836

Wackers P, Dollé MET, van Oostrom CTM, van Kerkhof LWM (2023). Exploration of genome-wide DNA methylation profiles in night shift workers. Epigenetics. 18(1):1. https://doi.org/10.1080/15592294.2022.2152637 PMID:36457290

Waidyanatha S, Black SR, Witt KL, Fennell TR, Swartz C, Recio L, et al. (2022). The common indoor air pollutant α-pinene is metabolised to a genotoxic metabolite α-pinene oxide. Xenobiotica. 52(3):301–11. https://doi.org/10.1080/00498254.2022.2070047https://doi.org/10.1080/00498254.2022.2070047 PMID:35473450

Waits A, Chen HC, Kuo PL, Wang CW, Huang HB, Chang WH, et al. (2020). Urinary phthalate metabolites are associated with biomarkers of DNA damage and lipid peroxidation in pregnant women – Tainan Birth Cohort Study (TBCS). Environ Res. 188:109863. https://doi.org/10.1016/j.envres.2020.109863https://doi.org/10.1016/j.envres.2020.109863 PMID:32846647

Wakamatsu N, Collins JB, Parker JS, Tessema M, Clayton NP, Ton TV, et al. (2008). Gene expression studies demonstrate that the K-ras/Erk MAP kinase signal transduction pathway and other novel pathways contribute to

the pathogenesis of cumene-induced lung tumors. Toxicol Pathol. 36(5):743–52. https://doi.org/10.1177/0192623308320801https://doi.org/10.1177/0192623308320801 PMID:18648096

Walker WH 2nd, Bumgarner JR, Walton JC, Liu JA, Meléndez-Fernández OH, Nelson RJ, et al. (2020). Light pollution and cancer. Int J Mol Sci. 21(24):9360. https://doi.org/10.3390/ijms21249360 PMID:33302582

Walker WH 2nd, Kvadas RM, May LE, Liu JA, Bumgarner JR, Walton JC, et al. (2021). Artificial light at night reduces anxiety-like behavior in female mice with exacerbated mammary tumor growth. Cancers (Basel). 13(19):4860. https://doi.org/10.3390/cancers13194860 PMID:34638343

Wan X, Zhu F, Zhuang P, Liu X, Zhang L, Jia W, et al. (2022). Associations of hemoglobin adducts of acrylamide and glycidamide with prevalent metabolic syndrome in a nationwide population-based study. J Agric Food Chem. 70(28):8755–66. https://doi.org/10.1021/acs.jafc.2c03016 PMID:35796657

Wang C, Gu Y, Zhou J, Zang J, Ling X, Li H, et al. (2022d). Leukocyte telomere length in children born following blastocyst-stage embryo transfer. Nat Med. 28(12):2646–53. https://doi.org/10.1038/s41591-022-02108-3 PMID:36522605

Wang H, Meng Z, Liu F, Zhou L, Su M, Meng Y, et al. (2020a). Characterization of boscalid-induced oxidative stress and neurodevelopmental toxicity in zebrafish embryos. Chemosphere. 238:124753. https://doi.org/10.1016/j.chemosphere.2019.124753 PMID:31545217

Wang H, Wang J, Cao Y, Chen J, Deng Q, Chen Y, et al. (2022a). Combined exposure to 33 trace elements and associations with the risk of oral cancer: a large-scale case-control study. Front Nutr. 9:913357. https://doi.org/10.3389/fnut.2022.913357 PMID:35873417

Wang H, Wei H, Ma J, Luo X (2000). The fumonisin B1 content in corn from North China, a high-risk area of esophageal cancer. J Environ Pathol Toxicol Oncol. 19(1–2):139–41. PMID:10905519

Wang J, Aldabagh B, Yu J, Arron ST (2014). Role of human papillomavirus in cutaneous squamous cell carcinoma: a meta-analysis. J Am Acad Dermatol. 70(4):621–9. https://doi.org/10.1016/j.jaad.2014.01.857 PMID:24629358

Wang J, Guo G, Li A, Cai WQ, Wang X (2021a). Challenges of phototherapy for neonatal hyperbilirubinemia (Review). Exp Ther Med. 21(3):231. https://doi.org/10.3892/etm.2021.9662 PMID:33613704

Wang J, Li J, Cheng D, Zhang K, Liu W, Xue Q, et al. (2023g). miR-132–3p promotes heat stimulation-induced esophageal squamous cell carcinoma tumorigenesis by targeting KCNK2. Mol Carcinog. 62(5):583–97. https://doi.org/10.1002/mc.23504 PMID:37014157

Wang JS, Busby WF Jr (1993). Induction of lung and liver tumors by fluoranthene in a preweanling CD-1 mouse bioassay. Carcinogenesis. 14(9):1871–4. https://doi.org/10.1093/carcin/14.9.1871 PMID:8403212

Wang JS, Busby WF, Wogan GN (1995). Tissue distribution of DNA adducts in pre-weanling BLU:Ha mice treated with a tumorigenic dose of fluoranthene. Cancer Lett. 92(1):9–19. https://doi.org/10.1016/0304-3835(95)03751-H PMID:7757965

Wang L, Asimakopoulos AG, Kannan K (2015). Accumulation of 19 environmental phenolic and xenobiotic heterocyclic aromatic compounds in human adipose tissue. Environ Int. 78:45–50. https://doi.org/10.1016/j.envint.2015.02.015 PMID:25749637

Wang L, Deng Q, Hu H, Liu M, Gong Z, Zhang S, et al. (2019a). Glyphosate induces benign monoclonal gammopathy and promotes multiple myeloma progression in mice. J Hematol Oncol. 12(1):70. https://doi.org/10.1186/s13045-019-0767-9 PMID:31277689

Wang L, Wang H, Wei S, Huang X, Yu C, Meng Q, et al. (2023b). *Toxoplasma gondii* induces MLTC-1 apoptosis via ERS pathway. Exp Parasitol. 244:108429. https://doi.org/10.1016/j.exppara.2022.108429 PMID:36403802

Wang L, Wang T, Gu JQ, Su HB (2018a). Volatile anesthetic sevoflurane suppresses lung cancer cells and miRNA interference in lung cancer cells. OncoTargets Ther. 11:5689–93. https://doi.org/10.2147/OTT.S171672 PMID:30254461

Wang L, Yan J, Hardy W, Mosley C, Wang S, Yu H (2005). Light-induced mutagenicity in *Salmonella* TA102 and genotoxicity/cytotoxicity in human T-cells by 3,3′-dichlorobenzidine: a chemical used in the manufacture of dyes and pigments and in tattoo inks. Toxicology. 207(3):411–8. https://doi.org/10.1016/j.tox.2004.10.010 PMID:15664269

Wang M, Yu N, Chen L, Villalta PW, Hochalter JB, Hecht SS (2006). Identification of an acetaldehyde adduct in human liver DNA and quantitation as N2-ethyldeoxyguanosine. Chem Res Toxicol. 19(2):319–24. https://doi.org/10.1021/tx0502948 PMID:16485909

Wang M, Yu Y, Tang Y, Pan C, Fei Q, Hu Z, et al. (2023h). 2,4-dihydroxybenzophenone and −2 UV-filters potently inhibit human, rat, and mouse gonadal 3β-hydroxysteroid dehydrogenases: structure–activity relationship and in silico docking analysis. J Steroid Biochem Mol Biol. 230:106279. https://doi.org/10.1016/j.jsbmb.2023.106279 PMID:36871834

Wang N, Liu F, Chen Y, Xie M, Gao B, Qiu Y, et al. (2023e). The role of rare earth elements and dietary intake in tongue cancer: a mediation analysis in southeast China. Front Public Health. 11:1058013. https://doi.org/10.3389/fpubh.2023.1058013 PMID:37181707

Wang R, Yang JF, Senay TE, Liu W, You J (2023a). Characterization of the impact of Merkel cell polyomavirus-induced interferon signalling on viral infection. J Virol. 97(4):e0190722. https://doi.org/10.1128/jvi.01907-22 PMID:36946735

Wang R, Zhang Y, Lan Q, Holford TR, Leaderer B, Zahm SH, et al. (2009). Occupational exposure to solvents and risk of non-Hodgkin lymphoma in Connecticut women. Am J Epidemiol. 169(2):176–85. https://doi.org/10.1093/aje/kwn300 PMID:19056833

Wang SK, Liu S, Yang LG, Shi RF, Sun GJ (2013). Effect of fumonisin B_1 on the cell cycle of normal human liver cells. Mol Med Rep. 7(6):1970–6. https://doi.org/10.3892/mmr.2013.1447 PMID:23625282

Wang SS, Deapen D, Voutsinas J, Lacey JV Jr, Lu Y, Ma H, et al. (2016). Breast implants and anaplastic large cell lymphomas among females in the California Teachers Study cohort. Br J Haematol. 174(3):480–3. https://doi.org/10.1111/bjh.13779 PMID:26456010

Wang T, Meng Y, Tu Y, Zhang G, Wang K, Gong S, et al. (2023d). Associations between DNA methylation and genotoxicity among lead-exposed workers in China. Environ Pollut. 316(Pt 1):120528. https://doi.org/10.1016/j.envpol.2022.120528 PMID:36341824

Wang W, Mu M, Zou Y, Li B, Cao H, Hu D, et al. (2022c). Inflammation and fibrosis in the coal dust-exposed lung described by confocal Raman spectroscopy. PeerJ. 10:e13632. https://doi.org/10.7717/peerj.13632 PMID:35765591

Wang W, Wu N, Zu YG, Fu YJ (2008). Antioxidative activity of *Rosmarinus officinalis* L. essential oil compared to its main components. Food Chem. 108(3):1019–22. https://doi.org/10.1016/j.foodchem.2007.11.046 PMID:26065766

Wang WQ, Duan HX, Pei ZT, Xu RR, Qin ZT, Zhu GC, et al. (2018c). Evaluation by the Ames assay of the mutagenicity of UV filters using benzophenone and 2,4-dihydroxybenzophenone. Int J Environ Res Public Health. 15(9):1907. https://doi.org/10.3390/ijerph15091907https://doi.org/10.3390/ijerph15091907 PMID:30200545

Wang X, Anadón A, Wu Q, Qiao F, Ares I, Martínez-Larrañaga MR, et al. (2018b). Mechanism of neonicotinoid toxicity: impact on oxidative stress and metabolism. Annu Rev Pharmacol Toxicol. 58(1):471–507. https://doi.org/10.1146/annurev-pharmtox-010617-052429 PMID:28968193

Wang X, Chen Y (2009). Determination of aromatic amines in food products and composite food packaging bags by capillary electrophoresis coupled with transient isotachophoretic stacking. J Chromatogr A. 1216(43):7324–8. https://doi.org/10.1016/j.chroma.2009.05.089 PMID:19524248

Wang X, Gao X, He B, Zhu J, Lou H, Hu Q, et al. (2017a). Cis-bifenthrin induces immunotoxicity in adolescent male C57BL/6 mice. Environ Toxicol. 32(7):1849–56. https://doi.org/10.1002/tox.22407 PMID:28251819

Wang X, Tang M, Ge J, Jiang W, Li Z, Xiao Q, et al. (2022b). Effects of intrauterine and lactational exposure to lanthanum nitrate on BALB/c offspring mice: developmental immunotoxicity and self-recovery. Toxicol Lett. 362:17–25. https://doi.org/10.1016/j.toxlet.2022.01.013 PMID:35091016

Wang X, Zhang C, Bao N (2023j). Molecular mechanism of palmitic acid and its derivatives in tumor progression. Front Oncol. 13:1224125. https://doi.org/10.3389/fonc.2023.1224125 PMID:37637038

Wang X, Zhu J, Kong B, He B, Wei L, Jin Y, et al. (2019c). $C_{9–13}$ chlorinated paraffins cause immunomodulatory effects in adult C57BL/6 mice. Sci Total Environ. 675:110–21. https://doi.org/10.1016/j.scitotenv.2019.04.199https://doi.org/10.1016/j.scitotenv.2019.04.199 PMID:31026635

Wang XR, Yu IT, Qiu H, Wang MZ, Lan YJ, Tse LY, et al. (2012). Cancer mortality among Chinese chrysotile asbestos textile workers. Lung Cancer. 75(2):151–5. https://doi.org/10.1016/j.lungcan.2011.06.013 PMID:21798615

Wang Y, Ronckers CM, van Leeuwen FE, Moskowitz CS, Leisenring W, Armstrong GT, et al.; International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer (2023f). Subsequent female breast cancer risk associated with anthracycline chemotherapy for childhood cancer. Nat Med. 29(9):2268–77. https://doi.org/10.1038/s41591-023-02514-1 PMID:37696934

Wang Y, Song H, Li L, Ma J, Yu F (2023i). Generation characteristics and spreading risk of VOCs released from a biological fermentation pharmaceutical factory. Environ Sci Process Impacts. 25(3):507–18. https://doi.org/10.1039/D2EM00378C PMID:36606575

Wang YW, Shu CM, Duh YS, Kao CS (2001). Thermal runaway hazards of cumene hydroperoxide with contaminants. Ind Eng Chem Res. 40(4):1125–32. https://doi.org/10.1021/ie990900s

Wang YX, Liu C, Shen Y, Wang Q, Pan A, Yang P, et al. (2019b). Urinary levels of bisphenol A, F and S and markers of oxidative stress among healthy adult men: variability and association analysis. Environ Int. 123:301–9. https://doi.org/10.1016/j.envint.2018.11.071 PMID:30553203

Wang Z, Cui Y, Zhang Y, Wang X, Li J, Li J, et al. (2023c). Twelve-week treadmill endurance training in mice is associated with upregulation of interleukin-15 and natural killer cell activation and increases apoptosis rate in Hepa1–6 cell-derived mouse hepatomas. Braz J Med Biol Res. 56:e12296. https://doi.org/10.1590/1414-431x2023e12296 PMID:37585912

Wang Z, Li X, Klaunig JE (2017b). Investigation of the mechanism of triclosan induced mouse liver tumors. Regul Toxicol Pharmacol. 86:137–47. https://doi.org/10.1016/j.yrtph.2017.03.001 PMID:28267557

Ward EM, Schulte PA, Straif K, Hopf NB, Caldwell JC, Carreón T, et al. (2010a). Research recommendations for selected IARC-classified agents. Environ Health Perspect. 118(10):1355–62. https://doi.org/10.1289/ehp.0901828 PMID:20562050

Ward MH, Jones RR, Brender JD, de Kok TM, Weyer PJ, Nolan BT, et al. (2018). Drinking water nitrate and human health: an updated review. Int J Environ Res Public Health. 15(7):1557. https://doi.org/10.3390/ijerph15071557https://doi.org/10.3390/ijerph15071557 PMID:30041450

Ward MH, Kilfoy BA, Weyer PJ, Anderson KE, Folsom AR, Cerhan JR (2010b). Nitrate intake and the risk of thyroid cancer and thyroid disease. Epidemiology. 21(3):389–95. https://doi.org/10.1097/EDE.0b013e3181d6201dhttps://doi.org/10.1097/EDE.0b013e3181d6201d PMID:20335813

Ward T, Lange T (2010). The impact of wood smoke on ambient $PM_{2.5}$ in northern Rocky Mountain valley communities. Environ Pollut. 158(3):723–9. https://doi.org/10.1016/j.envpol.2009.10.016 PMID:19897293

Warden H, Richardson H, Richardson L, Siemiatycki J, Ho V (2018). Associations between occupational exposure to benzene, toluene and xylene and risk of lung cancer in Montréal. Occup Environ Med. 75(10):696–702. https://doi.org/10.1136/oemed-2017-104987 PMID:29764994

Waris S, Patel A, Ali A, Mahmood R (2020). Acetaldehyde-induced oxidative modifications and morphological changes in isolated human erythrocytes: an in vitro study. Environ Sci Pollut Res Int. 27(14):16268–81. https://doi.org/10.1007/s11356-020-08044-4 PMID:32124282

Warnasuriya GD, Elcombe BM, Foster JR, Elcombe CR (2010). A mechanism for the induction of renal tumours in male Fischer 344 rats by short-chain chlorinated paraffins. Arch Toxicol. 84(3):233–43. https://doi.org/10.1007/s00204-009-0489-9https://doi.org/10.1007/s00204-009-0489-9 PMID:20069279

Warner FM, Darvishian M, Boyle T, Brooks-Wilson AR, Connors JM, Lai AS, et al. (2020). Tattoos and hematologic malignancies in British Columbia, Canada. Cancer Epidemiol Biomarkers Prev. 29(10):2093–5. https://doi.org/10.1158/1055-9965.EPI-20-0515 PMID:32699076

Wastesson JW, Martikainen JE, Zoëga H, Schmidt M, Karlstad Ø, Pottegård A (2018). Trends in use of paracetamol in the Nordic countries. Basic Clin Pharmacol Toxicol. 123(3):301–7. https://doi.org/10.1111/bcpt.13003 PMID:29527817

Waszynski E (1977). Nonneoplastic and neoplastic changes in the kidneys and other organs in rodents fed lead acetate and sulfathiazole chronically. Pathol Pol. 28:101–111.

Watson ATD, Johnson VJ, Luster MI, Burleson GR, Fallacara DM, Sparrow BR, et al. (2021). Immunotoxicity studies of sulfolane following developmental exposure in Hsd:Sprague Dawley SD rats and adult exposure in B6C3F$_1$/N mice. J Immunotoxicol. 18(1):1–12. https://doi.org/10.1080/1547691X.2020.1869355 PMID:34357831

Watson IR, Takahashi K, Futreal PA, Chin L (2013). Emerging patterns of somatic mutations in cancer. Nat Rev Genet. 14(10):703–18. https://doi.org/10.1038/nrg3539 PMID:24022702

Weber GL, Steenwyk RC, Nelson SD, Pearson PG (1995). Identification of N-acetylcysteine conjugates of 1,2-dibromo-3-chloropropane: evidence for cytochrome P450 and glutathione mediated bioactivation pathways. Chem Res Toxicol. 8(4):560–73. https://doi.org/10.1021/tx00046a010 PMID:7548736

Wei F, Mortimer M, Cheng H, Sang N, Guo L-H (2021b). Parabens as chemicals of emerging concern in the environment and humans: a review. Sci Total Environ. 778:146150. https://doi.org/10.1016/j.scitotenv.2021.146150 PMID:34030374

Wei H, Liang F, Meng G, Nie Z, Zhou R, Cheng W, et al. (2016). Redox/methylation mediated abnormal DNA methylation as regulators of ambient fine particulate matter-induced neurodevelopment related impairment in human neuronal cells. Sci Rep. 6(1):33402. https://doi.org/10.1038/srep33402 PMID:27624276

Wei TT, Chandy M, Nishiga M, Zhang A, Kumar KK, Thomas D, et al. (2022). Cannabinoid receptor 1 antagonist genistein attenuates marijuana-induced vascular inflammation. Cell. 185(10):1676–1693.e23. https://doi.org/10.1016/j.cell.2022.04.005 PMID:35489334

Wei W, Wu BJ, Wu Y, Tong ZT, Zhong F, Hu CY (2021a). Association between long-term ambient air pollution exposure and the risk of breast cancer: a systematic review and meta-analysis. Environ Sci Pollut Res Int. 28(44):63278–96. https://doi.org/10.1007/s11356-021-14903-5 PMID:34227005

Wei Y, Zhu J (2016a). Associations between urinary concentrations of 2,5-dichlorophenol and metabolic syndrome among non-diabetic adults. Environ Sci Pollut Res Int. 23(1):581–8. https://doi.org/10.1007/s11356-015-5291-z PMID:26330318

Wei Y, Zhu J (2016b). Para-dichlorobenzene exposure is associated with thyroid dysfunction in US adolescents. J Pediatr. 177:238–43. https://doi.org/10.1016/j.jpeds.2016.06.085 PMID:27476635

Wei YY, Wang HR, Fan YM, Gu JH, Zhang XY, Gong XH, et al. (2023). Acute liver injury induced by carbon tetrachloride reversal by Gandankang aqueous extracts through nuclear factor erythroid 2-related factor 2 signalling pathway. Ecotoxicol Environ Saf. 251:114527. https://doi.org/10.1016/j.ecoenv.2023.114527 PMID:36628874

Weis LM, Rummel AM, Masten SJ, Trosko JE, Upham BL (1998). Bay or baylike regions of polycyclic aromatic hydrocarbons were potent inhibitors of gap junctional intercellular communication. Environ Health Perspect. 106(1):17–22. https://doi.org/10.1289/ehp.9810617 PMID:9417772

Weissenborn SJ, Nindl I, Purdie K, Harwood C, Proby C, Breuer J, et al. (2005). Human papillomavirus-DNA loads in actinic keratoses exceed those in non-melanoma skin cancers. J Invest Dermatol. 125(1):93–7. https://doi.org/10.1111/j.0022-202X.2005.23733.x PMID:15982308

Weller M, Clemence D, Lau A, Rawlings M, Robertson A, Sankaran B (2024). An assessment of worker exposure to respirable dust and crystalline silica in workshops fabricating engineered stone. Ann Work Expo Health. 68(2):170–9. https://doi.org/10.1093/annweh/wxad072 PMID:38096573

Wen H, Lin X, Sun D (2022). The association between different hormone replacement therapy use and the incidence of lung cancer: a systematic review and meta-analysis. J Thorac Dis. 14(2):381–95. https://doi.org/10.21037/jtd-22-48 PMID:35280481

Wen J, Geng S, Zhu L, Yao X, Zhou Y, Shen F, et al. (2023). Urinary antibiotic concentrations in preschool children from eastern China and health risk assessment. Environ Sci Pollut Res Int. 30(34):82547–59. https://doi.org/10.1007/s11356-023-28209-1 PMID:37326733

Wen L-P, Madani K, Fahrni JA, Duncan SR, Rosen GD (1997). Dexamethasone inhibits lung epithelial cell apoptosis induced by IFN-γ and Fas. Am J Physiol. 273(5):L921–9. PMID:9374718

Wendeu-Foyet MG, Cénée S, Koudou Y, Trétarre B, Rébillard X, Cancel-Tassin G, et al. (2020). Circadian genes polymorphisms, night work and prostate cancer risk: findings from the EPICAP study. Int J Cancer. 147(11):3119–29. https://doi.org/10.1002/ijc.33139 PMID:32506468

Weng JR, Tsai CH, Kulp SK, Chen CS (2008). Indole-3-carbinol as a chemopreventive and anti-cancer agent. Cancer Lett. 262(2):153–63. https://doi.org/10.1016/j.canlet.2008.01.033 PMID:18314259

Weng SS, Huang YT, Huang YT, Li YP, Chien LY (2022). Assisted reproductive technology and risk of childhood cancers. JAMA Netw Open. 5(8):e2230157. https://doi.org/10.1001/jamanetworkopen.2022.30157 PMID:36044210

Wentzensen N, Poole EM, Trabert B, White E, Arslan AA, Patel AV, et al. (2016). Ovarian cancer risk factors by histologic subtype: an analysis from the ovarian cancer cohort consortium. J Clin Oncol. 34(24):2888–98. https://doi.org/10.1200/JCO.2016.66.8178 PMID:27325851

Wesseling C, Ahlbom A, Antich D, Rodriguez AC, Castro R (1996). Cancer in banana plantation workers in Costa Rica. Int J Epidemiol. 25(6):1125–31. https://doi.org/10.1093/ije/25.6.1125 PMID:9027515

Westendorf J, Groth G, Steinheider G, Marquardt H (1985). Formation of DNA-adducts and induction of DNA-crosslinks and chromosomal aberrations by the new potent anthracycline antitumor antibiotics: morpholinodaunomycin, cyanomorpholinodaunomycin and cyanomorpholinoadriamycin. Cell Biol Toxicol. 1(2):87–101. https://doi.org/10.1007/BF00717794 PMID:3917129

Westendorf J, Mohr U, Marquardt H (1987). Induction of malignant transformation in vitro and mammary tumors in rats by two new potent anthracycline antitumor antibiotics, morpholinodaunomycin and cyanomorpholinoadriamycin. Cell Biol Toxicol. 3(1):17–21. https://doi.org/10.1007/BF00117822 PMID:3507246

Westerlund J, Graff P, Bryngelsson IL, Westberg H, Eriksson K, Löfstedt H (2015). Occupational exposure to trichloramine and trihalomethanes in Swedish indoor swimming pools: evaluation of personal and stationary monitoring. Ann Occup Hyg. 59(8):1074–84. https://doi.org/10.1093/annhyg/mev045 PMID:26155991

Westra S, Goldberg MS, Labrèche F, Baumgartner J, Ho V (2023). The association between the incidence of postmenopausal breast cancer and occupational exposure to selected organic solvents, Montreal, Canada, 2008–2011. Am J Ind Med. 66(11):911–27. https://doi.org/10.1002/ajim.23525 PMID:37565624

White AJ, Bradshaw PT, Hamra GB (2018). Air pollution and breast cancer: a review. Curr Epidemiol Rep. 5(2):92–100. https://doi.org/10.1007/s40471-018-0143-2 PMID:30271702

White AJ, Gregoire AM, Taylor KW, Eberle C, Gaston S, O'Brien KM, et al. (2021a). Adolescent use of hair dyes, straighteners and perms in relation to breast cancer risk. Int J Cancer. 148(9):2255–63. https://doi.org/10.1002/ijc.33413 PMID:33252833

White AJ, Sandler DP, Gaston SA, Jackson CL, O'Brien KM (2021b). Use of hair products in relation to ovarian cancer risk. Carcinogenesis. 42(9):1189–95. https://doi.org/10.1093/carcin/bgab056 PMID:34173819

White AJ, Weinberg CR, Park YM, D'Aloisio AA, Vogtmann E, Nichols HB, et al. (2017). Sleep characteristics, light at night and breast cancer risk in a prospective cohort. Int J Cancer. 141(11):2204–14. https://doi.org/10.1002/ijc.30920 PMID:28791684

Whittaker P, Clarke JJ, San RH, Begley TH, Dunkel VC (2008). Evaluation of the butter flavoring chemical diacetyl and a fluorochemical paper additive for mutagenicity and toxicity using the mammalian cell gene mutation assay in L5178Y mouse lymphoma cells. Food Chem Toxicol. 46(8):2928–33. https://doi.org/10.1016/j.fct.2008.06.001https://doi.org/10.1016/j.fct.2008.06.001 PMID:18585428

WHO (1984). Tetrachloroethylene. Environmental health criteria 31. International Programme on Chemical Safety. Geneva, Switzerland: World Health Organization. Available from: https://www.inchem.org/documents/ehc/ehc/ehc31.htm, accessed September 2024.

WHO (1987). Diaminotoluenes. Environmental health criteria 74. International Programme On Chemical Safety. Geneva, Switzerland: World Health Organization. Available from: https://www.inchem.org/documents/ehc/ehc/ehc74.htm, accessed September 2024.

WHO (1991). Selenium. Environmental health criteria 58. International Programme on Chemical Safety. Geneva, Switzerland: World Health Organization. Available from: https://www.inchem.org/documents/ehc/ehc/ehc58.htm, accessed September 2024.

WHO (1992). Diethylhexyl phthalate. Environmental health criteria 131. International Programme On Chemical Safety. Geneva, Switzerland: World Health Organization. Available from: https://www.inchem.org/documents/ehc/ehc/ehc131.htm, accessed September 2024.

WHO (1993). Guidelines for drinking-water quality. 2nd edition: volume 1 – recommendations. Geneva, Switzerland: Water, Sanitation, Hygiene and Health (WSH), World Health Organization. Available from: https://www.who.int/publications/i/item/924154460O, accessed June 2024.

WHO (1995a) Cresols. Environmental health criteria 168. International Programme on Chemical Safety. Geneva, Switzerland: World Health Organization. Available from: https://iris.who.int/bitstream/handle/10665/41245/9241571681-eng.pdf?sequence=1, accessed March 2024.

WHO (1995b). Acetaldehyde. Environmental health criteria 167. International Programme on Chemical Safety. Geneva, Switzerland: World Health Organization. Available from: https://www.inchem.org/documents/ehc/ehc/ehc167.htm, accessed March 2024.

WHO (1997). Methanol. Environmental health criteria 196. International Programme on Chemical Safety. Geneva, Switzerland: World Health Organization. Available from: https://www.inchem.org/documents/ehc/ehc/ehc196.htm, accessed December 2023.

WHO (1999a). Butyl benzyl phthalate. Concise international chemical assessment document 17. Geneva, Switzerland: World Health Organization. Available from: https://www.inchem.org/documents/cicads/cicads/cicad17.htm, accessed September 2024.

WHO (1999b). Carbon tetrachloride. Environmental health criteria 208. International Programme of Chemical Safety. Geneva, Switzerland: World Health Organization. Available from: https://www.inchem.org/documents/ehc/ehc/ehc208.htm, accessed September 2024.

WHO (2000). Fumonisin B1. Environmental health criteria 219. Geneva, Switzerland: World Health Organization. Available from: https://iris.who.int/bitstream/handle/10665/42269/WHO_EHC_219.pdf, accessed September 2024.

WHO (2002a). Carbon disulfide. Concise international chemical assessment document 46. Geneva, Switzerland: World Health Organization. Available from: https://www.inchem.org/documents/cicads/cicads/cicad46.htm, accessed March 2024.

WHO (2002b). Formaldehyde. Concise international chemical assessment document 40. Geneva, Switzerland: World Health Organization. Available from: https://www.inchem.org/documents/cicads/cicads/cicad40.htm, accessed June 2024.

WHO (2003). Toxicological evaluation of certain veterinary drug residues in food. World Health Organization food additives series: 51. Prepared by the sixtieth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JEFCA). Available from: https://iris.who.int/bitstream/handle/10665/42800/924166051X.pdf?sequence=1, accessed January 2024.

WHO (2004). Brominated acetic acids in drinking-water. Background document for development of WHO guidelines for drinking-water quality. Report WHO/SDE/WSH/03.04/79. Geneva, Switzerland: World Health Organization. Available from: https://cdn.who.int/media/docs/default-source/wash-documents/wash-chemicals/brominatedaceticacids.pdf?sfvrsn=5307a55_4, accessed September 2024.

WHO (2005). Bromate in drinking-water. Background document for development of WHO Guidelines for drinking-water quality. Report WHO/SDE/WSH/05.08/78. Geneva, Switzerland: World Health Organization. Available from: https://cdn.who.int/media/docs/default-source/wash-documents/wash-chemicals/bromate-backgound.pdf?sfvrsn=a676385a_4, accessed September 2020.

WHO (2007). Electromagnetic fields and public health. Exposure to extremely low frequency fields. Geneva, Switzerland: World Health Organization. https://www.who.int/teams/environment-climate-change-and-health/radiation-and-health/non-ionizing/exposure-to-extremely-low-frequency-field, accessed February 2024.

WHO (2009a). Guidelines for drinking-water quality, fourth edition. Aluminium. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/docs/default-source/wash-documents/wash-chemicals/aluminium-chemical-fact-sheet.pdf?sfvrsn=3dd7e5b3_4, accessed June 2024.

WHO (2009b). WHO handbook on indoor radon: a public health perspective. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/publications/i/item/9789241547673, accessed September 2024.

WHO (2011). Toxicological and health aspects of bisphenol A. Joint FAO/WHO expert meeting report. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/publications/i/item/toxicological-and-health-aspects-of-bisphenol-a, accessed September 2024.

WHO (2016). Nitrate and nitrite in drinking-water. Background document for development of WHO guidelines for drinking-water quality. Report WHO/FWC/WSH/16.52. Geneva, Switzerland: World Health Organization. Available from: https://cdn.who.int/media/docs/default-source/wash-documents/wash-chemicals/nitrate-nitrite-background-jan17.pdf?sfvrsn=1c1e1502_4, accessed March 2024.

WHO (2018). Elimination of asbestos related diseases. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/news-room/fact-sheets/detail/asbestos-elimination-of-asbestos-related-diseases, accessed September 2024.

WHO (2019). The WHO recommended classification of pesticides by hazard and guidelines to classification 2019. Geneva, Switzerland: World Health Organization. Available from: https://iris.who.int/bitstream/handle/10665/332193/9789240005662-eng.pdf?ua=1, accessed June 2024.

WHO (2020a). Transmission of SARS-CoV-2: implications for infection prevention precautions. Scientific brief. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions, accessed May 2024.

WHO (2020b). Chemical safety: pesticides. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/news-room/questions-and-answers/item/chemical-safety-pesticides, accessed March 2024.

WHO (2021a). Obesity and overweight. Fact sheets. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight, accessed September 2024.

WHO (2021b). WHO global air quality guidelines: particulate matter ($PM_{2.5}$ and PM_{10}), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneva, Switzerland: World Health Organization. Available from: https://iris.who.int/bitstream/handle/10665/345329/9789240034228-eng.pdf, accessed September 2024.

WHO (2021c). Report of the informal global WHO consultation with policymakers in dental public health. Report Geneva, Switzerland: World Health Organization. Available from: https://www.unep.org/globalmercurypartnership/resources/report/report-informal-global-who-consultation-policymakers-dental-public-health-2021, accessed March 2024.

WHO (2021d). Piperonyl butoxide (CAS No. 51-03-6). A synergist in insecticide-treated nets. Generic risk assessment – human health. Geneva, Switzerland: World Health Organization. Available from: https://extranet.who.int/prequal/sites/default/files/document_files/WHO_VCP_GRA%20_ITN-PIPERONYL-BUTOXIDE.pdf, accessed March 2024.

WHO (2022a). Post COVID condition (long COVID). Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition, accessed January 2024.

WHO (2022b). Global status report on physical activity 2022. Geneva, Switzerland: World Health Organization. Available from: https://iris.who.int/bitstream/handle/10665/363607/9789240059153-eng.pdf?sequence=1, accessed September 2024.

WHO (2022c). Dietary and inhalation exposure to nano- and microplastic particles and potential implications for human health. Geneva, Switzerland: Nutrition and Food Safety (NFS), Standards & Scientific Advice on Food Nutrition (SSA), World Health Organization. Available from: https://www.who.int/publications/i/item/9789240054608, accessed May 2024.

WHO (2023a). Schistosomiasis. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/news-room/fact-sheets/detail/schistosomiasis, accessed February 2024.

WHO (2023b). World Health Organization model list of essential medicines – 23rd list, 2023. In: The selection and use of essential medicines 2023. Web annex A. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02, accessed September 2024.

WHO (2023c) Carbadox (addendum). Food additives series: 51. International Programme on Chemical Safety (IPCS). Geneva, Switzerland: World Health Organization. https://inchem.org/documents/jecfa/jecmono/v51je05.htm, accessed January 2024.

WHO (2024a). WHO COVID-19 dashboard. Number of COVID-19 cases reported to WHO. Geneva, Switzerland: World Health Organization. Available from: https://data.who.int/dashboards/covid19/cases?n=c, accessed May 2024.

WHO (2024b). WHO occupational burden of disease application tool. WHO/ILO joint estimates of the work-related burden of disease and injury. Environment, climate change and health. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/teams/environment-climate-change-and-health/monitoring/who-ilo-joint-estimates, accessed March 2024.

WHO (2024c). WHO global report on trends in prevalence of tobacco use 2000–2030. Geneva, Switzerland: World Health Organization. Available from: https://iris.who.int/bitstream/handle/10665/375711/9789240088283-eng.pdf, accessed March 2024.

WHO (2024d). Drinking-water quality guidelines. Water sanitation and health. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/teams/environment-climate-change-and-health/water-sanitation-and-health/water-safety-and-quality/drinking-water-quality-guidelines, accessed March 2024.

Wichert K, Rabstein S, Stang A, Erbel R, Eisele L, Arendt M, et al. (2020). Associations between shift work and risk of colorectal cancer in two German cohort studies. Chronobiol Int. 37(8):1235–43. https://doi.org/10.1080/07420528.2020.1782930 PMID:32654542

Wichmann G, Herbarth O, Lehmann I (2002). The mycotoxins citrinin, gliotoxin, and patulin affect interferon-γ rather than interleukin-4 production in human blood cells. Environ Toxicol. 17(3):211–8. https://doi.org/10.1002/tox.10050 PMID:12112629

Wickremasinghe AC, Kuzniewicz MW, Grimes BA, McCulloch CE, Newman TB (2016). Neonatal phototherapy and infantile cancer. Pediatrics. 137(6):e20151353. https://doi.org/10.1542/peds.2015-1353 PMID:27217478

Wiegand DM, Methner MM, Grimes GR, Couch JR, Wang L, Zhang L, et al. (2020). Occupational exposure to secondhand cannabis smoke among law enforcement officers providing security at outdoor concert events. Ann Work Expo Health. 64(7):705–14. https://doi.org/10.1093/annweh/wxaa025 PMID:32219297

Wielsøe M, Long M, Ghisari M, Bonefeld-Jørgensen EC (2015). Perfluoroalkylated substances (PFAS) affect oxidative stress biomarkers in vitro. Chemosphere. 129:239–45. https://doi.org/10.1016/j.chemosphere.2014.10.014 PMID:25455676

Wiemann C, Melching-Kollmuss S, Hambruch N, Wiss L, Stauber F, Richert L (2023). Boscalid shows increased thyroxin-glucuronidation in rat but not in human hepatocytes in vitro. J Appl Toxicol. 43(6):828–44. https://doi.org/10.1002/jat.4427 PMID:36549901

Wiencke JK, Cervenka J, Kennedy BJ, Prlina J, Gorlin R (1982). Sister-chromatid exchange induction by cis-platinum/adriamycin cancer chemotherapy. Mutat Res. 104(1–3):131–6. https://doi.org/10.1016/0165-7992(82)90133-6 PMID:7200570

Wiesner G, Schiewe-Langgartner F, Lindner R, Gruber M (2008). Increased formation of sister chromatid exchanges, but not of micronuclei, in anaesthetists exposed to low levels of sevoflurane. Anaesthesia. 63(8):861–4. https://doi.org/10.1111/j.1365-2044.2008.05498.xhttps://doi.org/10.1111/j.1365-2044.2008.05498.x PMID:18540930

Wilcosky TC, Checkoway H, Marshall EG, Tyroler HA (1984). Cancer mortality and solvent exposures in the rubber industry. Am Ind Hyg Assoc J. 45(12):809–11. https://doi.org/10.1080/15298668491400683 PMID:6549104

Wilking H, Thamm M, Stark K, Aebischer T, Seeber F (2016). Prevalence, incidence estimations, and risk factors of *Toxoplasma gondii* infection in Germany: a representative, cross-sectional, serological study. Sci Rep. 6(2016):22551. https://doi.org/10.1038/srep22551 PMID:26936108

Willett KL, Randerath K, Zhou GD, Safe SH (1998). Inhibition of CYP1A1-dependent activity by the polynuclear aromatic hydrocarbon (PAH) fluoranthene. Biochem Pharmacol. 55(6):831–9. https://doi.org/10.1016/S0006-2952(97)00561-3 PMID:9586956

Wills CA, Drago D, Pietrusko RG (2023). Clinical holds for cell and gene therapy trials: risks, impact, and lessons learned. Mol Ther Methods Clin Dev. 31:101125. https://doi.org/10.1016/j.omtm.2023.101125 PMID:37886603

Wilson CL, Ness KK, Neglia JP, Hammond S, Shnorhavorian M, Leisenring WL, et al. (2013). Renal carcinoma after childhood cancer: a report from the childhood cancer survivor study. J Natl Cancer Inst. 105(7):504–8. https://doi.org/10.1093/jnci/djt014 PMID:23515901

Wilson NM, Laursen M, Lidegaard Ø (2012). Oral contraception in Denmark 1998–2010. Acta Obstet Gynecol Scand. 91(7):810–5. https://doi.org/10.1111/j.1600-0412.2012.01416.x PMID:22486520

Wilson PM, La DK, Froines JR (1996). Hemoglobin and DNA adduct formation in Fischer-344 rats exposed to 2,4- and 2,6-toluene diamine. Arch Toxicol. 70(10):591–8. https://doi.org/10.1007/s002040050317 PMID:8870951

Wilson R, McConnell EE, Ross M, Axten CW, Nolan RP (2008). Risk assessment due to environmental exposures to fibrous particulates associated with taconite ore. Regul Toxicol Pharmacol. 52(1):S232–45. https://doi.org/10.1016/j.yrtph.2007.11.005 PMID:18207296

Wilson RA (1987) Cercariae to liver worms: development and migration in the mammalian host. ln: Rollinson, D, Simpson AJG, eds, The biology of schistosomes. From genes to latrines. London, UK: Academic Press.

Wilson RW, Steingrube VA, Böttger EC, Springer B, Brown-Elliott BA, Vincent V, et al. (2001). *Mycobacterium immunogenum* sp. nov., a novel species related to *Mycobacterium abscessus* and associated with clinical disease, pseudo-outbreaks and contaminated metalworking fluids: an international cooperative study on mycobacterial taxonomy. Int J Syst Evol Microbiol. 51(Pt 5):1751–64. https://doi.org/10.1099/00207713-51-5-1751 PMID:11594606

Win-Shwe TT, Fujimaki H (2011). Nanoparticles and neurotoxicity. Int J Mol Sci. 12(9):6267–80. https://doi.org/10.3390/ijms12096267 PMID:22016657

Winitthana T, Lawanprasert S, Chanvorachote P (2014). Triclosan potentiates epithelial-to-mesenchymal transition in anoikis-resistant human lung cancer cells. PLoS One. 9(10):e110851. https://doi.org/10.1371/journal.pone.0110851 PMID:25329306

Winker R, Roos G, Pilger A, Rüdiger HW (2008). Effect of occupational safety measures on micronucleus frequency in semiconductor workers. Int Arch Occup Environ Health. 81(4):423–8. https://doi.org/10.1007/s00420-007-0229-5 PMID:17653756

Winograd-Katz SE, Levitzki A (2006). Cisplatin induces PKB/Akt activation and p38(MAPK) phosphorylation of the EGF receptor. Oncogene. 25(56):7381–90. https://doi.org/10.1038/sj.onc.1209737 PMID:16785992

Winquist A, Hodge JM, Diver WR, Rodriguez JL, Troeschel AN, Daniel J, et al. (2023). Case–cohort study of the association between PFAS and selected cancers among participants in the American Cancer Society's Cancer Prevention Study II LifeLink Cohort. Environ Health Perspect. 131(12):127007. https://doi.org/10.1289/EHP13174 PMID:38088576

Winthrop KL, Melmed GY, Vermeire S, Long MD, Chan G, Pedersen RD, et al. (2018). Herpes zoster infection in patients with ulcerative colitis receiving tofacitinib. Inflamm Bowel Dis. 24(10):2258–65. https://doi.org/10.1093/ibd/izy131 PMID:29850873

Wise LA, Wang TR, Ncube CN, Lovett SM, Abrams J, Boynton-Jarrett R, et al. (2023). Use of chemical hair straighteners and fecundability in a North American preconception cohort. Am J Epidemiol. 192(7):1066–80. https://doi.org/10.1093/aje/kwad079 PMID:37005071

Withrow DR, Anderson H, Armstrong GT, Hawkins M, Journy N, Neglia JP, et al. (2022). Pooled analysis of meningioma risk following treatment for childhood cancer. JAMA Oncol. 8(12):1756–64. https://doi.org/10.1001/jamaoncol.2022.4425 PMID:36201196

Witt KL, Knapton A, Wehr CM, Hook GJ, Mirsalis J, Shelby MD, et al. (2000). Micronucleated erythrocyte frequency in peripheral blood of B6C3F(1) mice from short-term, prechronic, and chronic studies of the NTP carcinogenesis bioassay program. Environ Mol Mutagen. 36(3):163–94. https://doi.org/10.1002/1098-

2280(2000)36:3<163::AID-EM1>3.0.CO;2-Phttps://doi.org/10.1002/1098-2280(2000)36:3<163::AID-EM1>3.0.CO;2-P PMID:11044899

Wiwanitkit V, Suwansaksri J, Soogarun S (2008). White blood cell sister chromatid exchange among a sample of Thai subjects exposed to lead: lead-induced genotoxicity. Toxicol Environ Chem. 90(4):765–8. https://doi.org/10.1080/02772240701712758

Włuka A, Woźniak A, Woźniak E, Michałowicz J (2020). Tetrabromobisphenol A, terabromobisphenol S and other bromophenolic flame retardants cause cytotoxic effects and induce oxidative stress in human peripheral blood mononuclear cells (in vitro study). Chemosphere. 261:127705. https://doi.org/10.1016/j.chemosphere.2020.127705 PMID:32731020

Wofford P, Segawa R, Schreider J, Federighi V, Neal R, Brattesani M (2014). Community air monitoring for pesticides. Part 3: using health-based screening levels to evaluate results collected for a year. Environ Monit Assess. 186(3):1355–70. https://doi.org/10.1007/s10661-013-3394-x PMID:24370859

Wojcicki JM, Medrano R, Lin J, Epel E (2018). Increased cellular aging by 3 years of age in Latino, preschool children who consume more sugar-sweetened beverages: a pilot study. Child Obes. 14(3):149–57. https://doi.org/10.1089/chi.2017.0159 PMID:29148828

Wojnowski W, Marć M, Kalinowska K, Kosmela P, Zabiegała B (2022). Emission profiles of volatiles during 3D printing with ABS, ASA, Nylon, and PETG polymer filaments. Molecules. 27(12):3814. https://doi.org/10.3390/molecules27123814 PMID:35744939

Wołejko E, Łozowicka B, Jabłońska-Trypuć A, Pietruszyńska M, Wydro U (2022). Chlorpyrifos occurrence and toxicological risk assessment: a review. Int J Environ Res Public Health. 19(19):12209. https://doi.org/10.3390/ijerph191912209 PMID:36231509

Wong ET, Luettich K, Krishnan S, Wong SK, Lim WT, Yeo D, et al. (2020). Reduced chronic toxicity and carcinogenicity in A/J mice in response to life-time exposure to aerosol from a heated tobacco product compared with cigarette smoke. Toxicol Sci. 178(1):44–70. https://doi.org/10.1093/toxsci/kfaa131 PMID:32780830

Woo JH, Baik HJ, Kim CH, Chung RK, Kim DY, Lee GY, et al. (2015). Effect of propofol and desflurane on immune cell populations in breast cancer patients: a randomized trial. J Korean Med Sci. 30(10):1503–8. https://doi.org/10.3346/jkms.2015.30.10.1503 PMID:26425050

Wood NR, Garritson J, Mathias A, Haughian JM, Hayward R (2022). Moderate intensity endurance and resistance exercise attenuates cachexia in tumor-bearing mice. Anticancer Res. 42(1):397–405. https://doi.org/10.21873/anticanres.15498https://doi.org/10.21873/anticanres.15498 PMID:34969750

Woollen BH, Hall MG, Craig R, Steel GT (1985). Dinitrotoluene: an assessment of occupational absorption during the manufacture of blasting explosives. Int Arch Occup Environ Health. 55(4):319–30. https://doi.org/10.1007/BF00377690 PMID:4008056

Woutersen RA, Appel MJ, Van Garderen-Hoetmer A (1999). Modulation of pancreatic carcinogenesis by antioxidants. Food Chem Toxicol. 37(9–10):981–4. https://doi.org/10.1016/S0278-6915(99)00093-9 PMID:10541454

Woźniak E, Sicińska P, Michałowicz J, Woźniak K, Reszka E, Huras B, et al. (2018). The mechanism of DNA damage induced by Roundup 360 Plus, glyphosate and AMPA in human peripheral blood mononuclear cells – genotoxic risk assessment. Food Chem Toxicol. 120:510–22. https://doi.org/10.1016/j.fct.2018.07.035 PMID:30055318

Woźniak K, Blasiak J (2003). In vitro genotoxicity of lead acetate: induction of single and double DNA strand breaks and DNA-protein cross-links. Mutat Res. 535(2):127–39. https://doi.org/10.1016/S1383-5718(02)00295-4 PMID:12581530

Wright J, Symons B, Angell J, Ross KE, Walker S (2021). Current practices underestimate environmental exposures to methamphetamine: inhalation exposures are important. J Expo Sci Environ Epidemiol. 31(1):45–52. https://doi.org/10.1038/s41370-020-00260-x PMID:32873859

Wróbel AM, Gregoraszczuk EŁ (2015). Action of methyl-, propyl- and butylparaben on GPR30 gene and protein expression, cAMP levels and activation of ERK1/2 and PI3K/Akt signalling pathways in MCF-7 breast cancer cells and MCF-10A non-transformed breast epithelial cells. Toxicol Lett. 238(2):110–6. https://doi.org/10.1016/j.toxlet.2015.08.001https://doi.org/10.1016/j.toxlet.2015.08.001 PMID:26253279

Wrzesien M (2018). Thyroid exposure during 18F-FDG production procedures. Radiat Prot Dosimetry. 182(4):464–71. https://doi.org/10.1093/rpd/ncy103 PMID:29931185

Wu AH, Franke AA, Wilkens LR, Tseng C, Conroy SM, Li Y, et al. (2021b). Urinary phthalate exposures and risk of breast cancer: the Multiethnic Cohort study. Breast Cancer Res. 23(1):44. https://doi.org/10.1186/s13058-021-01419-6https://doi.org/10.1186/s13058-021-01419-6 PMID:33823904

Wu AH, Franke AA, Wilkens LR, Tseng C, Conroy SM, Li Y, et al. (2021c). Risk of breast cancer and prediagnostic urinary excretion of bisphenol A, triclosan and parabens: The Multiethnic Cohort Study. Int J Cancer. 149(7):1426–34. https://doi.org/10.1002/ijc.33692https://doi.org/10.1002/ijc.33692 PMID:34013527

Wu C, Du X, Tang L, Wu J, Zhao W, Guo X, et al. (2020a). *Schistosoma japonicum* SjE16.7 protein promotes tumor development via the receptor for advanced glycation end products (RAGE). Front Immunol. 11:1767. https://doi.org/10.3389/fimmu.2020.01767 PMID:32973746

Wu H, Weinstein S, Moore LE, Albanes D, Wilson RT (2022b). Coffee intake and trace element blood concentrations in association with renal cell cancer among smokers. Cancer Causes Control. 33(1):91–9. https://doi.org/10.1007/s10552-021-01505-2 PMID:34652593

Wu JC, Hseu YC, Tsai JS, Chen LC, Chye SM, Chen CH, et al. (2011). Fenthion and terbufos induce DNA damage, the expression of tumor-related genes, and apoptosis in HEPG2 cells. Environ Mol Mutagen. 52(7):529–37. https://doi.org/10.1002/em.20652 PMID:21538558

Wu M, Gordon RE, Herbert R, Padilla M, Moline J, Mendelson D, et al. (2010). Case report: lung disease in World Trade Center responders exposed to dust and smoke: carbon nanotubes found in the lungs of World Trade Center patients and dust samples. Environ Health Perspect. 118(4):499–504. https://doi.org/10.1289/ehp.0901159 PMID:20368128

Wu N, Feng YQ, Lyu N, Wang D, Yu WD, Hu YF (2022a). *Fusobacterium nucleatum* promotes colon cancer progression by changing the mucosal microbiota and colon transcriptome in a mouse model. World J Gastroenterol. 28(18):1981–95. https://doi.org/10.3748/wjg.v28.i18.1981 PMID:35664967

Wu N-X, Deng L-J, Xiong F, Xie J-Y, Li X-J, Zeng Q, et al. (2022c). Risk of thyroid cancer and benign nodules associated with exposure to parabens among Chinese adults in Wuhan, China. Environ Sci Pollut Res Int. 29(46):70125–34. https://doi.org/10.1007/s11356-022-20741-w PMID:35581467

Wu S, Bai YN, Pu HQ, He J, Zheng TZ, Li HY, et al. (2015b). Dynamic changes in DNA damage and repair biomarkers with employment length among nickel smelting workers. Biomed Environ Sci. 28(9):679–82. https://doi.org/10.3967/bes2015.095 PMID:26464256

Wu S, Rhee KJ, Albesiano E, Rabizadeh S, Wu X, Yen HR, et al. (2009). A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat Med. 15(9):1016–22. https://doi.org/10.1038/nm.2015 PMID:19701202

Wu WT, Lin YJ, Li CY, Tsai PJ, Yang CY, Liou SH, et al. (2015a). Cancer attributable to asbestos exposure in shipbreaking workers: a matched-cohort study. Sci Rep. 10(7):e0133128. https://doi.org/10.1371/journal.pone.0133128PMID:26192180

Wu X, Cui L, Wang H, Xu J, Zhong Z, Jia X, et al. (2023b). Impact of dietary sucralose and sucrose-sweetened water intake on lipid and glucose metabolism in male mice. Eur J Nutr. 62(1):199–211. https://doi.org/10.1007/s00394-022-02980-2 PMID:35933635

Wu XJ, Lu WQ, Roos PH, Mersch-Sundermann V (2005). Vinclozolin, a widely used fungizide, enhanced BaP-induced micronucleus formation in human derived hepatoma cells by increasing CYP1A1 expression. Toxicol Lett. 159(1):83–8. https://doi.org/10.1016/j.toxlet.2005.04.010 PMID:15979257

Wu Y, Gui SY, Fang Y, Zhang M, Hu CY (2021a). Exposure to outdoor light at night and risk of breast cancer: a systematic review and meta-analysis of observational studies. Environ Pollut. 269:116114. https://doi.org/10.1016/j.envpol.2020.116114 PMID:33280921

Wu Y, Yang Z, Su S, Xu X, Li Y, Li X, et al. (2023a). Differential epitranscriptome and proteome modulation in the brain of neonatal mice exposed to isoflurane or sevoflurane. Cell Biol Toxicol. 39(5):2133–48. https://doi.org/10.1007/s10565-022-09701-9 PMID:35249202

Wu Z, He C, Han W, Song J, Li H, Zhang Y, et al. (2020b). Exposure pathways, levels and toxicity of polybrominated diphenyl ethers in humans: a review. Environ Res. 187:109531. https://doi.org/10.1016/j.envres.2020.109531 PMID:32454306

Xia Q, Feng X, Huang H, Du L, Yang X, Wang K (2011). Gadolinium-induced oxidative stress triggers endoplasmic reticulum stress in rat cortical neurons. J Neurochem. 117(1):38–47. https://doi.org/10.1111/j.1471-4159.2010.07162.x PMID:21198628

Xia Q, Zhao Y, Von Tungeln LS, Doerge DR, Lin G, Cai L, et al. (2013). Pyrrolizidine alkaloid-derived DNA adducts as a common biological biomarker of pyrrolizidine alkaloid-induced tumorigenicity. Chem Res Toxicol. 26(9):1384–96. https://doi.org/10.1021/tx400241c PMID:23937665

Xia Y, Cheng S, Bian Q, Xu L, Collins MD, Chang HC, et al. (2005). Genotoxic effects on spermatozoa of carbaryl-exposed workers. Toxicol Sci. 85(1):615–23. https://doi.org/10.1093/toxsci/kfi066 PMID:15615886

Xia Y, Niu Y, Cai J, Lin Z, Liu C, Li H, et al. (2018). Effects of personal short-term exposure to ambient ozone on blood pressure and vascular endothelial function: a mechanistic study based on DNA methylation and metabolomics. Environ Sci Technol. 52(21):12774–82. https://doi.org/10.1021/acs.est.8b03044 PMID:30259740

Xiao K, Shang J, Liu Y, Chen Z, Wang L, Long Q (2022). Effect of NLRP3 repression on NLRP3 inflammasome activation in human corneal epithelial cells with black carbon exposure. Cutan Ocul Toxicol. 41(2):107–12. https://doi.org/10.1080/15569527.2022.2050746 PMID:35298317

Xiao L, Miwa N (2017). Hydrogen-rich water achieves cytoprotection from oxidative stress injury in human gingival fibroblasts in culture or 3D-tissue equivalents, and wound-healing promotion, together with ROS-scavenging and relief from glutathione diminishment. Hum Cell. 30(2):72–87. https://doi.org/10.1007/s13577-016-0150-x PMID:27804028

Xiao Q, Gierach GL, Bauer C, Blot WJ, James P, Jones RR (2021a). The association between outdoor artificial light at night and breast cancer risk in black and white women in the Southern Community Cohort Study. Environ Health Perspect. 129(8):87701. https://doi.org/10.1289/EHP9381 PMID:34379524

Xiao Q, James P, Breheny P, Jia P, Park Y, Zhang D, et al. (2020). Outdoor light at night and postmenopausal breast cancer risk in the NIH-AARP diet and health study. Int J Cancer. 147(9):2363–72. https://doi.org/10.1002/ijc.33016 PMID:32488897

Xiao Q, Jones RR, James P, Stolzenberg-Solomon RZ (2021b). Light at night and risk of pancreatic cancer in the NIH-AARP Diet and Health Study. Cancer Res. 81(6):1616–22. https://doi.org/10.1158/0008-5472.CAN-20-2256 PMID:33514513

Xie H, Wise SS, Holmes AL, Xu B, Wakeman TP, Pelsue SC, et al. (2005). Carcinogenic lead chromate induces DNA double-strand breaks in human lung cells. Mutat Res. 586(2):160–72. https://doi.org/10.1016/j.mrgentox.2005.06.002 PMID:16112599

Xie J, Terry KL, Poole EM, Wilson KM, Rosner BA, Willett WC, et al. (2013). Acrylamide hemoglobin adduct levels and ovarian cancer risk: a nested case-control study. Cancer Epidemiol Biomarkers Prev. 22(4):653–60. https://doi.org/10.1158/1055-9965.EPI-12-1387 PMID:23417989

Xie S, Friesen MC, Baris D, Schwenn M, Rothman N, Johnson A, et al. (2024b). Occupational exposure to organic solvents and risk of bladder cancer. J Expo Sci Environ Epidemiol. 34(3):546–53. https://doi.org/10.1038/s41370-024-00651-4 PMID:38365975

Xie S, Wei L, Liu Y, Meng J, Cao W, Qiu B, et al. (2024a). Size-tunable nanogels for cascaded release of metronidazole and chemotherapeutic agents to combat *Fusobacterium nucleatum*-infected colorectal cancer. J Control Release. 365:16–28. https://doi.org/10.1016/j.jconrel.2023.11.018 PMID:37956925

Xie X, Zhou J, Hu L, Shu R, Zhang M, Xiong Z, et al. (2021). Exposure to hexafluoropropylene oxide dimer acid (HFPO-DA) disturbs the gut barrier function and gut microbiota in mice. Environ Pollut. 290:117934. https://doi.org/10.1016/j.envpol.2021.117934 PMID:34416495

Xing L-G, Wu Y-L, Zheng H-N, Jia Y-Y, Wu G-F, Yang C (2018). Induction of esophageal cancers by nitenpyram (NIT) in rats. Eur Rev Med Pharmacol Sci. 22(24):8698–711. https://www.europeanreview.org/article/16635 PMID:30575910

Xiong L, Huang J, Wang S, Yuan Q, Yang D, Zheng Z, et al. (2022). Yttrium chloride-induced cytotoxicity and DNA damage response via ROS generation and inhibition of Nrf2/PPARγ pathways in H9c2 cardiomyocytes. Arch Toxicol. 96(3):767–81. https://doi.org/10.1007/s00204-022-03225-1 PMID:35088107

Xu J, Alexander DB, Futakuchi M, Numano T, Fukamachi K, Suzui M, et al. (2014). Size- and shape-dependent pleural translocation, deposition, fibrogenesis, and mesothelial proliferation by multiwalled carbon nanotubes. Cancer Sci. 105(7):763–9. https://doi.org/10.1111/cas.12437 PMID:24815191

Xu J, Niehoff NM, White AJ, Werder EJ, Sandler DP (2022b). Fossil-fuel and combustion-related air pollution and hypertension in the Sister Study. Environ Pollut. 315:120401. https://doi.org/10.1016/j.envpol.2022.120401 PMID:36228848

Xu K, Li S, Whitehead TP, Pandey P, Kang AY, Morimoto LM, et al. (2021a). Epigenetic biomarkers of prenatal tobacco smoke exposure are associated with gene deletions in childhood acute lymphoblastic leukemia. Cancer Epidemiol Biomarkers Prev. 30(8):1517–25. https://doi.org/10.1158/1055-9965.EPI-21-0009 PMID:34020997

Xu M, Legradi J, Leonards P (2023b). A comprehensive untargeted metabolomics study in zebrafish embryos exposed to perfluorohexane sulfonate (PFHxS). Sci Total Environ. 887:163770. https://doi.org/10.1016/j.scitotenv.2023.163770 PMID:37146801

Xu Q, Li M, Yang M, Yang J, Xie J, Lu X, et al. (2018). α-pinene regulates *miR-221* and induces G_2/M phase cell cycle arrest in human hepatocellular carcinoma cells. Biosci Rep. 38(6):BSR20180980. https://doi.org/10.1042/BSR20180980https://doi.org/10.1042/BSR20180980 PMID:30473536

Xu S, Wang H, Liu Y, Zhang C, Xu Y, Tian F, et al. (2021b). Hair chemicals may increase breast cancer risk: a meta-analysis of 210319 subjects from 14 studies. PLoS One. 16(2):e0243792. https://doi.org/10.1371/journal.pone.0243792 PMID:33539348

Xu S, Yu S, Dong D, Lee LTO (2019b). G protein-coupled estrogen receptor: a potential therapeutic target in cancer. Front Endocrinol (Lausanne). 10:725. https://doi.org/10.3389/fendo.2019.00725https://doi.org/10.3389/fendo.2019.00725 PMID:31708873

Xu T, Wang B, Wang X, Yang S, Cao L, Qiu W, et al. (2021c). Associations of urinary carbon disulfide metabolite with oxidative stress, plasma glucose and risk of diabetes among urban adults in China. Environ Pollut. 272:115959. https://doi.org/10.1016/j.envpol.2020.115959 PMID:33250290

Xu Y, Xu H, Ling T, Cui Y, Zhang J, Mu X, et al. (2023a). Inhibitor of nuclear factor kappa B kinase subunit epsilon regulates murine acetaminophen toxicity via RIPK1/JNK. Cell Biol Toxicol. 39(6):2709–24. https://doi.org/10.1007/s10565-023-09796-8 PMID:36757501

Xu Y, Zhang Z, Wang B, He X, Tang J, Peng W, et al. (2022a). *Flammulina velutipes* polysaccharides modulate gut microbiota and alleviate carbon tetrachloride-induced hepatic oxidative injury in mice. Front Microbiol. 13:847653. https://doi.org/10.3389/fmicb.2022.847653 PMID:35401429

Xu ZP, Chang H, Ni YY, Li C, Chen L, Hou M, et al. (2019a). *Schistosoma japonicum* infection causes a reprogramming of glycolipid metabolism in the liver. Parasit Vectors. 12(1):388. https://doi.org/10.1186/s13071-019-3621-6 PMID:31375125

Yadav H, Sharma RS, Singh R (2022). Immunotoxicity of radiofrequency radiation. Environ Pollut. 309:119793. https://doi.org/10.1016/j.envpol.2022.119793 PMID:35863710

Yafune A, Kawai M, Itahashi M, Kimura M, Nakane F, Mitsumori K, et al. (2013). Global DNA methylation screening of liver in piperonyl butoxide-treated mice in a two-stage hepatocarcinogenesis model. Toxicol Lett. 222(3):295–302. https://doi.org/10.1016/j.toxlet.2013.08.006https://doi.org/10.1016/j.toxlet.2013.08.006 PMID:23968726

Yafune A, Taniai E, Morita R, Akane H, Kimura M, Mitsumori K, et al. (2014). Immunohistochemical cellular distribution of proteins related to M phase regulation in early proliferative lesions induced by tumor promotion in rat two-stage carcinogenesis models. Carcinogenesis. 66(1):1–11. https://doi.org/10.1016/j.etp.2013.07.001PMID:23890812

Yahia S, Shabaan AE, Gouida M, El-Ghanam D, Eldegla H, El-Bakary A, et al. (2015). Influence of hyperbilirubinemia and phototherapy on markers of genotoxicity and apoptosis in full-term infants. Eur J Pediatr. 174(4):459–64. https://doi.org/10.1007/s00431-014-2418-z PMID:25209224

Yakupova EI, Bobyleva LG, Vikhlyantsev IM, Bobylev AG (2019). Congo Red and amyloids: history and relationship. Biosci Rep. 39(1):BSR20181415. https://doi.org/10.1042/BSR20181415 PMID:30567726

Yamada T, Asano H, Miyata K, Rhomberg LR, Haseman JK, Greaves P, et al. (2019). Toxicological evaluation of carcinogenicity of the pyrethroid imiprothrin in rats and mice. Regul Toxicol Pharmacol. 105:1–14. https://doi.org/10.1016/j.yrtph.2019.03.012 PMID:30905765

Yamamoto Y, Kamiya T, Yano M, Huyen VT, Oishi M, Nishio M, et al. (2023). Oral microbial profile analysis in patients with oral and pharyngeal cancer reveals that tumoral *Fusobacterium nucleatum* promotes oral cancer progression by activating YAP. Microorganisms. 11(12):2957. https://doi.org/10.3390/microorganisms11122957 PMID:38138101

Yamano S, Goto Y, Takeda T, Hirai S, Furukawa Y, Kikuchi Y, et al. (2022b). Pulmonary dust foci as rat pneumoconiosis lesion induced by titanium dioxide nanoparticles in 13-week inhalation study. Part Fibre Toxicol. 19(1):58. https://doi.org/10.1186/s12989-022-00498-3 PMID:36100920

Yamano S, Takeda T, Goto Y, Hirai S, Furukawa Y, Kikuchi Y, et al. (2022a). No evidence for carcinogenicity of titanium dioxide nanoparticles in 26-week inhalation study in rasH2 mouse model. Sci Rep. 12(1):14969. https://doi.org/10.1038/s41598-022-19139-y PMID:36056156

Yamaori S, Yokozuka H, Sasama A, Funahashi T, Kimura T, Yamamoto I, et al. (2005). Hepatic metabolism of methyl anthranilate and methyl *N*-methylanthranilate as food flavoring agents in relation to allergenicity in the guinea pig. J Health Sci. 51(6):667–75. https://doi.org/10.1248/jhs.51.667

Yamashita K, Takeno S, Hoshino S, Shiwaku H, Aisu N, Yoshida Y, et al. (2016). Triclosan sutures for surgical site infection in colorectal cancer. J Surg Res. 206(1):16–21. https://doi.org/10.1016/j.jss.2016.06.070 PMID:27916357

Yan S, Wu H, Qin J, Zha J, Wang Z (2017). Halogen-free organophosphorus flame retardants caused oxidative stress and multixenobiotic resistance in Asian freshwater clams (*Corbicula fluminea*). Environ Pollut. 225:559–68. https://doi.org/10.1016/j.envpol.2017.02.071 PMID:28318792

Yan WK, Liu YN, Song SS, Kang JW, Zhang Y, Lu L, et al. (2022). Zearalenone affects the growth of endometriosis via estrogen signalling and inflammatory pathways. Ecotoxicol Environ Saf. 241:113826. https://doi.org/10.1016/j.ecoenv.2022.113826 PMID:36068753

Yan Y, Wang C, Zheng Z, Qu L, Zeng D, Li M (2019). Renal injury following long-term exposure to carbon disulfide: analysis of a case series. BMC Nephrol. 20(1):377. https://doi.org/10.1186/s12882-019-1553-1 PMID:31623563

Yang B, Petrick JL, Chen J, Hagberg KW, Sahasrabuddhe VV, Graubard BI, et al. (2016b). Associations of NSAID and paracetamol use with risk of primary liver cancer in the Clinical Practice Research Datalink. Cancer Epidemiol. 43:105–11. https://doi.org/10.1016/j.canep.2016.06.009 PMID:27420633

Yang H, Ma Z, Peng L, Kuhn C, Rahmeh M, Mahner S, et al. (2021a). Comparison of Histone H3K4me3 between IVF and ICSI technologies and between boy and girl offspring. Int J Mol Sci. 22(16):8574. https://doi.org/10.3390/ijms22168574 PMID:34445278

Yang H, Zhang X, Liu H, Cui W, Zhang Q, Li Y, et al. (2016a). Lanthanum nitrate genotoxicity evaluation: Ames test, mouse micronucleus assay, and chromosome aberration test. Mutat Res Genet Toxicol Environ Mutagen. 810:1–5. https://doi.org/10.1016/j.mrgentox.2016.09.008 PMID:27776686

Yang J, Chen W, Li X, Sun J, Guo Q, Wang Z (2014). Relationship between urinary nickel and methylation of p15, p16 in workers exposed to nickel. J Occup Environ Med. 56(5):489–92. https://doi.org/10.1097/JOM.0000000000000168 PMID:24806561

Yang JM, Han DW, Liang QC, Zhao JL, Hao SY, Ma XH, et al. (1997). Effects of endotoxin on expression of ras, p53 and bcl-2 oncoprotein in hepatocarcinogenesis induced by thioacetamide in rats. World J Gastroenterol. 3(4):213–7. https://doi.org/10.3748/wjg.v3.i4.213 PMID:27053867

Yang L, Chen J, Feng H, Ai S, Liu Y, Chen X, et al. (2022a). Night shift work, MTNR1B rs10830963 polymorphism, and prostate cancer risk: findings from a prospective, population-based study. Cancer Epidemiol Biomarkers Prev. 31(4):728–35. https://doi.org/10.1158/1055-9965.EPI-21-1108

Yang L, Xu JB, Zhen L, Sun ZW, Shi L, Jin MH, et al. (2005). DNA damage of germ cell of rat induced by nitrotoluene chemicals. J Environ Sci (China). 17(1):84–90. https://content.iospress.com/articles/journal-of-environmental-sciences/jes17-1-17 PMID:15900764

Yang L, Zha J, Guo Y, Zhou B (2020b). Evaluation and mechanistic study of chlordecone-induced thyroid disruption: based on in vivo, in vitro and in silico assays. Sci Total Environ. 716:136987. https://doi.org/10.1016/j.scitotenv.2020.136987 PMID:32044482

Yang S, Diem M, Liu JDH, Wesseling S, Vervoort J, Oostenbrink C, et al. (2020a). Cellular levels and molecular dynamics simulations of estragole DNA adducts point at inefficient repair resulting from limited distortion of the double-stranded DNA helix. Arch Toxicol. 94(4):1349–65. https://doi.org/10.1007/s00204-020-02695-5 PMID:32185416

Yang W, Yang X, Jiang L, Song H, Huang G, Duan K, et al. (2022b). Combined biological effects and lung proteomics analysis in mice reveal different toxic impacts of electronic cigarette aerosol and combustible cigarette smoke on the respiratory system. Arch Toxicol. 96(12):3331–47. https://doi.org/10.1007/s00204-022-03378-z PMID:36173423

Yang WJ, Wu HB, Zhang C, Zhong Q, Hu MJ, He JL, et al. (2021b). Exposure to 2,4-dichlorophenol, 2,4,6-trichlorophenol, pentachlorophenol and risk of thyroid cancer: a case-control study in China. Environ Sci Pollut Res Int. 28(43):61329–43. https://doi.org/10.1007/s11356-021-14898-z PMID:34173948

Yang X, Ni Y, Yuan Z, Chen H, Plymoth A, Jin L, et al. (2018). Very hot tea drinking increases esophageal squamous cell carcinoma risk in a high-risk area of China: a population-based case-control study. Clin Epidemiol. 10:1307–20. https://doi.org/10.2147/CLEP.S171615 PMID:30310324

Yang Y, Wang XY, Duan C, Wang ZJ, Sheng HY, Xu XL, et al. (2023). Clinicopathological characteristics and its association with digestive system tumors of 1111 patients with *Schistosomiasis japonica*. Sci Rep. 13(1):15115. https://doi.org/10.1038/s41598-023-42456-9 PMID:37704736

Yang Z, Bjorkman PJ (2008). Structure of UL18, a peptide-binding viral MHC mimic, bound to a host inhibitory receptor. Proc Natl Acad Sci USA. 105(29):10095–100. https://doi.org/10.1073/pnas.0804551105 PMID:18632577

Yanguas J, Pinazo-Henandis S, Tarazona-Santabalbina FJ (2018). The complexity of loneliness. Acta Biomed. 89(2):302–14. PMID:29957768

Yanicostas C, Soussi-Yanicostas N (2021). SDHI fungicide toxicity and associated adverse outcome pathways: what can zebrafish tell us? Int J Mol Sci. 22(22):12362. https://doi.org/10.3390/ijms222212362 PMID:34830252

Yano BL, Young JT, Mattsson JL (2000). Lack of carcinogenicity of chlorpyrifos insecticide in a high-dose, 2-year dietary toxicity study in Fischer 344 rats. Toxicol Sci. 53(1):135–44. https://doi.org/10.1093/toxsci/53.1.135 PMID:10653531

Yao W, Xu J, Tang W, Gao C, Tao L, Yu J, et al. (2023a). Developmental toxicity of perfluorohexane sulfonate at human relevant dose during pregnancy via disruption in placental lipid homeostasis. Environ Int. 177:108014. https://doi.org/10.1016/j.envint.2023.108014 PMID:37315490

Yao YN, Wang Y, Zhang H, Gao Y, Zhang T, Kannan K (2023b). A review of sources, pathways, and toxic effects of human exposure to benzophenone ultraviolet light filters. Eco Environ Health. 3(1):30–44. https://doi.org/10.1016/j.eehl.2023.10.001https://doi.org/10.1016/j.eehl.2023.10.001 PMID:38162868

Yarmolinsky J, Bonilla C, Haycock PC, Langdon RJQ, Lotta LA, Langenberg C, et al.; PRACTICAL Consortium (2018). Circulating selenium and prostate cancer risk: a mendelian randomization analysis. J Natl Cancer Inst. 110(9):1035–8. https://doi.org/10.1093/jnci/djy081 PMID:29788239

Yazdani HO, Kaltenmeier C, Morder K, Moon J, Traczek M, Loughran P, et al. (2021). Exercise training decreases hepatic injury and metastases through changes in immune response to liver ischemia/reperfusion in mice. Hepatology. 73(6):2494–509. https://doi.org/10.1002/hep.31552https://doi.org/10.1002/hep.31552 PMID:32924145

Ye L, Guo J, Ge RS (2014). Environmental pollutants and hydroxysteroid dehydrogenases. Vitam Horm. 94:349–90. https://doi.org/10.1016/B978-0-12-800095-3.00013-4 PMID:24388197

Ye L, Su ZJ, Ge RS (2011). Inhibitors of testosterone biosynthetic and metabolic activation enzymes. Molecules. 16(12):9983–10001. https://doi.org/10.3390/molecules16129983 PMID:22138857

Yeh CN, Lin KJ, Hsiao IT, Yen TC, Chen TW, Jan YY, et al. (2008). Animal PET for thioacetamide-induced rat cholangiocarcinoma: a novel and reliable platform. Mol Imaging Biol. 10(4):209–16. https://doi.org/10.1007/s11307-008-0141-8 PMID:18491193

Yeh CN, Maitra A, Lee KF, Jan YY, Chen MF (2004). Thioacetamide-induced intestinal-type cholangiocarcinoma in rat: an animal model recapitulating the multi-stage progression of human cholangiocarcinoma. Carcinogenesis. 25(4):631–6. https://doi.org/10.1093/carcin/bgh037 PMID:14656942

Yen YC, Ku CH, Yao TC, Tsai HJ, Peng CY, Chen YC (2023). Personal exposure to aldehydes and potential health risks among schoolchildren in the city. Environ Sci Pollut Res Int. 30(45):101627–36. https://doi.org/10.1007/s11356-023-29578-3 PMID:37653197

Yesalis CE, Bahrke MS (2002). Anabolic–androgenic steroids and related substances. Curr Sports Med Rep. 1(4):246–52. https://doi.org/10.1249/00149619-200208000-00009 PMID:12831702

Yiin JH, Anderson JL, Daniels RD, Seel EA, Fleming DA, Waters KM, et al. (2009). A nested case–control study of multiple myeloma risk and uranium exposure among workers at the Oak Ridge gaseous diffusion plant. Radiat Res. 171(6):637–45. https://doi.org/10.1667/RR1607.1 PMID:19580470

Yilmaz S, Yilmaz Sezer N, Gönenç İM, İlhan SE, Yilmaz E (2018). Safety of clomiphene citrate: a literature review. Cytotechnology. 70(2):489–95. https://doi.org/10.1007/s10616-017-0169-1 PMID:29159661

Yin L, Lin S, Summers AO, Roper V, Campen MJ, Yu X (2021). Children with amalgam dental restorations have significantly elevated blood and urine mercury levels. Toxicol Sci. 184(1):104–26. https://doi.org/10.1093/toxsci/kfab108 PMID:34453845

Ying Y, Pan P, Zou C, Wang Y, Tang Y, Hou X, et al. (2021). Tebuconazole exposure disrupts placental function and causes fetal low birth weight in rats. Chemosphere. 264(Pt 2):128432. https://doi.org/10.1016/j.chemosphere.2020.128432 PMID:33049508

Yong M, Anderle L, Levy L, McCunney RJ (2019). Carbon black and lung cancer mortality – a meta-regression analysis based on three occupational cohort studies. J Occup Environ Med. 61(11):949–0. https://doi.org/10.1097/JOM.0000000000001713 PMID:31513042

Yongxing W, Xiaorong W, Zichun H (2000). Genotoxicity of lanthanum (III) and gadolinium (III) in human peripheral blood lymphocytes. Bull Environ Contam Toxicol. 64(4):611–6. https://doi.org/10.1007/s001280000047 PMID:10754061

Yonis M, Haim A, Zubidat AE (2019). Altered metabolic and hormonal responses in male rats exposed to acute bright light-at-night associated with global DNA hypo-methylation. J Photochem Photobiol B. 194:107–18. https://doi.org/10.1016/j.jphotobiol.2019.03.020 PMID:30953912

Yoo HJ, Pyo MC, Park Y, Kim BY, Lee KW (2021). Hexafluoropropylene oxide dimer acid (GenX) exposure induces apoptosis in HepG2 cells. Heliyon. 7(11):e08272. https://doi.org/10.1016/j.heliyon.2021.e08272 PMID:34765786

Yoon C, Kim S, Park D, Choi Y, Jo J, Lee K (2020). Chemical use and associated health concerns in the semiconductor manufacturing industry. Saf Health Work. 11(4):500–8. https://doi.org/10.1016/j.shaw.2020.04.005 PMID:33329917

Yoon J, Cho HJ, Lee E, Choi YJ, Kim YH, Lee JL, et al. (2017). Rate of humidifier and humidifier disinfectant usage in Korean children: a nationwide epidemiologic study. Environ Res. 155:60–3. https://doi.org/10.1016/j.envres.2017.01.030 PMID:28189074

Yoshida T, Andoh K, Fukuhara M (2002a). Urinary 2,5-dichlorophenol as biological index for p-dichlorobenzene exposure in the general population. Arch Environ Contam Toxicol. 43(4):481–5. https://doi.org/10.1007/s00244-002-1228-x PMID:12399920

Yoshida T, Andoh K, Kosaka H, Kumagai S, Matsunaga I, Akasaka S, et al. (2002b). Inhalation toxicokinetics of p-dichlorobenzene and daily absorption and internal accumulation in chronic low-level exposure to humans. Arch Toxicol. 76(5–6):306–15. https://doi.org/10.1007/s00204-002-0341-y PMID:12107648

Yoshida T, Mimura M, Sakon N (2021). Estimating household exposure to pyrethroids and the relative contribution of inhalation pathway in a sample of Japanese children. Environ Sci Pollut Res Int. 28(15):19310–24. https://doi.org/10.1007/s11356-020-12060-9 PMID:33394402

Yoshizawa T, Yamashita A, Luo Y (1994). Fumonisin occurrence in corn from high- and low-risk areas for human esophageal cancer in China. Appl Environ Microbiol. 60(5):1626–9. https://doi.org/10.1128/aem.60.5.1626-1629.1994 PMID:8017941

Young HA, Mills PK, Riordan DG, Cress RD (2005). Triazine herbicides and epithelial ovarian cancer risk in central California. J Occup Environ Med. 47(11):1148–56. https://doi.org/10.1097/01.jom.0000177044.43959.e8 PMID:16282876

Ytterberg SR, Bhatt DL, Connell CA (2022b). Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. Reply.. N Engl J Med. 386(18):1768. PMID:35507493

Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, et al.; ORAL Surveillance Investigators (2022a). Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med. 386(4):316–26. https://doi.org/10.1056/NEJMoa2109927 PMID:35081280

Yu C, Tang H, Guo Y, Bian Z, Yang L, Chen Y, et al.; China Kadoorie Biobank Collaborative Group (2018). Hot tea consumption and its interactions with alcohol and tobacco use on the risk for esophageal cancer: a population-based cohort study. Ann Intern Med. 168(7):489–97. https://doi.org/10.7326/M17-2000 PMID:29404576

Yu G, Murphy G, Michel A, Weinstein SJ, Männistö S, Albanes D, et al. (2013). Seropositivity to *Helicobacter pylori* and risk of pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 22(12):2416–9. https://doi.org/10.1158/1055-9965.EPI-13-0680 PMID:24089457

Yu L, Wu J, Zhai Q, Tian F, Zhao J, Zhang H, et al. (2019a). Metabolomic analysis reveals the mechanism of aluminum cytotoxicity in HT-29 cells. PeerJ. 7:e7524. https://doi.org/10.7717/peerj.7524 PMID:31523502

Yu P, Guo S, Xu R, Ye T, Li S, Sim MR, et al. (2021b). Cohort studies of long-term exposure to outdoor particulate matter and risks of cancer: a systematic review and meta-analysis. Innovation (Camb). 2(3):100143. https://doi.org/10.1016/j.xinn.2021.100143 PMID:34557780

Yu S, Jia B, Liu N, Yu D, Zhang S, Wu A (2021c). Fumonisin B1 triggers carcinogenesis via HDAC/PI3K/Akt signalling pathway in human esophageal epithelial cells. Sci Total Environ. 787:147405. https://doi.org/10.1016/j.scitotenv.2021.147405 PMID:34000555

Yu X, Peng W, Wang Y, Xu W, Chen W, Huang L, et al. (2023). Palmitic acid inhibits the growth and metastasis of gastric cancer by blocking the STAT3 signalling pathway. Cancers (Basel). 15(2):388. https://doi.org/10.3390/cancers15020388 PMID:36672337

Yu X, Wu Y, Deng M, Liu Y, Wang S, He X, et al. (2019b). Tetracycline antibiotics as PI3K inhibitors in the Nrf2-mediated regulation of antioxidative stress in zebrafish larvae. Chemosphere. 226:696–703. https://doi.org/10.1016/j.chemosphere.2019.04.001 PMID:30959454

Yu X, Yin H, Peng H, Lu G, Liu Z, Dang Z (2019c). OPFRs and BFRs induced A549 cell apoptosis by caspase-dependent mitochondrial pathway. Chemosphere. 221:693–702. https://doi.org/10.1016/j.chemosphere.2019.01.074 PMID:30669111

Yu Y, Wang J, Wang X, Gu P, Lei Z, Tang R, et al. (2021a). Schistosome eggs stimulate reactive oxygen species production to enhance M2 macrophage differentiation and promote hepatic pathology in schistosomiasis. Sci Rep. 15(8):e0009696. https://doi.org/10.1371/journal.pntd.0009696PMID:34398890

Yu Z, Zhang L, Wu D, Liu F (2005). Anti-apoptotic action of zearalenone in MCF-7 cells. Ecotoxicol Environ Saf. 62(3):441–6. https://doi.org/10.1016/j.ecoenv.2004.10.003 PMID:16216639

Yuan C, Zhang C, Qi Y, Li D, Hu Y, Huang D (2020). 2,4-Dichlorophenol induced feminization of zebrafish by down-regulating male-related genes through DNA methylation. Ecotoxicol Environ Saf. 189:110042. https://doi.org/10.1016/j.ecoenv.2019.110042 PMID:31816500

Yuan JM, Gao YT, Wang R, Chen M, Carmella SG, Hecht SS (2012). Urinary levels of volatile organic carcinogen and toxicant biomarkers in relation to lung cancer development in smokers. Carcinogenesis. 33(4):804–9. https://doi.org/10.1093/carcin/bgs026 PMID:22298640

Yuan L, Ni J, Lu W, Yan Q, Wan X, Li Z (2023a). Association between domain-specific sedentary behaviour and endometrial cancer: a systematic review and meta-analysis. BMJ Open. 13(6):e069042. https://doi.org/10.1136/bmjopen-2022-069042 PMID:37280028

Yuan Y, Wang X, Ge J, Jiang W, Li Z, Wang Z, et al. (2023b). Developmental immunotoxicity of maternal exposure to yttrium nitrate on BALB/c offspring mice. Environ Toxicol. 38(8):1939–50. https://doi.org/10.1002/tox.23820 PMID:37102272

Yue H, Tian Y, Wu X, Yang X, Xu P, Zhu H, et al. (2023b). Exploration of the damage and mechanisms of BPS exposure on the uterus and ovary of adult female mice. Sci Total Environ. 868:161660. https://doi.org/10.1016/j.scitotenv.2023.161660 PMID:36690098

Yueh MF, Taniguchi K, Chen S, Evans RM, Hammock BD, Karin M, et al. (2014). The commonly used antimicrobial additive triclosan is a liver tumor promoter. Proc Natl Acad Sci USA. 111(48):17200–5. https://doi.org/10.1073/pnas.1419119111 PMID:25404284

Yuk JS, Kim M (2023). Effects of menopausal hormone therapy on the risk of ovarian cancer: health insurance database in South Korea-based cohort study. Menopause. 30(5):490–6. https://doi.org/10.1097/GME.0000000000002176 PMID:37022299

Yuri T, Tsukamoto R, Miki K, Uehara N, Matsuoka Y, Tsubura A (2006). Biphasic effects of zeranol on the growth of estrogen receptor-positive human breast carcinoma cells. Oncol Rep. 16(6):1307–12. https://doi.org/10.3892/or.16.6.1307 PMID:17089054

Zabrodskii PF, Maslyakov VV, Gromov MS (2016). [Effect of 4-methylpyrazole on immune response, function of Th1 and Th2 lymphocytes, and cytokine concentration in rat blood after acute methanol poisoning]. Eksp Klin Farmakol. 79(3):37–40. PMID:27455577 [Russian]

Zackular JP, Baxter NT, Iverson KD, Sadler WD, Petrosino JF, Chen GY, et al. (2013). The gut microbiome modulates colon tumorigenesis. MBio. 4(6):e00692–13. https://doi.org/10.1128/mBio.00692-13 PMID:24194538

Zahm S, Bonde JP, Chiu WA, Hoppin J, Kanno J, Abdallah M, et al. (2023). Carcinogenicity of perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS). Lancet Oncol. 25(1):16–7. https://doi.org/10.1016/S1470-2045(23)00622-8https://doi.org/10.1016/S1470-2045(23)00622-8 PMID:38043561

Zainab B, Ayaz Z, Rashid U, Al Farraj DA, Alkufeidy RM, AlQahtany FS, et al. (2021). Role of persistent organic pollutants in breast cancer progression and identification of estrogen receptor alpha inhibitors using in-silico mining and drug–drug interaction network approaches. Biology (Basel). 10(7):681. https://doi.org/10.3390/biology10070681https://doi.org/10.3390/biology10070681 PMID:34356536

Zanchi MM, Marafon F, Marins K, Bagatini MD, Zamoner A (2024). Redox imbalance and inflammation: a link to depression risk in Brazilian pesticide-exposed farmers. Toxicology. 501:153706. https://doi.org/10.1016/j.tox.2023.153706 PMID:38097130

Zand MS, Vo T, Huggins J, Felgar R, Liesveld J, Pellegrin T, et al. (2005). Polyclonal rabbit antithymocyte globulin triggers B-cell and plasma cell apoptosis by multiple pathways. Transplantation. 79(11):1507–15. https://doi.org/10.1097/01.TP.0000164159.20075.16 PMID:15940039

Zang X, Qin W, Xiong Y, Xu A, Huang H, Fang T, et al. (2023). Using three statistical methods to analyze the association between aldehyde exposure and markers of inflammation and oxidative stress. Environ Sci Pollut Res Int. 30(32):79437–50. https://doi.org/10.1007/s11356-023-27717-4 PMID:37286832

Zani F, Blagih J, Gruber T, Buck MD, Jones N, Hennequart M, et al. (2023). The dietary sweetener sucralose is a negative modulator of T cell-mediated responses. Nature. 615(7953):705–11. https://doi.org/10.1038/s41586-023-05801-6 PMID:36922598

Zare Sakhvidi MJ, Lequy E, Goldberg M, Jacquemin B (2020). Air pollution exposure and bladder, kidney and urinary tract cancer risk: a systematic review. Environ Pollut. 267:115328. https://doi.org/10.1016/j.envpol.2020.115328 PMID:32871482

Zargar S, Alonazi M, Rizwana H, Wani TA (2019). Resveratrol reverses thioacetamide-induced renal assault with respect to oxidative stress, renal function, DNA damage, and cytokine release in Wistar rats. Oxid Med Cell Longev. 2019:1702959. https://doi.org/10.1155/2019/1702959 PMID:31583036

Zawirska B (1981). The role of the kidneys in disorders of porphyrin metabolism during carcinogenesis induced with lead acetate. Environ Res. 24(2):391–408. https://doi.org/10.1016/0013-9351(81)90168-7

Zawirska B, Medraś K (1968). [Tumors and disorders of porphyrin metabolism in rats with chronic experimental lead poisoning. I. Morphological studies]. Zentralbl Allg Pathol. 111(1):1–12. [German] PMID:4906497

Zawirska B, Medraś K (1972). The role of the kidneys in disorders of porphyrin metabolism during carcinogenesis induced with lead acetate. Arch Immunol Ther Exp (Warsz). 20(2):257–72. PMID:5024632

Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K (1992). Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ Mol Mutagen. 19 Suppl 21:2–141. https://doi.org/10.1002/em.2850190603https://doi.org/10.1002/em.2850190603 PMID:1541260

Zeiner GM, Boothroyd JC (2010). Use of two novel approaches to discriminate between closely related host microRNAs that are manipulated by *Toxoplasma gondii* during infection. RNA. 16(6):1268–74. https://doi.org/10.1261/rna.2069310 PMID:20423977

Zeljezic D, Mladinic M, Kopjar N, Radulovic AH (2016). Evaluation of genome damage in subjects occupationally exposed to possible carcinogens. Toxicol Ind Health. 32(9):1570–80. https://doi.org/10.1177/0748233714568478 PMID:25653038

Zeljezic D, Vinkovic B, Kasuba V, Kopjar N, Milic M, Mladinic M (2017). The effect of insecticides chlorpyrifos, α-cypermethrin and imidacloprid on primary DNA damage, TP 53 and c-Myc structural integrity by comet-FISH assay. Chemosphere. 182:332–8. https://doi.org/10.1016/j.chemosphere.2017.05.010 PMID:28505574

Zendehdel R, Yu IJ, Hajipour-Verdom B, Panjali Z (2019). DNA effects of low level occupational exposure to extremely low frequency electromagnetic fields (50/60 Hz). Toxicol Ind Health. 35(6):424–30. https://doi.org/10.1177/0748233719851697 PMID:31138035

Zeng J, Lei L, Zeng Q, Yao Y, Wu Y, Li Q, et al. (2020). Ozone therapy attenuates NF-κB-mediated local inflammatory response and activation of Th17 cells in treatment for psoriasis. Int J Biol Sci. 16(11):1833–45. https://doi.org/10.7150/ijbs.41940 PMID:32398953

Zeng JY, Chen PP, Liu C, Deng YL, Miao Y, Zhang M, et al. (2022). Bisphenol A analogues in associations with serum hormone levels among reproductive-aged Chinese men. Environ Int. 167:107446. https://doi.org/10.1016/j.envint.2022.107446 PMID:35940031

Zeng Y, Bai J, Deng LC, Xie YP, Zhao F, Huang Y (2016). Association of the glutathione S-transferase T1 null genotype with risk of gastric cancer: a meta-analysis in Asian populations. Asian Pac J Cancer Prev. 17(3):1141–8. https://doi.org/10.7314/APJCP.2016.17.3.1141 PMID:27039739

Zhang C, Li D, Ge T, Han J, Qi Y, Huang D (2020a). 2,4-Dichlorophenol induces feminization of zebrafish (Danio rerio) via DNA methylation. Sci Total Environ. 708:135084. https://doi.org/10.1016/j.scitotenv.2019.135084 PMID:31780173

Zhang C, Luo Y, Qiu S, Huang X, Jin K, Li J, et al. (2022d). Associations between urinary concentrations of bisphenols and serum concentrations of sex hormones among US males. Environ Health. 21(1):135. https://doi.org/10.1186/s12940-022-00949-6 PMID:36550468

Zhang C, Xu C, Gao X, Yao Q (2022a). Platinum-based drugs for cancer therapy and anti-tumor strategies. Theranostics. 12(5):2115–32. https://doi.org/10.7150/thno.69424 PMID:35265202

Zhang D, Jones RR, James P, Kitahara CM, Xiao Q (2021a). Associations between artificial light at night and risk for thyroid cancer: a large US cohort study. Cancer. 127(9):1448–58. https://doi.org/10.1002/cncr.33392 PMID:33554351

Zhang GQ, Chen JL, Luo Y, Mathur MB, Anagnostis P, Nurmatov U, et al. (2021b). Menopausal hormone therapy and women's health: an umbrella review. PLoS Med. 18(8):e1003731. https://doi.org/10.1371/journal.pmed.1003731 PMID:34339416

Zhang H, Li J, An Y, Wang D, Zhao J, Zhan M, et al. (2022e). Concentrations of bisphenols, benzophenone-type ultraviolet filters, triclosan, and triclocarban in the paired urine and blood samples from young adults: partitioning between urine and blood. Chemosphere. 288(Pt 2):132563.

https://doi.org/10.1016/j.chemosphere.2021.132563https://doi.org/10.1016/j.chemosphere.2021.132563 PMID:34653480

Zhang J, Haines C, Watson AJM, Hart AR, Platt MJ, Pardoll DM, et al. (2019b). Oral antibiotic use and risk of colorectal cancer in the United Kingdom, 1989–2012: a matched case-control study. Gut. 68(11):1971–8. https://doi.org/10.1136/gutjnl-2019-318593 PMID:31427405

Zhang J, Zhou Y, Wu YJ, Li MJ, Wang RJ, Huang SQ, et al. (2013a). Hyper-methylated miR-203 dysregulates ABL1 and contributes to the nickel-induced tumorigenesis. Toxicol Lett. 223(1):42–51. https://doi.org/10.1016/j.toxlet.2013.08.007 PMID:23968727

Zhang JH, Zhou SJ, Kuang Z, Qin ZH, Tan LW, Shao YT (2023d). [Expression profile of circular RNA in inflammatory response in human bronchial epithelial cells induced by carbon black nanoparticles]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 41(8):576–81. [Chinese] https://rs.yiigle.com/cmaid/1472331 PMID:37667152

Zhang JJ, Dong X, Liu GH, Gao YD (2023c). Risk and protective factors for COVID-19 morbidity, severity, and mortality. Clin Rev Allergy Immunol. 64(1):90–107. https://doi.org/10.1007/s12016-022-08921-5 PMID:35044620

Zhang JJ, Wei Y, Fang Z (2019a). Ozone pollution: a major health hazard worldwide. Front Immunol. 10:2518. https://doi.org/10.3389/fimmu.2019.02518 PMID:31736954

Zhang L, Wang B, Li K, Wang Z, Xu D, Su Y, et al. (2023f). Non-negligible health risks caused by inhalation exposure to aldehydes and ketones during food waste treatments in megacity Shanghai. Environ Pollut. 325:121448. https://doi.org/10.1016/j.envpol.2023.121448 PMID:36931489

Zhang L, Wang B, Wang Z, Li K, Fang R, Su Y, et al. (2022f). Spatiotemporal footprints of odor compounds in megacity's food waste streams and policy implication. J Hazard Mater. 437:129423. https://doi.org/10.1016/j.jhazmat.2022.129423 PMID:35752052

Zhang L, Yang L, Luo Y, Dong L, Chen F (2023g). Acrylamide-induced hepatotoxicity through oxidative stress: mechanisms and interventions. Antioxid Redox Signal. 38(16–18):1122–37. https://doi.org/10.1089/ars.2022.0055 PMID:36322716

Zhang L, Zhang J, Fan S, Zhong Y, Li J, Zhao Y, et al. (2023e). A case–control study of urinary concentrations of bisphenol A, bisphenol F, and bisphenol S and the risk of papillary thyroid cancer. Chemosphere. 312(Pt 1):137162. https://doi.org/10.1016/j.chemosphere.2022.137162 PMID:36347349

Zhang L, Zhang J, Yang L, Dong Y, Zhang Y, Xie Z (2013b). Isoflurane and sevoflurane increase interleukin-6 levels through the nuclear factor-kappa B pathway in neuroglioma cells. Br J Anaesth. 110 Suppl 1:i82–91. https://doi.org/10.1093/bja/aet115 PMID:23604542

Zhang M, Shi J, Meng Y, Guo W, Li H, Liu X, et al. (2019c). Occupational exposure characteristics and health risk of PBDEs at different domestic e-waste recycling workshops in China. Ecotoxicol Environ Saf. 174:532–9. https://doi.org/10.1016/j.ecoenv.2019.03.010 PMID:30861441

Zhang Q, Hu M, Wu H, Niu Q, Lu X, He J, et al. (2021d). Plasma polybrominated diphenyl ethers, urinary heavy metals and the risk of thyroid cancer: a case–control study in China. Environ Pollut. 269:116162. https://doi.org/10.1016/j.envpol.2020.116162 PMID:33303234

Zhang Q, Liu X, Gao M, Li X, Wang Y, Chang Y, et al. (2022b). The study of human serum metabolome on the health effects of glyphosate and early warning of potential damage. Chemosphere. 298:134308. https://doi.org/10.1016/j.chemosphere.2022.134308 PMID:35302001

Zhang Q, Matsuura K, Kleiner DE, Zamboni F, Alter HJ, Farci P (2016a). Analysis of long noncoding RNA expression in hepatocellular carcinoma of different viral etiology. J Transl Med. 14(1):328. https://doi.org/10.1186/s12967-016-1085-4https://doi.org/10.1186/s12967-016-1085-4 PMID:27894309

Zhang Q, Yu S, Chen X, Fu L, Dai W, Gu S (2021c). Stereoisomeric selectivity in the endocrine-disrupting potential of cypermethrin using in vitro, in vivo, and in silico assays. J Hazard Mater. 414:125389. https://doi.org/10.1016/j.jhazmat.2021.125389 PMID:33677314

Zhang RQ, Sun XF, Wu RY, Cheng SF, Zhang GL, Zhai QY, et al. (2018). Zearalenone exposure elevated the expression of tumorigenesis genes in mouse ovarian granulosa cells. Toxicol Appl Pharmacol. 356:191–203. https://doi.org/10.1016/j.taap.2018.08.013 PMID:30138655

Zhang S, Li J, Li Y, Liu Y, Guo H, Xu X (2017). Nitric oxide synthase activity correlates with OGG1 in ozone-induced lung injury animal models. Front Physiol. 8:249. https://doi.org/10.3389/fphys.2017.00249 PMID:28496412

Zhang W, Huang J, Peng G, Ding Q, Chen J, Hua Y, et al. (2013c). Null genotype of glutathione *S*-transferase T1 contributes to increased risk of gastric cancer in Asian population. Tumour Biol. 34(3):1461–6. https://doi.org/10.1007/s13277-013-0669-3 PMID:23397542

Zhang X, Li H, Qiu Q, Qi Y, Huang D, Zhang Y (2014). 2,4-Dichlorophenol induces global DNA hypermethylation through the increase of S-adenosylmethionine and the upregulation of DNMTs mRNA in the liver of goldfish *Carassius auratus.* Comp Biochem Physiol C Toxicol Pharmacol. 160:54–9. https://doi.org/10.1016/j.cbpc.2013.11.008 PMID:24316013

Zhang X, Wallace AD, Du P, Kibbe WA, Jafari N, Xie H, et al. (2012b). DNA methylation alterations in response to pesticide exposure in vitro. Environ Mol Mutagen. 53(7):542–9. https://doi.org/10.1002/em.21718 PMID:22847954

Zhang X, Zha J, Li W, Yang L, Wang Z (2008). Effects of 2,4-dichlorophenol on the expression of vitellogenin and estrogen receptor genes and physiology impairments in Chinese rare minnow (*Gobiocypris rarus*). Environ Toxicol. 23(6):694–701. https://doi.org/10.1002/tox.20375 PMID:18348291

Zhang X, Zhao L, Ducatman A, Deng C, von Stackelberg KE, Danford CJ, et al. (2023a). Association of per- and polyfluoroalkyl substance exposure with fatty liver disease risk in US adults. JHEP Rep Innov Hepatol. 5(5):100694. https://doi.org/10.1016/j.jhepr.2023.100694https://doi.org/10.1016/j.jhepr.2023.100694 PMID:36968216

Zhang Y, Bao J, Gong X, Shi W, Liu T, Wang X (2022c). Transcriptomics and metabolomics revealed the molecular mechanism of the toxic effect of mancozeb on liver of mice. Ecotoxicol Environ Saf. 243:114003. https://doi.org/10.1016/j.ecoenv.2022.114003https://doi.org/10.1016/j.ecoenv.2022.114003 PMID:36007320

Zhang Y, Birmann BM, Han J, Giovannucci EL, Speizer FE, Stampfer MJ, et al. (2020b). Personal use of permanent hair dyes and cancer risk and mortality in US women: prospective cohort study. BMJ. 370:m2942. https://doi.org/10.1136/bmj.m2942 PMID:32878860

Zhang Y, Dong Y, Wu X, Lu Y, Xu Z, Knapp A, et al. (2010). The mitochondrial pathway of anesthetic isoflurane-induced apoptosis. J Biol Chem. 285(6):4025–37. https://doi.org/10.1074/jbc.M109.065664 PMID:20007710

Zhang Y, Huo X, Cao J, Yang T, Xu L, Xu X (2016b). Elevated lead levels and adverse effects on natural killer cells in children from an electronic waste recycling area. Environ Pollut. 213:143–50. https://doi.org/10.1016/j.envpol.2016.02.004 PMID:26895538

Zhang Y, Lv J, Fan YJ, Tao L, Xu J, Tang W, et al. (2023b). Evaluating the effect of gestational exposure to perfluorohexane sulfonate on placental development in mice combining alternative splicing and gene expression analyses. Environ Health Perspect. 131(11):117011. https://doi.org/10.1289/EHP13217 PMID:37995155

Zhang Y, Xu Z, Wang H, Dong Y, Shi HN, Culley DJ, et al. (2012a). Anesthetics isoflurane and desflurane differently affect mitochondrial function, learning, and memory. Ann Neurol. 71(5):687–98. https://doi.org/10.1002/ana.23536 PMID:22368036

Zhang Y, Zhang Y, Ye Z, Yang S, Liu M, Wu Q, et al. (2024). Mobile phone use and risks of overall and 25 site-specific cancers: a prospective study from the UK Biobank Study. Cancer Epidemiol Biomarkers Prev. 33(1):88–95. https://doi.org/10.1158/1055-9965.EPI-23-0766 PMID:37870426

Zhang Z, Guo S, Liu X, Gao X (2015). Synergistic antitumor effect of α-pinene and β-pinene with paclitaxel against non-small-cell lung carcinoma (NSCLC). Drug Res (Stuttg). 65(4):214–8. https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0034-1377025 PMID:25188609

Zhao GP, Wang XY, Li JW, Wang R, Ren FZ, Pang GF, et al. (2021b). Imidacloprid increases intestinal permeability by disrupting tight junctions. Ecotoxicol Environ Saf. 222:112476. https://doi.org/10.1016/j.ecoenv.2021.112476 PMID:34214772

Zhao HZ, Guo ZW, Wang ZL, Wang C, Luo XY, Han NN, et al. (2024). A comparative study of the effects of electronic cigarette and traditional cigarette on the pulmonary functions of C57BL/6 male mice. Nicotine Tob Res. 26(4):474–83. https://doi.org/10.1093/ntr/ntad139 PMID:37535700

Zhao J, Liu X, Chen Y, Zhang LS, Zhang YR, Ji DR, et al. (2021a). STAT3 promotes schistosome-induced liver injury by inflammation, oxidative stress, proliferation, and apoptosis signal pathway. Infect Immun. 89(3):e00309–20. https://doi.org/10.1128/IAI.00309-20 PMID:33257536

Zhao S, Fan Z, Hu J, Zhu Y, Lin C, Shen T, et al. (2020b). The differential effects of isoflurane and sevoflurane on neonatal mice. Sci Rep. 10(1):19345. https://doi.org/10.1038/s41598-020-76147-6 PMID:33168900

Zhao TT, Jin F, Li JG, Xu YY, Dong HT, Liu Q, et al. (2019). Dietary isoflavones or isoflavone-rich food intake and breast cancer risk: a meta-analysis of prospective cohort studies. Clin Nutr. 38(1):136–45. https://doi.org/10.1016/j.clnu.2017.12.006 PMID:29277346

Zhao X, Wang Y, Liu JL, Zhang JH, Zhang SC, Ouyang Y, et al. (2020a). Fumonisin B1 affects the biophysical properties, migration and cytoskeletal structure of human umbilical vein endothelial cells. Cell Biochem Biophys. 78(3):375–82. https://doi.org/10.1007/s12013-020-00923-4 PMID:32504355

Zhao Y, Chen R, Wang Y, Yang Y (2018). α-Pinene inhibits human prostate cancer growth in a mouse xenograft model. Chemotherapy. 63(1):1–7. https://doi.org/10.1159/000479863https://doi.org/10.1159/000479863 PMID:29069647

Zhao Z, Hua Z, Luo X, Li Y, Yu L, Li M, et al. (2022). Application and pharmacological mechanism of methotrexate in rheumatoid arthritis. Biomed Pharmacother. 150:113074. https://doi.org/10.1016/j.biopha.2022.113074 PMID:35658215

Zheng C, Zeng H, Lin H, Wang J, Feng X, Qiu Z, et al. (2017). Serum microcystin levels positively linked with risk of hepatocellular carcinoma: a case–control study in southwest China. Hepatology. 66(5):1519–28. https://doi.org/10.1002/hep.29310 PMID:28599070

Zheng W, McLaughlin JK, Gao YT, Silverman DT, Gao RN, Blot WJ (1992). Bladder cancer and occupation in Shanghai, 1980–1984. Am J Ind Med. 21(6):877–85. https://doi.org/10.1002/ajim.4700210611 PMID:1621696

Zheng Y, Izumi K, Li Y, Ishiguro H, Miyamoto H (2012). Contrary regulation of bladder cancer cell proliferation and invasion by dexamethasone-mediated glucocorticoid receptor signals. Mol Cancer Ther. 11(12):2621–32. https://doi.org/10.1158/1535-7163.MCT-12-0621 PMID:23033490

Zhivagui M, Ng AWT, Ardin M, Churchwell MI, Pandey M, Renard C, et al. (2019). Experimental and pan-cancer genome analyses reveal widespread contribution of acrylamide exposure to carcinogenesis in humans. Genome Res. 29(4):521–31. https://doi.org/10.1101/gr.242453.118 PMID:30846532

Zhong C, Franklin M, Wiemels J, McKean-Cowdin R, Chung NT, Benbow J, et al. (2020). Outdoor artificial light at night and risk of non-Hodgkin lymphoma among women in the California Teachers Study cohort. Cancer Epidemiol. 69:101811. https://doi.org/10.1016/j.canep.2020.101811 PMID:33002844

Zhong C, Wang R, Morimoto LM, Longcore T, Franklin M, Rogne T, et al. (2023a). Outdoor artificial light at night, air pollution, and risk of childhood acute lymphoblastic leukemia in the California Linkage Study of Early-Onset Cancers. Sci Rep. 13(1):583. https://doi.org/10.1038/s41598-022-23682-z PMID:36631468

Zhong GC, Zhu Q, Cai D, Hu JJ, Dai X, Gong JP, et al. (2023b). Ultra-processed food consumption and the risk of pancreatic cancer in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Int J Cancer. 152(5):835–44. https://doi.org/10.1002/ijc.34290 PMID:36094042

Zhong S, Ye W, Lin SH, Liu JY, Leong J, Ma C, et al. (2011). Zeranol induces cell proliferation and protein disulfide isomerase expression in mammary gland of ACI rat. Anticancer Res. 31(5):1659–65. https://ar.iiarjournals.org/content/31/5/1659.long PMID:21617224

Zhong T, Qing QJ, Yang Y, Zou WY, Ye Z, Yan JQ, et al. (2014). Repression of contexual fear memory induced by isoflurane is accompanied by reduction in histone acetylation and rescued by sodium butyrate. Br J Anaesth. 113(4):634–43. https://doi.org/10.1093/bja/aeu184 PMID:24838805

Zhong Y, Yang C, Wang N, Pan D, Wang S, Sun G (2022). Hot tea drinking and the risk of esophageal cancer: a systematic review and meta-analysis. Nutr Cancer. 74(7):2384–91. https://doi.org/10.1080/01635581.2021.2007963 PMID:34818954

Zhou C, Li J, Guo C, Zhou Z, Yang Z, Zhang Y, et al. (2023a). Alterations in gut microbiome and metabolite profile of patients with *Schistosoma japonicum* infection. Parasit Vectors. 16(1):346. https://doi.org/10.1186/s13071-023-05970-3 PMID:37798771

Zhou G, Lü M, Xiu Z, Wang S, Zhang H, Zhou Y, et al. (2006). Controlled synthesis of high-quality PbS star-shaped dendrites, multipods, truncated nanocubes, and nanocubes and their shape evolution process. J Phys Chem B. 110(13):6543–8. https://doi.org/10.1021/jp0549881 PMID:16570952

Zhou J, Zhang D, Yang Y, Zhou L, Tao L (2016). Association between *Helicobacter pylori* infection and carcinoma of the larynx or pharynx. Head Neck. 38 Suppl 1:E2291–6. https://doi.org/10.1002/hed.24214 PMID:26316145

Zhou R, Zhang L, Sun Y, Yan J, Jiang H (2023b). Association of urinary bisphenols with oxidative stress and inflammatory markers and their role in obesity. Ecotoxicol Environ Saf. 266:115546. https://doi.org/10.1016/j.ecoenv.2023.115546 PMID:37827096

Zhou Y, Irshad H, Dye WW, Wu G, Tellez CS, Belinsky SA (2021). Voltage and e-liquid composition affect nicotine deposition within the oral cavity and carbonyl formation. Tob Control. 30(5):485–91. https://doi.org/10.1136/tobaccocontrol-2020-055619 PMID:32587113

Zhou Y, Zhao H, Peng C (2015). Association of sedentary behavior with the risk of breast cancer in women: update meta-analysis of observational studies. Ann Epidemiol. 25(9):687–97. https://doi.org/10.1016/j.annepidem.2015.05.007 PMID:26099193

Zhu CC, Hou YJ, Han J, Cui XS, Kim NH, Sun SC (2014). Zearalenone exposure affects epigenetic modifications of mouse eggs. Mutagenesis. 29(6):489–95. https://doi.org/10.1093/mutage/geu033 PMID:25155023

Zhu L, Xue J, He Y, Xia Q, Fu PP, Lin G (2022). Correlation investigation between pyrrole–DNA and pyrrole–protein adducts in male ICR mice exposed to retrorsine, a hepatotoxic pyrrolizidine alkaloid. Toxins (Basel). 14(6):377. https://doi.org/10.3390/toxins14060377https://doi.org/10.3390/toxins14060377 PMID:35737038

Zhu L, Xue J, Xia Q, Fu PP, Lin G (2017). The long persistence of pyrrolizidine alkaloid-derived DNA adducts in vivo: kinetic study following single and multiple exposures in male ICR mice. Arch Toxicol. 91(2):949–65. https://doi.org/10.1007/s00204-016-1713-zhttps://doi.org/10.1007/s00204-016-1713-z PMID:27125825

Zhu L, Yuhan J, Huang K, He X, Liang Z, Xu W (2021a). Multidimensional analysis of the epigenetic alterations in toxicities induced by mycotoxins. Food Chem Toxicol. 153:112251. https://doi.org/10.1016/j.fct.2021.112251 PMID:33961929

Zhu M, Wu J, Ma X, Huang C, Wu R, Zhu W, et al. (2019). Butyl benzyl phthalate promotes prostate cancer cell proliferation through miR-34a downregulation. Toxicol In Vitro. 54:82–8. https://doi.org/10.1016/j.tiv.2018.09.007 PMID:30243731

Zhu S, Jiao W, Xu Y, Hou L, Li H, Shao J, et al. (2021d). Palmitic acid inhibits prostate cancer cell proliferation and metastasis by suppressing the PI3K/Akt pathway. Life Sci. 286:120046. https://doi.org/10.1016/j.lfs.2021.120046https://doi.org/10.1016/j.lfs.2021.120046 PMID:34653428

Zhu S, Rong Y, Kiang TKL (2021c). Effects of *p*-cresol on oxidative stress, glutathione depletion, and necrosis in HepaRG cells: comparisons to other uremic toxins and the role of *p*-cresol glucuronide formation. Pharmaceutics. 13(6):857. https://doi.org/10.3390/pharmaceutics13060857https://doi.org/10.3390/pharmaceutics13060857 PMID:34207666

Zhu X, Pan D, Wang N, Wang S, Sun G (2021b). Relationship between selenium in human tissues and breast cancer: a meta-analysis based on case–control studies. Biol Trace Elem Res. 199(12):4439–46. https://doi.org/10.1007/s12011-021-02574-9 PMID:33420696

Zhu ZH, Sun ML, Li ZS, Yang ZC, Zhang TB, Heng ZC, et al. (1987). [An investigation of the maximum allowable concentration of sulfolane in surface water]. Hua Xi Yi Ke Da Xue Xue Bao. 18(4):376–80. [Chinese] PMID:3449430

Zimmerman MA, Budish RA, Kashyap S, Lindsey SH (2016). GPER-novel membrane oestrogen receptor. Clin Sci (Lond). 130(12):1005–16. https://doi.org/10.1042/CS20160114https://doi.org/10.1042/CS20160114 PMID:27154744

Zimmermann FK, Mohr A (1992). Formaldehyde, glyoxal, urethane, methyl carbamate, 2,3-butanedione, 2,3-hexanedione, ethyl acrylate, dibromoacetonitrile and 2-hydroxypropionitrile induce chromosome loss in *Saccharomyces cerevisiae*. Mutat Res. 270(2):151–66. https://doi.org/10.1016/0027-5107(92)90126-M PMID:1383732

Zober A, Hoffmann G, Ott MG, Will W, Germann C, van Ravenzwaay B (1995). Study of morbidity of personnel with potential exposure to vinclozolin. Occup Environ Med. 52(4):233–41. https://doi.org/10.1136/oem.52.4.233 PMID:7795738

Zong Z, Wei Y, Ren J, Zhang L, Zhou F (2021). The intersection of COVID-19 and cancer: signalling pathways and treatment implications. Mol Cancer. 20(1):76. https://doi.org/10.1186/s12943-021-01363-1 PMID:34001144

Zorrilla LM, Gibson EK, Stoker TE (2010). The effects of simazine, a chlorotriazine herbicide, on pubertal development in the female Wistar rat. Reprod Toxicol. 29(4):393–400. https://doi.org/10.1016/j.reprotox.2010.03.010 PMID:20381603

Zubidat AE, Fares B, Fares F, Haim A (2018). Artificial light at night of different spectral compositions differentially affects tumor growth in mice: interaction with melatonin and epigenetic pathways. Cancer Control. 25(1):1073274818812908. https://doi.org/10.1177/1073274818812908 PMID:30477310

Zumkeller N, Brenner H, Zwahlen M, Rothenbacher D (2006). *Helicobacter pylori* infection and colorectal cancer risk: a meta-analysis. Helicobacter. 11(2):75–80. https://doi.org/10.1111/j.1523-5378.2006.00381.x PMID:16579836

Zúñiga-González GM, Gómez-Meda BC, Lemus-Varela ML, Zamora-Perez AL, Armendáriz-Borunda J, Barros-Hernández A, et al. (2012). Micronucleated erythrocytes in preterm newborns exposed to phototherapy and/or oxygentherapy. J Photochem Photobiol B. 107:79–83. https://doi.org/10.1016/j.jphotobiol.2011.12.002 PMID:22209030

Zweig G, Leffingwell JT, Popendorf W (1985). The relationship between dermal pesticide exposure by fruit harvesters and dislodgeable foliar residues. J Environ Sci Health B. 20(1):27–59. https://doi.org/10.1080/03601238509372467 PMID:3921591

Zwirner-Baier I, Kordowich FJ, Neumann HG (1994). Hydrolyzable hemoglobin adducts of polyfunctional monocyclic N-substituted arenes as dosimeters of exposure and markers of metabolism. Environ Health Perspect. 102(Suppl 6) suppl 6:43–5. https://doi.org/10.1289/ehp.94102s643 PMID:7889857

List of Abbreviations

AADC	aromatic L-amino acid decarboxylase
AARP	American Association of Retired Persons
AAV	adeno-associated viruses
ABS	acrylonitrile-butadiene-styrene
ACE	angiotensin converting enzyme
ACGIH	American Conference of Governmental Industrial Hygienists
AChE	acetylcholinesterase
ADHD	attention deficit hyperactivity disorder
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AdV	adenoviruses
AFFF	aqueous film-forming foam
AGRICAN	AGRiculture & CANcer
AHR	arhyl receptor
AHS	Agricultural Health Study
ALAN	artificial light at night
ALCL	anaplastic large-cell lymphoma
ALD	adrenoleukodystrophy
ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia
AMPA	aminomethylphosphonic acid
AOEL	acceptable operator exposure level
AOPP	advanced oxidation protein products
AR	androgen receptor
ARG	arginase
ART	assisted reproductive techniques
ASB	artificially sweetened beverages
ATG	anti-thymocyte globulin
ATP	adenosine triphosphate
BaP	benzo[*a*]pyrene
BAX	BCL2 associated X, apoptosis regulator
BBN	*N*-butyl-*N*-(4-hydroxybutyl)nitrosamine
BBP	butyl benzyl phthalate
BCAC	Breast Cancer Association Consortium
BCC	basal cell carcinoma
BCE	black cohosh extracts
BMI	body mass index
BPA	bisphenol A
BPD	bronchopulmonary dysplasia
BPF	bisphenol F
BPS	bisphenol S
BRAF	B-Raf proto-oncogene
BTX	benzene, toluene, xylene
CAR	constitutive androstane receptor
CAREX	CARcinogen EXposure
CAS	chemical abstracts service
CAT	catalase

CBMC	cord blood mononuclear cells
CDC	Centers for Disease Control and Prevention
CHO	chinese hamster ovary
CHOP	cyclophosphamide, daunorubicin, vincristine, and prednisone
CI	confidence interval
CIC	Carcinogen Identification Committee
CLL	chronic lymphocytic leukaemia
CNF	carbon nanofibres
CNS	central nervous system
COC	cumulus–oocyte complexes
COSMOS	European Cohort Study of Mobile Phone Use and Health
CRC	colorectal cancer
CYP	cytochrome P450
DBCP	1,2-Dibromo-3-chloropropane
DBP	dibutyl phthalate
DD	dopamine-deficient mice
DEET	*N*,*N*-diethyl-*meta*-toluamide
DEHP	Di(2-ethylhexyl) phthalate
DEN	diethylnitrosamine
DHFR	dihydrofolate reductase
DINCH	diisononyl cyclohexane-1,2-dicarboxylate
DINP	diisononyl phthalate
DLBCL	diffuse large B-cell lymphoma
DMBA	7,12-dimethylbenz[*a*]anthracene
DMSO	dimethyl sulfoxide
DMSP	Defense Meteorological Satellite Program
DWCNT	double-walled carbon nanotube
EARLI	Early Autism Risk Longitudinal Investigation
EBDC	ethylenebisdithiocarbamate
EBV	Epstein–Barr virus
ECHA	European Chemicals Agency
ECS	e-cigarette smoke
EDA	ethylenediamine
EDBC	ethylenedithiocarbamate
EFSA	European Food Safety Authority
EGFR	epidermal growth factor receptor protein
ELF	extremely low-frequency magnetic fields
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMF	electromagnetic field
EMP	elongate mineral particles
EMT	epithelial–mesenchymal transition
ENDS	electronic nicotine delivery systems
EPIC	European Prospective Investigation into Cancer and Nutrition
EPICAP	EPIdemiological study of Prostate CAncer
EPTC	*S*-ethyl-*N*,*N*-dipropylthiocarbamate
ER	estrogen receptor
ESCCAPE	Esophageal Squamous Cell Carcinoma African Prevention Research
EtO	ethylene oxide

ETU	ethylene thiourea
EV	epidermodysplasia verruciformis
FD&C	Federal Food Drug and Cosmetic Act
FISH	fluorescence in situ hybridization
FMO	flavin-containing monooxygenase
FSH	follicle-stimulating hormone
GBCA	gadolinium-based contrast agents
GDM	global DNA methylation
GDNF	glial cell line-derived neurotrophic factor
GF	germ-free
GJIC	gap junctional intercellular communication
GLP	Good Laboratory Practice
GM	geometric mean
GPER	g protein-coupled estrogen receptor
GRAS	generally recognized as safe
GSH	glutathione
GSTT1	glutathione *S*-transferase theta 1
GTH	gonadotropin hormone
HAA	haloacetic acid
HAPI	highly aggressively proliferating immortalized
HBP	hydroxybiphenyl
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCMV	human cytomegalovirus
HCV	hepatitis C virus
HDV	hepatitis D virus
HFR	halogen flame retardants
HL	Hodgkin lymphoma
HMBP	2-Hydroxy-4-methoxybenzophenone
HPRT	hypoxanthine-guanine phosphoribosyl transferase
HPV	human papillomavirus
HR	hazard ratio
HRT	hormone replacement therapy
HSCT	haematopoietic stem cell transplantation
HUVEC	human umbilical vein endothelial cells
HWSB	healthy worker survivor bias
ICC	intrahepatic cholangiocarcinoma
ICSI	intra-cytoplasmic sperm injection
IFN	interferon
IgA	immunoglobulin A
IgG	immunoglobulin G
INCHEM	Internationally Peer Reviewed Chemical Safety Information
INN	international nonproprietary name
ILO	International Labour Organization
IPCS	International Programme on Chemical Safety
IPL	intense pulsed light
IPSE	IL-4 inducing principle from *S. mansoni* eggs
ISA	Integrated Science Assessment
IUD	intrauterine device

IVF	in vitro fertilization
JAK	janus kinase
JBRC	Japan Bioassay Research Center
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
JNK	jun N-terminal kinase
KC	KCs of carcinogens
KSHV	kaposi sarcoma-associated herpesvirus
LAN	light at night
LCV	leukocytoclastic vasculitis
LED	light-emitting diode
LGBTQ	lesbian, gay, bisexual, transgender, or queer
LH	luteinizing hormone
LMIC	low- and middle-income countries
LNCaP	Lymph Node Carcinoma of the Prostate cell line
LPC	long-term progestin-only contraceptives
LPS	lipopolysaccharide
LT	large T antigen
LV	lentivirus
MALT	mucosa associated lymphoid tissue
MAPK	mitogen-activated protein kinase
MBzP	monobenzyl phthalate
MCC	merkel cell carcinoma
MCL	mantle cell lymphoma
MCV	merkel cell polyomavirus
MDA	malondialdehyde
MDP	muramyl dipeptide
MDS	myelodysplastic syndrome
MDSC	myeloid-derived suppressor cells
MEK	anti-MAPK kinase
MELN	ERE-βGlob-Luc-SVNeo plasmid
MGUS	monoclonal gammopathy of undetermined significance
MIG	monokine induced by IFNγ
MINCH	monoisononyl ester
MLD	metachromatic leukodystrophy
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
MWCNT	multiwalled carbon nanotubes
MYC	MYC proto-oncogene
NADH	nicotinamide adenine dinucleotide
NAFLD	non-alcoholic fatty liver disease
NANoREG	EU framework for the safety assessment of nanomaterials
NAPP	North American Pooled Project
NCE	normochromatic erythrocytes
NCTR	National Center for Toxicological Research
NHANES	National Health and Nutrition Examination Survey
NHBE	normal human bronchial epithelial
NHL	non-Hodgkin lymphoma
NIOSH	National Institute for Occupational Safety and Health

NK	natural killer
NMDA	*N*-methyl-D-aspartate
NMSC	non-melanoma skin cancer
NNK	4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone
NNN	*N′*-nitrosonornicotine
NOAEL	no observed adverse effect level
NOCCA	Nordic Occupational Cancer Study
NSW	night shift work
NTA	nitrilotriacetic acid
NTP	National Toxicology Program
OBESO	Origen Bioquímico y Epigenético del Sobrepeso y la Obesidad
OECD	Organisation for Economic Co-operation and Development
OMEGA	Ovariumstimulatie en Gynecologische Aandoeningen
ORAL	Oral Rheumatoid Arthritis Trial
OSHA	Occupational Safety and Health Administration
PA	pyrrolizidine alkaloids
PAH	polycyclic aromatic hydrocarbons
PAMS	PA mutational signature
PBDE	pentabromodimethyl ether
PBO	piperonyl butoxide
PBL	peripheral blood lymphocytes
PBMC	peripheral blood mononuclear cells
PCB	polychlorinated biphenyls
PCE	polychromatic erythrocytes
PCNA	proliferating cell nuclear antigen
PCR	polymerase chain reaction
PCT	procalcitonin
PDC	plasmacytoid dendritic cells
PEF	peak expiratory flow
PFAS	per- and polyfluoroalkyl substances
PHMG	polyhexamethylene guanidine
PLA	polylactic acid
PLCO	prostate, lung, colorectal, and ovarian
PLD	pegulated liposomal doxorubicin
PM	particulate matter
PMS	premenstrual syndrome
PMTDI	provisional maximum tolerable daily intake
PON1	paraoxonase-1
PPAR	peroxisome proliferator-activated receptor
PR	progesterone receptor
PRS	polygenic risk score
PTEN	phosphatase and tensin homologue
PTLD	post-transplant lymphoproliferative disorder
PTWI	provisional tolerable weekly intake
PUMA	Pooled Uranium Miners Analysis
PVC	polyvinyl chloride
PXR	pregnane X receptor
RB	retinoblastoma
RCF	refractory ceramic fibres

RCS	respirable crystalline silica
REE	rare earth elements
ROS	reactive oxygen species
RR	Relative risk
SAM	*S*-adenosylmethionine
SAN	styrene–acrylonitrile
SBC	subsequent breast cancer
SCC	squamous cell carcinoma
SCE	sister-chromatid exchange
SCID	severe combined immunodeficiency
SDH	succinate dehydrogenase
SEA	soluble egg antigens
SEER	Surveillance, Epidemiology, and End Results
SH	sulfhydryl
SHGB	sex hormone-binding globulin
SIR	standardized incidence ratio
SLL	Small B-cell lymphocytic lymphoma
SMART	*drosophila* Wing Spot Test
SMR	Standardized mortality ratio
SNP	single-nucleotide polymorphism
SOD	superoxide dismutase
SSB	sugar-sweetened beverage
StAR	steroidogenic acute regulatory protein
SWCNT	single-walled carbon nanotubes
TBARS	thiobarbituric acid-reactive substances
TBP	2,4,6-Tribromophenol
TCEP	tris(2-chloroethyl) phosphate
TCPP	tris(chloropropyl) phosphate
TGFA	transforming growth factor alpha
THM	trihalomethanes
THS	tobacco heating system
TIDES	The Infant Development and the Environment Study
TIPS	transtracheal intrapulmonary spraying
TLV	threshold limit value
TNFα	tumour necrosis factor alpha
TPA	12-*O*-tetradecanoylphorbol-13-acetate
TSH	thyroid-stimulating hormone
TSNA	tobacco-specific nitrosamines
TWA	time-weighted average
UDS	unscheduled DNA synthesis
UFP	ultra-fine particles
UK	United Kingdom
UPF	ultra-processed food
US	United States
US EPA	United States Evironmental Protection Agency
US FDA	United States Food and Drug Administration
UV	ultraviolet
UVB	ultraviolet B radiation
VEGF	vascular endothelial growth factor

VIIRS	visible Infrared Imaging Radiometer Suite
VZV	varicella zoster virus
WHI	Women's Health Initiative
YAP	yes-activating protein

Annex 1. List of participants

IARC Monographs on the Identification of Carcinogenic Hazards to Humans

Advisory Group to Recommend Priorities for the *IARC Monographs* during 2025–2029

Lyon, France: 19–22 March 2024

LIST OF PARTICIPANTS

IARC requests that Meeting Observers and others outside the Advisory Group do not contact or lobby Advisory Group Members, send them written materials, or offer favours that could appear to be linked to their participation. (You may send pertinent written materials to IARC.) IARC will ask participants to report all such contacts and will publicly reveal any attempt to influence the meeting. Thank you for your cooperation.

Advisory Group Members serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only.

Members

Robert Barouki, Institut national de la santé et de la recherche médicale (INSERM), France
Silvia Berlanga de Moraes Barros, University of São Paulo (retired), Brazil
Dinesh Barupal, Icahn School of Medicine, Mount Sinai, USA[1]
Laura Beane Freeman, Division of Cancer, Epidemiology and Genetics, National Cancer Institute, USA
Amy Berrington de González, The Institute of Cancer Research, UK
Parveen Bhatti, British Columbia Cancer Research Institute, Canada
Gloria Calaf, Instituto de Alta Investigacion, Universidad de Tarapacá, Chile
Rajesh Dikshit, Center for Cancer Epidemiology, Tata Memorial Hospital, India (withdrew)
Joakim Dillner, Karolinska Institutet, Sweden
Karima El Rhazi, Department of Epidemiology and Public Health, Faculty of Medicine of Fez, Morocco
Renée Turzanski Fortner, Cancer Registry of Norway and German Cancer Research Center, Norway
Lin Fritschi, Curtin University, Australia
Shoji Fukushima, Japan Bioassay Research Center, Japan
Lode Godderis, Leuven University and Belgian Service for Prevention and Protection (IDEWE), Belgium
Manolis Kogevinas, Barcelona Institute for Global Health, Spain
Dirk Lachenmeier, Chemical and Veterinary Investigation Agency Karlsruhe (CVUA), Germany
Daniele Mandrioli, Ramazzini Institute, Italy
Scott Masten, National Institute of Environmental Health Sciences, USA

[1] Dr Barupal reported receiving personal consultancy fees from Brightseed Bio Inc. for processing untargeted high-resolution mass spectrometry metabolomics datasets and for generating mass spectral libraries for authentic chemical standards. Brightseed Bio's products do not appear to present a competing interest for the agents considered at the present meeting.

Mazvita Molleen Muchengeti, National Cancer Registry, National Health Laboratory Service, South Africa
Richard T. Niemeier, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, USA
Jane Pappas, Health Canada, Canada
Susan Peters, Institute for Risk Assessment Sciences, Utrecht University, The Netherlands
Jingbo Pi, Key Laboratory of Environmental Stress and Chronic Disease Control and Prevention, Ministry of Education, China Medical University, China
Mark Purdue, Division of Cancer Epidemiology and Genetics, National Cancer Institute, USA
Elio Riboli, School of Public Health, Imperial College London, UK
Teresa Rodriguez, Autonomous University of Nicaragua (retired), Nicaragua
Tiina Santonen, Finnish Institute of Occupational Health, Finland
Vivi Schlünssen, Department of Public Health, Aarhus University, Denmark
Marianna G. Yakubovskaya, NN Blokhin National Medical Research Center of Oncology, Russian Federation

Invited Specialists

None

Representatives of national and international health agencies

Yoonjoo Choi, National Cancer Center, Republic of Korea
Byungmi Kim, National Cancer Center, Republic of Korea

Observers

Remi Bars, Regulatory Science Associates, France[2]
Janice Britt, ToxStrategies, USA[3]

IARC Secretariat

Ayat Ahmadi, *IARC Monographs* Programme
Lamia Benbrahim-Tallaa, *IARC Monographs* Programme
Shirisha Chittiboyina, *IARC Monographs* Programme
Aline de Conti, *IARC Monographs* Programme
Caterina Facchin, *IARC Monographs* Programme
Zdenko Herceg, IARC Epigenomics and Mechanisms Branch
Shalini Kulasingam, *IARC Monographs* Programme
Béatrice Lauby-Secretan, *IARC Handbooks* Programme
Richard MacLehose, *IARC Monographs* Programme
Federica Madia, *IARC Monographs* Programme

[2] Dr Bars reported being a salaried employee of Regulatory Science Associates and that CropLife International will sponsor his travel to and attendance at the present meeting.
[3] Dr Britt reported being a salaried employee of ToxStrategies LLC, which will sponsor her travel to and attendance at the present meeting.

Heidi Mattock, *IARC Monographs* Programme (Editor)
Elisa Pasqual, *IARC Monographs* Programme
Moez Sanaa, Department of Nutrition and Food Safety Standards / Scientific Advice on Food and Nutrition, WHO
Mary Schubauer-Berigan, *IARC Monographs* Programme (Programme Head & Responsible Officer)
Joachim Schüz, IARC Environment and Lifestyle Epidemiology Branch[4]
Eero Suonio, *IARC Monographs* Programme
Roland Wedekind, *IARC Monographs* Programme
Jiri Zavadil, IARC Epigenomics and Mechanisms Branch

NOTE REGARDING CONFLICTS OF INTERESTS: Each participant first received a preliminary invitation with the request to complete and sign the IARC/WHO Declaration of Interests, which covers employment and consulting activities, individual and institutional research support, and other financial or non-financial interests (e.g. public statements and positions related to the subject of the meeting).

Official invitations were extended after careful assessment of any declared interests that might constitute a conflict of interest. Pertinent and significant conflicts are disclosed here. Information about other potential conflicts that are not disclosed may be sent to the Head of the *IARC Monographs* programme at imo@iarc.who.int.

The Declarations were updated and reviewed again at the opening of the meeting.

[4] Dr Schüz reports that this spouse is a salaried employee of Merck group. None of the pharmaceutical agents at the meeting are produced by Merck group.

Annex 2. Meeting agenda

IARC Monographs on the Identification of Carcinogenic Hazards to Humans
Advisory Group to Recommend Priorities for IARC Monographs during 2025–2029
Lyon, France, 19-22 March 2024

Tuesday, 19 March 2024

09:00-09:30	Registration, lobby
09:30-10:30	Plenary session: introductions and discussion of prioritization criteria
10:30-11:00	Group photo followed by coffee break, lobby
11:00-11:30	Presentation from Dr Dinesh K. Barupal, Mount Sinai School of Medicine
11:30-13:00	Discipline subgroup sessions: exposure, human cancer, cancer bioassays, mechanisms
13:00-14:00	Lunch, IARC cafeteria
14:00-16:00	Discipline subgroup sessions: exposure, human cancer, cancer bioassays, mechanisms
16:00-16:30	Coffee break and payment of *per diem* & dinner reservation, lobby
16:30-18:00	Subgroup sessions: exposure, human cancer, cancer bioassays, mechanisms
18:00 - 19:00	Chairs' coordination meeting

Wednesday, 20 March 2024

09:00-9:30	Plenary session: progress report from discipline subgroups
09:30-10:30	Discipline subgroup sessions: exposure, human cancer, cancer bioassays, mechanisms
10:30-11:00	Coffee break, lobby
11:00-13:00	Discipline subgroup sessions: exposure, human cancer, cancer bioassays, mechanisms
13:00-14:00	Lunch, IARC cafeteria
14:00-16:00	Discipline subgroup sessions: exposure, human cancer, cancer bioassays, mechanisms
16:00-16:30	Coffee break and payment of *per diem* & dinner reservation, lobby
16:30-18:00	Subgroup sessions: exposure, human cancer, cancer bioassays, mechanisms
18:00 - 19:00	Chairs' coordination meeting

Thursday, 21 March 2024

09:00-10:30	Plenary session: results of discipline subgroups; overview of agent-type subgroup work
10:30-11:00	Coffee break, lobby
11:00-13:00	Agent-type subgroup sessions (A-E)
13:00-14:00	Lunch, IARC cafeteria
14:00-15:45	Agent-type subgroup sessions (A-E)
15:45-16:15	Coffee break, lobby
16:15-17:30	Agent-type subgroup sessions (A-E)
17:30-18:00	Chairs' coordination meeting
18:30-21:00	Group apéritif dînatoire, Salons d'Anthouard, 249 Rue Marcel Mérieux, 69007 Lyon

Friday, 22 March 2024

09:00-10:30	Plenary session: Finalize prioritizations
10:30-11:00	Coffee break, lobby
11:00-13:00	Plenary session: Finalize prioritizations
13:00-14:00	Lunch, IARC cafeteria
14:00-15:45	Plenary session: Advice on miscellaneous topics
15:45-16:15	Coffee break, lobby
16:15-18:00	Plenary session: report finalization and closing remarks

Annex 3. Search terms used to identify studies for detailed narrative descriptions

Narrative descriptions – search terms used	
Search string label	**Search terms**
Human exposure	AGENT NAME AND (exposure OR exposed OR occurrence OR biomonitoring) AND human* [MeSH Terms]
Tumor search	AGENT NAME AND (neoplasm* OR carcinogen* OR malignan* OR tumor OR tumors OR tumour OR tumours OR carcinoma OR cancer OR cancers OR mesothelioma OR lymphoma OR melanom* OR leukemia OR myeloma OR sarcoma) AND ("bioassay" OR "initiation-promotion" OR "co-carcinogenicity" OR “neoplasms”)
Cancer epidemiology	AGENT NAME AND (neoplasm* OR carcinogen* OR malignan* OR tumor OR tumors OR tumour OR tumours OR carcinoma OR cancer OR cancers OR mesothelioma OR lymphoma OR melanom* OR leukemia OR myeloma OR sarcoma) AND (“Epidemiology"[Mesh] OR "Epidemiologic Studies"[Mesh] OR epidemiolog* OR case-referent OR case-control OR "Occupational Exposure"[Mesh] OR workers OR cohort)
Absorption, distribution, metabolism, and excretion	AGENT NAME AND (ADME[tiab] OR tissue-distribut*[tiab] OR "distribution"[All Fields] OR protein-bound[tiab] OR protein-bind*[tiab] OR plasma-protein[tiab] OR "pharmacokinetics"[Subheading] OR "pharmacokinetics"[tw] OR "toxicokinetics"[tw] OR "pharmacokinetics"[MeSH Terms] OR Metabolite*[tiab] OR metabolism[tiab] OR Metabolic*[tiab] OR Biotransformation[tiab] OR bioavailability[tiab] OR excretion[tw] OR elimination[tw] OR urine[tiab] OR Urination[tiab] OR feces[tiab] OR fecal[tiab] OR biliary[tiab] OR Bile[tiab] OR Renal Elimination[mh])
Causes DNA alterations (KC 1-3)	AGENT NAME AND (("Mutation"[Mesh] OR "Cytogenetic Analysis"[Mesh] OR "Mutagens"[Mesh] OR "Oncogenes"[Mesh] OR "Genetic Processes"[Mesh] OR "genomic instability"[MesH] OR chromosom* OR clastogen* OR "genetic toxicology" OR "strand break" OR "unscheduled DNA synthesis" OR "DNA damage" OR "DNA adducts" OR "SCE" OR "chromatid" OR micronucle* OR mutagen* OR "DNA repair" OR "UDS" OR "DNA fragmentation" OR "DNA cleavage"))
Induces epigenetic alterations (KC 4)	AGENT NAME AND ("rna"[MeSH] OR "epigenesis, genetic"[MesH] OR rna OR "rna, messenger"[MeSH] OR "rna" OR "messenger rna" OR mrna OR "histones"[MeSH] OR histones OR epigenetic OR miRNA OR methylation)
Induces oxidative stress (KC 5)	AGENT NAME AND ("reactive oxygen species"[MeSH Terms] OR "reactive oxygen species"[All Fields] OR "oxygen radicals"[All Fields] OR "oxidative stress"[MeSH Terms] OR "oxidative"[All Fields] OR "oxidative stress"[All Fields] OR "free radicals"[All Fields])
Induces chronic inflammation (KC 6)	AGENT NAME AND ((chronic[tw] AND inflammation[MH]) OR chronic inflamm*[tw] OR inflammatory response*[tw] OR inflammatory marker*[tw] OR markers of inflammation[tw] OR inflammatory index[tw] OR systemic inflamm*[tw] OR tissue inflammation[tw] OR inflammatory potential[tw] OR inflammatory foci[tw] OR inflammatory state*[tw] OR inflammatory condition*[tw] OR IL-8[tw] OR interleukin-8[tw] OR IL-6[tw] OR interleukin-6[tw])
Causes immunosuppression (KC 7)	AGENT NAME AND (Immunosuppression[MH] OR Killer Cells, Natural[MH] OR CD4-Positive T-Lymphocytes[MH] OR immunosuppress*[tw] OR immune response*[tw] OR immune function*[tw] OR immune status[tw] OR immune state*[tw] OR immune competence[tw] OR immune impairment[tw] OR immune dysregulation[tw] OR humoral immunity[tw] OR cell-mediated immunity[tw] OR NK[tw] OR Natural Killer[tw] OR CD4[tw] OR T4 Cell*[tw] OR T4 Lymphocyte[tw] OR IgM)

Narrative descriptions – search terms used

Search string label	Search terms
Modulates receptor mediated effects (KC 8)	AGENT NAME AND (Androgen Antagonists[Mesh:NoExp] OR Androgen Receptor Antagonists[Mesh:NoExp] or Estrogen Antagonists[MH] or Estrogen Receptor Modulators[MH:NoExp] or Gonadal Hormones[MH] or Thyroid Hormones[MH] or Melatonin[MH] OR Endocrine Disruptors[MH] OR Receptors, Steroid[MH] OR Receptors, Cytoplasmic and Nuclear[MH] OR Receptors, Aryl Hydrocarbon[MH] OR Androgen*[tw] OR Estradiol[tw] OR Estrogen*[tw] OR Progesterone[tw] OR Testosterone[tw] OR thyroid[tw] OR Melatonin[tw] OR Endocrine disrupt*[tw] OR Peroxisome Proliferator-Activated Receptor[tw] OR PPAR[tw] OR constitutive androstane receptor [tw] OR farnesoid X-activated receptor[tw] OR liver X receptor[tw] OR Retinoid X receptor[tw] OR Aryl hydrocarbon receptor[tw] OR Ah receptor[tw])
Causes immortalization (KC 9)	AGENT NAME AND (Cell Transformation, Neoplastic[MH:NoExp] OR Cell Transformation, Viral[MH] OR Telomere[MH] OR Telomere Shortening[MH] OR Telomere Homeostasis[MH] OR cell transformation[tw] OR tumorigen transformation[tw] tumorigenic transformation[tw] OR neoplastic transformation[tw] OR carcinogen transformation[tw] OR carcinogenic transformation[tw] OR viral transformation[tw] OR immortalization[tw] OR Telomer*[tw])
Alters cell proliferation, cell death & nutrient supply (KC 10)	AGENT NAME AND (Cell Proliferation[MH] OR DNA Replication[MH] OR Cell Cycle[MH] OR Hyperplasia[MH] OR Metaplasia[MH:NoExp] OR Neovascularization, Pathologic[MH:NoExp] OR Apoptosis[MH] OR Angiogenesis Modulating Agents[MH:NoExp] OR Angiogenesis Inducing Agents[MH] OR Heat-Shock Proteins[MH] OR Extracellular Matrix[MH:NoExp] OR Cell proliferation[tw] OR Cellular proliferation[tw] OR Cell multiplication[tw] OR Cell division[tw] OR Proliferative activity[tw] OR Sustained proliferation[tw] OR DNA replication[tw] OR DNA synthesis[tw] OR tumor growth[tw] OR neoplastic growth[tw] OR malignant growth[tw] OR Hyperplasia[tw] OR Metaplasia[tw] OR Apoptosis inhibition[tw] OR Angiogenesis[tw] OR heat shock protein[tw] OR extracellular matrix[tw])

Annex 4. Text mining for prioritizing agents for *IARC Monographs* evaluations

Text mining – search terms used

PubMed Filter Label	PubMed Filters	Additional filter for human studies*
Cancer all	(neoplasm*[All Fields] OR carcinogen*[All Fields] OR malignan*[All Fields] OR tumor[All Fields] OR tumors[All Fields] OR tumour[All Fields] OR tumours[All Fields] OR cancer[All Fields] OR cancers[All Fields])	
Cancer epidemiology	((neoplasm*[All Fields] OR carcinogen*[All Fields] OR malignan*[All Fields] OR tumor[All Fields] OR tumors[All Fields] OR tumour[All Fields] OR tumours[All Fields] OR cancer[All Fields] OR cancers[All Fields]) AND (cohort[All Fields] OR case*[All Fields] OR epidemiolog*[All Fields] OR Epidemiology[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Occupational Exposure"[Mesh] OR workers[All Fields]))	
Causes DNA alterations (KC 1-3)	("Mutation"[Mesh] OR "Cytogenetic Analysis"[Mesh] OR "Mutagens"[Mesh] OR "Oncogenes"[Mesh] OR "Genetic Processes"[All Fields] OR "genomic instability"[MesH] OR chromosom*[All Fields] OR clastogen*[All Fields] OR "genetic toxicology"[All Fields] OR "strand break"[All Fields] OR "unscheduled DNA synthesis"[All Fields] OR "DNA damage"[All Fields] OR "DNA adducts"[All Fields] OR "SCE"[All Fields] OR "chromatid"[All Fields] OR micronucle*[All Fields] OR mutagen*[All Fields] OR "DNA repair"[All Fields] OR "UDS"[All Fields] OR "DNA fragmentation"[All Fields] OR "DNA cleavage"[All Fields])	(children OR girls OR girl OR men OR women OR boys OR boy OR participants OR participant OR individual OR individuals OR patients OR patient OR human OR "Homo Sapiens" OR subjects OR subject OR person OR persons OR farmers OR farmer OR people OR cases OR recruited OR enrolled)
Induces epigenetic alterations (KC 4)	("rna"[MeSH] OR "epigenesis, genetic"[MesH] OR rna OR "rna, messenger"[MeSH] OR "rna"[All Fields] OR "messenger rna"[All Fields] OR mrna[All Fields] OR "histones"[MeSH] OR histones[All Fields] OR epigenetic[All Fields] OR miRNA[All Fields] OR methylation[All Fields])	(children OR girls OR girl OR men OR women OR boys OR boy OR participants OR participant OR individual OR individuals OR patients OR patient OR human OR "Homo Sapiens" OR subjects OR subject OR person OR persons OR farmers OR farmer OR people OR cases OR recruited OR enrolled)
Induces oxidative stress (KC 5)	("reactive oxygen species"[MeSH Terms] OR "reactive oxygen species"[All Fields] OR "oxygen radicals"[All Fields] OR "oxidative stress"[MeSH Terms] OR "oxidative"[All Fields] OR "oxidative stress"[All Fields] OR "free radicals"[All Fields])	(children OR girls OR girl OR men OR women OR boys OR boy OR participants OR participant OR individual OR individuals OR patients OR patient OR human OR "Homo Sapiens" OR subjects OR subject OR person OR persons OR farmers OR farmer OR people OR cases OR recruited OR enrolled)

Text mining – search terms used

PubMed Filter Label	PubMed Filters	Additional filter for human studies*
Induces chronic inflammation (KC 6)	((chronic[All Fields] AND "inflammation"[MeSH Terms]) OR (chronic inflamm*[All Fields]))	(children OR girls OR girl OR men OR women OR boys OR boy OR participants OR participant OR individual OR individuals OR patients OR patient OR human OR "Homo Sapiens" OR subjects OR subject OR person OR persons OR farmers OR farmer OR people OR cases OR recruited OR enrolled)
Causes immunosuppression (KC 7)	(Immunosuppression[MH] OR "Killer Cells, Natural"[MH] OR "CD4-Positive T-Lymphocytes"[MH] OR immunosuppress*[tw] OR immune response*[tw] OR immune function*[tw] OR "immune status"[tw] OR "immune state*"[tw] OR "immune competence"[tw] OR "immune impairment"[tw] OR "immune dysregulation"[tw] OR "humoral immunity"[tw] OR "cell-mediated immunity"[tw] OR NK[tw] OR "Natural Killer"[tw] OR CD4[tw] OR "T4 Cell*"[tw] OR T4 Lymphocyte[tw])	(children OR girls OR girl OR men OR women OR boys OR boy OR participants OR participant OR individual OR individuals OR patients OR patient OR human OR "Homo Sapiens" OR subjects OR subject OR person OR persons OR farmers OR farmer OR people OR cases OR recruited OR enrolled)
Modulates receptor mediated effects (KC 8)	("Androgen Antagonists"[Mesh:NoExp] OR "Androgen Receptor Antagonists"[Mesh:NoExp] OR "Estrogen Antagonists"[MH] OR "Estrogen Receptor Modulators"[MH:NoExp] OR "Gonadal Hormones"[MH] OR "Thyroid Hormones"[MH] OR "Endocrine Disruptors"[MH] OR "Receptors, Steroid"[MH] OR "Receptors, Cytoplasmic and Nuclear"[MH] OR "Receptors, Aryl Hydrocarbon"[MH] OR Androgen*[tw] OR Estradiol[tw] OR Estrogen*[tw] OR Progesterone[tw] OR Testosterone[tw] OR thyroid[tw] OR "Endocrine disrupt*"[tw] OR "Peroxisome Proliferator-Activated Receptor"[tw] OR PPAR[tw] OR "constitutive androstane receptor"[tw] OR "farnesoid X-activated receptor"[tw] OR "liver X receptor"[tw] OR "Retinoid X receptor"[tw] OR "Aryl hydrocarbon receptor"[tw] OR "Ah receptor"[tw])	(children OR girls OR girl OR men OR women OR boys OR boy OR participants OR participant OR individual OR individuals OR patients OR patient OR human OR "Homo Sapiens" OR subjects OR subject OR person OR persons OR farmers OR farmer OR people OR cases OR recruited OR enrolled)
Causes immortalization (KC 9)	("Cell Transformation, Neoplastic"[MH:NoExp] OR "Cell Transformation, Viral"[MH] OR Telomere[MH] OR "Telomere Shortening"[MH] OR "Telomere Homeostasis"[MH] OR "cell transformation"[tw] OR "tumorigen transformation"[tw] "tumorigenic transformation"[tw] OR "neoplastic transformation"[tw] OR "carcinogen transformation"[tw] OR "carcinogenic transformation"[tw] OR "viral transformation"[tw] OR immortalization[tw] OR Telomer*[tw])	(children OR girls OR girl OR men OR women OR boys OR boy OR participants OR participant OR individual OR individuals OR patients OR patient OR human OR "Homo Sapiens" OR subjects OR subject OR person OR persons OR farmers OR farmer OR people OR cases OR recruited OR enrolled)
Alters cell proliferation, cell death & nutrient supply (KC 10)	("Cell Proliferation"[MH] OR "DNA Replication"[MH] OR "Cell Cycle"[MH] OR Hyperplasia[MH] OR Metaplasia[MH:NoExp] OR "Neovascularization, Pathologic"[MH:NoExp] OR Apoptosis[MH] OR?"Angiogenesis Modulating Agents"[MH:NoExp] OR "Angiogenesis Inducing Agents"[MH] OR "Heat-Shock Proteins"[MH] OR "Extracellular Matrix"[MH:NoExp] OR "Cell proliferation"[tw] OR "Cellular proliferation"[tw] OR "Cell multiplication"[tw] OR "Cell division"[tw] OR "Proliferative activity"[tw] OR "Sustained proliferation"[tw] OR "DNA replication"[tw]	(children OR girls OR girl OR men OR women OR boys OR boy OR participants OR participant OR individual OR individuals OR patients OR patient OR human OR "Homo Sapiens" OR subjects OR subject OR person OR persons OR farmers OR farmer OR people OR cases OR recruited OR enrolled)

Text mining – search terms used

PubMed Filter Label	PubMed Filters	Additional filter for human studies*
	OR "DNA synthesis"[tw] OR "tumor growth"[tw] OR "neoplastic growth"[tw] OR "malignant growth"[tw] OR Hyperplasia[tw] OR Metaplasia[tw] OR "Apoptosis inhibition"[tw] OR Angiogenesis[tw] OR "heat shock protein"[tw] OR "extracellular matrix"[tw])	

*additional search terms used to identify studies in exposed humans.

		All KC papers								
Unique agent name	Agent Class	All KCs (Unique of papers in KC1-10)*	(KC 1-3)	(KC 4)	(KC 5)	(KC 6)	(KC 7)	(KC 8)	(KC 9)	(KC 10)
Gene therapy/Cell therapy/Vectors	A: Biologicals_other	53663	34710	40758	5890	4278	177034	11617	1604	52161
Dysbiotic microbiota	A: Biologicals_other	16991	743	9501	1968	1472	4587	1227	22	970
Helicobacter pylori	A: Biologicals_other	10198	2381	2860	816	984	1793	193	92	4133
Fusobacterium nucleatum	A: Biologicals_other	662	129	280	85	48	162	6	2	141
Merkel cell polyomavirus	A: Biologicals_other	247	73	81	0	4	78	11	2	66
Schistosoma mansoni	A: Biologicals_parasites	2648	290	849	249	58	1261	90	5	359
Schistosoma japonicum	A: Biologicals_parasites	931	75	429	83	15	393	20	3	146
Opisthorchis felineus	A: Biologicals_parasites	253	40	84	37	43	66	8	1	74
Severe acute respiratory syndrome coro	A: Biologicals_virus	23022	3054	16510	1140	627	12184	1012	52	849
Human cytomegalovirus (HCMV)	A: Biologicals_virus	9738	1718	2653	134	171	5157	151	88	1887
Human papilloma virus (beta and some	A: Biologicals_virus	2911	656	1318	62	28	740	70	134	907
Hepatitis D virus	A: Biologicals_virus	1468	221	1327	7	38	120	7	3	57
Salmonella typhi	A: Biologicals_virus	1355	525	224	81	21	522	25	0	176
Obesity	A: Complex_exposure	36093	5487	13355	6745	3935	2899	13504	263	5006
Insomnia / Sleep	A: Complex_exposure	23933	4129	7283	3757	1280	3403	5186	259	2844
Haloacetic acids and other disinfection	A: Complex_exposure	1836	422	579	638	8	44	241	5	376
Second hand smoke and active smokin	A: Complex_exposure	1715	500	477	524	100	189	147	18	304
Social isolation and loneliness	A: Complex_exposure	1034	97	402	74	36	136	291	16	122
Sedentary behaviour	A: Complex_exposure	636	28	155	233	77	66	146	25	66
Electronic nicotine delivery systems (E	A: Complex_exposure	548	112	125	297	17	36	21	1	87
Combustion of biomass	A: Complex_exposure	339	73	79	199	10	10	8	1	14
Chronic circadian dysfunction	A: Complex_exposure	199	44	57	25	5	26	68	4	10
Cannabis smoking	A: Complex_exposure	180	30	66	16	6	50	16	0	20
Night shift work	A: Complex_exposure	177	11	51	20	14	27	80	5	13
Long working days (> 12 hours per day	A: Complex_exposure	98	6	31	12	12	20	33	3	8
2,4,6-Tribromophenol (disinfection bypro	A: Complex_exposure	47	10	16	16	0	0	17	0	5
Metalworking fluid	A: Complex_exposure	26	6	10	3	1	4	0	0	5
Anatase-type nano-TiO2 and other nano	A: Dusts_particles_fibres	39173	6436	17955	22570	678	6450	2077	381	24574
Ultrafine particles	A: Dusts_particles_fibres	12098	2615	3399	4844	688	1566	870	120	2051
Silica dust	A: Dusts_particles_fibres	11438	1602	3625	3372	264	834	583	76	3315
Outdoor air pollution	A: Dusts_particles_fibres	5232	1233	1484	1833	278	526	507	72	517
Multiwalled carbon nanotubes	A: Dusts_particles_fibres	3154	472	667	1350	43	194	168	31	887
Micro- and nano- plastics	A: Dusts_particles_fibres	1971	193	357	1424	10	149	174	0	161
Acrylonitrile-Butadiene-Styrene particles	A: Dusts_particles_fibres	1701	43	177	105	9	80	56	1	1339
Asbestos	A: Dusts_particles_fibres	1552	591	336	501	74	125	28	38	497
Nitrogen dioxide	A: Dusts_particles_fibres	917	122	187	473	27	78	42	10	106
Engineered stone	A: Dusts_particles_fibres	441	87	108	189	13	15	9	5	112
Carbon black, bulk and nanoscale	A: Dusts_particles_fibres	390	70	104	232	10	24	20	6	57
Coal dust	A: Dusts_particles_fibres	146	49	28	64	9	4	8	2	28
Taconite	A: Dusts_particles_fibres	1	0	1	1	0	0	0	0	0

Table 1. Class of agents A: biologicals, complex exposures, dust particles and fibres

Count of unique papers in PubMed across the KCs *Note: When the paper count is > 10 000 for a KC, only the first 10 000 are used due to the limitation of PubMed APIs.

		All KC papers								
Unique agent name	Agent Class	All KCs (Unique of papers in KC1-10)*	(KC 1-3)	(KC 4)	(KC 5)	(KC 6)	(KC 7)	(KC 8)	(KC 9)	(KC 10)
Selenium and selenium compounds	B: Metals_metalloids	8039	923	2109	4006	114	760	1276	31	1514
Rare earth elements	B: Metals_metalloids	6052	788	1446	1740	101	345	501	28	2023
Metallic nickel	B: Metals_metalloids	4645	1291	1554	1412	42	401	163	58	880
Inorganic lead compounds	B: Metals_metalloids	4564	836	1363	1730	32	285	548	38	764
Dental amalgam	B: Metals_metalloids	197	33	41	52	15	21	18	0	37
Phosphorescent paints [e.g: strontium	B: Metals_metalloids	1	0	0	0	0	1	0	0	1
Anthracyclines as mechanistic class	B: Pharmaceutical	28647	21524	7576	4737	85	2390	2593	187	14310
Daunorubicin (anthracycline)	B: Pharmaceutical	27506	20830	7101	4531	82	2243	2188	181	13863
Doxorubicin (anthracycline)	B: Pharmaceutical	26225	19248	6316	4345	74	1944	2099	164	12867
Assisted reproductive techniques (ART)	B: Pharmaceutical	22754	6930	4173	1393	47	704	12833	118	3777
Methotrexate	B: Pharmaceutical	16230	8107	1681	576	396	5270	1050	23	2580
Hormone replacement therapy	B: Pharmaceutical	11276	563	426	259	44	184	22101	21	1118
Progestogen-only contraceptives	B: Pharmaceutical	9498	214	593	63	13	110	9205	11	1035
Anaesthetics, volatile (isoflurane, sevoflu	B: Pharmaceutical	7723	238	6894	542	9	123	145	1	764
Anti-thymocyte globulin	B: Pharmaceutical	7624	901	185	10	19	6976	170	9	493
Reversible AChE inhibitors such as Riva	B: Pharmaceutical	3852	501	1834	991	22	298	287	7	388
Tetracycline	B: Pharmaceutical	3497	1289	1123	533	55	179	285	11	720
Paracetamol	B: Pharmaceutical	3416	480	850	1767	49	203	359	5	604
Clomiphene citrate	B: Pharmaceutical	2950	105	61	23	1	11	2814	0	161
Methamphetamine	B: Pharmaceutical	2511	193	1637	523	17	131	166	5	283
Epirubicin (anthracycline)	B: Pharmaceutical	2489	1832	259	122	3	91	362	11	481
Gadolinium based contrast agents	B: Pharmaceutical	1465	179	372	244	49	167	96	0	584
Platinum-based chemotherapies as mec	B: Pharmaceutical	1241	561	263	220	2	81	47	18	458
Melanoma Tx - Vemurafenib	B: Pharmaceutical	1015	715	188	33	3	55	94	4	352
Tofacitinib and other JAK kinase inhibito	B: Pharmaceutical	833	105	152	28	123	433	28	13	122
Melanoma Tx - Dabrafenib	B: Pharmaceutical	493	392	50	7	3	23	70	3	95
Breast implants	B: Pharmaceutical	387	42	40	16	72	102	47	0	118
Carbadox	B: Pharmaceutical	176	176	13	2	0	4	3	0	6
Alefacept	B: Pharmaceutical	123	0	4	0	12	111	0	0	7
Melanoma Tx - Encorafenib	B: Pharmaceutical	92	85	7	0	0	1	0	0	11
GLP-1 analogues	B: Pharmaceutical	6	0	0	2	1	0	3	0	1
Neonatal phototherapy	B: Physical_agents	16022	1314	2337	6156	327	2629	442	46	6777
Extremely low frequency magnetic fields	B: Physical_agents	2566	564	481	599	17	145	238	15	1195
RF/EMF from wireless mobile radiation	B: Physical_agents	84	20	16	24	1	9	7	0	27
Very hot beverages and very hot food	B: Physical_agents	40	11	11	8	3	2	4	1	10
Intense pulsed light (IPL)	B: Physical_agents	28	3	5	4	10	4	2	0	8
Artificial light at night (ALAN)	B: Physical_agents	16	0	3	6	0	2	3	1	2
Radon-222 and its decay products	B: Physical_agents	2	2	0	0	0	0	0	0	0

Table 2. Class of agents B: metals and metalloids, pharmaceuticals, physical agents

Count of unique papers in PubMed across the KCs *Note: When the paper count is > 10 000 for a KC, only the first 10 000 are used due to the limitation of PubMed APIs.

		All KC papers								
Unique agent name	Agent Class	All KCs (Unique of papers in KC1-10)*	(KC 1-3)	(KC 4)	(KC 5)	(KC 6)	(KC 7)	(KC 8)	(KC 9)	(KC 10)
Pyrethrins and pyrethroids	C: Chemical_pesticide	2699	929	997	655	10	134	364	5	328
Atrazine and other 2-chlor	C: Chemical_pesticide	1171	212	320	381	0	48	398	0	106
Chlorpyrifos	C: Chemical_pesticide	1169	198	520	421	3	50	156	2	167
Glyphosate	C: Chemical_pesticide	1163	321	510	346	1	35	150	3	136
Malathion	C: Chemical_pesticide	583	165	217	170	1	39	60	3	79
Cypermethrin (pyrethroid)	C: Chemical_pesticide	549	153	191	184	1	34	87	2	102
Permethrin (pyrethroid)	C: Chemical_pesticide	414	157	143	77	7	34	54	0	37
Biphenyl	C: Chemical_pesticide	371	64	167	74	1	5	47	1	75
Carbaryl	C: Chemical_pesticide	259	75	126	36	0	16	30	0	29
Vinclozolin	C: Chemical_pesticide	247	28	103	11	1	3	209	0	29
2,4-Dichlorophenol	C: Chemical_pesticide	210	63	49	90	0	3	31	0	10
Chlordecone	C: Chemical_pesticide	163	14	30	14	0	7	105	1	36
Mancozeb	C: Chemical_pesticide	149	44	23	59	0	8	39	0	34
Tebuconazole	C: Chemical_pesticide	139	45	48	40	0	3	37	0	14
1,2-Dibromo-3-chloropropa	C: Chemical_pesticide	121	80	14	8	0	0	39	0	8
Alachlor	C: Chemical_pesticide	119	40	38	33	0	2	21	1	23
Bifenthrin	C: Chemical_pesticide	108	18	46	37	0	4	33	0	15
para-Dichlorobenzene	C: Chemical_pesticide	56	25	8	11	0	0	7	0	17
Pendimethalin	C: Chemical_pesticide	52	20	10	24	1	3	6	0	14
Boscalid	C: Chemical_pesticide	48	19	20	14	0	1	4	0	1
Ethylenedithiocarbamates	C: Chemical_pesticide	47	11	19	5	0	3	11	0	10
Cyfluthrin	C: Chemical_pesticide	44	10	18	16	0	1	3	0	4
Neonicotinoid insecticides	C: Chemical_pesticide	44	9	21	15	0	1	3	0	3
Phosmet	C: Chemical_pesticide	30	9	18	5	0	0	2	0	2
Ametryn	C: Chemical_pesticide	25	9	3	15	0	0	1	0	0
Hexythiazox	C: Chemical_pesticide	13	2	13	1	0	0	0	0	2
Terbufos	C: Chemical_pesticide	11	5	5	3	0	0	0	0	2
Fonofos	C: Chemical_pesticide	7	2	3	2	0	0	1	0	0
Proquinazid	C: Chemical_pesticide	2	0	1	0	0	1	0	0	0
Metyltetraprole	C: Chemical_pesticide	1	1	0	0	0	0	0	0	0
Estragole	C: Nutritional	108	62	54	11	1	1	6	0	13
Sucralose	C: Nutritional	63	12	20	20	1	3	4	0	14
Sweetened beverage cons	C: Nutritional	23	2	9	6	3	1	4	1	3
Ultra-processed food cons	C: Nutritional	13	0	2	7	2	1	1	0	0
Semi-conductor industry	C: Occupations	632	109	217	192	3	23	32	5	105
Textile manufacturing indu	C: Occupations	368	100	84	171	5	13	19	0	11
E-waste workers	C: Occupations	209	38	61	85	1	15	40	5	5
Laboratory work & occupa	C: Occupations	133	41	33	2	2	31	20	0	10
Occupation as a pesticide	C: Occupations	68	26	20	10	0	3	20	2	5

Table 3. Class of agents C: pesticides, nutritional, occupations

Count of unique papers in PubMed across the KCs *Note: When the paper count is > 10 000 for a KC, only the first 10 000 are used due to the limitation of PubMed APIs.

		All KC papers								
Unique agent name	Agent Class	All KCs (Unique of papers in KC1-10)*	(KC 1-3)	(KC 4)	(KC 5)	(KC 6)	(KC 7)	(KC 8)	(KC 9)	(KC 10)
Hair straightening products	D: Chemical_dye	489	180	66	192	7	24	82	0	40
Congo red	D: Chemical_dye	447	172	141	72	12	17	24	1	87
Hair colouring products (personal us	D: Chemical_dye	325	151	34	158	1	13	23	0	31
Tattoos and permanent make up	D: Chemical_dye	200	17	37	19	20	48	13	0	55
para-Phenylenediamine (1,4-benzer	D: Chemical_dye	198	67	45	94	0	22	6	0	33
2,4-Diaminotoluene	D: Chemical_dye	134	134	11	5	0	1	4	0	10
Red dye no. 3 (Erythrosine)	D: Chemical_dye	84	26	14	26	0	4	16	0	19
3,3'-Dimethoxybenzidine (ortho-Dian	D: Chemical_dye	80	19	10	52	1	0	5	0	2
Methyl anthranilate	D: Chemical_dye	67	3	67	2	0	0	1	0	2
o-Aminoazotoluene	D: Chemical_dye	45	18	20	0	0	3	6	0	13
p-Nitrotoluene	D: Chemical_dye	25	12	8	3	0	1	3	0	4
3,3'-Dimethylbenzidine (ortho-Tolidin	D: Chemical_dye	14	11	2	3	0	0	2	0	0
para-Cresidine (2-Methoxy-5-methyl	D: Chemical_dye	12	8	1	0	0	1	0	0	5
Ethyl anthranilate	D: Chemical_dye	2	1	1	0	0	0	0	0	0
Menthyl anthranilate	D: Chemical_dye	2	0	0	2	0	0	0	0	0
5-Nitro-*ortho*-toluidine	D: Chemical_dye	0	0	0	0	0	0	0	0	0
Bisphenol A	D: Chemical_POPs	5878	389	1236	954	15	142	4934	20	812
Phthalates (e.g., DEHP)	D: Chemical_POPs	2650	349	768	612	11	95	1622	8	558
Dibutyl phthalate	D: Chemical_POPs	801	96	213	183	2	25	492	0	140
Perfluorooctanesulfonic acid (PFOS)	D: Chemical_POPs	696	59	187	179	2	64	314	15	138
Bisphenol S and Bisphenol F	D: Chemical_POPs	389	27	94	99	1	13	299	1	66
Pentabromodiphenyl ethers	D: Chemical_POPs	382	42	108	113	0	17	202	2	60
Butyl benzyl phthalate	D: Chemical_POPs	164	21	48	19	1	5	121	2	35
Diisononyl phthalate	D: Chemical_POPs	88	7	19	23	0	8	51	0	13
Hexafluoropropylene Oxide (HFPO)	D: Chemical_POPs	87	5	40	23	1	5	36	3	14
Chlorinated paraffins	D: Chemical_POPs	55	9	11	15	0	1	32	0	8
Perfluorohexanesulfonic acid (PFHx	D: Chemical_POPs	44	4	13	8	0	3	24	2	3
Tris(chloropropyl)phosphate	D: Chemical_POPs	12	3	6	7	1	0	1	0	2
Methanol	D: Chemical_solvent	4895	783	2731	1081	38	104	287	5	561
Carbon tetrachloride	D: Chemical_solvent	4034	362	1352	1837	96	184	298	16	1286
Gasoline oxygenated additives (MTE	D: Chemical_solvent	2974	252	1625	1291	26	57	97	9	251
Automotive gasoline	D: Chemical_solvent	906	227	532	203	2	17	31	0	51
Xylenes	D: Chemical_solvent	895	215	446	186	22	39	39	4	96
Isoprene	D: Chemical_solvent	354	78	205	124	0	2	2	0	15
Tetrachloroethylene (perchloroethyle	D: Chemical_solvent	240	76	109	59	0	11	7	0	19
p-Cresol	D: Chemical_solvent	203	48	90	59	6	6	11	0	35
Allyl alcohol	D: Chemical_solvent	161	30	56	59	1	1	6	0	24
Cumene	D: Chemical_solvent	40	10	14	24	0	1	4	0	1
Sulfolane	D: Chemical_solvent	14	4	6	3	0	3	0	0	1

Table 4. Class of agents D: dyes, POPs, solvents

Count of unique papers in PubMed across the KCs *Note: When the paper count is > 10 000 for a KC, only the first 10 000 are used due to the limitation of PubMed APIs.

POP, persistent organic pollutant

		All KC papers								
Unique agent name	Agent Class	All KCs (Unique of papers in KC1-10)*	(KC 1-3)	(KC 4)	(KC 5)	(KC 6)	(KC 7)	(KC 8)	(KC 9)	(KC 10)
Toxoplasma gondii /	E: Biol_natural_toxins	4063	610	1075	232	63	2060	81	9	831
Aflatoxins	E: Biol_natural_toxins	3514	1878	1091	666	18	274	203	31	575
Zearalenone	E: Biol_natural_toxins	1400	187	308	265	8	73	942	2	332
Patulin	E: Biol_natural_toxins	883	883	67	76	0	14	10	0	59
Fumonisin B1	E: Biol_natural_toxins	549	139	139	150	1	37	26	2	293
Safrole	E: Biol_natural_toxins	259	121	90	48	1	8	30	0	45
Alpha pinene	E: Biol_natural_toxins	176	23	74	78	0	3	3	0	38
Pyrrolizidine alkaloic	E: Biol_natural_toxins	27	24	4	1	0	0	0	0	5
Black cohosh extrac	E: Biol_natural_toxins	2	1	2	1	1	0	0	0	0
Nitrite-producing bac	E: Biol_natural_toxins	0	0	0	0	0	0	0	0	0
Glutathione	E: Chemical_other	25556	6289	6899	30718	322	1136	1815	61	7590
Nitrate in drinking wa	E: Chemical_other	8753	1857	3155	3573	141	285	578	7	1090
Formaldehyde	E: Chemical_other	5987	1829	2782	745	148	434	410	25	849
Ozone	E: Chemical_other	4341	490	840	2857	90	219	254	16	418
Palmitic acid	E: Chemical_other	2586	482	1079	701	53	94	341	3	796
Acetaldehyde	E: Chemical_other	1834	629	594	633	12	82	86	4	289
Parabens (cosmetic	E: Chemical_other	1409	157	766	194	0	22	591	1	101
Acrylamide	E: Chemical_other	1095	448	254	391	6	18	101	9	233
Triclosan	E: Chemical_other	1037	141	372	215	5	33	441	3	92
Thioacetemide	E: Chemical_other	894	86	343	339	25	26	61	8	354
1,2-Dihydroxybenzer	E: Chemical_other	755	315	183	279	3	15	50	0	108
Ethylene oxide	E: Chemical_other	636	382	141	103	3	12	14	0	79
Nitrilotriacetic acid	E: Chemical_other	595	462	87	301	1	8	15	3	112
Cumyl hydroperoxid	E: Chemical_other	499	109	64	445	0	1	23	0	40
Bromate compounds	E: Chemical_other	387	146	51	287	5	7	28	1	59
2,3-Butanedione (dia	E: Chemical_other	280	92	106	59	2	3	9	1	60
Carbon disulfide	E: Chemical_other	213	43	78	51	1	8	38	1	17
1,4-dioxane	E: Chemical_other	184	54	65	63	0	2	5	1	21
Piperonyl butoxide	E: Chemical_other	184	42	74	66	1	5	19	1	26
Fluoranthene	E: Chemical_other	166	75	46	44	1	5	19	0	19
Glycidamide	E: Chemical_other	112	86	15	24	0	0	9	1	16
Polyhexamethylene	E: Chemical_other	40	4	15	9	2	5	0	0	18
Butyraldehyde	E: Chemical_other	24	9	13	7	0	0	2	0	2
1,2-CYCLOHEXANE	E: Chemical_other	15	2	1	6	0	0	9	0	1
2,4-Dimethylphenol	E: Chemical_other	11	3	6	2	0	0	0	0	2
Atraric acid (Methyl	E: Chemical_other	9	1	4	0	0	0	6	0	6
Benzophenone-1	E: Chemical_other	9	1	4	1	0	0	5	0	2

Table 5. Class of agents E: biotoxins and other chemicals

Count of unique papers in PubMed across the KCs *Note: When the paper count is > 10 000 for a KC, only the first 10 000 are used due to the limitation of PubMed APIs.