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February 11, 2020

Honorable Freda L. Wolfson, Chief Judge
United States District Court
Clarkson S. Fisher Building & US Courthouse
402 East State Street
Trenton, NJ 08608

Re: ***In Re: Johnson & Johnson Talcum Powder Products Marketing, Sales Practices and Products Liability Litigation*** **(MDL No. 2738)**

Dear Chief Judge Wolfson:

The Plaintiffs' Steering Committee writes to provide the Court with additional scientific materials that support the PSC's general causation experts' opinions that Johnson & Johnson's talcum powder products can cause ovarian cancer.

The International Agency for the Research on Cancer (IARC) recently published the "Report of the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020-2024," attached as Exhibit A. IARC classified talc *without* asbestiform fibers as a possible carcinogen (Group 2B) in 2010. The Working Group, having reviewed studies published since this initial review was completed in 2006, has made it a high priority to re-evaluate domestic talc products, i.e., talc-based body powders. *See* Ex. A at 73. In support of their recommendation, the Working Group cited the Penninkilampi (2018) study, which was relied upon by the PSC's experts and which summarizes new studies, including prospective cohort studies, reporting a "modestly elevated but precise overall odds ratio of 1.31 (95% confidence interval [CI], 1.24-1.39)." *Id.* at 72. They noted that there was a slight gradient in risk or dose response with increased exposure. *Id.* IARC also noted that mechanistic evidence has been updated since 2006:

> There is evidence to suggest that when talc is used in the genital area, talc enters the vagina and migrates to the upper genital tract (Cramer et

> al., 2007), where it may induce inflammatory reactions capable of damaging genital tissue DNA. Serous subtypes originate in the fallopian tube; this may enhance the plausibility of the observed associations in epidemiological studies. An in vitro study of epithelial ovarian and normal cells found that both were stimulated by talc to exhibit oxidative stress (Fletcher et al., 2019 [Saed]). Ovarian toxicity in rats was also observed after talc exposure (Yumrutas et al., 2015), and the pilot study of Sprague-Dawley rats noted above found inflammatory changes in the reproductive system, including increased numbers of follicles (Keskin et al., 2009).

Id. at 73. These studies and the purposes for which IARC cites them support the opinions of the PSC's experts.

In addition, the U.S. Food and Drug Administration (FDA) has formed an Interagency Working Group on Asbestos in Consumer Products (IWGACP). The working group is composed of representatives from the FDA, National Institutes for Occupational Safety and Health (NIOSH), National Institute of Health (NIH)/ National Institute of Environmental Health Sciences (NIEHS), Occupational Safety and Health Administration (OSHA), Environmental Protection Agency (EPA), Consumer Product Safety Commission (CPSC), the National Institute of Standards & Technology (NIST), and the Department of Interior's U.S. Geological Survey (USGS).

On January 6, 2020, the IWGACP issued preliminary recommendations on testing methods for asbestos in talc and consumer products containing talc. *See* Exhibit B. The IWGACP "strongly recommended the use of TEM with energy dispersive X-ray spectroscopy (EDS) and selected area electron diffraction (SAED) analyses to reliably detect and identify chrysotile and asbestiform and non-asbestiform amphibole minerals." *Id.* at 5 (¶5). They recommended that "testing laboratories report all EMPs having length ≥ 0.5 µ." *Id.* (¶ 2). They recommended that individual fibers be reported instead of a "mass percent, a unit that is frequently used to express content of asbestos in commercial bulk materials." *Id.* (¶4, 6).

The IWGACP's recommended methodology for testing talc for asbestiform minerals (asbestos and fibrous talc) are entirely consistent with and supportive of the methodology that Drs. Longo and Rigler used when testing Johnson & Johnson's historical samples. As recently as February 4, 2020, the FDA held a public hearing

to solicit public comment on the IWGACP's testing recommendations. Scientists and medical experts with experience in numerous disciplines including a few PSC experts participated along with interested persons in the all-day meeting. The PSC will provide to the Court relevant statements, power point presentations and official hearing transcripts when all are made available.

Lastly, in its December 24, 2019 submission to the Court, the PSC brought to the Court's attention the recent scientific publication, Steffen, JE., et al. *Serous Ovarian Cancer Caused by Exposure to Asbestos in Cosmetic Talc Powders – A Case Series Serous Ovarian Cancer Caused by Asbestos in Cosmetic Talc*. Journal of Occupational and Environmental Medicine. DOI: 10.1097/JOM.0000000000001800. (published ahead of print) (Dec. 23, 2019). At that time, the only version available was a pre-publication galley proof. The PSC now attaches for the record a published version of the manuscript. *See* Exhibit C.

We thank the Court for its consideration of these additional scientific publications.

Respectfully submitted,

/s/ Michelle A. Parfitt
Michelle A. Parfitt

/s/ P. Leigh O'Dell
P. Leigh O'Dell

cc: All counsel of record via ECF notification

Exhibit A

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 2020–2024

CONTENTS

Introduction

An IARC Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 met in Lyon, France, on 25–27 March 2019. 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 the IARC RSS news feed, 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 IARC personnel, including the recommended priorities remaining from a similar Advisory Group meeting convened in 2014 (Straif et al., 2014), and the priorities nominated by the Advisory Group.

The list of Advisory Group members and all other meeting participants is provided in Annex 1 (see https://monographs.iarc.fr/wp-content/uploads/2019/02/AGP-ListofParticipants.pdf); the preliminary agenda is provided in Annex 2. Dr Matilde Marques (Portugal) served as Meeting Chair, and Dr Amy Berrington de González (USA) served as Meeting Vice Chair. The Subgroup Chairs were Frederick Beland (USA), Patience Browne (France), Paul Demers (Canada), and Dirk Lachenmeier (Germany).

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 recently refined in the Preamble to the *IARC Monographs* (IARC, 2019a).

The Advisory Group considered more than 170 unique candidate agents nominated for consideration. Short draft summaries of each nomination were prepared before the meeting. These drafts summarized the evidence on human exposure (including any evidence of exposure in low- and middle-income countries), cancer epidemiology, cancer bioassays in experimental animals, and carcinogen mechanisms, in line with the evaluation approach that was recently refined in the Preamble to the *IARC Monographs* (IARC, 2019a).

A complementary approach assessed all nominations using a chemoinformatics, text mining, and chemical similarity analysis workflow (Guha et al., 2016) to help reveal coverage and gaps in the extent of evidence across data streams, to support decisions on individual agents and groups of chemically related nominations. 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 chemical similarity maps as well as hierarchical clustering heat maps. The literature search terms used, the chemical similarity maps, and the heat maps are provided in Annex 3.

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. metals, fibres, chemicals, biological agents, and complex mixtures), 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. Agents not meeting these criteria were not recommended for evaluation.

Determining priority

In line with the Preamble to the *IARC Monographs* (IARC, 2019a), priority was assigned for:

(a) A new evaluation of an agent.

(b) An agent reviewed in a previous *Monograph* 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 in a previous *Monograph* 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 may focus on these new tumour sites.

Priority was assigned on the basis of (i) evidence of human exposure and (ii) the extent 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*). Agents without evidence of human exposure or evidence for evaluating carcinogenicity were not recommended for further consideration.

Priorities for the *IARC Monographs* during 2020–2024

The types of recommendations encompassed individual agents as well as groups of related agents, taking into account the advice of the Advisory Group. 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. A tabular summary of the evaluations is provided in Annex 4. Summaries of the recommendations are provided in the sections that follow.

The Advisory Group recognized that agents related to the identified priorities may also warrant evaluation. Furthermore, 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.

In line with coordination and communication mechanisms agreed between IARC and WHO headquarters and set out in the interim standard operating procedure (SOP) adopted by the IARC Governing Council (see http://governance.iarc.fr/GC/GC60/En/Docs/GC60_13_CoordinationWHO.pdf), the *IARC Monographs* programme will conduct an evaluation only if IARC and WHO headquarters agree that this does not duplicate work or present a risk of contradictory evaluations across the hazard identification and risk assessment programmes. In keeping with the interim SOP adopted by the IARC Governing Council, IARC will consider this advice when selecting agents for future *Monographs* evaluations according to the Preamble to the *IARC Monographs* (IARC, 2019a, b).

Acetaldehyde (CAS No. 75-07-0)

Acetaldehyde was classified by the *IARC Monographs* as *possibly carcinogenic to humans* (Group 2B) (IARC, 1999b), on the basis of *inadequate evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. In addition, "acetaldehyde associated with the consumption of alcoholic beverages" was evaluated by IARC as *carcinogenic to humans* (Group 1) (IARC, 2012c). This upgrade was based on sufficient epidemiological evidence showing that humans who are deficient in the oxidation of acetaldehyde to acetate have a substantially increased risk for the development of alcohol-related cancers, in particular cancers of the oesophagus and the upper aerodigestive tract.

Exposure Data

In addition to its occurrence in association with alcoholic beverages, both as their natural constituent and as the first metabolite of ethanol, acetaldehyde occurs as a natural compound in various foods and alcohol-free beverages, in tobacco smoke, and also in the environment. Acetaldehyde is also used in industry, so that human exposure from occupational, environmental, and lifestyle sources is ubiquitous.

Acetaldehyde is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Cancer in Humans

Since the most recent review of acetaldehyde in 2012, new genetic epidemiological data have been reported, including case–control and cohort studies and several meta-analyses, which strengthen the association of acetaldehyde (as a metabolite of alcohol consumption) with oesophageal cancer and also provide associations with gastric and hepatocellular cancers, specifically in humans with inactive aldehyde dehydrogenase 2 (Yu et al., 2018). Associations were also observed of genes in alcohol metabolism pathways, alcohol consumption, and risks of colorectal cancer (Crous-Bou et al., 2013; Offermans et al., 2018). Positive associations of head and neck cancer subsites and long-term and frequent use of mouthwash were observed in a pooled analysis of data from 12 case–control studies, although there was a limited ability to examine nonsmokers or non-alcohol drinkers (Boffetta et al., 2016). Positive associations of prenatal or early-life exposure to acetaldehyde (as well as other correlated pollutants) in ambient air and childhood central nervous system primitive neuroectodermal tumour (PNET), Wilms tumour, and retinoblastoma were observed in case–control studies conducted in California, USA (Shrestha et al., 2014; Heck et al., 2015; von Ehrenstein et al., 2016); however, these studies are confounded by co-exposures to other air pollutants.

Cancer in Experimental Animals

In the previous evaluation (IARC, 1999b), there was *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde.

Mechanistic Evidence

Studies in experimental animals exposed directly to acetaldehyde, or indirectly through alcohol drinking, have detected acetaldehyde-specific DNA adducts. These adducts were found in tissues of rats exposed to acetaldehyde for 50 days in atmospheric air, as well as in tissues of rhesus monkeys exposed to alcohol drinking over their lifetime.

In mechanistic studies in vitro and in vivo, acetaldehyde exhibited several key characteristics of carcinogens, such as electrophilicity, genotoxicity, alteration of DNA repair, induction of epigenetic alterations, and oxidative stress. Acetaldehyde also belongs to a class of agents (aldehydes) for which one member – formaldehyde – has been classified as *carcinogenic to humans* (Group 1) (IARC, 2012b).

Key References

The following key references were also identified: Woutersen et al. (1986); Eriksson (2015); Lachenmeier & Salaspuro (2017); Mizumoto et al. (2017).

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

Acrolein (CAS No. 107-02-8)

Acrolein was evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1995).

Exposure Data

Acrolein is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Acrolein is formed during combustion of fuels, wood, and plastics, and is present in cigarette smoke. In commercial kitchens, there are measurable amounts of acrolein in the air from high-temperature roasting and deep-fat frying. Acrolein is routinely measured in studies monitoring ambient air pollution in the USA, and it has been identified in various combustion emissions in numerous reports. Firefighters are also exposed.

Cancer in Humans

No epidemiological studies of carcinogenicity have been reported (IARC, 1995). Acrolein is a metabolite of cyclophosphamide and is speculated to be the cause of cancer of the bladder in cancer patients treated with anticancer drugs over the long term.

Cancer in Experimental Animals

Since the previous IARC evaluation, new animal inhalation carcinogenicity studies, reported in 2016, obtained positive results in both rats and mice. In the nasal cavity, squamous cell carcinoma, which was not

observed in the Japan Bioassay Research Center historical controls, was found in one male rat exposed to 2 ppm acrolein. The incidence of tumours of the nasal cavity (rhabdomyoma and squamous cell carcinoma combined) was significantly increased in the high-dose groups in female rats. The incidence of adenomas in the nasal cavity was increased in female mice exposed to 1.6 ppm acrolein (JBRC, 2016).

Mechanistic Evidence

Several new studies have been reported in which the types of DNA adducts and mutations induced by acrolein have been identified. Acrolein forms adducts on guanine that are processed into G → T and G → A mutations at a frequency similar to that found in the *TP53* gene in smoking-associated tumours of the lung (IARC, 1995).

Key References

The following key references were also identified: Tang et al. (2011); Wang et al. (2012b); Roth-Walter et al. (2017); Sarkar (2019).

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

Acrylamide (CAS No. 79-06-1)

Acrylamide has been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1987, 1994a) and since Volume 60 is classified as *probably carcinogenic to humans* (Group 2A) (IARC, 1994a), on the basis of *sufficient evidence* of carcinogenicity in experimental animals, *inadequate evidence* of carcinogenicity in humans (from occupational exposures), and mechanistic evidence on DNA adduct formation and genotoxicity of acrylamide and its metabolite glycidamide.

Exposure Data

Acrylamide is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Acrylamide is a vinyl monomer chemical that has been produced and used since the mid-1950s (IARC, 1994a), primarily to make polyacrylamide and acrylamide copolymers for use in various industrial processes (e.g. production of paper, dyes, and plastics; drinking-water and wastewater treatment) (NCI, 2017). In 2002, it was discovered that acrylamide can form naturally in carbohydrate-rich foods during high-temperature cooking (e.g. frying, roasting, or baking) (EFSA, 2015). 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, 2015); levels vary with several factors, including the method, timing, and temperature of the cooking process (NCI, 2017). Acrylamide is also present in cigarette smoke (EFSA, 2015); in the general population, smoking is a more substantial source of exposure to acrylamide than is food (NCI, 2017). Occupational exposure can also occur in workplaces where acrylamide is present.

Cancer in Humans

Since the most recent *IARC Monographs* evaluation, several epidemiological studies have examined the relationship between estimated dietary consumption of acrylamide and specific cancer types, mostly with inconclusive or inconsistent results. These results are not very informative, 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 potential bias towards the null. The evidence is suggestive of modest associations for cancer of the kidney, and for cancers of the endometrium and the ovary in never-smokers. Haemoglobin adducts of acrylamide or glycidamide were not associated with risks of cancer of the ovary or the endometrium in nonsmoking postmenopausal women in the USA (Xie et al., 2013) and in European cohort studies (Obón-Santacana et al., 2016).

Cancer in Experimental Animals

In the previous evaluation (IARC, 1994a), there was *sufficient evidence* of carcinogenicity in experimental animals.

Mechanistic Evidence

Several recent mechanistic studies are relevant to key characteristics of carcinogens, particularly whether acrylamide is genotoxic and induces oxidative stress (Besaratinia & Pfeifer, 2005; Huang et al., 2018b; Zhivagui et al., 2019). Furthermore, the Advisory Group considered that an updated evaluation of the newly available evidence in humans may be useful.

Key References

The following key references were also identified: Hogervorst et al. (2016); Kotemori et al. (2018).

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

Acrylonitrile (CAS No. 107-13-1)

Acrylonitrile was classified by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) (IARC, 1999b), on the basis of *inadequate evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. In Supplement 7, it had been classified as *probably carcinogenic to humans* (Group 2A) (IARC, 1987), on the basis of *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. It was first reviewed by IARC in 1979 (IARC, 1979a).

Exposure Data

Acrylonitrile is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Acrylonitrile is used in the manufacture of various plastics, resins, elastomers, fibres, and synthetic rubber. Exposure may result from migration of acrylonitrile into food from packaging, and consumer exposures from contact with residual levels in products and in processes such as three-dimensional printing and plastics recycling (He et al., 2015b), as well as from smoking and exposure to second-hand smoke (Sleiman et al., 2014). Occupational exposures occur during the production and manufacture of goods.

Cancer in Humans

The finding of *inadequate evidence* of carcinogenicity of humans in 1999 noted that early indications of carcinogenicity were not confirmed by later studies. Some relevant studies have subsequently been published. Although an update of a cohort of workers in fibre production showed null results, there was no control for smoking (Symons et al., 2008). A United States National Institute for Occupational Safety and Health-National Cancer Institute cohort reported increased but not significant lung cancer risk only when internal rates were used (Marsh et al., 2001). A meta-analysis showed that risk of lung cancer increased after adjustment for the healthy worker effect (Sponsiello-Wang et al., 2006). A second meta-analysis reported increased incidence of bladder cancer but associated it with facilities with aromatic amines (Collins & Acquavella, 1998). A positive association between acrylonitrile and incident lung cancer was found in a large case–control study with good control for smoking (Scélo et al., 2004). Null findings were reported for a cohort of Dutch workers; excesses of brain cancer were found in some exposure categories (NTP, 2016g).

Cancer in Experimental Animals

The finding of *sufficient evidence* of carcinogenicity in experimental animals in 1999 was based on an inhalation study that found "glial cell tumours of the central nervous system found in several previous studies that had not been fully reported", and that in addition found malignancies of the mammary gland, Zymbal gland, liver, and extrahepatic circulatory system.

Additional evidence of carcinogenicity in experimental animals not considered in previous volumes exists: gavage (in water) studies in mice (NTP, 2001), finding tumours of the Harderian gland and the forestomach in males and females; a gavage study in rats (Bio/dynamics Inc., 1980a; Johannsen & Levinskas, 2002a), finding tumours of the brain, Zymbal gland, and forestomach in both sexes, of the intestine in males (females not examined), and of the mammary gland in females (males not examined); drinking-water studies in two strains of rats (Bio/dynamics Inc., 1980b, c; Johannsen & Levinskas, 2002a, b), finding tumours of the brain, spinal cord, Zymbal gland, and forestomach in both strains and both sexes; drinking-water studies in rats (Quast, 2002), finding tumours of the brain, spinal cord, forestomach, tongue, and Zymbal gland in males and females, as well as of the small intestine and mammary gland in females; drinking-water three-generation study (Beliles et al., 1980; Friedman & Beliles, 2002), finding tumours of the brain (astrocytomas) in the F_1 generation and of the Zymbal gland in the F_1 and F_2 generations; and inhalation studies in rats (Quast et al., 1980), finding tumours of the brain, spinal cord, and Zymbal gland in males and females, of the mammary gland in females, and of the small intestine in males.

Mechanistic Evidence

Acrylonitrile is genotoxic after activation; this is thought to be through the formation of 2-cyanoethylene oxide. Additional studies indicative of genotoxicity have been published since the IARC review in 1999. The IARC review and other reviews (NTP, 2001; ECHA, 2017, 2018c) point to the greater extent of positive in vitro chromosomal damage assays compared with in vivo findings, but data are limited. The recent review by the European Chemicals Agency (ECHA, 2018d) reported DNA damage and chromosomal aberrations in two recent studies of exposed workers, and reported a recent rodent comet assay via oral gavage as weakly positive. In an additional study in workers in China, the genetic damage status of exposed workers (buccal cell micronuclei) was elevated compared with that of non-exposed workers (Fan et al., 2006). The review by the European Chemicals Agency also found the evidence for oxidative stress compelling.

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

Aflatoxins (CAS No. 1402-68-2)

Aflatoxins have been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1987, 1993a, 2002, 2012b). In Supplement 7, they were classified as *carcinogenic to humans* (Group 1) (IARC, 1987), on the basis of *sufficient evidence* of carcinogenicity both in experimental animals and in humans. The current evaluation (IARC, 2012b) specifies that aflatoxins cause cancer of the liver (hepatocellular carcinoma) and that there is strong evidence that the carcinogenicity of aflatoxins operates by a genotoxic mechanism of action that involves metabolic activation to a genotoxic epoxide metabolite, formation of DNA adducts, and modification of the *TP53* gene.

Exposure Data

Aflatoxins can naturally contaminate food crops and pose a serious health threat to humans and livestock all over the world. Aflatoxins also impose a significant economic burden, causing an estimated 25% or more of the world's food crops to be destroyed annually. Two closely related species of fungi are mainly responsible for producing the aflatoxins of public health significance: *Aspergillus flavus* and *A. parasiticus*. Under favourable conditions (including high temperatures and high humidity), typically found in tropical and subtropical regions, these moulds, which are usually found on dead and decaying vegetation, can invade food crops. Food crops can become contaminated both before and after harvesting. Pre-harvest contamination with aflatoxins is mainly limited to maize, cottonseed, peanuts, and tree nuts. Post-harvest contamination can be found in a variety of other crops, such as coffee, rice, and spices. Improper storage under conditions that favour the growth of mould (warm and humid storage environments) can typically lead to levels of contamination much higher than those found in the field (WHO, 2018).

Cancer in Humans

Two new case–control studies showed an association between aflatoxins and cancer of the gall bladder in Chile and Shanghai, China (Nogueira et al., 2015; Koshiol et al., 2017). The Advisory Group noted that the results of prospective studies are expected within 5 years.

The Advisory Group considered that the new epidemiological evidence appears to support the classification of additional cancer sites to either the *sufficient* or *limited* evidence category.

Key References

The following key references were also identified: Williams (2012); Mulder et al. (2015); Erkekoglu et al. (2017); Livingstone et al. (2017); Marchese et al. (2018); Rushing & Selim (2019).

Recommendation: Medium priority

Air pollutants and underlying mechanisms for breast cancer

The nomination of this agent indicated that there was new mechanistic evidence for the role of specific traffic-related air pollutants in making the *BRCA1/2* tumour suppressor systems dysfunctional.

Outdoor air pollution and particulate matter in outdoor air pollution have been classified by IARC as *carcinogenic to humans* (Group 1), on the basis of *sufficient evidence* for cancer of the lung in humans (IARC, 2016a).

"Outdoor air pollution/Urban air pollutants" was also separately nominated as a priority for other cancer sites, and more information about air pollution generally can be found in that nomination.

Cancer in Humans

Epidemiological evidence for traffic-related air pollution was mixed. Case–control studies based on modelled exposure data provided evidence of increased risk, including in studies that considered early-life exposures and menopausal status. However, the findings from prospective cohort studies were mostly null, possibly because they used different methods to estimate air pollution or because they did not evaluate early-life exposure or menopausal status.

Mechanistic Evidence

A 2018 review article on 134 environmental chemicals previously identified as mammary gland toxicants, including polycyclic aromatic hydrocarbons (PAHs), air pollution, and vehicular exhaust, summarized the role of several gene variants, including *BRCA1*, in modifying the association between PAH–DNA adducts and breast cancer (Rodgers et al., 2018). Although genes associated with DNA repair and apoptotic signalling did appear to modify the association, polymorphisms of methylation status (including *BRCA1*) did not. However, these results were based on small sample sizes or single studies.

The Advisory Group noted that from the mechanistic standpoint, this topic could be expanded beyond traffic-related exposures, including in occupational settings. In addition, this topic could be further explored

in a workshop format to clarify the mechanisms and the particular exposure settings that, in general, may contribute to breast cancer in women. This could be an important next step to elucidate the types of agents that could be grouped together and evaluated by the *IARC Monographs* programme. This merits further consideration with these clarifications.

Key References

The following key references were also identified: Callahan et al. (2018); White et al. (2015).

Recommendation: No evaluation

Airborne gram-negative bacterial endotoxins

Airborne gram-negative bacterial endotoxins have not been previously evaluated by the *IARC Monographs* programme.

Endotoxin is a component of gram-negative bacterial cell walls and is widespread in many industrial settings and in the ambient environment. Environments with high exposures include livestock farms, cotton textile facilities, and sawmills. Exposures may be particularly increased in tropical countries, because of high humidity and temperatures and poorly maintained ventilation systems. Concentrations are highly variable in non-occupational settings. Endotoxin causes inflammation and can lead to clinical symptoms such as fever, rigors, and respiratory problems. Paradoxically, given the probable role of inflammation in carcinogenesis, it has been suggested that endotoxin may prevent cancer and limit tumour growth (Lundin & Checkoway, 2009), particularly for cancer of the lung (Ben Khedher et al., 2017; Garcia et al., 2018a; Lerro et al., 2019). The Advisory Group noted the scant evidence for a carcinogenic role.

Recommendation: No evaluation

Alachlor (chloroacetanilide herbicide) (CAS No. 15972-60-8)

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

Exposure Data

Alachlor is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Alachlor is a chloroacetanilide herbicide that is used primarily on corn and soybeans. It has been banned in Canada and the European Union (EC, 2007) but is still authorized in the USA; its use has declined since a peak in the 1980s. Alachlor is listed in Annex III of the Rotterdam Convention and is subject to consent to import in many countries, particularly in Africa, Asia, and Central and South America (Rotterdam Convention, 2011a).

Cancer in Humans

There are some epidemiological studies on alachlor of cancer in humans. Two population-based case–control studies found no association of self-reported use and leukaemia or non-Hodgkin lymphoma (Lerro et al., 2018a). In the United States National Cancer Institute (NCI) Agricultural Health Study, an earlier analysis found evidence for an association with all lymphohaematopoietic cancers and non-statistically significantly elevated risks for multiple myeloma and leukaemia (Lee et al., 2004a; Weichenthal et al., 2010). A recent updated analysis of the NCI Agricultural Health Study found a strong positive association with laryngeal cancer and a weaker association with myeloid leukaemia (Lerro et al., 2018a).

Cancer in Experimental Animals

Primarily on the basis of evidence of benign and/or malignant tumours of the thyroid, stomach, and nasal cavity in rats, in 1986 the United States Environmental Protection Agency classified alachlor as a "probable human carcinogen". Although thyroid tumours were observed at very high doses, stomach and nasal tumours occurred at doses more relevant to human exposures (EPA, 1998b).

Mechanistic Evidence

The relevance to humans of tumours of the stomach in rats has been questioned based on mechanistic considerations (EFSA, 2004; Furukawa et al., 2014). In vitro, alachlor metabolites form DNA adducts and induce DNA single-strand breaks (EFSA, 2004).

Alachlor was evaluated in ToxCast and was active in cell-cycle and DNA binding assays below the cytotoxicity threshold.

Recommendation: Medium priority

Aluminium (CAS No. 7429-90-5)

Aluminium metal and aluminium compounds have not been previously evaluated by the *IARC Monographs* programme. The process of aluminium production is classified as *carcinogenic to humans* (Group 1) (IARC, 2012b), on the basis of a large number of epidemiological studies in aluminium production, which showed a consistent excess of cancer of the bladder and a somewhat less consistent excess of cancer of the lung. Pitch smokes and polycyclic aromatic hydrocarbons released by evaporation of pitch were identified as possible causal agents.

Exposure Data

Aluminium is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Aluminium is a metal that is widely used in the building, transportation, food processing, pharmacy, and water treatment industries. In humans, the main routes of chronic exposure to aluminium are oral (food,

water, oral medication), cutaneous (cosmetic, antiperspirant), and respiratory (dust inhalation). Occupational exposures occur mainly by inhalation during the production of metal in foundries, the production of powder, and the working of metals with welding.

Cancer in Humans

Several epidemiological studies have suggested that work at secondary aluminium smelters is associated with risk of bladder cancer and lung cancer; however, workers at these smelters have many co-exposures that may be a source of confounding in these studies (Seldén et al, 1997; Maltseva et al, 2016). Some studies suggesting that the use of antiperspirants containing aluminium salts may be associated with an increasing incidence of breast cancer have sparked scientific controversy, and this relationship has not been confirmed (Linhart et al, 2017; Mandriota 2017). The Advisory Group noted that "secondary aluminium smelting" could be considered as an agent, but that more clarification would be needed to differentiate the agent from metallic aluminium and aluminium compounds.

Cancer in Experimental Animals

The previous IARC evaluation indicated *sufficient evidence* in experimental animals for the carcinogenicity of airborne particulate polynuclear organic matter from aluminium production plants (IARC, 2012b).

Mechanistic Evidence

There is some evidence from both studies in experimental animals and studies in humans for a genotoxic mechanism underlying the effects of occupational exposures during aluminium production.

Better definition of the agent is needed (e.g. whether it has to do with salts), especially given that there is already an evaluation in Group 1 related to production and no new data are available to clarify that classification.

Key Reference

The following key reference was also identified: Darbre (2016).

Recommendation: Low priority

Amitrole (amino-triazole) (CAS No. 61-82-5)

Amitrole was previously evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3), on the basis of *inadequate evidence* of cancer in humans, *sufficient evidence* of cancer in experimental animals, and a mechanistic downgrade in consideration of the available mechanistic information.

Exposure Data

Amitrole is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Amitrole has been used as a commercial pesticide since the 1950s. In the USA, the registration for use on food crops was cancelled in 1971, and since then, it has been used primarily as a terrestrial herbicide in non-agricultural outdoor areas. Use is also restricted on land for feeding or grazing animals and direct application to water and wetlands in the USA. There has been no reported production in the USA since 1978. However, amitrole is commercially available in the USA and is produced by one manufacturer in Europe and two in East Asia. Reported use steadily declined in the 1970s, 1980s, and 1990s. Current release is reported to be less than 1000 lb (453.6 kg) per year. The European Food Safety Authority (EFSA, 2014b) conducted a risk assessment on amitrole used on food crops (orchards, vineyards, and olives) and roads and railways in Europe. When amitrole is released in air, it has a half-life of 3 days. In water and soil, amitrole is expected to rapidly undergo biodegradation by microorganisms. Under aerobic conditions, the half-life is expected to be 57 days in water and 22–26 days in soil.

Cancer in Humans

Inhalation, dermal, and ingestion occupational exposures are possible during manufacture and application. European estimates indicate that occupational exposures may exceed the acceptable operator exposure level (EFSA, 2014b).

Epidemiological studies of a small cohort of railroad workers in Sweden noted a significant increase in all cancers among workers who sprayed herbicides, but not among those primarily exposed to amitrole alone (Axelson et al., 1980). The United States National Toxicology Program (NTP, 2011b) considered the available epidemiological data to be inadequate for evaluating the relationship between cancer in humans and exposure to specifically amitrole.

Cancer in Experimental Animals

In one study in mice, thyroid follicular cell and hepatocellular tumours were produced after oral administration of amitrole. In one study in rats, amitrole administered orally induced follicular cell adenomas and carcinomas of the thyroid in males and females, and a marginal increase in the incidence of pituitary adenomas in female rats at the highest dose (IARC, 1987, 2001).

Mechanistic Evidence

The mechanisms of carcinogenicity in rodents have been thought to have limited relevance to humans (IARC, 2001; NTP, 2011b; EFSA, 2014b).

However, mechanistic studies indicate that amitrole may have variable effects on oxidative stress. Furukawa et al. (2010) reported an increase in oxidative DNA damage (as indicated by 8-oxo-7,8-dihydro-2′-deoxyguanosine) by the amitrole metabolite 3-amino-5-mercapto-1,2,4-triazole,

which was also noted to induce DNA lesions at guanine residues, suggesting that oxidative DNA damage may contribute to carcinogenicity of amitrole. In contrast, Jing et al. (2015) suggested that amitrole can inhibit inflammatory responses via downregulation of Cyp2E1; administration of amitrole increased survival in mice with oxidative hepatitis induced by acetaminophen overdose by altering catalase and plasma aminotransferase activity. Ruiz-Ojeda et al. (2016) reported increased hydrogen peroxide levels due to inhibition of catalase and glutathione peroxidase, with elevated superoxide dismutase activity, resulting in an overall decrease in reactive oxygen species in human adipose-derived stem cells after treatment with amitrole for 24 h. It is difficult to draw conclusions from these studies.

Recommendation: No evaluation

Androstenedione (CAS No. 63-05-8)

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

Exposure Data

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. Elevated serum androstenedione may be associated with some forms of congenital adrenal hyperplasia and is found among women with polycystic ovary syndrome, with and without accompanying elevated serum testosterone. Androstenedione is produced commercially as an intermediate in synthesis of steroid hormones for pharmaceutical uses (e.g. anti-inflammatory drugs, contraceptives) and was available as an athletic dietary supplement before the restriction of over-the-counter sales in 2005.

Cancer in Humans

In a 2019 systematic literature review of hormone levels during pregnancy and subsequent risk of maternal cancer of the breast and ovary, a single study reported significantly greater risk of sex-cord stromal tumours of the ovary associated with elevated androstenedione levels during pregnancy (Iqbal et al., 2019). Doubling of female androstenedione levels was reportedly associated with a 21% reduction in the risk of serious invasive ovarian epithelial cancers (Ose et al., 2015). A 2010 report from the United States National Toxicology Program (NTP) did not find an association between serum androstenedione and cancer of the prostate or other types of cancer (NTP, 2010a). A search of PubMed using IARC's cancer epidemiological search terms associated with androstenedione for the past 5 years did not identify publications suggesting recent developments on the association between androstenedione and risk of cancer in humans.

Cancer in Experimental Animals

The NTP technical report in 2010 described results of subchronic and chronic studies conducted in rats and mice dosed with androstenedione for 2 weeks, 3 months, or 2 years by oral gavage. Examination of the adrenal glands of female mice indicated that subchronic exposure to androstenedione had androgenic effects but was not dose-limiting at the highest treatment level (50 mg/kg/day), consistent with an increase in female body weight of treated animals compared with controls in the same studies. Androstenedione was associated with decreased incidence of mammary gland adenomas in female rats and testicular interstitial adenomas in male rats in the 2-year study (NTP, 2010a). Equivocal findings for bronchioloalveolar adenoma and adenoma or carcinoma (combined) were reported for male rats treated with 20 mg/kg and 50 mg/kg doses. Equivocal findings were also reported for mononuclear cell leukaemia in female rats at all dose levels. An increased incidence of hepatocellular adenoma and carcinomas and pancreatic islet adenomas was reported for male and female mice compared with controls. Results of the 2-year oral gavage treatment with androstenedione provided clear evidence of hepatocellular carcinogenicity in male mice. There was also an increased incidence of pancreatic islet adenomas in male and female mice, which was considered to be treatment-related (NTP, 2010a).

Mechanistic Evidence

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 (EPA, 2019a). The genetic toxicity of androstenedione was tested in several strains of *Salmonella* and *Escherichia coli*, and in rat bone marrow and mouse peripheral blood (NTP, 2010a).

Recommendation: Low priority

Angiotensin inhibitors and blockers

Exposure Data

Antihypertensives are some of the leading drugs prescribed. For example, lisinopril, an angiotensin-converting enzyme inhibitor (ACEI), was the second leading drug prescribed in the USA in 2010–2012 (Kantor et al., 2015), with more than 100 million prescriptions (ClinCalc, 2019). It has been estimated that there are more than 1 billion adults worldwide with hypertension, and this number is likely to grow by 56% in the next 6 years (Jarari et al., 2016). Moreover, a survey of the period 2001–2010 found that use of angiotensin receptor blockers (ARBs) increased by 100% and use of ACEIs by 31% (Gu et al., 2012).

Cancer in Humans

The role of antihypertensive drugs in cancer is the subject of continuing debate, because of conflicting results. There is a considerable body of evidence, including several large, well-conducted prospective studies, which have reported both harmful and protective associations. The disparate results occur across all cancer types combined and for specific sites, including cancers of the breast, lung, and skin (including melanoma). Of the positive associations, the hazard ratio of 1.14 (95% confidence interval [CI], 1.01–1.29) was reported for cancer of the lung for ACEI use of longer than 5 years (Hicks et al., 2018), the odds ratio of 2.86 (95% CI, 2.13–3.83) was reported for basal cell carcinoma (skin) for ARB use, and the odds ratio of 2.22 (95% CI, 1.37–3.61) was reported for squamous cell carcinoma for ARB use (Nardone et al., 2017).

Cancer in Experimental Animals

No animal cancer bioassays were identified.

Mechanistic Evidence

Very little is known about the underlying mechanism or mechanisms; however, there are probably more than one. Phototoxicity may play a role, as shown in the case of psoralens and photochemotherapy with squamous cell carcinoma (skin), because some antihypertensives are phototoxic. Induction of type II angiotensin receptors and their differential regulation of angiogenesis may also play a role (Walther et al., 2003). A third potential mechanism may be the increased exposure of the cells to co-carcinogens, through reduced efflux of multidrug resistance protein 1 (also known as P-glycoprotein 1) (Weiss et al., 2010). Finally, for lung neoplasia specifically, the undesirable accumulation of bradykinin in the lung (due to ACEI treatment), where it may bind bradykinin receptors, thereby stimulating lung cancer cell proliferation and angiogenesis, may play a role. This list is not exhaustive.

The study of the role of antihypertensive drugs in cancer may benefit from a systematic data assembly across the members of the class to ascertain the various levels of available evidence.

Recommendation: No evaluation

Aniline (CAS No. 62-53-3)

Aniline was evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1982, 1987).

Exposure Data

Aniline is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Aniline is used as a starting material in several industries, including the manufacture of a variety of plastics, rubber additives, colourants, and drugs. The worldwide annual production capacity of aniline is

more than 100 million tons. Aniline is also a component of cigarette smoke. Exposure occurs predominantly in occupational settings, but the general population can also be exposed to aniline in the environment, for example via industrial effluents.

Exposure to aniline occurs by inhalation, ingestion, and dermal absorption (Piotrowski, 1957; Dutkiewicz & Piotrowski, 1961; Korinth et al., 2012).

Since the previous IARC evaluation, the National Institute for Occupational Safety and Health has classified aniline and its homologs as occupational carcinogens (NIOSH, 2007, 2011), and there are occupational exposure limits in the European Union (2 ppm in air and 0.2 mg/L in urine), Germany (2 ppm in air and 1 mg/L in post-shift urine) (Käfferlein et al., 2014), and the USA (2 ppm in air). Aniline is classified as a "probable human carcinogen" by the United States Environmental Protection Agency's Integrated Risk Information System (IRIS) programme (EPA, 1990) and is listed as causing cancer in the Proposition 65 list by the California Office of Environmental Health Hazard Assessment (OEHHA, 2019a).

Cancer in Humans

Significantly elevated incidence of bladder cancer has been reported in two occupational cohorts with exposure to aniline in manufacturing plants, one in the USA (Carreón et al., 2014b) and one in Wales (Sorahan, 2008). In these cohorts, risk of bladder cancer increased with increasing exposure, with clear evidence of a dose–response relationship. Supporting evidence comes from a case series of 10 bladder cancer cases identified among workers in a dye and pigment manufacturing plant in Japan (Nakano et al., 2018).

However, the major limitation of these studies is that exposure to aniline was concurrent with exposure to several other chemical agents, including *ortho*-toluidine. In the 2008 study in Wales, the statistically significant association between aniline and bladder cancer was attenuated after adjustment for exposure to the other chemicals. These studies have generally concluded that exposure to *ortho*-toluidine is more likely than exposure to aniline to be the cause of the increased cancer risk.

Cancer in Experimental Animals

When administered in the diet for 2 years to CD-F rats (130 rats per sex per group) at levels of 0, 200, 600, and 2000 ppm, aniline hydrochloride increased the incidence of primary splenic sarcomas in male rats in the high-dose group (CIIT, 1982). Stromal hyperplasia and fibrosis of the splenic red pulp, which may be a precursor lesion of sarcoma, was also observed in the high-dose male rats and, to a lesser degree, in the female rats.

In an earlier study of dietary aniline hydrochloride administered at 0, 3000, or 6000 ppm to 50 male and 50 female Fischer 344 rats for 103 weeks (NCI, 1978a), male rats showed statistically significant dose-related trends in incidence of haemangiosarcomas and sarcomas or fibrosarcomas. The males also had statistically significantly increased incidence of haemangiosarcoma in the spleen and fibrosarcoma and

sarcoma (not otherwise specified) in the body cavity and the spleen, and a significant dose-related trend in incidence of malignant pheochromocytoma.

Mechanistic Evidence

Several studies relevant to key characteristics of carcinogens are available, particularly on whether aniline is genotoxic or induces oxidative stress (Parodi et al., 1982; Bomhard & Herbold, 2005; Koenig et al., 2018). For example, in a study of repeat gavage exposure to *para*-chloroaniline and aniline for 28 days in Big Blue TgF344 rats, results showed an increase in micronuclei, significant reductions in red blood cells, increases in absolute reticulocytes, and increased levels of methaemoglobin (Koenig et al., 2018). Aniline caused an increased frequency of sister chromatid exchange in vivo in mouse bone marrow cells (Parodi et al., 1982) and was also genotoxic in various tests in vitro.

Key References

The following key references were also identified: EC (2015); Wang et al. (2016b).

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

Anisidine

The term anisidine may refer to any of the three possible isomers (*para*, *ortho*, and *meta*) of methoxyaniline. The reference CAS No. 29191-52-4 corresponds to a mixture of the isomers (unspecified proportions). Carcinogenicity does not appear to have been tested in anisidine mixtures.

para-Anisidine/*para*-anisidine hydrochloride

para-Anisidine (CAS No. 104-94-9) was evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1987).

Exposure Data

Anisidine is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

para-Anisidine is used primarily as an intermediate in the manufacture of azo dyes and has been identified in tobacco smoke (IARC, 1982). It is routinely used in the laboratory setting as a reagent, in a colorimetric test that evaluates the formation of secondary lipid oxidation products (expressed as the anisidine value) in edible oils (Viau et al., 2016).

Cancer in Humans

No epidemiological studies evaluating the relationship between cancer in humans and exposure to *para*-anisidine were identified.

Cancer in Experimental Animals

When tested in 2-year carcinogenicity studies, *para*-anisidine hydrochloride was not carcinogenic in female rats and male or female mice and gave equivocal evidence of carcinogenic activity in male rats (NTP, 1978c). Similarly, *para*-anisidine was negative in several short-term carcinogenicity bioassays using transgenic mouse models (Tennant et al., 1995; Maronpot et al., 2000).

Mechanistic Evidence

para-Anisidine causes anoxia through the formation of methaemoglobin. It tested positive in some bacterial mutation assays and negative in others (Haworth et al., 1983; Thompson et al., 1992; Zeiger et al., 1992), was positive in in vitro cytogenetic assays (Galloway et al., 1987), and was negative in the in vivo bone marrow micronucleus assay (Pritchard et al., 2003). Although a C8-deoxyguanosine adduct through the arylamine nitrogen of *para*-anisidine was obtained by a synthetic method that mimicked the putative bioactivation pathway via *N*-hydroxylation and subsequent *O*-acetylation (Meier & Boche, 1991), *para*-anisidine gave no indication of causing DNA damage in rodents in vivo (Takasawa et al., 2015).

***meta*-Anisidine**

meta-Anisidine (CAS No. 536-90-3) has not been previously evaluated by the *IARC Monographs* programme.

meta-Anisidine is an intermediate in the manufacture of azo dyes and is associated with tobacco, as a natural component of tobacco, a pyrolysis product in tobacco smoke, or an additive (Rodgman & Perfetti, 2013).

Cancer in Humans

No epidemiological studies evaluating the relationship between cancer in humans and exposure to *meta*-anisidine were identified.

Cancer in Experimental Animals

No cancer studies in experimental animals appear to have been performed with *meta*-anisidine.

Mechanistic Evidence

meta-Anisidine tested positive in some bacterial mutation assays and negative in others (Haworth et al., 1983; Zeiger et al., 1992) and was positive in in vitro cytogenetic assays (Galloway et al., 1987).

***ortho*-Anisidine/*ortho*-anisidine hydrochloride**

ortho-Anisidine (CAS No. 90-04-0) is classified as *possibly carcinogenic to humans* (Group 2B) (IARC, 1987, 1999a), on the basis of *sufficient evidence* of carcinogenicity in experimental animals.

Exposure Data

ortho-Anisidine is used as an intermediate in the manufacture of dyes and pigments and the production of pharmaceuticals (e.g. guaiacol). It is also used as a corrosion inhibitor and antioxidant and has been identified in tobacco smoke as well as in wastewater from chemical plants and oil refineries (IARC, 1999a). In addition to occupational exposure, individuals may be exposed to *ortho*-anisidine that is present in the environment. The compound was detected in human urine from subjects of the general population in Germany (Weiss & Angerer, 2002; Kütting et al., 2009), and haemoglobin adducts from *ortho*-anisidine were identified in blood samples from children in three cities in Germany, regardless of exposure to environmental tobacco smoke (Richter et al., 2001).

Cancer in Humans

No epidemiological studies evaluating the relationship between cancer in humans and specific exposure to *ortho*-anisidine were identified. In a recent report of 10 cases of bladder cancer among workers in two dye and pigment manufacturing plants in Japan, an association was made with high exposure to *ortho*-toluidine (present at higher levels), although the workers were co-exposed to other aniline derivatives, including *ortho*-anisidine (Nakano et al., 2018).

Cancer in Experimental Animals

When tested in 2-year carcinogenicity studies, *ortho*-anisidine hydrochloride caused transitional cell carcinomas of the urinary bladder in male and female mice and rats. It also caused kidney cancer and increased the incidence of tumours (benign and malignant combined) of the thyroid in male rats (NCI, 1978b).

Mechanistic Evidence

ortho-Anisidine causes anoxia through the formation of methaemoglobin and is weakly mutagenic (IARC, 1999a), including in the urinary bladder of transgenic *lacI* (Big Blue) mice (Ashby et al., 1994). Mutagenicity was enhanced in a *Salmonella typhimurium* tester strain expressing elevated *N*-acetyltransferase activity (Thompson et al., 1992).

When administered to rodents, *ortho*-anisidine caused organ-specific DNA damage in the urinary bladder of mice (Sasaki et al., 1998), and *ortho*-anisidine hydrochloride produced DNA single-strand breaks and DNA adducts in the urinary bladder urothelium of rats (Iatropoulos et al., 2015). *ortho*-Anisidine has been found to undergo oxidative activation by peroxidase and cytochrome P450 enzymes to species capable of binding proteins and DNA in vitro (Thompson & Eling, 1991; Stiborová et al., 2002, 2005; Naiman et al., 2010, 2011). The same adducts detected in DNA incubated with *ortho*-anisidine and human microsomes in vitro were found in several organs of rats treated with the compound; higher levels were detected in the urinary bladder (Stiborová et al., 2005). These were identified as deoxyguanosine adducts stemming from cytochrome P450-mediated *N*-hydroxylation of *ortho*-anisidine, with some involvement of subsequent

O-sulfation (Stiborová et al., 2005; Naiman et al., 2008). The major adduct formed in vitro and in vivo was identified as *N*-(deoxyguanosin-8-yl)-2-methoxyaniline (Naiman et al., 2012). The metabolic bioactivation mechanism and DNA adduct profile, as well as the target organ for carcinogenicity, are similar to those observed for other aromatic amines, such as 4-aminobiphenyl, which is classified by IARC as *carcinogenic to humans* (Group 1) (IARC, 2010a).

The Advisory Group noted that it could be useful to consider *ortho*-nitro-anisole, which is classified as *possibly carcinogenic to humans* (Group 2B) (IARC, 1996), at the same time, because of structural similarity. It could be interesting to consider whether it belongs to the same mechanistic class as 4-aminobiphenyl (Group 1).

Key Reference

The following key reference was also identified: Hobbs et al. (2015).

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

Anthracene (CAS No. 120-12-7)

Anthracene (CAS No. 120-12-7) was first evaluated by the *IARC Monographs* in Volume 32 (IARC, 1983a). The most recent evaluation was in Volume 92 (IARC, 2010b). The compound was evaluated as *not classifiable as to its carcinogenicity to humans* (Group 3).

Exposure Data

Anthracene is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical. Anthracene is used primarily as an intermediate in the synthesis of dyes; other uses include in smoke screens, scintillation counter crystals, and organic semiconductor research.

Cancer in Humans

No epidemiological studies evaluating the relationship between cancer in humans and exposure to anthracene were identified.

Cancer in Experimental Animals

The cancer studies in rodents reviewed by previous *IARC Monographs* Working Groups (IARC, 1983a, 2010b) were negative, regardless of the route of administration. Additional data from a good laboratory practice (GLP) study in rodents demonstrated the carcinogenicity of anthracene in female rats (increase in the incidence of renal cell adenoma or carcinoma, combined), female mice (induction of hepatocellular carcinoma), and male rats (induction of hepatocellular carcinoma and transitional cell carcinoma of the bladder) (JBRC, 1998).

Mechanistic Evidence

Anthracene was not mutagenic in standard assays but displayed photomutagenicity (IARC 1983a, 2010b). Anthracene 1,2-dihydrodiol was identified as the major metabolite formed in incubations with rat liver preparations. The 1,2-dihydrodiol, as well as 9,10-anthraquinone, the 9,10-dihydrodiol, and 2,9,10-trihydroxyanthracene, have been identified in rat urine, along with conjugates consistent with formation of the 1,2-epoxide (IARC, 1983a). No additional data relevant to evaluation of anthracene carcinogenicity were identified in the recent literature.

Recommendation: Medium priority

Antidepressants

Exposure Data

Antidepressants are one of the leading prescription drug types in many countries, including Canada and the USA. Data from the National Health and Nutrition Examination Survey (NHANES) show that in 2011–2014, 12.7% of people in the USA aged 12 years and older (16.5% of females; 8.6% of males) had taken antidepressants in the previous month (Pratt et al., 2017). Even more strikingly, 25% of those who had taken antidepressants in the previous month had done so for the previous 10 years. Several selective serotonin reuptake inhibitors (SSRIs) make up the list of the most prescribed psychiatric drugs by primary mechanism of action and are among the top antidepressant types sold.

Cancer in Humans

Numerous studies aiming to determine whether the use of antidepressants in general is associated with cancer development or recurrence either have not found such an association or have found a protective effect. The most studied cancer types originate in the breast, prostate, bone, endometrium, ovary, or colon. However, a recent study with more than 5500 subjects found that chronic therapy with SSRIs specifically is associated with an increased incidence of death during the first 2 years after cancer diagnosis (Boursi et al., 2018). The hazard ratios for the risk of death upon continuous use of SSRIs were 2.02 (95% confidence interval [CI], 1.24–3.28) for melanoma, 1.91 (95% CI, 1.53–2.38) for breast cancer, 1.79 (95% CI, 1.38–2.33) for prostate cancer, 1.51 (95% CI, 1.21–1.72) for lung cancer, and 1.44 (95% CI, 1.19–1.75) for colorectal cancer. Previous studies aiming to determine whether the use of SSRIs is associated with cancer found varied results, from protective effects (for cancers of the colon and breast, and haematological malignancies) to increased incidence (for cancers of the lung and breast). In the study that found harmful effects, the following odds ratios were found in current SSRI users with treatment initiation occurring more than 1 year before the index date: 1.27 (95% CI, 1.16–1.38) for lung cancer and 1.12 (95% CI, 1.06–1.18) for breast cancer (Boursi et al., 2015). This was a large study, with more than 535 000 subjects, including more than 109 000 patients with cancer, and such an association had already been shown previously for

breast cancer (Cotterchio et al., 2000; Ashbury et al., 2012). Even more recently, yet another large study (with more than 23 000 patients with breast cancer) uncovered an association between SSRI use and breast cancer, with 27% higher mortality in SSRI users than in non-users (95% CI, 1.16–1.40) (Busby et al., 2018). The Advisory Group noted that in light of the mixed human cancer evidence, attention may be merited for specific classes of antidepressants, such as SSRIs, rather than the overall drug class.

Cancer in Experimental Animals

No positive associations were found in animal cancer bioassays with tumours of the lung or breast.

Mechanistic Evidence

Overall, the mechanism or mechanisms underlying an association between SSRI use and cancer remain unclear. However, several mechanisms have been suggested. One consists of SSRI binding to growth-regulatory intracellular histamine receptors, with anti-estrogenic effects, as described in rodents (Brandes et al., 1992). Another consists of paroxetine binding and inhibiting CYP2D6, thereby lowering the concentrations of metabolites of the anticancer drug tamoxifen in the circulation (Kelly et al., 2010). A third suggested mechanism includes an immunological one, such as the reduction of pro-inflammatory cytokines IL-1β, TNF-α, IL-6, and/or IFN-γ, the augmentation of the anti-inflammatory cytokine IL-10 (Kalkman & Feuerbach, 2016), or the reduction of T cells (including CD8+ cytotoxic T lymphocytes), potentially leading to reduced tumour cell visibility by the immune system. SSRIs cause oxidative stress in rat C6 glioma and human 1321N1 astrocytoma cell lines (Slamon & Pentreath, 2000). This list is not exhaustive.

In the future, certain members of this group may merit closer scrutiny, for example paroxetine (mentioned above). It may also be useful to consider some of the group separately, because of the diversity in terms of chemical structure, activity, and potential to cause or prevent cancer.

Key Reference

The following key reference was also identified: Hallett et al. (2016).

Recommendation: No evaluation

Antimony trioxide (CAS No. 1309-64-4)

Antimony trioxide (Sb_2O_3) was classified by IARC as *possibly carcinogenic to humans* (Group 2B) (IARC, 1989a), on the basis of *inadequate evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals.

Exposure Data

Antimony trioxide is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Antimony trioxide is an oxide of trivalent antimony and exists in nature in minerals. It can be interconverted to and from other forms of antimony in the environment, during commercial processing, and in vivo. Occupational, consumer, and environmental exposures result from its production and commercial use in the manufacture of flame retardants, polyethylene terephthalate plastic beverage containers, and specialty glasses, paints, and pigments.

Cancer in Humans

The most reliable epidemiological evidence comes from cohorts of antimony and tin smelter workers, and a case–control study of art glass workers (NTP, 2018g). Although lung cancer mortality was elevated in the smelter studies and stomach cancer risk was elevated in one antimony smelter study and the case–control study, confounding (including from co-exposures) and exposure misclassification were concerns for three of the studies (e.g. Jones et al., 2007). One cohort study in smelters, for which confounding and exposure misclassification were less of a concern, had elevated lung cancer mortality (ever exposure) and increased response with duration of employment (confidence bounds not given; see NTP, 2018g). A large cohort study in the USA found no association between antimony as a component of air pollution (at a single time point) and incidence of breast cancer (White et al., 2019). A nationally representative cross-sectional study in the USA found no association of antimony in blood with overall cancer prevalence (Guo et al., 2016).

Cancer in Experimental Animals

The conclusion of *sufficient evidence* of carcinogenicity in experimental animals in the IARC evaluation in 1989 (IARC, 1989a) was based on two inhalation studies in female rats showing lung tumours. Since then, additional inhalation studies have observed lung cancer in male and female mice and lung and adrenal tumours in male and female rats. Another inhalation study in male and female rats did not report increases in tumours (IARC, 1989a).

Mechanistic Evidence

Overall, there is considerable evidence that antimony trioxide is electrophilic and genotoxic (DNA damage and cytogenetic effects in vivo) and induces oxidative stress. Although antimony trioxide was not directly tested for inhibition of DNA repair, other trivalent antimony compounds in in vitro studies decreased DNA repair in human cells. In high-throughput assays, trivalent antimony compounds showed antagonist effects on nuclear receptors (cited in NTP, 2018g). There are a few studies in exposed humans and in human cell lines contributing to the overall mechanistic evidence (Paton & Allison, 1972; Gebel et al., 1997; Elliott et al., 1998; Cavallo et al., 2002).

Recommendation: Medium priority

Arecoline (CAS No. 63-75-2)

Arecoline has not been previously evaluated by the *IARC Monographs* programme. Arecoline is the primary active ingredient of the areca nut, which is classified as *carcinogenic to humans* (Group 1) (IARC, 2012c).

Exposure Data

Areca nut is widely cultivated in India, Bangladesh, Sri Lanka, Malaysia, the Philippines, and Japan. It has been estimated that more than 10% of the world's population chew areca nut, for its mild psychoactive effects.

Arecoline is an alkaloid that has been compared to nicotine; however, nicotine acts primarily on the nicotinic acetylcholine receptor. Arecoline is a partial agonist of the muscarinic acetylcholine receptors M1, M2, M3, and M4, and this is believed to be the primary cause of its parasympathetic effects (e.g. pupillary constriction, bronchial constriction). Because of its muscarinic and nicotinic agonist properties, arecoline has been shown to cause improvement in the learning ability of healthy volunteers as well as modest improvement in verbal and spatial memory in patients with Alzheimer's disease, although because of the possible carcinogenic properties of arecoline, it is not the first drug of choice for this degenerative disease. Arecoline has also been used medicinally as an anthelmintic.

Cancer in Humans

No studies were identified of cancer in humans specifically related to arecoline.

Cancer in Experimental Animals

IARC Monographs Volume 85 (IARC, 2004a) summarized the evidence from animal bioassays on arecoline; there was *limited evidence* in experimental animals for the carcinogenicity of arecoline. Arecoline given by gavage produced lung adenocarcinomas, stomach squamous cell carcinomas, and liver haemangiomas in male mice. It did not produce tumours when given by gavage to female mice, when given in the drinking-water to male and female hamsters, when injected subcutaneously into male mice, or when administered intraperitoneally to male mice. Since Volume 85 (IARC, 2004a), no new bioassays on arecoline have been published.

Mechanistic Evidence

As also described in Volume 85 (IARC, 2004a) and in more recent studies, mechanistic evidence relevant to various key characteristics of carcinogens is available for arecoline. Arecoline and other areca nut alkaloids gave positive responses in most bacterial mutagenicity assays, and induced chromosomal aberrations, micronucleus formation, and sister chromatid exchange in mammalian cells, both in vitro and in vivo. Arecoline also depletes glutathione in mice and in cultured human cells, and inhibits immune responses in mice. In addition, it inhibits matrix metalloproteinases.

Key References

The following key references were also identified: Liu et al. (2016); Wang et al. (2016a); Hsieh et al. (2017); Lin et al. (2017); Peng et al. (2017).

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

Aspartame (CAS No. 22839-47-0)

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

Exposure Data

Aspartame is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Aspartame is a non-nutritive sweetener. It is widely used as a tabletop sweetener, in low-calorie beverages, and in prepared foods. Use of aspartame is currently authorized in more than 90 countries.

Cancer in Humans

Studies in humans have mostly reported no association between aspartame intake and cancer risk, with the exception of an association for multiple myeloma and non-Hodgkin lymphoma in men but not in women in a prospective study in the USA (Schernhammer et al., 2012) and in two case–control studies, for adenocarcinoma of the exocrine pancreas (Chan et al., 2009) and urinary tract tumours (Andreatta et al, 2008). In all studies, aspartame intake was assessed indirectly from intake of low-calorie and non-calorie beverages and use of artificial sweeteners.

Cancer in Experimental Animals

Numerous studies in rats and mice, including standard cancer animal bioassays, studies in transgenic mice, tumour promotion studies, and studies in specific cancer types, have been conducted by the manufacturer, regulatory agencies, and independent researchers (NTP, 2005b; EFSA, 2013). Safety reviews have been conducted after concerns were raised by a few studies in animals about the potential adverse effect on the brain, including brain tumours. Lifetime studies in rats showed an increased risk of lymphomas, leukaemia, and transitional cell carcinomas of the pelvis, ureter, and bladder in a dose-dependent manner within ranges of aspartame intake that are considered to be safe for human consumption (Soffritti et al., 2014).

Mechanistic Evidence

Some mechanistic studies relevant to the key characteristics of carcinogens are available in the published literature, which may merit further review (e.g. Kamenickova et al., 2013; Saunders et al., 1980).

Aspartame was evaluated in ToxCast and showed estrogen response element binding, for which it was given a model score.

The major gut hydrolysis products of aspartame are L-phenylalanine, aspartic acid, and methanol (EFSA, 2013); however, the amount of methanol produced (about 10% by mass) is probably too low for concern.

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

Atrazine (CAS No. 1912-24-9) and other 2-chloro-*s*-triazine herbicides

Atrazine was previously reviewed by the *IARC Monographs* programme (IARC 1991, 1999a). The most recent IARC evaluation was *not classifiable as to its carcinogenicity to humans* (Group 3), on the basis of *sufficient evidence* of carcinogenicity in experimental animals and *strong* evidence that the mechanism by which atrazine increases the incidence of mammary gland tumours in Sprague-Dawley rats is not relevant to humans. The 2014 Priorities Advisory Group assigned atrazine a medium priority (IARC, 2014).

Exposure Data

Atrazine is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Atrazine is a herbicide that is used to control broad-leafed weeds and selected grasses on certain crops and on evergreen tree farms. Occupational exposure to atrazine can occur during manufacturing, formulation, and application tasks. Non-occupational exposure may occur from spray drifts and from drinking-water. In low-income countries, atrazine is one of the main pollutants of drinking-water, a fact that motivated the European Union to ban its use in 2004.

In 2003, the United States Environmental Protection Agency concluded that atrazine was “not likely to be carcinogenic to humans”, and in 2011 it was re-evaluated by a scientific advisory panel, which concluded that the information to assess the carcinogenicity of atrazine was inadequate.

Cancer in Humans

Some case–control studies showed weak associations of atrazine with non-Hodgkin lymphoma and have suggested an increased risk of cancers of the ovary and prostate. The United States National Cancer Institute Agricultural Health Study found suggestive associations with non-Hodgkin lymphoma, multiple myeloma, and cancers of the bladder and lung among applicators, but none were statistically significant. A suggestive association with thyroid cancer was found for participants with higher atrazine use, but this association remains to be confirmed. There was a non-statistically significant increased risk of ovarian cancer among female applicators who reported ever using atrazine compared with those who did not; however, this observation was based on a small number of cases among atrazine users.

Cancer in Experimental Animals

When atrazine was evaluated in 1999 (IARC, 1999a), there was *sufficient evidence* in experimental animals for the carcinogenicity of atrazine.

Mechanistic Evidence

Since the most recent *IARC Monographs* evaluation, some studies have provided new insights into carcinogenic and genotoxic activity of atrazine. Atrazine causes mammary tumours in rats by affecting the hypothalamus and pituitary gland, altering luteinizing hormone cycling, and thus leading to increasing endogenous estrogen and prolactin levels. However, this mechanism appears not to work in humans. Atrazine is an endocrine disruptor with both estrogenic and anti-estrogenic properties, which could be related with the etiology of both prostate cancer and ovarian cancer.

Several studies have indicated that atrazine may cause carcinogenesis by damaging the integrity of DNA and the stability of the cell genome; other studies have suggested that the genotoxic effect of atrazine is minimal. Early precancerous lesions in patient tissues, as well as specific oncogene activation in different tumour models, have been linked to DNA double-strand breaks and the activation of DNA damage checkpoints. Overall, there are a significant number of new mechanistic studies, both positive and negative and of variable quality.

Key References

The following key references were also identified: Kligerman et al. (2000); Tennant et al. (2001); Hopenhayn-Rich et al. (2002); MacLennan et al. (2002); Young et al. (2005); Liu et al. (2006); Zeljezic et al. (2006); Fan et al. (2007); Koutros et al. (2010); Cavas (2011); Huang et al. (2014); Deziel et al. (2018); Cook et al. (2019).

Recommendation: Medium priority

Automotive gasoline (leaded and unleaded)

Gasoline was classified by IARC as *possibly carcinogenic to humans* (Group 2B) (IARC, 1989b), on the basis of *inadequate evidence* of carcinogenicity in humans, *limited evidence* of carcinogenicity in experimental animals of unleaded automotive gasoline, and supporting evidence from in vivo and in vitro studies showing unscheduled DNA synthesis, as well as evidence on the carcinogenicity of the constituents benzene and butadiene.

Exposure Data

Gasoline is a flammable, highly refined, and blended mixture of petroleum-derived aromatic and aliphatic compounds, used as fuel in internal combustion engines used in transportation. Increased exposures occur to gasoline station attendants (Moro et al., 2017), residents living in close proximity to

gasoline stations, consumers fuelling their tanks, and workers in gasoline production, distribution, and storage.

Cancer in Humans

Since 1989, there have been several new epidemiological studies that have reported increased risk, and others that have not. These include studies reporting: leukaemia in a community cohort associated with exposures from a large gasoline spill (Patel et al., 2004; Talbott et al., 2011); elevated Hodgkin lymphoma in residents living near a non-operational petroleum refinery with a history of gasoline leaks (Dahlgren et al., 2008); acute childhood leukaemia in residents living near gasoline stations or repair garages in a case–control study in France (Brosselin et al., 2009); acute myeloid leukaemia in young adults that increased with car density in Sweden (Nordlinder & Järvholm, 1997); an elevated but not statistically significant increased risk of childhood leukaemia with proximity to main roads and gasoline stations in the United Kingdom (Harrison et al., 1999); null results in service station workers for haematopoietic cancers (Lynge et al., 1997); kidney cancers after occupational exposures in case–referent studies (Partanen et al., 1991; Mellemgaard et al., 1994; Mandel et al., 1995); and kidney and nasal cancer in a prospective cohort study of gasoline station workers in Nordic countries (Lynge et al., 1997).

Studies have also been conducted of other occupations that can involve exposures to gasoline, such as workers in the oil refinery and petroleum product distribution industry.

Cancer in Experimental Animals

With respect to studies in experimental animals that were not evaluated in *Monographs* Volume 45 (IARC, 1989b), gasoline was not found to be carcinogenic in a mouse dermal bioassay (Broddle et al., 1996) and was reported to increase the total number of malignant tumours when administered by stomach tube, in olive oil, once daily, 4 days per week, for 104 weeks, to male and female Sprague-Dawley rats (Maltoni et al., 1997). In addition, gasoline vapour condensate, with and without methyl *tert*-butyl ether (MTBE), was tested; the vapour condensate without MTBE induced renal tubule carcinomas (Benson et al., 2011).

Mechanistic Evidence

Studies of genotoxic effects in gasoline station workers and other workers exposed to gasoline fumes have exhibited a variety of outcomes indicative of genotoxicity (e.g. Sellappa et al., 2010; Rekhadevi et al., 2011; Tunsaringkarn et al., 2011; Moro et al., 2015; Beceren et al., 2016; Martinez-Valenzuela et al., 2017; Filho et al., 2018; Salem et al., 2018; Shaikh et al., 2018); the studies variously reported elevated micronucleus frequency, DNA fragmentation and other damage, chromosomal instability, chromosomal aberrations, and sister chromatid exchange.

Increased oxidative protein damage and decreased antioxidant capacity as well as immunological alterations have been observed in gasoline station attendants (Moro et al., 2015).

Genotoxicity, oxidative stress, and inflammation are observed in rats exposed to gasoline vapours (Ek-Wakf et al., 2019).

Cases of myeloproliferative disorders have been associated with the use of gasoline as a degreaser and solvent (Bernardini et al., 2005), and myelodysplastic syndrome has been observed in terminal workers involved in loading gasoline.

Other relevant information includes human, animal, and mechanistic evidence from studies on gasoline constituents and on interactions of constituents.

In summary, the Advisory Group considered that the new epidemiological, bioassay, and mechanistic evidence merited evaluation by an *IARC Monographs* Working Group to determine whether it could lead to a change in classification for this agent.

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

Benzophenone-1 (2,4-dihydroxybenzophenone) (UV blocker) (CAS No. 131-56-6)

Benzophenone-1 (also known as 2,4-dihydroxybenzophenone) has not been previously evaluated by the *IARC Monographs* programme. It is a member of the benzophenones. Benzophenone, another member of this class, was classified by IARC as *possibly carcinogenic to humans* (Group 2B), with no data in humans and *sufficient evidence* of carcinogenicity in experimental animals by oral administration (IARC, 2013c). However, benzophenone-1 was not mentioned in the *Monograph* on benzophenone.

Exposure Data

Benzophenone-1 is an ultraviolet-radiation blocker that is used in many cosmetic products (e.g. sunscreens, hair products, lipsticks, and nail polishes) as well as in paints and plastics.

Cancer in Humans

No epidemiological studies of cancer in humans with benzophenone-1, or benzophenones in general, were identified.

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified for benzophenone-1.

Mechanistic Evidence

There are some recent in vitro studies indicating that benzophenone-1 exerts endocrine-disrupting properties in estrogen receptor and androgen receptor signalling pathways. These studies suggest that benzophenone-1 stimulates the proliferation of BG-1 ovarian cancer cells like 17-β estradiol does (Park et al., 2013) and has the ability to induce ovarian cancer metastasis via regulation of the expression of epithelial–mesenchymal transition markers and migration of estrogen receptor-expressing BG-1 ovarian cancer cells (Shin et al., 2016). There are also in vitro studies showing that benzophenone-1 may accelerate growth of MCF-7 breast cancer cells and enhance the progression of prostate cancer by regulating cell

cycle-related genes (In et al., 2015) and may promote cancer metastasis through amplification of metastasis-related markers (Kim et al., 2015). These data are corroborated by the results of high-throughput and computational methods to evaluate the endocrine bioactivity used in the United States Environmental Protection Agency Endocrine Disruptor Screening Program, which showed that benzophenone-1 had significant estrogen receptor (Browne et al, 2015) and androgen receptor activity (positive in 17 estrogen receptor assays out of 31, and in 6 androgen receptor assays out of 15). It is relevant to mention that benzophenone and benzophenone-1 had different results for these tests. Benzophenone-1 estrogenic activity was measured in the ovariectomized rat uterotrophic assay, which indicated that it is a weak estrogenic compound (Koda et al., 2005).

Key Reference

The following key reference was also identified: EPA (2019f).

Recommendation: Low priority

o-Benzyl-*p*-chlorophenol (CAS No. 120-32-1)

o-Benzyl-*p*-chlorophenol has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

o-Benzyl-*p*-chlorophenol is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

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 United States National Institute for Occupational Safety and Health has statistically estimated that 347 634 workers (244 212 of them female) were potentially exposed to *o*-benzyl-*p*-chlorophenol in the USA (NIOSH, 2006). 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 data are available on carcinogenicity in humans.

Cancer in Experimental Animals

Toxicity and carcinogenicity studies were conducted by administering *o*-benzyl-*p*-chlorophenol (~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 increases in tumours were seen in male F344/N rats that received 30, 60, or 120 mg/kg body weight for 2 years or in female B6C3F$_1$ mice that received 120, 240, or 480 mg/kg body weight for 2 years (NTP, 1994a). In male B6C3F$_1$ mice, there was increased incidence of renal tubule adenoma and renal tubule adenoma or carcinoma (combined).

Mechanistic Evidence

Genetic toxicity studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, L5178Y mouse lymphoma cells, and cultured human lymphoblast cells (NTP, 1995a). In tests performed with and without exogenous metabolic activation, *o*-benzyl-*p*-chlorophenol did not induce gene mutations in various *S. typhimurium* strains (TA98, TA100, TA1535, or TA1537) and did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells. However, positive results were obtained in gene mutation tests conducted with LS178Y mouse lymphoma cells and TK6 human lymphoblast cells in the absence of S9. Other mechanistic data were sparse.

In summary, *o*-benzyl-*p*-chlorophenol is widely used. There is a lack of data in humans and weak evidence from animal carcinogenicity and genetic toxicity studies.

Recommendation: Medium priority

Biphenyl (CAS No. 92-52-4)

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

Exposure Data

Biphenyl is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical. Biphenyl is used in many products and processes, including as a fungicide and as a component of agricultural chemicals.

Cancer in Humans

The few available human health hazard data consist of limited assessments of workers exposed to biphenyl during the production or use of biphenyl-impregnated fruit-wrapping paper, in which signs of hepatic and nervous system effects were observed (IARC, 2014).

Cancer in Experimental Animals

Biphenyl has been studied in rats and mice. Bladder tumours were found in the male rats, as evidenced by significantly increased incidence of carcinoma and papilloma of the transitional cells as well as one rarely observed case of both carcinoma and papilloma of the squamous cells. In mice, incidence of hepatocellular adenoma and hepatocellular carcinoma was increased in females (Umeda et al., 2002, 2005).

Mechanistic Evidence

With respect to the key characteristics of carcinogens, studies are available on whether biphenyl is genotoxic, indicating some capability of inducing genetic damage under certain conditions. Bacterial mutagenicity assays were uniformly negative, even with metabolic activation; however, several in vitro mammalian cell assays were able to detect weak evidence of mutagenicity with activation. Indications of the ability to induce chromosomal aberrations were also observed with the addition of metabolic activation, although this was accompanied by cytotoxicity in one study without metabolic activation. In addition, evidence of DNA strand breaks was observed in mice in several organs, whereas micronuclei were not found in mouse bone marrow. Micronuclei were observed in primary human lymphocytes (EPA, 2012).

Recommendation: Medium priority

Bisphenol A (CAS No. 80-05-7)

Bisphenol A (BPA) has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

BPA is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

BPA is a carbon-based synthetic compound that is widely used in the production of polycarbonate plastics, epoxy and phenolic resins, and polyester. These products have broad applications in consumer products, such as storage containers for foods and beverages. Leaching from plastics is a primary source of ubiquitous environmental contamination, resulting in exposure via dietary pathways (FAO/WHO, 2010).

Cancer in Humans

In contrast to studies in animals, new epidemiological data on long-term exposure to BPA and cancer are sparse. Tarapore et al. (2014) reported an association between urinary levels of BPA and prostate cancer in a survey of 60 urology patients. A case–control study of prostate cancer in patients in China reported a positive dose–response association with BPA (Tse et al., 2017). However, a case–control study in Poland found no evidence of an association between a urinary BPA biomarker and risk of postmenopausal breast cancer (Trabert et al., 2014).

Cancer in Experimental Animals

Numerous studies have been published, comprising mainly in vivo and in vitro animal experiments. In particular, a 2-year bioassay in rats as part of the Consortium Linking Academic and Regulatory Insights on Bisphenol A Toxicity (CLARITY-BPA) was completed in 2018 (NTP, 2018d). The 2014 Priorities Advisory Group considered completion of this study key to obtaining sufficient data for a *Monographs* review (IARC, 2014). The study did not demonstrate a distinct pattern of consistent responses within or across organs within the stop-dose and continuous-dose arms and various sacrifice times. Differences in treatment groups were not dose-responsive, sometimes occurring in only one low-dose or intermediate-dose group.

Mechanistic Evidence

BPA is not genotoxic, and mechanistic effects appear to involve several complex molecular and epigenetic mechanisms involving the endocrine and reproductive systems (Caserta et al., 2014; Mallozzi et al., 2017; Shafei et al., 2018).

In summary, BPA is an estrogen-like endocrine-disrupting chemical with some evidence of associations between exposure and increased risk of hormone-dependent tumours such as cancers of the breast, ovary, and prostate, among others.

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

Breast implants

Breast implants have not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Breast (mammary) implants are used in breast augmentation as well as reconstruction after mastectomy (Pittet et al., 2005). These medical devices differ by the composition of their shell (e.g. silicone or other), their texture (e.g. smooth, modified, or coated), and their filler (e.g. gel or saline) (Bondurant et al., 2000). Foreign substances have been used to augment or reconstruct the breast since the late 1800s, and silicone breast implants were introduced in the early 1960s (Bondurant et al., 2000). In 2000, up to 2 million women in the USA were estimated to have breast implants (Bondurant et al., 2000). In the United Kingdom, 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 Digital, 2018).

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 breast cancer survivor. Since then, more than 257 incident cases have been reported in the USA, a formal name for this cancer has been adopted (breast implant-associated anaplastic large-cell

lymphoma [BIA-ALCL]), and the incidence of this malignancy has been increasing over time. A 2018 study estimated an odds ratio of 421.8 (95% confidence interval, 52.6–3385.2) for the association between breast implants and ALCL (de Boer et al., 2018). Of particular note, almost all cases have arisen in conjunction with a "textured" versus a "smooth" type of implant, in spite of the substantially greater number of smooth implant types in current use. The average interval between implant placement and diagnosis is currently estimated at 10 years. The vast majority of studies of this malignancy have been conducted by breast cancer surgeons and have had a distinct clinical orientation, as is the usual course for a putatively newly discovered malignancy. However, it appears that enough work has been done to establish this as a new malignancy, the incidence of which seems to be increasing. The Advisory Group also noted emerging case reports on buttock implants, which may warrant a broadening of this agent to consider cosmetic implants more generally.

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

Studies relevant to key characteristics of carcinogens were identified.

Key Reference

The following key reference was also identified: Collett et al. (2019.

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

Bromate compounds (CAS No. 15541-45-4)

Potassium bromate was classified by IARC as *possibly carcinogenic to humans* (Group 2B) (IARC, 1999a), on the basis of *sufficient evidence* of carcinogenicity in experimental animals. Bromate has also been classified as a carcinogen by the United States Environmental Protection Agency's Integrated Risk Information System (IRIS) programme (EPA, 2001) and by the California Office of Environmental Health Hazard Assessment (OEHHA, 2009).

Exposure Data

Bromate is a disinfection by-product (EPA, 2001), and bromate compounds such as potassium bromate have various uses, including as a maturing agent for flour, as an oxidizing agent, and in explosives (IARC, 1999a).

Cancer in Humans

No studies of cancer in humans were identified.

Cancer in Experimental Animals

Potassium bromate, and to a lesser extent sodium bromate, have been tested for carcinogenicity in experimental animals, yielding positive results (IARC, 1999a). The bioassay for potassium bromate would suffice for characterizing the bromate anion.

Mechanistic Evidence

With respect to the key characteristics of carcinogens, several studies are available on whether bromate is genotoxic and induces oxidative stress. Bromate is genotoxic in experimental systems in vivo and in rodent cells in vitro (IARC, 1999a), and a few more recent studies, including in human cells in vitro, are available (Richardson et al., 2007; Platel et al., 2009, 2010; Bausinger & Speit, 2014).

Recommendation: Medium priority

1,3-Butadiene (CAS No. 106-99-0)

1,3-Butadiene has been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1987, 1992, 1999b, 2008, 2012b) and since Volume 97 is classified as *carcinogenic to humans* (Group 1), on the basis of *sufficient evidence* both in experimental animals and in humans; 1,3-butadiene causes lymphohaematopoietic malignancies. Furthermore, there is strong evidence that 1,3-butadiene is genotoxic. This evaluation was confirmed in Volume 100F (IARC, 2012b).

Exposure Data

1,3-Butadiene is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Cancer in Humans

Early-life exposure to butadiene as an environmental air toxic was associated with childhood cancers in three studies published since 2009; one study each reported an association with childhood acute myeloid leukaemia, childhood acute lymphoblastic leukaemia, and childhood brain cancer (Heck et al., 2014; Symanski et al., 2016; von Ehrenstein et al., 2016). There is no emerging consistent pattern of environmental exposure to 1,3-butadiene and childhood cancer.

Overall, the new epidemiological evidence appears to remain insufficient for the classification of additional cancer sites to either the *sufficient* or *limited* evidence category (Heck et al., 2014; Symanski et al., 2016; von Ehrenstein et al., 2016).

Recommendation: No evaluation

2,3-Butanedione (CAS No. 431-03-8)

2,3-Butanedione has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

2,3-Butanedione (also known as diacetyl) is commonly used in the production of artificial flavour formulations. Examples of flavoured food products 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 United States Food and Drug Administration 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 is primarily by inhalation of vapours (NTP, 2018c).

Cancer in Humans

Occupational exposure to 2,3-butanedione has been associated with the occurrence of bronchiolitis obliterans. No data are available pertaining to the carcinogenicity of 2,3-butanedione in humans (NTP, 2018c)

Cancer in Experimental Animals

Female A/He mice treated by intraperitoneal injection with 2,3-butanedione weekly for 24 weeks had a dose-dependent increase in the incidence and multiplicity of lung tumours. This response was not observed in a repetition of the experiment or in male A/He mice treated in a similar manner (Stoner et al., 1973). Male Wistar Han rats exposed to 2,3-butanedione by inhalation for 2 years had a low, although statistically significant, increase in the incidence of squamous cell papilloma or carcinoma of the nose. Female Wistar Han rats had a low (non-significant) incidence of squamous cell carcinoma of the nose. Female B6C3F$_1$/N mice exposed in a similar manner had a low (non-significant) incidence of adenocarcinoma of the nose (NTP, 2018c).

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). In B6C3F$_1$/N mice and Sprague-Dawley rats treated with 2,3-butanedione, approximately 0.1% of the dose in mice and 0.3% of the dose in rats bound to albumin and haemoglobin. Mass spectral analyses indicated that the binding was through arginine (Fennell et al., 2015).

There is evidence that 2,3-butanedione is genotoxic. 2,3-Butanedione is mutagenic in *Salmonella 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, 2018c).

Recommendation: Medium priority

4-*tert*-Butylcatechol (CAS No. 98-29-3)

4-*tert*-Butylcatechol has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

4-*tert*-Butylcatechol is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

4-*tert*-Butylcatechol is used as an antioxidant, stabilizer, and polymerization inhibitor for styrene, butadiene, neoprene, and other olefins and reactive monomers. In addition, 4-*tert*-butylcatechol is used as an activator for insecticides, a clay strengthener in building materials, a corrosion and radical inhibitor, an anti-skinning additive, an emulsion breaker, a pour-point depressant, a chemical intermediate for organic syntheses, and a component of shoe adhesives.

Cancer in Humans

No epidemiological studies or case reports associating 4-*tert*-butylcatechol exposure with cancer risk in humans were identified in the literature.

Cancer in Experimental Animals

A 1-year tumour promotion study indicated that 4-*tert*-butylcatechol may be weakly carcinogenic (Hirose et al., 1988). New animal feeding carcinogenicity studies were reported in 2013. The incidence of forestomach tumour (squamous cell papilloma) was increased in male and female rats fed 4-*tert*-butylcatechol. The incidence of forestomach tumour (squamous cell papilloma) was increased in male mice. In female mice, there were no exposure-related neoplastic lesions (JBRC, 2013).

Mechanistic Evidence

No metabolism studies of 4-*tert*-butylcatechol were reported. As well as being a skin and eye irritant, 4-*tert*-butylcatechol is moderately toxic when ingested or absorbed dermally. Systemic toxic effects similar to those induced by phenols might be expected to occur, as with the parent compound catechol. No studies or reports of reproductive or developmental toxicity of 4-*tert*-butylcatechol in animals or humans were identified. Negative results were reported for 4-*tert*-butylcatechol in a battery of short-term mutagenicity tests, including bacterial gene mutation assays with *Salmonella typhimurium* strains and *Escherichia coli*, a test for mitotic gene conversion in *Saccharomyces*, and an assay for induced chromosomal aberrations in

metabolically competent cultured rat liver cells. In contrast, increases in mutant frequencies were observed in L5178Y mouse lymphoma cells (NTP, 2002c).

Recommendation: No evaluation

Butyl methacrylate (CAS No. 97-88-1)

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

Exposure Data

Butyl methacrylate is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Butyl methacrylate is used by industry to make polymers. Polymers based on butyl methacrylate are used in the manufacture of automotive coatings, lacquers and enamels, adhesives, oil additives (lubricants), dental products, and emulsions for textile, leather, and paper refinishing.

Cancer in Humans

No epidemiology data of carcinogenicity are available (OECD, 2004a).

Cancer in Experimental Animals

Inhalation carcinogenicity studies in experimental animals were reported in 2019 (JBRC, 2019). The incidence of splenic mononuclear cell leukaemia in male rats was statistically increased, by the Peto trend test. The incidence of hepatocellular adenoma in male mice was significantly increased, by the Peto trend test. The incidence of histiocytic sarcoma in all organs in male mice was also significantly increased, by the Peto trend test. The incidence of pituitary adenoma in the anterior lobe in female mice was significantly increased, by the Peto trend test. The incidence of haemangiosarcoma in all organs in female mice was also increased, by the Peto trend test, but the incidence of haemangioma was not increased (JBRC, 2019).

Mechanistic Evidence

Sparse data relevant to key characteristics of carcinogens are available.

Recommendation: Low priority

C.I. Direct Blue 218 (CAS No. 28407-37-6)

C.I. Direct Blue 218 has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

C.I. Direct Blue 218 is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

C.I. Direct Blue 218 is a copper-chelated dye used for cellulose, acetate, nylon, silk, wool, tissue, papers, and textile goods with a urea–formaldehyde finish (NTP, 1994b).

Cancer in Humans

No epidemiological evidence is available on the carcinogenic effects of C.I. Direct Blue 218.

Cancer in Experimental Animals

Carcinogenicity of C.I. Direct Blue 218 has been observed in animals, by the oral route (feed). In one oral study in Fischer rats (NTP, 1994b), C.I. Direct Blue 218 increased the occurrence of pharyngeal neoplasms in male F344/N rats. Squamous cell neoplasms of the forestomach may have been chemical-related. In one oral study in B6C3F_1 mice (NTP, 1994b), C.I. Direct Blue 218 increased the incidence of hepatocellular adenoma and carcinoma in male and female mice. The occurrence of a few neoplasms of the kidney and the small intestine in male mice may have been related to treatment with C.I. Direct Blue 218.

Mechanistic Evidence

C.I. Direct Blue 218 was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 tested with and without exogenous metabolic activation (S9). It was also tested in a modified *Salmonella* test protocol that used reductive metabolism supplied by flavin mononucleotide or rat caecal bacteria, followed by oxidative metabolism; results of this test using strain TA1538 were also negative. C.I. Direct Blue 218 induced a small but significant increase in sister chromatid exchanges in Chinese hamster ovary cells at the highest dose tested without S9. No increase in chromosomal aberrations was observed in Chinese hamster ovary cells with or without S9. C.I. Direct Blue 218 did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* (NTP, 1994b).

Recommendation: Medium priority

Cadmium (CAS No. 7440-43-9) and cadmium compounds

Cadmium and cadmium compounds have been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1987, 1993b, 2012d) and since Volume 58 are classified as *carcinogenic to humans* (Group 1), on the basis of *sufficient evidence* both in experimental animals and in humans. The current evaluation (IARC, 2012d) specifies that cadmium and cadmium compounds cause cancer of the lung.

Exposure Data

Cadmium is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Cancer in Humans

Positive associations have been observed between exposure to cadmium and cadmium compounds and cancers of the kidney and of the prostate. A small number of epidemiological studies investigating associations between cadmium and breast cancer were identified, but the results have been inconsistent.

Overall, the new epidemiological evidence appears to remain insufficient for the classification of additional cancer sites to either the *sufficient* or *limited* evidence category.

Key References

The following key references were also identified: Larsson et al. (2015); Van Maele-Fabry et al. (2016).

Recommendation: No evaluation

Cannabis smoking

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

Exposure Data

The plant *Cannabis sativa* is the source of the world's most widely used recreational drug, which can also be used for medicinal purposes. It is used in three forms: the dried leaves and flowering tops, a resin made from the pressed secretions of the plant, and an oil created through distillation or extraction. All of these forms can either be smoked or consumed as part of an edible product.

Cancer in Humans

When this agent was considered by the 2014 Priorities Advisory Group, four case–control studies and two cohort studies were evaluated. In 2015, a review and meta-analysis was published that considered four cohort studies and 30 case–control studies. The upper aerodigestive tract studies had mixed results. Most lung cancer studies were negative, and challenges related to potential confounding by tobacco were noted. A prospective cohort study of servicemen in Sweden and three case–control studies in the USA have all reported increased risks of testicular cancer. The study in Sweden found a relative risk of 2.57 (95% confidence interval, 1.02–6.50) among "heavy" cannabis users (Callaghan et al., 2017). A pooled re-analysis of the three case–control studies found an association specifically with non-seminoma testicular cancer.

Cancer in Experimental Animals

There were no studies identified of cancer in experimental animals for cannabis. However, many studies have examined the risk of cancer associated with similar combustion products, such as tobacco, biomass, coal, diesel, gasoline, and cooking oil, which may be relevant.

Mechanistic Evidence

There are more than 30 carcinogens in common to tobacco smoke and marijuana smoke. Numerous studies relevant to the key characteristics of carcinogens are available. In vitro studies of marijuana smoke condensates have found them to have similar effects to tobacco smoke in terms of mutagenicity and cytotoxicity, but to be significantly more potent. There is cross-talk between the endocannabinoid system and the hypothalamic–pituitary–gonadal system, and data are available for evaluating the key characteristic "modulates receptor-mediated effects".

Key References

The following key references were also identified: Gurney et al. (2015); Huang et al. (2015).

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

Carbamates

Several carbamates have been evaluated by the *IARC Monographs* programme, and most are categorized as *not classifiable as to their carcinogenicity to humans* (Group 3) (IARC, 1987), on the basis of less than sufficient evidence of carcinogenicity in experimental animals and no data in humans. Dimethylcarbamoyl chloride, an intermediate in the manufacture of several pharmaceuticals and carbamate pesticides, is classified as *probably carcinogenic to humans* (Group 2A) (IARC, 1987, 1999b), on the basis of *inadequate evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals and taking into account that it is a direct-acting alkylating agent with a wide spectrum of genotoxic activity, including activity in somatic cells in vivo.

Exposure Data

Carbamate pesticides are derived from carbamic acid (IPCS, 1986). They are widely used in agriculture as insecticides, fungicides, herbicides, nematocides, or sprout inhibitors and may also be used as biocides for industrial or household applications (IPCS, 1986; Fishel, 2017). Similar to organophosphates, these chemicals inhibit cholinesterase enzymes, affecting the transmission of nerve impulses (Fishel, 2017). The first carbamate, carbaryl, was released for use in 1956 (Fishel, 2017); since then, more than 50 other carbamates have been synthesized and sold (IPCS, 1986).

Cancer in Humans

Recent epidemiological studies reported an association between exposure to carbamate pesticides and brain cancer (Piel et al., 2018). Estimated lifetime exposure to each of 19 registered carbamate insecticides and the incidence of tumours of the central nervous system, overall and by histological subtype, was analysed. Increased risks of tumours of the central nervous system were reported with overall exposure to carbamate insecticides, as well as linear trends with duration of use of each carbamate. Hazard ratios for gliomas ranged from 1.2 for thiofanox to 4.6 for formetanate, and those for meningiomas tanged from 1.5 for carbaryl to 3.7 for thiofanox. Another analysis of the same cohort assessed exposure to each of 14 registered carbamate and thiocarbamate herbicides and 16 registered carbamate and dithiocarbamate fungicides and associations with the incidence of tumours of the central nervous system. Positive associations were reported for specific carbamates, including some fungicides (mancozeb, maneb, and metiram) and herbicides (chlorpropham, propham, and diallate).

Cancer in Experimental Animals

Animal cancer bioassays are available for various carbamates (e.g. mancozeb and carbaryl).

Mechanistic Evidence

Mechanistic data relevant to key characteristics of carcinogens are available (e.g. Xia et al., 2005; Srivastava et al., 2012; Luzy et al., 2013; Li et al., 2014a). Because the mechanisms of potential carcinogenesis may differ from those of carcinogenic action, grouping by class may have limitations.

Although there is evidence of carcinogenicity for individual pesticides within the class of carbamates, the Advisory Group recommended that specific carbamates, rather than the whole class, be considered for evaluation, as described elsewhere in this report.

Recommendation: No evaluation

Carbaryl (carbamate insecticide) (CAS No. 63-25-2)

Carbaryl (1-naphthyl methylcarbamate) was evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1987), because of the unavailability of information on the carcinogenic effects of carbaryl in humans and *inadequate evidence* of carcinogenicity in experimental animals. The 2014 Priorities Advisory Group assigned carbaryl a high priority (IARC, 2014).

Exposure Data

Carbaryl is a contact broad-spectrum insecticide that is also used as an acaricide and a molluscicide in crops, such as rice, cotton, berries, and fruit trees. It has also been used in nurseries, landscaping, garden care, flea treatments for pets, and mosquito control. In some countries, carbaryl is still used for the treatment of lice on humans.

In 2004, the United States Environmental Protection Agency classified carbaryl as "likely to be carcinogenic to humans".

Cancer in Humans

Several case–control studies of non-Hodgkin lymphoma among farmers in the USA reported a relationship with carbaryl handling. Other case–control studies of non-Hodgkin lymphoma observed odds ratios that were elevated but not significant, or odds ratios that were close to the null. A case–control study of prostate cancer in farmers reported a significant association with exposure to carbaryl. The United States National Cancer Institute Agricultural Health Study reported a small increase in risk of non-Hodgkin lymphoma with exposure to carbaryl, although none of the findings were statistically significant; risk of melanoma was elevated compared with subjects who never used carbaryl. Associations have also been observed with multiple myeloma. No associations were observed with other examined cancer types. The prospective Agriculture and Cancer (AGRICAN) cohort in France reported an association with gliomas and haemangiomas.

Cancer in Experimental Animals

In a good laboratory practice (GLP) study reviewed by the United States Environmental Protection Agency (EPA, 1993) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 1996), carbaryl caused an increase 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. In another GLP study reviewed by JMPR (JMPR, 1996), carbaryl caused an increase in the incidence of bladder papilloma and carcinoma in male rats and female rats (at doses probably greater than the maximum tolerated dose).

Mechanistic Evidence

Since the previous IARC evaluation in (IARC, 1987), new mechanistic data on carbaryl carcinogenesis have been produced. Although carbaryl seems negative in the Ames test, evidence from in vitro studies indicates that carbaryl may have genotoxic effects. Carbaryl induced sister chromatid exchanges, 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 was positive in assays for cell-cycle and DNA binding and estrogen agonism.

Key References

The following key references were also identified: Quarles & Tennant (1975); Hoar et al. (1986); Shukla et al. (1992); Hoppin et al. (2002, 2007); Alavanja et al. (2003, 2005); De Roos et al. (2003); Xia et al. (2005); Mahajan et al. (2007); Andreotti et al. (2009); Band et al. (2011); Kachuri et al. (2013); Presutti et al. (2016); Ferrucio et al. (2017); Piel et al. (2018).

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

Carbon black

Carbon black was classified by IARC as *possibly carcinogenic to humans* (Group 2B) (IARC, 2010e), on the basis of *inadequate evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals.

Exposure Data

Carbon black is a generic term for a particulate form of elemental carbon that is used in rubber and plastic products. Most of the consumption of carbon black is in the manufacture of tires (Carbon Black Sales, 2016). Carbon black is listed by the Organisation for Economic Co-operation and Development (for year 2007) as a High Production Volume chemical. Since 1970, personal geometric mean exposures to inhalable dust have been decreasing in the USA and western Europe (IARC, 2010e). However, no data were available to quantify the exposure levels of carbon black.

Cancer in Humans

There have been five cohort studies (Morfeld & McCunney, 2007, 2009, 2010; Sorahan & Harrington, 2007; Dell et al., 2015) and one case–control study (Ramanakumar et al., 2008) since IARC classified carbon black as *possibly carcinogenic to humans* (Group 2B) in *Monographs* Volume 93 (IARC, 2010e). Results from one positive and informative study (Sorahan & Harrington, 2007), which showed that recent exposures to carbon black are more likely to explain excess lung cancer mortality, were not supported by less-informative studies conducted in Germany (Morfeld & McCunney, 2007, 2009, 2010) or the USA (Dell et al., 2015). Two case–control studies for risk of lung cancer in relation to carbon black exposure, which adjusted for several potential confounders, including smoking in Montreal, Canada, showed no excess risk of lung cancer (Ramanakumar et al., 2008).

Cancer in Experimental Animals

In the previous evaluation (IARC, 2010e), there was *sufficient evidence* in experimental animals for the carcinogenicity of carbon black.

Among two studies in rodents, one study that treated rats by instillation of ultrafine carbon black caused benign and malignant lung tumours (Kolling et al., 2011), and one study in rasH2 mice caused spleen haemangioma and lung adenoma after ultrafine carbon black was administered by subcutaneous injection (Takanashi et al., 2012).

Mechanistic Evidence

Several studies in mice given ultrafine carbon black by intranasal instillation have shown that this agent may influence the brain immune function and increase the risk of dysfunction and disorder in their offspring

(Tin Tin Win et al., 2006; Onoda et al., 2014). Inhalation exposure to carbon black nanoparticles in pregnant mice induced DNA damage in the liver of the mothers and their offspring (Jackson et al., 2012). The biological effects of carbon black are dependent on the particle size (Tin Tin Win et al., 2006; Yamamoto et al., 2006). As observed in previous studies in experimental animals, ultrafine carbon black could cause oxidative stress in human lung epithelial cells.

Key References

The following key references were also identified: Shwe et al. (2005); Valberg et al. (2006); Chang et al. (2007); Chuang et al. (2013); Kyjovska et al. (2015); Senthong & Boriboon (2017).

Recommendation: Low priority

Carbon disulfide (CAS No. 75-15-0)

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

Exposure Data

Carbon disulfide is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Carbon disulfide is used in large quantities as an industrial chemical for the production of viscose rayon fibres (WHO, 2000a) and cellophane film (Newhook et al., 2002). Not only workers but also residents living near the viscose industry, natural gas processing plants, and sites with sulfur-containing natural gas flares (Newhook et al., 2002) are likely to be exposed to carbon disulfide (WHO, 2000a). Because of its ubiquitous characteristics, routes of human exposure include air, drinking-water, food, and dermal absorption (WHO, 2000a). Workplace concentrations of carbon disulfide and biological concentrations of the metabolite 2-thio-1,3-thiazolidine-4-carboxylic acid in urine have decreased during recent decades (WHO, 2000a; Chung et al., 2017).

Cancer in Humans

Few studies of cancer in humans are available for carbon disulfide. Early mortality studies provided no evidence of increased cancer risk in exposed populations (Nurminen & Hernberg, 1984; Pepłlońska et al., 2001). In a United States National Institute for Occupational Safety and Health cohort study of chemical manufacturing workers, two thirds were exposed to carbon disulfide (and had other co-exposures, including vinyl chloride, *ortho*-toluidine, and shift work); excesses of non-Hodgkin lymphoma were observed but were not associated with duration of employment (Carreón et al., 2014a). Landgren et al. (2009) found a 4-fold increase in risk of monoclonal gammopathy of undetermined significance (MGUS), a precursor of multiple myeloma, associated with exposure to the fumigant mixture carbon tetrachloride/carbon disulfide. The Advisory Group considered that these studies could not rule out confounding by co-exposures.

Cancer in Experimental Animals

Carbon disulfide caused a significant increase in the incidence of pulmonary adenoma in strain A/J mice (Adkins et al., 1986).

Mechanistic Evidence

A case–control study conducted in China showed that long-term exposure to low concentrations of carbon disulfide was associated with damage to human buccal cell DNA (Chen & Tan, 2004). In addition, a cross-sectional study in workers in Taiwan, China, indicated that exposure to carbon disulfide could result in oxidative stress and decrease the levels of antioxidant enzymes (Luo et al., 2011). Several studies of exposure to carbon disulfide in mice showed DNA damage (Hu et al., 2013) and oxidative stress resulting in embryo loss (Zhang et al., 2013a; Yang et al., 2014).

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

β-Carotene (CAS No. 7235-40-7)

β-Carotene has not been previously evaluated by the *IARC Monographs* programme.

Starting decades ago, a long series of studies identified high levels of consumption of fruits and vegetables with a lower subsequent risk of multiple types of malignancies and cancer overall. Among the many markers of vegetable consumption was β-carotene, which showed consistent evidence of protection with increased consumption. In the 1980s, this led to two randomized clinical trials of high-dose dietary supplementation with β-carotene in cigarette smokers in an attempt to lower their risk of cancer of the lung. Instead, in both studies this resulted in an excess of cases of and deaths from cancer of the lung and of overall mortality in the groups randomized to β-carotene. This led to a policy of advising against the use of β-carotene supplementation. In the two studies, the exposed groups returned to no increased risk within 2 years after stopping supplementation, perhaps indicating that the exposure acted as a promoter rather than an initiator.

Although the *Monographs* programme could formally review the existing data for β-carotene, there may not be public health urgency, because the data described above have already led to an intervention. What may be more useful in the foreseeable future is evaluating the current attempts to discover the underlying biology of the associations of high levels of consumption of fruits and vegetables with reduced risk of cancer. With the burgeoning of new technologies to pursue specific agents and their underlying pathways, future studies may be able to focus on potentially real causes rather than ethereal markers.

Key References

The following key references were also identified: Heinonen et al. (1998); Albanes (1999); Neuhouser et al. (2009); Virtamo et al. (2014); Middha et al. (2018).

Recommendation: No evaluation

Casiopeinas

Casiopeinas have not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Casiopeinas are a group of copper complexes that are being investigated for antineoplastic activity, primarily in vitro (Ruiz-Azuara & Bravo-Gómez, 2010). Because these drugs are currently in the phase I stage of clinical trials, some humans (typically 20–100) may be exposed. In addition, the laboratory technicians and synthetic chemists involved in development of the drugs may potentially be exposed (Ruiz-Azuara et al., 2014).

Cancer in Humans

No studies of cancer in exposed humans were identified.

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

Several studies relevant to key characteristics of carcinogens are available, most of which are from a single research group. These copper complexes exhibit cytostatic, cytotoxic, and genotoxic activity (M Vidal et al., 2017; Álvarez-Barrera et al., 2017; Rodríguez-Mercado et al., 2017; Espinal-Enríquez et al., 2016).

Recommendation: No evaluation

Catechol (CAS No. 120-80-9)

Catechol (1,2-dihydroxybenzene) has been classified since 1999 (IARC, 1999b) as *possibly carcinogenic to humans* (Group 2B), on the basis of *inadequate evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in animals.

Exposure Data

Catechol is a feedstock that 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, such as onions, beet sugar, coffee, and smoked fish, and is present in cigarette smoke.

Cancer in Humans

No epidemiological studies were identified.

Cancer in Experimental Animals

Since Volume 71 (IARC, 1999b), additional carcinogenesis studies have been conducted in rats, showing glandular stomach tumours (Hirose et al., 1999; Hagiwara et al., 2001); catechol co-administered with *N*-diethylnitrosamine induced forestomach and glandular tumours (Yafune et al., 2014), and forestomach initiation treatment followed by catechol caused forestomach tumours (Taniai et al., 2012; Kobayashi et al., 1999).

Mechanistic Evidence

Catechol induces oxidative DNA damage (Oikawa et al., 2001). Dietary catechol was observed to increase oxidative DNA damage in livers of mice treated with acetaminophen (Ishii et al., 2009). Catechol and sodium nitrite subacute co-exposure increased levels of 8-hydroxydeoxyguanosine in forestomach epithelium, followed by epithelial injury and hyperplasia (Ishii et al., 2006).

Catechol alters cell proliferation and cell death. In vivo apoptosis and cell proliferation are observed (Hirose et al., 1999; Taniai et al., 2012). Catechol was found to induce glioblastoma cell death, mainly by apoptosis (de Oliveira et al., 2010). In an exploration of cancer therapeutic effect, catechol suppressed anchorage-independent growth of murine KP2 and human H460 lung cancer cell lines, downregulated total c-Myc, and inhibited the growth of both allograft and xenograft lung cancer tumours in vivo (Lim et al., 2016).

Recommendation: Low priority

Chlordecone (organochlorine insecticide) (CAS No. 143-50-0)

Chlordecone was classified by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) (IARC, 1987), on the basis of *sufficient evidence* of carcinogenicity in experimental animals; there was *inadequate evidence* of carcinogenicity in humans.

Exposure Data

Chlordecone (also known as kepone) is an organochlorine insecticide that has been used as an insecticide on bananas, non-bearing citrus trees, tobacco plants, lawns, and flowers. It is a persistent organic

pollutant listed in Annex A of the Stockholm Convention (Stockholm Convention, 2004b) and has been banned worldwide since 2011. Although it is not used or produced anymore, chlordecone is highly persistent in the environment, has a high potential for bioaccumulation and biomagnification, and can be transported over long distances.

Cancer in Humans

Since 1987, some epidemiological studies have been published, specifically the results of studies in the French West Indies (Guadeloupe and Martinique), where chlordecone was intensively applied to banana fields from 1973 to 1993 and the population continues to be exposed to this chemical through consumption of contaminated foodstuffs. A population-based case–control study found a significant positive association between chlordecone concentration in blood and prostate cancer, the most commonly diagnosed cancer in men in Guadeloupe (Multigner et al., 2010). A reanalysis of these data confirmed the significant positive association (Emeville et al., 2015). However, in a study in Martinique, the highest incidence of prostate cancer was observed in urban zones, which had the lowest levels of soil contamination by chlordecone (Dieye et al., 2014).

Cancer in Experimental Animals

The *IARC Monographs* programme concluded in 1987 (IARC, 1979b, 1987) that there was *sufficient evidence* of carcinogenicity in experimental animals, on the basis of an increase in the incidence of tumours in mice and rats.

Mechanistic Evidence

Since the IARC evaluation, several in vitro studies have shown that chlordecone has estrogenic properties, with positive results for estrogen receptor (ER) binding and transactivation activities (Okubo et al., 2004; Lemaire et al., 2006; Li et al., 2006; Thomas & Dong, 2006; Benachour et al., 2007; Ray et al., 2007; Lee et al., 2008; Wu et al., 2008; Browne et al., 2015; EPA, 2019d). Chlordecone is classified by the Interagency Coordinating Committee on the Validation of Alternative Methods as an in vitro ER agonist reference chemical (ICCVAM, 2011). There are also results showing that chlordecone is an antagonist of the androgen receptor (Kleinstreuer et al., 2017). A study in middle-aged men in the French West Indies found no association between serum concentrations of various hormones and the level of exposure to chlordecone (Emeville et al., 2015). Some in vivo studies showed that chlordecone has pro-angiogenic effects through the involvement of ERα (Clere et al., 2012; Alabed Alibrahim et al., 2019) and that it accelerates the development of autoimmunity (Sobel et al., 2005, 2006; Wang et al., 2007, 2008b; Tabet et al., 2018).

Key References

The following key references were also identified: NTP (2011e); Multigner et al. (2016).

Recommendation: Low priority

Chlorinated paraffins (CAS No. 108171-27-3)

Short-chain chlorinated paraffins have not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Short-chain chlorinated paraffins are found worldwide in the environment, wildlife, and humans (EPA, 2009a). 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, 1990a). In particular, chlorinated paraffins C23 (43% chlorine) is an extreme-pressure lubricant and flame retardant (NTP, 1986a).

Cancer in Humans

One small registry-based case–control study showed a possible excess risk of cancer of the biliary tract with any exposure to chlorinated paraffins (odds ratio, 3.9; 95% confidence interval, 0.9–17) (Bardin et al., 2005). However, this study had few exposed cases, and the resulting confidence intervals are wide.

Cancer in Experimental Animals

Carcinogenicity of chlorinated paraffins has been observed in animals, by the oral route. In one oral study in Fischer rats (NTP, 1986a), pheochromocytomas of the adrenal gland medulla occurred with an increased incidence in female rats exposed to chlorinated paraffins (C23, 43% chlorine). In one oral study in $B6C3F_1$ mice (NTP, 1986a), the incidence of malignant lymphomas was increased in dosed male mice. Female mice that received a high dose showed a marginal increase in the incidence of hepatocellular carcinoma and in the incidence of adenoma or carcinoma (combined).

Mechanistic Evidence

Chlorinated paraffins (C23, 43% chlorine) were not mutagenic in various *Salmonella typhimurium* strains (TA97, TA98, TA100, or TA1535) in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 when assayed according to the pre-incubation protocol (NTP, 1986a). Few other data relevant to key characteristics of carcinogens are available. Structure–activity relationships may help to define whether and when to move forward to an evaluation.

Recommendation: Medium priority

Chlorpyrifos (organophosphate insecticide) (CAS No. 2921-88-2)

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

Exposure Data

Chlorpyrifos is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical. Chlorpyrifos is a broad-spectrum organophosphate insecticide and acaricide that is used in many countries (in homes and on farms).

Cancer in Humans

For chlorpyrifos, epidemiological data are available from the United States National Cancer Institute (NCI) Agricultural Health Study (AHS) (see Flower et al., 2004; Lee et al., 2005; Andreotti et al., 2009). For rectal cancer (Lee et al., 2004b, 2007) and lung cancer (Alavanja et al., 2004), the AHS findings were consistent for significantly increased risk of exposure to chlorpyrifos. Three AHS studies showed modestly increased risks of breast cancer associated with ever use of chlorpyrifos among premenopausal women (Engel et al., 2005, 2017; Lerro et al., 2015). There was a significantly increased risk of prostate cancer among users of chlorpyrifos with a family history of prostate cancer (Alavanja et al., 2003). For all lymphohaematopoietic cancers combined, leukaemia, and brain cancer, only applicators in the highest categories of intensity-weighted exposure days to chlorpyrifos had increased risk (for brain cancer, a significant non-monotonic exposure–response pattern was observed, based on small numbers of exposed cases) (Lee et al., 2004b). Chlorpyrifos was identified as a possible risk factor for non-Hodgkin lymphoma in a pooled analysis of three case–control studies (Waddell et al., 2001); this was not confirmed by AHS cohort results (Lee et al., 2004b).

Cancer in Experimental Animals

Chlorpyrifos was tested in long-term dietary studies in mice, rats, and dogs and showed limited evidence of carcinogenicity (lung adenoma in male CD-1 mice) (Warner et al., 1980; JMPR, 1982; Yano et al., 2000).

Mechanistic Evidence

There are several mechanistic studies on chlorpyrifos, but they are mainly related to developmental neurotoxicity. The available studies do not support a concern about mutagenicity; neither gene mutation nor clastogenic effects were seen for chlorpyrifos (EFSA, 2014a; EPA, 2015, 2019b). Literature studies using high doses showed mutagenic results (Sandhu et al., 2013), whereas lower exposures did not. However, there are several literature studies on DNA damage, showing in vitro and in vivo positive results in a comet assay (Rahman et al., 2002; Vindas et al., 2004; Ojha & Srivastava, 2014; Ezzi et al., 2016; Sultana Shaik et al., 2016), and one recent study showing chromosome loss and mis-segregation (Mužinić et al., 2019).

Chlorpyrifos has significant estrogen receptor and androgen receptor activity in high-throughput screens (Andersen et al., 2002; EPA, 2019b). In the steroidogenesis assay, at high test concentrations, chlorpyrifos increased estradiol levels and decreased testosterone levels. However, in vitro effects were not supported by higher-tiered mammalian data, such as the uterotrophic assay, the Hershberger assay, and the female and the male pubertal assays (EPA, 2015).

Key Reference

The following key reference was also identified: Svensson et al. (2013).

Recommendation: Medium priority

Cholesterol (CAS No. 57-88-5)

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

Exposure Data

Cholesterol is listed by the United States Environmental Protection Agency as a High Production Volume chemical.

Exposure to both dietary and endogenous cholesterol is universal. Endogenous cholesterol is essential to several physiological processes. In most people, dietary intakes of cholesterol have very little impact on endogenous cholesterol levels, as measured in blood. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) are the structures that carry cholesterol around the body. High levels of LDL have been linked with atherosclerosis and heart disease. Levels of HDL and LDL are influenced by dietary consumption of fats and carbohydrates.

In 2008, the global prevalence of raised total cholesterol (which combines LDL, HDL, and triglyceride measures) in adults (≥ 5.0 mmol/L) was 39% (37% for men and 40% for women) (WHO, 2019b). The prevalence of raised total cholesterol increased noticeably according to the income level of the country. In low-income countries, about one quarter of adults had raised total cholesterol, and in lower-middle-income countries this proportion was about one third of the population for both sexes (WHO, 2019b). In high-income countries, more than 50% of adults had raised total cholesterol, more than double the proportion in low-income countries (WHO, 2019b).

Statins are a class of drugs that act to reduce the level of LDLs in the blood. Statins are widely used for primary prevention of cardiovascular disease. Dietary cholesterol was reviewed by the *IARC Monographs* in Volume 31 (IARC, 1983b). Evidence of carcinogenicity in humans of cholesterol was considered inadequate, with some evidence that high cholesterol lowered the risk of cancer, no evidence of carcinogenicity in in vitro or in vivo assays, and an inadequate animal model. Similarly, in Supplement 7 (IARC, 1987) it was concluded that there were no data on genetic or related effects in humans, cells, or bacteria.

Cancer in Humans

Since 1987, new large observational cohorts have reported a protective effect of cholesterol for various cancer types in men and women; however, reverse causality cannot be ruled out. A Mendelian randomization analysis of people with genetically determined lower plasma cholesterol (APOE2 carriers) demonstrated that low cholesterol did not increase the risk of cancer. Some large cohort studies showed that statins decrease recurrence of and mortality from breast cancer in cases, an effect attributed to a decrease in LDL levels.

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

A substantial number of studies relevant to key characteristics of carcinogens are available. Mechanistic studies in vivo and in vitro demonstrated that LDL cholesterol upregulates the LDL receptor, causing adiponectin deficiency and thus inhibiting the tumour suppressor effect of this adipokine. In mice, the LDL receptor increased cell proliferation, and LDL caused oxidative stress, changed the expression of 87 genes in the MAP kinase pathway, and caused intestinal inflammation. In animals, cholesterol increased angiogenesis. Its metabolite 27-hydroxycholesterol is a ligand for the estrogen receptor and the liver X receptor, increasing growth and metastasis of breast cancers.

Key References

The following key references were also identified: Järvinen et al. (2001); Whitlock et al. (2001); Clarke et al. (2002); Bahl et al. (2005); Wiréhn et al. (2005); Montero et al. (2008); Trompet et al. (2009); Llaverias et al. (2011); Shafique et al. (2012); Alikhani et al. (2013); Cruz et al. (2013); Liu et al. (2013b); Nelson et al. (2013); Strohmaier et al. (2013); Taylor et al. (2013); dos Santos et al. (2014); National Clinical Guideline Centre UK (2014); Pelton et al. (2014); dos Santos et al. (2014); Chen et al. (2015b); Murai (2015); Kuzu et al. (2016); Mansourian et al. (2016); Gallagher et al. (2017); Wang et al. (2017c).

Recommendation: No evaluation

Cinidon ethyl (CAS No. 142891-20-1)

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

Exposure Data

Cinidon ethyl is a dicarboximide herbicide with applications on cereal crops (e.g. wheat and rye). It is “suspected of causing cancer” by the European Chemicals Agency (ECHA, 2018a) and is classified as “Carc. 2” by the European Commission (EC, 2016a).

Cancer in Humans

No studies of cancer in humans were identified for cinidon ethyl.

Cancer in Experimental Animals

In a 2-year dietary study in rats, cinidon ethyl induced tumours of the liver and parathyroid gland (EC, 2002).

Mechanistic Evidence

In mechanistic studies, cinidon ethyl showed no initiating potential for placental glutathione *S*-transferase positive foci in the liver. It induced a reversible selective increase in cell proliferation, mainly in perivenous areas, in the liver of rats. Other data relevant to key characteristics of carcinogens are sparse.

Recommendation: Low priority

Coal dust

Coal dust was evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1997a), on the basis of *inadequate evidence* of carcinogenicity both in humans and in experimental animals, although there was some evidence of increased risk of cancers of the lung and stomach among coal miners. The 2014 Priorities Advisory Group assigned coal dust a medium priority but suggested that the evidence on lung carcinogenicity had increased after extended follow-up of coal miners in multiple countries (IARC, 2014).

Exposure Data

Coal is the second largest energy source worldwide, and global consumption appears to be increasing. Coal dust is a heterogeneous by-product of coal mining comprising a mixture of more than 50 different elements and their oxides. Exposure to coal dust occurs predominantly in coal mining and to a lesser degree via other industrial processes and environmental air pollution.

Cancer in Humans

Since 2014, a dose–response relationship between exposure to coal dust and lung cancer mortality was reported in a recent study of coal miners in the USA (Graber et al., 2014). A case–control study using 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) and when restricted to workers with coal-workers' pneumoconiosis (Tomášková et al., 2017).

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

Evidence on mechanisms has increased since the previous IARC evaluation. Recent experimental data suggest that the induction of oxidative stress and inflammation are important mechanisms (León-Mejía et al., 2016; Matzenbacher et al., 2017; Espitia-Pérez et al., 2018). Exposure-related genotoxicity in oral mucosa cells in coal miners has been observed (da Silva Júnior et al., 2018). In other studies of exposed workers, exposure-related genotoxic, epigenetic, and cytostatic effects, including increased frequency of binucleated lymphocytes with micronuclei, nucleoplasmic bridges, and protrusions, as well as decreased telomere length and DNA hypermethylation, have been reported (Rohr et al., 2013; Sinitsky et al., 2016; de Souza et al., 2018). Recent studies in experimental animals have also reported inflammation, DNA damage, bronchoalveolar reactive hyperplasia, and epigenetic effects related to exposure to coal dust (Kania et al., 2014; León-Mejía et al., 2018).

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

Cobalt and cobalt compounds (CAS No. 7440-48-4)

The most recent *IARC Monographs* evaluation of the carcinogenicity of cobalt and cobalt compounds was in 2006 (IARC, 2006a). Cobalt metal without tungsten carbide, as well as cobalt sulfate and other soluble cobalt(II) salts were classified as *possibly carcinogenic to humans* (Group 2B). Metallic cobalt in combination with tungsten carbide was classified as *probably carcinogenic to humans* (Group 2A). These evaluations were based on *limited evidence* in humans for the carcinogenicity of cobalt metal with tungsten carbide, from data on lung cancer in hard-metal workers, and *sufficient* evidence in experimental animals for the carcinogenicity of cobalt sulphate and of cobalt-metal powder. There was *inadequate evidence* in humans for the carcinogenicity of cobalt metal without tungsten carbide.

Exposure Data

Cobalt is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Cobalt is a naturally occurring element that is used to make metal alloys and other metal compounds used for a variety of application, such as military, industrial, or medical equipment and rechargeable batteries. The highest exposure occurs in the workplace, from industries that refine cobalt from ores and produce cobalt, alloys, hard metals, drying agents, pigments, and catalysts, and during diamond polishing. Exposure also occurs in workers who use cobalt-containing products and recycle cobalt-containing electronics. People are potentially exposed to cobalt from failed surgical implants. The public may also be exposed to low levels of cobalt through food, contaminated drinking-water, and living near industrial sites.

Cancer in Humans

No new studies suggest that occupational exposure to cobalt (with or without tungsten carbide) is associated with an increased overall cancer risk or lung cancer risk among cobalt workers.

Cancer in Experimental Animals

In the previous evaluation (IARC, 2006a), there was *sufficient* evidence in experimental animals for the carcinogenicity of cobalt sulphate and of cobalt-metal powder. Both rats and mice exposed to cobalt metal or cobalt compounds developed tumours at various tissue sites (lung, adrenal gland, pancreas, and immune system) and through different routes of exposure, including inhalation.

Mechanistic Evidence

The release of cobalt ions into the body can lead to cell death and DNA damage. Mechanistic data provide strong support that inhibition of DNA repair, oxidative stress, and activation of hypoxia-inducible factors are likely to contribute to cobalt-induced neoplastic development and progression. All of these mechanisms are relevant to humans.

Key References

The following key references were also identified: Annangi et al. (2015); NTP (2016j); Marsh et al. (2017); Sauni et al. (2017).

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

Combustion of biomass

Indoor emissions from household combustion of biomass fuel (primarily wood) have been classified as *probably carcinogenic to humans* (Group 2A) (IARC, 2010c), on the basis of *sufficient evidence* in experimental animals for the carcinogenicity of wood-smoke extracts and *limited evidence* of carcinogenicity in humans supported by a positive association with cancer of the lung. The Working Group also noted mechanistic and other data including (i) the presence of polycyclic aromatic hydrocarbons and other carcinogenic compounds in wood smoke, (ii) evidence of mutagenicity of wood smoke, and (iii) multiple studies that showed cytogenetic damage in humans who are exposed to wood smoke.

Exposure Data

Biomass fuels include wood, branches, twigs, dung, and coal (IARC, 2010c). 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. Women and young children who are at home for most of the day are considered to be the most highly exposed groups (IARC, 2010c).

Cancer in Humans

Since the previous IARC evaluation, a meta-analysis including 14 case–control studies of biomass cooking or heating reported odds ratios for lung cancer risk of 1.17 with biomass for cooking and/or heating overall and of 1.15 with biomass for cooking only (Bruce et al., 2015). Sensitivity analyses restricted to studies with adequate adjustments for potential confounders and a clean-fuel reference category resulted in odds ratios of 1.21 (95% confidence interval [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. Results of analyses of associations of oesophageal cancer risk in the Golestan Cohort Study are forthcoming.

Cancer in Experimental Animals

No new cancer bioassays are available.

Mechanistic Evidence

Numerous recent studies relevant to key characteristics of carcinogens are available, for example characterizing the mutagenicity of components (e.g. Mutlu et al., 2016) or assessing effects in experimental animal models or in exposed humans (e.g. Lu et al., 2017b; Weinstein et al., 2017).

Key References

The following key reference was also identified: Smith et al. (2014).

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

Computed tomography scans

X- and gamma-radiation has been evaluated repeatedly by the *IARC Monographs* programme (IARC, 2000b, 2012f) and is classified as *carcinogenic to humans* (Group 1), on the basis of *sufficient evidence* both in experimental animals and in humans; X- and gamma-radiation causes cancer of the salivary gland, oesophagus, stomach, colon, lung, bone, skin (basal cell carcinoma), female breast, urinary bladder, kidney, brain and central nervous system, and thyroid, and leukaemia (excluding chronic lymphoblastic leukaemia), as well as for multiple sites after in utero exposure. Also, positive associations have been observed for several other sites (IARC, 2012f).

Exposure Data

Human exposure to X-radiation through computed tomography (CT) scans is markedly increasing, particularly in high-income countries. Doses are typically up to approximately 60 mSv per scan for children, and up to approximately 150 mSv per scan for adults.

Cancer in Humans

Several recent (2012–2019) epidemiological studies of patients exposed as children indicated an increase in the risk of cancer of the brain and of leukaemia. Multiple modelling studies have quantified the number of cases of cancer caused by exposure in various clinical contexts.

Because CT scans represent a specific exposure condition for an agent already classified as *carcinogenic to humans* (Group 1), no new evaluation for certain cancer sites is anticipated. The Advisory Group considered that a re-evaluation with a focus on quantitative risk characterization is outside the scope of the *IARC Monographs* programme.

Key References

The following key references were also identified: Journy et al. (2015); Berrington de Gonzalez et al. (2016); Meulepas et al. (2016, 2019).

Recommendation: No evaluation

Crotonaldehyde (2-butenal) (CAS No. 4170-30-3)

Currently, crotonaldehyde (also known as 2-butenal) is categorized by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1995).

Exposure Data

Crotonaldehyde is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Crotonaldehyde, a very reactive electrophilic α,β-unsaturated aldehyde (WHO, 2008), is an acutely toxic chemical intermediate that is used mainly in the manufacture of sorbates, solvents, pharmaceutical products, and aroma chemicals (WHO, 2008). Emissions of crotonaldehyde into the atmosphere are from combustion of vehicle fuels, wood combustion, tobacco smoking, and thermal treatment of foodstuffs (WHO, 2008).

In the National Health and Nutrition Examination Study (NHANES) in the USA, smokers were found to have statistically significantly higher adjusted levels than nonsmokers for a urinary metabolite of crotonaldehyde (*N*-acetyl-*S*-(3-hydroxypropyl-1-methyl)-L-cysteine [HPMMA]) (Jain, 2015a). In addition, female smokers had higher adjusted level of HPMMA than male smokers (Jain, 2015a). Compared with nonsmoking, non-alcohol-drinking women randomly selected from the Singapore Chinese Health Study as

controls, increased exposure to crotonaldehyde and other volatile organic compounds was reported in nonsmoking Chinese women who regularly cook with Chinese-style wok cooking (Hecht et al., 2010). This finding was supported by a study of nonsmoking Chinese women in Singapore who regularly cook at home (Hecht et al., 2015). In NHANES 2011–2012, children had statistically significantly higher levels of HPMMA than nonsmoking adults (Jain, 2015b).

Cancer in Humans

In a nested case–control study in the Shanghai Cohort Study, none of the metabolites of the volatile organic compounds including crotonaldehyde were associated with overall lung cancer (Yuan et al., 2014).

Cancer in Experimental Animals

After long-term oral administration to male rats, a significant increase in the incidence of liver nodules (adenomas) was reported, although it was not dose-related (IARC, 1995; WHO, 2008). In another study in male and female rats, rare nasal cavity adenomas were induced in males (JBRC, 2001).

Mechanistic Evidence

Crotonaldehyde has given positive results in a range of in vitro tests for genotoxicity: gene mutation in bacteria, chromosomal aberrations in Chinese hamster ovary cells, and comet assay in mammalian cells (WHO, 2008). Exposure to crotonaldehyde can result in formation of DNA adducts, which lead to DNA damage in almost all tissues from rats and mice. DNA and protein adducts have been found endogenously and after exogenous administration of crotonaldehyde in almost all investigated tissues from rats and mice (WHO, 2008). In addition, crotonaldehyde induces mutagenicity in cells in mice (Demir et al., 2011) and inflammatory and oxidative injuries of renal tissues in rats (Zhang et al., 2018a).

DNA adducts have also been detected in human oral tissue (WHO, 2008). Crotonaldehyde induces cell oxidative stress, caspase-dependent apoptosis, alteration of gene expression profile (Liu et al., 2010a, b), and autophagy-mediated cytotoxicity in human cells via various pathways (Wang et al., 2017b). Crotonaldehyde can also inhibit DNA repair and enhance hepatocyte mutational sensitivity, which leads to hepatocarcinogenesis in human hepatocytes (Weng et al., 2017).

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

Cumene (CAS No. 98-82-8)

Cumene (isopropylbenzene) has been classified by IARC as *possibly carcinogenic to humans* (Group 2B) (IARC, 2013c), on the basis of *sufficient evidence* of carcinogenicity in experimental animals.

Exposure Data

Cumene is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Cumene is a feedstock that is used in the manufacture of acetone, phenol, and other chemicals; it is also used as a solvent for fats and resins and as a thinner for paints. It occurs naturally in petroleum and is present in fossil fuels. It also has been measured in a variety of fruits and vegetables, wine, dairy products, cooked foods, and various non-food plants, as well as in cigarette smoke. It occurs in outdoor air in both urban and rural settings.

Cancer in Humans

No epidemiological studies of cancer were identified.

Cancer in Experimental Animals

In 2013, IARC based its determination of *sufficient evidence* of carcinogenicity in experimental animals on whole-body inhalation studies conducted by the United States National Toxicology Program (NTP) in male and female rats and mice. Observations included nasal cavity tumours in male and female rats, lung tumours in male and female rats, kidney tumours in male rats, haemangiosarcoma (spleen) in male mice, and liver tumours in female mice. No additional animal carcinogenesis studies of cumene were identified that were published after the 2013 IARC review.

IARC (2013c) also noted that after exposure to its likely metabolite α-methylstyrene, kidney tumours in male rats and liver tumours in female mice were seen; liver tumours were also seen in male mice after exposure to the metabolite.

Mechanistic Evidence

No significant new data on mechanisms published after the 2013 IARC review were identified. Cumene per se has not tested positive in yeast, with or without metabolic activation; however, some of its metabolites, such as α-methylstyrene, have. K-*ras* and *Tp53* mutations were far more frequent in mouse lung tumours in mice treated with cumene than in spontaneous lung tumours in mice. NTP (2016h) noted that the molecular alterations seen were similar to those in human lung cancers.

Recommendation: Low priority

Cupferron (CAS No. 135-20-6)

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

Exposure Data

Cupferron (*N*-nitroso-*N*-phenylhydroxylamine, ammonium salt) is used to separate and precipitate metals such as copper, iron, vanadium, and thorium. It is used to separate tin from zinc and to separate copper and iron from other metals. In analytical laboratories, cupferron is a reagent used for quantitative determination of vanadates and titanium and for the colorimetric determination of aluminium.

Cancer in Humans

No epidemiological studies were identified that evaluated the relationship between cancer in humans and exposure specifically to cupferron.

Cancer in Experimental Animals

Cupferron has been reviewed by the United States National Toxicology Program (NTP, 2016a). Oral exposure to cupferron caused tumours at several different tissue sites in mice and rats. Dietary administration of cupferron caused cancer of the blood vessels (haemangiosarcoma or haemangioma) in male and female rats and mice and cancer of the liver (hepatocellular carcinoma) in male and female rats and in female mice. It also caused cancer of the skin of the ear (carcinoma of the auditory sebaceous gland) in female rats and mice, cancer of the forestomach (squamous cell carcinoma) in male and female rats, and benign tumours of the Harderian gland (adenoma) in female mice (NTP, 1978a).

Mechanistic Evidence

No in vivo genotoxicity studies are available. In vitro, reverse mutation, chromosomal aberration, and sister chromatid exchange tests are positive. Cupferron was studied for the synthesis of novel nitric oxide (NO)-releasing agents. The alkylation occurred regioselectively at the terminal oxygen, leading to a single product, *N*-(alkyloxy)-*N'*-phenyldiimide *N'*-oxide, as indicated by nuclear magnetic resonance (NMR) and X-ray analysis. The *O*-alkyl derivatives exhibited significantly improved stability compared with their parent compound, cupferron. It was demonstrated that the cupferron *O*-alkyl derivatives could function as photoreleasing NO donor compounds.

N-(*N''*-acetylphenylalanylmethylenyloxy)-*N'*-phenyldiimide *N'*-oxide), which linked the cupferron portion with an amino acid via an acetal moiety, was synthesized as a model NO prodrug where controlled NO release would occur either by increasing pH or by a protease-catalysed hydrolysis (HSDB, 2012a).

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

Cyclopeptide cyanotoxins

Microcystin-LR has previously been classified by IARC as *possibly carcinogenic to humans* (Group 2B), on the basis of *strong* mechanistic evidence, and nodularin was evaluated as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 2010d).

Exposure Data

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, 2010d). Although climate warming is known to lead to increased eutrophication, new experimental data suggest that warmer water temperatures may significantly reduce production of microcystin from *Microcystis* strains (Bui et al., 2018). 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, 2010d).

Cancer in Humans

Several studies of hepatocellular carcinoma and one study of colorectal carcinoma reviewed in the previous *IARC Monograph* that evaluated microcystin-LR showed higher incidence in populations using surface water compared with well water, whereas details of microcystin concentrations, other contaminants, and potential confounders were not reported. Since 2010, several studies in China, Portugal, and Serbia have pointed to a strengthened association between exposure to microcystins and cancer (Drobac et al., 2011; Svirčev et al., 2013; Zheng et al., 2017). For example, in a case–control study in southwestern China in patients positive for microcystin-LR in their serum, the reported odds ratio for hepatocellular carcinoma was 2.9 (95% confidence interval [CI], 1.5–5.5), and infection with hepatitis B virus and excess alcohol consumption were found to positively interact (synergism indices, 3.0; 95% CI, 2.0–4.5 and 4.0; 95% CI, 1.7–9.5, respectively) (Zheng et al., 2017). Other studies, such as those conducted in the USA (Soward, 2011) and Canada (Labine et al., 2015), were inconclusive (Soward, 2011) or did not find an association (Labine et al., 2015). In addition, there is increasing evidence linking microcystins and primary liver cancer (Svirčev et al., 2017).

Cancer in Experimental Animals

Data from animal carcinogenicity studies are sparse. Studies in experimental animals and in vitro show that microcystins may damage organs at various sites (reviewed in Massey et al., 2018), notably even

inducing hepatocarcinogenesis (He et al., 2018b; Xu et al., 2018). New data (on microcystin-LR) include: (i) induction of MMP13 and migration/invasion, possibly through PI3K/AKT activation in the DLD-1 xenograft model (Miao et al., 2016); and (ii) increased proliferation, mobility, and clone and tumour formation via gankyrin activation in the rat model (He et al., 2018b).

Mechanistic Evidence

Once absorbed into the blood, microcystins are distributed to various organs, including the liver, intestine, brain, kidney, lung, heart and reproductive system.

Before 2010, it was known that microcystins: (i) inhibit cellular serine/threonine protein phosphatases, altering phosphorylation homeostasis and affecting cell structures and functions; (ii) act as tumour promoters (experimental data for the liver and the colon); and (iii) alter the expression of certain oncogenes, early response genes, and tumour necrosis factor α (TNF-α), thereby affecting cell division, survival, and apoptosis. Since then, many more experimental studies on microcystins (especially microcystin-LR) and associated cellular pathologies have been published, with results including: (i) oxidative stress through an increase in reactive oxygen species and/or depletion of glutathione (reviewed in Campos & Vasconcelos, 2010); (ii) cytoskeletal disruption (reviewed in Zhou et al., 2015b); (iii) immunotoxicity (reviewed in Lone et al., 2016); (iv) migration and/or invasion via various matrix metalloproteases in various colon and breast cancer lines (Zhang et al., 2013b; Miao et al., 2016; Ren et al., 2017; Zhu et al., 2018); (v) genotoxicity via nitric oxide synthesis in human–hamster hybrid cells (Wang et al., 2015b); (vi) promotion of epithelial–mesenchymal transition via SMAD2 expression in DLD-1 and HT-29 cells (Ren et al., 2017); (vii) increase in expression of oncogenes and decrease in expression of tumour suppressor genes in human primary liver cancer cells (Li et al., 2017); (viii) induction of the inflammatory response via NF-κB, COX-2, iNOS, TNF-α, IL-1B, and IL-6 in HepG2 cells (Ma et al., 2018); and (ix) increase in proliferation, mobility, and clone and tumour formation via gankyrin activation in the rat model (He et al., 2018b). This list is not exhaustive.

Key References

The following key references were also identified: Zhang et al. (2012); Bellém et al. (2013); Lin et al. (2016); Wang et al. (2016c); Liu et al. (2017b); Svirčev et al. (2014).

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

Depleted uranium (CAS No. 7440-61-1)

Implanted foreign bodies of depleted uranium were evaluated as *not classifiable as to their carcinogenicity to humans* (Group 3) (IARC, 1999c), on the basis of *inadequate evidence* in experimental animals for the carcinogenicity of implants of depleted uranium. In humans, the available studies were judged as inadequate to permit reliable and accurate estimates of long-term effects of depleted uranium.

Because of the low specific radioactivity of depleted uranium, the long-term toxicity was thought to be due to chemical effects rather than radiation effects.

Since then, studies on depleted uranium have been reviewed as part of the evaluation of X- and gamma-radiation (with respect to mechanistic evidence) and as part of the evaluation of alpha radiation (both in Volume 100D; IARC, 2012f). The evaluation of internalized radionuclides that emit alpha particles as *carcinogenic to humans* (Group 1) was based on *sufficient evidence* of carcinogenicity in experimental animals for $^{234, 235, 238}$U (natural, enriched, and depleted uranium), *limited evidence* of carcinogenicity in humans for mixtures of uranium isotopes, and other evidence.

Exposure Data

Depleted uranium was used extensively in various military conflicts, including in Bosnia and Herzegovina, Iraq, and Kosovo, in projectiles, armoured vehicles, and improvised explosive devices (IEDs). These uses caused exposure of military personnel of various countries via various routes, including inhalation or implantation of small fragments of depleted uranium shrapnel. It is estimated that more than 9 tons of depleted uranium was used by North Atlantic Treaty Organization (NATO) forces in Kosovo in 1999 alone. The military use of depleted uranium also resulted in post-war environmental exposure of the general population (Carvalho & Oliveira, 2010; Faa et al., 2018; Yue et al., 2018).

Cancer in Humans

Interpretation of the epidemiological studies remains challenging. Because depleted uranium represents a specific exposure condition for an agent already classified as *carcinogenic to humans* (Group 1), no new evaluation for certain cancer sites is anticipated.

Cancer in Experimental Animals

Three independent cancer bioassays using implanted military-grade depleted uranium pellets have shown malignant, potentially metastatic tumours formed near the implantation site and distant tumours in a leukaemia model. Tumours caused by depleted uranium occur in both rats and mice, and there is evidence for a dose–response relationship in two studies.

Mechanistic Evidence

There is some supportive mechanistic evidence, including of DNA hypomethylation and of in vitro malignant transformation.

The Advisory Group considered that quantitative risk characterization based on observational studies of cancer in exposed humans would also be challenging.

Key References

The following key references were also identified: Miller et al. (1998, 2001b, 2002a, b, 2005, 2009, 2017); Yang et al. (2002); Busby et al. (2010); Xie et al. (2010).

Recommendation: No evaluation

Dichloromethane (CAS No. 75-09-2)

Dichloromethane has been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1987, 1999b, 2017a) and is classified as *probably carcinogenic to humans* (Group 2A), on the basis of *sufficient evidence* of carcinogenicity in experimental animals and *limited evidence* of carcinogenicity in humans, supported by positive associations between exposure to dichloromethane and cancer of the biliary tract and non-Hodgkin lymphoma.

Exposure Data

Dichloromethane is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Dichloromethane has been used in the manufacture of polycarbonate plastics, hydrofluorocarbons, synthetic fibres, and photographic films; as an aerosol propellant; for paint stripping, metal cleaning, and printing-ink removal; and as an extraction solvent for some foods (IARC, 2017a). Global production of dichloromethane was estimated to range from 764 000 to 814 000 metric tonnes per year from 2005 to 2010 (OECD, 2011). Exposure of the general population may occur through air, water, or food, or during the use of consumer products that contain dichloromethane (ATSDR, 2000). Occupational exposure may occur during the production and processing of dichloromethane or during the use of products that contain dichloromethane, particularly when the end product is sprayed or otherwise aerosolized (IARC, 2017a).

Cancer in Humans

Since the most recent *IARC Monographs* evaluation, several new epidemiological studies have been published, including in Cyprus, Spain, and Italy. However, the only study on cancer of the biliary tract is in the same population of printers in Japan that was already reviewed in Volume 110 (IARC, 2017a) and does not provide additional support for an association with dichloromethane. All other studies are single studies on different cancer sites (head and neck, breast, brain, kidney) and childhood cancer, and would therefore not support a new evaluation for any of these cancer sites, although the large number of new studies was noted.

Cancer in Experimental Animals

In the previous evaluation (IARC, 2017a), there was *sufficient evidence* of carcinogenicity in experimental animals.

Mechanistic Evidence

New studies relevant to key characteristics of carcinogens are available, particularly on whether dichloromethane is genotoxic and induces oxidative stress, and there are a few such studies in exposed humans (e.g. Mimaki et al., 2016; Zeljezic et al., 2016).

Key References

The following key references were also identified: Sobue et al. (2015); Barul et al. (2017); Carton et al. (2017); Park et al. (2017); Purdue et al. (2017); García-Pérez et al. (2018); Makris & Voniatis (2018).

Recommendation: Low priority

Dietary iron overload (CAS No. 7439-89-6)

Iron–dextran complex was classified by IARC as *possibly carcinogenic to humans* (Group 2B), and iron–dextrin complex and iron sorbitol–citric acid complex as *not classifiable as to their carcinogenicity to humans* (Group 3) (IARC, 1987). Dietary iron and iron used as supplements or for medical purposes were listed as high priorities by the 2014 Priorities Advisory Group (IARC, 2014).

Exposure Data

Iron is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Iron is essential for life and is maintained in the body within strict physiological limits. It is an essential metal nutrient that is present in food, supplements, and water, among others.

Cancer in Humans

Vast amounts of data on a role for iron in cancer causation have accumulated that have not been addressed by an *IARC Monograph*. Examples of studies in humans include cancers linked to genetic or dietary iron overload disorders (hereditary haemochromatosis, thalassaemia, African overload syndrome). In these disorders, iron accumulates in tissues, including the liver, where an association with hepatocellular carcinoma is highly suspected, generally, but not exclusively, with cirrhosis. For example, a recent hereditary haemochromatosis cohort study showed that a higher age at diagnosis (longer exposure to high liver iron levels) strongly predicted development of hepatocellular carcinoma. Many further examples could be cited. Overall, such genetic disorders causing iron overload are suspected to have a prevalence of up to 0.5% of the world's population. In populations without genetic anomalies, increased iron intake may increase the risk of aggressive cancers of the prostate, and reducing body iron load decreases cancer risks. Increased or decreased body iron load can alter cancer rates accordingly, although this is not universally seen. Recent studies suggest that intake of iron may be associated with a higher risk of colorectal cancer. A

positive association has been found between haem iron from meat intake and oesophageal and gastric cancer.

Cancer in Experimental Animals

Genetically modified mice that could duplicate liver disease after iron overload have recently been developed (Preziosi et al., 2017). Pre-treating or treating concurrently with iron can increase tumour formation induced by other agents at numerous sites, such as the liver, skin, and kidney, in rodents (Smith et al., 1993; Asare et al., 2006).

Mechanistic Evidence

Mechanistic studies and supportive rodent models point towards oxidative stress caused by iron as a primary mechanism.

The Advisory Group concluded that, although there is some new evidence of colorectal and hepatocellular carcinoma, especially among those with iron overload conditions, other well-conducted studies (e.g. in the European Prospective Investigation into Cancer and Nutrition) are null for gastric cancer. The Advisory Group was uncertain about the applicability of the agent to the *Monographs* programme, specifically noting that any excess seen in cancer may be a result of an endogenous condition (e.g. haemochromatosis), which may not be a suitable topic for a *Monographs* evaluation.

Key References

The following key references were also identified: Bhasin et al. (2004); Choi et al. (2008); Zacharski et al. (2008); Chua et al. (2010); Jakszyn et al. (2012); Ward et al. (2012); Ashmore et al. (2013); Tirnitz-Parker et al. (2013); Torti & Torti (2013); Zhu et al. (2014); Chung et al. (2015); Lagergren et al. (2016); Leone et al. (2016); Lv et al. (2016); Manz et al. (2016); Finianos et al. (2018); Nowak et al. (2018).

Recommendation: No evaluation

Dietary salt intake (NaCl)

Dietary salt intake has not been previously evaluated by the *IARC Monographs* programme. Chinese-style salted fish is classified as *carcinogenic to humans* (Group 1) (IARC, 2012c). Pickled vegetables (traditional Asian) are classified as *possibly carcinogenic to humans* (Group 2B) (IARC, 1993a).

Exposure Data

Salt (sodium chloride) is listed by the Organisation for Economic Co-operation and Development (for year 2007) as a High Production Volume chemical.

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

There is considerable evidence from ecological, case–control, and cohort studies that consumption of foods preserved by salting increases the risk of stomach cancer in humans (D'Elia et al., 2012; WCRF/AICR, 2018). The limitations of epidemiological studies include (i) that salt intake is mainly indirectly assessed as consumption of salted or preserved foods, preference for salty foods, and use of table salt, and (ii) the possibility of confounding by infection with *Helicobacter pylori*, which is classified by IARC as *carcinogenic to humans* (Group 1) and is a recognized cause of gastric adenocarcinoma. The geographical differences in the incidence of gastric cancer worldwide and changes in incidence over time have been explained by the synergistic interaction between *H. pylori* infection and dietary factors, including salt intake (Tsugane & Sasazuki, 2007).

Cancer in Experimental Animals

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

In vitro, an increase of sodium chloride concentration in the culture medium leads to increased expression of the bacterial oncoprotein CagA (Loh et al., 2018) and to altered expression of multiple *H. pylori* genes (Noto et al., 2018). A few studies in mice and a cross-sectional study in humans have shown that a high-salt diet induces atrophic gastritis and intestinal metaplasia, two steps in gastric carcinogenesis (Song et al., 2017).

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

Dimethyl hydrogen phosphite (CAS No. 868-85-9)

Dimethyl hydrogen phosphite was evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1999b).

Exposure Data

Dimethyl hydrogen phosphite is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Dimethyl hydrogen phosphite is used as a flame retardant on nylon 6 fibres, as a chemical intermediate in the production of pesticides, and in lubricant additives and adhesives. No data on occupational exposure

levels were available. A potential source of exposure to this chemical is from its occurrence as a degradation product of the chemical intermediate trimethyl phosphite and of pesticides such as trichlorfon and malathion (IARC, 1990a).

Cancer in Humans

No studies of cancer in humans were identified for dimethyl hydrogen phosphite.

Cancer in Experimental Animals

In gavage studies in male F344/N rats that received dimethyl hydrogen phosphite, there was increased incidence of bronchioloalveolar adenomas, bronchioloalveolar carcinomas, and squamous cell carcinomas of the lung and of neoplasms of the forestomach. There was also marginally increased incidence of bronchioloalveolar carcinomas of the lung and of neoplasms of the forestomach. There was no evidence of carcinogenicity in male or female $B6C3F_1$ mice that received dimethyl hydrogen phosphite (NTP, 1985).

Mechanistic Evidence

In vitro data indicate that dimethyl hydrogen phosphite has mutagenic and clastogenic potential. The available in vivo data are limited to the bone marrow, and the results are conflicting, with one study indicating clastogenicity. Dimethyl hydrogen phosphite should be regarded as having genotoxic potential in vivo. It is rapidly absorbed via the oral and dermal routes. The main metabolic pathway in rodents is demethylation to monomethyl hydrogen phosphite and further oxidation to CO_2. Dimethyl hydrogen phosphite was mainly eliminated via urine and expired air. Over the studied dose range between 10 and 200 mg/kg body weight and 5×200 mg/kg body weight, respectively, only little evidence of bioaccumulation or saturation of absorption and elimination was observed (OECD, 2004b).

Recommendation: Medium priority

Dimethyl morpholinophosphoramidate (CAS No. 597-25-1)

Dimethyl morpholinophosphoramidate (DMMPA) has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

DMMPA was developed as a simulant for the physical properties of nerve agents for use in chemical defence training. There is no identified commercial production or use.

Cancer in Humans

No studies of cancer in humans were identified for this agent.

Cancer in Experimental Animals

There are no peer-reviewed publications other than those associated with the carcinogenicity studies of the United States National Toxicology Program (NTP). In the NTP 2-year gavage studies (NTP, 1986b), DMMPA administered to male and female F344/N rats caused an increased incidence of mononuclear cell leukaemia at the highest dose of 600 mg/kg, at which there was also a significant decrease in survival. There were no neoplasms attributed to exposure to DMMPA in mice (NTP, 1986b).

Mechanistic Evidence

There is some evidence of genotoxicity of DMMPA. DMMPA was not mutagenic to bacteria; it was mutagenic in the mouse lymphoma assay and induced chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells.

Recommendation: No evaluation

Diphenylamine (CAS No. 122-39-4)

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

Exposure Data

Diphenylamine is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Diphenylamine is used as industrial antioxidant, fungicide, and anthelmintic. It is used in the manufacture of dyes and pesticides, as a stabilizer of nitrocellulose explosives and celluloids, and as an antioxidant on apple foliage.

Cancer in Humans

No epidemiological studies of cancer are available for diphenylamine (ACGIH, 2001).

Cancer in Experimental Animals

In several carcinogenicity studies in rats and dogs, results were negative (Thomas et al., 1967a, b). In more recent animal feeding carcinogenicity studies, positive results were obtained in both rats and mice (JBRC, 2011a, b). In rats, there was an increased incidence of vascular tumours in the spleen and an increased incidence of vascular tumours of the sum of all organs, including in the spleen and the subcutis, in males and an increased incidence of adenocarcinomas in the mammary gland in females (JBRC, 2011a). In mice, there was an increased incidence of vascular tumours in the spleen and an increased incidence of vascular tumours of the sum of all organs, including in the spleen and the liver (JBRC, 2011b).

Mechanistic Evidence

Studies are available on several key characteristics of carcinogens. Diphenylamine gave negative results in most genotoxicity studies. Based on the available data for diphenylamine, the rat metabolism study with diphenylamine, and the open literature data for diphenylamine and metabolites, there is no evidence that the *N*-nitroso metabolite of diphenylamine would be formed in rats or humans in vivo (EPA, 1998a).

Recommendation: Medium priority

Domestic talc products

Talc-based body powder was classified by IARC as *possibly carcinogenic to humans* (Group 2B) (IARC, 2010e), on the basis of *limited evidence* in humans of carcinogenicity (cancer of the ovary) from perineal use of talcum powder, and *limited evidence* of carcinogenicity in experimental animals. The 2014 Priorities Advisory Group assigned the re-evaluation of talc a medium priority (IARC, 2014).

Exposure Data

Domestic talc products are listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical. Talc-based body powder is widely used and is globally available.

Cancer in Humans

The previous IARC evaluation of perineal use of talcum powder was largely based on case–control studies, which demonstrated a consistent association of low magnitude, in which sources of bias could not be ruled out. Since then, several new studies, including prospective cohort studies, have been published. These were summarized in a recent meta-analysis (Penninkilampi & Eslick, 2018), which reported a modestly elevated but precise overall odds ratio of 1.31 (95% confidence interval [CI], 1.24–1.39), with stronger evidence from case–control studies than from cohort studies. A slight gradient in risk with increased exposure was observed. The meta-analysis also found heterogeneity by subtype, with an association shown for serous and endometrioid subtypes but not for mucinous or clear cell subtypes. The role of confounding, for example by douching practices, as an explanation for these findings has also been advanced (Gonzalez et al., 2016). A strong elevation in risk of endometrial cancer among women who used talcum powder on diaphragms was observed in postmenopausal women in a large, well-designed cohort study (hazard ratio, 3.06; 95% CI, 2.00–4.70) (Crawford et al., 2012).

Cancer in Experimental Animals

Few animal bioassay studies of tumours have been published since the previous IARC evaluation (IARC, 2010e). A 3-month study in two groups of seven Sprague-Dawley rats exposed to talc by intravaginal or perineal application found no evidence of neoplastic changes (Keskın et al., 2009).

Mechanistic Evidence

The mechanistic evidence has been updated since the previous IARC evaluation (IARC, 2010e). There is evidence to suggest that when talc is used in the genital area, talc enters the vagina and migrates to the upper genital tract (Cramer et al., 2007), where it may induce inflammatory reactions capable of damaging genital tissue DNA. Serous subtypes originate in the fallopian tube; this may enhance the plausibility of the observed associations in epidemiological studies. An in vitro study of epithelial ovarian and normal cells found that both were stimulated by talc to exhibit oxidative stress (Fletcher et al., 2019). Ovarian toxicity in rats was also observed after talc exposure (Yumrutas et al., 2015), and the pilot study of Sprague-Dawley rats noted above found inflammatory changes in the reproductive system, including increased numbers of follicles (Keskın et al., 2009).

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

Dry cleaning

"Dry cleaning" is a cleaning process for clothing and textiles that uses a chemical solvent other than water. It has been nearly 25 years since "dry cleaning (occupational exposures in)" was evaluated by the *IARC Monographs* programme. It is currently listed as *possibly carcinogenic to humans* (Group 2B) (IARC, 1995). More recently, the two major solvents used historically in dry cleaning have been evaluated. Tetrachloroethylene was classified in Group 2A, on the basis of *limited* evidence in humans for several cancer types (including cancer of the bladder and kidney) and *sufficient evidence* in experimental animals (IARC, 2013d). Trichloroethylene was classified in Group 1 on the basis of *sufficient evidence* in humans for kidney cancer and *sufficient evidence* in experimental animals (IARC, 2013d).

Exposure Data

A major source of concern for this occupational group has been the extensive use of organic solvents, including agents recently classified in Group 1 (trichloroethylene) or Group 2A (tetrachloroethylene). The dry cleaning process dates back to the 19th century, originally with the use of petroleum-based solvents. Because of concerns about flammability, dry cleaners began using chlorinated solvents, and the use of tetrachloroethylene emerged in the 1930s. Tetrachloroethylene has been prominently used in the dry cleaning industry since the 1950s, and was estimated to be used by nearly all dry cleaning facilities in the USA from the 1960s until the 1990s (decreasing to 70% by 2007) (IARC, 2013d). Tetrachloroethylene remains one of the most widely used solvents in dry cleaning, although health and safety regulations implemented in many countries in recent decades have led to alternative cleaning methods.

Cancer in Humans

Several case–control studies and two cohort studies of dry cleaning exposures, the most recent of which was published in March 2019, have suggested a relatively high level of increased risk of cancers of the

kidney and bladder, particularly among people who are heavily exposed (e.g. Duh & Asal, 1984; Blair et al., 2003; Lynge et al., 2006; Calvert et al., 2011; Seldén & Ahlborg, 2011; Vlaanderen et al., 2013, 2014; Callahan et al., 2019). The confidence intervals have been somewhat wide, and the issue has been raised of the adequacy of control for certain variables, such as smoking, although when controlled for, it has not had an impact on risk estimates.

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

Genotoxicity has been observed among dry cleaners exposed to tetrachloroethylene (e.g. Azimi et al., 2017).

Although the Advisory Group recommended no individual evaluation for dry cleaning as an agent, it could be considered for evaluation along with tetrachloroethylene in a future *Monograph*.

Key References

The following key references were also identified: Blair et al. (1979, 1990); Brandt et al. (1987); Lynge & Thygesen (1990); McCredie & Stewart (1993); Ruder et al. (1994, 2001); Lynge et al. (1995); McGregor et al. (1995); Vaughan et al. (1997); Travier et al. (2002); Bakke et al. (2007); Ma et al. (2009); National Research Council (2010); Babiker et al. (2012); Habib et al. (2018).

Recommendation: No evaluation

1,1-Dimethylhydrazine (CAS No. 57-14-7)

1,1-Dimethylhydrazine, commonly referred to as unsymmetrical dimethylhydrazine (UDMH), has been classified by IARC as *possibly carcinogenic to humans* (Group 2B) (IARC, 1987), on the basis of *sufficient evidence* of carcinogenicity in experimental animals. It was first reviewed by IARC in 1974 (IARC, 1974) and was most recently reviewed in 1999 (IARC, 1999b).

Exposure Data

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. Environmental contamination results from its use as rocket fuel and as a plant growth regulator.

Cancer in Humans

No epidemiological studies of cancer from exposure to 1,1-dimethylhydrazine were identified.

Cancer in Experimental Animals

High incidence of haemangiosarcoma and lung tumours was observed in drinking-water studies in male and female mice; kidney and liver tumours were also observed in male mice. In an intraperitoneal study, peripheral nerve sheath tumours were observed in male and female hamsters.

Monographs Volume 71 (IARC, 1999b) did not report on a drinking-water study in hamsters observing caecum tumours in males, angiomas and angiosarcomas in both sexes, and adrenal cortical adenoma in females (Toth, 1977). Two series of bioassays are also available. The first series is of drinking-water studies conducted at the International Research and Development Corporation (Goldenthal, 1989). Incidence and study design are reported in Gold et al. (1995) and partially summarized by the United States Environmental Protection Agency (EPA, 2009c) and the International Programme on Chemical Safety (IPCS, 1991a). Tumours of the blood vessels and the lung were observed in male and female mice, and tumours of the liver in female rats. The second is a series of inhalation studies conducted by the United States Air Force (Haun et al., 1979, 1984) and reported by the United States Environmental Protection Agency (EPA, 2009c). In one set of studies in female mice and male rats, tumours were observed, but contamination of the test substance with nitrosodimethylamine was a concern. In the second set of studies, after exposure for 1 year using purified 1,1-dimethylhydrazine followed by observation for 1 year, benign tumours of the lung, liver, lymphatic system, nasal mucosa, bone, and circulatory system were increased in female mice.

Mechanistic Evidence

Few recent data relevant to the key characteristics of carcinogens are available for 1,1-dimethylhydrazine. The 1999 IARC review (IARC, 1999b) noted conflicting evidence of mutagenicity in bacteria, but noted adduct formation, micronucleus formation, and DNA fragmentation in vivo. In vivo metabolic oxidation to reactive derivatives appears to be involved (Sedgwick, 1992).

Recommendation: Low priority

1,2-Dimethylhydrazine (CAS No. 540-73-8)

1,2-Dimethylhydrazine has been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1987, 1999b). 1,2-Dimethylhydrazine is classified as *probably carcinogenic to humans* (Group 2A), on the basis of *sufficient evidence* of carcinogenicity in experimental animals and mechanistic evidence that 1,2-dimethylhydrazine is consistently mutagenic in a wide range of test systems and gives rise to a similar pattern of DNA damage in human and animal tissues in vitro.

Exposure Data

Occupational exposure may occur in laboratories; no data on exposure in humans were identified.

Cancer in Humans

Studies of cancer in humans exposed to 1,2-dimethylhydrazine were not identified.

Cancer in Experimental Animals

Several new studies of 1,2-dimethylhydrazine-induced colon cancer in rodents have investigated potentially protective agents and their attendant mechanisms (Senedese et al., 2019; Khan et al., 2018).

Mechanistic Evidence

Although the database of studies in rodents has expanded since the most recent *IARC Monographs* evaluation, new mechanistic evidence relevant to key characteristics of carcinogens from studies in exposed humans is sparse.

Key References

The following key references were also identified: Manju & Nalini (2005); Ertekin et al. (2013); Ulger et al. (2013); Gurley et al. (2015); Saleem et al. (2015); Ilhan et al. (2016); Kuugbee et al. (2016); Ríos-León et al. (2017); Sun et al. (2017).

Recommendation: No evaluation

Dysbiotic microbiota

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

Exposure Data

The human body is colonized by many microorganisms; the gut microbiota has emerged as an important consideration in clinical oncology. The microbiome not only acts at a local epithelial level in the gut but also modifies immune responses within intestinal and extraintestinal tumours.

Cancer in Humans

A host's microbiota may increase, decrease, or have no effect on cancer susceptibility. Assigning causal roles in cancer to specific microbes and microbiotas, unravelling host–microbiota interactions with environmental factors in carcinogenesis, and exploiting such knowledge for cancer diagnosis and treatment are areas of intensive interest.

A few studies have identified specific bacteria – notably *Fusobacterium* and *pks*+ *Escherichia coli* – that may be involved in the etiology of colorectal adenomas and carcinomas in the context of dysbiotic gut microbiota. Specifically; a recent case–control study in the USA showed that colorectal cancer cases had a

significantly decreased overall microbial diversity and increased carriage of *Fusobacterium* and *Porphyromonas*. In addition, *pks*+ *E. coli* are found at a significantly higher percentage in the gut microbiota of patients with inflammatory bowel disease or colorectal cancer.

However, the results of these studies of specific bacteria have been limited by potential confounding and the inability to rule out reverse causation. Furthermore, studies of specific bacteria may not reflect the impact of the microbiota more generally. The Advisory Group recommended that the agent be more specifically defined, perhaps limited to specific pathogenic strains.

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

Microbiota may contribute to carcinogenesis by at least three mechanisms, whether by enhancing or diminishing a host's risk: (i) altering the balance of host cell proliferation and death; (ii) influencing metabolism of host-produced factors, ingested foodstuffs, and pharmaceuticals; and (iii) guiding immune system function.

In an azoxymethane/interleukin-10 knockout (AOM/*Il10*$^{-/-}$) mouse model, *pks*+ *E. coli* have a carcinogenic effect independent of inflammation. Deletion of the *pks* genotoxic islands from *E. coli* NC101 decreased tumour multiplicity and invasion in these mice, without altering intestinal inflammation. Data from these studies suggested that in mice, colitis can promote tumorigenesis by altering microbial composition and inducing the expansion of microorganisms with genotoxic capabilities. Through a series of experimental studies in vitro and in vivo, mechanisms were investigated by which *Fusobacterium nucleatum* in the gut could be associated with colorectal carcinoma. It was suggested that *Fusobacterium* spp., via binding of *Fusobacterium* adhesin A (FadA) to receptors on host epithelial cells, can alter barrier function, increase inflammation by modulating the tumour microenvironment, and activate pro-oncogenic signals to promote colorectal carcinoma.

The Advisory Group noted that it may be highly useful to focus on certain species, including *Fusobacterium* species and *pks*+ *E. coli*.

Key References

The following key references were also identified: Murphy et al. (2019); Herrington et al. (2019); Lucas et al. (2017); Koliarakis et al. (2018); Flemer et al. (2018); Kang & Martin (2017); Garrett (2015).

Recommendation: Low priority

Electronic nicotine delivery systems and nicotine

Electronic nicotine delivery systems (ENDS; also known as electronic cigarettes or e-cigarettes) have not been previously evaluated by the *IARC Monographs* programme. The 2014 Priorities Advisory Group assigned them a high priority (IARC, 2014).

Exposure Data

Electronic cigarettes are battery-powered devices designed to deliver nicotine without combusting tobacco. They generate aerosols by heating a liquid ("e-liquid") composed of nicotine and flavours in propylene glycol (propane-1,2-diol) and/or glycerol (propane-1,2,3-triol). There has been an exponential increase in the use of electronic cigarettes in the past decade, and it is currently estimated that in the USA, 14% of middle school students, 38% of high school students, 36% of young adults (ages 18–24 years), and 16% of adults (ages ≥ 25 years) have used electronic cigarettes (Balbo & Stepanov, 2018).

Upon heating, glycerol and propylene glycol give rise to a variety of carbonyl compounds, including formaldehyde (IARC Group 1) and acetaldehyde (IARC Group 2B), as well as acrolein, propanal, glyoxal, and methylglyoxal (IARC Group 3) (Bekki et al., 2014; Pisinger & Døssing, 2014; Pisinger, 2015; Kim et al., 2016). Volatile organic compounds have also been detected in the vapour, including benzene (IARC Group 1), styrene (IARC Group 2A), ethylene benzene (IARC Group 2B), and toluene (IARC Group 3) (Pisinger & Døssing, 2014; Pisinger, 2015; Kim et al., 2016). Other substances that have been reported include nanoparticles, heavy metals such as cadmium (IARC Group 1), mercury (IARC Group 3), and lead (IARC Group 2B), and tobacco-specific nitrosamines such as *N*′-nitrosonornicotine (NNN) (IARC Group 1) and 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) (IARC Group 1) (Goniewicz et al., 2014; Pisinger & Døssing, 2014; Pisinger, 2015; Kim et al., 2016). Electronic cigarette refill fluids ("e-liquids") contain an extensive variety of flavouring chemicals, some of which are toxic to cultured mouse neural stem cells and human bronchial epithelial cells (Hua et al., 2019).

The most frequent adverse effects of use of electronic cigarettes are light-headedness, irritation of the throat, dizziness, and coughing. Other effects include increased airway resistance, an increased heart rate, and an elevated diastolic blood pressure (Pisinger & Døssing, 2014; Pisinger, 2015; Kim et al., 2016).

Cancer in Humans

No data are available pertaining to the carcinogenicity of electronic cigarettes in humans.

Cancer in Experimental Animals

Nicotine administered in the drinking-water induced urothelial hyperplasia in female Wistar Han rats and to a lesser extent in female C57BL/6 mice (Dodmane et al., 2014). In a subsequent study, rats initiated with *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN) and then given nicotine in the drinking-water had a dose-dependent increase in the incidence of urothelial carcinoma of the urinary bladder (Suzuki et al., 2018).

This may be due to a receptor-mediated mechanism involving nicotinic acetylcholine receptors (Grando, 2014.)

Mechanistic Evidence

4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL, a metabolite of NNK), acrolein, 2-naphthylamine (IARC Group 1), and *ortho*-toluidine (IARC Group 1) have been detected in the urine of users of electronic cigarettes (Pisinger & Døssing, 2014; Pisinger, 2015; Fuller et al., 2018). Benzene, toluene, and 2,5-dimethylfuran have been found in the breath of users of electronic cigarettes (Pisinger & Døssing, 2014; Pisinger, 2015). Increased levels of acrolein-derived DNA adducts have been detected in oral cells from individuals who use electronic cigarettes (Dator et al., 2018). Increased levels of O^6-methyldeoxyguanosine and an acrolein-derived DNA adduct have been reported in human lung and bladder cells exposed in vitro to nicotine. This was accompanied by decreased nucleotide excision and base excision repair activity and lower levels of XPC and OGG1/2 DNA repair proteins. Nicotine also enhanced the mutant frequency and cell transformation in cultured human lung and bladder cells (Lee et al., 2018).

Mice exposed to vapour from electronic cigarettes had elevated levels of O^6-methyldeoxyguanosine and an acrolein-derived DNA adduct in DNA isolated from lung, bladder, heart, and liver tissue, as assessed by immunoassays and ^{32}P-postlabelling assays. Lung tissue from the mice exposed to electronic cigarette vapour had decreased nucleotide excision and base excision repair activity and lower levels of XPC and OGG1/2 DNA repair proteins (Lee et al., 2018).

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

Estrogen: estradiol and estrogen–progestogen

Estrogen–progestogen oral contraceptives and estrogen–progestogen menopausal therapy have been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1987, 1999d, 2007b, 2012a) and are classified as *carcinogenic to humans* (Group 1) since Supplement 7 (IARC, 1987) and Volume 92 (IARC, 2010b), respectively. The current evaluation (IARC, 2012a) specifies that estrogen–progestogen oral contraceptives cause cancers of the breast, cervix, and liver, and estrogen–progestogen menopausal therapy causes cancers of the breast and the endometrium.

Exposure Data

Estrogen–progestogen combinations are used for the prevention of conception in women, in menopausal therapy, and in the treatment of moderate acne vulgaris or premenstrual disorders in some individuals. More than 100 million women worldwide (10% of all women of reproductive age) use combined hormonal contraceptives; a higher proportion of women receive these drugs in high-income countries (16%) than in low- and middle-income countries (6%). At the peak of use for menopausal therapy

in 1999, approximately 20 million women in high-income countries used combined hormone therapy; use has fallen by more than 50% since 2002 (IARC, 2012a).

Conjugated estrogens, estradiol and its semisynthetic esters (especially estradiol valerate), are the main estrogens used in the treatment of menopausal disorders. Estrogens are also used in the treatment of a variety of other conditions associated with a deficiency of estrogenic hormones, including female hypogonadism, castration, and primary ovarian failure. In addition, estrogens may be used in the treatment of abnormal uterine bleeding caused by hormonal imbalance not associated with an organic pathology. After a substantial increase in use in the 1960s and early 1970s, the use of estrogen-only treatment regimens for menopausal symptoms declined after 1975, when a strong association with endometrial cancer was noted. Estrogen-only menopausal therapy is still prescribed for women who have undergone hysterectomy (IARC, 2012a).

Cancer in Humans

A major pooled analysis of more than 50 prospective studies published after the most recent *IARC Monographs* evaluation reported a statistically significant increased risk of ovarian cancer (Beral et al., 2015). The risk increase was similar for estrogen-only and estrogen–progestogen combinations, but differed across the four main tumour types and was increased for the two most common types, serous and endometrioid.

The Advisory Group considered that the new epidemiological evidence appears to support the classification of additional cancer sites to either the *sufficient* or *limited* evidence category for estrogen-only menopausal therapy. The Advisory Group noted that before embarking on a re-evaluation of estrogen–progestogen menopausal therapy and ovarian cancer, further expert solicitation and umbrella reviews about estrogen-only menopausal therapy, estrogen–progestogen oral contraceptives, estrogen–progestogen menopausal therapy, and perhaps also diethylstilbestrol may be warranted to specify the scope of the re-evaluations with regard to different hormone therapies for various indications and increased or reduced cancer risk in humans.

Key References

The following key references were also identified: Cavalieri et al. (2001, 2002, 2012); Cavalieri & Rogan (2002, 2006); Yu (2002); Russo & Russo (2006); Laviolette et al. (2010); Samavat & Kurzer (2015); Ziegler et al. (2015); Zane et al. (2017).

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

Ethanol (inhalation and dermal exposure) (CAS No. 64-17-5)

Ethanol has been evaluated repeatedly by the *IARC Monographs* programme as “ethanol in alcoholic beverages” (IARC, 2010g, 2012c) and is classified as *carcinogenic to humans* (Group 1), on the basis of

sufficient evidence in experimental animals for the carcinogenicity of ethanol, *sufficient evidence* in humans for the carcinogenicity of alcohol consumption for several cancer sites, and other considerations.

Ethanol is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical. Occupational exposure to ethanol is primarily via inhalation; dermal absorption seems to be negligible. Studies of carcinogenic effects of ethanol under conditions of inhalation or other non-oral routes of exposure in the workplace were not identified; all available cancer bioassays are via oral exposure. Several national agencies or committees have concluded that the occupational exposure is negligible compared with endogenous production of ethanol.

Key References

The following key references were identified: MAK (1999); Dutch Health Council (2006); Anses/Afsset (2010).

Recommendation: No evaluation

Ethyl carbamate (urethane) (CAS No. 51-79-6)

Ethyl carbamate has been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1987, 2010g) and is classified as *probably carcinogenic to humans* (Group 2A), on the basis of *sufficient evidence* of carcinogenicity in experimental animals, *inadequate evidence* of carcinogenicity in humans, and mechanistic evidence including (i) similarities in the metabolic pathways of the activation of ethyl carbamate in rodents and humans; and (ii) that the formation of DNA-reactive metabolites, thought to play a major role in ethyl carbamate-induced carcinogenesis in rodents, probably also occurs in human cells.

Exposure Data

Ethyl carbamate (also known as urethane) is a naturally occurring component of all fermented foods and beverages. Ethyl carbamate can also be made commercially through reactions with ethanol. It was historically used in medical practice as a hypnotic agent, as an antineoplastic agent (in particular for multiple myeloma), and in analgesics. There is no evidence that ethyl carbamate is currently used in human medicine, although it is used as an anaesthetic in veterinary medicine. Workers may be exposed in various occupations, and the general population may be exposed to ethyl carbamate via ingestion of fermented foods and alcoholic beverages. Levels in foods have been regulated and significantly reduced in recent decades.

Cancer in Humans

No new studies of cancer in humans were identified since the most recent *IARC Monographs* evaluation.

Cancer in Experimental Animals

In the previous evaluation (IARC, 2010g), there was *sufficient evidence* of carcinogenicity in experimental animals.

Mechanistic Evidence

New mechanistic evidence is available, primarily from exposure to ethyl carbamate in alcoholic beverages. This includes not only considerable evidence that urethane is metabolized to an electrophile, inducing direct DNA damage, and is genotoxic, but also evolving understanding that urethane exhibits other key characteristics of carcinogens, including modulating receptor-mediated effects, causing chronic inflammation, and modulating cellular proliferation and cell death pathways.

Key References

The following key references were also identified: FDA (1997); Lachenmeier et al. (2010); Cerreti et al. (2016); Lee et al. (2016); Pflaum et al. (2016); Choi et al. (2017).

Recommendation: No evaluation

Ethylenethiourea (CAS No. 96-45-7)

Ethylenethiourea was classified by IARC as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 2001), on the basis of *inadequate evidence* of carcinogenicity in humans, *sufficient evidence* of carcinogenicity in experimental animals, with a mechanistic downgrade.

Exposure Data

Ethylenethiourea is used as a vulcanization accelerator in the rubber industry. It is a degradation product of and an impurity in ethylenebisdithiocarbamate fungicides, and field workers may be exposed to ethylenethiourea while applying these fungicides. Ethylenethiourea is the major metabolite of the fungicide mancozeb (EPA, 2013). The general population may be exposed to low concentrations of residues of ethylenethiourea in foods.

Cancer in Humans

No studies of cancer in humans were identified.

Cancer in Experimental Animals

In experimental animals, ethylenethiourea was tested for carcinogenicity by oral administration in two studies in three strains of mice, with perinatal exposure in one study. It was also tested in five studies in rats by oral administration, with perinatal exposure in one study. In mice, it produced follicular cell tumours of the thyroid and tumours of the liver and anterior pituitary gland. In rats, it consistently produced follicular

cell adenomas and carcinomas of the thyroid. Ethylenethiourea did not cause neoplasms in one strain of hamsters (IARC, 2001).

Mechanistic Evidence

Data relevant to key characteristics of carcinogens, as well as on the human relevance of tumours in experimental animals (Capen et al., 1999), are available. In mechanistic studies, ethylenethiourea was not genotoxic in bacterial assays, in cultured mammalian cells, or in rodents in vivo. It induced chromosomal recombination and aneuploidy in yeast and cell transformation in mammalian cells. In rats, ethylenethiourea altered thyroid hormone homeostasis and produced enlargement of the thyroid. Ethylenethiourea induced follicular cell hypertrophy and hyperplasia in rats and in mice.

Recommendation: No evaluation

S-Ethyl-*N*,*N*-dipropylthiocarbamate (EPTC) (CAS No. 759-94-4)

S-Ethyl-*N*,*N*-dipropylthiocarbamate (EPTC) has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

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 United States Environmental Protection Agency classified EPTC as “not likely to be carcinogenic to humans” (EPA, 2008c).

EPTC is listed by the Organisation for Economic Co-operation and Development (for year 2007) as a High Production Volume chemical.

Cancer in Humans

An earlier report of the United States National Cancer Institute (NCI) Agricultural Health Study (AHS) showed a modestly increased risk of non-Hodgkin lymphoma among farmers who applied carbamate pesticides when compared with non-farmers. An update from the NCI AHS reported an excess risk of cancers of the colorectum and pancreas. There was a suggestion of an association with leukaemia and non-Hodgkin lymphoma. No other associations were observed. A case–control study of pancreatic cancer nested in the NCI AHS found statistically significant exposure–response associations for EPTC.

Cancer in Experimental Animals

The Advisory Group noted the lack of carcinogenic potential noted in the available studies (EPA, 1999, 2011a).

Mechanistic Evidence

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.

Key References

The following key references were also identified: Dickie (1987); Zheng et al. (2001); Lee et al. (2004c); Health Canada (2008); van Bemmel et al. (2008); Andreotti et al. (2009); Wofford et al. (2014); EPA (2017c).

Recommendation: Low priority

E-waste burn sites

Exposure Data

Several exposures from electronic and electrical waste (e-waste) burn sites have been recorded in the surrounding environment (Wang et al., 2012a; Zheng et al., 2013, 2016; reviewed in Grant et al., 2013) or in patients with cancer (Zhao et al., 2009). Several of these exposures have been identified as human carcinogens and/or persistent organic pollutants, including brominated flame retardants, polybrominated diphenyl ethers, polychlorinated biphenyls, dioxin and similar compounds (polychlorinated dibenzodioxins and dibenzofurans, dioxin-like polychlorinated biphenyls, and perfluoroalkyls), polycyclic aromatic hydrocarbons, metals or elements (lead, chromium or hexavalent chromium, cadmium, mercury, zinc, nickel, lithium, barium, and beryllium), and air pollutants (particulate matter with particles of aerodynamic diameter < 2.5 μm [$PM_{2.5}$]). Exposure of the population may occur through food, house dust, groundwater or drinking-water, air pollution, and soil.

Cancer in Humans

The proposal to evaluate exposures from e-waste burn sites originates from an increased cancer risk found in children around a large e-waste burn site in the West Bank. Bailony et al. (2011) analysed patterns in the incidence of childhood cancer in the West Bank Cancer Registry for 1998–2007. One of the two areas with the highest rates was a rural area of southwest Hebron, and within this area a cluster of childhood lymphoma was observed. This site was later shown (Davis & Garb, 2019) to be the centre of an extensive informal e-waste dismantling industry, which has been operating for almost two decades. At the site, there was extensive open burning of e-waste components to extract valuable components or dispose of waste. This problem is not limited to this area. E-waste from high-income countries is regularly transferred to low- and middle-income countries such as China, India, and African countries, where e-waste is processed using

less advanced technology and with less strict controls than those in the countries that produce the e-waste. Several exposure studies (and some with accompanying risk assessment estimates) have been conducted in China. The Advisory Group noted that this is an exposure circumstance of major concern, particularly for low- and middle-income countries, which could include potential exposure to several established carcinogens, and therefore suggested that it may be more suited for a risk assessment process rather than hazard identification.

Cancer in Experimental Animals

Because this is an exposure circumstance, it is not easy to obtain data in experimental animals.

Mechanistic Evidence

Mechanistic data exist, for specific exposures (e.g. cadmium, benzo[*a*]pyrene) rather than for the exposure mixture that surrounds the e-waste sites.

In summary, the potential for a carcinogenic risk around e-waste sites is present. The main 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. Exposures are heterogeneous between e-waste sites, and this is not a scenario that enables a meaningful *IARC Monographs* assessment to be made. For these sites it would be important to perform quantitative risk assessment on the basis of existing knowledge on the toxicity of specific exposures and knowledge of exposure levels at the e-waste sites.

Recommendation: No evaluation

Fertility treatment

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

Exposure Data

Drugs to stimulate ovulation were introduced for fertility treatment in the 1960s. Use has increased in recent years, although access is still very limited in low- and middle-income countries. Treatment typically involves the use of ovulation-stimulating agents, including selective estrogen receptor modulators such as clomiphene citrate, gonadotropins, gonadotropin-releasing hormone agonists and antagonists, and human chorionic gonadotropin.

Cancer in Humans

It has been hypothesized that these drugs could cause cancers in the treated women (particularly cancer of the ovary, endometrium, or breast) and possibly in their offspring. Clomiphene citrate was evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1987), because of *inadequate evidence* in humans and in experimental animals. Epidemiological studies of cancer

after fertility treatment have been challenging because of the relative rarity of exposure, insufficient follow-up time, lack of data on the number of cycles or doses, and potential confounding by subfertility for cancers of the ovary, endometrium, or breast. Cochrane reviews and multiple meta-analyses of more than 20 studies have generally concluded that there is no clear evidence of increased risks of cancer of the breast or endometrium, and the possible excess risk of borderline ovarian tumours could be due to intrinsic characteristics of these tumours or surveillance bias (Rizzuto et al., 2013; Gennari et al., 2015; van den Belt-Dusebout et al., 2016; Skalkidou et al., 2017; Williams et al., 2018). Large new studies due to be published in 2019–2020 include an expansion of the OMEGA cohort in the Netherlands and a cohort in Israel that includes women with more than 20 treatment cycles. Several studies have reported increased risk of cancer (particularly haematological malignancies) in the offspring, but few have examined specific drugs and results have not been consistent (Hargreave et al., 2013; Reigstad et al., 2017; Wang et al., 2018a; Spaan et al., 2019). An expansion of the OMEGA cohort, which has some of the most detailed data on treatments and potential confounders, is still several years from completion.

Cancer in Experimental Animals

Direct experimental evidence of cancer risk in animal models is still lacking. There are some rodent studies of gonadotropins demonstrating that they stimulate proliferation of the ovarian surface epithelium, supporting that fertility treatment and hormone therapy could affect risk of ovarian cancer in this context. However, this area of research is limited in that ovarian surface epithelium-derived tumours are essentially non-existent; thus, historically the view was that there were not adequate models in which to test the hypothesis. Given recent changes in the understanding of the fallopian tube origin of many invasive ovarian cancers, there may be an opportunity for this area of research in fallopian tube-derived cancer models.

Mechanistic Evidence

Experimental studies consistently suggest that endogenous as well as exogenous sex hormones play an important role in the development of cancers of the female reproductive tract. Exogenously administered fertility drugs increase the woman's endogenous levels of gonadotrophins, estrogen, and progesterone. Based on the mechanisms of action, fertility treatments modulate receptor-mediated effects and alter cell proliferation, cell death, or nutrient supply and may warrant additional investigation based on the pharmacology.

Additional mechanisms for development of ovarian cancer include "incessant ovulation" and damage to the ovarian surface epithelium.

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

Firefighting exposure

Firefighting was classified by IARC as *possibly carcinogenic to humans* (Group 2B) (IARC, 2010f), on the basis of *limited evidence* of carcinogenicity in humans and *inadequate evidence* of carcinogenicity in experimental animals. Data in humans generally lacked exposure–response information, and findings among studies were inconsistent, although the evidence of excess risk appeared strongest for cancers of the testis and prostate and non-Hodgkin lymphoma.

Exposure Data

There are approximately 4.7 million firefighters worldwide. The term "firefighter" describes a heterogeneous group of professionals and volunteers, working in municipal, wildland, and industrial settings, who perform a wide array of tasks related to firefighting. Firefighting predominantly involves potential exposures to complex mixtures of gases, vapours, and particulates, including many known or suspected carcinogens, found in volatilized combustion and pyrolysis products or debris. Exposure is via all routes of entry, and sources involve multiple pathways. Firefighters also work irregular hours; this may disrupt biological functions.

Cancer in Humans

Since 2010, several new studies have been published, including large multicentre longitudinal designs (Ahn et al., 2012; Daniels et al., 2014, 2015; Pukkala et al., 2014; Ahn & Jeong, 2015; Amadeo et al., 2015; Tsai et al., 2015; Bigert et al., 2016; Glass et al., 2016, 2017, 2019; Harris et al., 2018; Kullberg et al., 2018; Muegge et al., 2018; Petersen et al., 2018a, b). Findings still differ by cancer site, although studies with longer follow-up and greater numbers report similar results (Daniels et al., 2014; Pukkala et al., 2014). A recent meta-analysis reported excess non-Hodgkin lymphoma, melanoma, and cancers of the colon, rectum, prostate, bladder, and kidney (Crawford et al., 2017). Dose–response information is sparse; however, a study of career firefighters in the USA reported positive dose–response associations for leukaemia and lung cancer (Daniels et al., 2015).

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

New mechanistic data are available. Biomarker studies have related firefighting exposure to increased urinary concentrations of polycyclic aromatic hydrocarbon (PAH) metabolites (Adetona et al., 2017; Keir et al., 2017; Hoppe-Jones et al., 2018; Oliveira et al., 2018). There is evidence of increased DNA damage and oxidative stress in structural and wildland firefighters compared with non-exposed subjects (Adetona et al., 2013; Abreu et al., 2017; Keir et al., 2017; Oliveira et al., 2018). In subjects completing a firefighting training course, DNA strand breaks in peripheral blood mononuclear cells were positively associated with

dermal exposure to pyrene and PAHs and urinary excretion of 1-hydroxypyrene (Andersen et al., 2018). There is also evidence of epigenetic changes in firefighters. A study reported that increased concentrations of PAH metabolites in firefighters were related to activation of the aryl hydrocarbon receptor and p53 cancer pathways (Hoppe-Jones et al., 2018). Changes in microRNA expression were observed in firefighters compared with non-exposed firefighter recruits (Jeong et al., 2018). These changes may be associated with activation of cancer pathways.

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

Flame retardants

Several individual flame retardants have been evaluated by the *IARC Monographs* programme. In Volume 48 (IARC, 1990a), six specific flame retardants were evaluated as *possibly carcinogenic to humans* (Group 2B), on the basis of *sufficient evidence* of carcinogenicity in experimental animals, or as *not classifiable as to their carcinogenicity to humans* (Group 3), on the basis of less than sufficient evidence of carcinogenicity in experimental animals. Two of these, BDE-209 and tris(2-chloroethyl) phosphate, were re-evaluated in Volume 71, with no change in the overall evaluation as *not classifiable as to their carcinogenicity to humans* (Group 3), on the basis of less than sufficient evidence of carcinogenicity in experimental animals (IARC, 1999b). More recently, tetrabromobisphenol A was classified as *probably carcinogenic to humans* (Group 2A) (IARC, 2018c), on the basis of *sufficient evidence* of carcinogenicity in experimental animals, *inadequate evidence* of carcinogenicity in humans, and mechanistic evidence that tetrabromobisphenol A can operate through three key characteristics of carcinogens and that these can be operative in humans. Specifically, the evidence was strong for the modulation of receptor-mediated effects, for the induction of oxidative stress, and for the induction of immunosuppression. Other agents, such as polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) (IARC, 2016c), may also have been used as flame retardants.

Exposure Data

Flame retardants are added or applied to various materials and products (e.g. electronics, furniture, and building materials) to prevent the start or growth of fires (IARC, 2016c, 2018c). The production and use of some flame retardants, such as PCBs and PBBs, was widely banned or discontinued by the 1980s (IARC, 2016c). The production and use of other flame retardants continues; for example, tetrabromobisphenol A is still produced in some non-European Union countries and is used primarily as a flame retardant in printed circuit boards (IARC, 2018c). Because of their tendency to persist and bioaccumulate, many flame retardants have been detected in most biotic and abiotic compartments worldwide. The general population is exposed to flame retardants through breast milk, diet, and ingestion of indoor dust. Occupational exposure may occur during the manufacture of electronic products. New exposures of concern have emerged more recently in occupational groups such as recyclers of electronic and electrical waste (e-waste).

Cancer in Humans

Epidemiological evidence of cancer is available relevant to the carcinogenicity of flame retardants (see also tris(2-chloroethyl) phosphate; pentabromodiphenyl ethers). Recently, two relatively small case–control studies observed an increased risk of papillary thyroid cancer associated with flame retardants (Hoffman et al., 2017; Leung, 2017). One observed an increased risk associated with decabromodiphenyl ether (BDE-209) in serum, and the other observed an increased risk associated with BDE-209 and tris(2-chloroethyl) phosphate in dust. Two other recent studies, one a cohort study and one a case–control study, did not observe an increased risk associated with polybrominated diphenyl ethers in serum. An additional case–control study did not find any associations with organophosphate flame retardants on the basis of urinary concentrations. All studies were relatively small, with limited power to examine specific congeners, and they used different media to measure exposure (serum, house dust, urine).

Cancer in Experimental Animals

Animal cancer bioassays are available or in progress for several flame retardants, such as DE-71 (NTP, 2016l), tris(2-chloroethyl) phosphate (NTP, 1991), and tris(chloropropyl) phosphate (NTP, 2019e).

Mechanistic Evidence

Studies relevant to key characteristics of carcinogens are available for several flame retardants, such as polybrominated diphenyl ethers and DE-71.

"Flame retardants" is a functional class that contains a diverse array of chemicals, making them difficult to study. Some chemicals in the class are structurally and mechanistically similar and could be grouped for evaluation.

Key References

The following key references were also identified: Terrell et al. (2016); Hoffman et al. (2017); Mughal & Demeneix (2017); Gorini et al. (2018).

Recommendation: No evaluation

Fonofos (CAS No. 944-22-9)

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

Exposure Data

Fonofos is an organothiophosphate insecticide that continues to be used widely in agriculture. The registration for use of fonofos as a soil insecticide for many crops (e.g. cereals, maize, vegetables, and fruit) has been cancelled in the USA, but use of related agents continues worldwide.

Cancer in Humans

Recent epidemiological evidence from the United States National Cancer Institute (NCI) Agricultural Health Study (AHS) has revealed an association with cancer of the prostate, with noteworthy indications of a significant interaction involving the link between genetic variants of 8q24 and risk of prostate cancer. The NCI AHS has also produced evidence to support associations between fonofos and cancers of the colon and breast and also non-Hodgkin lymphoma and leukaemia.

Cancer in Experimental Animals

Results of chronic cancer bioassays in rats and in mice reviewed by the United States Environmental Protection Agency (EPA, 2008a) were equivocal.

Mechanistic Evidence

Potential mechanisms relevant to carcinogenicity have been reported. Fonofos alters steroid hormone metabolism and inhibits testosterone.

Key References

The following key references were also identified: Alavanja et al. (1996); Folsom et al. (1996); Hodgson & Rose (2006); Mahajan et al. (2006); Engel et al. (2017).

Recommendation: Low priority

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

Fumonisin B_1 was classified as *possibly carcinogenic to humans* (Group 2B) (IARC, 2002), on the basis of *sufficient evidence* of carcinogenicity in experimental animals and *inadequate evidence* of carcinogenicity for fumonisins in humans.

Exposure Data

Fumonisin B_1 is a mycotoxin that is produced primarily by *Fusarium verticillioides* and *Fusarium proliferatum*. Fumonisins, primarily fumonisin B_1 and to a lesser extent fumonisin B_2, are widespread natural contaminants of corn (maize) and corn-based foods and animal feeds. Although more than 30 fumonisin analogues have been characterized, fumonisin B_1 appears to be the most important from a toxicological perspective. Exposure to fumonisins is generally low in western Europe, North America, and Japan but can be much higher in parts of Africa, China, and Central America (Voss & Riley, 2013).

Cancer in Humans

Observational and epidemiological studies have suggested an association between exposure to fumonisin B_1, from the consumption of corn, and cancers of the oesophagus and liver; however, the data are

not conclusive and in the case of liver cancer are confounded by simultaneous exposure to aflatoxin B_1 (Voss & Riley, 2013).

Cancer in Experimental Animals

The carcinogenicity of fumonisin B_1 in experimental animals was thoroughly reviewed in the 2002 *IARC Monograph* (IARC, 2002). On the basis of the results obtained from a 2-year dietary study in male and female $B6C3F_1$ mice, a 2-year dietary study in male and female F344/N rats, and a 2-year dietary study in male BDIX rats, the Working Group concluded that there was *sufficient evidence* in experimental animals for the carcinogenicity of fumonisin B_1.

After the 2002 IARC evaluation (IARC, 2002), an additional study was published in which male p53 heterozygous ($p53^{+/-}$) and p53 homozygous ($p53^{+/+}$) transgenic mice were fed fumonisin B_1 for 26 weeks. At the highest dose tested, 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 fumonisin B_1 is due to a non-genotoxic mode of action (Bondy et al., 2012).

Mechanistic Evidence

There is little support for the view that fumonisin B_1 interacts directly with DNA or is metabolized to a metabolite that interacts with DNA. Fumonisin B_1 is inactive in bacterial mutagenesis assays but induces DNA damage in vitro and in vivo, perhaps as a consequence of oxidative damage.

Fumonisin B_1 is a potent and specific inhibitor of ceramide synthase, which results in a disruption in sphingolipid metabolism and an accumulation of sphinganine and sphingosine. These sphingoid bases are thought to be involved in the induction of apoptosis in renal tubule cells and hepatocytes. Other aspects associated with the inhibition of ceramide synthase by fumonisin B_1 include (i) increased mRNA expression of genes modulating apoptosis; (ii) increased expression of tumour necrosis factor α; (iii) increased expression of genes involved in mitosis or regulating cell-cycle progression, particularly the G1/S transition; (iv) oxidative stress and secondary damage to macromolecules; and (v) altered lipid biosynthesis and changes in the composition of lipids in cell membranes (Voss & Riley, 2013). An elevation of phosphorylated sphingoid bases in mouse embryonic fibroblasts treated with fumonisin B_1 has been associated with decreased histone deacetylase activity and an increased acetylation of histone lysines (Gardner et al., 2016).

Evidence has been presented for the inhibition of ceramide synthase in people in Guatemala who consume corn-based foods with a high content of fumonisin B_1 (Riley et al., 2015). Individuals from this region also have a high incidence of liver cancer, although this is confounded by the presence of aflatoxin B_1 (Torres et al., 2015).

Recent evidence demonstrates that urinary fumonisin B_1 may be used to assess continuing exposure to fumonisin B_1 in population-based studies. The use of this biomarker may increase the power of current and

future epidemiological studies to uncover relationships between fumonisin B_1 exposure and the development of preneoplastic lesions and/or cancer (Riley et al., 2015; Torres et al., 2015)

Rats treated sequentially with aflatoxin B_1 and fumonisin B_1 had a synergistic increase in the number of preneoplastic liver foci compared with rats treated with either mycotoxin alone (Qian et al., 2016).

In summary, substantial new information has become available since the previous *IARC Monographs* evaluation.

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

Furan (CAS No. 110-00-9)

Furan was evaluated by the *IARC Monographs* as *possibly carcinogenic to humans* (Group 2B) (IARC, 1995), on the basis of *inadequate evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals.

Exposure Data

Furan is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

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 (NCTR, 2015; Von Tungeln et al., 2017).

Cancer in Humans

No data were identified pertaining to the carcinogenicity of furan in humans.

Cancer in Experimental Animals

Since furan was evaluated in 1995, additional bioassays have been conducted in experimental animals. Female $B6C3F_1$ mice treated orally with furan for 2 years had a dose-dependent increase in hepatocellular tumours (Moser et al., 2009). Infant male $B6C3F_1$ mice treated intraperitoneally with furan had increased incidence of hepatocellular tumours (Johansson et al., 1997). Male F344 rats exposed to furan developed malignant mesothelioma on membranes surrounding the epididymis and on the testicular tunics. There was also a dose-related increase in the incidence of mononuclear cell leukaemia. Non-neoplastic liver lesions were observed; the most sensitive were cholangiofibrosis (NCTR, 2015; Von Tungeln et al., 2017).

Mechanistic Evidence

There is evidence that furan is electrophilic. Furan is extensively metabolized, primarily by hepatic cytochrome P450 2E1, to *cis*-2-butene-1,4-dial, a highly reactive metabolite. Glutathione conjugates of *cis*-2-butene-1,4-dial have been detected in experimental animals treated with furan, and evidence has been presented for urinary *cis*-2-butene-1,4-dial amino acid adducts resulting from the degradation of proteins in rats treated with furan. DNA adducts have been characterized from the reaction of *cis*-2-butene-1,4-dial with the exocyclic nitrogens of deoxycytidine, deoxyadenosine, and deoxguanosine; however, evidence for the formation of DNA adducts derived from *cis*-2-butene-1,4-dial is minimal in tissues from rats treated with furan, even at high doses and for extended exposure times (NCTR, 2015; Von Tungeln et al., 2017).

There is evidence that furan is genotoxic. Furan is weakly mutagenic or non-mutagenic in *Salmonella typhimurium* TA100. *cis*-2-Butene-1,4-dial is mutagenic in *S. typhimurium* TA104, a strain sensitive to aldehydes. Incubation of L51788Ytk$^{+/-}$ mouse cells with furan did not result in an increase in DNA strand breaks (comet assay), whereas an increase in strand breaks was observed in incubations conducted with *cis*-2-butene-1,4-dial. Male Big Blue transgenic rats treated with furan had a significant increase in strand breaks (comet assay), but the mutant frequency was not increased (*Pig-a*, *Hprt*, or *cII*). Strand breaks were also observed in male F344 rats given furan (NCTR, 2015). The mutant frequency was assessed in male and female *gpt* delta rats administered carcinogenic doses of furan. An increase was not detected (Hibi et al., 2017).

There is evidence that furan causes epigenetic changes. Gene expression and epigenetic changes were examined in male Sprague-Dawley rats administered furan. Significant changes were observed in the expression of several genes associated with the cell cycle, apoptosis, and DNA damage. In addition to changes in gene expression, furan treatment was associated with alterations in microRNA expression, gene-specific changes in DNA methylation, and a decrease in global DNA methylation in tumour tissues. More recent studies demonstrated the occurrence of several types of tightly connected epigenetic alterations (e.g. gene-specific hypermethylation and histone H3K9me3 and H3K27me3 enrichment, gene-specific hypomethylation and histone H3K9ac and H3K27ac enrichment, and microRNA dysregulation) (de Conti et al., 2017).

Although there is a rich database of mechanistic studies relevant to key characteristics of carcinogens, such data from human systems appear sparse, but if available would justify higher prioritization.

Recommendation: Medium priority

Furfural (CAS No. 98-01-1)

Furfural was previously evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1995), on the basis of *inadequate evidence* of carcinogenicity in humans and *limited evidence* of carcinogenicity in experimental animals.

Exposure Data

Furfural is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Furfural is used widely as a solvent in petroleum refining, in the production of phenolic resins, and in a variety of other applications. Human exposure to furfural occurs during its production and use, as a result of its natural occurrence in many foods as well as its use as a food flavouring additive, and from the combustion of coal and wood (WHO, 2000b; EFSA, 2004).

Cancer in Humans

No epidemiological studies of cancer in humans were identified.

Cancer in Experimental Animals

Since the most recent IARC evaluation, no new long-term animal bioassays have been conducted. In a 13-week dietary study in rats, minor hepatocellular alterations were observed in males, but not in females (NTP, 1990).

Mechanistic Evidence

With respect to the key characteristics of carcinogens, limited evidence for genotoxicity in vitro was described. Furfuryl alcohol, evaluated by IARC as *possibly carcinogenic to humans* (Group 2B) (IARC, 2019d), is metabolized to furfural.

Recommendation: No evaluation

Furmecyclox (CAS No. 60568-05-0)

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

Exposure Data

Furmecyclox is a furamide fungicide and a wood preservative. It is “suspected of causing cancer” by the European Chemicals Agency (ECHA, 2018b), is classified as “Carc. 2” by the European Commission (EC, 2016b), is classified as B2 (“probable human carcinogen - based on sufficient evidence of carcinogenicity in animals”) by the United States Environmental Protection Agency (EPA, 1988a), and is listed as causing cancer in the Proposition 65 list by the California Office of Environmental Health Hazard Assessment (OEHHA, 2019b).

Cancer in Humans

Studies of cancer in humans were not available.

Cancer in Experimental Animals

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 (EPA, 1988b).

Mechanistic Evidence

Data relevant to key characteristics of carcinogens are sparse. Furmecyclox was negative in *Salmonella* and in an unscheduled DNA synthesis assay in marmoset hepatocytes (EPA, 1988b).

Recommendation: Low priority

Gasoline oxygenated additives

Methyl *tert*-butyl ether (MTBE) was evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1999a).

Ethyl *tert*-butyl ether (ETBE), diisopropyl ether (DIPE), *tert*-amyl methyl ether (TAME), and *tert*-butyl alcohol (TBA) have not been previously evaluated by the *IARC Monographs* programme.

The 2014 Priorities Advisory Group assigned high priority to MTBE, ETBE, and TBA (IARC, 2014).

Exposure Data

Oxygenates are gasoline additives used to improve the combustion process and, more specifically, to significantly reduce carbon monoxide emissions of motor vehicles, especially at low temperatures during winter months (Straif et al., 2014). They are also intended to dilute toxic compounds in fuels. Currently, the most widely used oxygenates are low-molecular-weight alcohols (e.g. ethanol, methanol, and isopropyl alcohol) and alcohol ethers (e.g. MTBE, ETBE, TAME, and DIPE). When mixed with gasoline, the ether oxygenates are less volatile and less water soluble than the alcohols. Therefore, ether oxygenates are less subject to evaporative loss or partitioning into water as a fuel contaminant than are alcohol additives, which improves year-round engine performance and makes for easier handling, transportation, and storage of the fuel. Most human exposure to oxygenates occurs passively through air and drinking-water. Several sources of atmospheric oxygenated additives have been identified, involving every step of production and use, from manufacture to distribution and to tailpipe emissions (Zhang et al., 2016c). Most of the atmospheric burden of oxygenated additives is due to tailpipe emissions, followed (distantly) by petroleum refineries and service stations; other sources contribute smaller amounts. Direct contamination of drinking-water may occur as a result of wastewater released during manufacture or from fuel spills and storage tank leaks. Because of their environmental mobility and resistance to biodegradation, oxygenated additives have the potential to contaminate and persist in groundwater and soil.

Cancer in Humans

Epidemiological studies have shown that the blood concentrations of MTBE and ETBE observed in exposed workers correlate positively with concentrations in their working environment (Moolenaar et al., 1994; Eitaki et al., 2011). However, very limited epidemiological evidence exists on the carcinogenic effects of oxygenates; for example, no studies of cancer in humans were identified for MTBE, ETBE, TAME, DIPE, or TBA.

Cancer in Experimental Animals

Carcinogenicity of MTBE has been observed in animals, by oral and inhalation routes. In one oral study in Sprague-Dawley rats (Belpoggi et al., 1995, 1999), MTBE was shown to cause an increase in lymphomas or leukaemias (mainly lymphoimmunoblastic lymphomas) in females and an increase in interstitial cell adenomas of the testis in males. In one inhalation study in Fischer rats performed by industry (Chun et al., 1992; Bird et al., 1997), MTBE caused an increase in interstitial cell adenoma of the testis and an increase in renal tubular tumours in males. In one inhalation study in CD-1 mice performed by industry (Burleigh-Flayer et al., 1992), a statistically significant increase in hepatocellular carcinomas was observed in males, and in adenomas and combined adenomas and carcinomas in females.

Carcinogenicity of ETBE has been observed in animals, by oral and inhalation routes. In one inhalation study in Fischer rats (JPEC, 2010; Saito et al., 2013), an increase in hepatocellular adenomas and carcinomas was observed. In one oral study in Sprague-Dawley rats (Maltoni et al., 1999), an increase in haemolymphoreticular neoplasia was observed in males and females. An initiation–promotion study by gavage in male Fischer rats suggested tumour promotion activity by ETBE (Hagiwara et al., 2011). One oral study in Fischer rats did not report significant findings (Suzuki et al., 2012).

Carcinogenicity of TAME has been observed in animals, by the oral route. In one oral study in Sprague-Dawley rats (Belpoggi et al., 2002a), an increased incidence of haemolymphoreticular neoplasias, carcinomas of the ear duct, and glial malignant tumours of the brain was observed in treated males and females; an increase in the incidence of interstitial cell adenomas of the testis was observed in males.

Carcinogenicity of DIPE has been observed in animals, by the oral route. In one oral study in Sprague-Dawley rats (Belpoggi et al., 2002a), an increased incidence of haemolymphoreticular neoplasias, carcinomas of the ear duct, and glial malignant tumours of the brain was observed in treated males and females. The onset of some interstitial cell adenomas of the testis was noted in the treated group, and a slight increase in malignant sarcomas of the uterus and vagina was observed in the treated group.

Carcinogenicity of TBA has been observed in animals, by the oral route. In one oral study in Fischer rats (NTP, 1995b), an increased incidence of renal tumours was observed in males. In one oral study in B6C3F$_1$ mice (NTP, 1995b), an increased incidence of thyroid tumours was observed in males and females.

MTBE has been considered as a carcinogenic chemical to be included in the Proposition 65 list by the California Office of Environmental Health Hazard Assessment (OEHHA, 1999), on the basis of the several findings in studies in experimental animals. ETBE is currently under review by the United States

Environmental Protection Agency's Integrated Risk Information System (IRIS) programme, and according to the draft report there is "suggestive evidence of carcinogenic potential" for ETBE in rats (EPA, 2016a). TBA is currently under review by the IRIS programme, and according to the draft report there is "suggestive evidence of carcinogenic potential" for TBA in rats and mice (EPA, 2016b).

Mechanistic Evidence

Oxygenated additives are rapidly absorbed through the respiratory and digestive systems, efficiently distributed to various tissues through blood circulation, and metabolized within hours. MTBE and ETBE are metabolically activated in the liver, leading to the generation of TBA as the major bioreactive metabolite (Hong et al., 1999).

Various studies relevant to the key characteristics of carcinogens are available. Because MTBE functions as a non-traditional genotoxicant, several mechanisms were suggested to explain its mode of action, including functioning as a cytotoxic as opposed to a mitogenic agent, involvement of hormonal mechanisms, and operating as a promoter instead of being a complete carcinogen. Some studies suggested that carcinogenicity of MTBE may be due to its two main metabolites, formaldehyde and tributanol. A role for DNA repair in MTBE carcinogenesis has been suggested, which may explain some but not all effects (Ahmed, 2001).

Mechanistic studies reported that deficient enzyme function of aldehyde dehydrogenase 2 (ALDH2) enhanced ETBE-induced genotoxicity in hepatocytes and leukocytes; this is suggestive of genotoxicity being mediated by the ETBE metabolite acetaldehyde, which is directly genotoxic (EPA, 2017a).

Key References

The following key references were also identified: Belpoggi et al. (1997); Benson et al. (2011); Borghoff & Williams (2000); Campo et al. (2016); Conaway et al. (1985); Gholami et al. (2015); Hagiwara et al. (2015); Hu et al. (2016); Li et al. (2007); Maltoni et al. (1997); McGregor (2006); O'Callaghan et al. (2014); Phillips et al. (2008); Prah et al. (2004); USDA Foreign Agricultural Service (2012); White et al. (1995); Williams et al. (2000).

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

Gentian violet (CAS No. 548-62-9)

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

Exposure Data

Gentian violet, a dye belonging to a chemical class known as di- and triaminophenylmethanes, is a mixture of crystal violet and methyl violet.

Gentian violet has been used in human medicine against fungi and intestinal parasites, in veterinary medicine against moulds and fungi, and for other uses.

Cancer in Humans

No epidemiological studies of cancer are available for gentian violet.

Cancer in Experimental Animals

Two animal bioassays were performed, one in mice and one in rats (Littlefield et al., 1985; 1989). The study in mice (Littlefield et al., 1985) was performed with 720 males and 720 females at dose levels of 0, 100, 300, and 600 ppm (mg/kg feed). Sacrifices were performed at 12, 18, and 24 months. A positive association for hepatocellular carcinoma was observed in males and females. Other dose-related toxicological responses, especially in females, included adenoma of the Harderian gland and the presence of type A reticular cell sarcomas in the urinary bladder, uterus, ovary, and vagina.

The study in rats (Littlefield et al., 1989) included 570 males and 570 females. The animals were fed gentian violet at 0, 100, 300, or 600 ppm (mg/kg feed) for 12, 18, and 24 months and then sacrificed. A significantly increased incidence of follicular cell adenocarcinomas of the thyroid was observed in both sexes at the highest exposure levels.

Mechanistic Evidence

A large number of animal and in vitro studies have been performed to study the toxicity of gentian violet (Diamante et al., 2009). With respect to the key characteristics of carcinogens, gentian violet is electrophilic and binds to DNA, inducing chromosomal breaks, as well as oxidative stress and receptor-mediated effects. There is some evidence from ToxCast assays that gentian violet has receptor-mediated effects.

Key Reference

The following key reference was also identified: JECFA (2013).

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

Glucocorticoids

Glucocorticoids have not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Glucocorticosteroids are synthetic analogues of the natural steroid hormones produced by the adrenal cortex.

Since their discovery in the 1940s, glucocorticosteroids have become one of the most widely used and effective treatments for various inflammatory and autoimmune disorders. They are widely used as replacement therapy in adrenal insufficiency; in the treatment of both acute and chronic inflammations,

including rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, psoriasis, and eczema; in the treatment of certain leukaemias; and in immunosuppressive regimes after organ transplantation (Liu et al, 2013c). Glucocorticoids (e.g. betamethasone and dexamethasone) are also routinely used in obstetrical practice in the management of women at risk of early preterm birth, which may lead to intrauterine exposure (Tegethoff et al., 2009).

Cancer in Humans

Among epidemiological studies, population-based case–control studies in the USA have reported significant positive associations of oral glucocorticoid use and risk of squamous cell carcinoma (Karagas et al., 2001) and of prolonged glucocorticoid use and incidence of bladder cancer, with a stronger association for invasive, TP53-positive (staining intensity ≥ 3) disease (Dietrich et al., 2009). In a more recent case–control study of early-onset basal cell carcinoma, there was no association with systemic glucocorticoid use (Troche et al., 2014). In studies in Denmark, there were significantly greater numbers of observed versus expected cases of both squamous cell carcinomas and basal cell carcinomas of the skin as well as non-Hodgkin lymphomas among individuals with glucocorticoid prescriptions in a record-linkage study (Sørensen et al., 2004). A population-based case–control study also reported a significant positive association of oral glucocorticoid use and risk of basal cell carcinoma (Jensen et al., 2009). There was no association of systemic glucocorticoid use and colorectal cancer risk, overall or by stage, or breast cancer risk or recurrence (Sørensen et al., 2012; Ostenfeld et al., 2013; Lietzen et al., 2014). Use of inhaled and systemic glucocorticoids was positively associated with risk of prostate cancer in the Melbourne Collaborative Cohort Study (Severi et al., 2010). Overall, the epidemiological evidence supports consistent positive associations with glucocorticoid use for several cancer sites.

Cancer in Experimental Animals

In studies in experimental animals, Zheng et al. (2012) examined the effects of dexamethasone in mouse xenograft models for bladder cancer. They found that glucocorticoids increased tumour cell proliferation while suppressing invasion and metastasis. Li et al. (2019) reported effects of corticosterone on colorectal carcinoma progression in mice.

Mechanistic Evidence

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.

Several other studies related to key characteristics of carcinogens are available, including on oxidative stress, DNA damage, receptor-mediated effects, and progression. Other studies in organ transplant recipients may provide additional supporting evidence relevant to an evaluation.

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

Glycerol (CAS No. 56-81-5)

Glycerol (glycerin) was nominated for evaluation on the basis of its commercial use and occupational exposure. No other justification was provided.

Exposure Data

Glycerol is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Glycerol is used in the food industry and in medical, pharmaceutical, and personal care applications, is a common component of electronic cigarette refill fluids ("e-liquids"), and has numerous other applications. From the National Occupational Exposure Survey 1981–1983 (NIOSH, 1983), the United States National Institute for Occupational Safety and Health statistically estimated that about 2 million people (> 50% female) were potentially exposed to glycerin in the USA. More recent estimates provide much lower estimates of the number of exposed workers. Occupational exposure to glycerin may occur through inhalation and dermal contact with this compound at workplaces where glycerin is produced or used. Use data and limited monitoring data indicate that the general population may be exposed to glycerin via ingestion of food, some pharmaceuticals, and drinking-water, and via dermal contact with consumer products containing glycerin.

Glycerol is a precursor for synthesis of triacylglycerols and of phospholipids in the liver and adipose tissue and is released into the bloodstream when the body uses stored fat as a source of energy.

Glycerol is considered a low-toxicity chemical, and irritant effects have been described only at high exposure levels.

Cancer in Humans

There is one occupational cohort study on synthetic fibre workers exposed to glycerol polyglycidyl ether (not the same as glycerol), which did not find an overall increased risk of cancer but showed increased mortality from tumours of the central nervous system (Lanes et al., 1994; Watkins et al., 2001).

Recent studies on metabolomics have examined glycerol in relation to prostate cancer and breast cancer. A breast cancer cohort study in France identified an association between baseline nuclear magnetic resonance (NMR) plasma metabolomic signatures including glycerol-based compounds and long-term risk of breast cancer (Lécuyer et al., 2018). A metabolomics study of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort of male smokers identified circulating 1-stearoylglycerol (and also

glycerol) as being statistically significantly inversely associated with risk of prostate cancer (i.e. men with higher serum 1-stearoylglycerol or glycerol levels were less likely to develop prostate cancer).

Cancer in Experimental Animals

Animal experiments have been performed and have not shown increased tumour incidence in the treated mice or rats (HSDB, 2012b). In a recent initiation–promotion study in Wistar rats on hepatocarcinogenesis, animals also received glycerol by gavage. Treatment with glycerol was found to reduce the volume of preneoplastic lesions by decreasing the proliferative status of liver foci (Capiglioni et al., 2018).

Mechanistic Evidence

Studies relevant to multiple key characteristics of carcinogens were identified.

In summary, glycerol is a chemical with a high volume of production and with presumably many workers exposed and also exposure of the general population. The limited evidence available does not indicate that it poses a cancer hazard to humans.

Key Reference

The following key reference was also identified: Mondul et al. (2015).

Recommendation: No evaluation

Glycidamide (CAS No. 5694-00-8)

Glycidamide has not been previously evaluated by the *IARC Monographs* programme. It was assigned a high priority by the 2014 Priorities Advisory Group (IARC, 2014).

Exposure Data

The primary use of glycidamide is as an intermediate in organic synthesis, for example as a synthetic intermediate in the production of dyes and plasticizers (NTP, 2014).

Glycidamide is a major metabolite of the α,β-unsaturated amide acrylamide. Therefore, the major source of human exposure to glycidamide occurs through exposure to acrylamide in occupational situations, through the diet, or by the use of tobacco products. Glycidamide has also been reported to be present in certain foods, at a level of less than 1% of that of acrylamide (NTP, 2014).

Cancer in Humans

Although the toxicity of acrylamide in humans is well documented, there are no toxicity data in humans from direct exposure to glycidamide. There are also no data pertaining to the carcinogenicity of glycidamide in humans (NTP, 2014).

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 10 mg or 50 mg of glycidamide per kg body weight (bw) 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 50 mg of glycidamide per kg bw (Olstørn et al., 2007). In another study, male $B6C3F_1$ mice injected intraperitoneally with 0.70 mmol glycidamide per kg bw on postnatal days 1, 8, and 15 had a significant increase in hepatocellular tumours that was associated with A → G and A → T mutations at codon 61 of the H-*ras* oncogene (Von Tungeln et al., 2012). Male and female $B6C3F_1$ mice exposed to glycidamide in the drinking-water at concentrations of up to 0.70 mM had significant dose-related increases in tumours of the Harderian gland, lung, forestomach, and skin. Female $B6C3F_1$ mice also had a 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 the 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 lung V79 cells, L5178Y/*Tk*$^{+/-}$ mouse 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 *Salmonella typhimurium* (various strains), L5178Y/*Tk*$^{+/-}$ mouse lymphoma cells (attributed to a clastogenic mode of action), Chinese hamster lung V79 cells (also chromosomal aberrations), Chinese hamster ovary cells, Big Blue mouse embryo fibroblasts (primarily substitutions), and human lymphoid TK6 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).

The Advisory Group recommended that an evaluation of glycidamide should be conducted together with that of acrylamide.

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

Glyphosate (CAS No. 1071-83-6)

Glyphosate was evaluated by the *IARC Monographs* programme in Volume 112 and is classified as *probably carcinogenic to humans* (Group 2A) (IARC, 2017c), on the basis of *sufficient evidence* of carcinogenicity in experimental animals and *limited evidence* of carcinogenicity in humans. In studies on cancer in humans, positive associations were observed between exposure to glyphosate and non-Hodgkin lymphoma (NHL), although the role of chance, bias, and confounding could not be ruled out. The classification of glyphosate was supported by strong evidence that (i) glyphosate or glyphosate-based formulations are genotoxic, based on studies in human cells in vitro and studies in experimental animals, and (ii) glyphosate, glyphosate-based formulations, and its major metabolite aminomethylphosphonic acid (AMPA) induce oxidative stress, based on studies in experimental animals and studies in human cells in vitro.

Exposure Data

Glyphosate is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Glyphosate is a widely used herbicide across the globe, as documented in IARC (2017c), including the use of aerial spraying of glyphosate in Latin America to reduce illegal production of cocaine, marijuana, and poppy seed. After the previous evaluation, several epidemiological studies measured levels of glyphosate and its major metabolite AMPA in environmental and biological samples.

Cancer in Humans

The recent IARC evaluation has stimulated additional research into the carcinogenicity of glyphosate. Since the evaluation in Volume 112, an extended follow-up of the United States National Cancer Institute (NCI) Agricultural Health Study (AHS) has been published (Andreotti et al., 2018). Results from an earlier follow-up of this cohort were already included and reviewed in Volume 112. Consistent with the previous results included in the *IARC Monograph*, the newly published AHS update did not find an association between NHL and glyphosate. However, the AHS update did report some evidence that glyphosate exposure may increase the risk of acute myeloid leukaemia, with a positive, non-significant association observed in the highest exposure category. The recently published Consortium of Agricultural Cohorts (AGRICOH) study, which is a pooled analysis of three large cohorts of agricultural workers (including the AHS) on exposure to several pesticides and risk of NHL reported an increased risk of a subtype of NHL (diffuse large B-cell lymphoma) but not of NHL overall (Leon et al., 2019). Other relevant epidemiological studies and analyses are in progress.

Cancer in Experimental Animals

The *IARC Monographs* evaluation (IARC, 2017c) concluded that there was *sufficient evidence* of carcinogenicity in experimental animals. Since then, additional cancer bioassay data have become publicly available (see Zhang et al., 2019a).

Mechanistic Evidence

Several new studies relevant to key characteristics of carcinogens are available, including in experimental animals and in human cells (e.g. Ghisi et al., 2016; Santovito et al., 2018; Woźniak et al., 2018).

In summary, the Advisory Group reviewed the evidence published since *IARC Monographs* Volume 112 and concluded that the evidence on cancer in humans appears to remain limited. In addition, no change is anticipated in the conclusions regarding cancer in experimental animals or mechanistic evidence. Therefore, a re-evaluation would not be warranted within the next 5 years.

Recommendation: No evaluation

Goldenseal

Goldenseal was classified by IARC as *possibly carcinogenic to humans* (Group 2B) (IARC, 2016b).

Exposure Data

Goldenseal (*Hydrastis canadensis* L.) is a perennial plant, which grows naturally in the eastern USA and Canada.

Powdered goldenseal root and leaf products are available as capsules and teas in combination with other herbs, in some over-the-counter herbal supplements. Worldwide sales of goldenseal root as a dietary supplement totalled US$ 25 million, of which appreciable sales occurred in Germany, France, and the USA (IARC, 2016b).

Goldenseal is also found in eardrops, feminine cleansing products, cold and flu remedies, allergy relief products, laxative products, and aids to digestion.

Cancer in Humans

No studies of cancer in humans are available for goldenseal root powder.

Cancer in Experimental Animals

Goldenseal was shown to induce an increase in liver tumours in rats and mice in the standard 2-year bioassay by the United States National Toxicology Program (NTP, 2010d).

Mechanistic Evidence

The toxicity of the five goldenseal alkaloid constituents was characterized in a study published in 2013. Berberine, followed by palmatine, appears to be the most potent DNA damage inducer in human hepatoma HepG2 cells. DNA damage was also observed when cells were treated with commercially available goldenseal extract (Chen et al., 2013).

Recommendation: No evaluation

Haloacetic acids (and other disinfection by-products)

Some haloacetic acids and other disinfection by-products have been previously evaluated by the *IARC Monographs* programme. Bromochloroacetic acid and dibromoacetic acid (IARC, 2013c) as well as trichloroacetic acid and dichloroacetic acid (IARC, 2013d) have been classified as *possibly carcinogenic to humans* (Group 2B). Bromodichloroacetic acid (CAS No. 71133-14-7), which was specifically nominated, has not been previously evaluated by the *IARC Monographs* programme. The 2014 Priorities Advisory Group assigned high priority to disinfection by-products in disinfected water used for showering, bathing, swimming, or drinking (IARC, 2014).

Exposure Data

Humans are exposed to haloacetic acids and trihalomethanes, including bromodichloroacetic acid, as the predominant by-products of drinking-water disinfection (WHO, 2004).

Exposures were considerably higher before the introduction in the 1980s of regulations limiting levels of trihalomethanes in drinking-water. Formation of haloacetic acid and other disinfection by-products is dependent on the relationship between chlorine, the most commonly used water disinfectant, and organic matter in the treated water, in addition to other physicochemical conditions during and after the disinfection process. In the USA, trihalomethanes make up the largest group of drinking-water disinfection by-products by weight (58%), followed by haloacetic acids (36%). Almost all people exposed to disinfected drinking-water are exposed to the associated disinfection by-products via plain tap water, instant drinks, and food. Dermal and inhalation exposures (e.g. from swimming pools and spa baths) are possible, as are occupational hazards (e.g. water treatment plant employees, swimming pool attendants). The United States National Toxicology Program (NTP) is evaluating the carcinogenicity of 13 haloacetic acids that are regulated by the United States Environmental Protection Agency or considered for regulation; 11 of these have been identified in disinfected water in the USA, and the remaining two may be formed under experimental conditions. Considerations include the carcinogenicity of individual drinking-water by-products, as well as whether these chemicals should be considered members of a class of carcinogens (NTP, 2018e).

Cancer in Humans

Hrudey et al. (2015) reported on the evaluation of an interdisciplinary panel convened to review scientific evidence on the association of chlorination disinfection by-products and human bladder cancer. The panel concluded that there was evidence for an association on the basis of 10 case–control studies with original data collected before 2001. More recent studies reflecting current exposure levels and using other study designs may provide additional data for judging the evidence of carcinogenicity in humans (Hrudey et al., 2015). Two meta-analyses of historical case–control studies indicated support for an association between chlorination disinfection by-products and bladder cancer, although it should be noted that the two meta-analyses share most of the same case studies. A plausible mechanism of action involving glutathione *S*-transferase theta 1 has been postulated (DeMarini et al., 1997; Pegram et al., 1997; Cantor et al., 2010; Cortés & Marcos, 2018).

Links between drinking-water disinfection by-products and various cancer types were evaluated in a cohort of postmenopausal women using historical water treatment and monitoring data. The Iowa Women's Health Study evaluated the risk of kidney cancer (Jones et al., 2017a), pancreatic cancer (Quist et al., 2018), and colorectal cancer (Jones et al., 2019). No positive associations were identified between exposure and pancreatic cancer or kidney cancer. Limited data indicate a positive association of exposure to haloacetic acids and trihalomethanes for rectal cancer, but "require further investigations in study populations with higher exposures" (Jones et al., 2019).

Cancer in Experimental Animals

Carcinogenicity of bromodichloroacetic acid has been observed in experimental animals, by the oral route. In one drinking-water study in Fischer rats (NTP, 2015a), male rats that received bromodichloroacetic acid had increased incidence of malignant mesothelioma and a variety of skin tumours. Exposed female rats had increased incidence of fibroadenoma and carcinoma of the mammary gland. There were a few occurrences of uncommon tumours of the oral cavity, large intestine, and mammary gland in exposed male rats and of uncommon brain tumours in exposed male and female rats. In one drinking-water study in $B6C3F_1$ mice (NTP, 2015a), increased incidence of malignant liver tumours (hepatocellular carcinomas and hepatoblastomas) was seen in male and female mice. Exposed male mice had increased incidence of adenomas and carcinomas of the Harderian gland (NTP, 2015a).

More broadly, the 2018 NTP monograph evaluating the carcinogenicity of drinking-water disinfection by-products summarized findings from 41 studies in experimental animals, 36 of which were carcinogenicity studies (NTP, 2018e). In these studies, the animals were exposed (at multiple doses) to 7 of the 13 haloacetic acids reviewed in the monograph. Studies were conducted in rats and mice, and all but 3 of the 41 studies exposed the animals by gavage or via drinking-water. In exposed rodents, di- and trihaloacetic acids increased liver neoplasms. In addition, malignant mesotheliomas were induced by the three bromide-containing haloacetic acids. Other specific haloacetic acids increased the incidence of mononuclear cell leukaemia, lung adenoma and adenoma or carcinoma (combined), large intestine

neoplasms, mammary gland fibroadenomas and other neoplasms, pancreatic islet adenomas, various skin and epithelial tumours, and brain neoplasms.

Mechanistic Evidence

Bromodichloroacetic acid was tested in two independent bacterial gene mutation assays. In the first assay, conducted with an uncharacterized sample of bromodichloroacetic acid, the compound was judged to be weakly positive on the basis of responses seen in *Salmonella typhimurium* strain TA97 in the presence of rat or hamster S9 metabolic activation enzymes; an equivocal response was obtained in TA97 in the absence of S9, and no mutagenic activity was seen in strains TA98, TA100, or TA1535. In the second assay, conducted with the same well-characterized lot of bromodichloroacetic acid that was used in the animal bioassays mentioned above, positive responses were seen in *S. typhimurium* strains TA97, TA98, and TA100 and the *Escherichia coli* strain WP2 uvrA/pkM101 in the absence of S9. With rat S9, equivocal responses were seen with the three *S. typhimurium* tester strains, and a positive response was observed in the *E. coli* strain (NTP, 2015a).

Gene expression analysis in rats exposed to bromodichloroacetic acid showed a positive trend in the number of genes associated with human breast cancer, with proportionately more genes represented in tumours from the group treated with bromodichloroacetic acid. In addition, a five-gene signature representing possible activation of the Tgfβ pathway was observed in adenocarcinomas from the group treated with bromodichloroacetic acid, suggesting that this pathway may be involved in the increased incidence of mammary tumours in animals exposed to bromodichloroacetic acid (Harvey et al., 2016).

More broadly, *Salmonella* mutagenicity assays indicate that chlorination or chloramination results in finished tap water that is mutagenic. Several bacterial and mammalian genotoxicity assays indicate that disinfection by-products are genotoxic, as do in vivo plant, *Caenorhabditis elegans*, and zebrafish assays (Cortés & Marcos, 2018). In vitro exposure of human urothelial (T24) cells to haloacetic acids indicated that acute exposures were genotoxic. After long-term exposure, cells developed resistance to oxidative stress (Marsà et al., 2018).

The NTP monograph (NTP, 2018e) summarized in vitro tests of individual haloacetic acids in human and rodent cell lines, supporting several key characteristics of carcinogens, including effects on oxidative stress, genotoxicity, and alteration of DNA repair. Furthermore, in vivo evidence of DNA and chromosomal damage after exposure is available in zebrafish, *Drosophila*, amphibians, rodents, and chickens (NTP, 2018e). Other relevant studies have assessed effects from swimming pool exposures (Kogevinas et al., 2010; Espín-Pérez et al., 2018; van Veldhoven et al., 2018).

Therefore, haloacetic acids express many of the key characteristics of carcinogens, including electrophilicity and the ability to cause oxidative stress, induce genotoxicity, alter DNA repair, alter the cell cycle, alter nuclear receptor signalling, and alter cell proliferation or cell death (Richardson et al., 2007; NTP, 2018e).

The Advisory Group noted that disinfection by-products are a complex mixture, not limited to haloacetic acids. Bromodichloroacetic acid is a haloacetic acid and should be considered together with others in this class of disinfection by-products.

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

Heavy metals (as a mixture)

Exposure Data

In the environment, living organisms are exposed to multiple xenobiotics, such as metals, through different routes as a result of environmental and occupational variability. Heavy metals are ubiquitous and generally persist in the environment, enabling them to biomagnify in the food chain. Although varied health effects are associated with exposure to single metals, information on toxicity and associated mechanisms for metal mixtures, especially in low doses, is limited.

Exposure to heavy metals presents significant health concerns in the human population. These elements have the ability to induce several adverse health effects. One of their more serious actions is their role in carcinogenesis.

Cancer in Humans

There is evidence from both studies in experimental animals and studies in humans to support heavy metals as risk factors for many types of cancer, including breast cancer, oral cancer, ovarian cancer, and lung cancer. In ecological studies, associations between concentrations of heavy metals in drinking-water and total cancer incidence were observed in Turkey (Colak et al., 2015). There were weak correlations between concentrations of heavy metals in soil and oral cancer mortality in Taiwan, China (Lin et al., 2014). There were few significant correlations between concentrations of heavy metals both in soil and in grain and levels of heavy metals in cancer tissue from patients with lung cancer, liver cancer, and gastric cancer in eastern China (Zhao et al., 2014). Positive associations between levels of heavy metals and metalloids in topsoil and digestive system tumour mortality were observed in Spain (Núñez et al., 2017). The Advisory Group noted that ecological studies provided limited evidence for causality.

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

Some studies have suggested associations between heavy metals in breast cancer tissue and indicators of tumour progression (Romaniuk et al., 2015; 2017). Heavy metals in cigarette smoke induced accumulation of reactive oxygen species and increased expression of anti-apoptotic markers in breast epithelial cells

(Mohapatra et al., 2014). In a mouse model, exposure to particulate matter from chromium-containing gas metal arc stainless steel welding was found to act in tumour promotion (Zeidler-Erdely et al., 2013).

Heavy metals, through different pathogenetic links, stimulate the progression of breast cancer and reduce its sensitivity to treatment. They can cause tumour progression and destabilization of the genome, which is reflected in increased DNA fragmentation. Exposure of biological systems to heavy metals may lead to oxidative stress, which may induce DNA damage, protein modification, lipid peroxidation, and other effects.

In summary, the Advisory Group noted that several individual heavy metals are already classified as *carcinogenic to humans* (Group 1), which would complicate the evaluation of heavy metals as a class, and a recommendation was made to continue to evaluate heavy metals individually.

Key References

The following key references were also identified: Chiu et al. (2004); Wang & Fowler (2008); Su et al. (2010); Antwi et al. (2015); Wu et al. (2016); Carver & Gallicchio (2017); Rockfield et al. (2017); Vigneri et al. (2017); Marouf (2018).

Recommendation: No evaluation

Hepatitis D virus

Hepatitis D virus (HDV) was evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1994c).

HDV, a small RNA virus that requires hepatitis B virus (HBV) for its life-cycle, is the most pathogenic hepatitis virus. Compared with individuals infected with HBV alone, people co-infected with HBV and HDV experience much more rapid progression of liver disease to cirrhosis and hepatocellular carcinoma (Mahale et al., 2019). Data on the prevalence of HDV infection are limited, but it is estimated that 15–20 million people worldwide are infected with HDV. In some countries, HDV infection may contribute substantially to the burden of hepatocellular carcinoma. For example, in Mongolia, the country with the highest incidence of hepatocellular carcinoma in the world, a recent population-based serosurvey found that more than half of individuals with chronic hepatitis B were co-infected with HDV. Limited data from sub-Saharan Africa suggest localized clusters of HDV endemicity in that region (Stockdale et al., 2017). There is no vaccine for HDV; successful HBV vaccination will prevent HDV infection. Currently, treatment for chronic hepatitis D is limited; however, several promising agents are in clinical trials. Some data suggesting potential mechanisms of carcinogenesis have been published (Negro, 2014; Diaz et al., 2018).

Recommendation: Low priority

Hexachlorobenzene (organochlorine fungicide) (CAS No. 118-74-1)

Hexachlorobenzene was classified by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) (IARC, 2001), on the basis of *inadequate evidence* of carcinogenicity in humans and *sufficient evidence* in experimental animals for the carcinogenicity of hexachlorobenzene.

Exposure Data

Hexachlorobenzene is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Hexachlorobenzene (also known as perchlorobenzene) is an organochlorine fungicide that was used as a seed treatment (for wheat, barley, oats, and rye) and has been restricted in its production and use since the early 1970s. It is a persistent organic pollutant listed in Annex III of the Rotterdam Convention (Rotterdam Convention, 2011b) with no consent to import in most countries of the world, except for Benin, Nigeria, Singapore, and Togo (only under specified conditions). Despite its prohibition in most countries, hexachlorobenzene residues persist in soil and rivers, resulting in widespread contamination of the general population, and measurable amounts are still found in human tissues.

Cancer in Humans

Since 2001, there have been new epidemiological studies or meta-analyses investigating the possible association between organochlorine pesticide levels in humans and various cancer types: cancers of the thyroid, prostate, breast, testis, and pancreas and non-Hodgkin lymphoma; however, the findings are not expected to change the current classification. The existing epidemiological data do not support the hypothesis that exposure to hexachlorobenzene is associated with an increased incidence of cancer of the thyroid (Lerro et al., 2018b), prostate (Lewis-Mikhael et al., 2015), or breast (López-Carrillo et al., 2002; Pavuk et al., 2003; Charlier et al., 2004; Iwasaki et al., 2008; Itoh et al., 2009; Arrebola et al., 2015). The studies on breast cancer investigated populations in different regions of the world: Japan, Mexico, Slovakia, and Tunisia. A case–control study of testicular cancer in Sweden found no significant differences in the concentrations of hexachlorobenzene between cases and controls, although in general mothers of cases had higher concentrations of hexachlorobenzene (Hardell et al., 2006). A study of exocrine pancreatic cancer in Sweden based on a low number of cases found a significantly increased concentration of hexachlorobenzene in the cases (Hardell et al., 2007). Population-based case–control studies in the USA and Canada showed conflicting results for the association of serum levels of hexachlorobenzene and risk of non-Hodgkin lymphoma (Cantor et al., 2003; Spinelli et al., 2007).

Cancer in Experimental Animals

IARC Monographs Volume 79 (IARC, 2001) concluded that there was *sufficient evidence* of carcinogenicity in experimental animals, on the basis of an increase in the incidence of cancers of the liver, thyroid, and kidney in oral studies.

Mechanistic Evidence

Numerous studies are available that investigated the possible mechanisms of hexachlorobenzene (Starek-Świechowicz et al., 2017) and are relevant to several key characteristics of carcinogens; however, it is not clear that they would support a revision of the current classification.

Recommendation: No evaluation

Human cytomegalovirus

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

Exposure Data

Human cytomegalovirus (HCMV), also known as human herpesvirus 5 (HHV-5), is a ubiquitous herpesvirus that leads to lifelong latent infection in most adults worldwide. Upon primary infection or reactivation, it can cause severe or fatal complications in fetuses and immunocompromised individuals (Sinclair & Sissons, 2006; Savva et al., 2013; Lichtner et al., 2014; Mc Bride et al., 2019).

Cancer in Humans

The role of HCMV in the pathogenesis of cancer has been investigated recently. The presence of the HCMV genome and RNA in tumour tissue has been reported for several cancer types, including cancers of the breast and colorectum (Chen & Chan, 2014; Pasquereau et al., 2017), medulloblastoma (Hortal et al., 2017), and glioblastoma (Xing et al., 2016; Yang et al., 2017a). There are currently very few cohort and case–control studies of cancer incidence. Recent case series and studies on survival in humans have pointed to a potential role, albeit inconclusive, for HCMV in glioblastoma. Studies have shown: (i) increased 2-year survival in patients with low-grade HCMV infection; (ii) positive results in an intervention study of antiviral treatment in patients with glioblastoma; (iii) increasing levels of anti-HCMV immunoglobulin G associated with decreasing risk of glioma; and (iv) HCMV-negative non-cancer cells in close proximity to the tumour (Rahbar et al., 2012; Lehrer, 2012; Amirian et al., 2013; Stragliotto et al., 2013). In 2011, a symposium on HCMV and glioma reached the consensus that HCMV exists in the majority of malignant glioma (Dziurzynski et al., 2012), and although a more recent meta-analysis also reported an association between HCMV and glioma (Farias et al., 2019), the authors pointed out that reverse causation has not been excluded as an explanation for the association.

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

A large literature has investigated how HCMV could be involved in cancer (reviewed in Herbein, 2018). Several mechanisms have been proposed, including "oncomodulation" (e.g. to favour the progression and the spread of the tumour), activation of pro-oncogenic pathways (e.g. leading to most hallmarks of cancer as described by Hanahan & Weinberg, 2011), and direct cell transformation.

The Advisory Group considered that although epidemiological evidence of a role for HCMV in cancer incidence is inconclusive, mechanistic evidence of such a role is more persuasive.

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

Human papillomavirus genus beta (β-HPV): cutaneous types

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

Exposure Data

Human papillomavirus types of genus beta (β-HPVs) are abundantly found on skin surfaces and hair follicles in the general population. DNA of β-HPVs can be detected very early in life, and the incidence increases with age. Transmission of β-HPVs occurs through direct skin contact, and asymptomatic infections may persist for several years (Sichero et al., 2019).

Cancer in Humans

Recently, there has been a growing focus on the prevalence, disease association, and functional analysis of β-HPVs. However, there are many challenges in finding relevant associations, because these viruses are not only highly heterogeneous but also ubiquitously distributed throughout the human body, thus hampering the identification of clinically relevant infections. Distinct biomarkers of infection with β-HPVs have been incorporated into numerous epidemiological studies investigating the association between infection with β-HPVs and non-melanoma skin cancer, especially in cutaneous squamous cell carcinoma (cSCC) (Sichero et al., 2019). A meta-analysis incorporating 14 studies indicated a significant association between overall β-HPV and cSCC, as well as a significant association between HPV subtypes 5, 8, 17, 20, 24, 38, respectively, and cSCC (Chahoud et al., 2016). Two prospective studies showed that multiplicity of β-HPV infection and higher β-HPV viral load were associated with development of cSCC among organ transplant recipients (Sichero et al., 2019). A recent nested case–control study showed that the detection of oral β1-HPV5 and β2-HPV38 types is associated with an increased risk of oropharyngeal, oral cavity, and

laryngeal SCCs (Agalliu et al., 2016). The Advisory Group noted that although case–control studies have shown associations of β-HPV with skin cancer, β-HPV has not been shown to integrate into tumour DNA (which is a known mechanism for HPV). β-HPV has also been shown to be associated with other skin lesions that are presumed to be non-causal.

Cancer in Experimental Animals

No new animal cancer bioassays are available.

Mechanistic Evidence

The oncogenic and transforming capacity of the epidermodysplasia verruciformis HPV types has been shown not only in transgenic mouse models but also in organotypic raft cultures under in vitro conditions.

Two kinds of mouse models have demonstrated a "hit-and-run" mechanism for an opportunistic role of β-HPVs in development of skin cancer. β-HPVs apparently interfere with their host cell at the beginning of the multi-step process of carcinogenesis, finally leading to an intracellular environment that counteracts episomal DNA replication (Hasche et al., 2018). Persistent β-HPV infections could possibly stimulate tumour progression by favouring the accumulation of ultraviolet radiation-induced mutations in the host genome, which would eventually result in cell transformation.

Human papillomavirus genus alpha (α-HPV): mucosal types

Several mucosal HPVs have been classified as *carcinogenic to humans* (Group 1). These are considered as high-risk mucosal HPVs and recognized as etiological agents of cervical cancer. Several other HPV types of the alpha genus that are closely related to the high-risk HPVs classified in Group 1 have been classified as *probably carcinogenic to humans* (Group 2A) or *possibly carcinogenic to humans* (Group 2B) because of limited evidence at the time of the most recent evaluation (IARC, 2012e). Testing for high-risk HPV types is being incorporated into cervical cancer screening to improve cervical cancer prevention. The screening tests used are based on the classification in *IARC Monographs* Volume 100B. Mucosal HPVs are also involved in carcinoma in other part of the genitalia and in cancers of the head and neck (Mena et al., 2018; de Sanjosé et al., 2019; ICO, 2019).

Recommendation: Low priority

Hydrazobenzene (CAS No. 122-66-7)

Hydrazobenzene has not been previously evaluated by the *IARC Monographs* programme, but it has been reviewed by the United States National Toxicology Program (NTP, 2016b).

Exposure Data

Hydrazobenzene (1,2-diphenylhydrazine) has been used as an industrial intermediate primarily in benzidine dye manufacturing. Benzidine dyes have not been produced for several decades in the USA, although they may still be used in other countries.

Cancer in Humans

No studies of cancer in humans were identified for hydrazobenzene.

Cancer in Experimental Animals

Evidence for carcinogenicity is almost entirely limited to an early NTP study (NTP, 1978b). In that study, administration of hydrazobenzene in feed caused an increased incidence of hepatocellular carcinoma and Zymbal gland squamous cell neoplasms in male rats, and of benign liver tumours and mammary adenocarcinomas in female rats. Exposure to hydrazobenzene also caused an increased incidence of hepatocellular carcinoma in female mice (NTP, 1978b).

Mechanistic Evidence

A more recent 13-week study in F344 rats administered hydrazobenzene via feed focused on the dose–response for hepatotoxicity (Dodd et al., 2012). Other mechanistic data are sparse.

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 for this chemical.

Recommendation: Medium priority

Hydrochlorothiazide (CAS No. 58-93-5)

Hydrochlorothiazide was classified by IARC as *possibly carcinogenic to humans* (Group 2B) (IARC, 2016b), on the basis of *limited evidence* for an association with squamous cell carcinoma of the skin and lip in humans; there was also *limited evidence* of carcinogenicity in experimental animals.

Exposure Data

Hydrochlorothiazide is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Hydrochlorothiazide is a commonly used diuretic in the treatment of hypertension and fluid retention. It is often used in combination with other antihypertensive medications. In addition to effects on the kidney, hydrochlorothiazide has photosensitizing properties, enhancing sensitivity of the skin to sunlight exposure.

Cancer in Humans

At the time of the previous evaluation, there were few epidemiological studies at other cancer sites, including the kidney, breast, gall bladder, colon, prostate, and endometrium, and potential confounding by drug indication was of concern. Among epidemiological studies published since the previous evaluation, a Danish registry-based case–control study reported a significant positive association of ever hydrochlorothiazide use and risk of squamous cell carcinoma of the lip (Pottegård et al., 2017). There was also a significant positive trend with category of cumulative dose. There were also significant positive associations of both ever use and high use of hydrochlorothiazide and risk of malignant melanoma (Pottegård et al., 2018), and significant positive trends of categories of cumulative hydrochlorothiazide dose and risk of non-melanoma skin cancer, particularly squamous cell carcinoma (Pedersen et al., 2018a), as well as risk of Merkel cell carcinoma and malignant adnexal skin tumours (Pedersen et al., 2019). Potential residual confounding by lifestyle factors, such as sun exposure or tobacco smoking, as well as skin phenotype may be of concern.

Cancer in Experimental Animals

No new animal carcinogenicity bioassays were identified since the *IARC Monographs* Volume 108 (IARC, 2016b) evaluation of *limited evidence* of carcinogenicity in experimental animals.

Mechanistic Evidence

Mechanistic evidence relevant to several key characteristics of carcinogens is available, but it is mixed. As described in Volume 108 (IARC, 2016b), hydrochlorothiazide was not mutagenic in bacterial assays, had cytotoxic effects and was mutagenic in the mouse lymphoma assay, and induced sister chromatid exchange, but not chromosomal aberration, in Chinese hamster ovary cells. It induced micronucleus formation and chromosome breakage in human lymphocytes.

In the presence of ultraviolet A irradiation, hydrochlorothiazide enhanced the production of DNA cyclobutane–pyrimidine dimers, both in isolated DNA and in the skin of mice deficient in DNA repair. The Advisory Group noted the possibility of drug-related photosensitization, which would cause DNA damage (production of dimers by hydrochlorothiazide in the presence of sunlight) and could also lead to a chronic inflammatory reaction in the skin. The Advisory Group noted that it may be worthwhile to consider evaluating other photosensitizing drugs together with hydrochlorothiazide.

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

Hydroquinone (CAS No. 123-31-9)

Hydroquinone was previously evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1999b), on the basis of *inadequate evidence* of carcinogenicity in humans and *limited evidence* of carcinogenicity in experimental animals.

Exposure Data

Hydroquinone is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Exposure to hydroquinone may occur during its production and its use as an inhibitor, antioxidant, and intermediate in the production of dyes, paints, motor fuels, and oils. Hydroquinone occurs naturally in certain plant species. Hydroquinone has been widely used in cosmetics as a skin-lightening agent. Hydroquinone may also be contained in tobacco smoke.

Cancer in Humans

No new epidemiological studies of cancer in humans were identified.

Cancer in Experimental Animals

Since the latest IARC evaluation, a new carcinogenicity study in experimental animals was conducted. The 10-month study in rats provided evidence that a metabolite of hydroquinone (2,3,5-tris(glutathion-*S*-yl)hydroquinone) may cause formation of renal adenomas and carcinomas (Lau et al., 2001).

Mechanistic Evidence

With respect to the key characteristics of carcinogens, limited data are available, with some evidence for genotoxicity as well as induction of oxidative stress and inflammation. There are assumptions that the carcinogenicity of benzene, classified by IARC as *carcinogenic to humans* (Group 1) (IARC, 2018b), may be – at least partially – mediated through hydroquinone as a metabolite, and this may provide indirect concern for the carcinogenicity of hydroquinone. Other, more recent results include the finding that hydroquinone induction of the FOXP3-ADAM17-Lyn-Akt-p21 signalling axis promotes malignant progression of human leukaemia U937 cells (Chen et al., 2017b). However, it should be noted that hydroquinone has also been found to have anticancer activity in mouse cancer cells (Byeon et al, 2018).

Key References

The following key references were also identified: Gowans et al. (2005); McGregor (2007).

Recommendation: No evaluation

2-Hydroxy-4-methoxybenzophenone (CAS No. 131-57-7)

2-Hydroxy-4-methoxybenzophenone (HMBP) has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

HMBP is listed by the United States Environmental Protection Agency as a High Production Volume chemical.

HMBP is an ultraviolet filter that is approved for use in sunscreen formulations and is also used to some extent in industrial products such as plastics and coatings. Because of its ubiquitous use, HMBP is found at high population frequency in human urine in biomonitoring studies. HMBP is effective at preventing ultraviolet radiation-induced DNA damage in animal models while also causing phototoxicity under certain conditions. Most investigative studies have focused on estrogenic and other endocrine effects, because this class of compounds (benzophenones) has been shown to affect estrogen receptor-mediated activities.

Cancer in Humans

No studies of cancer in humans were identified.

Cancer in Experimental Animals

The United States National Toxicology Program (NTP) has conducted 2-year chronic toxicity and carcinogenicity studies of HMBP in rats and mice. Results of these studies are available in the form of data file downloads on the NTP website, and a technical report (TR-597) is in preparation (NTP, 2019g). The available data files indicate a significant increase in the incidence of thyroid adenoma or carcinoma and uterus stromal polyp or sarcoma in female rats for only one of the treatment groups.

Mechanistic Evidence

A few recent publications described inflammatory effects in human cells, association with oxidative stress in exposed people, and increased cell proliferation in mice in vivo. HMBP was included in the Tox21 and ToxCast programmes. The United States Environmental Protection Agency CompTox dashboard indicates that it was active in 57 of 500 assays. Responses that occurred below cytotoxic concentrations included nuclear receptor activation (estrogen receptor, pregnane X receptor) and induction of inflammatory cytokines (IL-1α, CCL26).

Key References

The following key references were also identified: Watkins et al. (2015); Phiboonchaiyanan et al. (2017); Ao et al. (2018); LaPlante et al. (2018); EPA (2019c).

Recommendation: Low priority

5-(Hydroxymethyl)-2-furfural (HMF) (CAS No. 67-47-0)

5-(Hydroxymethyl)-2-furfural (HMF) has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

HMF is a common product of the Maillard reaction and is found in many foods and beverages, including bread, coffee, and alcoholic beverages, leading to ubiquitous exposure of the population worldwide (Husøy et al., 2008; Monakhova & Lachenmeier, 2012).

Cancer in Humans

There were no studies identified of cancer in humans exposed to HMF.

Cancer in Experimental Animals

In several studies in experimental animals, HMF promoted azoxymethane-initiated aberrant crypt foci and microadenoma. In bioassays performed by the United States National Toxicology Program, HMF gave negative results in rats and male mice but caused liver tumours in female mice (NTP, 2010b).

Mechanistic Evidence

Although HMF gave negative results in standard assays for genotoxicity, its sulfotransferase-catalysed metabolite, 5-sulfoxymethyl-2-furfural, exhibits several key characteristics of carcinogens, such as being electrophilic, genotoxic, and cytotoxic; this may be important for humans, who have higher expression of sulfotransferases than rodents do (Surh et al., 1994).

Recommendation: No evaluation

Indole-3-carbinol (CAS No. 700-06-1)

Indole-3-carbinol (I3C) has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

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).

Cruciferous vegetables are considered to have a protective effect on cancer, which has been attributed in part to isothiocyanates and indoles (Bosetti et al., 2012), including I3C (Katz et al., 2018; Bosetti et al., 2012; Baena Ruiz & Salinas Hernández, 2016).

Cancer in Humans

Epidemiological evidence of a potentially protective association has come from case–control, cohort, and clinical trials, but there have been some conflicting results (e.g. Thomson et al., 2017; Kiselev et al., 2018; Zhao et al 2017).

Cancer in Experimental Animals

In a bioassay performed by the United States National Toxicology Program (NTP, 2017), I3C increased 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, hepatocellular carcinoma, hepatoblastoma, and their combination (NTP, 2017). I3C has been shown to inhibit tumorigenesis in rodents (Benninghoff & Williams, 2013; Baena Ruiz & Salinas Hernández, 2016; de Moura et al., 2018).

Mechanistic Evidence

In mechanistic studies, I3C exhibits a broad spectrum of effects relevant to key characteristics of carcinogens and/or cancer prevention, including impacts on apoptosis, cell-cycle progression, hormonal homeostasis, DNA repair, angiogenesis, and multiple drug resistance (Weng et al., 2008). I3C undergoes metabolic transformation in vivo through a process of acid-catalysed dehydration and condensation to form oligomeric metabolites, which include 3,3′-diindoylmethane and indolo[3,2-*b*]-carbazole as well as a linear trimer, a cyclic trimer, and a cyclic tetramer (Weng et al., 2008).

Key References

The following key references were also identified: Verhoeven et al. (1996); Liu et al. (2012, 2013a); Liu & Lv (2013); Wu et al. (2013a, b, 2019); Zhao & Zhao (2013); Han et al. (2014); Angelino et al. (2015); Li et al. (2015b); Adwas et al. (2016); Fujioka et al. (2016); Schwingshackl & Hoffmann (2016); He et al. (2017).

Recommendation: Medium priority

Inorganic lead compounds

Inorganic lead compounds have been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1987, 2006b) and are classified as *probably carcinogenic to humans* (Group 2A), on the basis of *sufficient evidence* of carcinogenicity in experimental animals and *limited evidence* of carcinogenicity in humans. Epidemiological evidence indicated positive associations of occupational exposures to lead with cancers of the stomach, lung, kidney, and brain, but not in all studies. The 2014 Priorities Advisory Group recommended a re-evaluation with medium priority, depending on the availability and results of pooled analyses of workers in the countries with biomonitoring for lead exposure (IARC, 2014).

Exposure Data

Lead (CAS No. 7439-92-1) is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Lead has been used in plumbing and tableware for thousands of years; its use increased progressively with industrialization. The use of lead in pipes and plumbing, paints and pigments, and gasoline additives has been phased out in many countries; currently, the predominant use of lead is in lead–acid batteries and, to a lesser extent, in construction materials and lead-based chemicals.

The dispersion of lead throughout the global environment and consequent human exposure have arisen predominantly from the widespread use of leaded gasoline. Some geographical areas, for example those near lead mines and smelters, have high environmental concentrations of lead. The past and present use of lead-based paints increases the potential for localized exposure to lead-contaminated dust. Despite the persistence of lead in the environment, human exposure has decreased substantially in countries where control measures have been implemented in recent decades.

Other sources of exposure to lead include individual activities (e.g. smoking, certain crafts and hobbies), occupational activities (e.g. mining, primary and secondary smelting, production of lead–acid batteries, pigment production, construction and demolition), and small-scale industries (e.g. jewellery making, ceramics, leaded glass).

Cancer in Humans

Results from new epidemiological studies are generally inconsistent; however, for some cancer sites the strength of the evidence is increasing. Significant positive trends with blood lead levels were reported for lung cancer, and borderline significant trends were reported for brain cancer, bladder cancer, and laryngeal cancer (e.g. Rajaraman et al., 2006; Chowdhury et al., 2014), including in a pooled cohort in Finland, the United Kingdom, and the USA (Steenland et al., 2017). Most results were consistent across all three cohorts. In a small subsample of the cohort in the USA, no association between smoking and blood lead levels was observed. Pooled incidence analyses from two of the three cohorts supported a positive association with brain cancer and lung cancer and also reported increased risks for other cancer types (Steenland et al., 2019). However, significant interactions by country were found for lung cancer and brain cancer: data from Finland showed strong positive trends, and data from Great Britain showed modest trends or no trends. Increased risks of meningioma in genetically susceptible individuals were observed in a study based on a small number of exposed cases with a variant genotype.

Cancer in Experimental Animals

The most recent IARC evaluation of inorganic lead compounds as *probably carcinogenic to humans* (Group 2A) (IARC, 2006b) was based on *sufficient evidence* of carcinogenicity in experimental animals.

Mechanistic Evidence

In both humans and experimental animals, absorbed lead is rapidly distributed from blood plasma simultaneously into erythrocytes, soft tissues, and bone. After oral ingestion, inorganic lead that has not been absorbed in the gastrointestinal tract is excreted in the faeces. Absorbed lead is excreted in the urine and, via the bile, in the faeces. Excretion of lead through sweat is of minor importance (IARC, 2006b).

Numerous studies have been published about the effects of inorganic lead compounds on the key characteristics of carcinogens. In particular, the genotoxic effect of inorganic lead compounds has been shown in many studies (García-Lestón et al., 2010). Inorganic lead induces DNA damage in humans in vivo and in vitro, and in non-mammalian experimental systems (García-Lestón et al., 2010; Carmona et al., 2011; McKelvey et al., 2015; Delmond et al., 2019). Mutagenicity was shown in workers from two different factories engaged in the production of lead–acid batteries and glass chips (García-Lestón et al., 2010). Several studies reported increases in the frequency of chromosomal aberrations in human populations exposed to inorganic lead compounds. Treatment of human leukocytes with lead acetate for 24 hours showed clearly elevated frequencies of achromatic lesions, chromatid breaks, and isochromatid breaks in 72-hour cultures (Beek and Obe, 1974; García-Lestón et al., 2010). Increases in the rate of chromosomal aberrations were found in several studies in mammalian and non-mammalian experimental systems (García-Lestón et al., 2010). Micronuclei were induced in exposed workers, in human cells in vitro, and in non-human mammals in vivo and in non-human mammalian systems in vitro (García-Lestón et al., 2010.

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

Isoflavones

Genistein, as well as isoflavones or phytoestrogens more broadly, have not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Genistein (CAS No. 446-72-0) is an isoflavone that possesses weak estrogenic activity. Human exposure derives primarily from consumption of soybeans and soy products as well as other legumes, and is highest in Asian countries (Spagnuolo et al., 2015; Applegate et al., 2018). A database on the isoflavone content of foods, including estimates for genistein specifically, is publicly available (Bhagwat et al., 2008).

Cancer in Humans

Several systematic reviews and meta-analyses have reviewed the epidemiological evidence of associations of genistein, and other phytoestrogens, as well as soy consumption more broadly with cancer risk; the numbers of included studies ranged from approximately 10 to 30, depending on the exposure metric considered. Inverse associations of dietary genistein and risk of prostate cancer (He et al., 2015a; Zhang et al., 2016a, 2017a; Applegate et al., 2018) and of serum genistein concentrations and risk of both breast and

prostate cancer (Rienks et al., 2017) were observed, particularly among studies in Asian populations. In contrast, there was no association of circulating genistein and prostate cancer risk in a nested case–control study in the European Prospective Investigation into Cancer and Nutrition study (Travis et al., 2012). A recent analysis in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial reported a positive association of dietary genistein and risk of advanced prostate cancer (Reger et al., 2018). There are fewer studies at other cancer sites. In an analysis of postmenopausal women in the Multiethnic Cohort Study, there was a significant inverse association of dietary genistein and risk of endometrial cancer (Ollberding et al., 2012). Although some studies have limitations, including heterogeneity in assessment of genistein exposure, small numbers of studies with biomarker-based approaches, a lack of data on genistein exposure over time, and potential residual confounding by other lifestyle factors, in general the weight of evidence supports a protective effect of isoflavones, including genistein, on cancer risk.

Cancer in Experimental Animals

In a report from the United States National Toxicology Program, in female rats continuously exposed from conception until age 2 years, tumours of the mammary gland and pituitary gland were observed (NTP, 2007a). In mice, genistein was shown to enhance proliferation and metastasis of patient-derived prostate cancer cells (Nakamura et al., 2011).

Mechanistic Evidence

Effects of genistein on apoptosis, the cell cycle, angiogenesis, and inhibition of metastasis have been described in several in vitro and in vivo studies (Spagnuolo et al., 2015). In rats, a phytoestrogen-rich diet was associated with reductions in serum testosterone concentrations (Ohno et al., 2003). In general, the mechanistic data are mixed, and it may be of interest to consider possible estrogenic effects in postmenopausal women and prepubertal boys.

In the context of the *IARC Monographs*, isoflavones could be considered together with phytoestrogens more broadly (e.g. lignans, coumestans, stilbenes) as part of an evaluation.

Recommendation: Low priority

Isophorone (CAS No. 78-59-1)

Isophorone (3,5,5-trimethylcyclohex-2-enone) has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Isophorone is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical. Isophorone is a widely used solvent and chemical intermediate.

Cancer in Humans

No epidemiological studies of cancer were identified.

Cancer in Experimental Animals

In bioassays performed by the United States National Toxicology Program (NTP, 1986c), administration of isophorone increased the incidence of renal tubule adenoma, renal tubule adenocarcinoma, and preputial gland carcinoma in male rats. In male mice, there was an increase in the incidence of hepatocellular adenoma or carcinoma (combined), mesenchymal tumours of the integumentary system, and malignant lymphoma (NTP, 1986c).

Mechanistic Evidence

Mechanistic data are sparse. In tests performed by the United States National Toxicology Program (NTP, 1986c), isophorone was not mutagenic in bacterial tests. In the absence of S9, isophorone was weakly mutagenic in the mouse L5178Y/TK$^{+/-}$ assay and induced sister chromatid exchanges (but not chromosomal aberrations) in Chinese hamster ovary cells.

Recommendation: Low priority

Isoprene (CAS No. 78-79-5)

Isoprene (2-methyl-1,3-butadiene) was classified by IARC as *possibly carcinogenic to humans* (Group 2B) (IARC, 1994a, 1999b), on the basis of *sufficient evidence* of carcinogenicity in experimental animals. Isoprene is structurally similar to 1,3-butadiene, which was classified by IARC as *carcinogenic to humans* (Group 1) (IARC, 2008).

Exposure Data

Isoprene is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Isoprene is the monomeric unit of natural rubber, terpenes, and steroids. It is emitted from vegetation and has been detected in tobacco smoke and automobile exhaust. Isoprene is formed endogenously in humans and other animals and is the major hydrocarbon in human breath. Globally, it is estimated to account for about 57% of the total natural emissions of volatile organic compounds. Isoprene is primarily produced as a by-product of the thermal cracking of naphtha or gas oil and is mostly used for the synthesis of synthetic rubber, styrene–isoprene–styrene block copolymers, and butyl elastomers (IARC, 1999b; NTP, 2011d). Because of the large global industrial production of synthetic isoprene, estimated to be close to 1 million metric tonnes per year (Morais et al., 2015), there is potential for significant occupational exposure to isoprene, although modern levels of exposure were reported to be below the recommended limits (Lynch, 2001).

Cancer in Humans

No epidemiological studies evaluating the relationship between cancer in humans and exposure to isoprene were identified.

Cancer in Experimental Animals

Exposure to isoprene by inhalation caused tumours at multiple tissues in male and female mice and rats (Melnick et al., 1994; Cox et al., 1996; Placke et al., 1996; NTP, 1999b). There were considerable species differences in the sites of neoplasia, with the mammary gland as the only common tumour site in rats and mice. Within each species, there were several common sites of tumour induction by isoprene and 1,3-butadiene (reviewed in Melnick & Sills, 2001).

Mechanistic Evidence

Similarly to 1,3-butadiene, isoprene is metabolized to monoepoxide and diepoxide intermediates by hepatic cytochrome P450 enzymes (particularly CYP2E1) from several species, including humans (IARC, 1999b). The stereochemistry and kinetics of monoepoxide and diepoxide formation in vitro have been compared in rats, mice, and humans (IARC, 1999b; Bogaards et al., 2001; Golding et al., 2003). These epoxides may undergo detoxification by epoxide hydrolase-mediated hydrolysis or conjugation with glutathione (Bogaards et al., 1999). Isoprene-specific mercapturate conjugates, likely stemming from catabolism of the glutathione adducts, have been detected in human urine (Alwis et al., 2016). Covalent binding to haemoglobin has been shown to occur in rodents in vivo (Fred et al., 2004, 2005) and human red blood cells in vitro (Tareke et al., 1998).

Neither isoprene nor its monoepoxide metabolites induced mutations in *Salmonella typhimurium*, but the diepoxide was mutagenic in strains TA98 and TA100 (IARC, 1994a). Isoprene was negative in genotoxicity assays performed in mammalian cells in vitro but caused sister chromatid exchange in bone marrow cells and micronucleus formation in peripheral blood erythrocytes in mice exposed in vivo (IARC, 1999b; NTP, 1999b). When tested in the presence of a metabolic activation system, isoprene caused DNA damage in human peripheral blood mononuclear cells and human HL-60 leukaemia cells. DNA damage by the isoprene monoepoxides and diepoxides was also shown in human cells (Fabiani et al., 2007; Li et al., 2014b), and DNA adducts from both isoprene monoepoxides have been characterized in vitro (Begemann et al., 2004, 2011). Genetic alterations in the *K*-ras and *H*-ras proto-oncogenes were observed in isoprene-induced tumours of the Harderian gland and forestomach in mice. In particular, tumours of the Harderian gland had a high frequency of unique *K*-ras A → T transversion mutations at codon 61 (Hong et al., 1997; Sills et al., 2001). The mutation spectrum was similar to that induced by 1,3-butadiene (Hong et al., 1997; Sills et al., 2001).

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

Job stress

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

There has been speculation for some time about a possible relationship between psychological and psychosocial factors, including stress from occupational and other sources, and increased risk of cancer. Although some attempts have been made to address these speculations, there is little consequential evidence to either support or refute them. In addition to the various hypothetical and incomplete ways of identifying the exposure and its intensity, other common challenges have included lack of control for confounding and the limiting of most efforts to all cancers combined or breast cancer in women. As more is learned about the underlying biology of carcinogenesis in humans, more insight may also be obtained into the likelihood of these exposures playing a significant role. For example, there is a growing body of evidence that socioeconomic disadvantage in childhood is associated with DNA methylation patterns that differ many years later, perhaps implying that there may be many potential confounders of psychological factors that will need to be considered in risk assessment. Therefore, the Advisory Group noted that there is much to learn before an adequate assessment can be made of the roles of psychological and psychosocial factors, including job stress, in carcinogenesis.

Key References

The following key references were identified: Engel et al. (2018); Mona et al. (2019).

Recommendation: No evaluation

Laboratory work and occupation as a chemist

Laboratory work and occupation as a chemist has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

The terms “laboratory workers” and “laboratorians” refer to a heterogeneous group of workers who are assigned tasks in multiple laboratory settings (e.g. inorganic and organic chemistry, molecular biology, and biochemistry research or production) involving potential exposures to a wide array of potentially harmful chemical, physical, and biological agents, including many known or suspected carcinogens. The potential for hazardous exposure is increased among laboratorians compared with most other workers, given the variety of different agents encountered and work that may include handling agents with unknown properties.

Cancer in Humans

An extensive literature stems mainly from case reports and observational studies comparing small numbers of workers with external referent populations. However, some nationally based longitudinal

studies are available for laboratorians in the United Kingdom (Hunter et al., 1993; Brown et al., 1996), the USA (Collins et al., 2014), Sweden (Wennborg et al., 1999, 2001), Finland (Kauppinen et al., 2003), Israel (Shaham et al., 2003a, b), and the Netherlands (van Barneveld et al., 2004). Site-specific findings are inconsistent; however, the reports that appear most often are of excess lymphohaematopoietic cancers (Li et al., 1969; Olin, 1978; Olin & Ahlbom, 1980, 1982; Hunter et al., 1993; Gustavsson et al., 1999; Kubale et al., 2008), digestive system cancers (Hunter et al., 1993; Cordier et al., 1995; Hansen et al., 2015), brain cancers (Carpenter et al., 1991; Beall et al., 2001; Sathiakumar et al., 2001; Alexander et al., 2013), and breast cancers (Walrath et al., 1985; Belli et al., 1990; Gustavsson et al., 1999, 2017; Shaham et al., 2003a, b). Laboratorians differ from the general population socioeconomically; therefore, healthy worker effects were common in most studies, resulting in risk deficits in mortality and outcomes largely affected by lifestyle factors. Studies generally lacked consideration of other known risk factors and dose–response information.

Cancer in Experimental Animals

Information from studies in experimental animals is not immediately relevant, given wide-ranging exposures.

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 and other organic solvents (Souza & Devi, 2014; Costa et al., 2015; de Aquino et al., 2016).

Recommendation: Low priority

Malachite green chloride (CAS No. 548-62-9) and leucomalachite green (CAS No. 129-73-7)

Malachite green chloride and leucomalachite green have not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Malachite green chloride is a triphenylmethane dye used in the fish industry as an antifungal agent. Leucomalachite green is formed by the reduction of malachite green chloride, and it persists in the tissues of exposed fish. Human exposure to malachite green chloride and leucomalachite green is relevant both for workers and for consumers of fish.

Cancer in Humans

No epidemiological studies of cancer are available for these compounds.

Cancer in Experimental Animals

Animal cancer bioassays were performed for both compounds (NTP, 2005a).

Groups of female rats were fed diets containing 0, 100, 300, or 600 ppm malachite green chloride for 2 years. Follicular cell adenomas and carcinomas of the thyroid occurred at the highest doses, and non-statistically significant excesses of hepatocellular adenomas and mammary gland carcinomas occurred in exposed rats. Malachite green chloride was also tested in groups of 48 female mice exposed to 100, 225, or 450 ppm for 2 years. No increased incidence of neoplasms was observed in exposed mice (NTP, 2005a).

Groups of 48 male and female rats were fed diets containing 0.91, 272, or 573 ppm leucomalachite green for 2 years. An increased incidence of interstitial cell adenoma of the testis and the occurrence of follicular cell adenoma or carcinoma (combined) of the thyroid was observed in exposed male rats. In female rats, a marginally increased incidence of hepatocellular adenoma and the occurrence of follicular cell adenoma or carcinoma (combined) of the thyroid were reported. Groups of 48 female mice were fed diets containing 0.91, 201, or 408 ppm leucomalachite green for 2 years. The incidence of hepatocellular hepatoma or carcinoma (combined) occurred with a positive trend (NTP, 2005a).

Mechanistic Evidence

With respect to the key characteristics of carcinogens, studies are available on whether malachite green and leucomalachite green are electrophilic and are genotoxic (inducing DNA damage) and induce oxidative stress in experimental animals (Manjanatha et al., 2004; Mittelstaedt et al., 2004; Donya et al., 2012; Gopinathan et al., 2015). Structural similarity to other carcinogens was also noted.

Key Reference

The following key reference was also identified: WHO (2009).

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

Malaria

Malaria is classified as *probably carcinogenic to humans* (Group 2A) (IARC, 2013f).

Exposure Data

Since the first *IARC Monographs* review of *Plasmodium falciparum* malaria (IARC, 2013f), new data have emerged relevant to the link between *Plasmodium* malaria and other cancer types in humans, to animal carcinogenicity, and to mechanistic data.

Cancer in Humans

With respect to the link between malaria and other cancer types in humans, epidemiological data indicate a linkage between malaria and the causal virus, Kaposi sarcoma-associated herpesvirus (KSHV). Evidence suggests that malaria enhances lytic replication of KSHV, which is thought to be a major risk factor, both for transmission to other people and for pathogenesis to Kaposi sarcoma (Wakeham et al., 2013; Nalwoga et al., 2015, 2018; Newton et al., 2018a, b). KSHV seroprevalence was higher in adults and children with malaria parasitaemia than in children without malaria parasitaemia, and malaria exposure (e.g. as measured by titres of anti-malaria antibodies) was higher in KSHV-seropositive children than in KSHV-seronegative children (Wakeham et al., 2013; Nalwoga et al., 2015, 2018). In a region of Uganda with high KSHV seroprevalence, malaria infection was associated with higher KSHV seroprevalence in both children and adults and with shedding of virus in saliva (Newton et al., 2018a, b). In addition, one case–control study in Cameroon showed that people with Kaposi sarcoma were less likely to use bed nets than were controls (Stolka et al., 2014).

Cancer in Experimental Animals

With respect to carcinogenicity in experimental animals of *P. falciparum* malaria, the previous IARC evaluation noted a lack of evidence of *Plasmodium*-induced carcinogenicity in animal models.

Mechanistic Evidence

A new study has directly documented that repeated infection of mice with the murine *P. chabaudi* resulted in B-cell lymphomas (Robbiani et al., 2008, 2015). These lymphomas had the c-myc translocation and phenotype consistent with Burkitt lymphoma. Furthermore, tumorigenesis induced by *P. chabaudi* infection required the enzyme activation-induced cytidine deaminase (AID). AID is required for the c-myc translocation characteristic of Burkitt lymphoma (Wilmore et al., 2016). A second study showed that *P. chabaudi* could induce aberrant AID activity in B cells outside the germinal centre (Robbiani et al., 2008). Providing the link to human Burkitt lymphoma, Grande et al. (2019) sequenced more than 100 Burkitt lymphoma genomes. They found that Epstein–Barr virus (EBV)-positive Burkitt lymphoma but not EBV-negative Burkitt lymphoma had evidence of a high level of AID activity, which they hypothesized was a critical event in malignant transformation. The EBV-positive Burkitt lymphoma tumours are predominantly the endemic form of Burkitt lymphoma, which is found where malaria transmission is high. Torgbor et al. (2014) showed that addition of *P. falciparum* extracts could induce AID in B cells. AID is also elevated in peripheral blood of children living in malaria endemic regions with a high risk of Burkitt lymphoma (Wilmore et al., 2015).

In summary, since the previous *IARC Monographs* evaluation, there are new data on animal carcinogenicity, mechanistic studies, and links to other cancer types to support a re-evaluation.

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

Mancozeb (CAS No. 8018-01-7)

Mancozeb (manganese ethylene-bis-dithiocarbamate) has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Mancozeb is a widely used fungicide. It is one of the most commonly used fungicides, and therefore it is relevant for production workers, applicators, residents in areas where it is used, and consumers.

Cancer in Humans

In an epidemiological study of about 50 000 pesticide applicators, a significant association was detected between cutaneous melanoma and exposure to maneb/mancozeb (Dennis et al., 2010). In a pooled analysis of two case–control studies on cutaneous melanoma and pesticide exposure, the odds ratio associated with exposure to fungicides (mancozeb and maneb are the most commonly used), adjusted for age, sex, centre, education, skin phototype, number of naevi, sunburn episodes in childhood, and family history of skin cancer, was 3.88 (95% confidence interval, 1.17–12.9), based on 19 exposed cases (Fortes et al., 2016).

Cancer in Experimental Animals

An animal cancer bioassay was performed on groups of 150 male and female Sprague-Dawley rats at concentrations of 1000, 500, 100, 10, and 0 ppm in feed for 104 weeks. Animals were followed up until spontaneous death. Mancozeb caused increases in total malignant tumours, malignant mammary tumours, carcinomas of the Zymbal gland and ear duct (in males), hepatocarcinomas (in males), malignant tumours of the pancreas (in males and females), malignant tumours of the thyroid (in males and females), osteosarcomas (in males and females), and lymphoreticular neoplasms (in males and females) (Belpoggi et al., 2002b). The progeny of pregnant Swiss albino mice administered mancozeb intraperitoneally showed an increased tumour incidence after promotion with 12-*O*-tetradecanoylphorbol-13-acetate or dimethylbenz[*a*]anthracene (Shukla & Arora, 2001).

Mechanistic Evidence

The increased tumour incidence observed in the above-mentioned transplacental initiation–promotion study suggests that mancozeb or its metabolites may cross the placental barrier and exert DNA damage and tumour-initiating consequences in fetal cells. The carcinogenic mechanisms of mancozeb were investigated in a proteome profile study of mancozeb-exposed (at 200 mg/kg body weight) and control mouse skin. After the treatment, calcyclin and calgranulin B were upregulated, thus suggesting their role in mancozeb-induced neoplastic alterations. This finding was confirmed in an in vitro model of human skin keratinocyte carcinogenesis. Different outcomes provided consistent responses (Tyagi et al., 2011).

Recommendation: Medium priority

Matrine (CAS No. 519-02-8)

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

Exposure Data

Matrine is one of the major tetracyclo-quinolizidine alkaloids extracted from the roots of the herb *Sophora flavescens* Aiton (Zhao et al., 2015; Rashid et al., 2019). It is a traditional herbal remedy used in the treatment of cardiovascular diseases, liver diseases, and asthma, as well as tumours (Zhao et al., 2015; Rashid et al., 2019). It is found in China, Japan, and some European countries.

Cancer in Humans

Preclinical and clinical studies have evaluated matrine as an anticancer agent for prevention and treatment of several cancer types, including gastric cancer, breast cancer, lung cancer, liver cancer, leukaemia, and myeloma (Rashid et al., 2019). Matrine is approved for cancer therapy by the Chinese State Food and Drug Administration (Rashid et al., 2019)

A total of 12 meta-analyses and systematic reviews of clinical trials were identified that analysed the use of matrine in the treatment of various cancer types. These studies show a superior clinical profile of matrine compared with other Chinese herbal therapies (Ge et al., 2016; Zhang et al., 2017b, 2018b, 2019b), including when used as a co-treatment with other chemotherapy regimens (Huang et al., 2011; Sun et al., 2011; Ma et al., 2016; Zhang et al., 2017c; Ao et al., 2019).

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

Several studies in experimental animals have been published that have investigated the inhibitory effect on tumour growth and progression in inoculated mice and rats (Chang et al., 2014; Shi et al., 2014; Zhang & Wang, 2018).

In mechanistic studies, matrine is reported to have a wide range of relevant effects (Rashid et al., 2019), such as inhibiting the proliferation of various cancer cells, disrupting cell-cycle regulation, and inducing apoptosis, as well as facilitating anti-angiogenesis by reducing secretion of vascular endothelial growth factor (Liu et al., 2014).

Key References

The following key references were also identified: Zhang et al. (2009, 2011, 2015a); Wang et al. (2014); Yanju et al. (2014); Guo et al. (2015); Hu et al. (2015); Sun & Xu (2015); Liu et al. (2017a); Gu et al. (2018).

Recommendation: No evaluation

Merkel cell polyomavirus (MCV)

Soon after its discovery, Merkel cell polyomavirus (MCV) was evaluated by the *IARC Monographs* programme and classified as *probably carcinogenic to humans* (Group 2A) (IARC, 2013f), on the basis of *inadequate evidence* of carcinogenicity in experimental animals and *limited evidence* of carcinogenicity in humans supported by a positive association between infection with MCV and Merkel cell carcinoma; there was also *strong* mechanistic evidence that MCV can directly contribute to the development of a large proportion of Merkel cell carcinomas.

Exposure Data

MCV was discovered in 2008 in Merkel cell carcinoma, a rare skin cancer (IARC, 2013f). MCV is acquired early in life and is asymptomatic; it is detected at various anatomical locations but most commonly in the skin (IARC, 2013f; Spurgeon & Lambert, 2013). MCV infection is prevalent in the general population; approximately 50–90% of adults are infected worldwide (IARC, 2013f). The mode of transmission, cellular tropism, and latency characteristics are unclear (IARC, 2013f).

Cancer in Humans

Since the *IARC Monographs* evaluation, several new epidemiological studies on the association between MCV and Merkel cell carcinoma have been published, with consistent findings of increased risk in epidemiological studies of populations in different geographical areas, a suggestion of a dose–response relationship, and supportive results from clinical and molecular studies.

Cancer in Experimental Animals

No new cancer bioassays are available.

Mechanistic Evidence

New mechanistic data have become available since the *IARC Monographs* evaluation.

The Advisory Group suggested that the *IARC Monographs* consider including other polyomaviruses in any updated evaluation.

Key References

The following key references were also identified: Becker et al. (2009, 2017); Martel-Jantin et al. (2013); Zhang et al. (2014); NTP (2016m); Álvarez-Argüelles et al. (2017); Knips et al. (2017); Verhaegen et al. (2017); Zanetti et al. (2017); Bhat et al. (2018); Coggshall et al. (2018); Harms et al. (2018); Liu et al. (2018); Nwogu et al. (2018); Kieny et al. (2019); Park et al. (2019); Riethdorf et al. (2019).

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

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

Nickel and nickel compounds have been evaluated repeatedly by the IARC *Monographs* programme (IARC, 1973, 1976, 1987, 1990b). Metallic nickel is currently listed as *possibly carcinogenic to humans* (Group 2B) (IARC, 1990b), on the basis of *sufficient evidence* of carcinogenicity in experimental animals and *inadequate evidence* of carcinogenicity in humans. However, *IARC Monographs* Volume 100C evaluated the metals classified as *carcinogenic to humans* (Group 1), which included nickel compounds but not metallic nickel or alloys (IARC, 2012d). In the process of reviewing the evidence for nickel compounds, the Working Group also reviewed evidence for metallic nickel. There was *sufficient evidence* in humans for the carcinogenicity of mixtures that include nickel compounds and nickel metal; these agents cause cancers of the lung and of the nasal cavity and paranasal sinuses.

Exposure Data

Metallic nickel is ubiquitous and occurs in soil, water, air, and the biosphere. It is found in a variety of industrial production and manufacturing processes and is used mainly in the production of stainless steel and other alloys with high corrosion and temperature resistance. Pure nickel metal is used in electroplating, as a chemical catalyst, and in the manufacture of products such as alkaline batteries, coins, welding products, magnets, electrical components, machinery parts, and medical implants or prostheses. Occupational exposure is widespread globally, occurring through exposure to nickel-containing dusts and fumes during welding and metal fabrication, nickel refining and smelting, electroplating, mining, steel production, and other processes (IPCS, 1991b). Metallic nickel is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Cancer in Humans

The evidence cited in Volume 100C includes a study of nickel refinery workers in Wales (Easton et al., 1992), in which risk of lung cancer was found to be associated with exposure to metallic nickel, and a study of nickel alloy workers (Arena et al., 1998), in which a small but statistically significant elevation in risk of lung cancer was found to be associated with exposure to metallic nickel.

Cancer in Experimental Animals

There was *sufficient evidence* in experimental animals for the carcinogenicity of nickel metal. Inhaled metallic nickel increased the incidence of adrenal pheochromocytomas in male rats and adrenal cortex tumours in female rats. Intratracheal administration of metallic nickel powder caused lung tumours in rats. Metallic nickel also caused local tumours in rats when administered by injection (intrapleural, subcutaneous, intramuscular, and intraperitoneal). However, the conclusions on the carcinogenicity to humans or animals were not carried over into an overall evaluation for metallic nickel. The overall conclusion indicated that nickel compounds are *carcinogenic to humans* (Group 1).

In the United States National Toxicology Program 14th report on carcinogens (NTP, 2016k), metallic nickel was reasonably anticipated to be a human carcinogen on the basis of sufficient evidence of carcinogenicity from studies in experimental animals.

Mechanistic Evidence

The hazard associated with a particular nickel compound is related largely to the compound's propensity to release ionic nickel in the body. Metallic nickel can slowly dissolve in the body and release ionic nickel, an active genotoxic and carcinogenic form of nickel, which suggests that metallic nickel has carcinogenic properties. There is no evidence to suggest that the mechanisms by which nickel causes tumours in experimental animals would not also operate in humans (NTP, 2016k; IARC, 2019a).

Numerous mechanistic studies relevant to the key characteristics of carcinogens are available. Many studies in cultured rodent and human cells have shown that a variety of nickel compounds, including both soluble and insoluble forms of nickel, caused genetic damage, including DNA strand breaks, mutations, chromosomal damage, cell transformation, and disrupted DNA repair. Chromosomal aberrations have been observed in humans occupationally exposed to nickel. Nickel can bind ionically to cellular components, including DNA. The reduction–oxidation activity of the nickel ion may produce reactive oxygen species that attack DNA, and exposure to nickel ion in vitro or in vivo can result in production of 8-hydroxy-2′-deoxyguanosine in target tissues for cancer caused by nickel (IARC 1990b, Kasprzak et al., 1990; Lu et al., 2005; NTP, 2016k; Chen & Costa, 2017). Nickel has been shown to promote hypermethylation of tumour suppressor genes such as E-cadherin and p16, which may be important in triggering carcinogenesis (Chen et al., 2019). In addition to DNA methylation, exposure to nickel has been found to alter global histone modifications both in vitro and in vivo (Chen et al., 2019).

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

Metalworking fluids

Metalworking fluids have not been previously evaluated by the *IARC Monographs* programme. They were assigned medium priority by the 2014 Priorities Advisory Group (Straif et al., 2014).

Exposure Data

Metalworking fluids are a complex mixture of water-based and/or oil-based fluids and additives that are used to lubricate and cool metals during cutting and grinding operations. Metalworking fluids 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). Dermal and inhalation exposure is likely in the course of a range of operations involving metal processing. Widespread use of metalworking fluids in automotive and other industries has resulted in workplace exposures that 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, 2015b). The United States National Toxicology Program (NTP) also recently tested a metalworking fluid used as a lubricant and coolant liquid and for cleaning tools and parts during cutting, drilling, milling, and grinding (NTP, 2016f).

Cancer in Humans

There is a large body of observational research examining occupational exposure to metalworking fluids and cancer risk, with mixed results. Modest positive associations are reported for several tumour sites, with the strongest evidence stemming from multiple investigations of 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 difficulties in assessing exposure, data in humans have generally lacked quantitative metrics in exposure–response information. However, there are several longitudinal studies using exposure surrogates to examine exposure–response that report 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).

A recent study provided evidence of gene–environment interactions for occupational exposures and susceptibility loci for bladder cancer. In particular, with respect to *GSTM1*, the authors noted the relevance of rs798766 (*TMEM129-TACC3-FGFR3*) with specific exposure to straight metalworking fluids (Figueroa et al., 2015).

Cancer in Experimental Animals

An NTP inhalation bioassay study for a common metalworking fluid (TRIM VX) has been published. In the exposed group in Wistar rats (NTP, 2016f), increased bronchioloalveolar adenoma or carcinoma of the lung was observed in males, and increased bronchioloalveolar adenoma of the lung was observed in females. In $B6C3F_1$ mice (NTP, 2016f), increased incidence of bronchioloalveolar adenoma or carcinoma of the lung was observed in males and females.

Another metalworking fluid, CIMSTAR 3800, was also tested by inhalation (NTP, 2015b). In the exposed group in Wistar rats, increased incidence of prostate gland adenoma or carcinoma was observed in males. Increased incidence of squamous cell papilloma or keratoacanthoma (combined) of the skin and adenocarcinoma or mixed malignant Müllerian tumour (combined) of the uterus was observed in female rats. In one inhalation study in $B6C3F_1$ mice (NTP, 2015b), increased incidence of follicular cell carcinoma of the thyroid and bronchioloalveolar adenoma or carcinoma (combined) of the lung was observed in female mice.

Mechanistic Evidence

TRIM VX gave no evidence of genotoxicity in bacterial mutation tests or in vivo tests for chromosomal damage (micronuclei) (NTP, 2016f). CIMSTAR 3800 was mutagenic in *Escherichia coli* strain WP2 uvrA/pKM101 in the absence of exogenous metabolic activation (S9); no mutagenic activity was observed in *Salmonella typhimurium* strains TA98 and TA100, with or without S9, or in the *E. coli* strain with S9 (NTP, 2015b). Sparse mechanistic studies are available in the published literature for these two metalworking fluids.

Experimental data are available on the carcinogenicity of certain components of metalworking fluids, including mineral oil. Mineral oil-based fluids (straight and soluble) contain polycyclic aromatic hydrocarbons (PAHs), which are classified in Group 1. These fluids may also contain naphthenes, paraffins, sulfur and chlorine additives, and fatty oil. Soluble fluids contain emulsifying agents to maintain the oil–water mix and water-based fluids (synthetic and soluble). Water-based fluids may also contain organic esters, polyglycols, biocides, and corrosion inhibitors. Among the anticorrosive agents are ethanolamines, which, when combined with nitrites, may form nitrosamines.

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

Methanol (CAS No. 67-56-1)

Methanol has not been previously evaluated by the *IARC Monographs* programme. The 2014 Priorities Advisory Group assigned methanol a medium priority (Straif et al., 2014).

Exposure Data

Methanol is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Methanol has many commercial uses. It is also found in fruit juices and other foods (IPCS, 1997). It is also produced from biomass, especially plant materials. Methanol may be exhaled in breath and body fluids. This substance is manufactured and/or imported in the European Economic Area at 10 million to 100 million metric tonnes per year (ECHA, 2019).

Cancer in Humans

Evidence on the carcinogenic effects of methanol in humans is sparse. A cohort study of 25 218 male workers found no positive association between methanol exposure and cancer mortality (Min et al., 2019).

Cancer in Experimental Animals

Carcinogenicity of methanol has been observed in animals in oral studies. In one oral study (drinking-water containing methanol) in Sprague-Dawley rats (Soffritti et al., 2002), increases in the incidence of carcinoma of the ear duct, osteosarcoma of the head, and haemolymphoreticular tumours were

reported in exposed male and female rats. In addition, an increase in the incidence of testicular interstitial cell adenomas was reported in males, and an increase in the incidence of sarcomas of the uterus was reported in females. A follow-up Pathology Working Group revision of the study confirmed fewer lesions and suggested further molecular and immunohistochemical characterization of the haemolymphoreticular tumours (Gift et al., 2013). In one oral study in Eppley Swiss Webster mice (Apaja, 1980), increases in the incidence of malignant lymphoma were reported in male and female mice.

Mechanistic Evidence

Gene expression profiles of methanol-treated baker's yeast were analysed using DNA microarrays. Among approximately 6000 open reading frames (ORFs), 314 were repressed and 375 were induced in response to methanol. The gene process category "energy" comprised the greatest number of induced genes, and "protein synthesis" comprised the greatest number of repressed genes. Products of genes induced by methanol were mainly integral membrane proteins or were localized to the plasma membrane (Yasokawa et al., 2010). Daily exposure of rats to methanol (at very high doses) by gavage for 5 days induced hydroxymethyl DNA adducts in multiple tissues in a dose-dependent manner (Lu et al., 2012). The relevance of these adducts to methanol exposure is unclear.

Recommendation: Low priority

Methyl isobutyl ketone (CAS No. 108-10-1)

Methyl isobutyl ketone (MIBK) was classified by the *IARC Monographs* programme as *possibly carcinogenic to humans* (Group 2B) (IARC, 2013c), on the basis of *sufficient evidence* of carcinogenicity in experimental animals.

Exposure Data

MIBK is used industrially as a solvent, occurs naturally in certain foods, and is also approved for use as a flavouring agent. MIBK is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Cancer in Humans

No studies of cancer in humans were identified.

Cancer in Experimental Animals

The evidence in experimental animals evaluated in *IARC Monographs* Volume 101 (IARC, 2013c) consisted of chronic inhalation studies. In a 2-year inhalation study in male and female mice and rats, MIBK increased the incidence of hepatocellular adenoma and of hepatocellular adenoma and carcinoma combined in male and female mice, and that of renal tubule adenoma and of renal tubule adenoma and carcinoma

combined in male rats, and caused two rare renal malignant mesenchymal tumours in female rats in the high-dose group (NTP, 2007b).

Mechanistic Evidence

MIBK was generally not genotoxic in a variety of systems. The strength of the evidence that the kidney tumours in male rats arise through a mechanism associated with α2u nephropathy is weak. There is no evidence that liver tumours in mice arise from a cytotoxic/regenerative cell proliferation mechanism, because no overt liver toxicity has been demonstrated. There is only weak evidence that the tumours arise through a receptor-mediated mechanism (IARC, 2013c). The only published mechanistic evidence since the previous IARC evaluation (IARC, 2013c) is two short-term studies (Borghoff et al., 2015; Hughes et al., 2016) exploring the possibility of rodent-specific mechanisms for mouse liver and rat kidney tumours. In one study, no hepatic cell proliferation was observed in CAR/PXR knockout mice exposed to MIBK. The other study demonstrated an exposure-related increase in specific measures of α2u nephropathy in male rats but not in female rats.

Recommendation: No evaluation

Methyl eugenol (CAS No. 93-15-2) and isoeugenol (CAS No. 97-54-1)

Methyl eugenol (1,2-dimethoxy-4-prop-2-enylbenzene) was evaluated by the *IARC Monographs* programme in Volume 101 (IARC, 2013c) and classified as *possibly carcinogenic to humans* (Group 2B), on the basis of *sufficient evidence* of carcinogenicity in experimental animals and no data on the carcinogenicity in humans. Isoeugenol (2-methoxy-4-prop-1-enylphenol) has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Methyl eugenol and isoeugenol belong to a class of plant-derived volatile chemicals called phenylpropenes. Methyl eugenol and isoeugenol are fragrant essential oils that are found (along with other phenylpropenes) in various spices and herbs, including calamus, savory, basil, ylang-ylang, clove, tuberose, jonquil, nutmeg, tobacco, sandalwood, dill seed, mace, gardenia, and petunia. Commercially, methyl eugenol and isoeugenol are prepared by the methylation or isomerization, respectively, of eugenol. Methyl eugenol and isoeugenol are added as flavouring agents to beverages, baked foods, confectionery, and chewing gums. The addition of methyl eugenol as a pure substance to foods is not permitted in the European Union because of concerns about genotoxicity and carcinogenicity. Similarly, the United States Food and Drug Administration no longer allows the use of methyl eugenol as a food additive. Isoeugenol is “generally recognized as safe (GRAS)” by the United States Food and Drug Administration for use in foods. Methyl eugenol and isoeugenol are incorporated as fragrances into household cleaning agents, perfumes, lotions, soaps, and detergents. There is also occupational exposure to methyl eugenol and isoeugenol (NTP, 2010c).

Cancer in Humans

No data were identified pertaining to the carcinogenicity of methyl eugenol or isoeugenol in humans.

Cancer in Experimental Animals

The carcinogenicity of methyl eugenol in experimental animals was thoroughly reviewed in *IARC Monographs* Volume 101 (IARC, 2013c). On the basis of the results obtained from a 2-year gavage study in male and female mice, a 2-year gavage study in male and female rats, and an intraperitoneal injection study in newborn male mice, the Working Group concluded that there was *sufficient evidence* for the carcinogenicity of methyl eugenol in experimental animals. The carcinogenicity of 1′-hydroxymethyleugenol, which is considered to be a proximate carcinogenic metabolite of methyl eugenol, was also evaluated in newborn male mice and was shown to be positive.

After the IARC evaluation in 2013 (IARC, 2013c), an additional study was published in which male F344 rats were treated intragastrically with methyl eugenol 3 times per week for 16 weeks and then placed on a control diet or a diet containing phenobarbital for 24 weeks. Methyl eugenol caused a dose-dependent induction of hepatocellular adenoma, the size of which was increased by phenobarbital (Williams et al., 2013).

Male F344/N rats treated by gavage for 2 years with isoeugenol (ratio of *Z*-isoeugenol to *E*-isoeugenol, 7:1) had a significant dose trend in benign or malignant thymoma of the thymus and mammary gland carcinoma. These neoplasms were observed only in the highest dose group (300 mg/kg), and the increase in incidence was not statistically significant; nonetheless, these are very rare tumours in that strain and sex of rats. Male B6C3F_1 mice treated by gavage for 2 years had a significant dose trend in hepatocellular adenoma, hepatocellular carcinoma, and combined hepatocellular adenoma or carcinoma, and the increase was significant at the lowest dose tested (75 mg/kg). Female B6C3F_1 mice treated by gavage for 2 years had a significant dose trend in histiocytic sarcoma (NTP, 2010c).

Mechanistic Evidence

Since the previous *IARC Monographs* evaluation (IARC, 2013c), substantial new mechanistic information has become available.

There is evidence that methyl eugenol is electrophilic. Incubation of methyl eugenol with rat hepatocytes resulted in the formation of two DNA adducts, as assessed by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS): N^6-(*trans*-methylisoeugenol-3′-yl)-2′-deoxyadenosine (N^6-MIE-dA) and N^2-(*trans*-methylisoeugenol-3′-yl)-2′-deoxyguanosine (N^2-MIE-dG). Higher levels of the same adducts were detected in incubations conducted with 10-fold lower concentrations of 1′-hydroxymethyleugenol (Cartus et al., 2012). N^2-MIE-dG was also detected (by HPLC-MS/MS) in the livers of rats treated with methyl eugenol (Alhusainy et al., 2014).

Of 30 DNA samples from human liver specimens, 29 had detectable levels of N^2-MIE-dG. Most of the samples also contained N^6-MIE-dA, at levels lower than those of N^2-MIE-dG (Herrmann et al., 2013). N^2-MIE-dG was also detected in 10 of 10 DNA samples from human lung specimens. Most of the samples also contained N^6-MIE-dA, at levels lower than those of N^2-MIE-dG (Monien et al., 2015).

N^2-MIE-dG and N^6-MIE-dA were found (by HPLC-MS/MS) in various tissues from transgenic mice expressing human SULT1A1/2, at levels much higher than those observed with wild-type mice (Herrmann et al., 2016; see also Herrmann et al., 2014). Hepatic DNA adduct levels of N^2-MIE-dG were associated with higher expression levels and higher copy numbers of SULT1A1 (Tremmel et al., 2017).

N^6-MIE-dA has been detected, by HPLC-MS/MS, in the urine of rats treated orally with methyl eugenol. Surprisingly, N^2-MIE-dG, which is formed to a much greater extent than N^6-MIE-dG, was not detected. N^6-MIE-dA was also detected in the urine of rats administered extracts of Asari radix, Acori tatarinowii rhizome, Myristicae semen (nutmeg), and Shi San Xiang, at levels comparable to the methyl eugenol content of the spices (Feng et al., 2018). In other work, Feng and colleagues demonstrated that methyl eugenol bound to cysteine residues in proteins (Feng et al., 2017).

There is also evidence that methyl eugenol is genotoxic. When it was evaluated by IARC (IARC, 2013c), methyl eugenol was considered to be not mutagenic in bacteria but did induce chromosomal aberrations in vitro. After that evaluation, the mutagenicity of the proximate methyl eugenol metabolite 1′-hydroxymethyleugenol was assessed in *Salmonella typhimurium* strains expressing human and murine sulfotransferases. An increase in mutations was detected with strains expressing human SULT1A1 and SULT1C2; fewer mutations were detected with SULT1A2 and SULT1E1. An increased mutation frequency was observed with strains expressing murine Sult1a1, but at higher substrate concentrations than with human sulfotransferases. The induction of mutations was associated with the formation of N^2-MIE-dG and N^6-MIE-dA (Herrmann et al., 2012).

Male and female F344 *gpt* delta transgenic rats treated by gavage with methyl eugenol for 13 weeks had dose-dependent increases in the *gpt* and Spi$^-$ mutant frequency (Jin et al., 2013).

Methyl eugenol significantly enhanced DNA damage in Chinese hamster V79 cells and HT29 human colon carcinoma cells as assessed by the comet assay (Groh et al., 2012, 2016). In a subsequent study, the same group demonstrated that methyl eugenol induced apoptotic cell death and this was associated with the induction of caspase 3 (Groh & Esselen, 2017).

Data on other mechanistic end-points are also available for methyl eugenol. In a recent study, male F344/N rats were treated with a hepatocarcinogenic dose of methyl eugenol to examine carcinogen-specific liver cell kinetics. The changes observed included increases in cell proliferation and upregulation of DNA damage-related genes (Kimura et al., 2016).

There is little or no evidence that isoeugenol is electrophilic. There is little evidence that isoeugenol is genotoxic. Dermal exposure to isoeugenol has been associated with moderate irritation and contact dermatitis.

Key Reference

The following key reference was also identified: Yao et al. (2016).

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

N-Methylolacrylamide (CAS No. 924-42-5)

N-Methylolacrylamide was previously evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1994a)

Exposure Data

N-Methylolacrylamide is a bifunctional monomer with reactive vinyl and hydroxyethyl groups. Thermoplastic polymers can be formed by copolymerization of *N*-methylolacrylamide with a variety of vinyl monomers by emulsion, solution, and suspension techniques. The uses of *N*-methylolacrylamide range from adhesives and binders in papermaking and textiles to a variety of surface coatings and resins for varnishes, films, and sizing agents (IARC, 1994a)

Cancer in Humans

No studies of cancer in humans were identified for *N*-methylolacrylamide.

Cancer in Experimental Animals

Carcinogenicity of *N*-methylolacrylamide has been observed in animals, by the oral route. In one oral study in Fischer rats (NTP, 1989b), there was no evidence of carcinogenic activity. In one oral study in $B6C3F_1$ mice (NTP, 1989b), there was increased incidence of adenomas of the Harderian gland, adenomas and carcinomas of the liver, and adenomas and carcinomas of the lung in males, and increased incidence of adenomas of the Harderian gland, adenomas of the liver, bronchioloalveolar adenomas or carcinomas (combined) of the lung, and granulosa cell tumours of the ovary in females.

Mechanistic Evidence

Mechanistic data relevant to key characteristics of carcinogens are sparse. *N*-Methylolacrylamide was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535 when tested with or without exogenous metabolic activation. *N*-Methylolacrylamide induced both sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells with and without metabolic activation. No increase in micronucleated polychromatic erythrocytes was observed in the bone marrow of $B6C3F_1$ mice after intraperitoneal injection of *N*-methylolacrylamide (NTP, 1989b).

Recommendation: Medium priority

Metronidazole (CAS No. 443-48-1)

Metronidazole was last evaluated by the *IARC Monographs* in 1987 (IARC, 1987), when it was classified as *possibly carcinogenic in humans* (Group 2B); there was *inadequate evidence* of carcinogenicity in humans.

Exposure Data

Metronidazole is used primarily as a drug for the treatment of infection by parasitic protozoans. It is included in the WHO Model List of Essential Medicines (WHO, 2017).

Cancer in Humans

Since the most recent *IARC Monographs* evaluation, subsequent epidemiological studies did not indicate a significantly increased risk of cancer. The studies are mostly of limited informativeness because of insufficient sample size or follow-up time.

Cancer in Experimental Animals

The previous evaluation concluded that there was *sufficient evidence* in experimental animals for the carcinogenicity of metronidazole. This has been confirmed in a subsequent bioassay.

Mechanistic Evidence

With respect to the key characteristics of carcinogens, metronidazole has been investigated in a substantial number of studies and is clearly genotoxic. This has been demonstrated in bacteria and to a lesser extent in mammalian systems.

Key References

The following key references were also identified: Falagas et al. (1998); Bendesky et al. (2002); Adil et al. (2018).

Recommendation: No evaluation

Multi-walled carbon nanotubes

Multi-walled carbon nanotubes (MWCNTs) were evaluated in 2014 (IARC, 2017b); MWCNT-7 was evaluated as *possibly carcinogenic to humans* (Group 2B), and MWCNTs other than MWCNT-7 were evaluated as *not classifiable as to their carcinogenicity to humans* (Group 3).

Exposure Data

MWCNTs are a special form of carbon nanotubes in which multiple single-walled carbon nanotubes are nested inside one another. They have many applications in fields as diverse as electronics, transportation, sporting goods, energy, and medicine. The worldwide production of carbon nanotubes has increased

substantially in the past decade, leading to occupational exposures. During the synthesis and handling of MWCNTs, bagging, maintenance of the reactor, and powder conditioning were associated with higher exposure levels in the production area (Kuijpers et al., 2016). Workers in facilities that produce or use carbon nanotubes have the potential for inhalation exposure when these particles become airborne and enter the workers' breathing zone.

Cancer in Humans

No epidemiological studies of cancer in humans have been reported. Because of *inadequate evidence* of carcinogenicity in humans, the data on carcinogenicity in experimental animals of specific MWCNTs provided the evidence base for the IARC classifications in 2014 (IARC, 2017b).

Cancer in Experimental Animals

MWCNTs were evaluated in 2014 (IARC, 2017b) as to their carcinogenicity in experimental animals; there was *sufficient evidence* for the carcinogenicity of MWCNT-7, *limited evidence* for two types of MWCNTs with dimensions similar to those of MWCNT-7, and *inadequate evidence* for MWCNTs other than MWCNT-7. Since then, MWCNT-7 was shown to cause lung carcinomas by inhalation in rats (Kasai et al., 2016, 2019); intratracheal instillation of MWCNT-N in rats caused mesotheliomas and lung cancers (Suzui et al., 2016), and intraperitoneal injection in rats of four different types of MWCNTs (A, B, C, and D) caused mesotheliomas (Rittinghausen et al., 2014). The Advisory Group was also aware of 2-year good laboratory practice (GLP) inhalation studies conducted on the 1020 Long MWCNT in male and female rats and mice (NTP, 2019c).

Mechanistic Evidence

The mechanistic evidence was not strong enough to support a modification of the classifications of MWCNT-7 as *possibly carcinogenic to humans* (Group 2B) and MWCNTs other than MWCNT-7 as *not classifiable as to their carcinogenicity to humans* (Group 3) (IARC, 2017b; Kuempel et al., 2017). MWCNTs have been shown to penetrate the outer surface of the lungs and enter the intrapleural space. Numerous short-term studies in vivo and in vitro have demonstrated that, like for fibres, the biological effects of nanotubes are dependent on their shape, size, and durability. Since the previous evaluation, some evidence of oxidative stress, chronic inflammation, and lung fibrosis was reported in exposed humans (Lee et al., 2015b; Fatkhutdinova et al., 2016).

Type of material and size are important determinants. Chemoinformatics analyses may be helpful to clarify which members of the class may merit evaluation.

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

Nanomaterials (e.g. titanium dioxide or nanosilica)

Multi-walled carbon nanotubes were evaluated in 2014 (IARC, 2017b); MWCNT-7 was classified as *possibly carcinogenic to humans* (Group 2B), and MWCNTs other than MWCNT-7 were evaluated as *not classifiable as to their carcinogenicity to humans* (Group 3). Other nanomaterials have not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

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) in 2008 (Gebel, 2012). The development of precision technology has raised concerns about the increase in these nanomaterials and their effects on the human body, but research on this topic is still limited. Human exposure to nanomaterials occurs through the respiratory tract and may occur through absorption in the skin, digestive tract, and eyes. However, 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). In addition, 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 are expected to increase exposure of the human body (Mackevica & Foss Hansen, 2016).

Cancer in Humans

In Canada, Europe, and the USA, epidemiological studies have been conducted on the association of exposure to titanium dioxide (TiO_2) with cancer of the lung, but not on nano-TiO_2. To date, 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 studies in experimental animals, evidence of carcinogenicity of nanomaterials such as nano-TiO_2 (Becker et al., 2011) and carbon nanotubes (Kobayashi et al., 2017) has been reviewed. Recently, long-term exposure to cerium oxide (CeO_2) and barium sulfate ($BaSO_4$) nanoparticles has been suggested to be carcinogenic in the lung in rats (Schwotzer et al., 2017).

Mechanistic Evidence

Genotoxicity was observed in zinc oxide and silica nanoparticles in mammalian models, suggesting that various nanomaterials are associated with carcinogenicity (Kwon et al., 2014). The main mechanistic hypothesis is that when nanomaterials enter the body through the respiratory tract, which is the main pathway to infiltration into the body, the inflammatory reaction is activated by the immune action, and the inflammatory reaction is sustained for a long period of time, leading to carcinogenicity (Luanpitpong et al., 2016).

The *IARC Monographs* have not made an overall assessment of nanomaterials. However, in animal experiments, carcinogenicity of several nanomaterials is emerging, and epidemiological studies on humans are under way.

Recommendation: Medium priority

Neonatal phototherapy

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

Exposure Data

Phototherapy uses visible light (390–470 nm, within the blue spectrum, optimally around 450 nm) to treat severe jaundice in the neonatal period (Pinto et al., 2015). Approximately 60% of full-term babies and 85% of preterm babies develop clinically apparent jaundice. Treatment with phototherapy is implemented to prevent the neurotoxic effects of high serum levels of unconjugated bilirubin.

Cancer in Humans

Recently, three cohort studies reported on the association between neonatal phototherapy and cancer. A retrospective cohort study in Canada found that infants who received neonatal phototherapy had more than 2 times the risk of any solid tumour between age 4 years and 11 years compared with non-exposed children (Auger et al., 2019). In a cohort of infants born in hospitals in California, USA, at ≥ 35 weeks' gestation, infants with diagnosis codes for phototherapy had a 60% increased risk of cancer compared with children without such codes (Wickremasinghe et al., 2016). In propensity-adjusted analyses, associations were seen between phototherapy and overall cancer (adjusted odds ratio [aOR], 1.4; 95% confidence interval [CI], 1.1–1.9), myeloid leukaemia (aOR, 2.6; 95% CI, 1.3–5.0), and kidney cancer (aOR, 2.5; 95% CI, 1.2–5.1). In a retrospective cohort study of children born in Kaiser Permanente Northern California hospitals, cancer incidence in children exposed to phototherapy was increased by 40% compared with that in non-exposed children (Newman et al., 2016). Phototherapy was associated with increased rates of any leukaemia (incidence rate ratio [IRR], 2.1; $P = 0.0007$), non-lymphocytic leukaemia (IRR, 4.0; $P = 0.0004$), and liver cancer (IRR, 5.2; $P = 0.04$). With adjustment for a propensity score, risks were attenuated and confidence intervals included the null value. The Advisory Group noted the lack of consistency between cancer sites in these studies and the possibility of confounding by indication, as suggested by the attenuation in risk with adjustment for propensity score.

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

Studies relevant to key characteristics of carcinogens were identified.

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

Nitrogen dioxide (NO_2) (CAS No. 10102-44-0)

Diesel engine exhaust was classified as *carcinogenic to humans* (Group 1) (IARC, 2013b), gasoline engine exhaust as *possibly carcinogenic to humans* (Group 2B) (IARC, 2013b), and outdoor air pollution as *carcinogenic to humans* (Group 1) (IARC, 2016a). Nitrogen dioxide (NO_2), a pollutant in both engine exhaust and air pollution, was not independently evaluated in previous *IARC Monographs*, because there were few studies available on the association between NO_2 and cancer, and the findings in those studies were ambiguous.

Exposure Data

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).

Cancer in Humans

Recently, a growing number of epidemiological studies, including long-term cohort and case–control studies, have explored the association between increasing exposure to NO_2 and mortality or morbidity from lung cancer, breast cancer, and other cancer types. A meta-analysis of 16 cohorts demonstrated that the hazard ratio for lung cancer mortality was 1.05 (95% confidence interval, 1.02–1.08) per 10 $\mu g/m^3$ increment in NO_2 (Atkinson et al., 2018). A review of eight case–control studies and nine cohort studies indicated that more consistent findings had been reported for elevated NO_2 and risk of breast cancer (White et al, 2018). A few studies suggested a potentially increasing risk of non-melanoma skin cancer, mouth and throat cancer, bladder cancer, and brain tumours (Jørgensen et al., 2016; Datzmann et al., 2018). However, some studies showed ambiguous results, and the Advisory Group noted that correlations among air pollutants make it difficult to ascribe causality to NO_2.

Cancer in Experimental Animals

Previous *IARC Monographs* have reviewed studies in experimental animals, in vivo and in vitro, most of which identified the carcinogenicity of whole engine exhaust and air pollution. To date, limited studies have provided the individual effect of NO_2 on cancer development.

Mechanistic Evidence

A substantial number of studies relevant to several key characteristics of carcinogens are available. Some studies evaluated whether NO_2 is genotoxic (Koehler et al., 2010), and others indicated that NO_2 may act via the induction of increased levels of oxidative free radicals and inflammation (Ahmad et al., 2009).

Recommendation: Medium priority

o-Nitrotoluene and *p*-nitrotoluene

o-Nitrotoluene (CAS No. 88-72-2) was evaluated by the *IARC Monographs* as *probably carcinogenic to humans* (Group 2A) (IARC, 2013c), and *p*-nitrotoluene (CAS No. 99-99-0) was evaluated as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1996).

Exposure Data

o-Nitrotoluene and *p*-nitrotoluene are listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as High Production Volume chemicals.

o-Nitrotoluene and *p*-nitrotoluene are used primarily to produce derivative compounds that are further processed to various dyes or colorants. Exposures to workers would occur in manufacturing or processing facilities where these compounds are used.

Cancer in Humans

No studies of cancer in humans were identified.

Cancer in Experimental Animals

Both compounds have been tested in chronic rodent carcinogenicity studies by the United States National Toxicology Program (NTP, 2002 a, b).

***o*-Nitrotoluene**

o-Nitrotoluene has been reviewed by the United States National Toxicology Program (NTP, 2011c).

In rats, *o*-nitrotoluene caused subcutaneous skin mammary gland tumours in both sexes, malignant mesothelioma and benign or malignant tumours of the liver and lung in males, and benign tumours of the liver in females. In mice, *o*-nitrotoluene caused haemangiosarcomas in both sexes, malignant tumours of the large intestine in males, and benign or malignant tumours of the liver in females (NTP, 2002a).

***p*-Nitrotoluene**

Administration of *p*-nitrotoluene resulted in a modest increase in the incidence of clitoral gland neoplasms in female rats, and slight increases in the incidence of subcutaneous skin neoplasms in male rats

and bronchioloalveolar neoplasms in male mice. There were no treatment-related differences in tumour incidence in female mice (NTP, 2002b).

Mechanistic Evidence

***o*-Nitrotoluene**

In factory workers exposed to *o*-nitrotoluene, *o*-nitrotoluene–haemoglobin adducts were detected in the blood (Jones et al., 2005a) and *o*-nitrobenzoic acid and *o*-nitrobenzyl alcohol were detected in the urine (Jones et al., 2005b), providing evidence that human exposure to *o*-nitrotoluene results in production of a reactive metabolite or metabolites. In addition, adducts between haemoglobin and 2-methylaniline (a metabolite of *o*-nitrotoluene) were identified in both exposed workers and exposed rats, and the level of 2-methylaniline–haemoglobin adducts in the blood of rats was proportional to the level of 2-methylaniline–DNA adducts in the livers of rats (Jones & Sabbioni, 2003; Jones & Sabbioni, 2003).

o-Nitrotoluene induced oxidative DNA damage (increased level of 8-oxo-7,8-dihydro-2′-deoxyguanosine) in cultured human HL-60 leukaemia cells (Watanabe et al., 2010). In rats exposed to *o*-nitrotoluene in vivo, DNA adducts were detected in the liver of males but not of females (NTP, 2008).

o-Nitrotoluene did not induce DNA repair in rat or human hepatocytes. In rats and mice exposed in vivo, *o*-nitrotoluene caused a slight increase in micronucleus formation in peripheral normochromatic erythrocytes in male mice at a high dose level; this finding was not considered conclusive. *o*-Nitrotoluene did not induce micronucleus formation in peripheral normochromatic erythrocytes in female mice or in polychromatic erythrocytes in the bone marrow of male rats or mice (NTP, 2002a, b). *o*-Nitrotoluene was not mutagenic to bacteria, and there were mixed results in studies of its ability to cause genetic damage in cultured mammalian cells (NTP, 2002a).

***p*-Nitrotoluene**

Evidence for genotoxicity is limited; *p*-nitrotoluene was not mutagenic to bacteria, had no effect on micronuclei in bone marrow of male rats or mice, and induced chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells.

The Advisory Group noted that data on similarity to *ortho*-toluidine may be relevant to a review of these compounds.

Recommendation for *p*-nitrotoluene: Medium priority

Recommendation for *o*-nitrotoluene: No evaluation

Non-ionizing radiation (radiofrequency) and extremely low-frequency magnetic fields

Radiofrequency electromagnetic fields (RF-EMF) were evaluated by the *IARC Monographs* as *possibly carcinogenic to humans* (Group 2B) (IARC, 2013e), on the basis of limited evidence of an increased risk of glioma. Extremely low-frequency magnetic fields (ELF-MF) were evaluated as *possibly carcinogenic to humans* (Group 2B) (IARC, 2002), on the basis of *limited evidence* of an increased risk of childhood leukaemia.

Exposure Data

Human exposures to RF-EMF can occur from use of personal devices (e.g. cell phones, cordless phones, and Bluetooth) and from environmental sources such as cell phone base stations, broadcast antennas, and medical applications. More than 5 billion people now have access to cell phone devices, and the technology is constantly evolving. Use has also expanded rapidly in low- and middle-income countries, where more than 75% of adults now report owning a cell phone; in high-income countries, the proportion is 96% (Pew Research Center, 2018).

Cancer in Humans

Since the previous *IARC Monographs* evaluation, several new epidemiological studies have been published on the association between RF-EMF and cancer, although the evidence remains mixed. In the Million Women Study cohort, there was no evidence of increased risk of glioma or meningioma, even among long-term users. There was an increased risk of acoustic neuromas with long-term use and a significant dose–response relationship (Benson et al., 2013). Updated follow-up in the Danish nationwide subscribers study did not find increased risks of glioma, meningioma, or vestibular schwannoma, even among those with subscriptions of 10 years or longer (Frei et al., 2011; Schüz et al., 2011). New reports from case–control studies that assessed long-term use also found mixed results; for example, increased risks of glioma and acoustic neuroma were reported by Hardell & Carlberg (2015) and Hardell et al. (2013), but no evidence of increased risks for these tumours were reported by Yoon et al. (2015) and Pettersson et al. (2014). Röösli et al. (2019) recently reviewed these new data. Several large-scale studies are still in progress and should report results within the next few years. Mobi-Kids is a multicentre case–control study of brain tumours in those aged 10–24 years. Cohort Study of Mobile Phone Use and Health (COSMOS) is a new European cohort of adult cell phone users. There will also be updated results from the Million Women Study.

Cancer in Experimental Animals

New data in experimental animals for exposure to RF-EMF have been published since the previous *IARC Monographs* evaluation. The large study by the United States National Toxicology Program found an increased risk of malignant schwannomas of the heart in male rats with high exposure to radiofrequency radiation at frequencies used by cell phones, as well as possible increased risks of certain types of tumours in

the brain and adrenal glands, but no increased risks in mice or female rats (NTP, 2018a, b). Another study in experimental animals also found an increase in schwannomas of the heart in highly exposed male rats and a possible increase in gliomas in female rats (Falcioni et al., 2018).

Mechanistic Evidence

The previous IARC evaluation concluded that there was weak evidence that radiofrequency radiation was genotoxic but that there was no evidence for mutagenicity (IARC, 2013e). Although there have been many new publications from a wide variety of experiments, uncertainty remains about the mechanisms, and there are few systematic reviews of the new data (Kocaman et al., 2018).

Although a future evaluation could be broadened to consider exposure to all non-ionizing radiation (including ELF-MF), ELF-MF were evaluated by IARC as *possibly carcinogenic to humans* (Group 2B), and the Advisory Group did not recommend an update, because of a lack of new informative epidemiological findings, no toxicological evidence, and little supporting mechanistic evidence.

Key References

The following key references were also identified: Coureau et al. (2014); Carlberg & Hardell (2015); Pedersen et al. (2017).

Recommendation for non-ionizing radiation (radiofrequency): High priority (and ready for evaluation within 5 years)

Recommendation for extremely low-frequency magnetic fields: No evaluation

Nuclear industry work

Different types of ionizing radiation have been evaluated repeatedly by the *IARC Monographs* programme (IARC, 2000b, 2012f), and all types have been classified as *carcinogenic to humans* (Group 1); overall evaluations are based on different evidence streams, often including *sufficient evidence* in humans for several cancer sites. New research in recent years has confirmed increased risks per unit of exposure to ionizing radiation for cancer sites and groups of cancer sites that have already been linked with ionizing radiation. No specific evaluation has been made in respect of work in the nuclear industry, which represents a specific exposure condition for agents already classified as *carcinogenic to humans* (Group 1).

Key References

The following key references were identified: Lee et al. (2015c); Leuraud et al. (2015); Richardson et al. (2015); Schubauer-Berigan et al. (2015); Grellier et al. (2017).

Recommendation: No evaluation

Occupational exposures to insecticides and childhood leukaemia (myeloid and lymphoid)

Occupational exposure to insecticides as a class of chemicals has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

In low-income countries, children who live in rural areas are in contact with agricultural pesticide formulations in a para-occupational way (e.g. via drift from the sprayed fields, the take-home pathway, helping their parents in the fields, and through prenatal exposure) and through child labour in agriculture. The International Labour Organization (ILO, 2019) has estimated that more than 98 million girls and boys (age 5–17 years) are working in agriculture worldwide. Child labour in farming may involve applying fertilizers and spraying pesticides. Some studies in Costa Rica and Nicaragua have shown that urinary pesticide residues in children in rural areas can be as high as those in pesticide applicators.

Exposure to pesticides in homes is widespread. In recent years there has been substantial development in methods to evaluate exposures and validate existing methods. These studies have shown that exposure assessments in epidemiological studies, including those based on self-report, were valid (Gunier, et al., 2011; Deziel, et al., 2015).

Cancer in Humans

The existing studies have evaluated direct exposure of the child after birth from drift/house dust, and direct exposure of the parents before conception and during pregnancy. There has been a major effort to pool epidemiological studies on childhood leukaemia. Recent pooled and meta-analyses of childhood acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) from the Childhood Leukemia International Consortium (the largest to date) showed increased risk with paternal exposure to pesticides at work and at home (Bailey et al., 2014a, 2015a). Studies in California, USA, using dust samples also showed an association with ALL (Metayer et al., 2013; Gunier et al., 2017). A recent study on residential use of pesticides in Costa Rica showed an increase only in boys, related to insecticides (Hyland et al., 2018).

The same studies have evaluated other exposures. Among the most consistent findings are those on solvents, although the findings are generally not as strong as those for pesticides.

Cancer in Experimental Animals

Because in most studies the assessment is performed on pesticides in general without specifying the compounds, there are no corresponding relevant data from animal bioassays.

Mechanistic Evidence

Relevant mechanistic evidence may be available from studies of individual compounds or from mixed exposures.

In summary, there is increasing evidence from high-quality studies that pesticides are associated with ALL and perhaps AML in children. Although there is a series of positive findings among studies of broad groups of pesticides, the studies will not be informative on the carcinogenicity of individual pesticides, which are the current focus of most cancer hazard identification. Accordingly, an evaluation on "pesticides" may not be meaningful within the context of the *IARC Monographs*.

Key References

The following key references were also identified: Rodríguez et al. (2012); van Wendel de Joode et al. (2012); ILO (2019).

Recommendation: No evaluation

Opisthorchis felineus

Opisthorchis felineus was last reviewed by the *IARC Monographs* programme in 1994 (IARC, 1994b); it was evaluated as *not classifiable as to its carcinogenicity to humans* (Group 3), because of a lack of evidence.

Exposure Data

The liver fluke *O. felineus* occurs primarily in the Russian Federation, especially in Western Siberia, and in Ukraine, Belarus, Kazakhstan, and the Baltic countries. However, it now increasingly occurs in other European regions, including in Italy, Greece, and Spain. It is responsible for about 10% of cases of opisthorchiasis – 1.6 million of 17 million cases per year – and can affect the liver, pancreas, and gall bladder. The risk factor for acquisition is consumption of raw or lightly cooked fish containing the parasite.

Cancer in Humans

Data in humans are limited to case reports (Kovshirina et al., 2019) and a single ecological study, which found no association between the incidence of *O. felineus* and the incidence of cancers of the liver and bile duct (Fedorova et al., 2017).

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

O. felineus is closely related to *O. viverrini*, which is classified as *carcinogenic to humans* (Group 1) (IARC, 2012e). Since the last evaluation of *O. felineus*, few additional data have become available to support a carcinogenic role, although several mechanistic models have been postulated based on rodent models (Gouveia et al., 2017; Maksimova et al., 2017).

In view of the sparse evidence, the Advisory Group concluded that further review is not likely to change the current classification.

Recommendation: Low priority

Outdoor air pollution/Urban air pollutants

Outdoor air pollution and particulate matter in outdoor air pollution were classified by IARC as *carcinogenic to humans* (Group 1) (IARC, 2016a), on the basis of *sufficient evidence* for cancer of the lung in humans. Positive associations of outdoor air pollution and cancer of the urinary bladder were also noted, but this evidence was deemed *limited*. Evidence for other cancers, including breast cancer, leukaemia, and lymphoma, and for other cancer sites was based on a small number of informative studies and was inconsistent. There was also *sufficient evidence* of carcinogenicity in experimental animals, as well as a range of genetic and related effects, including oxidative stress and sustained inflammation. Results of recent studies in experimental animals and mechanistic evidence for ambient benzene exposure are summarized in IARC (2018b).

Exposure Data

Sources of human exposure are widespread and are both natural and anthropogenic, including, for example, emissions from mobile sources, power generation, industrial processes, residential heating and cooking, and dust storms. Many important species are also secondarily formed in the atmosphere. It was estimated that 87% of the world's population live in areas exceeding the WHO Air Quality Guideline of 10 $\mu g/m^3$ for particulate matter with particles of aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) (Brauer et al., 2016). Trends vary by pollutant and by region. Large increases in global population-weighted $PM_{2.5}$ concentrations were noted in recent decades, driven largely by increases in South Asia, South-East Asia, and China (Brauer et al., 2016). In contrast, there were decreasing trends in many high-income countries.

Cancer in Humans

Results from several large-scale epidemiological studies of cancer types other than cancer of the lung have been published since the previous IARC evaluation, including in Europe, North America, and Asia, although findings are generally mixed, including in studies of bladder cancer (Turner et al., 2017; Pedersen et al., 2018b) and breast cancer (Andersen et al., 2017; Hart et al., 2018), and appear to remain insufficient for the classification of additional cancer sites to either the *sufficient* or *limited* evidence category. Some studies have noted positive associations with cancers of the digestive tract (Pan et al., 2015; Wong et al., 2016; Turner et al., 2017). The previous IARC evaluation also noted some weak suggestive associations with childhood leukaemia, although they were inconsistent. A recent meta-analysis reported significant positive associations of traffic-related air pollution (as an indicator of ambient benzene exposure) and childhood leukaemia, which were stronger for acute myeloid leukaemia than for acute lymphoblastic

leukaemia (Carlos-Wallace et al., 2016). Some positive associations have also been noted with different indicators of ambient air pollution in other recent studies (Houot et al., 2015; Lavigne et al., 2017), although limitations associated with exposure assessment, confounding, and bias remain of concern. In one study, early-life exposure to air pollution was associated with DNA methylation of tumour suppressor genes in human breast tumours (Callahan et al., 2018).

The Advisory Group considered that the new epidemiological evidence appears to support the classification of additional cancer sites to either the *sufficient* or *limited* evidence category.

Recommendation: Low priority

Oxymetholone (CAS No. 434-07-1)

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

Exposure Data

Oxymetholone is a 17α-alkylated anabolic–androgenic steroid synthesized from testosterone (Pavlatos et al., 2001; NTP, 2016d). Oxymetholone was first described in 1959 (Pavlatos et al., 2001). It is used for treatment of several conditions, including hypogonadism, delayed puberty, and hereditary angioneurotic oedema, and to stimulate production of red blood cells (NTP, 2016d). Oxymetholone is also used to stimulate weight gain (Hengge et al., 1996). In addition, athletes abuse it in attempts to improve performance (Socas et al., 2005).

Cancer in Humans

There is a paucity of information from epidemiological studies evaluating the association between exposure to oxymetholone and cancer in humans. Most of the evidence has come from case reports with small sample sizes. A large number of case reports on liver tumours in patients with aplastic anaemia, Fanconi anaemia, paroxysmal nocturnal haemoglobinuria, and other disorders treated with oxymetholone alone or in combination with other androgenic drugs have been published (IARC, 1977; NTP, 2016d).

In a review performed in 2004 on the association of exposure to anabolic steroids and cancer development in patients with and without anaemia, hepatocellular carcinomas were associated with exposure to oxymetholone (Velazquez & Alter, 2004). The authors highlighted that even in the absence of anaemia, treatment with oxymetholone was associated with hepatocellular carcinoma. The study also showed that oxymetholone was one of the anabolic steroids used most often (Velazquez & Alter, 2004).

Cancer in Experimental Animals

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 relevant to key characteristics of carcinogens are available, particularly on receptor-mediated effects. Oxymetholone was not mutagenic in bacterial assays, did not induce chromosomal aberrations in cultured Chinese hamster ovary cells, and was negative in the mouse micronucleus assay (NTP, 1999a).

Key Reference

The following key reference was also identified: Zhang et al. (2016b).

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

Ozone (O_3) (CAS No. 10028-15-6)

Ozone (O_3) has not been previously evaluated by the *IARC Monographs* programme. Outdoor air pollution was classified as *carcinogenic to humans* (Group 1) (IARC, 2016a), and specifically particulate matter in outdoor air pollution was classified as *carcinogenic to humans* (Group 1) (IARC, 2016a). Ozone, a pollutant in both engine exhaust and air pollution, was found to show an increasing risk of cancer. However, the results were inconsistent, as summarized in *IARC Monographs* Volume 109 (IARC, 2016a).

Exposure Data

Ozone is listed by the Organisation for Economic Co-operation and Development (for year 2007) as a High Production Volume chemical.

As a major component of photochemical smog, ozone is formed in the atmosphere through reactions of nitrogen oxides with volatile organic compounds and carbon monoxide, or through natural processes (e.g. in the stratosphere). The levels of ozone in pre-industrial ages were approximately 30 $\mu g/m^3$. However, background levels are currently about twice that level, corresponding to worldwide anthropogenic emissions of nitrogen oxides and volatile organic compounds. The concentration in urban areas sometimes reaches about 400 $\mu g/m^3$, more than 10 times the general background level.

Cancer in Humans

Epidemiological cohort studies and case–control studies cited in *IARC Monographs* Volume 109 (IARC, 2016a) demonstrated null associations between exposure to ozone and risk of cancer. Since 2016, a few studies have been published, including several cohort studies and two meta-analyses (Atkinson et al., 2016; Yang et al., 2016). Most of them found no evidence of associations between ozone exposure and cancer risk.

Cancer in Experimental Animals

The few animal experiments cited in *IARC Monographs* Volume 109 (IARC, 2016a) showed the individual effect of ozone from the mixture of air pollutants. However, in a 2-year good laboratory practice (GLP) study, ozone caused a marginal increase in the incidence of bronchioloalveolar adenoma or carcinoma (combined) in male mice and of bronchioloalveolar carcinoma and bronchioloalveolar adenoma or carcinoma (combined) 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, 1994c).

Mechanistic Evidence

A substantial number of studies relevant to key characteristics of carcinogens are available. Since the previous evaluation, studies in experimental animals and in vivo have indicated that ozone can produce oxidative stress and induce genetic effects (Di Mauro et al., 2019).

Key Reference

The following key reference was also identified: Lipfert (2018).

Recommendation: Medium priority

Paints and solvents and risk of childhood leukaemia

In the context of a re-evaluation of occupational exposure as a painter, classified as *carcinogenic to humans* (Group 1) (IARC, 1989a, 2010f, 2012b), the Working Group of *IARC Monographs* Volume 98 also concluded that there is *limited evidence* of carcinogenicity in humans, primarily on the basis of studies of maternal exposure, and that painting is associated with childhood leukaemia. This evaluation was confirmed in Volume 100F.

Benzene has been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1987, 2012b, 2018b) and since Supplement 1 is classified as *carcinogenic to humans* (Group 1). The current evaluation (IARC, 2018b) is based on *sufficient evidence* both in experimental animals and in humans; in addition, the Working Group also concluded for the first time that a positive association has been observed between exposure to benzene and childhood acute myeloid leukaemia (AML).

Recent pooled and meta-analyses of childhood AML and acute lymphoblastic leukaemia (ALL) from the Childhood Leukemia International Consortium (the largest to date) showed no increased risk with paternal and maternal exposure to paints at work, although a positive association with exposure at home was reported for defined periods before and during pregnancy and after birth (Bailey et al., 2014b, 2015b). However, because exposure to paints at home represents a specific exposure condition where a determination of *limited evidence* already exists, no further evaluation is warranted.

Key References

The following additional key references were also identified: Metayer et al. (2016b); Whitehead et al. (2016).

Recommendation: No evaluation

Parabens

Parabens have not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Parabens are a group of chemicals that are widely used as preservatives in cosmetics, personal care products, pharmaceuticals, some food commodities, and industrial products (Barr et al., 2012; Kirchoff & De Gannes, 2013; Błędzka et al., 2014). Parabens were introduced in the mid-1930s as a preservative in drug products, and their use has increased since then (Kirchoff & De Gannes, 2013). The main sources of human exposure to parabens are use of cosmetics and pharmaceuticals (Błędzka et al., 2014; Ramaswamy et al., 2011). Parabens have a ubiquitous presence in the environment and have been found in water sources, soil in agricultural fields, sediments, indoor air, and dust (Błędzka et al., 2014). Parabens have been detected in human tissue and bodily fluids, including in breast cancer tissue (Barr et al., 2012; Darbre & Harvey, 2014).

Cancer in Humans

Epidemiological studies on parabens and cancer are sparse. One study investigated use of underarm deodorant with underarm shaving as a proxy for exposure to parabens. That study found that in 437 women diagnosed with breast cancer, use of underarm deodorant with underarm shaving was associated with earlier diagnosis of breast cancer (McGrath, 2003). However, the level of exposure to parabens from use of underarm deodorant with underarm shaving is not well characterized. An earlier study (Mirick et al., 2002) did not show an association between underarm shaving and breast cancer.

Cancer in Experimental Animals

In female and male ICR/Jcl mice aged 8 weeks, oral administration of butylparaben (0.15%, 0.3%, or 0.6%) in the diet for up to 102 weeks produced neoplasms in the haematopoietic system, including thymic lymphoma, non-thymic lymphoid leukaemia, and myeloid leukaemia. In addition, a moderately high incidence of lung adenomas and adenocarcinomas and of soft tissue myosarcomas and osteosarcomas was found. However, the tumour incidence was not significantly different from that in the control group (Inai et al., 1985; NTP, 2005c). One oral study in mice and one oral study in rats with butylparaben were negative (Odashima, 1980). In a xenograft study in ovariectomized female nu/nu mice implanted with a patient-derived xenograft breast tumour line plus MCF-7 cells, methylparaben increased tumour proliferation and xenograft MCF-7 tumour formation (Lillo et al., 2017).

Mechanistic Evidence

Studies relevant to key characteristics of carcinogens have investigated potential effects relevant to whether parabens modulate receptor-mediated effects. Parabens are considered as endocrine-disrupting (Lillo et al., 2017), and estrogenic activity (including uterotropic activity in mice) has been observed in experimental animals (Karpuzoglu et al., 2013; Błędzka et al., 2014). The estrogenic activities of the parabens increase as the length and branching of the alkyl ester increase (Darbre et al., 2004).

Parabens bind to human estrogen receptors, although with significantly lower affinity than to estradiol (Kirchoff & De Gannes, 2013). In vitro assays have shown that, once bound to the estrogen receptors, ligand-based transcription factors elicit expression of genes involved in cell proliferation (Wróbel & Gregoraszczuk, 2014, 2015). Parabens were negative in genetic toxicity tests conducted by the United States National Toxicology Program (NTP, 2019a).

The Advisory Group noted that the evaluation could be organized based on structure or structure–activity relationship.

Key References

The following key references were also identified: Alan & Williams (2004); Wróbel & Gregoraszczuk (2013); Patel (2017).

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

Pendimethalin (dinitroaniline herbicide) (CAS No. 40487-42-1)

Pendimethalin has not been previously evaluated by the *IARC Monographs* programme. The 2014 Priorities Advisory Group assigned pendimethalin a high priority (IARC, 2014).

Exposure Data

Pendimethalin is a dinitroaniline herbicide with unrestricted use that is applied to crops, lawns, and gardens by farmers, professional applicators, and homeowners. In agriculture it is applied to cotton, rice, onions, fruit trees, corn, sorghum, and tomatoes and is used for the control of suckers in tobacco.

In 1997, the United States Environmental Protection Agency classified pendimethalin as a "possible human carcinogen" (Group C).

Cancer in Humans

Recent epidemiological data from the United States National Cancer Institute Agricultural Health Study have suggested that pendimethalin is associated with an excess risk of cancers of the lung and other sites. Overall cancer incidence did not increase with increasing lifetime pendimethalin use.

Cancer in Experimental Animals

Two long-term bioassays in experimental animals reviewed by the United States Environmental Protection Agency (EPA, 1996) reported increases in the incidence of follicular cell adenoma of the thyroid in male and/or female rats.

Mechanistic Evidence

Recent high-throughput data also provided new insights into the extent of biological activity. Pendimethalin significantly enhanced the oxidative stress markers (protein carbonylation and lipid peroxidation) and decreased or suppressed antioxidant defences (glutathione, superoxide dismutase, catalase, glutathione *S*-transferase) in liver and kidney tissues of rats. The histopathological changes observed in the liver and kidney included leukocyte infiltration, pyknotic nuclei, necrosis, enlargement of the Bowman space, and shrinkage of the renal cortex. Although it was not positive in other genotoxicity tests, pendimethalin induced DNA damage in lymphocytes and V79 cells through the activation of oxidative stress pathways and chromosomal damage.

Key References

The following key references were also identified: Hurley (1998); Alavanja et al. (2004); Hou et al. (2006); Weichenthal et al. (2010); Bonner et al. (2017); Ahmad et al. (2018); Sarıgöl Kılıç et al. (2018).

Recommendation: Medium priority

Pentabromodiphenyl ethers (CAS No. 32534-81-9)

Pentabromodiphenyl ethers have not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

The pentabromodiphenyl ether mixture DE-71 (technical grade) is listed by the United States Environmental Protection Agency as a High Production Volume chemical.

DE-71 (technical grade) is a pentabromodiphenyl ether mixture that is used as a flame retardant, often in furniture materials. The use of pentabromodiphenyl ethers has been discontinued in the European Union and in the USA, but pentabromodiphenyl ethers have been found in the environment, in humans, and in various food products.

Cancer in Humans

No epidemiological studies of cancer are available for pentabromodiphenyl ethers. 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., 2018a). In small case–control studies, no association was observed between polybrominated diphenyl ethers and cancer of the prostate in Singapore (Pi et al., 2016) and cancer of the thyroid in the USA (Aschebrook-Kilfoy et al., 2015).

Cancer in Experimental Animals

In a bioassay performed by the United States National Toxicology Program (NTP, 2016c), administration of DE-71 significantly increased the incidence of: hepatocellular adenoma or carcinoma (combined) and hepatocholangioma, hepatocellular adenoma, or hepatocellular carcinoma (combined) in male and female rats; adenoma in the pars distalis of the pituitary gland in male rats; follicular cell carcinoma in female rats; and hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) in male and female mice (NTP, 2016c).

Mechanistic Evidence

Studies relevant to key characteristics of carcinogens are available, particularly indicating that DE-71 is not genotoxic but induces oxidative stress and has receptor-mediated effects; in addition, there is some evidence of immunosuppression as well as hyperplasia in rodents. DE-71 was negative in various genetic toxicology tests (in bacteria, mouse bone marrow cells, and mouse peripheral blood erythrocytes) conducted by the United States National Toxicology Program (NTP, 2016c).

The Advisory Group recommended that the pentabromodiphenyl ether mixture DE-71 be evaluated together with other polybrominated diphenyl ethers and/or components.

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

Pesticide spraying (occupational exposure to)

Occupational exposures to non-arsenical insecticides have been classified as *probably carcinogenic to humans* (Group 2A) (IARC, 1991), solely on the basis of *limited evidence* of carcinogenicity in humans. Occupational exposure to pesticides was recommended for re-evaluation with high priority in 2014 (IARC, 2014). However, the 2014 Priorities Advisory Group recommended framing occupational evaluations as narrowly as possible (IARC, 2014), noting that the grouping "non-arsenical insecticides" that was evaluated in 1991 was very broad and included multiple classes of differently acting pesticides, somewhat limiting the utility of the evaluation as Group 2A.

Exposure Data

"Pesticides" include a wide range of chemical insecticides, herbicides, fungicides, or nematode control agents that are used to prevent, destroy, or mitigate pests (EPA, 2019e). "Pesticide application" refers to the practical way in which these agents are delivered to their biological targets (e.g. pest, crop, or other plant), such as during seed treatment, where pesticides are applied to seeds before planting, and spraying of pre- and post-emergent crops (i.e. before and after the target weeds have emerged from the soil) (Matthews, 2000). It has been estimated that nearly 2 billion people worldwide are engaged in agriculture; most use pesticides to protect their products (Alavanja, 2009). Outside of agriculture, public health employees, landscapers, and other types of workers may also be exposed. Occupational exposure to pesticides may occur during a worker's preparation, application, or entry into an area where pesticides have been applied (e.g. during crop picking) (EPA, 2019e). Exposures may occur through multiple exposure routes (oral, dermal, and inhalation), depending on the type of pesticide and its use (EPA, 2019e). In many low- and middle-income countries, measures to control exposures are limited or non-existent (Alavanja, 2009). In addition, there is potential for exposures to occur not only in agriculture but also in recreational areas and in households.

Cancer in Humans

Many pesticide workers are exposed to a wide variety of different pesticides during their employment, which makes specific epidemiological evaluations difficult. Since 1991, several new epidemiological reports have been published that examined associations between specific pesticides and cancer, such as in the United States National Cancer Institute Agricultural Health Study.

Cancer in Experimental Animals

No new cancer bioassays are available.

Mechanistic Evidence

Mechanistic information relevant to key characteristics of carcinogens for specific pesticides has been identified or become available.

In summary, available epidemiological and mechanistic information, together with publicly available animal cancer bioassay data, has supported first-time or updated evaluations of several particular pesticides (e.g. IARC, 2017c, 2018d, 2019e). A published chemoinformatics analysis on pesticides (see http://pesticide.barupal.org and Guha et al., 2016) informed consideration of the individual pesticides evaluated, also taking into account specific agents and agent classes recommended by the 2014 Priorities Advisory Group. The Advisory Group suggested that the approach of evaluating specific agents may provide greater clarity about the potential carcinogenicity of pesticides relevant for understanding cancer hazards from occupational exposures from pesticide spraying.

Key References

The following key references were also identified: Blair et al. (1993); Pesatori et al. (1994); Becher et al. (1996); Alavanja et al. (2004); Walker et al. (2005); González et al. (2006, 2007); Weichenthal et al. (2010); Alavanja & Bonner (2012); Ojha & Srivastava (2014); Zafiropoulos et al. (2014); Jones et al. (2015); Tual et al. (2016); Bonner et al. (2017); Engel et al. (2017); Louis et al. (2017); EPA (2017b); Wang et al. (2017a); Korea Crop Protection Association (2018); van der Plaat et al. (2018).

Recommendation: No evaluation

Phenyl and octyl tin compounds

These compounds have not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Organotin compounds are substances composed of tin, directly bound to several organic groups. Organotin compounds are mostly known for their biocidal effects. They have been used for multiple applications as biocides and pesticides, as stabilizers for polyvinyl chloride (PVC), and as catalysts for various products. Phenyl and octyl tin compounds are used as antifouling agents and have potentially widespread human and environmental exposures that are of great public health concern.

Cancer in Humans

Very few epidemiological studies have assessed the potential health impact of chronic low-level exposure to organotin compounds. There is currently no epidemiological evidence that tin or tin compounds cause cancer in humans. Some studies have reported metabolic or endocrine-disrupting effects in newborns (weight gain, cryptorchidism).

Cancer in Experimental Animals

Some studies in experimental animals showed that a specific organotin, triphenyltin hydroxide, can produce cancer in animals after long-term oral administration.

Mechanistic Evidence

The main carcinogenic action of phenyl and octyl tin compounds appears to be hormonal. Organotin compounds have been shown to produce endocrine-disrupting effects in aquatic species and rodent models, raising concerns about effects on human reproduction and development. Some in vitro tests demonstrating placental estrogen stimulation or adipogenic effects strengthen the consideration of organotin compounds as endocrine-active compounds. Organotin compounds inhibit the enzymatic activity of aromatase. Activation of the peroxisome proliferator-activated receptor gamma (PPARγ) and/or the retinoid X receptor (RXR) has been proposed as a novel mechanism for organotin-induced effects in mammals.

Key References

The following key references were also identified: ATSDR (2005); WHO (2006); MAK (2007); Nakanishi (2008); Varela-Ramirez et al. (2011); Rantakokko et al. (2014); NTP (2016e).

Recommendation: No evaluation

Polychlorinated biphenyls (dietary exposure)

Polychlorinated biphenyls (PCBs) have been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1987, 2016c) and since Volume 107 are classified as *carcinogenic to humans* (Group 1), on the basis of *sufficient evidence* of carcinogenicity both in experimental animals (for some individual PCBs and some commercial mixtures of PCBs) and in humans. The current evaluation (IARC, 2016c) specifies that PCBs cause malignant melanoma. Also, positive associations have been observed between exposure to PCBs and non-Hodgkin lymphoma and cancer of the breast. In addition, dioxin-like PCBs have been classified as *carcinogenic to humans* (Group 1), based on strong evidence to support a receptor-mediated mechanism for carcinogenesis associated with dioxin-like PCBs in humans.

The previous review (IARC, 2016c) encompassed dietary exposures to PCBs and cancer in humans, cancer bioassays with dietary exposures to PCBs, and absorption, distribution, metabolism, and excretion as well as mechanistic studies based on dietary exposures to PCBs. Recently published studies on dietary exposures to PCBs for any cancer site (including cancers of the prostate, breast, endometrium, and ovary) have not provided strong evidence of an association (Ali et al., 2016; Donat-Vargas et al., 2016, 2017).

In summary, dietary exposure to PCBs represents a specific exposure condition for an agent already classified as *carcinogenic to humans* (Group 1), which was previously reviewed across the full *Monograph* and for which no new evaluation for certain cancer sites is anticipated.

Recommendation: No evaluation

Polycyclic aromatic hydrocarbons as a group

Polycyclic aromatic hydrocarbons (PAHs) as a group have not been previously evaluated by the *IARC Monographs* programme. The 2014 Priorities Advisory Group assigned this group a low priority (IARC, 2014). As noted at the time, a considerable number of individual PAHs were evaluated by the *IARC Monographs* (IARC, 2010b). Several types of complex mixtures containing PAHs were also evaluated, including household use of solid fuels (IARC, 2010c), bitumens and bitumen emissions (IARC, 2013a), diesel and gasoline engine exhausts (IARC, 2013b), and outdoor air pollution (IARC, 2016a). Individual PAHs currently span the whole spectrum of IARC evaluations, from *carcinogenic to humans* (Group 1) to *not classifiable as to its carcinogenicity to humans* (Group 3), and different preferential metabolic pathways and mechanisms of action have been identified (Moorthy et al., 2015). This variability, along with the fact that complex mixtures in which PAHs are present also typically contain other potential carcinogens (e.g. nitro-PAHs and heterocyclic PAHs, aromatic amines), presents difficulties for the accurate evaluation of PAHs as a group, because limited studies are available on exposure to pure, well-characterized mixtures of PAHs. Nonetheless, exposure to PAHs as a group is a more realistic exposure scenario in occupational and environmental settings than exposure to the individual compounds.

Cancer in Humans

A few epidemiological studies reporting an increased risk of cancer in association with occupational and environmental exposure to PAHs as a group have been published in recent years. Positive results have been found for cancers of the breast (White et al., 2016; Shen et al., 2017; Lee et al., 2019) and larynx (Wagner et al., 2015). Associations with cancers of the lung (Olsson et al., 2010; Petit et al., 2019) and bladder (Boada et al., 2015), as well as lymphatic and haematopoietic neoplasms (Alicandro et al., 2016), were weak or were not found.

Cancer in Experimental Animals

There was no evaluation of carcinogenicity in experimental animals of PAHs as a group in the *IARC Monographs* evaluation on PAHs (IARC, 2010b). However, *IARC Monographs* Volume 92 reported on a significant number of positive inhalation, skin application, and subcutaneous or intraperitoneal injection studies of environmental or laboratory mixtures of PAHs in mice and rats showing an increase in the incidence of benign or malignant tumours at various organ or tissue sites. In addition, there is *sufficient evidence* of carcinogenicity in experimental animals for numerous individual PAHs (IARC, 2010b).

Mechanistic Evidence

Mechanistic data relevant to key characteristics, especially concerning whether PAHs are genotoxic, are available.

The Advisory Group concluded that an evaluation of the risk of cancer in humans for all PAHs as a group is difficult because of the heterogeneity in the likely effects. Although the group of PAHs as a whole

is too diverse to be considered as a single class, the Advisory Group considered that subgroups of PAHs could be developed on the basis of mechanistic and structure–activity considerations. These could then be used to identify the classes for evaluation and be based on well-studied chemicals in the class and information from new approach methods in toxicology.

Recommendation: No evaluation

Poor oral hygiene

Poor oral hygiene has not been previously evaluated by the *IARC Monographs* programme. Of the infectious agents that are implicated, some are classified as *carcinogenic to humans* (Group 1): the viruses human papillomavirus (HPV), linked to oropharyngeal cancer; Epstein–Barr virus (EBV), linked to endemic Burkitt lymphoma; and Kaposi sarcoma-associated herpesvirus (KSHV), linked to Kaposi sarcoma. Others (e.g. the bacterium *Porphyromonas gingivalis*, linked to pancreatic cancer) are not.

Exposure Data

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-East 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 has been examined predominantly in relation to cancers of the digestive tract. Many case–control studies have evaluated poor oral hygiene. Positive associations with cancers of the oral cavity were observed for infrequent or no tooth brushing, for example in Beijing, China (Zheng et al, 1990), in Fujian, China in never-smoker, never-drinker women (Chen et al., 2017a), in Nigeria (Oji & Chukwuneke, 2012), in southern Sweden (Rosenquist, 2005), and in India (Balaram et al., 2002). For squamous cell oesophageal cancer, positive associations of increased tooth loss, decayed, missing, or filled teeth (DMFT) score, and poor oral hygiene were found in Golestan, Islamic Republic of Iran, not confounded by alcohol consumption or tobacco use (Abnet et al., 2008), and similar positive associations were found in Kashmir, India (Dar et al., 2013), in China, and in Kenya (Menya et al., 2018). Although the epidemiological evidence

for associations between poor oral hygiene and cancers is reasonably strong (Joshy et al., 2016), there is concern that some may be confounded by other key factors (e.g. tobacco use, socioeconomic factors) and that a causal relationship may be difficult to establish. Recent meta-analyses have concluded that the evidence for causality is scant (Corbella et al., 2018; Xie et al., 2018).

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

There are no clear animal models and only limited data on the proposed mechanisms, which include inflammation after infections in the oral cavity or carcinogenic processes associated with dysbiosis of the oral microbiome. Carcinogenic pathways associated with alterations of the oral microbiome have been hypothesized, for example production of acetaldehyde by oral microbes, by *Streptococcus* and *Candida* species, alone or after ingestion of ethanol or endogenous production of *N*-nitroso compounds or reactive oxygen species.

Key References

The following key references were also identified: Abnet et al. (2005); Huang et al. (2016); Yang et al. (2017b); Thistle et al. (2018).

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

Riddelliine (pyrrolizidine alkaloids) (CAS No. 23246-96-0)

Riddelliine was evaluated by the *IARC Monographs* as *possibly carcinogenic to humans* (Group 2B) (IARC, 2002). The 2014 Priorities Advisory Group assigned riddelliine a medium priority, and it was recommended that any re-evaluation include other pyrrolizidine alkaloids that appear to act through a similar mechanism (Straif et al., 2014).

Exposure Data

The riddelliine-containing plant *Senecio longilobus* has been used in medicinal herb preparations in the USA, and *S. jacobaea* and *S. vulgaris*, both of which have been shown to contain riddelliine, are used in medicinal preparations in other parts of the world.

Cancer in Humans

There were no data on the carcinogenicity of riddelliine in humans, and no epidemiological studies have been reported since the previous evaluation.

Cancer in Experimental Animals

Since the previous evaluation, no additional bioassays on riddelliine have been reported.

Mechanistic Evidence

There have been several studies on the mechanism for the genotoxicity and induction of tumours by riddelliine. Publications since the 2014 Advisory Group review (Straif et al., 2014) further explored mechanisms (e.g. cytotoxicity, protein and DNA binding) of cancer and non-cancer outcomes using in vitro and in vivo models.

The proposed mechanism appears to apply to other carcinogenic pyrrolizidine alkaloids: retrorsine (Group 3), monocrotaline (Group 2B), lasiocarpine (Group 2B), heliotrine, clivorine, and senkirkine (Group 3).

The Advisory Group considered that it may be important to consider other pyrrolizidine alkaloids at the same time, because of the similarity in the reactive intermediate or intermediates.

Key References

The following key references were also identified: NTP (2003, 2016i).

Recommendation: Low priority

Salmonella typhi

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

Exposure Data

Humans are the main reservoir for *S. typhi*, and transmission occurs by sewage-polluted crops and food items, as well as person-to-person transmission. The 2014 Priorities Advisory Group assigned *S. typhi* a medium priority (IARC, 2014).

Cancer in Humans

Diverse epidemiological studies (prospective, retrospective, cross-sectional, ecological, and meta-analysis) have consistently linked chronic carriage of *S. typhi* to cancer of the gall bladder. A limitation of the studies in humans is that *S. typhi* may not be viable in the host at the time of diagnosis of gall bladder cancer, but its effect may persist.

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

Data from mechanistic studies support the findings from epidemiological studies. New mechanistic data from Asia, Europe, USA, and Latin America provide more evidence on the potential carcinogenicity of *S. typhi*. The typhoid toxin and the cytolethal distending toxins have carcinogenic potential associated with DNA damage. The biofilm formation of *S. typhi*, associated with polyamine metabolites, is also a potential carcinogenic factor. Bacterial degradation, bile salts, and other bacterial products could cause gall bladder cancer. The latter two mechanisms have been described in colon cancer associated with intestinal bacteria.

Studies in mouse models of *S. typhi* infection and gall bladder cancer reported that gallstones and *S. typhi* caused inflammation, but only *S. typhi* infection caused premalignant lesions.

Key References

The following key references were identified: Axelrod et al. (1971); Welton et al. (1979); Mellemgaard & Gaarslev (1988); Csendes et al. (1994); Caygill et al. (1994, 1995); Strom et al. (1995); Singh et al. (1996); Nath et al. (1997, 2010); Roa et al. (1999); Dutta et al. (2000); Shukla et al. (2000); Serra et al. (2002); Pandey & Shukla (2003); Hazrah et al. (2004); Yagyu et al. (2004); Vaishnavi et al. (2005); Mager (2006); Sharma et al. (2007); Capoor et al. (2008); Tewari et al. (2010); Guerra et al. (2011); Safaeian et al. (2011); Gonzalez-Escobedo et al. (2013); Guidi et al. (2013a, b); Nagaraja & Eslick (2014a, b); Scanu et al. (2015); Zhang et al. (2015b); Del Bel Belluz et al. (2016); Frisan (2016); Koshiol et al. (2016); Pratap et al. (2016); Taieb et al. (2016); Walawalkar et al. (2016a, b); Di Domenico et al. (2017); Kim et al. (2017); Mittal et al. (2018); Nickerson et al. (2018); Tsuchiya et al. (2018).

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

Schistosoma mansoni

Schistosoma mansoni was evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1994b), on the basis of *inadequate evidence* both in humans and in experimental animals.

Exposure Data

S. mansoni is a trematode that lives for years in the mesenteric veins of humans, where it produces hundreds of eggs per day. Half of the eggs migrate to the intestinal lumen and are passed out of the body. Once in the environment, they infect a snail, in which the adult worm develops. These snails infect humans through the skin. Half of the eggs go into the blood and into the liver, where they get trapped. Current evidence suggests that human oncogenicity in the intestines or the liver is caused by *S. mansoni* eggs.

Cancer in Humans

Well-designed studies of cancer in humans remain scarce. Most are case reports and retrospective studies of hepatocellular carcinoma (HCC), of which most lack comparison groups, which makes it difficult to interpret their findings. Some studies in humans have suggested synergy of *S. mansoni* with hepatitis C virus or with aflatoxin in the development of HCC.

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

Since 1994, new evidence of carcinogenicity of *S. mansoni* for HCC has been published from mechanistic studies, in vivo and in human cells. Experimental studies in animals (hamsters) demonstrated the mechanism by which *S. mansoni* eggs maintain activation of hepatic cells and the DNA proliferation process that promotes HCC. Another study in mice showed synergy between *S. mansoni* and diethylnitrosamine in promoting HCC. An example of a mechanism comes from 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., 2018).

It may be useful to investigate whether there is evidence of chronic inflammation to support prioritization.

In conclusion, new well-designed studies in experimental animals provide evidence in favour of liver carcinogenicity of *S. mansoni*. However, evidence in humans has not improved substantially.

Key References

The following key references were also identified: Haese & Bueding (1976); Basílio-de-Oliveira et al. (2002); Palumbo (2007); Mazigo et al. (2010); Anthony et al. (2012); Abdel-Rahman et al. (2013); El-Tonsy et al. (2013, 2016); Pérez del Villar et al. (2013); Ndeffo-Mbah et al. (2014); Chalmers et al. (2015); Toda et al. (2015); Herman et al. (2017); Omar et al. (2017); Rujeni et al. (2017); van Tong et al. (2017); Filgueira et al. (2018); Vicentino et al. (2018); Weiskirchen et al. (2018).

Recommendation: Medium priority

Sedentary behaviour

Sedentary behaviour has not been previously evaluated by the *IARC Monographs* programme. Physical inactivity and sedentary behaviour are closely intertwined. Sedentary work is an emerging area of research that has been investigated as a risk factor for cancer independent of recreational levels of physical activity. Physical inactivity and sedentary work were reviewed jointly by the 2014 Priorities Advisory Group (Straif et al., 2014). Although the combined topic was ranked as a high priority, that Advisory Group encouraged

IARC "to assess whether or not physical activity would be a more relevant topic for the *Handbooks of Cancer Prevention* (update), rather than evaluating physical inactivity for the *Monographs* programme." Physical activity is currently under consideration as a topic for the *IARC Handbooks* programme.

Exposure Data

The prevalence of low average weekly physical activity at work, at home, transport-related, and recreational (defined as < 8000 total metabolic equivalent minutes per week) was estimated to be 46.6% (95% confidence interval [CI], 42.0–50.3%) for men and 39.4% (95% CI, 35.0–43.4%) for women worldwide, leading to more than 1.6 million (95% CI, 1.3–2.0 million) all-cause deaths and 35 million (95% CI, 27–42 million) disability-adjusted life years in 2015 (Forouzanfar et al., 2016). 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 were also estimated to be attributable to low physical activity in 2015.

Cancer in Humans

A systematic review and meta-analysis of domain-specific physical activity in relation to cancers of the colon and rectum reported that increased levels of occupational, recreational, and transport-related activity were associated with lower risk of colon cancer. Furthermore, increased levels of occupational sedentary behaviour were associated with increases in risk of colon cancer.

A meta-analysis of sedentary behaviour and incident cancer based on 17 prospective studies reported that sedentary behaviour was associated with a 20% increased risk of cancer (relative risk [RR], 1.20; 95% CI, 1.12–1.28). In subgroup analysis, there were statistically significant associations between sedentary behaviour and specific cancer types, including endometrial cancer (RR, 1.28; 95% CI, 1.08–1.53), colorectal cancer (RR, 1.30; 95% CI, 1.12–1.49), breast cancer (RR, 1.17; 95% CI, 1.03–1.33), and lung cancer (RR, 1.27; 95% CI, 1.06–1.52). There was no association of sedentary behaviour with ovarian cancer (RR, 1.26; 95% CI, 0.87–1.82), renal cell carcinoma (RR, 1.11; 95% CI, 0.87–1.41), or non-Hodgkin lymphoid neoplasms (RR=1.09; 95% CI, 0.82–1.43).

In two additional meta-analyses of sedentary behaviour and breast cancer risk, one found a slightly increased risk and the other found no association between high levels of sedentary behaviour and breast cancer. A pooled analysis of two population-based case–control studies, more specifically focused on sedentary work, found no association between self-reported sedentary work and breast cancer risk among either premenopausal or postmenopausal women.

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

Physical activity may be related to cancer prevention through multiple mechanisms. Mechanistic studies of physical inactivity and cancer in both human and animal populations have been described related to

sustaining proliferative signalling, evading growth suppressors, activating invasion and metastasis, resisting cell death, and inducing angiogenesis (Ruiz-Casado et al., 2017).

In summary, consistent evidence has been found of positive associations with colon cancer or colorectal cancer in large studies. The Advisory Group suggested 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 may demonstrate independent effects.

Key References

The following key references were also identified: Schmid & Leitzmann (2014); Shen et al. (2014); Zhou et al. (2015a); Boyle et al. (2016); Mahmood et al. (2017).

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

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

Selenium and selenium compounds were previously evaluated by the *IARC Monographs* as *not classifiable as to their carcinogenicity to humans* (Group 3) (IARC, 1975, 1987), on the basis of *inadequate evidence*.

Exposure Data

Human exposure to selenium and selenium compounds occurs mainly through drinking-water and the food chain but also through air. Selenium has nutritional and toxicological implications. Both deficiency and excessive intake of this chemical agent have adverse effects on health.

Cancer in Humans

A large number of epidemiological studies have considered populations with high selenium intake. Ecological and analytical studies have been based on both environmental and biological monitoring, yielding conflicting findings. An inverse association between exposure indicators and cancer incidence has been repeatedly observed. 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. These contradictory findings present a confusing picture of the potential carcinogenicity of different forms of selenium, which may be difficult to reconcile in a *Monograph*.

Cancer in Experimental Animals

Animal bioassays on selenium had been evaluated in the above-mentioned *IARC Monograph*, which concluded that there was *inadequate evidence* of carcinogenicity in experimental animals. A study from the United States National Toxicology Program (NTP, 1980) (gavage study) was positive but was not reviewed.

Mechanistic Evidence

After the randomized clinical trials, a large number of mechanistic studies relevant to key characteristics of carcinogens were published.

Key References

The following key references were also identified: Lippman et al. (2009); Türker et al. (2011); Hatfield et al. (2014); Kristal et al. (2014); Vinceti et al. (2017, 2018); Brigelius-Flohé & Arnér (2018); Chaudhary et al. (2018); Fernandes et al. (2018); Peters et al. (2018); Wang et al. (2018b); Yarmolinsky et al. (2018); Zhao et al. (2018).

Recommendation: Low priority

Semiconductor manufacturing

Semiconductor manufacturing has not been previously evaluated by the *IARC Monographs* programme. Known or suspected carcinogens involved in semiconductor manufacturing include acid mists, antimony trioxide, trichloroethylene, arsenic (and arsenical compounds), formaldehyde, nickel, naphthalene, titanium dioxide, and others (Galea & Cherrie, 2010; Marano et al., 2010; Choi et al., 2018; Park, 2018).

Exposure Data

Semiconductor manufacturing involves complex and diverse industrial processes using a wide variety of chemicals, including organic solvents, toxic gases, pyrophoric gases, and metals. Many process chemicals are trade secrets, lacking information on hazards, and chemical inventories are constantly changing because of evolving technology (Choi et al., 2018; Jang et al., 2019). In the course of employment, workers are potentially exposed to these process chemicals, to their by-products, and to non-ionizing radiation (radiofrequency and ultraviolet) and ionizing radiation. Work areas are controlled environments (cleanrooms) designed to reduce airborne contaminants that adversely affect product quality; therefore, workers' exposures are generally constrained to low levels and are well below existing occupational exposure limits.

Cancer in Humans

The literature includes recent reviews (Kim et al., 2014; Park, 2018), case reports (Kim et al., 2012), and several industry-based longitudinal studies (McElvenny et al., 2003; Beall et al., 2005; Nichols & Sorahan, 2005; Bender et al., 2007; Boice et al., 2010; Lee et al., 2011, 2015a; Darnton et al., 2012). Findings among studies are mixed, although there are reports of excess cancers of the brain, prostate, lung, pancreas, thyroid, and lymphohaematopoietic sites and melanoma among workers. Most studies lack adequate exposure characterization and consideration of other known risk factors. Among the few studies that examined dose–response, most relied on employment duration as a proxy for exposure (Beall et al., 2005; Bender et al., 2007; Boice et al., 2010). One case–control study used a detailed hygiene assessment to assign exposures based on processes and individual work practices (Darnton et al., 2012). Consistent dose–response patterns were not evident.

Cancer in Experimental Animals

Information from studies in experimental animals is not immediately relevant to this work activity.

Mechanistic Evidence

Mechanistic data are not directly applicable; however, information 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 compared with non-exposed controls. In replicate analysis, the difference disappeared after the implementation of protective measures for lowering exposures, described only as a “complex mixtures of chemical waste products” (Winker et al., 2008).

Recommendation: Low priority

Silymarin (CAS No. 65666-07-1)

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

Exposure Data

Silymarin, a natural polyphenolic flavonoid, is a medicinal plant extract of *Silybum marianum* (milk thistle) (Cheung et al., 2010; Federico et al., 2017). Milk thistle is a frequently sold herbal remedy for liver disorders and a common dietary supplement (Agarwal et al., 2013; Bosch-Barrera & Menendez, 2015). Silymarin and its major active constituent silibinin have also been reported to influence treatment of liver disorders, diabetes mellitus, mushroom poisoning, neurodegenerative and neurotoxic diseases, certain types of nephrotoxicity, and numerous types of cancer (Cheung et al., 2010).

Cancer in Humans

Most of the epidemiological evidence on silymarin and cancer has come from clinical trials investigating the effects of co-treatment in cancer and its effect in reducing side-effects of therapy (e.g. Elyasi et al., 2017). There is an apparent lack of other types of epidemiological studies, including systematic reviews.

Cancer in Experimental Animals

A feeding study conducted by the United States National Toxicology Program of milk thistle extract in male and female rats and mice (NTP, 2011a) was negative.

Mechanistic Evidence

Numerous studies relevant to key characteristics of carcinogens and/or potential chemopreventive action are available, showing anti-inflammatory, apoptotic, anti-metastatic, and anti-angiogenic effects. Silymarin tested positive in the Ames assay (NTP, 2019b).

Key References

The following key references were also identified: Giacomelli et al. (2002); Singh et al. (2004); Schröder et al. (2005); Flaig et al. (2007, 2010); Wang et al. (2008a); Rho et al. (2010); Vidlar et al. (2010); Becker-Schiebe et al. (2011); Chang et al. (2011); Skorupski et al. (2011); Ho et al. (2012); Cufí et al. (2013a, b); Siegel et al. (2014); Nambiar et al. (2015); Shahbazi et al. (2015); Bosch-Barrera et al. (2016, 2017); Elyasi et al. (2016); Lazzeroni et al. (2016); Li et al. (2016); Li & Wang (2016); Megna et al. (2016).

Recommendation: No evaluation

Sleep

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

Exposure Data

There has been speculation for some time about a potential role of sleeping habits in cancer risk, with a particular focus on risk of breast cancer, and to a lesser extent on cancers of the lung, colorectum, prostate, ovary, and endometrium.

Cancer in Humans

Studies of sleep and cancer risk tend to focus on two aspects of sleep: sleep duration and sleep quality. There is some evidence to indicate that there have been reductions in habitual sleep duration over the past 20–30 years, although reductions in sleep duration have not been consistently reported. Studies of sleep

quality have been somewhat more consistent, with reported increases in the prevalence of self-reported poor-quality sleep ranging from 5% to almost 40%.

Studies investigating sleep duration and cancer risk are more common than those investigating sleep quality; however, the measurements of both of these aspects of sleep have the same limitations, and the results have been similarly inconclusive. Studies of sleep duration and cancer risk have reported results finding higher risk, lower risk, and no association for both shorter and longer durations of sleep. Studies of sleep quality and cancer risk have generally reported no association. However, studies with sufficiently large sample sizes have relied on self-reported sleep habits, which are not well suited to capture a highly variable trait such as sleep and rarely correlate well with objective measures of sleep.

Another area of active research is that of obstructive sleep apnoea. This is a condition of repetitive collapse of the upper airway during sleep, causing cyclic hypoxaemia and hypercapnia, leading to reopening of the airway by arousal from sleep and a variety of surges in the sympathetic nervous system along with sleep fragmentation. The prevalence of this condition is higher among obese people, and it is currently thought to affect 17% of middle-aged men and 9% of middle-aged women, most of whom remain undiagnosed. Recent investigations have assessed overall cancer incidence and mortality in these groups. Although the results are provocative, most remain non-significant because of limited sample sizes. Efforts are under way to increase the sample sizes and combine cohorts to address risk questions.

Cancer in Experimental Animals

Studies of cancer in experimental animals were not identified.

Mechanistic Evidence

The results of studies of carcinogen mechanisms were not clear.

Key References

The following key references were also identified: Girschik et al. (2012); Bai et al. (2016); Lu et al. (2017a); Chen et al. (2018); Sillah et al. (2018).

Recommendation: Medium priority

Some anthracyclines

Certain anthracyclines have been evaluated by the *IARC Monographs* programme. Daunomycin is classified as *possibly carcinogenic to humans* (Group 2B) (IARC, 1987), on the basis of *sufficient evidence* of carcinogenicity in experimental animals. Adriamycin is classified as *probably carcinogenic to humans* (Group 2A) (IARC, 1987), on the basis of *sufficient evidence* of carcinogenicity in experimental animals, *inadequate evidence* of carcinogenicity in humans, and mechanistic evidence (including chromosomal aberrations and sister chromatid exchanges in treated patients; chromosomal aberrations, micronuclei, sister

chromatid exchanges, and DNA damage in human cells in vitro; and chromosomal aberrations, micronuclei, sister chromatid exchanges, and DNA damage in rodents in vivo). Doxorubicin, idarubicin, and other compounds in this class have not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Anthracyclines are antibiotics that are found primarily as natural products of the family *Streptomyces* and other Actinomycetales fungi (Bachur, 2002). Anthracyclines have been used as anticancer agents since the 1960s (Bachur, 2002); they act by damaging the DNA in cancer cells (NCI, 2019). Anthracyclines are included in the WHO Model List of Essential Medicines (WHO, 2017) and are used to treat many different types of cancers. Doxorubicin, daunorubicin, epirubicin, and idarubicin are the four most common anthracyclines (McGowan et al., 2017).

Cancer in Humans

An increase in the risk of subsequent solid cancers and cancer of the breast has been reported with prior chemotherapy involving anthracyclines and other drugs. In the Childhood Cancer Survivor Study, a 4-fold increased risk of breast cancer was observed in survivors without a history of chest radiotherapy when compared with the general population. The risk was highest among survivors of sarcoma and leukaemia. Chemotherapy with alkylators and anthracyclines was associated with an increased risk of breast cancer in a dose-dependent manner. Another cohort study of childhood cancer survivors reported dose-dependent doxorubicin-related increased risks of all solid cancers ($P_{trend} < 0.001$) and breast cancer ($P_{trend} < 0.001$). The Advisory Group noted that additional evidence from a new childhood cancer study on two anthracyclines may be available in the next several years.

Cancer in Experimental Animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of daunomycin and of adriamycin (IARC, 1987). Doxorubicin and idarubicin have not been evaluated by the *IARC Monographs* programme.

Mechanistic Evidence

Potential mechanisms include: regulated intramembrane proteolysis, where a membrane-bound protein is cleaved to liberate a soluble messenger, playing a role in a variety of cellular processes (Lal & Caplan, 2011); synthesis of ceramide, followed by activation of the transcription factor CREB3L1 (Denard et al., 2012); histone eviction from open chromatin (Pang et al., 2013); and epithelial–mesenchymal transition via upregulation of transforming growth factor β signalling (Li et al., 2015a), for example.

Key References

The following key references were also identified: Henderson et al. (2016); Teepen et al. (2017).

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

Some perfluorinated compounds (e.g. PFOA)

Of the perfluorinated compounds, perfluorooctanoic acid (PFOA) was evaluated by the *IARC Monographs* (IARC 2017a). PFOA was classified as *possibly carcinogenic to humans* (Group 2B), on the basis of *limited evidence* of carcinogenicity in humans, and a positive association was observed for cancers of the testis and kidney.

Exposure Data

Perfluorinated compounds, including PFOA, perfluorooctanesulfonic acid, GenX, and C8, are widely used in applications such as the production of Teflon and other coatings, as well as in fire-fighting foam. They are characterized by a fully fluorinated hydrophobic linear carbon chain attached to one or more hydrophilic head groups. These compounds have been listed by the Stockholm Convention because they are persistent, bioaccumulative, and toxic and have been detected globally (Stockholm Convention, 2004a).

Studies relevant to cancer in humans, to cancer in experimental animals, and to mechanisms are available to varying degrees for several perfluorinated compounds. Additional perfluoroalkylated substances are being prioritized for additional tiered toxicity and toxicokinetic testing (Patlewicz et al., 2019).

Cancer in Humans

Among epidemiological studies published since the last *IARC Monographs* evaluation, a case–control study nested in the California Teachers Study reported no clear association of risk of breast cancer with levels of serum PFOA or other perfluoroalkylated and polyfluoroalkylated substances measured after diagnosis (Hurley et al., 2018). A small case–control study of breast cancer risk among Inuit women in Greenland reported significant positive associations with serum levels of PFOA as well as other perfluoroalkyl acids (Wielsøe et al., 2017). In a cohort of workers exposed to PFOA in the USA, there was a positive but non-significant trend of lifetime cumulative serum PFOA levels (both occupational and drinking-water exposure estimates combined) with incidence of prostate cancer and a significant inverse trend with incidence of bladder cancer (Steenland et al., 2015). Analysis of kidney cancer or testicular cancer incidence was not performed, because of small numbers.

Cancer in Experimental Animals

There was *limited evidence* in experimental animals for the carcinogenicity of PFOA. However, a bioassay by the United States National Toxicology Program (NTP) that is in progress may provide new evidence relevant to the carcinogenicity in experimental animals (NTP, 2019d).

Mechanistic Evidence

Data relevant to key characteristics of carcinogens are available. PFOA is not DNA-reactive, but other studies have examined whether PFOA induces oxidative stress and mediates receptor-mediated effects. NTP data are available on the immunotoxicity of PFOA. Work that is in progress in the USA (Environmental Protection Agency and NTP) may be informative for selecting additional agents from the class for evaluation.

Although perfluorinated compounds as a whole are too diverse to be considered as a single class, the Advisory Group considered that subgroups of these chemicals could be developed on the basis of mechanistic and structure–activity considerations. These could then be used to identify the classes for evaluation (see, for example, Patlewicz et al., 2019) and be based on well-studied chemicals in the class and information from new approach methods in toxicology.

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

Some pyrethroids (i.e. permethrin, cypermethrin, deltamethrin)

Permethrin was evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1991). The 2014 Priorities Advisory Group assigned permethrin a high priority (IARC, 2014).

Deltamethrin was evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1991).

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

Exposure Data

Pyrethroids are insecticides that are used worldwide in agricultural, veterinary, domestic, and public health applications. Their public health uses include the disinsection of buildings and aircraft and the treatment of mosquito nets and army uniforms. Permethrin is also used in shampoo for the treatment of head lice and scabies.

The United States Environmental Protection Agency classified permethrin as “likely to be carcinogenic to humans” in 2007. Deltamethrin was classified as “not likely to be carcinogenic to humans” in 2003. Cypermethrin was classified as a “possible human carcinogen” in 1988.

Cancer in Humans

For permethrin, an increased risk of multiple myeloma has been reported in the United States National Cancer Institute Agricultural Health Study. No associations between permethrin and all malignant neoplasms combined, or between permethrin and melanoma, non-Hodgkin lymphoma, leukaemia, or cancers of the colon, rectum, lung, or prostate were found. A case–control study of infant and childhood leukaemia conducted in Brazil found that prenatal exposure was associated with acute lymphoblastic leukaemia (odds ratio, 2.5; 95% confidence interval, 1.2–5.2) and acute myeloid leukaemia (odds ratio, 7.3; 95% confidence interval, 2.6–20) for children aged 0–11 months (Ferreira et al., 2013).

Deltamethrin has been found to be associated with chronic lymphocytic leukaemia, small lymphocytic lymphoma, and benign skin tumours**.** No studies of cancer in humans were identified for cypermethrin.

Cancer in Experimental Animals

Since the previous IARC evaluation of *inadequate evidence* for the carcinogenicity of permethrin in experimental animals (IARC, 1991), increased incidences of bronchioloalveolar adenoma and carcinoma in female mice, and of hepatocellular adenoma in male and female mice, have been observed in one study reviewed by the United States Environmental Protection Agency, and a high-dose study has shown an increased incidence of lung adenoma in female mice (EPA, 2007).

Mechanistic Evidence

Mechanistic studies relevant to the key characteristics of carcinogens are available for permethrin and other pyrethroids. At high doses, permethrin can induce oxidative stress, DNA damage, and genotoxicity in bone marrow, and disruption of the immune system. Permethrin affects certain signalling pathways involved in the regulation of cell proliferation. Molecular mechanisms that have been proposed for carcinogenicity are a reduction in the activity of an enzyme involved in the breakdown of the amino acid tryptophan, inhibition of gap-junctional intercellular communication, endocrine disruption, and genotoxicity. Permethrin have the potential to induce breaks in the *KMT2A* and *IGH* genes, which could be the first step in the origin of lymphoma and leukaemia.

Cypermethrin promoted metastasis of Lewis lung cancer cells in both in vitro and in vivo models. It could promote tumour metastasis by inhibiting development of pro-inflammatory M1 macrophages. Cypermethrin is an endocrine disruptor; it has estrogen receptor activity and could facilitate cell proliferation. Androgen receptor activity and thyroid receptor activity were also reported. β-Cypermethrin and the general pyrethroid metabolite 3-phenoxybenzoic acid induce cytotoxicity, block granulocytic cell differentiation, and induce apoptosis in human neuroblastoma cell lines.

Key References

The following key references were also identified: Ishmael & Lithfield (1988); Hakoi et al. (1992); Go et al. (1999); Shukla et al. (2001); Alavanja et al. (2003, 2004, 2014); ATSDR (2003); Borkhardt et al. (2003); Gabbianelli et al. (2004); Kim et al. (2004); Menegaux et al. (2006); EPA (2006); Lee et al. (2007);

Andreotti et al. (2009); Osimitz & Lake (2009); Rusiecki et al. (2009); George et al. (2011); Koutros et al. (2013, 2016); Lokhov et al (2013); Ferreira et al. (2013); Presutti et al. (2016); Bonner et al. (2017); Navarrete-Meneses et al. (2017); He et al. (2018c); Huang et al. (2018a); Leon et al. (2019).

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

Spinal cord injury

Spinal cord injuries have not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

The Global Burden of Diseases, Injuries, and Risk Factors Study estimated that there were 0.93 million (95% uncertainty interval [UI], 0.78–1.16 million) new cases of spinal cord injuries worldwide in 2016, with an age-standardized incidence rate of approximately 13 (95% UI, 11–16) per 100 000 population (GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators, 2019). Age-standardized incidence rates varied by country and region; rates were higher in countries with high Socio-demographic Index (25 [95% UI, 20–31] per 100 000) than in countries with middle (8 [95% UI, 7–9] per 100 000) or low (12 [95% UI, 9–18] per 100 000) Socio-demographic Index. The leading cause of spinal cord injuries was falls. There were an estimated 27.04 million (95% UI, 24.98–30.15 million) prevalent cases of spinal cord injuries worldwide in 2016.

Cancer in Humans

In one study in the USA of 45 486 patients with traumatic spinal cord injuries, a standardized mortality ratio for deaths from bladder cancer of 6.7 (95% confidence interval [CI], 5.4–8.1) overall was observed compared with the general population (Nahm et al., 2015). However, there was no increase in bladder cancer mortality among ventilator users, those with motor incomplete injuries, or those injured for less than 10 years. In a registry-based study in Taiwan, China, of 1815 patients with spinal cord injuries, a hazard ratio for bladder cancer incidence of 6.51 (95% CI, 2.56–16.52) was observed compared with a reference cohort of age- and sex-matched individuals (Ho et al., 2015). However, results of other studies are not entirely consistent, and in one study a significantly reduced risk of prostate cancer was observed (Lee et al., 2014). The Advisory Group noted that the proposed causal agent in this instance would need to be reframed, because spinal cord injury was not considered a modifiable risk factor for cancer. In addition, it was thought that the observed relationship with bladder cancer may be mediated by aspects of management of spinal cord injuries, such as long-term catheterization.

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified.

Mechanistic Evidence

In rats, expression of microRNA-1949 in bladders was dysregulated and abundant after spinal cord injury, and a role in the translational regulation of retinoblastoma 1 and in bladder tumorigenesis was suggested (Wang et al., 2015a). Another study in rats observed disruption to bladder interstitial cells after spinal cord injury (Johnston et al., 2012).

Recommendation: No evaluation

Styrene–acrylonitrile trimer (SAN Trimer)

Styrene–acrylonitrile trimer (SAN Trimer) has not been previously evaluated by the *IARC Monographs* programme. Acrylonitrile is classified as *possibly carcinogenic to humans* (Group 2B) (IARC, 1999b), and styrene is classified as *probably carcinogenic to humans* (Group 2A) (IARC, 2019c).

SAN Trimer exists as a mixture of isomers composed of two structural forms: 4-cyano-1,2,3,4-tetrahydro-α-methyl-1-naphthaleneacetonitrile (THNA; CAS No. 57964-39-3) and 4-cyano-1,2,3,4-tetrahydro-1-naphthalenepropionitrile (THNP; CAS No. 57964-40-6). These, in turn, consist of four and two stereoisomers, respectively.

Exposure Data

SAN Trimer is formed by the condensation of two moles of acrylonitrile and one mole of styrene. 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) (EPA, 2014).

Cancer in Humans

Several epidemiological studies evaluated incidence of childhood cancer in New Jersey, including three ecological studies and a case–control study (ATSDR, 2008). In an epidemiological study, there was increased incidence of soft tissue sarcomas in a subgroup (females aged ≤ 19 years in 2004–2005) in both the Toms River Township and sub-Township area.

Cancer in Experimental Animals

In one study of cancer in experimental animals, male and female F344 rats were exposed to SAN Trimer during gestation, during nursing through their mothers' milk, and throughout their lifetimes through feed. There was no significant increase in the incidence of any tumours (NTP, 2012b).

Mechanistic Evidence

A few studies relevant to key characteristics of carcinogens are available. SAN Trimer was tested for genotoxicity by the United States National Toxicology Program. 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.

Recommendation: Medium priority

Sucralose (CAS No. 56038-13-2)

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

Exposure Data

Sucralose is a widely used non-nutritive sweetener, originally approved for use as a food ingredient in Canada in 1991. In 1998, the United States Food and Drug Administration 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 European Union approved the use of sucralose in a variety of products. The acceptable daily intake level of sucralose was established at 5 mg/kg body weight in the USA and at 15 mg/kg body weight in the European Union. Sucralose is currently approved for use in more than 80 countries.

Cancer in Humans

There are no studies on sucralose of cancer in humans, but there have been studies of non-nutritive sweeteners and cancer risk. In those studies, most of the intake of non-nutritive sweeteners is from saccharin or aspartame and not from sucralose.

Cancer in Experimental Animals

One study in mice and one in rats were negative (Mann et al., 2000a, b). A more recent lifespan study, starting from prenatal life, reported a significant dose-related increase in incidence of malignant tumours in male Swiss mice treated with sucralose in their feed (Soffritti et al., 2016).

Mechanistic Evidence

Sucralose is minimally absorbed after oral administration. Sucralose safety tests have indicated no acute, subchronic, or chronic toxicity at levels well above expected human intakes.

Sucralose has also been tested over a wide range of concentrations in several genotoxicity screening assays with no demonstration of genotoxicity, with the exception of an independent comet assay published in 2002 that reported induced DNA strand breaks in mice for the glandular stomach, colon, and lungs at the highest dose tested.

Recommendation: Low priority

Sulfluramid (perfluorinated pesticide) (CAS No. 4151-50-2)

Sulfluramid (*N*-ethylperfluorooctanesulfonamide) has not been previously evaluated by the *IARC Monographs* programme, but IARC has evaluated perfluorooctanoic acid, which – with perfluorooctylsulfonate (PFOS) – belongs to a vast group of fluorinated compounds called perfluoroalkylated substances (PFAS). Perfluorooctanoic acid was classified as *possibly carcinogenic to humans* (Group 2B) (IARC, 2017a), on the basis of *limited evidence* of carcinogenicity in humans (positive association for cancers of the testis and kidney) and *limited evidence* of carcinogenicity in experimental animals.

Exposure Data

Sulfluramid, a pesticide that is used to combat leaf-cutting ants, degrades into PFOS. Use of sulfluramid was banned in 2009 by the Stockholm Convention, although China and countries in Central and South America (Argentina, Brazil, Colombia, Costa Rica, Ecuador, and Venezuela) were allowed to continue using it (Löfstedt Gilljam et al., 2016; Meng et al., 2018; Rauert et al., 2018), because alternatives to PFOS are available for some applications, but this is not always the case in low- and middle-income countries.

Cancer in Humans

No epidemiological studies of cancer in humans were identified for sulfluramid. Some studies are available in workers exposed to PFOS, which have not shown convincing evidence of increased cancer risk (for cancers of the bladder, prostate, and colorectum) (Alexander et al., 2003; Alexander & Olsen, 2007; EFSA, 2008; Eriksen et al., 2009; EPA, 2009b; Innes et al., 2014).

Cancer in Experimental Animals

The carcinogenicity of PFOS in experimental animals (Thomford, 2002) was evaluated by the Organisation for Economic Co-operation and Development (OECD, 2002), Health Canada (Health Canada, 2004), the United States Environmental Protection Agency (EPA, 2009b), and the European Food Safety Authority (EFSA, 2008).

In summary, PFOS induced liver tumours in rats, and the evidence for induction of thyroid and mammary tumours in this species was difficult to evaluate because of the lack of a dose–response relationship.

Mechanistic Evidence

On the basis of negative results in a large series of in vitro and/or in vivo short-term tests at the gene and/or chromosome or DNA repair levels, the weight of evidence indicates an indirect (non-genotoxic) mechanism for the carcinogenicity of PFOS (EFSA, 2008; Eriksen et al., 2010; Kawamoto et al., 2010; Florentin et al., 2011). The induction of hepatocellular tumours does not appear to be directly related to peroxisome proliferation; however, the increased incidence of tumours was observed at doses above those associated with non-neoplastic toxic effects. Thyroid tumours are likely to be secondary to hormonal imbalance (EFSA, 2008).

The Advisory Group suggested that the *IARC Monographs* consider the evaluation of PFAS as a group, not only sulfluramid.

Key Reference

The following key reference was also identified: EPA (2008b).

Recommendation: No evaluation

Tepraloxydim (cyclohexanedione herbicide) (CAS No. 149979-41-9)

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

Exposure Data

Tepraloxydim is a cyclohexanedione herbicide that inhibits acetyl coenzyme A carboxylase and can be used in various crops: field bean, canola, cotton, potato, sugar beet, pea, oilseed rape, and soybean. It is authorized in some countries, such as Australia, Brazil, Canada, and Japan, but it is not authorized in the European Union (since 2017) or in the USA (since 2014) (renewal not submitted by the applicant).

Cancer in Humans

No epidemiological studies of cancer in humans were identified.

Cancer in Experimental Animals

No studies of cancer in experimental animals were identified in the open literature, but pesticide regulatory agencies analysed several regulatory studies in mice and rats. Tepraloxydim was reviewed by Australia (APVMA, 2003), the European Union (EC, 2004), Japan (Food Safety Commission of Japan, 2015), and the USA (EPA, 2011b). The Advisory Group noted that evidence of carcinogenicity in cancer studies conducted in rats and mice was equivocal.

Mechanistic Evidence

Tepraloxydim is considered as non-genotoxic. Publicly available mechanistic data relevant to key characteristics of carcinogens are sparse.

Recommendation: No evaluation

Terbufos (CAS No. 13071-79-9)

Terbufos has not been previously evaluated by the *IARC Monographs* programme, nor have other members of this class of insecticides.

Exposure Data

Terbufos is an organothiophosphate insecticide that continues to be used widely in agriculture.

Cancer in Humans

Recent epidemiological evidence from the United States National Cancer Institute (NCI) Agricultural Health Study (AHS) has revealed an association with cancer of the prostate, with noteworthy indications of a significant interaction involving the link between genetic variants of 8q24 and risk of prostate cancer. Additional evidence from the AHS has also supported possible associations between terbufos and elevated risks of all cancers combined, non-Hodgkin lymphoma, and breast cancer, although the evidence for breast cancer is marginal. An association between terbufos and non-Hodgkin lymphoma was observed in the recently published Consortium of Agricultural Cohorts (AGRICOH) study, which is a pooled study of the Agriculture and Cancer (AGRICAN) study in France, the AHS in the USA, and the Cancer in the Norwegian Agricultural Population (CNAP) study in Norway (Leon et al., 2019).

Cancer in Experimental Animals

Studies in mice and rats reviewed by the United States Environmental Protection Agency and by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) were considered negative.

Mechanistic Evidence

Potential mechanisms for carcinogenicity have been reported, including that terbufos may influence risk of prostate cancer by altering cancer signalling pathways involved in cellular adhesion, proliferation, and differentiation. Terbufos also alters steroid hormone metabolism and inhibits testosterone.

Key References

The following key references were also identified: Alavanja et al. (1996); Folsom et al. (1996); Hodgson & Rose (2006); Mahajan et al. (2006); Engel et al. (2017).

Recommendation: Medium priority

2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (TCDD) (dioxin) (CAS No. 1746-01-6)

2,3,7,8-Tetrachlorodibenzo-*para*-dioxin has been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1987, 1997b, 2012b). It has been classified as *carcinogenic to humans* (Group 1) since Volume 69 (IARC, 1997b), in one of the first mechanistic upgrades of an agent to Group 1. There is strong evidence to support a receptor-mediated mechanism that operates in humans for carcinogenesis associated with 2,3,7,8-tetrachlorodibenzo-*para*-dioxin. The current evaluation is based on *sufficient evidence* of carcinogenicity both in experimental animals and in humans; the strongest evidence in humans for the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin is for all cancers combined. Also, a positive association has been observed between exposure to 2,3,7,8-tetrachlorodibenzo-*para*-dioxin and soft tissue sarcoma, non-Hodgkin lymphoma, and cancer of the lung. However, the new epidemiological evidence appears to remain insufficient for the classification of additional cancer sites to either the *sufficient* or *limited* evidence category.

Recommendation: No evaluation

Tetrachloroethylene (perchloroethylene) (CAS No. 127-18-4)

Tetrachloroethylene has been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1987, 1995, 2013d) and is classified as *probably carcinogenic to humans* (Group 2A), on the basis of *sufficient evidence* of carcinogenicity in experimental animals and *limited evidence* of carcinogenicity in humans, supported by positive associations between exposure to tetrachloroethylene and cancer of the bladder. Several other studies suggested an association with cancer of the kidney and non-Hodgkin lymphoma, but results were not consistent across studies.

Exposure Data

Tetrachloroethylene is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Tetrachloroethylene (also known as perchloroethylene) is used as a cleaning agent for dry cleaning and degreasing. Inhalation exposure is almost inevitable, and there is potential for dermal and other routes of exposure. The solvent is also a ubiquitous contaminant of groundwater, soil, and ambient and urban air, and is one of the most common pollutants present in many hazardous waste sites (IARC, 2014).

Cancer in Humans

Since the most recent *IARC Monographs* evaluation (IARC, 2013d), some new epidemiological studies have been published (Hadkhale et al., 2017; Purdue et al., 2017; Callahan et al., 2019). In an extended follow-up of a cohort of dry cleaning workers in the USA, strong exposure–response relationships with estimated solvent exposure were reported for bladder cancer (hazard ratio [HR], 4.2 for medium exposure and 9.2 for high exposure, both vs no exposure) and kidney cancer (HR, 4.1 for medium exposure and 24.4 for high exposure). High exposure was also associated with lymphohaematopoietic malignancies (HR, 4.3). In a case–control study of kidney cancer, high cumulative exposure to tetrachloroethylene was associated with increased risk, both overall and after excluding participants with 50% or higher exposure probability for trichloroethylene.

Cancer in Experimental Animals

In the previous evaluation (IARC, 2013d), there was *sufficient evidence* of carcinogenicity in experimental animals.

Mechanistic Evidence

A few new studies relevant to key characteristics of carcinogens are available, of which a few are in exposed humans (e.g. Azimi et al., 2017). Furthermore, it has been noted that tetrachloroethylene has some toxicological similarity to trichloroethylene (Cichocki et al., 2016), which has been classified as *carcinogenic to humans* (Group 1), on the basis of *sufficient evidence* of carcinogenicity in humans for cancer of the kidney and *limited evidence* for cancer of the liver and non-Hodgkin lymphoma.

The Advisory Group recommended that, if a re-evaluation of the carcinogenicity of tetrachloroethylene is undertaken by the *Monographs* programme, consideration should also be given to re-evaluating dry cleaning (using tetrachloroethylene) as an occupation.

Key References

The following key references were also identified: Kauppinen et al. (2000); ECSA (2012); Cichocki et al. (2017).

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

Tetracyclines and other photosensitizing drugs

Some psoralens have been evaluated by the *IARC Monographs* programme (IARC, 1987). Notably, methoxsalen plus ultraviolet A radiation has been classified as *carcinogenic to humans* (Group 1) (IARC, 1987, 2012a). Tetracyclines have not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Tetracyclines are a group of antibiotics that can be isolated from several types of *Streptomyces* bacteria or can be produced semisynthetically (Encyclopaedia Britannica, 2019). Tetracyclines are included in the WHO Model List of Essential Medicines (WHO, 2017). This broad-spectrum group of drugs is inexpensive and has been administered, typically orally, to treat a range of infections, including cholera, trachoma, and brucellosis, as well as acne (Chopra & Roberts, 2001; Encyclopaedia Britannica, 2019). The first tetracyclines (chlortetracycline and oxytetracycline) were discovered in 1948; since then, additional drugs in this class have been identified and marketed (Chopra & Roberts, 2001). Like some other widely prescribed medications, including quinolone antibiotics and psoralens, various tetracycline derivatives are photosensitizers. These chemicals enhance the erythema response to sunlight.

Cancer in Humans

There is an emerging epidemiological literature on the association between the use of tetracyclines and an increased risk of non-melanoma skin cancer, in particular basal cell carcinoma. The associations were observed in a study based on three large cohorts in the USA (hazard ratio, 1.11; 95% confidence interval [CI], 1.02–1.21) (Li et al., 2018), in a Danish national registry-based cohort study (incidence rate ratio, 1.3; 95% CI, 1.3–1.4) (Kaae et al., 2010), and in a population-based case–control study in the USA (odds ratio, 1.5; 95% CI, 1.1–2.1) (Robinson et al., 2013), with stronger evidence for early-onset basal cell carcinoma and longer duration of tetracycline use. The main indications for tetracycline in the study populations were acne and other skin conditions. Some of the studies also reported associations of non-melanoma skin cancers and other photosensitizing medications.

Cancer in Experimental Animals

A feeding study conducted by the United States National Toxicology Program of tetracycline hydrochloride in male and female rats and mice (NTP, 1989a) was negative.

Mechanistic Evidence

Tetracycline is known to induce photosensitivity, increasing the vulnerability of the epidermis and dermis to ultraviolet radiation-induced damage (Blakely et al., 2019).

Key Reference

The following key reference was also identified: Richards et al. (2011).

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

Thioacetamide (CAS No. 62-55-5)

Thioacetamide is currently classified as *possibly carcinogenic to humans* (Group 2B) (IARC, 1987), on the basis of *sufficient evidence* of carcinogenicity in experimental animals.

Exposure Data

Thioacetamide (C_2H_5NS) is a crystalline compound that is soluble in water and ethanol. It was used as a solvent, vulcanization accelerator, and motor fuel stabilizer. However, it is currently used only as a laboratory reagent in place of hydrogen sulfide in qualitative analyses (HSDB, 2001) and as a reactant in making metal salt nanoparticles (Liddell & Summers, 2004; Jin et al., 2006). The primary routes of potential human exposure to thioacetamide are inhalation and dermal contact. Occupational exposure to thioacetamide may occur during the production and use of thioacetamide.

Cancer in Humans

No epidemiological studies on carcinogenicity in humans were identified.

Cancer in Experimental Animals

Thioacetamide is known to induce carcinogenesis in the liver and the biliary tree in experimental animal models. When rats or mice were administered thioacetamide intraperitoneally (100–200 mg/kg body weight) or orally (200 mg/L drinking-water), they showed liver fibrosis, hepatocellular carcinoma, or cholangiocarcinoma (Becker, 1983; Honda et al., 2002; Wallace et al., 2015). In several studies, when rats were administered thioacetamide intraperitoneally at 200 mg/kg body weight twice per week for 6 consecutive weeks, they showed necrosis of hepatocytes, bridging fibrosis, and superficial liver nodules (Tsai et al., 2010; El-Mihi et al., 2017; Dwivedi & Jena, 2018). Also, a study of rats injected with diethylnitrosamine and exposed to 0.03% thioacetamide in the drinking-water for 39 weeks showed that septal fibrosis, cirrhosis, and hepatocarcinoma developed at 9, 20, and 40 weeks, respectively (Lim, 2002; Park et al., 2001). Cholangiocarcinoma was induced by oral administration of thioacetamide (0.03% in tap water) for 40 weeks (Liu et al., 2008). Rats administered thioacetamide at 300 mg/L drinking-water every day developed biliary dysplasia and cholangiocarcinoma (Yeh et al., 2004, 2008).

Mechanistic Evidence

Several studies have investigated the molecular mechanisms of the toxicity of thioacetamide (Clawson et al., 1987; El-Ashmawy et al., 2014). Thioacetamide itself is not toxic to the liver, but its metabolic intermediates (in particular TAA-S-oxide, a reactive oxygen species) covalently bind to hepatic macromolecules, impair the function of mitochondria, and damage DNA in hepatic cells, leading to cellular damage and necrosis of hepatocytes (Staňková et al., 2010; Jaeschke et al., 2013).

Recommendation: No evaluation

Tobacco smoking and second-hand tobacco smoke

Tobacco smoking has been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1986, 2004b, 2012c) and since Volume 38 (Supplement 7) is classified as *carcinogenic to humans* (Group 1) (IARC, 1987), on the basis of *sufficient evidence* both in experimental animals and in humans (for an increasing number of cancer sites). Second-hand tobacco smoke has been evaluated repeatedly by the *IARC Monographs* programme (IARC, 2004b, 2012c) and since Volume 83 is classified as *carcinogenic to humans* (Group 1), on the basis of *sufficient evidence* both in experimental animals (for sidestream tobacco smoke condensates) and in humans; second-hand tobacco smoke causes cancer of the lung (IARC, 2012c). There was *limited evidence* for breast cancer for active smoking (since Volume 100E), but not for second-hand tobacco smoke. For childhood leukaemia (myeloid and lymphoid), Volume 100E summarized 2 cohort studies, 27 case–control studies, and 2 meta-analyses on the association of exposure to parental tobacco smoking (paternal, maternal, or both) with childhood haematopoietic malignancies (leukaemia and lymphoma). The body of evidence suggested an association of leukaemia (and lymphoma) with paternal smoking before conception and with combined parental smoking, but not with maternal smoking during pregnancy.

Exposure Data

In 2015, more than 1.1 billion people worldwide smoked tobacco (cigarettes, cigars, pipes, and other tobacco products); the prevalence is much higher in males than in females. Although the prevalence of tobacco smoking is declining globally, it appears to be increasing in the WHO Eastern Mediterranean Region and the WHO African Region (WHO, 2019a).

Involuntary smoking occurs when a nonsmoking individual is exposed to second-hand tobacco smoke (composed of both exhaled mainstream smoke and sidestream smoke that is released between puffs into the air from the burning cone). In 2004 it was estimated that 40% of children, 33% of male nonsmokers, and 35% of female nonsmokers were exposed to second-hand smoke globally (Oberg et al., 2011). Findings from Global Youth Tobacco Surveys conducted in 132 countries between 1999 and 2005 indicated that a large proportion of students in every WHO region were exposed to second-hand smoke at home (43.9%), and many (46.5%) had parents who smoked (GTSS Collaborative Group, 2006).

Cancer in Humans

Since the most recent *IARC Monographs* evaluation, about 15 cohort studies have reported a positive association between breast cancer and smoking (active smoking, involuntary smoking, or both), and several recent reviews have concluded that there is an association between smoking and a higher risk of breast cancer, especially for women who started smoking before first childbirth (e.g. Catsburg et al., 2015; Jones et al., 2017b).

Since the most recent *IARC Monographs* evaluation, numerous studies have been published on childhood leukaemia associated with parental smoking (e.g. Liu et al., 2011; Milne et al., 2012; Metayer et

al., 2016a). For example, recent pooled and meta-analyses of childhood acute myeloid leukaemia (AML) from the Childhood Leukemia International Consortium (the largest to date) reported an increased risk and a dose–response relationship of paternal smoking with childhood AML. The literature remains complex for maternal smoking. Furthermore, meta-analyses of paternal smoking suggest an association with childhood acute lymphoblastic leukaemia (ALL).

The Advisory Group considered that the new epidemiological evidence appears to support the classification of additional cancer sites to either the *sufficient* or *limited* evidence category.

Key References

The following key references were also identified: Whitehead et al. (2016); de Smith et al. (2017).

Recommendation: Medium priority

1,1,1-Trichloroethane (CAS No. 71-55-6)

1,1,1-Trichloroethane was previously evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1999b).

Exposure Data

1,1,1-Trichloroethane is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

1,1,1-Trichloroethane is used as a solvent for adhesives, in metal degreasing, and in the manufacture of vinylidene chloride. Other applications include its use in pesticides, textile processing, cutting fluids, aerosols, lubricants, cutting oil formulations, drain cleaners, shoe polishes, spot cleaners, printing inks, and stain repellents.

Cancer in Humans

In the previous IARC evaluation (IARC, 1999b), the few reported studies of cancer in humans were determined to be inadequate. A new study of solvent-exposed workers in Nordic countries reported non-significant elevations in chronic lymphocytic leukaemia associated with 1,1,1-trichloroethane (Talibov et al., 2017).

Cancer in Experimental Animals

New animal inhalation carcinogenicity studies were reported in 2013. In male rats, the incidence of bronchioloalveolar adenomas and peritoneal mesotheliomas was significantly increased. In male mice, a significant positive trend with dose was shown for incidence of bronchioloalveolar carcinomas, combined incidence of bronchioloalveolar adenomas or carcinomas and hepatocellular adenomas, adenomas of the Harderian gland, and malignant lymphomas of the spleen. In female mice, the incidence of

bronchioloalveolar adenomas or carcinomas (combined), of hepatocellular adenomas, and of hepatocellular adenomas or carcinomas (combined) was significantly increased (Ohnishi et al., 2013).

Mechanistic Evidence

1,1,1-Trichloroethane is neurotoxic and hepatotoxic, after high exposure concentrations in people and also in rodents. No structural damage has been reported in reproductive toxicity studies in rats and mice, but delayed development was reported. 1,1,1-Trichloroethane covalently bound to DNA, RNA, and protein in mice and rats but did not induce micronuclei or abnormal sperm head morphology in mice in vivo. It induced chromosomal aberrations and cell transformation in mammalian cell cultures. It did not induce unscheduled DNA synthesis or gene mutation in mammalian cells in vitro. 1,1,1-Trichloroethane did not cause mutation in plants or sex-linked mutation in *Drosophila*. It did not induce DNA damage, gene conversion, mutation or aneuploidy in yeast, or genetic crossing-over or aneuploidy in fungi, but it was mutagenic to some bacterial strains (IARC, 1999b). Since the most recent *IARC Monographs* evaluation of the compound, there has been a micronucleus test by the United States National Toxicology Program (NTP, 2018f), which was negative.

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

Trichloroethylene (CAS No. 79-01-6)

Trichloroethylene has been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1987, 1995, 2013d) and since Volume 106 is classified as *carcinogenic to humans* (Group 1), on the basis of *sufficient evidence* both in experimental animals and in humans. The current evaluation (IARC, 2013d) specifies that trichloroethylene causes cancer of the kidney. Also, positive associations have been observed between exposure to trichloroethylene and both non-Hodgkin lymphoma and cancer of the liver.

Trichloroethylene is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

Trichloroethylene was widely used for degreasing metal parts until the 1990s, and in dry cleaning from the 1930s to the 1950s (IARC, 2013d). Currently, its main use is in production of chlorinated chemicals; approximately 80% of the current production of trichloroethylene in the European Union is used for this purpose (ECSA, 2012). An estimated 276 000 workers in the European Union were exposed to trichloroethylene in the early 1990s (Kauppinen et al., 2000). The general population is exposed through consumer products, food, and contaminated water (IARC, 2013d).

The Advisory Group determined that, overall, the new epidemiological evidence appears to remain insufficient for the classification of additional cancer sites to either the *sufficient* or *limited* evidence category.

Recommendation: No evaluation

Tris(2-chloroethyl) phosphate (CAS No. 115-96-8)

Tris(2-chloroethyl) phosphate (TCEP) was evaluated by the *IARC Monographs* as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1999b).

Exposure Data

TCEP is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical.

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

In a single small case–control study, there were higher levels of TCEP in household dust from homes of individuals with papillary thyroid cancer than from those of controls (Hoffman et al., 2017).

Cancer in Experimental Animals

In the 2-year gavage studies performed by the United States National Toxicology Program (NTP), the incidence of renal tubule adenoma, thyroid follicular cell adenoma or carcinoma combined (in females), and mononuclear cell leukaemia (in males) was increased in rats. There were non-significant increases in the incidence of renal tubule cell neoplasms and adenomas of the Harderian gland in exposed male and female mice, respectively (NTP, 1991).

Mechanistic Evidence

TCEP was not mutagenic in bacterial assays and caused equivocal or no effect on chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells. Evidence beyond the NTP studies is sparse. TCEP was active in a pregnane X receptor (PXR) nuclear receptor assay in ToxCast (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., 2019).

The Advisory Group recommended that this compound should be considered in conjunction with tris(chloropropyl) phosphate. 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 for these chemicals. Close structurally related compounds are carcinogenic to rodents.

Key Reference

The following key reference was also identified: Zhang et al. (2017d).

Recommendation: Medium priority

Tris(chloropropyl) phosphate (CAS No. 13674-84-5)

Tris(chloropropyl) phosphate has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Tris(chloropropyl) phosphate is listed by the Organisation for Economic Co-operation and Development (for year 2007) and the United States Environmental Protection Agency as a High Production Volume chemical. Tris(chloropropyl) phosphate is a flame retardant that is used primarily in polyurethane foams.

Cancer in Humans

No epidemiological studies of cancer are available.

Cancer in Experimental Animals

A bioassay by the United States National Toxicology Program (NTP) is in progress (see NTP, 2012a).

Mechanistic Evidence

In genetic toxicology tests performed by NTP, tris(chloropropyl) phosphate was positive in the micronucleus test in male (but not in female) B6C3F$_1$ mice. It was negative in the micronucleus test in rats and was negative in bacterial tests. From a chemical structure point of view, it may be an alkylating agent; computational tools may aid in clarifying.

This compound should be considered in conjunction with tris(2-chloroethyl) phosphate. 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 for these chemicals. Close structurally related compounds are carcinogenic to rodents.

The Advisory Group recommended that the priority of this chemical should be reconsidered after the NTP bioassay data become available.

Recommendation: Medium priority

Underground mining

Exposure to a variety of agents classified as *carcinogenic to humans* (Group 1) has been documented in underground mining, including (but not limited to) crystalline silica dust, radon and its decay products, diesel engine exhaust, and various metals, depending on the ores mined. Hundreds of thousands of people, mainly men, are employed worldwide in underground mining across all high-, middle- and low-income countries.

When the available epidemiological studies pertain to a mixture, process, occupation, or industry, the Preamble to the *IARC Monographs* recommends that the evaluation is focused as narrowly as the available data on exposure and other aspects permit. The Advisory Group considered that a generic evaluation of underground mining, which represents a specific exposure condition for agents already classified as *carcinogenic to humans* (Group 1), is inconsistent with the guidance provided by the Preamble.

Key References

The following key references were identified: Vermeulen et al. (2010); Patra et al. (2016); Sodhi-Berry et al. (2017).

Recommendation: No evaluation

Uracil (CAS No. 66-22-8)

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

Exposure Data

Uracil is a constituent of RNA. Cultivated plants, such as cereals and pulses, have a high content of RNA equivalents, as do vegetables (Lassek & Montag, 1990).

Cancer in Humans

No data were identified pertaining to the carcinogenicity of uracil in humans.

Cancer in Experimental Animals

When uracil was administered at high levels in the diet (3%), a significant increase in the incidence of transitional cell papilloma and carcinoma of the urinary bladder was observed in male F344 rats; a significant increase in the incidence of transitional cell carcinoma was also observed in female F344 rats and female B6C3F_1 mice (Fukushima et al., 1992). The induction of these tumours is associated with the formation of bladder calculi, and possibly irritation and cell proliferation (Kagawa et al., 1992; Fukushima & Murai, 1999). When sodium chloride was co-administered with the uracil, incidence of both neoplasms and urinary calculi decreased (Fukushima et al., 1992).

Male F344 rats initiated with *N*-methyl-*N*-nitrosourea and then administered 3% uracil in the diet had a high incidence of urinary bladder carcinoma (Masui et al., 1989). Male F344 rats initiated with acrolein and then administered 3% uracil in the diet had a high incidence of urinary bladder papilloma (Cohen et al., 1992). In other experiments, female F344 rats co-administered *N*-ethyl-*N*-hydroxyethylnitrosamine and 3% uracil had a significant increase in the incidence of adenocarcinoma of the kidneys. This was not observed with 1.5% uracil (Takashi et al., 1994). In a subsequent experiment with a similar design, Wistar rats were shown to be more sensitive than F344 rats to the induction of renal adenocarcinoma (Yamada et al., 1995).

Mechanistic Evidence

It has been demonstrated that co-administration of dihydrouracil, a metabolite of uracil, and sodium nitrite increased the level of 7-(2′-carboxyethyl)guanine in liver DNA of rats (Wang et al., 2013). Data in humans are sparse. Two studies have shown that under folate-deficient conditions, high levels of uracil become incorporated into DNA, which results in strand breaks and global hypomethylation (Blount et al., 1997; McGlynn et al., 2013).

Recommendation: No evaluation

Very hot foods and beverages

Drinking very hot beverages at temperatures above 65 °C has previously been evaluated by the *IARC Monographs* programme (IARC, 2018a) and was classified as *probably carcinogenic to humans* (Group 2A), on the basis of *limited evidence* of carcinogenicity both in humans and in experimental animals for cancer of the oesophagus.

Exposure Data

Although there is no universally accepted definition of hot or very hot foods or beverages and the standards may vary according to the type of food or beverage and geographical location, people in certain geographical areas do appear to have a preference for the consumption of food or beverages at temperatures above 60 °C. This preference appears to be focused predominantly in low- and middle-income areas, including Asia, the Middle East, and South America.

Cancer in Humans

A meta-analysis summarized 11 case–control studies of the consumption of very hot foods with oesophageal cancer and reported consistently increased risk, with an overall risk estimate (odds ratio) of 2.09 (95% confidence interval [CI], 1.71–2.56). A significant limitation of all the included studies is that food temperature was based on self-report, and not on objective temperature measurement, and is therefore likely to be subject to reporting bias. A recent case–control study in China used objective food temperature measurement and reported an odds ratio of 2.98 (95% CI, 1.89–4.12) but did not describe the method of temperature measurement. However, a high-quality cohort study with prospectively and objectively

measured tea drinking temperatures has reported significant associations with oesophageal cancer and tea drunk at 60 °C or above (hazard ratio, 1.41; 95% CI, 1.10–1.81). This new study would provide strong supporting evidence for the mechanisms underlying both very hot foods and very hot beverages. The Advisory Group noted that the agent could be expanded to include both food and beverages that are consumed very hot (Islami et al., 2019).

Cancer in Experimental Animals

No data on cancer in experimental animals were identified.

Mechanistic Evidence

No data on mechanisms were identified; the relevant mechanistic data in Volume 116 (IARC, 2018a) were sparse.

Key References

The following key references were also identified: Chen et al. (2015a); Tai et al. (2017).

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

Vinclozolin (CAS No. 50471-44-8)

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

Exposure Data

Vinclozolin is listed by the Organisation for Economic Co-operation and Development (for year 2007) as a High Production Volume chemical (OECD, 2009). 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 classified as a "possible human carcinogen" by the United States Environmental Protection Agency in 2000. In the USA, since the early 2000s, its use is restricted to canola and turf used on golf courses and industrial sites. In the USA, the only food import allowed after use of vinclozolin is wine grapes. Some other countries continue to use this fungicide (HSDB, 2017).

Cancer in Humans

No studies of cancer in humans were identified.

Cancer in Experimental Animals

In a study of carcinogenicity in C57BL/6 mice at dietary levels of 0, 15, 150, 3000, or 8000 ppm, hepatocellular carcinomas were seen at 8000 ppm. There was evidence of toxicity at 3000 ppm, including hepatotoxicity, Leydig cell hyperplasia, atrophy of accessory sex glands, atrophic uteri, and lipidosis in the corticomedullary region of the adrenals (JMPR, 1995).

In rats, the long-term toxicity and carcinogenicity of vinclozolin has recently been investigated in three studies using dietary levels between 25 ppm and 4500 ppm. An increased incidence of Leydig cell tumours was seen in rats treated at 150 ppm and above, together with atrophy of accessory sex glands. Benign sex cord stromal tumours in the ovaries were seen in rats treated at 500 ppm and above, and uterine adenocarcinomas were detected in rats treated at 3000 ppm (the highest dose tested in the carcinogenicity study). Adrenal tumours were seen in rats treated at 1500 ppm and above. Hepatocellular carcinomas were seen in males treated at 4500 ppm (JMPR, 1995).

Mechanistic Evidence

Several studies relevant to key characteristics of carcinogens are available, primarily on whether vinclozolin induces epigenetic effects and modulates receptor-mediated effects (Hrelia et al., 1996; Lioi et al., 1998a, b; Skinner, 2016; Pietryk et al., 2018).

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

Water pipe (narghile, hookah, shisha)

Tobacco smoking has been evaluated repeatedly by the *IARC Monographs* programme (IARC, 1986, 2004b, 2012c) and since Volume 38 (Supplement 7) is classified as *carcinogenic to humans* (Group 1) (IARC, 1987), on the basis of *sufficient evidence* both in experimental animals and in humans (for an increasing number of cancer sites). Water pipe, as a particular mode of exposure to tobacco smoke, was considered in the exposure section of the *Monograph* on tobacco smoking (IARC, 2012c) and is explicitly described to be included as part of the classification of this agent as *carcinogenic to humans* (Group 1).

Exposure Data

Use of water pipes is highly prevalent in some low- and middle-income countries, as well as among some particular age, socioeconomic, and ethnic groups in high-income countries. About 100 million people worldwide use water pipes.

Cancer in Humans

Four recent reviews and meta-analyses reported statistically significant increased risks for lung cancer, oesophageal cancer, or oral cancer (Awan et al., 2017; Mamtani et al., 2017; Montazeri et al., 2017; Waziry et al., 2017). However, some of the meta-analyses as well as some of the original studies seem to have methodological issues; for example, one of the reviews and meta-analyses on oral cancer was based only on cross-sectional studies (Waziry et al., 2017).

Use of water pipe was reviewed by the 2014 Priorities Advisory Group, which concluded that a review and evaluation constrained to this mode of exposure to tobacco smoke, which represents a specific exposure condition for an agent already classified as *carcinogenic to humans* (Group 1), was unjustified given the

high likelihood that this particular mode of exposure to tobacco smoke causes cancer. The same conclusion was retained by the current Advisory Group.

Recommendation: No evaluation

Weapons-grade tungsten/nickel/cobalt alloy

Different alloys of cobalt-based alloys were evaluated in *IARC Monographs* Volume 74. Implanted foreign bodies of cobalt-based alloys were evaluated as *not classifiable as to their carcinogenicity to humans* (Group 3) (IARC, 1999c), on the basis of *limited evidence* in experimental animals for the carcinogenicity of implants of alloys containing cobalt.

Cobalt metal with tungsten carbide was classified as *probably carcinogenic to humans* (Group 2A) (IARC, 2006a), on the basis of *limited evidence* in humans for the carcinogenicity of cobalt metal with tungsten carbide and *sufficient evidence* in experimental animals for the carcinogenicity of cobalt-metal powder.

Weapons-grade tungsten/nickel/cobalt alloy has not been previously evaluated by the *IARC Monographs* programme.

Exposure Data

Cobalt metal and tungsten carbide powders are produced widely with high purity for use in the hard-metal industry, in the manufacture of superalloys, and for other industrial and military applications. Hard metals are materials in which metallic carbides are bound together or cemented by a soft and ductile metal binder, usually cobalt or nickel. Tungsten carbide ranks among the most important carbides for the production of hard metals; it is often used in armour-piercing ammunition, because it is extremely hard and very dense. Tungsten alloys have been used in the production of military materials and weapons since the 18th century (Lansdown, 2014). Occupational exposure to cobalt–tungsten carbide may occur during its manufacture (NTP, 2016k); exposure in military personnel via internalization of shrapnel may also occur (Lansdown, 2014).

A military-grade tungsten/nickel/cobalt alloy (W/Ni/Co; 91%/6%/3%) was used in battlefield ballistics, particularly for armour-piercing rounds but also in small-calibre ammunition. Typically, a military-grade tungsten/nickel/cobalt alloy is favoured because of its ability to penetrate armour. It has been replaced with "green" tungsten alloys that do not contain cobalt. Use in military conflicts of tungsten-based projectiles has caused exposure of military personnel via various routes, including inhalation of particles or implantation of fragments after survival of a friendly fire incident.

Cancer in Humans

No epidemiological literature was identified for military-grade tungsten alloy for either exposed military personnel or potentially exposed local populations.

Cancer in Experimental Animals

Recently, three separate, well-conducted chronic rodent studies were published in which a military-grade tungsten/nickel/cobalt alloy (W/Ni/Co; 91%/6%/3%) was used to mimic shrapnel loads. When embedded in thigh muscle, pellets of these alloys induced malignant rhabdomyosarcomas at a high rate (80–100%) in both rats (two studies) and mice, with indication of a dose–response relationship (Kalinich et al., 2005; Emond et al., 2015a). Replacing cobalt with iron in the pellets before implantation abolished tumour response in mice and rats and blocked pellet dissolution, as assessed by urinary nickel and cobalt levels, indicating that corrosion is a key to cancer formation, as opposed to simple local irritation (Schuster et al., 2012). A subsequent 2-year study in mice investigated implanted pellets made of biologically inert tantalum plus the exact amount of original pellet component metals separately (W, Ni, or Co alone or W+Ni, W+Co, or Ni+Co) in mice and found a much lower (maximum, 20%) or no tumour response (Emond et al., 2015b). The data indicate that when alloyed, tungsten uniquely acts as a sort of metallurgic generator for cobalt and nickel that corrosively releases these two rodent carcinogens.

Mechanistic Evidence

Significant increases in both urinary and serum levels of tungsten, nickel, and cobalt have been shown in rats implanted with weapons-grade tungsten alloy (W/Ni/Co) pellets (Kalinich et al., 2008). With regard to the key characteristics of carcinogens, tungsten alloy (W/Ni/Co) induced cell transformation (Miller et al., 2001a), DNA strand breaks (Harris et al., 2015), and changes in gene expression (Miller et al., 2004) in human cells in vitro. In rats in vitro, DNA damage and cell death (Harris et al., 2011; 2015), pulmonary inflammation, and altered expression of genes associated with oxidative and metabolic stress and toxicity were observed (Harris et al., 2011; Roedel et al., 2012; Bardack et al., 2014; Adams et al., 2015). Epigenetic modifications were induced in mice in vitro (Verma et al., 2011).

Key References

The following key references were also identified: Bolt et al. (2015); Laulicht et al. (2015); NTP (2016n, 2019f).

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

Zidovudine (AZT) (CAS No. 30516-87-1)

Zidovudine, also known as azidothymidine (AZT), was last reviewed by the *IARC Monographs* in Volume 76 (IARC, 2000a) and was classified as *possibly carcinogenic to humans* (Group 2B), on the basis of *sufficient evidence* of carcinogenicity in experimental animals; there was *inadequate evidence* of carcinogenicity in humans. The 2014 Priorities Advisory Group assigned zidovudine a medium priority (Straif et al., 2014).

Exposure Data

Zidovudine is a nucleoside analogue that has been used in the treatment and prevention of HIV infection in adults and children. It is included in the WHO Model List of Essential Medicines (WHO, 2017).

Cancer in Humans

Since the most recent *IARC Monographs* evaluation, there has been one large epidemiological study that evaluated the incidence of cancer in uninfected children born to mothers infected with HIV (Benhammou et al., 2008). The overall cancer incidence did not differ significantly from that expected for the general population. Another study reported that the incidence of cancers of the liver and lung and of Hodgkin lymphoma was increased in individuals who received highly active antiretroviral therapy (HAART) compared with the general population, but this was attributed to the use of non-nucleoside reverse transcriptase inhibitors rather than to use of zidovudine.

Cancer in Experimental Animals

As indicated above, there is *sufficient evidence* in experimental animals for the carcinogenicity of zidovudine (IARC, 2000a).

Mechanistic Evidence

With respect to the key characteristics of carcinogens, studies have confirmed the genotoxicity of zidovudine, including in humans in vivo (Poirier et al., 2004; Escobar et al., 2007; Olivero, 2007). The compound also terminates DNA replication and induces epigenetic alterations and oxidative stress. Some evidence is emerging that it may have protective effects against cancer and potential utility in cancer therapy.

Key References

The following key references were also identified: NTP (1999c); Walker et al. (2007); Benhammou et al. (2008); Koczor et al. (2015).

Recommendation: No evaluation

References

Abdel-Rahman M, El-Sayed M, El Raziky M, Elsharkawy A, El-Akel W, Ghoneim H, et al. (2013). Coinfection with hepatitis C virus and schistosomiasis: fibrosis and treatment response. World J Gastroenterol. 19(17):2691–6. https://doi.org/10.3748/wjg.v19.i17.2691 PMID:23674877

Abnet CC, Kamangar F, Dawsey SM, Stolzenberg-Solomon RZ, Albanes D, Pietinen P, et al. (2005). Tooth loss is associated with increased risk of gastric non-cardia adenocarcinoma in a cohort of Finnish smokers. Scand J Gastroenterol. 40(6):681–7. https://doi.org/10.1080/00365520510015430 PMID:16036528

Abnet CC, Kamangar F, Islami F, Nasrollahzadeh D, Brennan P, Aghcheli K, et al. (2008). Tooth loss and lack of regular oral hygiene are associated with higher risk of esophageal squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev. 17(11):3062–8. https://doi.org/10.1158/1055-9965.EPI-08-0558 PMID:18990747

Abreu A, Costa C, Pinho E Silva S, Morais S, do Carmo Pereira M, Fernandes A, et al. (2017). Wood smoke exposure of Portuguese wildland firefighters: DNA and oxidative damage evaluation. J Toxicol Environ Health A. 80(13–15):596–604. https://doi.org/10.1080/15287394.2017.1286896 PMID:28524757

ACGIH (2001). Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th ed. Cincinnati (OH), USA: American Conference of Governmental Industrial Hygienists.

Adams VH, Dennis WE, Bannon DI (2015). Toxic and transcriptional responses of PC12 cells to soluble tungsten alloy surrogates. Toxicol Rep. 2:1437–44. https://doi.org/10.1016/j.toxrep.2015.09.005 PMID:28962486

Adetona O, Simpson CD, Li Z, Sjodin A, Calafat AM, Naeher LP (2017). Hydroxylated polycyclic aromatic hydrocarbons as biomarkers of exposure to wood smoke in wildland firefighters. J Expo Sci Environ Epidemiol. 27(1):78–83. https://doi.org/10.1038/jes.2015.75 PMID:26555473

Adetona O, Zhang JJ, Hall DB, Wang JS, Vena JE, Naeher LP (2013). Occupational exposure to woodsmoke and oxidative stress in wildland firefighters. Sci Total Environ. 449:269–75. https://doi.org/10.1016/j.scitotenv.2013.01.075 PMID:23434577

Adil M, Iqbal W, Adnan F, Wazir S, Khan I, Khayam MU, et al. (2018). Association of metronidazole with cancer: a potential risk factor or inconsistent deductions? Curr Drug Metab. 19(11):902–9. https://doi.org/10.2174/1389200219666180329124130 PMID:29595104

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

Adwas AA, Elkhoely AA, Kabel AM, Abdel-Rahman MN, Eissa AA (2016). Anti-cancer and cardioprotective effects of indol-3-carbinol in doxorubicin-treated mice. J Infect Chemother. 22(1):36–43. https://doi.org/10.1016/j.jiac.2015.10.001 PMID:26603425

Agalliu I, Gapstur S, Chen Z, Wang T, Anderson RL, Teras L, et al. (2016). Associations of oral α-, β-, and γ-human papillomavirus types with risk of incident head and neck cancer. JAMA Oncol. 2(5):599–606. https://doi.org/10.1001/jamaoncol.2015.5504 PMID:26794505

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

Agarwal C, Wadhwa R, Deep G, Biedermann D, Gažák R, Křen V, et al. (2013). Anti-cancer efficacy of silybin derivatives – a structure-activity relationship. PLoS One. 8(3):e60074. https://doi.org/10.1371/journal.pone.0060074 PMID:23555889

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 R, Rasheed Z, Ahsan H (2009). Biochemical and cellular toxicology of peroxynitrite: implications in cell death and autoimmune phenomenon. Immunopharmacol Immunotoxicol. 31(3):388–96. https://doi.org/10.1080/08923970802709197 PMID:19555204

Ahmed FE (2001). Toxicology and human health effects following exposure to oxygenated or reformulated gasoline. Toxicol Lett. 123(2–3):89–113. https://doi.org/10.1016/S0378-4274(01)00375-7 PMID:11641038

Ahn YS, Jeong KS (2015). Mortality due to malignant and non-malignant diseases in Korean professional emergency responders. PLoS One. 10(3):e0120305. https://doi.org/10.1371/journal.pone.0120305 PMID:25756281

Ahn YS, Jeong KS, Kim KS (2012). Cancer morbidity of professional emergency responders in Korea. Am J Ind Med. 55(9):768–78. https://doi.org/10.1002/ajim.22068 PMID:22628010

Alabed Alibrahim E, Legeay S, Billat PA, Bichon E, Guiffard I, Antignac JP, et al. (2019). In vivo comparison of the proangiogenic properties of chlordecone and three of its dechlorinated derivatives formed by in situ chemical reduction. Environ Sci Pollut Res Int. [Epub ahead of print] https://doi.org/10.1007/s11356-019-04353-5 PMID:30710326

Alan J, Williams G (2004). Letter to the Editor. Acta Paediatr. 52(s150):20–6.

Alavanja MC, Bonner MR (2012). Occupational pesticide exposures and cancer risk: a review. J Toxicol Environ Health B Crit Rev. 15(4):238–63. https://doi.org/10.1080/10937404.2012.632358 PMID:22571220

Alavanja MC, Dosemeci M, Samanic C, Lubin J, Lynch CF, Knott C, et al. (2004). Pesticides and lung cancer risk in the Agricultural Health Study cohort. Am J Epidemiol. 160(9):876–85. https://doi.org/10.1093/aje/kwh290 PMID:15496540

Alavanja MC, Hofmann JN, Lynch CF, Hines CJ, Barry KH, Barker J, et al. (2014). 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

Alavanja MC, Samanic C, Dosemeci M, Lubin J, Tarone R, Lynch CF, et al. (2003). Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. Am J Epidemiol. 157(9):800–14. https://doi.org/10.1093/aje/kwg040 PMID:12727674

Alavanja MC, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, Lynch CF, et al. (1996). The Agricultural Health Study. Environ Health Perspect. 104(4):362–9. https://doi.org/10.1289/ehp.96104362 PMID:8732939

Alavanja MCR (2009). Introduction: pesticides use and exposure extensive worldwide. Rev Environ Health. 24(4):303–9. https://doi.org/10.1515/REVEH.2009.24.4.303 PMID:20384038

Alavanja MCR, Sandler DP, Lynch CF, Knott C, Lubin JH, Tarone R, et al. (2005). Cancer incidence in the Agricultural Health Study. Scand J Work Environ Health. 31(Suppl 1):39–45, discussion 5–7. PMID:16190148

Albanes D (1999). Beta-carotene and lung cancer: a case study. Am J Clin Nutr. 69(6):1345S–50S. https://doi.org/10.1093/ajcn/69.6.1345S PMID:10359235

Alexander BH, Mandel JH, Scott LLF, Ramachandran G, Chen YC (2013). Brain cancer in workers employed at a specialty chemical research facility. Arch Environ Occup Health. 68(4):218–27. https://doi.org/10.1080/19338244.2012.701248 PMID:23697694

Alexander BH, Olsen GW (2007). Bladder cancer in perfluorooctanesulfonyl fluoride manufacturing workers. Ann Epidemiol. 17(6):471–8. https://doi.org/10.1016/j.annepidem.2007.01.036 PMID:17448680

Alexander BH, Olsen GW, Burris JM, Mandel JH, Mandel JS (2003). Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility. Occup Environ Med. 60(10):722–9. https://doi.org/10.1136/oem.60.10.722 PMID:14504359

Alhusainy W, Williams GM, Jeffrey AM, Iatropoulos MJ, Taylor S, Adams TB, et al. (2014). The natural basil flavonoid nevadensin protects against a methyleugenol-induced marker of hepatocarcinogenicity in male F344 rat. Food Chem Toxicol. 74:28–34. https://doi.org/10.1016/j.fct.2014.08.016 PMID:25218219

Ali I, Julin B, Glynn A, Högberg J, Berglund M, Johansson JE, et al. (2016). Exposure to polychlorinated biphenyls and prostate cancer: population-based prospective cohort and experimental studies. Carcinogenesis. 37(12):1144–51. https://doi.org/10.1093/carcin/bgw105 PMID:27742691

Alicandro G, Rota M, Boffetta P, La Vecchia C (2016). Occupational exposure to polycyclic aromatic hydrocarbons and lymphatic and hematopoietic neoplasms: a systematic review and meta-analysis of cohort studies. Arch Toxicol. 90(11):2643–56. https://doi.org/10.1007/s00204-016-1822-8 PMID:27530719

Alikhani N, Ferguson RD, Novosyadlyy R, Gallagher EJ, Scheinman EJ, Yakar S, et al. (2013). Mammary tumor growth and pulmonary metastasis are enhanced in a hyperlipidemic mouse model. Oncogene. 32(8):961–7. https://doi.org/10.1038/onc.2012.113 PMID:22469977

Álvarez-Argüelles ME, Melón S, Rojo S, Fernandez-Blázquez A, Boga JA, Palacio A, et al. (2017). Detection and quantification of Merkel cell polyomavirus. Analysis of Merkel cell carcinoma cases from 1977 to 2015. J Med Virol. 89(12):2224–9. https://doi.org/10.1002/jmv.24896 PMID:28681977

Álvarez-Barrera L, Rodríguez-Mercado JJ, López-Chaparro M, Altamirano-Lozano MA (2017). Genotoxicity of Casiopeina III-Ea in mouse bone marrow cells. Drug Chem Toxicol. 40(3):333–8. https://doi.org/10.1080/01480545.2016.1229787 PMID:27784184

Alwis KU, Bailey TL, Patel D, Wang L, Blount BC (2016). Measuring urinary *N*-acetyl-S-(4-hydroxy-2-methyl-2-buten-1-yl)-L-cysteine (IPMA3) as a potential biomarker of isoprene exposure. Anal Chim Acta. 941:61–6. https://doi.org/10.1016/j.aca.2016.08.023 PMID:27692379

Amadeo B, Marchand JL, Moisan F, Donnadieu S, Gaëlle C, Simone MP, et al. (2015). French firefighter mortality: analysis over a 30-year period. Am J Ind Med. 58(4):437–43. https://doi.org/10.1002/ajim.22434 PMID:25708859

Amirian ES, Marquez-Do D, Bondy ML, Scheurer ME (2013). Anti-human-cytomegalovirus immunoglobulin G levels in glioma risk and prognosis. Cancer Med. 2(1):57–62. https://doi.org/10.1002/cam4.44 PMID:24133628

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 MHG, Saber AT, Clausen PA, Pedersen JE, Løhr M, Kermanizadeh A, et al. (2018). Association between polycyclic aromatic hydrocarbon exposure and peripheral blood mononuclear cell DNA damage in human volunteers during fire extinction exercises. Mutagenesis. 33(1):105–15. https://doi.org/10.1093/mutage/gex021 PMID:29045708

Andersen ZJ, Stafoggia M, Weinmayr G, Pedersen M, Galassi C, Jørgensen JT, et al. (2017). Long-term exposure to ambient air pollution and incidence of postmenopausal breast cancer in 15 European cohorts within the ESCAPE project. Environ Health Perspect. 125(10):107005. https://doi.org/10.1289/EHP1742 PMID:29033383

Andreatta MM, Muñoz SE, Lantieri MJ, Eynard AR, Navarro A (2008). Artificial sweetener consumption and urinary tract tumors in Cordoba, Argentina. Prev Med. 47(1):136–9. https://doi.org/10.1016/j.ypmed.2008.03.015 PMID:18495230

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, 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

Angelino D, Dosz EB, Sun J, Hoeflinger JL, Van Tassell ML, Chen P, et al. (2015). Myrosinase-dependent and -independent formation and control of isothiocyanate products of glucosinolate hydrolysis. Front Plant Sci. 6:831. https://doi.org/10.3389/fpls.2015.00831 PMID:26500669

Annangi B, Bach J, Vales G, Rubio L, Marcos R, Hernández A (2015). Long-term exposures to low doses of cobalt nanoparticles induce cell transformation enhanced by oxidative damage. Nanotoxicology. 9(2):138–47. https://doi.org/10.3109/17435390.2014.900582 PMID:24713074

Anses/Afsset (2010). L'éthanol en population professionnelle: évaluation des risques de l'éthanol en population professionnelle. Paris, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (Anses/Afsset). Available from: https://www.anses.fr/fr/system/files/CHIM-Ra-Ethanol.pdf.

Anthony BJ, Ramm GA, McManus DP (2012). Role of resident liver cells in the pathogenesis of schistosomiasis. Trends Parasitol. 28(12):572–9. https://doi.org/10.1016/j.pt.2012.09.005 PMID:23099112

Antwi SO, Eckert EC, Sabaque CV, Leof ER, Hawthorne KM, Bamlet WR, et al. (2015). Exposure to environmental chemicals and heavy metals, and risk of pancreatic cancer. Cancer Causes Control. 26(11):1583–91. https://doi.org/10.1007/s10552-015-0652-y PMID:26293241

Ao J, Yuan T, Gao L, Yu X, Zhao X, Tian Y, et al. (2018). Organic UV filters exposure induces the production of inflammatory cytokines in human macrophages. Sci Total Environ. 635:926–35. https://doi.org/10.1016/j.scitotenv.2018.04.217 PMID:29710614

Ao M, Xiao X, Li Q (2019). Efficacy and safety of compound Kushen injection combined with chemotherapy on postoperative patients with breast cancer: a meta-analysis of randomized controlled trials. Medicine (Baltimore). 98(3):e14024. https://doi.org/10.1097/MD.0000000000014024 PMID:30653109

Apaja M (1980). Evaluation of toxicity and carcinogenicity of malonaldehyde: an experimental study in Swiss mice [thesis]. Oulu, Finland: University of Oulu.

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

APVMA (2003). Public release summary on evaluation of the new active tepraloxydim in the product Aramo herbicide. Canberra, Australia: Australian Pesticides and Veterinary Medicines Authority. Available from: https://apvma.gov.au/sites/default/files/publication/14056-prs-tepraloxydim.pdf, accessed 27 February 2019.

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

Arrebola JP, Belhassen H, Artacho-Cordón F, Ghali R, Ghorbel H, Boussen H, et al. (2015). Risk of female breast cancer and serum concentrations of organochlorine pesticides and polychlorinated biphenyls: a case-control study in Tunisia. Sci Total Environ. 520:106–13. https://doi.org/10.1016/j.scitotenv.2015.03.045 PMID:25804877

Asare GA, Paterson AC, Kew MC, Khan S, Mossanda KS (2006). Iron-free neoplastic nodules and hepatocellular carcinoma without cirrhosis in Wistar rats fed a diet high in iron. J Pathol. 208(1):82–90. https://doi.org/10.1002/path.1875 PMID:16278820

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

Ashbury JE, Lévesque LE, Beck PA, Aronson KJ (2012). Selective serotonin reuptake inhibitor (SSRI) antidepressants, prolactin and breast cancer. Front Oncol. 2:177. https://doi.org/10.3389/fonc.2012.00177 PMID:23227451

Ashby J, Short JM, Jones NJ, Lefevre PA, Provost GS, Rogers BJ, et al. (1994). Mutagenicity of *o*-anisidine to the bladder of lacI^{-} transgenic B6C3F$_1$ mice: absence of ^{14}C or ^{32}P bladder DNA adduction. Carcinogenesis. 15(10):2291–6. https://doi.org/10.1093/carcin/15.10.2291 PMID:7955069

Ashmore JH, Lesko SM, Miller PE, Cross AJ, Muscat JE, Zhu J, et al. (2013). Association of dietary and supplemental iron and colorectal cancer in a population-based study. Eur J Cancer Prev. 22(6):506–11. https://doi.org/10.1097/CEJ.0b013e32836056f8 PMID:23492957

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

ATSDR (2000). Toxicological profile for methylene chloride. Atlanta (GA), USA: Agency for Toxic Substances and Disease Registry. Available from: http://www.atsdr.cdc.gov/toxprofiles/tp14.pdf.

ATSDR (2003). Toxicological profile for pyrethrins and pyrethroids. Atlanta (GA), USA: Agency for Toxic Substances and Disease Registry.

ATSDR (2005). Toxicological profile for tin. Atlanta (GA), USA: Agency for Toxic Substances and Disease Registry. Available from: http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=543&tid=98.

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.

Auger N, Laverdière C, Ayoub A, Lo E, Luu TM (2019). Neonatal phototherapy and future risk of childhood cancer. Int J Cancer. 145(8):2061–69. https://doi.org/10.1002/ijc.32158 PMID:30684392

Awan KH, Siddiqi K, Patil Sh, Hussain QA (2017). Assessing the effect of waterpipe smoking on cancer outcome - a systematic review of current evidence. Asian Pac J Cancer Prev. 18(2):495–502. https://doi.org/10.22034/APJCP.2017.18.2.495 PMID:28345836

Axelrod L, Munster AM, O'Brien TF (1971). Typhoid cholecystitis and gallbladder carcinoma after interval of 67 years. JAMA. 217(1):83. https://doi.org/10.1001/jama.1971.03190010065032 PMID:5108716

Axelson O, Sundell L, Andersson K, Edling C, Hogstedt C, Kling H (1980). Herbicide exposure and tumor mortality. An updated epidemiologic investigation on Swedish railroad workers. Scand J Work Environ Health. 6(1):73–9. https://doi.org/10.5271/sjweh.2631 PMID:7384770

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

Babiker M, Dillon MF, Bass G, Walsh TN (2012). Oesophageal carcinoma in a married couple following long-term exposure to dry cleaning agents. Occup Environ Med. 69(7):525. https://doi.org/10.1136/oemed-2011-100407 PMID:22146992

Bachur NR (2002). Anthracyclines. In: Bertino JR, editor. Encyclopedia of cancer. 2nd ed. Academic Press; pp. 57–61. https://doi.org/10.1016/B0-12-227555-1/00006-X

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

Bahl M, Ennis M, Tannock IF, Hux JE, Pritchard KI, Koo J, et al. (2005). Serum lipids and outcome of early-stage breast cancer: results of a prospective cohort study. Breast Cancer Res Treat. 94(2):135–44. https://doi.org/10.1007/s10549-005-6654-9 PMID:16261412

Bai Y, Li X, Wang K, Chen S, Wang S, Chen Z, et al. (2016). Association of shift-work, daytime napping, and nighttime sleep with cancer incidence and cancer-caused mortality in Dongfeng-Tongji cohort study. Ann Med. 48(8):641–51. https://doi.org/10.1080/07853890.2016.1217037 PMID:27558895

Bailey HD, Fritschi L, Infante-Rivard C, Glass DC, Miligi L, Dockerty JD, et al. (2014a). Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: findings from the Childhood Leukemia International Consortium. Int J Cancer. 135(9):2157–72. https://doi.org/10.1002/ijc.28854 PMID:24700406

Bailey HD, Fritschi L, Metayer C, Infante-Rivard C, Magnani C, Petridou E, et al. (2014b). Parental occupational paint exposure and risk of childhood leukemia in the offspring: findings from the Childhood Leukemia International Consortium. Cancer Causes Control. 25(10):1351–67. https://doi.org/10.1007/s10552-014-0441-z PMID:25088805

Bailey HD, Infante-Rivard C, Metayer C, Clavel J, Lightfoot T, Kaatsch P, et al. (2015a). Home pesticide exposures and risk of childhood leukemia: findings from the Childhood Leukemia International Consortium. Int J Cancer. 137(11):2644–63. https://doi.org/10.1002/ijc.29631 PMID:26061779

Bailey HD, Metayer C, Milne E, Petridou ET, Infante-Rivard C, Spector LG, et al. (2015b). Home paint exposures and risk of childhood acute lymphoblastic leukemia: findings from the Childhood Leukemia International Consortium. Cancer Causes Control. 26(9):1257–70. https://doi.org/10.1007/s10552-015-0618-0 PMID:26134047

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

Bailony MR, Hararah MK, Salhab AR, Ghannam I, Abdeen Z, Ghannam J (2011). Cancer registration and healthcare access in West Bank, Palestine: a GIS analysis of childhood cancer, 1998-2007. Int J Cancer. 129(5):1180–9. https://doi.org/10.1002/ijc.25732 PMID:20957630

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. 31:14. https://doi.org/10.1186/s12302-019-0195-z

Bakke B, Stewart PA, Waters MA (2007). Uses of and exposure to trichloroethylene in U.S. industry: a systematic literature review. J Occup Environ Hyg. 4(5):375–90. https://doi.org/10.1080/15459620701301763 PMID:17454505

Balaram P, Sridhar H, Rajkumar T, Vaccarella S, Herrero R, Nandakumar A, et al. (2002). Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. Int J Cancer. 98(3):440–5. https://doi.org/10.1002/ijc.10200 PMID:11920597

Balbo S, Stepanov I (2018). The Wild West of e-cigarettes. Chem Res Toxicol. 31(9):823–4. https://doi.org/10.1021/acs.chemrestox.8b00214 PMID:30188707

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

Bardack S, Dalgard CL, Kalinich JF, Kasper CE (2014). Genotoxic changes to rodent cells exposed in vitro to tungsten, nickel, cobalt and iron. Int J Environ Res Public Health. 11(3):2922–40. https://doi.org/10.3390/ijerph110302922 PMID:24619124

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;2-0 PMID:9219653

Bardin JA, Gore RJ, Wegman DH, Kriebel D, Woskie SR, Eisen EA (2005). Registry-based case-control studies of liver cancer and cancers of the biliary tract nested in a cohort of autoworkers exposed to metalworking fluids. Scand J Work Environ Health. 31(3):205–11. https://doi.org/10.5271/sjweh.870 PMID:15999572

Barr L, Metaxas G, Harbach CA, Savoy LA, Darbre PD (2012). Measurement of paraben concentrations in human breast tissue at serial locations across the breast from axilla to sternum. J Appl Toxicol. 32(3):219–32. https://doi.org/10.1002/jat.1786 PMID:22237600

Barul C, Fayossé A, Carton M, Pilorget C, Woronoff A-S, Stücker I, et al. (2017). Occupational exposure to chlorinated solvents and risk of head and neck cancer in men: a population-based case-control study in France. Environ Health. 16(1):77. https://doi.org/10.1186/s12940-017-0286-5 PMID:28738894

Basílio-de-Oliveira CA, Aquino A, Simon EF, Eyer-Silva WA (2002). Concomitant prostatic schistosomiasis and adenocarcinoma: case report and review. Braz J Infect Dis. 6(1):45–9. https://doi.org/10.1590/S1413-86702002000100007 PMID:11980603

Bausinger J, Speit G (2014). Induction and repair of DNA damage measured by the comet assay in human T lymphocytes separated by immunomagnetic cell sorting. Mutat Res. 769:42–8. https://doi.org/10.1016/j.mrfmmm.2014.07.005 PMID:25771724

Beall C, Bender TJ, Cheng H, Herrick R, Kahn A, Matthews R, et al. (2005). Mortality among semiconductor and storage device-manufacturing workers. J Occup Environ Med. 47(10):996–1014. https://doi.org/10.1097/01.jom.0000183094.42763.f0 PMID:16217241

Beall C, Delzell E, Rodu B, Sathiakumar N, Myers S (2001). Cancer and benign tumor incidence among employees in a polymers research complex. J Occup Environ Med. 43(10):914–24. https://doi.org/10.1097/00043764-200110000-00011 PMID:11665461

Beceren A, Akdemir N, Omurtag GZ, Tarlipinar ME, Sardas S (2016). DNA damage in gasoline station workers caused by occupational exposures to petrol vapour in Turkey. Acta Pharmaceutica Sciencia. 54(1):53–62. https://doi.org/10.23893/1307-2080.APS.0545

Becher H, Flesch-Janys D, Kauppinen T, Kogevinas M, Steindorf K, Manz A, et al. (1996). Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins. Cancer Causes Control. 7(3):312–21. https://doi.org/10.1007/BF00052936 PMID:8734824

Becker FF (1983). Thioacetamide hepatocarcinogenesis. J Natl Cancer Inst. 71(3):553–8. PMID:6577229

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

Becker JC, Schrama D, Houben R (2009). Merkel cell carcinoma. Cell Mol Life Sci. 66(1):1–8. https://doi.org/10.1007/s00018-008-8483-6 PMID:19023519

Becker JC, Stang A, DeCaprio JA, Cerroni L, Lebbé C, Veness M, et al. (2017). Merkel cell carcinoma. Nat Rev Dis Primers. 3:17077. https://doi.org/10.1038/nrdp.2017.77 PMID:29072302

Becker-Schiebe M, Mengs U, Schaefer M, Bulitta M, Hoffmann W (2011). Topical use of a silymarin-based preparation to prevent radiodermatitis: results of a prospective study in breast cancer patients. Strahlenther Onkol. 187(8):485–91. https://doi.org/10.1007/s00066-011-2204-z PMID:21786113

Beek B, Obe G (1974). Effect of lead acetate on human leukocyte chromosomes in vitro. Experientia. 30(9):1006–7. https://doi.org/10.1007/BF01938974 PMID:4413065

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

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 B6C3F$_1$ 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

Beliles RP, Paulin JH, Makris MG, Weir RJ (1980). Three-generation reproduction study of rats receiving acrylonitrile in drinking water. Litton Bionetics, Inc. Prepared for the Chemical Manufacturers Association, as cited in US Environmental Protection Agency, Health Assessment Document for Acrylonitrile, Office of Health and Environmental Assessment. EPA-600/8-82-007F, October 1983. Washington (DC), USA: United States Environmental Protection Agency.

Bellém F, Nunes S, Morais M (2013). Cyanobacteria toxicity: potential public health impact in South Portugal populations. J Toxicol Environ Health A. 76(4–5):263–71. https://doi.org/10.1080/15287394.2013.757204 PMID:23514068

Belli S, Comba P, De Santis M, Grignoli M, Sasco AJ (1990). Cancer mortality patterns among laboratory workers. Lancet. 335(8705):1597–8. https://doi.org/10.1016/0140-6736(90)91432-A PMID:1972521

Belpoggi F, Soffritti M, Filippini F, Maltoni C (1997). Results of long-term experimental studies on the carcinogenicity of methyl *tert*-butyl ether. Ann N Y Acad Sci. 837(1):77–95. https://doi.org/10.1111/j.1749-6632.1997.tb56865.x PMID:9472331

Belpoggi F, Soffritti M, Guarino M, Lambertini L, Cevolani D, Maltoni C (2002b). 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

Belpoggi F, Soffritti M, Maltoni C (1995). Methyl-tertiary-butyl ether (MTBE) – a gasoline additive – causes testicular and lymphohaematopoietic cancers in rats. Toxicol Ind Health. 11(2):119–49. https://doi.org/10.1177/074823379501100202 PMID:7491630

Belpoggi F, Soffritti M, Maltoni C (1999). Immunoblastic lymphomas in Sprague-Dawley rats following exposure to the gasoline oxygenated additives methyl-tertiary-butyl ether (MTBE) and ethyl-tertiary-butyl ether (ETBE): early observations on their natural history. Eur J Oncol. 4:563–72.

Belpoggi F, Soffritti M, Minardi F, Bua L, Cattin E, Maltoni C (2002a). Results of long-term carcinogenicity bioassays on *tert*-amyl-methyl-ether (TAME) and di-isopropyl-ether (DIPE) in rats. Ann N Y Acad Sci. 982(1):70–86. https://doi.org/10.1111/j.1749-6632.2002.tb04925.x PMID:12562629

Ben Khedher S, Neri M, Guida F, Matrat M, Cenée S, Sanchez M, et al.; ICARE Study Group (2017). Occupational exposure to endotoxins and lung cancer risk: results of the ICARE Study. Occup Environ Med. 74(9):667–79. https://doi.org/10.1136/oemed-2016-104117 PMID:28490662

Benachour N, Moslemi S, Sipahutar H, Seralini GE (2007). Cytotoxic effects and aromatase inhibition by xenobiotic endocrine disrupters alone and in combination. Toxicol Appl Pharmacol. 222(2):129–40. https://doi.org/10.1016/j.taap.2007.03.033 PMID:17599374

Bender TJ, Beall C, Cheng H, Herrick RF, Kahn AR, Matthews R, et al. (2007). Cancer incidence among semiconductor and electronic storage device workers. Occup Environ Med. 64(1):30–6. https://doi.org/10.1136/oem.2005.023366 PMID:16847035

Bendesky A, Menéndez D, Ostrosky-Wegman P (2002). Is metronidazole carcinogenic? Mutat Res. 511(2):133–44. https://doi.org/10.1016/S1383-5742(02)00007-8 PMID:12052431

Benhammou V, Warszawski J, Bellec S, Doz F, André N, Lacour B, et al.; ANRS-Enquête Périnatale Française (2008). Incidence of cancer in children perinatally exposed to nucleoside reverse transcriptase inhibitors. AIDS. 22(16):2165–77. https://doi.org/10.1097/QAD.0b013e328311d18b PMID:18832880

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 JM, Gigliotti AP, March TH, Barr EB, Tibbetts BM, Skipper BJ, et al. (2011). Chronic carcinogenicity study of gasoline vapor condensate (GVC) and GVC containing methyl tertiary-butyl ether in F344 rats. J Toxicol Environ Health A. 74(10):638–57. https://doi.org/10.1080/15287394.2011.538837 PMID:21432714

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

Beral V, Gaitskell K, Hermon C, Moser K, Reeves G, Peto R; Collaborative Group On Epidemiological Studies Of Ovarian Cancer (2015). Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet. 385(9980):1835–42. https://doi.org/10.1016/S0140-6736(14)61687-1 PMID:25684585

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

Bernardini P, Giannandrea F, Voso MT, Sica S (2005). Myeloproliferative disorders due to the use of gasoline as a solvent: report of three cases. Med Lav. 96(2):119–25. PMID:16001511 [in Italian]

Berrington de Gonzalez A, Salotti JA, McHugh K, Little MP, Harbron RW, Lee C, et al. (2016). Relationship between paediatric CT scans and subsequent risk of leukaemia and brain tumours: assessment of the impact of underlying conditions. Br J Cancer. 114(4):388–94. https://doi.org/10.1038/bjc.2015.415 PMID:26882064

Besaratinia A, Pfeifer GP (2005). DNA adduction and mutagenic properties of acrylamide. Mutat Res. 580(1–2):31–40. https://doi.org/10.1016/j.mrgentox.2004.10.011 PMID:15668105

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.3193 PMID:21901243

Bhagwat S, Haytowitz DB, Holden JM (2008). USDA database for the isoflavone content of selected foods, release 2.0. Washington (DC), USA: United States Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory. Available from: http://www.ars.usda.gov/nutrientdata/isoflav.

Bhasin G, Kauser H, Athar M (2004). Free radical generating agents lead to the rapid progression of benign skin tumors to carcinoma in iron-overloaded mice. Arch Toxicol. 78(3):139–46. https://doi.org/10.1007/s00204-003-0525-0 PMID:14647977

Bhat VK, Krump C, Bernhart E, Becker JC, Sattler W, Ghaffari-Tabrizi-Wizsy N (2018). A short-term in vivo model for Merkel cell carcinoma. Exp Dermatol. 27(6):684–7. https://doi.org/10.1111/exd.13529 PMID:29509994

Bigert C, Gustavsson P, Straif K, Taeger D, Pesch B, Kendzia B, et al. (2016). Lung cancer among firefighters: smoking-adjusted risk estimates in a pooled analysis of case-control studies. J Occup Environ Med. 58(11):1137–43. https://doi.org/10.1097/JOM.0000000000000878 PMID:27820764

Bio/dynamics Inc. (1980a). A twenty-four month oral toxicity/carcinogenicity study of acrylonitrile administered by intubation to Spartan rats, Project No. 77-1746 (BDN-77-29). Final report submitted to Monsanto Company, 30 June 1980.

Bio/dynamics Inc. (1980b). A twenty-four month oral toxicity/carcinogenicity study of acrylonitrile administered to Spartan rats in the drinking water, Project No. 77-1745 (BDN-77-28). Final report submitted to Monsanto Company, 30 June 1980.

Bio/dynamics Inc. (1980c). A twenty-four month oral toxicity/carcinogenicity study of acrylonitrile administered in the drinking water to Fischer 344 rats, Project No. 77-1744 (BDN-77-27). Final report submitted to Monsanto Company, 30 June 1980.

Bird MG, Burleigh-Flayer HD, Chun JS, Douglas JF, Kneiss JJ, Andrews LS (1997). Oncogenicity studies of inhaled methyl tertiary-butyl ether (MTBE) in CD-1 mice and F-344 rats. J Appl Toxicol. 17(Suppl 1):S45–55. https://doi.org/10.1002/(SICI)1099-1263(199705)17:1+<S45::AID-JAT410>3.3.CO;2-B PMID:9179727

Blair A, Decoufle P, Grauman D (1979). Causes of death among laundry and dry cleaning workers. Am J Public Health. 69(5):508–11. https://doi.org/10.2105/AJPH.69.5.508 PMID:434285

Blair A, Dosemeci M, Heineman EF (1993). Cancer and other causes of death among male and female farmers from twenty-three states. Am J Ind Med. 23(5):729–42. https://doi.org/10.1002/ajim.4700230507 PMID:8506851

Blair A, Petralia SA, Stewart PA (2003). Extended mortality follow-up of a cohort of dry cleaners. Ann Epidemiol. 13(1):50–6. https://doi.org/10.1016/S1047-2797(02)00250-8 PMID:12547485

Blair A, Stewart PA, Tolbert PE, Grauman D, Moran FX, Vaught J, et al. (1990). Cancer and other causes of death among a cohort of dry cleaners. Br J Ind Med. 47(3):162–8. https://doi.org/10.1136/oem.47.3.162 PMID:2328223

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

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

Błędzka D, Gromadzińska J, Wąsowicz W (2014). Parabens. From environmental studies to human health. Environ Int. 67:27–42. https://doi.org/10.1016/j.envint.2014.02.007 PMID:24657492

Blount BC, Mack MM, Wehr CM, MacGregor JT, Hiatt RA, Wang G, et al. (1997). Folate deficiency causes uracil misincorporation into human DNA and chromosome breakage: implications for cancer and neuronal damage. Proc Natl Acad Sci USA. 94(7):3290–5. https://doi.org/10.1073/pnas.94.7.3290 PMID:9096386

Boada LD, Henríquez-Hernández LA, Navarro P, Zumbado M, Almeida-González M, Camacho M, et al. (2015). Exposure to polycyclic aromatic hydrocarbons (PAHs) and bladder cancer: evaluation from a gene-environment perspective in a hospital-based case-control study in the Canary Islands (Spain). Int J Occup Environ Health. 21(1):23–30. https://doi.org/10.1179/2049396714Y.0000000085 PMID:25291984

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

Bogaards JJ, Freidig AP, van Bladeren PJ (2001). Prediction of isoprene diepoxide levels in vivo in mouse, rat and man using enzyme kinetic data in vitro and physiologically-based pharmacokinetic modelling. Chem Biol Interact. 138(3):247–65. https://doi.org/10.1016/S0009-2797(01)00276-9 PMID:11714482

Bogaards JJ, Venekamp JC, Salmon FG, van Bladeren PJ (1999). Conjugation of isoprene monoepoxides with glutathione, catalyzed by α, μ, π and θ-class glutathione *S*-transferases of rat and man. Chem Biol Interact. 117(1):1–14. https://doi.org/10.1016/S0009-2797(98)00094-5 PMID:10190541

Boice JD Jr, Marano DE, Munro HM, Chadda BK, Signorello LB, Tarone RE, et al. (2010). Cancer mortality among US workers employed in semiconductor wafer fabrication. J Occup Environ Med. 52(11):1082–97. https://doi.org/10.1097/JOM.0b013e3181f7e520 PMID:21063186

Bolt AM, Sabourin V, Molina MF, Police AM, Negro Silva LF, Plourde D, et al. (2015). Tungsten targets the tumor microenvironment to enhance breast cancer metastasis. Toxicol Sci. 143(1):165–77. https://doi.org/10.1093/toxsci/kfu219 PMID:25324207

Bomhard EM, Herbold BA (2005). Genotoxic activities of aniline and its metabolites and their relationship to the carcinogenicity of aniline in the spleen of rats. Crit Rev Toxicol. 35(10):783–835. https://doi.org/10.1080/10408440500442384 PMID:16468500

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.

Bondy G, Mehta R, Caldwell D, Coady L, Armstrong C, Savard M, et al. (2012). Effects of long term exposure to the mycotoxin fumonisin B_1 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

Borghoff SJ, Poet TS, Green S, Davis J, Hughes B, Mensing T, et al. (2015). Methyl isobutyl ketone exposure-related increases in specific measures of α2u-globulin (α2u) nephropathy in male rats along with in vitro evidence of reversible protein binding. Toxicology. 333:1–13. https://doi.org/10.1016/j.tox.2015.02.003 PMID:25797582

Borghoff SJ, Williams TM (2000). Species-specific tumor responses following exposure to methyl *tert*-butyl ether. CIIT Activities. 20:1–9.

Borkhardt A, Wilda M, Fuchs U, Gortner L, Reiss I (2003). Congenital leukaemia after heavy abuse of permethrin during pregnancy. Arch Dis Child Fetal Neonatal Ed. 88(5):F436–7. https://doi.org/10.1136/fn.88.5.F436 PMID:12937054

Bosch-Barrera J, Menendez JA (2015). Silibinin and STAT3: a natural way of targeting transcription factors for cancer therapy. Cancer Treat Rev. 41(6):540–6. https://doi.org/10.1016/j.ctrv.2015.04.008 PMID:25944486

Bosch-Barrera J, Queralt B, Menendez JA (2017). Targeting STAT3 with silibinin to improve cancer therapeutics. Cancer Treat Rev. 58:61–9. https://doi.org/10.1016/j.ctrv.2017.06.003 PMID:28686955

Bosch-Barrera J, Sais E, Cañete N, Marruecos J, Cuyàs E, Izquierdo A, et al. (2016). Response of brain metastasis from lung cancer patients to an oral nutraceutical product containing silibinin. Oncotarget. 7(22):32006–14. https://doi.org/10.18632/oncotarget.7900 PMID:26959886

Bosetti C, Filomeno M, Riso P, Polesel J, Levi F, Talamini R, et al. (2012). Cruciferous vegetables and cancer risk in a network of case-control studies. Ann Oncol. 23(8):2198–203. https://doi.org/10.1093/annonc/mdr604 PMID:22328735

Boursi B, Lurie I, Haynes K, Mamtani R, Yang YX (2018). Chronic therapy with selective serotonin reuptake inhibitors and survival in newly diagnosed cancer patients. Eur J Cancer Care (Engl). 27(1):e12666. https://doi.org/10.1111/ecc.12666 PMID:28252230

Boursi B, Lurie I, Mamtani R, Haynes K, Yang YX (2015). Anti-depressant therapy and cancer risk: a nested case-control study. Eur Neuropsychopharmacol. 25(8):1147–57. https://doi.org/10.1016/j.euroneuro.2015.04.010 PMID:25934397

Boyle T, Fritschi L, Kobayashi LC, Heyworth JS, Lee DG, Si S, et al. (2016). Sedentary work and the risk of breast cancer in premenopausal and postmenopausal women: a pooled analysis of two case-control studies. Occup Environ Med. 73(11):735–41. https://doi.org/10.1136/oemed-2015-103537 PMID:27540104

Brandes LJ, Arron RJ, Bogdanovic RP, Tong J, Zaborniak CL, Hogg GR, et al. (1992). Stimulation of malignant growth in rodents by antidepressant drugs at clinically relevant doses. Cancer Res. 52(13):3796–800. PMID:1617649

Brandt L, Kolstad H, Rasmussen K (1987). Health risks of dry cleaning. Ugeskr Laeger. 149(5):319–23. PMID:3824612 [in Danish]

Brauer M, Freedman G, Frostad J, van Donkelaar A, Martin RV, Dentener F, et al. (2016). Ambient air pollution exposure estimation for the Global Burden of Disease 2013. Environ Sci Technol. 50(1):79–88. https://doi.org/10.1021/acs.est.5b03709 PMID:26595236

Brigelius-Flohé R, Arnér ESJ (2018). Selenium and selenoproteins in (redox) signaling, diseases, and animal models - 200 year anniversary issue. Free Radic Biol Med. 127:1–2. https://doi.org/10.1016/j.freeradbiomed.2018.09.026 PMID:30274914

Broddle WD, Dennis MW, Kitchen DN, Vernot EH (1996). Chronic dermal studies of petroleum streams in mice. Fundam Appl Toxicol. 30(1):47–54. https://doi.org/10.1006/faat.1996.0042 PMID:8812220

Brosselin P, Rudant J, Orsi L, Leverger G, Baruchel A, Bertrand Y, et al. (2009). Acute childhood leukaemia and residence next to petrol stations and automotive repair garages: the ESCALE study (SFCE). Occup Environ Med. 66(9):598–606. https://doi.org/10.1136/oem.2008.042432 PMID:19213757

Brown TP, Paulson J, Pannett B, Coupland C, Coggon D, Chilvers CED, et al. (1996). Mortality pattern among biological research laboratory workers. Br J Cancer. 73(9):1152–5. https://doi.org/10.1038/bjc.1996.221 PMID:8624280

Browne P, Judson RS, Casey WM, Kleinstreuer NC, Thomas RS (2015). Screening chemicals for estrogen receptor bioactivity using a computational model. Environ Sci Technol. 49(14):8804–14. https://doi.org/10.1021/acs.est.5b02641 PMID:26066997

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

Bui T, Dao TS, Vo TG, Lürling M (2018). Warming affects growth rates and microcystin production in tropical bloom-forming *Microcystis* strains. Toxins (Basel). 10(3):123. https://doi.org/10.3390/toxins10030123 PMID:29538312

Burleigh-Flayer HD, Chun JS, Kintigh WJ (1992). Methyl tertiary butyl ether: vapor inhalation oncogenicity study in CD-1 mice. Bushy Run Research Center Report No. 91N0013A.

Busby C, Hamdan M, Ariabi E (2010). Cancer, infant mortality and birth sex-ratio in Fallujah, Iraq 2005-2009. Int J Environ Res Public Health. 7(7):2828–37. https://doi.org/10.3390/ijerph7072828 PMID:20717542

Busby J, Mills K, Zhang S-D, Liberante FG, Cardwell CR (2018). Selective serotonin reuptake inhibitor use and breast cancer survival: a population-based cohort study. Breast Cancer Res. 20(1):4. https://doi.org/10.1186/s13058-017-0928-0 PMID:29351761

Byeon SE, Yi YS, Lee J, Yang WS, Kim JH, Kim J, et al. (2018). Hydroquinone exhibits in vitro and in vivo anti-cancer activity in cancer cells and mice. Int J Mol Sci. 19(3):pii:E903. https://doi.org/10.3390/ijms19030903 PMID:29562668

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, Bonner MR, Nie J, Han D, Wang Y, Tao MH, et al. (2018). Lifetime exposure to ambient air pollution and methylation of tumor suppressor genes in breast tumors. Environ Res. 161:418–24. https://doi.org/10.1016/j.envres.2017.11.040 PMID:29197760

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

Calvert GM, Ruder AM, Petersen MR (2011). Mortality and end-stage renal disease incidence among dry cleaning workers. Occup Environ Med. 68(10):709–16. https://doi.org/10.1136/oem.2010.060665 PMID:21172794

Campo L, Rossella F, Mercadante R, Fustinoni S (2016). Exposure to BTEX and ethers in petrol station attendants and proposal of biological exposure equivalents for urinary benzene and MTBE. Ann Occup Hyg. 60(3):318–33. https://doi.org/10.1093/annhyg/mev083 PMID:26667482

Campos A, Vasconcelos V (2010). Molecular mechanisms of microcystin toxicity in animal cells. Int J Mol Sci. 11(1):268–87. https://doi.org/10.3390/ijms11010268 PMID:20162015

Cantor KP, Strickland PT, Brock JW, Bush D, Helzlsouer K, Needham LL, et al. (2003). Risk of non-Hodgkin's lymphoma and prediagnostic serum organochlorines: beta-hexachlorocyclohexane, chlordane/heptachlor-related compounds, dieldrin, and hexachlorobenzene. Environ Health Perspect. 111(2):179–83. https://doi.org/10.1289/ehp.4347 PMID:12573902

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

Capen CC, Dybing E, Rice JM, Wilbourn JD, editors (1999). Species differences in thyroid, kidney and urinary bladder carcinogenesis (IARC Scientific Publications, No. 147). Lyon, France: International Agency for Research on Cancer.

Capiglioni AM, Lorenzetti F, Quiroga AD, Parody JP, Ronco MT, Pisani GB, et al. (2018). Attenuation of liver cancer development by oral glycerol supplementation in the rat. Eur J Nutr. 57(3):1215–24. https://doi.org/10.1007/s00394-017-1404-4 PMID:28255652

Capoor MR, Nair D, Rajni, Khanna G, Krishna SV, Chintamani MS, et al. (2008). Microflora of bile aspirates in patients with acute cholecystitis with or without cholelithiasis: a tropical experience. Braz J Infect Dis. 12(3):222–5. http://dx.doi.org/10.1590/S1413-86702008000300012 PMID:18839486

Carbon Black Sales (2016). Carbon black – world consumption. Available from: https://carbonblacksales.com/carbon-black-reinforcing-agent/.

Carlberg M, Hardell L (2015). Pooled analysis of Swedish case-control studies during 1997-2003 and 2007-2009 on meningioma risk associated with the use of mobile and cordless phones. Oncol Rep. 33(6):3093–8. https://doi.org/10.3892/or.2015.3930 PMID:25963528

Carlos-Wallace FM, Zhang L, Smith MT, Rader G, Steinmaus C (2016). Parental, in utero, and early-life exposure to benzene and the risk of childhood leukemia: a meta-analysis. Am J Epidemiol. 183(1):1–14. https://doi.org/10.1093/aje/kwv120 PMID:26589707

Carmona ER, Creus A, Marcos R (2011). Genotoxicity testing of two lead-compounds in somatic cells of *Drosophila melanogaster*. Mutat Res. 724(1–2):35–40. https://doi.org/10.1016/j.mrgentox.2011.05.008 PMID:21645631

Carpenter L, Beral V, Roman E, Swerdlow AJ, Davies G (1991). Cancer in laboratory workers. Lancet. 338(8774):1080–1. https://doi.org/10.1016/0140-6736(91)91938-Q PMID:1681382

Carreón T, Hein MJ, Hanley KW, Viet SM, Ruder AM (2014a). 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

Carreón T, Hein MJ, Hanley KW, Viet SM, Ruder AM (2014b). Bladder cancer incidence among workers exposed to *o*-toluidine, aniline and nitrobenzene at a rubber chemical manufacturing plant. Occup Environ Med. 71(3):175–82. https://doi.org/10.1136/oemed-2013-101873 PMID:24368697

Carton M, Barul C, Menvielle G, Cyr D, Sanchez M, Pilorget C, et al.; ICARE Study Group (2017). Occupational exposure to solvents and risk of head and neck cancer in women: a population-based case-control study in France. BMJ Open. 7(1):e012833. https://doi.org/10.1136/bmjopen-2016-012833 PMID:28069619

Cartus AT, Herrmann K, Weishaupt LW, Merz KH, Engst W, Glatt H, et al. (2012). Metabolism of methyleugenol in liver microsomes and primary hepatocytes: pattern of metabolites, cytotoxicity, and DNA-adduct formation. Toxicol Sci. 129(1):21–34. https://doi.org/10.1093/toxsci/kfs181 PMID:22610610

Carvalho FP, Oliveira JM (2010). Uranium isotopes in the Balkan's environment and foods following the use of depleted uranium in the war. Environ Int. 36(4):352–60.

Carver A, Gallicchio VS (2017). Heavy metals and cancer. In: Atroshi F, editor. Cancer causing substances. London, UK: IntechOpen. Available from: https://www.intechopen.com/books/cancer-causing-substances/heavy-metals-and-cancer.

Caserta D, Di Segni N, Mallozzi M, Giovanale V, Mantovani A, Marci R, et al. (2014). Bisphenol A and the female reproductive tract: an overview of recent laboratory evidence and epidemiological studies. Reprod Biol Endocrinol. 12(1):37. https://doi.org/10.1186/1477-7827-12-37 PMID:24886252

Catsburg C, Miller AB, Rohan TE (2015). Active cigarette smoking and risk of breast cancer. Int J Cancer. 136(9):2204–9. https://doi.org/10.1002/ijc.29266 PMID:25307527

Cavalieri E, Rogan E (2006). Catechol quinones of estrogens in the initiation of breast, prostate, and other human cancers: keynote lecture. Ann N Y Acad Sci. 1089(1):286–301. https://doi.org/10.1196/annals.1386.042 PMID:17261777

Cavalieri E, Saeed M, Zahid M, Cassada D, Snow D, Miljkovic M, et al. (2012). Mechanism of DNA depurination by carcinogens in relation to cancer initiation. IUBMB Life. 64(2):169–79. https://doi.org/10.1002/iub.586 PMID:22162200

Cavalieri EL, Devanesan P, Bosland MC, Badawi AF, Rogan EG (2002). Catechol estrogen metabolites and conjugates in different regions of the prostate of Noble rats treated with 4-hydroxyestradiol: implications for estrogen-induced initiation of prostate cancer. Carcinogenesis. 23(2):329–33. https://doi.org/10.1093/carcin/23.2.329 PMID:11872641

Cavalieri EL, Kumar S, Todorovic R, Higginbotham S, Badawi AF, Rogan EG (2001). Imbalance of estrogen homeostasis in kidney and liver of hamsters treated with estradiol: implications for estrogen-induced initiation of renal tumors. Chem Res Toxicol. 14(8):1041–50. https://doi.org/10.1021/tx010042g PMID:11511178

Cavalieri EL, Rogan EG (2002). A unified mechanism in the initiation of cancer. Ann N Y Acad Sci. 959(1):341–54. https://doi.org/10.1111/j.1749-6632.2002.tb02105.x PMID:11976208

Cavallo D, Iavicoli I, Setini A, Marinaccio A, Perniconi B, Carelli G, et al. (2002). Genotoxic risk and oxidative DNA damage in workers exposed to antimony trioxide. Environ Mol Mutagen. 40(3):184–9. https://doi.org/10.1002/em.10102 PMID:12355552

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

Caygill CPJ, Braddick M, Hill MJ, Knowles RL, Sharp JCM (1995). The association between typhoid carriage, typhoid infection and subsequent cancer at a number of sites. Eur J Cancer Prev. 4(2):187–93. https://doi.org/10.1097/00008469-199504000-00010 PMID:7767246

Caygill CPJ, Hill MJ, Braddick M, Sharp JC (1994). Cancer mortality in chronic typhoid and paratyphoid carriers. Lancet. 343(8889):83–4. https://doi.org/10.1016/S0140-6736(94)90816-8 PMID:7903779

Cerreti M, Fidaleo M, Benucci I, Liburdi K, Tamborra P, Moresi M (2016). Assessing the potential content of ethyl carbamate in white, red, and rosé wines as a key factor for pursuing urea degradation by purified acid urease. J Food Sci. 81(7):C1603–12. https://doi.org/10.1111/1750-3841.13344 PMID:27239804

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

Chalmers IW, Fitzsimmons CM, Brown M, Pierrot C, Jones FM, Wawrzyniak JM, et al. (2015). Human IgG1 responses to surface localised *Schistosoma mansoni* Ly6 family members drop following praziquantel treatment. PLoS Negl Trop Dis. 9(7):e0003920. https://doi.org/10.1371/journal.pntd.0003920 PMID:26147973

Chan JM, Wang F, Holly EA (2009). Sweets, sweetened beverages, and risk of pancreatic cancer in a large population-based case-control study. Cancer Causes Control. 20(6):835–46. https://doi.org/10.1007/s10552-009-9323-1 PMID:19277880

Chang C, Rao DL, Qiu XM, Wang H, Xiong L (2014). The inhibitory effect of matrine on the growth of human colorectal cancer HT29 cells: an experimental observation. Zhongguo Zhong Xi Yi Jie He Za Zhi. 34(1):62–5. PMID:24520790 [in Chinese]

Chang CC, Chen SH, Ho SH, Yang CY, Wang HD, Tsai ML (2007). Proteomic analysis of proteins from bronchoalveolar lavage fluid reveals the action mechanism of ultrafine carbon black-induced lung injury in mice. Proteomics. 7(23):4388–97. https://doi.org/10.1002/pmic.200700164 PMID:17963277

Chang HR, Chen PN, Yang SF, Sun YS, Wu SW, Hung TW, et al. (2011). Silibinin inhibits the invasion and migration of renal carcinoma 786-O cells in vitro, inhibits the growth of xenografts in vivo and enhances chemosensitivity to 5-fluorouracil and paclitaxel. Mol Carcinog. 50(10):811–23. https://doi.org/10.1002/mc.20756 PMID:21574189

Charlier C, Foidart JM, Pitance F, Herman P, Gaspard U, Meurisse M, et al. (2004). Environmental dichlorodiphenyltrichlorethane or hexachlorobenzene exposure and breast cancer: is there a risk? Clin Chem Lab Med. 42(2):222–7. https://doi.org/10.1515/CCLM.2004.040 PMID:15061365

Chaudhary S, Chauhan P, Kumar R, Bhasin KK (2018). Toxicological responses of surfactant functionalized selenium nanoparticles: a quantitative multi-assay approach. Sci Total Environ. 643:1265–77. https://doi.org/10.1016/j.scitotenv.2018.06.296 PMID:30189543

Chen F, He BC, Yan LJ, Qiu Y, Lin LS, Cai L (2017a). Influence of oral hygiene and its interaction with standard of education on the risk of oral cancer in women who neither smoked nor drank alcohol: a hospital-based, case-control study. Br J Oral Maxillofac Surg. 55(3):260–5. https://doi.org/10.1016/j.bjoms.2016.11.316 PMID:27908460

Chen H, Qin S, Wang M, Zhang T, Zhang S (2015b). Association between cholesterol intake and pancreatic cancer risk: evidence from a meta-analysis. Sci Rep. 5(1):8243. https://doi.org/10.1038/srep08243 PMID:25649888

Chen H-P, Chan YJ (2014). The oncomodulatory role of human cytomegalovirus in colorectal cancer: implications for clinical trials. Front Oncol. 4:314. https://doi.org/10.3389/fonc.2014.00314 PMID:25452935

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 (2019). 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, Wan L, Couch L, Lin H, Li Y, Dobrovolsky VN, et al. (2013). Mechanism study of goldenseal-associated DNA damage. Toxicol Lett. 221(1):64–72. https://doi.org/10.1016/j.toxlet.2013.05.641 PMID:23747414

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 [in Chinese]

Chen Y, Tan F, Wei L, Li X, Lyu Z, Feng X, et al. (2018). Sleep duration and the risk of cancer: a systematic review and meta-analysis including dose-response relationship. BMC Cancer. 18(1):1149. https://doi.org/10.1186/s12885-018-5025-y PMID:30463535

Chen Y, Tong Y, Yang C, Gan Y, Sun H, Bi H, et al. (2015a). Consumption of hot beverages and foods and the risk of esophageal cancer: a meta-analysis of observational studies. BMC Cancer. 15(1):449. https://doi.org/10.1186/s12885-015-1185-1 PMID:26031666

Chen YJ, Liu WH, Chang LS (2017b). Hydroquinone-induced FOXP3-ADAM17-Lyn-Akt-p21 signaling axis promotes malignant progression of human leukemia U937 cells. Arch Toxicol. 91(2):983–97. https://doi.org/10.1007/s00204-016-1753-4 PMID:27307158

Cheung CWY, Gibbons N, Johnson DW, Nicol DL (2010). Silibinin – a promising new treatment for cancer. Anticancer Agents Med Chem. 10(3):186–95. https://doi.org/10.2174/1871520611009030186 PMID:20015009

Chiu A, Katz AJ, Beaubier J, Chiu N, Shi X (2004). Genetic and cellular mechanisms in chromium and nickel carcinogenesis considering epidemiologic findings. Mol Cell Biochem. 255(1–2):181–94. https://doi.org/10.1023/B:MCBI.0000007274.25052.82 PMID:14971659

Choi B, Ryu D, Kim CI, Lee JY, Choi A, Koh E (2017). Probabilistic dietary exposure to ethyl carbamate from fermented foods and alcoholic beverages in the Korean population. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 34(11):1885–92. https://doi.org/10.1080/19440049.2017.1364433 PMID:28783003

Choi JY, Neuhouser ML, Barnett MJ, Hong CC, Kristal AR, Thornquist MD, et al. (2008). Iron intake, oxidative stress-related genes (*MnSOD* and *MPO*) and prostate cancer risk in CARET cohort. Carcinogenesis. 29(5):964–70. https://doi.org/10.1093/carcin/bgn056 PMID:18296681

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):E1162. https://doi.org/10.3390/ijerph15061162 PMID:29865268

Chopra I, Roberts M (2001). Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol Mol Biol Rev. 65(2):232–60. https://doi.org/10.1128/MMBR.65.2.232-260.2001 PMID:11381101

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

Chua AC, Klopcic B, Lawrance IC, Olynyk JK, Trinder D (2010). Iron: an emerging factor in colorectal carcinogenesis. World J Gastroenterol. 16(6):663–72. https://doi.org/10.3748/wjg.v16.i6.663 PMID:20135713

Chuang HC, Cheng YL, Lei YC, Chang HH, Cheng TJ (2013). Protective effects of pulmonary epithelial lining fluid on oxidative stress and DNA single-strand breaks caused by ultrafine carbon black, ferrous sulphate and organic extract of diesel exhaust particles. Toxicol Appl Pharmacol. 266(3):329–34. https://doi.org/10.1016/j.taap.2012.12.004 PMID:23261976

Chun JS, Burleigh-Flayer HD, Kintigh WJ (1992). Methyl tertiary ether: vapor inhalation oncogenicity study in Fischer 344 rats. Bushy Run Research Center Report No. 91N0013B.

Chung H, Youn K, Kim K, Park K (2017). Carbon disulfide exposure estimate and prevalence of chronic diseases after carbon disulfide poisoning-related occupational diseases. Ann Occup Environ Med. 29(1):52. https://doi.org/10.1186/s40557-017-0208-6 PMID:29093821

Chung WS, Lin CL, Lin CL, Kao CH (2015). Thalassaemia and risk of cancer: a population-based cohort study. J Epidemiol Community Health. 69(11):1066–70. https://doi.org/10.1136/jech-2014-205075 PMID:25922472

Cichocki JA, Furuya S, Venkatratnam A, McDonald TJ, Knap AH, Wade T, et al. (2017). Characterization of variability in toxicokinetics and toxicodynamics of tetrachloroethylene using the collaborative cross mouse population. Environ Health Perspect. 125(5):057006. https://doi.org/10.1289/EHP788 PMID:28572074

Cichocki JA, Guyton KZ, Guha N, Chiu WA, Rusyn I, Lash LH (2016). Target organ metabolism, toxicity, and mechanisms of trichloroethylene and perchloroethylene: key similarities, differences, and data gaps. J Pharmacol Exp Ther. 359(1):110–23. https://doi.org/10.1124/jpet.116.232629 PMID:27511820

CIIT (Chemical Industry Institute of Toxicology) (1982). 104-Week chronic toxicity study in rats: Aniline hydrochloride. Final report.

Clarke R, Lewington S, Youngman L, Sherliker P, Peto R, Collins R (2002). Underestimation of the importance of blood pressure and cholesterol for coronary heart disease mortality in old age. Eur Heart J. 23(4):286–93. https://doi.org/10.1053/euhj.2001.2781 PMID:11812064

Clawson GA, Button JD, Woo CH (1987). Hepatocarcinogen-induced alterations in nuclear RNA compartmentation. Carcinogenesis. 8(9):1235–8. https://doi.org/10.1093/carcin/8.9.1235 PMID:2441886

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

ClinCalc (2019). Lisinopril. Drug usage statistics, United States, 2006-2016. ClinCalc DrugStats Database version 19.1. Available from: https://clincalc.com/DrugStats/Drugs/Lisinopril.

Coggshall K, Tello TL, North JP, Yu SS (2018). Merkel cell carcinoma: an update and review: pathogenesis, diagnosis, and staging. J Am Acad Dermatol. 78(3):433–42. https://doi.org/10.1016/j.jaad.2017.12.001 PMID:29229574

Cohen SM, Garland EM, St John M, Okamura T, Smith RA (1992). Acrolein initiates rat urinary bladder carcinogenesis. Cancer Res. 52(13):3577–81. PMID:1617627

Colak EH, Yomralioglu T, Nisanci R, Yildirim V, Duran C (2015). Geostatistical analysis of the relationship between heavy metals in drinking water and cancer incidence in residential areas in the Black Sea region of Turkey. J Environ Health. 77(6):86–93. PMID:25619041

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-2017-104666 PMID:29374095

Collett DJ, Rakhorst H, Lennox P, Magnusson M, Cooter R, Deva AK (2019). Current risk estimate of breast implant-associated anaplastic large cell lymphoma in textured breast implants. Plast Reconstr Surg. 143(3S):30S–40S. https://doi.org/10.1097/PRS.0000000000005567 PMID:30817554

Collins JJ, Acquavella JF (1998). Review and meta-analysis of studies of acrylonitrile workers. Scand J Work Environ Health. 24(Suppl 2):71–80. PMID:9714515

Collins JJ, Bender TJ, Bonner EM, Bodner KM, Kreft AM (2014). Brain cancer in workers employed at a laboratory research facility. PLoS One. 9(12):e113997. https://doi.org/10.1371/journal.pone.0113997 PMID:25493437

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-2013-102056 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

Conaway CC, Schroeder RE, Snyder NK, Holdsworth CE (1985). Teratology evaluation of methyl tertiary butyl ether in rats and mice. J Toxicol Environ Health. 16(6):797–809. https://doi.org/10.1080/15287398509530789 PMID:4093995

Cook LE, Finger BJ, Green MP, Pask AJ (2019). Exposure to atrazine during puberty reduces sperm viability, increases weight gain and alters the expression of key metabolic genes in the liver of male mice. Reprod Fertil Dev. 31(5):920–31. https://doi.org/10.1071/RD18505 PMID:30636190

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

Cordier S, Mousel ML, Le Goaster C, Gachelin G, Le Moual N, Manderèau L, et al. (1995). Cancer risk among workers in biomedical research. Scand J Work Environ Health. 21(6):450–9. https://doi.org/10.5271/sjweh.61 PMID:8824751

Cortés C, Marcos R (2018). Genotoxicity of disinfection byproducts and disinfected waters: a review of recent literature. Mutat Res Genet Toxicol Environ Mutagen. 831:1–12. https://doi.org/10.1016/j.mrgentox.2018.04.005 PMID:29875071

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

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.0b013e3181fce4b8 PMID:20975563

Cotterchio M, Kreiger N, Darlington G, Steingart A (2000). Antidepressant medication use and breast cancer risk. Am J Epidemiol. 151(10):951–7. https://doi.org/10.1093/oxfordjournals.aje.a010138 PMID:10853633

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

Cox LA Jr, Bird MG, Griffis L (1996). Isoprene cancer risk and the time pattern of dose administration. Toxicology. 113(1–3):263–72. https://doi.org/10.1016/0300-483X(96)03455-5 PMID:8901907

Cramer DW, Welch WR, Berkowitz RS, Godleski JJ (2007). Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. Obstet Gynecol. 110(2 Pt 2):498–501. https://doi.org/10.1097/01.AOG.0000262902.80861.a0 PMID:17666642

Crawford JO, Winski T, McElvenny D, Graveling R, Dixon K (2017). Firefighters and cancer: the epidemiological evidence. Research report TM/17/01. Edinburgh, UK: Institute of Occupational Medicine; pp. 1–157.

Crawford L, Reeves KW, Luisi N, Balasubramanian R, Sturgeon SR (2012). Perineal powder use and risk of endometrial cancer in postmenopausal women. Cancer Causes Control. 23(10):1673–80. https://doi.org/10.1007/s10552-012-0046-3 PMID:22875750

Crous-Bou M, Rennert G, Cuadras D, Salazar R, Cordero D, Saltz Rennert H, et al. (2013). Polymorphisms in alcohol metabolism genes *ADH1B* and *ALDH2*, alcohol consumption and colorectal cancer. PLoS One. 8(11):e80158. https://doi.org/10.1371/journal.pone.0080158 PMID:24282520

Cruz PM, Mo H, McConathy WJ, Sabnis N, Lacko AG (2013). The role of cholesterol metabolism and cholesterol transport in carcinogenesis: a review of scientific findings, relevant to future cancer therapeutics. Front Pharmacol. 4:119. https://doi.org/10.3389/fphar.2013.00119 PMID:24093019

Csendes A, Becerra M, Burdiles P, Demian I, Bancalari K, Csendes P (1994). Bacteriological studies of bile from the gallbladder in patients with carcinoma of the gallbladder, cholelithiasis, common bile duct stones and no gallstones disease. Eur J Surg. 160(6–7):363–7. PMID:7948355

Cufí S, Bonavia R, Vazquez-Martin A, Corominas-Faja B, Oliveras-Ferraros C, Cuyàs E, et al. (2013a). Silibinin meglumine, a water-soluble form of milk thistle silymarin, is an orally active anti-cancer agent that impedes the epithelial-to-mesenchymal transition (EMT) in EGFR-mutant non-small-cell lung carcinoma cells. Food Chem Toxicol. 60:360–8. https://doi.org/10.1016/j.fct.2013.07.063 PMID:23916468

Cufí S, Bonavia R, Vazquez-Martin A, Oliveras-Ferraros C, Corominas-Faja B, Cuyàs E, et al. (2013b). Silibinin suppresses EMT-driven erlotinib resistance by reversing the high miR-21/low miR-200c signature in vivo. Sci Rep. 3(1):2459. https://doi.org/10.1038/srep02459 PMID:23963283

D'Elia L, Rossi G, Ippolito R, Cappuccio FP, Strazzullo P (2012). Habitual salt intake and risk of gastric cancer: a meta-analysis of prospective studies. Clin Nutr. 31(4):489–98. https://doi.org/10.1016/j.clnu.2012.01.003 PMID:22296873

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

Dahlgren J, Klein J, Takhar H (2008). Cluster of Hodgkin's lymphoma in residents near a non-operational petroleum refinery. Toxicol Ind Health. 24(10):683–92. https://doi.org/10.1177/0748233708100553 PMID:19141572

Daniels RD, Bertke S, Dahm MM, Yiin JH, Kubale TL, Hales TR, et al. (2015). Exposure-response relationships for select cancer and non-cancer health outcomes in a cohort of U.S. firefighters from San Francisco, Chicago and Philadelphia (1950-2009). Occup Environ Med. 72(10):699–706. https://doi.org/10.1136/oemed-2014-102671 PMID:25673342

Daniels RD, Kubale TL, Yiin JH, Dahm MM, Hales TR, Baris D, et al. (2014). Mortality and cancer incidence in a pooled cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950-2009). Occup Environ Med. 71(6):388–97. https://doi.org/10.1136/oemed-2013-101662 PMID:24142974

Dar NA, Islami F, Bhat GA, Shah IA, Makhdoomi MA, Iqbal B, et al. (2013). Poor oral hygiene and risk of esophageal squamous cell carcinoma in Kashmir. Br J Cancer. 109(5):1367–72. https://doi.org/10.1038/bjc.2013.437 PMID:23900216

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, Aljarrah A, Miller WR, Coldham NG, Sauer MJ, Pope GS (2004). Concentrations of parabens in human breast tumours. J Appl Toxicol. 24(1):5–13. https://doi.org/10.1002/jat.958 PMID:14745841

Darbre PD, Harvey PW (2014). Parabens can enable hallmarks and characteristics of cancer in human breast epithelial cells: a review of the literature with reference to new exposure data and regulatory status. J Appl Toxicol. 34(9):925–38. https://doi.org/10.1002/jat.3027 PMID:25047802

Darnton A, Miller BG, Maccalman L, Galea KS, Wilkinson S, Cherrie JW, et al. (2012). An updated investigation of cancer incidence and mortality at a Scottish semiconductor manufacturing facility with case-control and case-only studies of selected cancers. Occup Environ Med. 69(10):767–9. https://doi.org/10.1136/oemed-2011-100606 PMID:22718705

Dator RP, Villalta PW, Hooyman CJ, Maertens LA, Balbo S (2018). Integrating multi-"omics"-mass spectrometry-based methods to characterize electronic cigarette exposure in humans. Abstract from 256th ACS National Meeting.

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

Davis JM, Garb Y (2019). A strong spatial association between e-waste burn sites and childhood lymphoma in the West Bank, Palestine. Int J Cancer. 144(3):470–5. https://doi.org/10.1002/ijc.31902 PMID:30259977

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 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 Conti A, Beland FA, Pogribny IP (2017). The role of epigenomic alterations in furan-induced hepatobiliary pathologies. Food Chem Toxicol. 109(Pt 1):677–82. https://doi.org/10.1016/j.fct.2017.07.049 PMID:28756210

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 DM, Pitanga BP, Grangeiro MS, Lima RM, Costa MF, Costa SL, et al. (2010). Catechol cytotoxicity in vitro: induction of glioblastoma cell death by apoptosis. Hum Exp Toxicol. 29(3):199–212. https://doi.org/10.1177/0960327109360364 PMID:20097727

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 Sanjosé SB, Serrano S, Tous M, Alejo B, Lloveras B, Quirós O, et al. (2019). Burden of human papillomavirus (HPV)-related cancers attributable to HPVs 6/11/16/18/31/33/45/52 and 58. JNCI Cancer Spectrum. 2(4):pky045. https://doi.org/10.1093/jncics/pky045 PMID:31360870

de Smith AJ, Kaur M, Gonseth S, Endicott A, Selvin S, Zhang L, et al. (2017). Correlates of prenatal and early-life tobacco smoke exposure and frequency of common gene deletions in childhood acute lymphoblastic leukemia. Cancer Res. 77(7):1674–83. https://doi.org/10.1158/0008-5472.CAN-16-2571 PMID:28202519

de Souza MR, Kahl VFS, Rohr P, Kvitko K, Cappetta M, Lopes WM, et al. (2018). Shorter telomere length and DNA hypermethylation in peripheral blood cells of coal workers. Mutat Res Genet Toxicol Environ Mutagen. 836(Pt B):36–41. https://doi.org/10.1016/j.mrgentox.2018.03.009 PMID:30442342

Del Bel Belluz L, Guidi R, Pateras IS, Levi L, Mihaljevic B, Rouf SF, et al. (2016). The typhoid toxin promotes host survival and the establishment of a persistent asymptomatic infection. PLoS Pathog. 12(4):e1005528. https://doi.org/10.1371/journal.ppat.1005528 PMID:27055274

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

Delmond KA, Vicari T, Guiloski IC, Dagostim AC, Voigt CL, Silva de Assis HC, et al. (2019). Antioxidant imbalance and genotoxicity detected in fish induced by titanium dioxide nanoparticles ($NpTiO_2$) and inorganic lead (PbII). Environ Toxicol Pharmacol. 67:42–52. https://doi.org/10.1016/j.etap.2019.01.009 PMID:30711874

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

Demir E, Kaya B, Soriano C, Creus A, Marcos R (2011). Genotoxic analysis of four lipid-peroxidation products in the mouse lymphoma assay. Mutat Res. 726(2):98–103. https://doi.org/10.1016/j.mrgentox.2011.07.001 PMID:21763450

Denard B, Lee C, Ye J (2012). Doxorubicin blocks proliferation of cancer cells through proteolytic activation of CREB3L1. eLife. 1:e00090. https://doi.org/10.7554/eLife.00090 PMID:23256041

Dennis LK, Lynch CF, Sandler DP, Alavanja MC (2010). Pesticide use and cutaneous melanoma in pesticide applicators in the Agricultural Health Study. Environ Health Perspect. 118(6):812–7. https://doi.org/10.1289/ehp.0901518 PMID:20164001

Deziel NC, Beane Freeman LE, Hoppin JA, Thomas K, Lerro CC, Jones RR, et al. (2018). An algorithm for quantitatively estimating non-occupational pesticide exposure intensity for spouses in the Agricultural Health Study. J Expo Sci Environ Epidemiol. https://doi.org/10.1038/s41370-018-0088-z PMID:30375516

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

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):E1887. 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

Diamante C, Bergfeld WF, Belsito DV, Klaassen CD, Marks JG Jr, Shank RC, et al. (2009). Final report on the safety assessment of Basic Violet 1, Basic Violet 3, and Basic Violet 4. Int J Toxicol. 28(6 Suppl 2):193S–204S. https://doi.org/10.1177/1091581809354649 PMID:20086192

Diaz G, Engle RE, Tice A, Melis M, Montenegro S, Rodriguez-Canales J, et al. (2018). Molecular signature and mechanisms of hepatitis D virus-associated hepatocellular carcinoma. Mol Cancer Res. 16(9):1406–19. https://doi.org/10.1158/1541-7786.MCR-18-0012 PMID:29858376

Dickie BC (1987). Two-year oral feeding study of the oncogenicity and chronic toxicity of EPTC in rats. Hazelton Laboratories America, Inc., PPG Industries, Inc., Study No. 6100-106. DPR Vol. 117-069, No. 55491.

Dietrich K, Schned A, Fortuny J, Heaney J, Marsit C, Kelsey KT, et al. (2009). Glucocorticoid therapy and risk of bladder cancer. Br J Cancer. 101(8):1316–20. https://doi.org/10.1038/sj.bjc.6605314 PMID:19773763

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

Dodd DE, Pluta LJ, Sochaski MA, Wall HG, Thomas RS (2012). Subchronic hepatotoxicity evaluation of hydrazobenzene in Fischer 344 rats. Int J Toxicol. 31(6):564–71. https://doi.org/10.1177/1091581812465322 PMID:23134713

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

Donat-Vargas C, Åkesson A, Berglund M, Glynn A, Wolk A, Kippler M (2016). Dietary exposure to polychlorinated biphenyls and risk of breast, endometrial and ovarian cancer in a prospective cohort. Br J Cancer. 115(9):1113–21. https://doi.org/10.1038/bjc.2016.282 PMID:27632375

Donat-Vargas C, Berglund M, Glynn A, Wolk A, Åkesson A (2017). Dietary polychlorinated biphenyls, long-chain n-3 polyunsaturated fatty acids and incidence of malignant melanoma. Eur J Cancer. 72:137–43. https://doi.org/10.1016/j.ejca.2016.11.016 PMID:28033525

Donya SM, Farghaly AA, Abo-Zeid MA, Aly HF, Ali SA, Hamed MA, et al. (2012). Malachite green induces genotoxic effect and biochemical disturbances in mice. Eur Rev Med Pharmacol Sci. 16(4):469–82. PMID:22696874

dos Santos CR, Domingues G, Matias I, Matos J, Fonseca I, de Almeida JM, et al. (2014). LDL-cholesterol signaling induces breast cancer proliferation and invasion. Lipids Health Dis. 13(1):16. https://doi.org/10.1186/1476-511X-13-16 PMID:24428917

Drobac D, Svircev Z, Tokodi N, Vidovic M, Baltic V, Bozic-Krstic V, et al. (2011). Microcystins – potential risk factors in carcinogenesis of primary liver cancer in Serbia. Geogr Pannon. 15(3):70–80. https://doi.org/10.5937/GeoPan1103070D

Duh RW, Asal NR (1984). Mortality among laundry and dry cleaning workers in Oklahoma. Am J Public Health. 74(11):1278–80. https://doi.org/10.2105/AJPH.74.11.1278 PMID:6496825

Dutch Health Council (2006). Summary of report of Dutch Health Council on ethanol (ethyl alcohol). Available from: https://www.gezondheidsraad.nl/documenten/adviezen/2006/07/10/ethanol-ethyl-alcohol.

Dutkiewicz T, Piotrowski J (1961). Experimental investigations on the quantitative estimation of aniline absorption in man. Pure Appl Chem. 31(1–2):319–24. https://doi.org/10.1351/pac196103010319

Dutta U, Garg PK, Kumar R, Tandon RK (2000). Typhoid carriers among patients with gallstones are at increased risk for carcinoma of the gallbladder. Am J Gastroenterol. 95(3):784–7. https://doi.org/10.1111/j.1572-0241.2000.01860.x PMID:10710075

Dwivedi DK, Jena GB (2018). Glibenclamide protects against thioacetamide-induced hepatic damage in Wistar rat: investigation on NLRP3, MMP-2, and stellate cell activation. Naunyn Schmiedebergs Arch Pharmacol. 391(11):1257–74. https://doi.org/10.1007/s00210-018-1540-2 PMID:30066023

Dziurzynski K, Chang SM, Heimberger AB, Kalejta RF, McGregor Dallas SR, Smit M, et al.; HCMV and Gliomas Symposium (2012). Consensus on the role of human cytomegalovirus in glioblastoma. Neuro-oncol. 14(3):246–55. https://doi.org/10.1093/neuonc/nor227 PMID:22319219

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 & Sons; pp. 603–19.

ECHA (2017). Annex 1, Background document in support of the Committee for Risk Assessment (RAC) evaluation of limit values for acrylonitrile in the workplace. ECHA/RAC/ O-0000001412-86-188/F, 9 March 2018. Available from: https://echa.europa.eu/documents/10162/13641/acrylonitrile_bg_annex1_en.pdf/600bc12b-f2b4-16f6-0164-25153b48743d.

ECHA (2018a). Cinidon ethyl. Substance information database. Available from: https://echa.europa.eu/substance-information/-/substanceinfo/100.120.583.

ECHA (2018b). N-cyclohexyl-N-methoxy-2,5-dimethyl-3-furamide. Available from:https://echa.europa.eu/substance-information/-/substanceinfo/100.056.620.

ECHA (2018c). Committee for Risk Assessment. Opinion on scientific evaluation of occupational exposure limits for acrylonitrile. ECHA/RAC/O-0000001412-86-188/F. Adopted 9 March 2018. Available from: https://echa.europa.eu/documents/10162/13641/acrylonitrile_opinion_en.pdf/102477c9-a961-2c96-5c4d-76fcd856ac19.

ECHA (2018d). Proposal by the European Chemical Agency (ECHA) in support of occupational exposure limit values for acrylonitrile in the workplace, p. 43. Available from: https://echa.europa.eu/documents/10162/614f9f4d-dc3d-cb88-0910-1f93c98b07fe.

ECHA (2019). Substance information: methanol. European Chemicals Agency. Available from: https://echa.europa.eu/substance-information/-/substanceinfo/100.000.599, accessed 18 March 2019.

ECSA (2012). Trichloroethylene legislation, markets and uses. European Chlorinated Solvent Association. Available from: http://www.eurochlor.org/media/8198/trichloroethylene-legislation-markets-uses.pdf.

EFSA (2004). Opinion of the Scientific Panel on Plant Health, Plant protection products and their residues on a request from the Commission related to the evaluation of Alachlor in the context of Council Directive 91/414/EEC (Question No EFSA-Q-2004-48) adopted on 28 October 2004. EFSA J. 2004(111):1–34.

EFSA (2008). Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts. Scientific opinion of the Panel on Contaminants in the Food Chain (Question No. EFSA-Q-2004-163. EFSA J. 653:1–131. https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2008.653

EFSA (2013). EFSA Panel on Food Additives and Nutrient Sources added to Food. Scientific opinion on the re-evaluation of aspartame (E 951) as a food additive. EFSA J. 11(12):3496.

EFSA (2014a). Conclusion on the peer review of the pesticide human health risk assessment of the active substance chlorpyrifos. EFSA J. 12(4):3640–74.

EFSA (2014b). Conclusion on the peer review of the pesticide risk assessment of the active substance amitrole. EFSA J. 12(7):3742. https://doi.org/10.2903/j.efsa.2014.3742

EFSA (2015). Scientific opinion on acrylamide in food. Parma, Italy: European Food Safety Authority. Available from: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2015.4104.

EFSA (2004). Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Furfural and Furfural Diethylacetal. Question number EFSA-Q-2003-236. EFSA J. 67:1–27. https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2004.67

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.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

Eitaki Y, Kawai T, Omae K (2011). Exposure assessment of ETBE in gas station workers and gasoline tanker truck drivers. J Occup Health. 53(6):423–31. https://doi.org/10.1539/joh.11-0111-OA PMID:21996930

Ek-Wakf AM, Abdrabouh AE, Elgarieb AM (2019). Effectiveness of steamed and cooked broccoli to attenuate bone marrow injury and suppressed haemopoiesis in male rats exposed to petrol vapours. J Environ Stud (Northborough). 76(1):102–17. https://doi.org/10.1080/00207233.2018.1502956

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-Mihi KA, Kenawy HI, El-Karef A, Elsherbiny NM, Eissa LA (2017). Naringin attenuates thioacetamide-induced liver fibrosis in rats through modulation of the PI3K/Akt pathway. Life Sci. 187:50–7. https://doi.org/10.1016/j.lfs.2017.08.019 PMID:28830755

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

El-Tonsy MM, Hussein HM, Helal T-S, Tawfik RA, Koriem KM, Hussein HM (2016). Human *Schistosomiasis mansoni* associated with hepatocellular carcinoma in Egypt: current perspective. J Parasit Dis. 40(3):976–80. https://doi.org/10.1007/s12639-014-0618-0 PMID:27605822

Elliott BM, Mackay JM, Clay P, Ashby J (1998). An assessment of the genetic toxicology of antimony trioxide. Mutat Res. 415(1–2):109–17. https://doi.org/10.1016/S1383-5718(98)00065-5 PMID:9711267

Elyasi S, Hosseini S, Niazi Moghadam MR, Aledavood SA, Karimi G (2016). Effect of oral silymarin administration on prevention of radiotherapy induced mucositis: a randomized, double-blinded, placebo-controlled clinical trial. Phytother Res. 30(11):1879–85. https://doi.org/10.1002/ptr.5704 PMID:27555604

Elyasi S, Shojaee FSR, Allahyari A, Karimi G (2017). Topical silymarin administration for prevention of capecitabine-induced hand-foot syndrome: a randomized, double-blinded, placebo-controlled clinical trial. Phytother Res. 31(9):1323–9. https://doi.org/10.1002/ptr.5857 PMID:28635153

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

Emond CA, Vergara VB, Lombardini ED, Mog SR, Kalinich JF (2015a). Induction of rhabdomyosarcoma by embedded military-grade tungsten/nickel/cobalt not by tungsten/nickel/iron in the B6C3F$_1$ mouse. Int J Toxicol. 34(1):44–54. https://doi.org/10.1177/1091581814565038 PMID:25544565

Emond CA, Vergara VB, Lombardini ED, Mog SR, Kalinich JF (2015b). The role of the component metals in the toxicity of military-grade tungsten alloy. Toxics. 3(4):499–514. https://doi.org/10.3390/toxics3040499 PMID:29051474

Encyclopaedia Britannica (2019). Tetracycline. Available from: https://www.britannica.com/science/tetracycline.

Engel CL, Sharima Rasanayagam M, Gray JM, Rizzo J (2018). Work and female breast cancer: the state of the evidence, 2002-2017. New Solut. 28(1):55–78. https://doi.org/10.1177/1048291118758460 PMID:29658425

Engel LS, Hill DA, Hoppin JA, Lubin JH, Lynch CF, Pierce J, et al. (2005). Pesticide use and breast cancer risk among farmers' wives in the Agricultural Health Study. Am J Epidemiol. 161(2):121–35. https://doi.org/10.1093/aje/kwi022 PMID:15632262

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

EPA (1988a). Furmecyclox. Integrated Risk Information System (IRIS). Washington (DC), USA: United States Environmental Protection Agency. Available from: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=362.

EPA (1988b). 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.

EPA (1990). Aniline. Integrated Risk Information System (IRIS). Chemical Assessment Summary. Washington (DC), USA: United States Environmental Protection Agency, National Center for Environmental Assessment. Available from: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0350_summary.pdf.

EPA (1993). Carbaryl review of mouse carcinogenicity study. Doc #010443. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/056801/056801-104.pdf.

EPA (1996). Reregistration Eligibility Decision (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 2 May 2019.

EPA (1998a). Reregistration Eligibility Decision (RED) for diphenylamine. EPA 738-R-97-010. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/reregistration/web/pdf/2210red.pdf.

EPA (1998b). Reregistration Eligibility Decision (RED) for alachlor. EPA 738-R-98-020. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/reregistration/web/pdf/0063.pdf.

EPA (1999). Reregistration Eligibility Decision (RED) for EPTC (S-Ethyl dipropylthiocarbamate). HED Risk Assessment. Chemical No. 041401. Case No. 0064. Barcode D244982. Washington (DC), USA: United States Environmental Protection Agency.

EPA (2001). Bromate. Integrated Risk Information System (IRIS). Washington (DC), USA: United States Environmental Protection Agency. Available from: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1002.

EPA (2006). Reregistration Eligibility Decision (RED) for permethrin: fact sheet. Washington (DC), USA: United States Environmental Protection Agency. Available from: http://www.epa.gov/oppsrrd1/REDs/factsheets/permethrin_fs.htm.

EPA (2007). Chemicals evaluated for carcinogenic potential by the Office of Pesticide Programs. Washington (DC), USA: Health Effects Division, Office of Pesticide Programs, United States Environmental Protection Agency.

EPA (2008a). Health effects support document for fonofos. EPA/822-R-08-009, January 2008. Washington (DC), USA: United States Environmental Protection Agency, Office of Water (4304T), Health and Ecological Criteria Division. Available from: https://www.epa.gov/sites/production/files/2014-09/documents/health_effects_support_document_for_fonofos.pdf.

EPA (2008b). Sulfluramid proposed registration review final decision. Registration review case 7411. Docket number EPA-HQ-OPP-2007-1082; 23 June 2008.

EPA (2008c). Health effects support document for *S*-ethyl dipropylthiocarbamate (EPTC). EPA/822-R-08-006, January 2008. Washington (DC), USA: United States Environmental Protection Agency, Office of Water (4304T), Health and Ecological Criteria Division. Available from: https://www.epa.gov/sites/production/files/2014-09/documents/health_effects_support_document_for_eptc.pdf.

EPA (2009a). Short-chain chlorinated paraffins (SCCPs) and other chlorinated paraffins action plan. 12/30/2009. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/sites/production/files/2015-09/documents/sccps_ap_2009_1230_final.pdf, accessed 18 March 2019.

EPA (2009b). Provisional health advisories for perfluoro-octanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). 8 January 2009. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/sites/production/files/2015-09/documents/pfoa-pfos-provisional.pdf.

EPA (2009c). Provisional peer-reviewed toxicity values for 1,1-dimethylhydrazine (CASRN 57-14-7). EPA/690/R-09/018F, 30 September 2009. Washington (DC), USA: National Center for Environmental Assessment, Office of Research and Development, United States Environmental Protection Agency. Available from: https://cfpub.epa.gov/ncea/pprtv/documents/Dimethylhydrazine11.pdf.

EPA (2011a). 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.

EPA (2011b). Tepraloxydim; pesticide tolerances. EPA-HQ-OPP-2010-0865; FRL-9330-2. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.govinfo.gov/content/pkg/FR-2011-12-30/pdf/2011-33477.pdf, accessed 27 February 2019.

EPA (2012). Biphenyl; CASRN 92-52-4. Integrated Risk Information System (IRIS). Washington (DC), USA: United States Environmental Protection Agency. Available from: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0013_summary.pdf

EPA (2013). Recognition and management of pesticide poisonings. 6th ed. EPA 735K13001. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/sites/production/files/2015-01/documents/rmpp_6thed_final_lowresopt.pdf; p.148.

EPA (2014). Provisional peer-reviewed toxicity values for styrene-acrylonitrile (SAN) trimer (various CASRNs). Report EPA/690/R-14/015F. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://cfpub.epa.gov/ncea/pprtv/documents/StyreneAcrylonitrileSANTrimer.pdf.

EPA (2015). EDSP: weight of evidence analysis of potential interaction with the estrogen, androgen or thyroid pathways. Chemical: chlorpyrifos. Washington (DC), USA: United States Environmental Protection Agency.

EPA (2016a). Toxicological review of ethyl tertiary butyl ether (CASRN 637-92-3). Washington (DC), USA: United States Environmental Protection Agency. Available from: http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=528998.

EPA (2016b). Toxicological review of *tert*-butyl alcohol (*tert*-butanol) (CAS No. 75-65-0). Washington (DC), USA: United States Environmental Protection Agency. Available from: http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=528030.

EPA (2017a). Toxicological review of ethyl tertiary butyl ether (CASRN 637-92-3) (external review draft). EPA/635/R-17/061a. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=326410, accessed 18 March 2019.

EPA (2017b). Pesticides industry sales and usage. 2008 and 2012 market estimates. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/sites/production/files/2017-01/documents/pesticides-industry-sales-usage-2016_0.pdf.

EPA (2017c). EPTC; pesticide tolerances. EPA-HQ-OPP-2015-0308; FRL-9965-71. Available from: https://www.federalregister.gov/documents/2017/09/13/2017-19452/eptc-pesticide-tolerances.

EPA (2019a). ToxCast: EPA ToxCast Screening Library. 4-Androstene-3,17-dione. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/dsstoxdb/results?abbreviation=TOXCAST&search=DTXSID8024523#invitrodb.

EPA (2019b). Chlorpyrifos. Executive summary. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID4020458#exec_sum.

EPA (2019c). ToxCast/Tox21. 2-Hydroxy-4-methoxybenzophenone. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID3022405#invitrodb-bioassays-toxcast-tox21.

EPA (2019d). Kepone. 143-50-0. CompTox Chemistry Dashboard. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/dsstoxdb/results?utf8=%EF%83%BC&search=143-50-0#details.

EPA (2019e). Pesticides. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://www.epa.gov/pesticides.

EPA (2019f). Executive summary. 2,4-Dihydroxybenzophenone. Washington (DC), USA: United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID8022406#exec_sum.

Eriksen KT, Raaschou-Nielsen O, Sørensen M, Roursgaard M, Loft S, Møller P (2010). Genotoxic potential of the perfluorinated chemicals PFOA, PFOS, PFBS, PFNA and PFHxA in human HepG2 cells. Mutat Res. 700(1–2):39–43. https://doi.org/10.1016/j.mrgentox.2010.04.024 PMID:20451658

Eriksen KT, Sørensen M, McLaughlin JK, Lipworth L, Tjønneland A, Overvad K, et al. (2009). Perfluorooctanoate and perfluorooctanesulfonate plasma levels and risk of cancer in the general Danish population. J Natl Cancer Inst. 101(8):605–9. https://doi.org/10.1093/jnci/djp041 PMID:19351918

Eriksson CJ (2015). Genetic-epidemiological evidence for the role of acetaldehyde in cancers related to alcohol drinking. Adv Exp Med Biol. 815:41–58. https://doi.org/10.1007/978-3-319-09614-8_3 PMID:25427900

Erkekoglu P, Oral D, Chao MW, Kocer-Gumusel B (2017). Hepatocellular carcinoma and possible chemical and biological causes: a review. J Environ Pathol Toxicol Oncol. 36(2):171–90. https://doi.org/10.1615/JEnvironPatholToxicolOncol.2017020927 PMID:29199597

Ertekin T, Ekinci N, Karaca O, Nisari M, Canoz O, Ulger H (2013). Effect of angiostatin on 1,2-dimethylhydrazine-induced colon cancer in mice. Toxicol Ind Health. 29(6):490–7. https://doi.org/10.1177/0748233712440137 PMID:22393105

Escobar PA, Olivero OA, Wade NA, Abrams EJ, Nesel CJ, Ness RB, et al. (2007). Genotoxicity assessed by the comet and GPA assays following in vitro exposure of human lymphoblastoid cells (H9) or perinatal exposure of mother-child pairs to AZT or AZT-3TC. Environ Mol Mutagen. 48(3–4):330–43. https://doi.org/10.1002/em.20285 PMID:17358027

Espín-Pérez A, Font-Ribera L, van Veldhoven K, Krauskopf J, Portengen L, Chadeau-Hyam M, et al. (2018). Blood transcriptional and microRNA responses to short-term exposure to disinfection by-products in a swimming pool. Environ Int. 110:42–50. https://doi.org/10.1016/j.envint.2017.10.003 PMID:29122314

Espinal-Enríquez J, Hernández-Lemus E, Mejía C, Ruiz-Azuara L (2016). Network analysis shows novel molecular mechanisms of action for copper-based chemotherapy. Front Physiol. 6:406. https://doi.org/10.3389/fphys.2015.00406 PMID:26793116

Espitia-Pérez L, da Silva J, Brango H, Espitia-Pérez P, Pastor-Sierra K, Salcedo-Arteaga S, et al. (2018). Genetic damage in environmentally exposed populations to open-pit coal mining residues: analysis of buccal micronucleus cytome (BMN-cyt) assay and alkaline, Endo III and FPG high-throughput comet assay. Mutat Res Genet Toxicol Environ Mutagen. 836(Pt B):24–35. https://doi.org/10.1016/j.mrgentox.2018.06.002 PMID:30442341

EC (2002). Review report for the active substance cinidon ethyl. EU pesticides database. Brussels, Belgium: European Commission. Available from: http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.ViewReview&id=344, accessed 27 February 2019.

EC (2004). Review report for the active substance tepraloxydim. EU pesticides database. Brussels, Belgium: European Commission. Available from:

https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.ViewReview&id=397, accessed 27 February 2019.

EC (2007). 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.

EC (2015). SCOEL/REC/153 aniline. Recommendation from the Scientific Committee on Occupational Exposure Limits. Brussels, Belgium: European Commission.

EC (2016a). Cinidon ethyl. EU pesticides database. Brussels, Belgium: European Commission. Available from: http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.detail&language=EN&selectedID=1141.

EC (2016b). Furmecyclox. EU pesticides database. Brussels, Belgium: European Commission. Available from: http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.detail&language=EN&selectedID=1427.

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

Faa A, Gerosa C, Fanni D, Floris G, Eyken PV, Lachowicz JI, et al. (2018). Depleted uranium and human health. Curr Med Chem. 25(1):49–64. https://doi.org/10.2174/0929867324666170426102343 PMID:28462701

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

Falagas ME, Walker AM, Jick H, Ruthazer R, Griffith J, Snydman DR (1998). Late incidence of cancer after metronidazole use: a matched metronidazole user/nonuser study. Clin Infect Dis. 26(2):384–8. https://doi.org/10.1086/516306 PMID:9502459

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, Wang WL, Ding S, Zhou YL, Jin FS (2006). Application of micronucleus test of buccal mucosal cells in assessing the genetic damage of workers exposed to acrylonitrile. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 24(2):106–8. PMID:16600117 [in Chinese]

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

FAO/WHO (2010). Joint FAO/WHO expert meeting to review toxicological and health aspects of bisphenol A: final report, including report of stakeholder meeting on bisphenol A, 1–5 November 2010. Ottawa, Canada. Geneva, Switzerland: Food and Agriculture Organization of the United Nations (FAO), World Health Organization; pp. 1–60. Available from: https://apps.who.int/iris/bitstream/handle/10665/44624/97892141564274_eng.pdf;jsessionid=897420789B92D4FCFD14F8B9614CC5D5?sequence=1.

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

Fatkhutdinova LM, Khaliullin TO, Vasil'yeva OL, Zalyalov RR, Mustafin IG, Kisin ER, et al. (2016). 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

FDA (1997). Ethyl carbamate preventative action manual. Available from: https://www.fda.gov/food/foodborneillnesscontaminants/chemicalcontaminants/ucm078546.htm.

Federico A, Dallio M, Loguercio C (2017). Silymarin/silybin and chronic liver disease: a marriage of many years. Molecules. 22(2):E191. https://doi.org/10.3390/molecules22020191 PMID:28125040

Fedorova OS, Kovshirina YV, Kovshirina AE, Fedotova MM, Deev IA, Petrovskiy FI, et al. (2017). *Opisthorchis felineus* infection and cholangiocarcinoma in the Russian Federation: a review of medical statistics. Parasitol Int. 66(4):365–71. https://doi.org/10.1016/j.parint.2016.07.010 PMID:27474689

Feng Y, Wang H, Wang Q, Huang W, Peng Y, Zheng J (2017). Chemical interaction of protein cysteine residues with reactive metabolites of methyleugenol. Chem Res Toxicol. 30(2):564–73. https://doi.org/10.1021/acs.chemrestox.6b00290 PMID:28107620

Feng Y, Wang S, Wang H, Peng Y, Zheng J (2018). Urinary methyleugenol-deoxyadenosine adduct as a potential biomarker of methyleugenol exposure in rats. J Agric Food Chem. 66(5):1258–63. https://doi.org/10.1021/acs.jafc.7b05186 PMID:29328669

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.2014.12.029 PMID:25559854

Fernandes J, Hu X, Ryan Smith M, Go Y-M, Jones DP (2018). Selenium at the redox interface of the genome, metabolome and exposome. Free Radic Biol Med. 127:215–27. https://doi.org/10.1016/j.freeradbiomed.2018.06.002 PMID:29883789

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

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

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

Filgueira NA, Saraiva CMA, Jucá NT, Bezerra MF, Lacerda CM (2018). Schistosomal liver fibrosis and hepatocellular carcinoma - case series of patients submitted to liver transplantation. Braz J Infect Dis. 22(4):352–4. https://doi.org/10.1016/j.bjid.2018.06.001 PMID:30017854

Filho APR, Silveira MAD, do Nascimento CB, d'Arce LPG (2018). Integrative study of cell damage and cancer risk in gas station attendants. Int J Environ Health Res. 28(1):1–7. https://doi.org/10.1080/09603123.2017.1415305 PMID:29232963

Finianos A, Matar CF, Taher A (2018). Hepatocellular carcinoma in β-thalassemia patients: review of the literature with molecular insight into liver carcinogenesis. Int J Mol Sci. 19(12):E4070. https://doi.org/10.3390/ijms19124070 PMID:30562917

Fishel FM (2017). Pesticide toxicity profile: carbamate pesticides (Rev 2). Available from: https://edis.ifas.ufl.edu/pi088.

Flaig TW, Glodé M, Gustafson D, van Bokhoven A, Tao Y, Wilson S, et al. (2010). A study of high-dose oral silybin-phytosome followed by prostatectomy in patients with localized prostate cancer. Prostate. 70(8):848–55. https://doi.org/10.1002/pros.21118 PMID:20127732

Flaig TW, Gustafson DL, Su LJ, Zirrolli JA, Crighton F, Harrison GS, et al. (2007). A phase I and pharmacokinetic study of silybin-phytosome in prostate cancer patients. Invest New Drugs. 25(2):139–46. https://doi.org/10.1007/s10637-006-9019-2 PMID:17077998

Flemer B, Warren RD, Barrett MP, Cisek K, Das A, Jeffery IB, et al. (2018). The oral microbiota in colorectal cancer is distinctive and predictive. Gut. 67(8):1454–63. https://doi.org/10.1136/gutjnl-2017-314814 PMID:28988196

Fletcher NM, Harper AK, Memaj I, Fan R, Morris RT, Saed GM (2019). Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer. Reprod Sci. [Epub ahead of print] https://doi.org/10.1177/1933719119831773 PMID:30819054

Florentin A, Deblonde T, Diguio N, Hautemaniere A, Hartemann P (2011). Impacts of two perfluorinated compounds (PFOS and PFOA) on human hepatoma cells: cytotoxicity but no genotoxicity? Int J Hyg Environ Health. 214(6):493–9. https://doi.org/10.1016/j.ijheh.2011.05.010 PMID:21676652

Flower KB, Hoppin JA, Lynch CF, Blair A, Knott C, Shore DL, et al. (2004). Cancer risk and parental pesticide application in children of Agricultural Health Study participants. Environ Health Perspect. 112(5):631–5. https://doi.org/10.1289/ehp.6586 PMID:15064173

Folsom AR, Zhang S, Sellers TA, Zheng W, Kushi LH, Cerhan JR (1996). Cancer incidence among women living on farms: findings from the Iowa Women's Health Study. J Occup Environ Med. 38(11):1171–6. https://doi.org/10.1097/00043764-199611000-00018 PMID:8941908

Food Safety Commission of Japan (2015). Risk assessment report: tepraloxydim (pesticides). FS/407/2015. Available from: http://www.fsc.go.jp/english/evaluationreports/pesticide/tepraloxydim_no_fs407_2015.pdf, accessed 27 February 2019.

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)31679-8 PMID:27733284

Fortes C, Mastroeni S, Segatto 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

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. PMID:10519391

Fred C, Cantillana T, Henderson AP, Golding BT, Törnqvist M (2004). Adducts of N-terminal valines in hemoglobin with isoprene diepoxide, a metabolite of isoprene. Rapid Commun Mass Spectrom. 18(18):2177–84. https://doi.org/10.1002/rcm.1608 PMID:15378724

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

Frei P, Poulsen AH, Johansen C, Olsen JH, Steding-Jessen M, Schüz J (2011). Use of mobile phones and risk of brain tumours: update of Danish cohort study. BMJ. 343:d6387. https://doi.org/10.1136/bmj.d6387 PMID:22016439

Friedman MA, Beliles RP (2002). Three-generation reproduction study of rats receiving acrylonitrile in drinking water. Toxicol Lett. 132(3):249–61. https://doi.org/10.1016/S0378-4274(02)00075-9 PMID:12044706

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/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

Frisan T (2016). Bacterial genotoxins: the long journey to the nucleus of mammalian cells. Biochim Biophys Acta. 1858(3):567–75. https://doi.org/10.1016/j.bbamem.2015.08.016 PMID:26299818

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

Fujioka N, Fritz V, Upadhyaya P, Kassie F, Hecht SS (2016). Research on cruciferous vegetables, indole-3-carbinol, and cancer prevention: a tribute to Lee W. Wattenberg. Mol Nutr Food Res. 60(6):1228–38. https://doi.org/10.1002/mnfr.201500889 PMID:26840393

Fukushima S, Murai T (1999). Calculi, precipitates and microcrystalluria associated with irritation and cell proliferation as a mechanism of urinary bladder carcinogenesis in rats and mice. In Capen CC, Dybing E, Rice JM, Wilbourn

JD, editors. Species differences in thyroid, kidney and urinary bladder carcinogenesis (IARC Scientific Publications, No. 147). Lyon, France: International Agency for Research on Cancer; pp. 159–174.

Fukushima S, Tanaka H, Asakawa E, Kagawa M, Yamamoto A, Shirai T (1992). Carcinogenicity of uracil, a nongenotoxic chemical, in rats and mice and its rationale. Cancer Res. 52(7):1675–80. PMID:1551098

Fuller TW, Acharya AP, Meyyappan T, Yu M, Bhaskar G, Little SR, et al. (2018). Comparison of bladder carcinogens in the urine of e-cigarette users versus non e-cigarette using controls. Sci Rep. 8(1):507. https://doi.org/10.1038/s41598-017-19030-1 PMID:29323232

Furukawa A, Oikawa S, Harada K, Sugiyama H, Hiraku Y, Murata M, et al. (2010). Oxidatively generated DNA damage induced by 3-amino-5-mercapto-1,2,4-triazole, a metabolite of carcinogenic amitrole. Mutat Res. 694(1–2):7–12. https://doi.org/10.1016/j.mrfmmm.2010.08.004 PMID:20732334

Furukawa S, Harada T, Thake D, Iatropoulos MJ, Sherman JH (2014). Consensus diagnoses and mode of action for the formation of gastric tumors in rats treated with the chloroacetanilide herbicides alachlor and butachlor. Toxicol Pathol. 42(2):386–402. https://doi.org/10.1177/0192623313484106 PMID:23599414

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

Galea KS, Cherrie JW (2010). Report on a historical hygiene assessment at National Semiconductor (NSUK). IOM Report 884-0010. Edinburgh, Scotland: Institute of Occupational Medicine; pp. 1–43.

Gallagher EJ, Zelenko Z, Neel BA, Antoniou IM, Rajan L, Kase N, et al. (2017). Elevated tumor LDLR expression accelerates LDL cholesterol-mediated breast cancer growth in mouse models of hyperlipidemia. Oncogene. 36(46):6462–71. https://doi.org/10.1038/onc.2017.247 PMID:28759039

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(S10):1–175. https://doi.org/10.1002/em.2850100502 PMID:3319609

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, Picciotto S, Neophytou AM, Bradshaw PT, Balmes JR, Eisen EA (2018a). Lung cancer mortality and exposure to synthetic metalworking fluid and biocides: controlling for the healthy worker survivor effect. Occup Environ Med. 75(10):730–5. https://doi.org/10.1136/oemed-2017-104812 PMID:29743185

García-Lestón J, Méndez J, Pásaro E, Laffon B (2010). Genotoxic effects of lead: an updated review. Environ Int. 36(6):623–36. https://doi.org/10.1016/j.envint.2010.04.011 PMID:20466424

García-Pérez J, Lope V, Pérez-Gómez B, Molina AJ, Tardón A, Díaz Santos MA, et al. (2018). Risk of breast cancer and residential proximity to industrial installations: new findings from a multicase-control study (MCC-Spain). Environ Pollut. 237:559–68. https://doi.org/10.1016/j.envpol.2018.02.065 PMID:29524878

Gardner NM, Riley RT, Showker JL, Voss KA, Sachs AJ, Maddox JR, et al. (2016). Elevated nuclear sphingoid base-1-phosphates and decreased histone deacetylase activity after fumonisin B_1 treatment in mouse embryonic fibroblasts. Toxicol Appl Pharmacol. 298:56–65. https://doi.org/10.1016/j.taap.2016.02.018 PMID:26905748

Garrett WS (2015). Cancer and the microbiota. Science. 348(6230):80–6. https://doi.org/10.1126/science.aaa4972 PMID:25838377

GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators (2019). Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 18(1):56–87. https://doi.org/10.1016/S1474-4422(18)30415-0 PMID:30497965

Ge L, Wang YF, Tian JH, Mao L, Zhang J, Zhang JH, et al. (2016). Network meta-analysis of Chinese herb injections combined with FOLFOX chemotherapy in the treatment of advanced colorectal cancer. J Clin Pharm Ther. 41(4):383–91. https://doi.org/10.1111/jcpt.12410 PMID:27338003

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

Gebel T, Christensen S, Dunkelberg H (1997). Comparative and environmental genotoxicity of antimony and arsenic. Anticancer Res. 17(4A) 4a:2603–7. PMID:9252688

Gennari A, Costa M, Puntoni M, Paleari L, De Censi A, Sormani MP, et al. (2015). Breast cancer incidence after hormonal treatments for infertility: systematic review and meta-analysis of population-based studies. Breast Cancer Res Treat. 150(2):405–13. https://doi.org/10.1007/s10549-015-3328-0 PMID:25744295

George J, Srivastava AK, Singh R, Shukla Y (2011). Cypermethrin exposure leads to regulation of proteins expression involved in neoplastic transformation in mouse skin. Proteomics. 11(22):4411–21. https://doi.org/10.1002/pmic.201100233 PMID:21919204

Ghisi NC, de Oliveira EC, Prioli AJ (2016). Does exposure to glyphosate lead to an increase in the micronuclei frequency? A systematic and meta-analytic review. Chemosphere. 145:42–54. https://doi.org/10.1016/j.chemosphere.2015.11.044 PMID:26688238

Gholami S, Ansari-Lari M, Khalili L (2015). Histologic and histomorphometric changes of testis following oral exposure to methyl tertiary-butyl ether in adult rat. Iran J Vet Res. 16(3):288–92. PMID:27175191

Giacomelli S, Gallo D, Apollonio P, Ferlini C, Distefano M, Morazzoni P, et al. (2002). Silybin and its bioavailable phospholipid complex (IdB 1016) potentiate in vitro and in vivo the activity of cisplatin. Life Sci. 70(12):1447–59. https://doi.org/10.1016/S0024-3205(01)01511-9 PMID:11883719

Gift JS, Caldwell JC, Jinot J, Evans MV, Cote I, Vandenberg JJ (2013). Scientific considerations for evaluating cancer bioassays conducted by the Ramazzini Institute. Environ Health Perspect. 121(11-12):1253–63. https://doi.org/10.1289/ehp.1306661 PMID:24045135

Girschik J, Fritschi L, Heyworth J, Waters F (2012). Validation of self-reported sleep against actigraphy. J Epidemiol. 22(5):462–8. https://doi.org/10.2188/jea.JE20120012 PMID:22850546

Glass DC, Del Monaco A, Pircher S, Vander Hoorn S, Sim MR (2017). Mortality and cancer incidence among male volunteer Australian firefighters. Occup Environ Med. 74(9):628–38. https://doi.org/10.1136/oemed-2016-104088 PMID:28391245

Glass DC, Del Monaco A, Pircher S, Vander Hoorn S, Sim MR (2019). Mortality and cancer incidence among female Australian firefighters. Occup Environ Med. 76(4):215–21. PMID:30674605

Glass DC, Pircher S, Del Monaco A, Hoorn SV, Sim MR (2016). Mortality and cancer incidence in a cohort of male paid Australian firefighters. Occup Environ Med. 73(11):761–71. https://doi.org/10.1136/oemed-2015-103467 PMID:27456156

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

Gold LS, Manley NB, Slone TH, Garfinkel GB, Ames BN, Rohrbach L, et al. (1995). Sixth plot of the carcinogenic potency database: results of animal bioassays published in the general literature 1989 to 1990 and by the National Toxicology Program 1990 to 1993. Environ Health Perspect. 103(Suppl 8):3–122. PMID:8741772

Goldenthal EI (1989). Two year oncogenicity study in rats [UDMH]. International Research and Development Corporation, No. 399-062.

Golding BT, Cottrell L, Mackay D, Zhang D, Watson WP (2003). Stereochemical and kinetic comparisons of mono- and diepoxide formation in the in vitro metabolism of isoprene by liver microsomes from rats, mice, and humans. Chem Res Toxicol. 16(7):933–44. https://doi.org/10.1021/tx034061x PMID:12870896

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

Gonzalez NL, O'Brien KM, D'Aloisio AA, Sandler DP, Weinberg CR (2016). Douching, talc use, and risk of ovarian cancer. Epidemiology. 27(6):797–802. https://doi.org/10.1097/EDE.0000000000000528 PMID:27327020

González NV, Soloneski S, Larramendy ML (2006). Genotoxicity analysis of the phenoxy herbicide dicamba in mammalian cells in vitro. Toxicol In Vitro. 20(8):1481–7. https://doi.org/10.1016/j.tiv.2006.05.001 PMID:16828255

González NV, Soloneski S, Larramendy ML (2007). The chlorophenoxy herbicide dicamba and its commercial formulation banvel induce genotoxicity and cytotoxicity in Chinese hamster ovary (CHO) cells. Mutat Res. 634(1–2):60–8. https://doi.org/10.1016/j.mrgentox.2007.06.001 PMID:17643342

Gonzalez-Escobedo G, La Perle KMD, Gunn JS (2013). Histopathological analysis of *Salmonella* chronic carriage in the mouse hepatopancreatobiliary system. PLoS One. 8(12):e84058. https://doi.org/10.1371/journal.pone.0084058 PMID:24349565

Gopinathan R, Kanhere J, Banerjee J (2015). Effect of malachite green toxicity on non target soil organisms. Chemosphere. 120:637–44. https://doi.org/10.1016/j.chemosphere.2014.09.043 PMID:25462308

Gorini F, Iervasi G, Coi A, Pitto L, Bianchi F (2018). The role of polybrominated diphenyl ethers in thyroid carcinogenesis: is it a weak hypothesis or a hidden reality? From facts to new perspectives. Int J Environ Res Public Health. 15(9):1834. https://doi.org/10.3390/ijerph15091834 PMID:30149577

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

Gowans ID, Lorimore SA, McIlrath JM, Wright EG (2005). Genotype-dependent induction of transmissible chromosomal instability by γ-radiation and the benzene metabolite hydroquinone. Cancer Res. 65(9):3527–30. https://doi.org/10.1158/0008-5472.CAN-04-4242 PMID:15867342

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

Grande BM, Gerhard DS, Jiang A, Griner NB, Abramson JS, Alexander TB, et al. (2019). Genome-wide discovery of somatic coding and noncoding mutations in pediatric endemic and sporadic Burkitt lymphoma. Blood. 133(12):1313–24. https://doi.org/10.1182/blood-2018-09-871418 PMID:30617194

Grando SA (2014). Connections of nicotine to cancer. Nat Rev Cancer. 14(6):419–29. https://doi.org/10.1038/nrc3725 PMID:24827506

Grant K, Goldizen FC, Sly PD, Brune MN, Neira M, van den Berg M, et al. (2013). Health consequences of exposure to e-waste: a systematic review. Lancet Glob Health. 1(6):e350–61. https://doi.org/10.1016/S2214-109X(13)70101-3 PMID:25104600

Grellier J, Atkinson W, Bérard P, Bingham D, Birchall A, Blanchardon E, et al. (2017). Risk of lung cancer mortality in nuclear workers from internal exposure to alpha particle-emitting radionuclides. Epidemiology. 28(5):675–84. https://doi.org/10.1097/EDE.0000000000000684 PMID:28520643

Groh IA, Cartus AT, Vallicotti S, Kajzar J, Merz KH, Schrenk D, et al. (2012). Genotoxic potential of methyleugenol and selected methyleugenol metabolites in cultured Chinese hamster V79 cells. Food Funct. 3(4):428–36. https://doi.org/10.1039/c2fo10221h PMID:22302122

Groh IA, Rudakovski O, Gründken M, Schroeter A, Marko D, Esselen M (2016). Methyleugenol and oxidative metabolites induce DNA damage and interact with human topoisomerases. Arch Toxicol. 90(11):2809–23. https://doi.org/10.1007/s00204-015-1625-3 PMID:26542539

Groh IAM, Esselen M (2017). Methyleugenol and selected oxidative metabolites affect DNA-damage signalling pathways and induce apoptosis in human colon tumour HT29 cells. Food Chem Toxicol. 108(Pt A):267–75. https://doi.org/10.1016/j.fct.2017.08.014 PMID:28818686

GTSS Collaborative Group (2006). A cross country comparison of exposure to secondhand smoke among youth. Tob Control. 15(Suppl 2):ii4–19. PMID:16731523

Gu Q, Burt VL, Dillon CF, Yoon S (2012). Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health and Nutrition Examination Survey, 2001 to 2010. Circulation. 126(17):2105–14. https://doi.org/10.1161/CIRCULATIONAHA.112.096156 PMID:23091084

Gu YY, Chen MH, May BH, Liao XZ, Liu JH, Tao LT, et al. (2018). Matrine induces apoptosis in multiple colorectal cancer cell lines in vitro and inhibits tumour growth with minimum side effects in vivo via Bcl-2 and caspase-3. Phytomedicine. 51:214–25. https://doi.org/10.1016/j.phymed.2018.10.004 PMID:30466620

Guerra L, Guidi R, Slot I, Callegari S, Sompallae R, Pickett CL, et al. (2011). Bacterial genotoxin triggers FEN1-dependent RhoA activation, cytoskeleton remodeling and cell survival. J Cell Sci. 124(Pt 16):2735–42. https://doi.org/10.1242/jcs.085845 PMID:21807938

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

Guidi R, Guerra L, Levi L, Stenerlöw B, Fox JG, Josenhans C, et al. (2013a). Chronic exposure to the cytolethal distending toxins of Gram-negative bacteria promotes genomic instability and altered DNA damage response. Cell Microbiol. 15(1):98–113. https://doi.org/10.1111/cmi.12034 PMID:22998585

Guidi R, Levi L, Rouf SF, Puiac S, Rhen M, Frisan T (2013b). *Salmonella enterica* delivers its genotoxin through outer membrane vesicles secreted from infected cells. Cell Microbiol. 15(12):2034–50. https://doi.org/10.1111/cmi.12172 PMID:23869968

Gunier RB, Kang A, Hammond SK, Reinier K, Lea CS, Chang JS, et al. (2017). A task-based assessment of parental occupational exposure to pesticides and childhood acute lymphoblastic leukemia. Environ Res. 156:57–62. https://doi.org/10.1016/j.envres.2017.03.001 PMID:28319818

Gunier RB, Ward MH, Airola M, Bell EM, Colt J, Nishioka M, et al. (2011). Determinants of agricultural pesticide concentrations in carpet dust. Environ Health Perspect. 119(7):970–6. https://doi.org/10.1289/ehp.1002532 PMID:21330232

Guo J, Su L, Zhao X, Xu Z, Chen G (2016). Relationships between urinary antimony levels and both mortalities and prevalence of cancers and heart diseases in general US population, NHANES 1999-2010. Sci Total Environ. 571:452–60. https://doi.org/10.1016/j.scitotenv.2016.07.011 PMID:27396316

Guo YM, Huang YX, Shen HH, Sang XX, Ma X, Zhao YL, et al. (2015). Efficacy of compound kushen injection in relieving cancer-related pain: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2015:840742. https://doi.org/10.1155/2015/840742 PMID:26504481

Gurley KE, Moser RD, Kemp CJ (2015). Induction of colon cancer in mice with 1,2-dimethylhydrazine. Cold Spring Harb Protoc. 2015(9):prot077453. https://doi.org/10.1101/pdb.prot077453 PMID:26330619

Gurney J, Shaw C, Stanley J, Signal V, Sarfati D (2015). Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis. BMC Cancer. 15(1):897. https://doi.org/10.1186/s12885-015-1905-6 PMID:26560314

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, 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

Habib S, Ahmed HO, Al-Muhairi N, Ziad R (2018). Preliminary study: environmental assessment of perchloroethylene in dry-cleaning facilities in the UAE. J Environ Public Health. 2018:1732906. https://doi.org/10.1155/2018/1732906 PMID:30186333

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

Haese WH, Bueding E (1976). Long-term hepatocellular effects of hycanthone and of two other anti-schistosomal drugs in mice infected with *Schistosoma mansoni*. J Pharmacol Exp Ther. 197(3):703–13. PMID:180276

Hagiwara A, Doi Y, Imai N, Nakashima H, Ono T, Kawabe M, et al. (2011). Medium-term multi-organ carcinogenesis bioassay of ethyl tertiary-butyl ether in rats. Toxicology. 289(2–3):160–6. https://doi.org/10.1016/j.tox.2011.08.007 PMID:21864636

Hagiwara A, Doi Y, Imai N, Suguro M, Kawabe M, Furukawa F, et al. (2015). Promotion of liver and kidney carcinogenesis by ethyl tertiary-butyl ether (ETBE) in male Wistar rats. J Toxicol Pathol. 28(4):189–95. https://doi.org/10.1293/tox.2015-0023 PMID:26538808

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

Hakoi K, Cabral R, Hoshiya T, Hasegawa R, Shirai T, Ito N (1992). Analysis of carcinogenic activity of some pesticides in a medium-term liver bioassay in the rat. Teratog Carcinog Mutagen. 12(6):269–76. https://doi.org/10.1002/tcm.1770120605 PMID:1363965

Hallett RM, Girgis-Gabardo A, Gwynne WD, Giacomelli AO, Bisson JNP, Jensen JE, et al. (2016). Serotonin transporter antagonists target tumor-initiating cells in a transgenic mouse model of breast cancer. Oncotarget. 7(33):53137–52. https://doi.org/10.18632/oncotarget.10614 PMID:27447971

Han B, Li X, Yu T (2014). Cruciferous vegetables consumption and the risk of ovarian cancer: a meta-analysis of observational studies. Diagn Pathol. 9(1):7. https://doi.org/10.1186/1746-1596-9-7 PMID:24444040

Hanahan D, Weinberg RA (2011). Hallmarks of cancer: the next generation. Cell. 144(5):646–74. https://doi.org/10.1016/j.cell.2011.02.013 PMID:21376230

Hansen J, Wagner P, Uhrskov AS, Larsen AI (2015). Increased pancreas cancer in a bio-technological research laboratory. Am J Ind Med. 58(7):788–90. https://doi.org/10.1002/ajim.22468 PMID:25940323

Hardell L, Bavel B, Lindström G, Eriksson M, Carlberg M (2006). In utero exposure to persistent organic pollutants in relation to testicular cancer risk. Int J Androl. 29(1):228–34. https://doi.org/10.1111/j.1365-2605.2005.00622.x PMID:16371110

Hardell L, Carlberg M (2015). Mobile phone and cordless phone use and the risk for glioma - analysis of pooled case-control studies in Sweden, 1997-2003 and 2007-2009. Pathophysiology. 22(1):1–13. https://doi.org/10.1016/j.pathophys.2014.10.001 PMID:25466607

Hardell L, Carlberg M, Hardell K, Björnfoth H, Wickbom G, Ionescu M, et al. (2007). Decreased survival in pancreatic cancer patients with high concentrations of organochlorines in adipose tissue. Biomed Pharmacother. 61(10):659–64. https://doi.org/10.1016/j.biopha.2007.04.006 PMID:17560068

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

Hargreave M, Jensen A, Toender A, Andersen KK, Kjaer SK (2013). Fertility treatment and childhood cancer risk: a systematic meta-analysis. Fertil Steril. 100(1):150–61. https://doi.org/10.1016/j.fertnstert.2013.03.017 PMID:23562045

Harms PW, Harms KL, Moore PS, DeCaprio JA, Nghiem P, Wong MKK, et al.; International Workshop on Merkel Cell Carcinoma Research (IWMCC) Working Group (2018). The biology and treatment of Merkel cell carcinoma: current understanding and research priorities. Nat Rev Clin Oncol. 15(12):763–76. https://doi.org/10.1038/s41571-018-0103-2 PMID:30287935

Harris MA, Kirkham TL, MacLeod JS, Tjepkema M, Peters PA, Demers PA (2018). Surveillance of cancer risks for firefighters, police, and armed forces among men in a Canadian census cohort. Am J Ind Med. 61(10):815–23. https://doi.org/10.1002/ajim.22891 PMID:30073696

Harris RM, Williams TD, Hodges NJ, Waring RH (2011). Reactive oxygen species and oxidative DNA damage mediate the cytotoxicity of tungsten-nickel-cobalt alloys in vitro. Toxicol Appl Pharmacol. 250(1):19–28. https://doi.org/10.1016/j.taap.2010.09.020 PMID:20934443

Harris RM, Williams TD, Waring RH, Hodges NJ (2015). Molecular basis of carcinogenicity of tungsten alloy particles. Toxicol Appl Pharmacol. 283(3):223–33. https://doi.org/10.1016/j.taap.2015.01.013 PMID:25620057

Harrison RM, Leung PL, Somervaille L, Smith R, Gilman E (1999). Analysis of incidence of childhood cancer in the West Midlands of the United Kingdom in relation to proximity to main roads and petrol stations. Occup Environ Med. 56(11):774–80. https://doi.org/10.1136/oem.56.11.774 PMID:10658564

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

Harvey JB, Hong HH, Bhusari S, Ton TV, Wang Y, Foley JF, et al. (2016). F344/NTac rats chronically exposed to bromodichloroacetic acid develop mammary adenocarcinomas with mixed luminal/basal phenotype and *Tgfβ* dysregulation. Vet Pathol. 53(1):170–81. https://doi.org/10.1177/0300985815571680 PMID:25732176

Hasche D, Vinzón SE, Rösl F (2018). Cutaneous papillomaviruses and non-melanoma skin cancer: causal agents or innocent bystanders? Front Microbiol. 9:874. https://doi.org/10.3389/fmicb.2018.00874 PMID:29770129

Hatfield DL, Tsuji PA, Carlson BA, Gladyshev VN (2014). Selenium and selenocysteine: roles in cancer, health, and development. Trends Biochem Sci. 39(3):112–20. https://doi.org/10.1016/j.tibs.2013.12.007 PMID:24485058

Haun CC, Hall A, Amster RL, et al. (1979). A six-month chronic inhalation exposure of animals to UDMH to determine its oncogenic potential. Proc. 9th Conf. Environ. Toxicol., March. Dayton (OH), USA: Aerospace Medical Research Laboratory, Aerosp. Med. Div., Air Force Systems Command, Wright-Paterson AFB; pp. 141−153, as cited in EPA (2009c).

Haun CC, Kinkead ER, Vernot EH, et al. (1984). Chronic inhalation toxicity of unsymmetrical dimethylhydrazine: oncogenic effects. AFAMRL-TR-85-020. Dayton (OH), USA: Aerospace Medical Research Laboratory, Aerosp. Med. Div., Air Force Systems Command, Wright-Paterson AFB; pp. 1–47, as cited in EPA (2009c).

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

Hazrah P, Oahn KTH, Tewari M, Pandey AK, Kumar K, Mohapatra TM, et al. (2004). The frequency of live bacteria in gallstones. HPB (Oxford). 6(1):28–32. https://doi.org/10.1080/13651820310025192 PMID:18333042

He B, Wang X, Wei L, Kong B, Jin Y, Xie X, et al. (2018c). 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 J, Gu Y, Zhang S (2017). Consumption of vegetables and fruits and breast cancer survival: a systematic review and meta-analysis. Sci Rep. 7(1):599. https://doi.org/10.1038/s41598-017-00635-5 PMID:28377568

He J, Wang S, Zhou M, Yu W, Zhang Y, He X (2015a). Phytoestrogens and risk of prostate cancer: a meta-analysis of observational studies. World J Surg Oncol. 13(1):231. https://doi.org/10.1186/s12957-015-0648-9 PMID:26228387

He L, Huang Y, Guo Q, Zeng H, Zheng C, Wang J, et al. (2018b). Chronic microcystin-LR exposure induces hepatocarcinogenesis via increased gankyrin in vitro and in vivo. Cell Physiol Biochem. 49(4):1420–30. https://doi.org/10.1159/000493446 PMID:30205410

He Y, Peng L, Zhang W, Liu C, Yang Q, Zheng S, et al. (2018a). 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 Z, Li G, Chen J, Huang Y, An T, Zhang C (2015b). Pollution characteristics and health risk assessment of volatile organic compounds emitted from different plastic solid waste recycling workshops. Environ Int. 77:85–94. https://doi.org/10.1016/j.envint.2015.01.004 PMID:25667057

Health Canada (2004). Perfluorooctane sulfonate, its salts and its precursors that contain the $C_8F_{17}SO_2$ or $C_8F_{17}SO_3$ moiety. Screening Assessment Report – Health. Available from: https://ec.gc.ca/lcpe-cepa/documents/substances/spfo-pfos/hc_sar_pfos_draft-eng.pdf.

Health Canada (2008). Re-evaluation decision: S-ethyl dipropylthiocarbamate (EPTC). Catalog No. H113-28/2008-6E. Ottawa (ON), Canada: Pest Management Regulatory Agency.

Hecht SS, Koh WP, Wang R, Chen M, Carmella SG, Murphy SE, et al. (2015). Elevated levels of mercapturic acids of acrolein and crotonaldehyde in the urine of Chinese women in Singapore who regularly cook at home. PLoS One. 10(3):e0120023. https://doi.org/10.1371/journal.pone.0120023 PMID:25807518

Hecht SS, Seow A, Wang M, Wang R, Meng L, Koh WP, et al. (2010). Elevated levels of volatile organic carcinogen and toxicant biomarkers in Chinese women who regularly cook at home. Cancer Epidemiol Biomarkers Prev. 19(5):1185–92. https://doi.org/10.1158/1055-9965.EPI-09-1291 PMID:20406956

Heck JE, Park AS, Qiu J, Cockburn M, Ritz B (2014). Risk of leukemia in relation to exposure to ambient air toxics in pregnancy and early childhood. Int J Hyg Environ Health. 217(6):662–8. https://doi.org/10.1016/j.ijheh.2013.12.003 PMID:24472648

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

Heinonen OP, Albanes D, Virtamo J, Taylor PR, Huttunen JK, Hartman AM, et al. (1998). Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. J Natl Cancer Inst. 90(6):440–6. https://doi.org/10.1093/jnci/90.6.440 PMID:9521168

Henderson TO, Moskowitz CS, Chou JF, Bradbury AR, Neglia JP, Dang CT, et al. (2016). Breast cancer risk in childhood cancer survivors without a history of chest radiotherapy: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 34(9):910–8. https://doi.org/10.1200/JCO.2015.62.3314 PMID:26700127

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

Herbein G (2018). The human cytomegalovirus, from oncomodulation to oncogenesis. Viruses. 10(8):E408. https://doi.org/10.3390/v10080408 PMID:30081496

Herman AM, Kishe A, Babu H, Shilanaiman H, Tarmohamed M, Lodhia J, et al. (2017). Colorectal cancer in a patient with intestinal schistosomiasis: a case report from Kilimanjaro Christian Medical Center Northern Zone Tanzania. World J Surg Oncol. 15(1):146. https://doi.org/10.1186/s12957-017-1217-1 PMID:28768520

Herrington CS, Poulsom R, Coates PJ (2019). Recent advances in pathology: the 2019 Annual Review issue of *The Journal of Pathology*. J Pathol. 247(5):535–8. https://doi.org/10.1002/path.5255 PMID:30734304

Herrmann K, Engst W, Appel KE, Monien BH, Glatt H (2012). Identification of human and murine sulfotransferases able to activate hydroxylated metabolites of methyleugenol to mutagens in *Salmonella typhimurium* and detection of associated DNA adducts using UPLC-MS/MS methods. Mutagenesis. 27(4):453–62. https://doi.org/10.1093/mutage/ges004 PMID:22337896

Herrmann K, Engst W, Florian S, Lampen A, Meinl W, Glatt HR (2016). The influence of the SULT1A status - wild-type, knockout or humanized - on the DNA adduct formation by methyleugenol in extrahepatic tissues of mice. Toxicol Res (Camb). 5(3):808–15. https://doi.org/10.1039/C5TX00358J PMID:30090391

Herrmann K, Engst W, Meinl W, Florian S, Cartus AT, Schrenk D, et al. (2014). Formation of hepatic DNA adducts by methyleugenol in mouse models: drastic decrease by Sult1a1 knockout and strong increase by transgenic human SULT1A1/2. Carcinogenesis. 35(4):935–41. https://doi.org/10.1093/carcin/bgt408 PMID:24318996

Herrmann K, Schumacher F, Engst W, Appel KE, Klein K, Zanger UM, et al. (2013). Abundance of DNA adducts of methyleugenol, a rodent hepatocarcinogen, in human liver samples. Carcinogenesis. 34(5):1025–30. https://doi.org/10.1093/carcin/bgt013 PMID:23334163

Hibi D, Yokoo Y, Suzuki Y, Ishii Y, Jin M, Kijima A, et al. (2017). Lack of genotoxic mechanisms in early-stage furan-induced hepatocellular tumorigenesis in *gpt* delta rats. J Appl Toxicol. 37(2):142–9. https://doi.org/10.1002/jat.3331 PMID:27143483

Hicks BM, Filion KB, Yin H, Sakr L, Udell JA, Azoulay L (2018). Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. BMJ. 363:k4209. https://doi.org/10.1136/bmj.k4209 PMID:30355745

Hirose M, Fukushima S, Kurata Y, Tsuda H, Tatematsu M, Ito N (1988). Modification of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine-induced forestomach and glandular stomach carcinogenesis by phenolic antioxidants in rats. Cancer Res. 48(18):5310–5. PMID:3409255

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

Ho BY, Lin CH, Apaya MK, Chao WW, Shyur LF (2012). Silibinin and paclitaxel cotreatment significantly suppress the activity and lung metastasis of triple negative 4T1 mammary tumor cell in mice. J Tradit Complement Med. 2(4):301–11. https://doi.org/10.1016/S2225-4110(16)30116-X PMID:24716145

Ho CH, Sung KC, Lim SW, Liao CH, Liang FW, Wang JJ, et al. (2015). Chronic indwelling urinary catheter increase the risk of bladder cancer, even in patients without spinal cord injury. Medicine (Baltimore). 94(43):e1736. https://doi.org/10.1097/MD.0000000000001736 PMID:26512566

Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, et al. (1986). Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA. 256(9):1141–7. https://doi.org/10.1001/jama.1986.03380090081023 PMID:3801091

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

Hobbs CA, Recio L, Streicker M, Boyle MH, Tanaka J, Shiga A, et al. (2015). Comet assay evaluation of six chemicals of known genotoxic potential in rats. Mutat Res Genet Toxicol Environ Mutagen. 786-788:172–81. https://doi.org/10.1016/j.mrgentox.2015.03.003 PMID:26212309

Hodgson E, Rose RL (2006). Organophosphorus chemicals: potent inhibitors of the human metabolism of steroid hormones and xenobiotics. Drug Metab Rev. 38(1–2):149–62. https://doi.org/10.1080/03602530600569984 PMID:16684654

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

Hogervorst JG, van den Brandt PA, Godschalk RW, van Schooten FJ, Schouten LJ (2016). The influence of single nucleotide polymorphisms on the association between dietary acrylamide intake and endometrial cancer risk. Sci Rep. 6(1):34902. https://doi.org/10.1038/srep34902 PMID:27713515

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

Honda H, Ikejima K, Hirose M, Yoshikawa M, Lang T, Enomoto N, et al. (2002). Leptin is required for fibrogenic responses induced by thioacetamide in the murine liver. Hepatology. 36(1):12–21. https://doi.org/10.1053/jhep.2002.33684 PMID:12085344

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 JY, Wang YY, Bondoc FY, Lee M, Yang CS, Hu WY, et al. (1999). Metabolism of methyl *tert*-butyl ether and other gasoline ethers by human liver microsomes and heterologously expressed human cytochromes P450: identification of CYP2A6 as a major catalyst. Toxicol Appl Pharmacol. 160(1):43–8. https://doi.org/10.1006/taap.1999.8750 PMID:10502501

Hopenhayn-Rich C, Stump ML, Browning SR (2002). Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. Arch Environ Contam Toxicol. 42(1):127–36. https://doi.org/10.1007/s002440010300 PMID:11706377

Hoppe-Jones C, Beitel S, Burgess JL, Snyder S, Flahr L, Griffin S, et al. (2018). Use of urinary biomarkers and bioassays to evaluate chemical exposure and activation of cancer pathways in firefighters. Occup Environ Med. 75(Suppl 2):A412–3. https://doi.org/10.1136/oemed-2018-ICOHabstracts.1178

Hoppin JA, Umbach DM, Kullman GJ, Henneberger PK, London SJ, Alavanja MCR, et al. (2007). Pesticides and other agricultural factors associated with self-reported farmer's lung among farm residents in the Agricultural Health Study. Occup Environ Med. 64(5):334–41. https://doi.org/10.1136/oem.2006.028480 PMID:17182642

Hoppin JA, Umbach DM, London SJ, Alavanja MCR, Sandler DP (2002). Chemical predictors of wheeze among farmer pesticide applicators in the Agricultural Health Study. Am J Respir Crit Care Med. 165(5):683–9. https://doi.org/10.1164/ajrccm.165.5.2106074 PMID:11874814

Hortal AM, Vermeulen JF, Van Hecke W, Bovenschen N (2017). Oncogenic role of cytomegalovirus in medulloblastoma? Cancer Lett. 408:55–9. https://doi.org/10.1016/j.canlet.2017.08.024 PMID:28844716

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

Houot J, Marquant F, Goujon S, Faure L, Honoré C, Roth MH, et al. (2015). Residential proximity to heavy-traffic roads, benzene exposure, and childhood leukemia – the GEOCAP Study, 2002–2007. Am J Epidemiol. 182(8):685–93. https://doi.org/10.1093/aje/kwv111 PMID:26377958

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

Hrudey SE, Backer LC, Humpage AR, Krasner SW, Michaud DS, Moore LE, et al. (2015). Evaluating evidence for association of human bladder cancer with drinking-water chlorination disinfection by-products. J Toxicol Environ Health B Crit Rev. 18(5):213–41. https://doi.org/10.1080/10937404.2015.1067661 PMID:26309063

HSDB (2001). Thioacetamide. CASRN: 62-55-5. Hazardous Substances Data Bank. Toxicology Data Network. Available from: https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+1318.

HSDB (2012a). Cupferron. Hazardous Substances Data Bank. Toxicology Data Network. Available from: https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+4109.

HSDB (2012b) Glycerin. Hazardous Substances Data Bank. Toxicology Data Network. Available from: https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+492, accessed 2 May 2019.

HSDB (2017). Vinclozolin. CASRN: 50471-44-8. Hazardous Substances Data Bank. Toxicology Data Network. Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+6747.

Hsieh CH, Hsu HH, Shibu MA, Day CH, Bau DT, Ho CC, et al. (2017). Down-regulation of β-catenin and the associated migration ability by Taiwanin C in arecoline and 4-NQO-induced oral cancer cells via GSK-3β activation. Mol Carcinog. 56(3):1055–67. https://doi.org/10.1002/mc.22570 PMID:27648737

Hu CX, Zhang BZ, Li CH, Wu YL, Yang L, Wang ZP (2013). DNA damage of splenic lymphocytes in pregnant mice exposed to carbon disulfide in implantation phase. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 31(8):576–80. PMID:24053955 [in Chinese]

Hu D, Yang J, Liu Y, Zhang W, Peng X, Wei Q, et al. (2016). Health risk assessment for inhalation exposure to methyl tertiary butyl ether at petrol stations in southern China. Int J Environ Res Public Health. 13(2):204. https://doi.org/10.3390/ijerph13020204 PMID:26861375

Hu G, Huang Z, Zhou X, Hu J, Huang B (2015). Matrine enhances the anticancer effect of cisplatin against hepatocellular carcinoma xenografts in nude mice by influencing expression of survivin/caspase-3. Zhonghua Gan Zang Bing Za Zhi. 23(9):669–74. PMID:26524360 [in Chinese]

Hua M, Omaiye EE, Luo W, McWhirter KJ, Pankow JF, Talbot P (2019). Identification of cytotoxic flavor chemicals in top-selling electronic cigarette refill fluids. Sci Rep. 9(1):2782. https://doi.org/10.1038/s41598-019-38978-w PMID:30808901

Huang F, Chen Z, Chen H, Lu W, Xie S, Meng QH, et al. (2018a). 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 J, Roosaar A, Axéll T, Ye W (2016). A prospective cohort study on poor oral hygiene and pancreatic cancer risk. Int J Cancer. 138(2):340–7. https://doi.org/10.1002/ijc.29710 PMID:26235255

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 S, Fan W, Liu P, Tian J (2011). Meta analysis of compound matrine injection combined with cisplatin chemotherapy for advanced gastric cancer. Zhongguo Zhong Yao Za Zhi. 36(22):3198–202. PMID:22375407 [in Chinese]

Huang YF, Huang CJ, Lu CA, Chen ML, Liou SH, Chiang SY, et al. (2018b). Feasibility of using urinary N7-(2-carbamoyl-2-hydroxyethyl) Guanine as a biomarker for acrylamide exposed workers. J Expo Sci Environ Epidemiol. 28(6):589–98. https://doi.org/10.1038/s41370-018-0018-0 PMID:29463903

Huang YH, Zhang ZF, Tashkin DP, Feng B, Straif K, Hashibe M (2015). An epidemiologic review of marijuana and cancer: an update. Cancer Epidemiol Biomarkers Prev. 24(1):15–31. https://doi.org/10.1158/1055-9965.EPI-14-1026 PMID:25587109

Hughes BJ, Thomas J, Lynch AM, Borghoff SJ, Green S, Mensing T, et al. (2016). Methyl isobutyl ketone-induced hepatocellular carcinogenesis in B6C3F$_1$ mice: a constitutive androstane receptor (CAR)-mediated mode of action. Regul Toxicol Pharmacol. 81:421–9. https://doi.org/10.1016/j.yrtph.2016.09.024 PMID:27664318

Hunter WJ, Henman BA, Bartlett DM, Le Geyt IP (1993). Mortality of professional chemists in England and Wales, 1965-1989. Am J Ind Med. 23(4):615–27. https://doi.org/10.1002/ajim.4700230409 PMID:8480770

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, Wang M, Park JS, Petreas M, Bernstein L, et al. (2018). Breast cancer risk and serum levels of per- and poly-fluoroalkyl substances: a case-control study nested in the California Teachers Study. Environ Health. 17(1):83. https://doi.org/10.1186/s12940-018-0426-6 PMID:30482205

Husøy T, Haugen M, Murkovic M, Jöbstl D, Stølen LH, Bjellaas T, et al. (2008). Dietary exposure to 5-hydroxymethylfurfural from Norwegian food and correlations with urine metabolites of short-term exposure. Food Chem Toxicol. 46(12):3697–702. https://doi.org/10.1016/j.fct.2008.09.048 PMID:18929614

Hyland C, Gunier RB, Metayer C, Bates MN, Wesseling C, Mora AM (2018). Maternal residential pesticide use and risk of childhood leukemia in Costa Rica. Int J Cancer. 143(6):1295–304. https://doi.org/10.1002/ijc.31522 PMID:29658108

IARC (1973). Some inorganic and organometallic compounds. IARC Monogr Eval Carcinog Risk Chem Man. 2:1–181. Available from: http://publications.iarc.fr/20.

IARC (1974). Some aromatic amines, hydrazine and related substances, *N*-nitroso compounds and miscellaneous alkylating agents. IARC Monogr Eval Carcinog Risk Chem Man. 4:1–286. Available from: http://publications.iarc.fr/22.

IARC (1975). Some aziridines, *N*-, *S*- and *O*-mustards and selenium. IARC Monogr Eval Carcinog Risk Chem Man. 9:1–268. Available from: http://publications.iarc.fr/27 PMID:1234596

IARC (1976). Cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general considerations on volatile anaesthetics. IARC Monogr Eval Carcinog Risk Chem Man. 11:1–306. Available from: http://publications.iarc.fr/29 PMID:992654

IARC (1977). Some miscellaneous pharmaceutical substances. IARC Monogr Eval Carcinog Risk Chem Man. 13:1–255. Available from: http://publications.iarc.fr/31 PMID:16821

IARC (1979a). Some monomers, plastics and synthetic elastomers, and acrolein. IARC Monogr Eval Carcinog Risk Chem Hum. 19:1–513. Available from: http://publications.iarc.fr/37 PMID:285915

IARC (1979b). Some halogenated hydrocarbons. IARC Monogr Eval Carcinog Risk Chem Hum. 20:1–609. Available from: http://publications.iarc.fr/38 PMID:296120

IARC (1982). Some aromatic amines, anthraquinones and nitroso compounds, and inorganic fluorides used in drinking-water and dental preparations. IARC Monogr Eval Carcinog Risk Chem Hum. 27:1–341. Available from: http://publications.iarc.fr/45 PMID:6955259

IARC (1983a). Polynuclear aromatic compounds, Part 1, chemical, environmental and experimental data. IARC Monogr Eval Carcinog Risk Chem Hum. 32:1–453. Available from: http://publications.iarc.fr/50 PMID:6586639

IARC (1983b). Some food additives, feed additives and naturally occurring substances. IARC Monogr Eval Carcinog Risk Chem Hum. 31:1–291. Available from: http://publications.iarc.fr/49 PMID:6579000

IARC (1986). Tobacco smoking. IARC Monogr Eval Carcinog Risk Chem Hum. 38:1–421. Available from: http://publications.iarc.fr/56.

IARC (1987). 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: http://publications.iarc.fr/139 PMID:3482203

IARC (1989a). Some organic solvents, resin monomers and related compounds, pigments and occupational exposures in paint manufacture and painting. IARC Monogr Eval Carcinog Risks Hum. 47:1–442. Available from: http://publications.iarc.fr/65 PMID:2636273

IARC (1989b). Occupational exposures in petroleum refining; crude oil and major petroleum fuels. IARC Monogr Eval Carcinog Risks Hum. 45:1–322. Available from: http://publications.iarc.fr/63 PMID:2664246

IARC (1990a). Some flame retardants and textile chemicals, and exposures in the textile manufacturing industry. IARC Monogr Eval Carcinog Risks Hum. 48:1–278. Available from: http://publications.iarc.fr/66 PMID:2374288

IARC (1990b). Chromium, nickel and welding. IARC Monogr Eval Carcinog Risks Hum. 49:1–648. Available from: http://publications.iarc.fr/67 PMID:2232124

IARC (1991). Occupational exposures in insecticide application, and some pesticides. IARC Monogr Eval Carcinog Risks Hum. 53:5–586. Available from: http://publications.iarc.fr/71 PMID:1688189

IARC (1992). Occupational exposures to mists and vapours from strong inorganic acids and other industrial chemicals. IARC Monogr Eval Carcinog Risks Hum. 54:1–310. Available from: http://publications.iarc.fr/72 PMID:1345371

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: http://publications.iarc.fr/74

IARC (1993b). Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. IARC Monogr Eval Carcinog Risks Hum. 58:1–415. Available from: http://publications.iarc.fr/76 PMID:8022054

IARC (1994a). Some industrial chemicals. IARC Monogr Eval Carcinog Risks Hum. 60:1–560. Available from: http://publications.iarc.fr/78 PMID:7869568

IARC (1994b). Schistosomes, liver flukes and *Helicobacter pylori*. IARC Monogr Eval Carcinog Risks Hum. 61:1–241. Available from: http://publications.iarc.fr/79 PMID:7715068

IARC (1994c). Hepatitis viruses. IARC Monogr Eval Carcinog Risks Hum. 59:1–255. Available from: http://publications.iarc.fr/77 PMID:7933461

IARC (1995). Dry cleaning, some chlorinated solvents and other industrial chemicals. IARC Monogr Eval Carcinog Risks Hum. 63:1–551. Available from: http://publications.iarc.fr/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: http://publications.iarc.fr/83 PMID:9148039

IARC (1997a). Silica, some silicates, coal dust and para-aramid fibrils. IARC Monogr Eval Carcinog Risks Hum. 68:1–475. Available from: http://publications.iarc.fr/86 PMID:9303953

IARC (1997b). Polychlorinated dibenzo-*para*-dioxins and polychlorinated dibenzofurans. IARC Monogr Eval Carcinog Risks Hum. 69:1–631. Available from: http://publications.iarc.fr/87 PMID:9379504

IARC (1999a). 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: http://publications.iarc.fr/91

IARC (1999b). Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. IARC Monogr Eval Carcinog Risks Hum. 71:1–315. Available from: http://publications.iarc.fr/89 PMID:10507919

IARC (1999c). Surgical implants and other foreign bodies. IARC Monogr Eval Carcinog Risks Hum. 74:1–409. Available from: http://publications.iarc.fr/92

IARC (1999d). Hormonal contraception and post-menopausal hormonal therapy. IARC Monogr Eval Carcinog Risks Hum. 72:1–660. Available from: http://publications.iarc.fr/90

IARC (2000a). Some antiviral and antineoplastic drugs, and other pharmaceutical agents. IARC Monogr Eval Carcinog Risks Hum. 76:1–522. Available from: http://publications.iarc.fr/94

IARC (2000b). Ionizing radiation, Part 1: X- and gamma (γ)-radiation, and neutrons. IARC Monogr Eval Carcinog Risks Hum. 75:1–492. Available from: http://publications.iarc.fr/93 PMID:11203346

IARC (2001). Some thyrotropic agents. IARC Monogr Eval Carcinog Risks Hum. 79:1–763. Available from: http://publications.iarc.fr/97

IARC (2002). Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. IARC Monogr Eval Carcinog Risks Hum. 82:1–556. Available from: http://publications.iarc.fr/100 PMID:12687954

IARC (2004a). Betel-quid and areca-nut chewing and some areca-nut derived nitrosamines. IARC Monogr Eval Carcinog Risks Hum. 85:1–334. Available from: http://publications.iarc.fr/103 PMID:15635762

IARC (2004b). Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum. 83:1–1438. Available from: http://publications.iarc.fr/101 PMID:15285078

IARC (2006a). Cobalt in hard metals and cobalt sulfate, gallium arsenide, indium phosphide and vanadium pentoxide. IARC Monogr Eval Carcinog Risks Hum. 86:1–294. Available from: http://publications.iarc.fr/104 PMID:16906675

IARC (2006b). Inorganic and organic lead compounds. IARC Monogr Eval Carcinog Risks Hum. 87:1–471. Available from: http://publications.iarc.fr/105 PMID:17191367

IARC (2007a). Human papillomaviruses. IARC Monogr Eval Carcinog Risks Hum. 90:1–636. Available from: http://publications.iarc.fr/108 PMID:18354839

IARC (2007b). Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. IARC Monogr Eval Carcinog Risks Hum. 91:1–528. Available from: http://publications.iarc.fr/109 PMID:18756632

IARC (2008). 1,3-Butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide). IARC Monogr Eval Carcinog Risks Hum. 97:1–510. Available from: http://publications.iarc.fr/115 PMID:20232717

IARC (2010a). Some aromatic amines, organic dyes, and related exposures. IARC Monogr Eval Carcinog Risks Hum. 99:1–658. Available from: http://publications.iarc.fr/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: http://publications.iarc.fr/110 PMID:21141735

IARC (2010c). Household use of solid fuels and high-temperature frying. IARC Monogr Eval Carcinog Risks Hum. 95:1–430. Available from: http://publications.iarc.fr/113 PMID:20701241

IARC (2010d). Ingested nitrate and nitrite, and cyanobacterial peptide toxins. IARC Monogr Eval Carcinog Risks Hum. 94:1–448. Available from: http://publications.iarc.fr/112 PMID:21141240

IARC (2010e). Carbon black, titanium dioxide, and talc. IARC Monogr Eval Carcinog Risks Hum. 93:1–413. Available from: http://publications.iarc.fr/111 PMID:21449489

IARC (2010f). Painting, firefighting, and shiftwork. IARC Monogr Eval Carcinog Risks Hum. 98:1–804. Available from: http://publications.iarc.fr/116 PMID:21381544

IARC (2010g). Alcohol consumption and ethyl carbamate. IARC Monogr Eval Carcinog Risks Hum. 96:1–1428. Available from: http://publications.iarc.fr/114 PMID:21735939

IARC (2012a). Pharmaceuticals. IARC Monogr Eval Carcinog Risks Hum. 100A:1–437. Available from: http://publications.iarc.fr/118 PMID:23189749

IARC (2012b). Chemical agents and related occupations. IARC Monogr Eval Carcinog Risks Hum. 100F:1–599. Available from: http://publications.iarc.fr/123 PMID:23189753

IARC (2012c). Personal habits and indoor combustions. IARC Monogr Eval Carcinog Risks Hum. 100E:1–575. Available from: http://publications.iarc.fr/122 PMID:23193840

IARC (2012d). Arsenic, metals, fibres, and dusts. IARC Monogr Eval Carcinog Risks Hum. 100C:1–499. Available from: http://publications.iarc.fr/120 PMID:23189751

IARC (2012e). Biological agents. IARC Monogr Eval Carcinog Risks Hum. 100B:1–441. Available from: http://publications.iarc.fr/119 PMID:23189750

IARC (2012f). Radiation. IARC Monogr Eval Carcinog Risks Hum. 100D:1–437. Available from: http://publications.iarc.fr/121 PMID:23189752

IARC (2013a). Bitumens and bitumen emissions, and some *N*- and *S*-heterocyclic polycyclic aromatic hydrocarbons. IARC Monogr Eval Carcinog Risks Hum. 103:9–303. Available from: http://publications.iarc.fr/127 PMID:24791350

IARC (2013b). Diesel and gasoline engine exhausts and some nitroarenes. IARC Monogr Eval Carcinog Risks Hum. 105:1–704. Available from: http://publications.iarc.fr/129 PMID:26442290

IARC (2013c). Some chemicals present in industrial and consumer products, food and drinking-water. IARC Monogr Eval Carcinog Risks Hum. 101:9–549. Available from: http://publications.iarc.fr/125 PMID:24772663

IARC (2013d). Trichloroethylene, tetrachloroethylene, and some other chlorinated agents. IARC Monogr Eval Carcinog Risks Hum. 106:1–514. Available from: http://publications.iarc.fr/130 PMID:26214861

IARC (2013e). Non-ionizing radiation, Part 2: Radiofrequency electromagnetic fields. IARC Monogr Eval Carcinog Risks Hum. 102:1–460. Available from: http://publications.iarc.fr/126 PMID:24772662

IARC (2013f). Malaria and some polyomaviruses (SV40, BK, JC, and Merkel cell viruses). IARC Monogr Eval Carcinog Risks Hum. 104:1–387. Available from: http://publications.iarc.fr/128 PMID:26173303

IARC (2014). Report of the Advisory Group to Recommend Priorities for IARC Monographs during 2015–2019. Internal Report 14/002. Lyon, France. Available from: https://monographs.iarc.fr/wp-content/uploads/2018/08/14-002.pdf.

IARC (2016a). Outdoor air pollution. IARC Monogr Eval Carcinog Risks Hum. 109:1–448. Available from: http://publications.iarc.fr/538.

IARC (2016b). Some drugs and herbal products. IARC Monogr Eval Carcinog Risks Hum. 108:1–422. Available from: http://publications.iarc.fr/132.

IARC (2016c). Polychlorinated biphenyls and polybrominated biphenyls. IARC Monogr Eval Carcinog Risks Hum. 107:1–502. Available from: http://publications.iarc.fr/131.

IARC (2017a). Some chemicals used as solvents and in polymer manufacture. IARC Monogr Eval Carcinog Risks Hum. 110:1–276. Available from: http://publications.iarc.fr/547.

IARC (2017b). Some nanomaterials and some fibres. IARC Monogr Eval Carcinog Risks Hum. 111:1–316. Available from: http://publications.iarc.fr/552.

IARC (2017c). Some organophosphate insecticides and herbicides. IARC Monogr Eval Carcinog Risks Hum. 112:1–452. Available from: http://publications.iarc.fr/549.

IARC (2018a). Drinking coffee, mate, and very hot beverages. IARC Monogr Eval Carcinog Risks Hum. 116:1–501. Available from: http://publications.iarc.fr/566.

IARC (2018b). Benzene. IARC Monogr Eval Carcinog Risks Hum. 120:1–300. Available from: http://publications.iarc.fr/576.

IARC (2018c). Some industrial chemicals. IARC Monogr Eval Carcinog Risks Hum. 115:1–292. Available from: http://publications.iarc.fr/563.

IARC (2018d). DDT, lindane, and 2,4-D. IARC Monogr Eval Carcinog Risks Hum. 113:1–501. Available from: http://publications.iarc.fr/550.

IARC (2019a). Preamble to the *IARC Monographs*. IARC Monographs on the Identification of Carcinogenic Hazards to Humans. Available from: https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf.

IARC (2019b). International Agency for Research on Cancer. Sixtieth Session of the IARC Governing Council. 2018. Available from: http://governance.iarc.fr/GC/GC60/index.php, http://governance.iarc.fr/GC/GC60/En/Docs/GC60_13_CoordinationWHO.pdf, accessed 12 April 2019.

IARC (2019c). Styrene, styrene-7,8-oxide, and quinoline. IARC Monogr Eval Carcinog Risks Hum. 121:1–346. Available from: http://publications.iarc.fr/582.

IARC (2019d). Some chemicals that cause tumours of the urinary tract in rodents. IARC Monogr Eval Carcinog Risks Hum. 119:1–272. Available from: http://publications.iarc.fr/575.

IARC (2019e). Pentachlorophenol and some related compounds. IARC Monogr Eval Carcinog Risks Hum. 117:1–324. Available from: http://publications.iarc.fr/574.

Iatropoulos MJ, Duan JD, Schmuck G, Williams GM (2015). The urinary bladder carcinogen propoxur does not produce genotoxic effects in the urinary bladder of Wistar male rats. Exp Toxicol Pathol. 67(9):453–8. https://doi.org/10.1016/j.etp.2015.06.002 PMID:26164753

ICCVAM (2011). The LUMI-CELL® ER (BG1Luc ER TA) test method: an in vitro assay for identifying human estrogen receptor agonist and antagonist activity of chemicals. Interagency Coordinating Committee on the Validation of Alternative Methods. Research Triangle Park (NC), USA: National Toxicology Program. Available from: https://ntp.niehs.nih.gov/iccvam/docs/endo_docs/erta-tmer/bg1lucer-ta-tmer-combined.pdf.

ICO (2019). Human papillomavirus and related diseases report. ICO/IARC Information Centre on HPV and Cancer. Barcelona, Spain: Institut Català d'Oncologia. Available from: https://www.hpvcentre.net/statistics/reports/XWX.pdf.

Ilhan N, Gungor H, Gul HF, Eroksuz H (2016). Expression of endoglin and vascular endothelial growth factor as prognostic markers in experimental colorectal cancer. Anticancer Res. 36(8):3953–9. PMID:27466499

ILO (2019). Child labour in agriculture. Geneva, Switzerland: International Labour Organization. Available from: https://www.ilo.org/ipec/areas/Agriculture/lang--en/index.htm.

In SJ, Kim SH, Go RE, Hwang KA, Choi KC (2015). Benzophenone-1 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/10.1080/15287394.2015.1010464 PMID:25849766

Inai K, Aoki Y, Akamizu H, Eto R, Nishida T, Tokuoka S (1985). Tumorigenicity study of butyl and isobutyl *p*-hydroxybenzoates administered orally to mice. Food Chem Toxicol. 23(6):575–8. https://doi.org/10.1016/0278-6915(85)90181-4 PMID:4040103

Innes KE, Wimsatt JH, Frisbee S, Ducatman AM (2014). Inverse association of colorectal cancer prevalence to serum levels of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in a large Appalachian population. BMC Cancer. 14(1):45. https://doi.org/10.1186/1471-2407-14-45 PMID:24468211

IPCS (1986). Environmental health criteria 64. Carbamate pesticides: a general introduction. Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety. Available from: http://www.inchem.org/documents/ehc/ehc/ehc64.htm.

IPCS (1991a). Daminozide. Pesticide residues in food: 1991 evaluations. Part II: Toxicology. Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety. Available from: http://www.inchem.org/documents/jmpr/jmpmono/v91pr09.htm.

IPCS (1991b). Environmental health criteria 108. Nickel. Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety; p. 13. Available from: http://www.inchem.org/documents/ehc/ehc/ehc108.htm.

IPCS (1997). Environmental health criteria 196. Methanol. Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety. Available from: http://www.inchem.org/documents/ehc/ehc/ehc196.htm.

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

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 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

Ishmael J, Lithfield MH (1988). Chronic toxicity and carcinogenic evaluation of permethrin in rats and mice. Fundam Appl Toxicol. 11(2):308–22. https://doi.org/10.1016/0272-0590(88)90156-X PMID:3220209

Islami F, Poustchi H, Pourshams A, Khoshnia M, Gharavi A, Kamangar F, et al. (2019). A prospective study of tea drinking temperature and risk of esophageal squamous cell carcinoma. Int J Cancer. [Epub ahead of print] https://doi.org/10.1002/ijc.32220 PMID:30891750

Itoh H, Iwasaki M, Hanaoka T, Kasuga Y, Yokoyama S, Onuma H, et al. (2009). Serum organochlorines and breast cancer risk in Japanese women: a case-control study. Cancer Causes Control. 20(5):567–80. https://doi.org/10.1007/s10552-008-9265-z PMID:19031103

Iwasaki M, Inoue M, Sasazuki S, Kurahashi N, Itoh H, Usuda M, et al.; Japan Public Health Center-based Prospective Study Group (2008). Plasma organochlorine levels and subsequent risk of breast cancer among Japanese women: a nested case-control study. Sci Total Environ. 402(2–3):176–83. https://doi.org/10.1016/j.scitotenv.2008.05.009 PMID:18555519

Jackson P, Hougaard KS, Boisen AM, Jacobsen NR, Jensen KA, Møller P, et al. (2012). 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

Jaeschke H, Williams CD, McGill MR, Xie Y, Ramachandran A (2013). Models of drug-induced liver injury for evaluation of phytotherapeutics and other natural products. Food Chem Toxicol. 55:279–89. https://doi.org/10.1016/j.fct.2012.12.063 PMID:23353004

Jain RB (2015a). Distributions of selected urinary metabolites of volatile organic compounds by age, gender, race/ethnicity, and smoking status in a representative sample of U.S. adults. Environ Toxicol Pharmacol. 40(2):471–9. https://doi.org/10.1016/j.etap.2015.07.018 PMID:26282484

Jain RB (2015b). Levels of selected urinary metabolites of volatile organic compounds among children aged 6-11 years. Environ Res. 142:461–70. https://doi.org/10.1016/j.envres.2015.07.023 PMID:26257031

Jakszyn P, Agudo A, Lujan-Barroso L, Bueno-de-Mesquita HB, Jenab M, Navarro C, et al. (2012). Dietary intake of heme iron and risk of gastric cancer in the European Prospective Investigation into Cancer and Nutrition study. Int J Cancer. 130(11):2654–63. https://doi.org/10.1002/ijc.26263 PMID:21717452

Jang M, Yoon C, Park J, Kwon O (2019). Evaluation of hazardous chemicals with material safety data sheet and by-products of a photoresist used in the semiconductor-manufacturing industry. Saf Health Work. 10(1):114–121. PMID:30949390

Jarari N, Rao N, Peela JR, Ellafi KA, Shakila S, Said AR, et al. (2016). A review on prescribing patterns of antihypertensive drugs. Clin Hypertens. 22(1):7. https://doi.org/10.1186/s40885-016-0042-0 PMID:27019747

Järvinen R, Knekt P, Hakulinen T, Rissanen H, Heliövaara M (2001). Dietary fat, cholesterol and colorectal cancer in a prospective study. Br J Cancer. 85(3):357–61. https://doi.org/10.1054/bjoc.2001.1906 PMID:11487265

JBRC (1998). GLP study. Report of the Ministry of Health, Labor and Welfare commissioned carcinogenicity test: multi-walled carbon nanotubes. Available from: http://anzeninfo.mhlw.go.jp/user/anzen/kag/carcino_report.htm. [in Chinese]

JBRC (2001). 2-Year inhalation study of crotonaldehyde – Tables. Study No. 0318. Available from: http://anzeninfo.mhlw.go.jp/user/anzen/kag/pdf/gan/0318_TABLES.pdf.

JBRC (2011a). Summary of feed carcinogenicity study of diphenylamine in B6D2F_1 mice. Japan Bioassay Research Center. Available from: http://anzeninfo.mhlw.go.jp/user/anzen/kag/pdf/gan/0685_DiphenylAmineMice.pdf.

JBRC (2011b). Summary of feed carcinogenicity study of diphenylamine in F344 rats. Japan Bioassay Research Center. Available from: http://anzeninfo.mhlw.go.jp/user/anzen/kag/pdf/gan/0684_DiphenylAmineRats.pdf.

JBRC (2013). 4-tert-Butylcatechol CAS 98-29-3. Japan Bioassay Research Center. Available from http://anzeninfo.mhlw.go.jp/user/anzen/kag/carcino_report.htm. [in Japanese]

JBRC (2016). Acrolein. Available from: https://www.mhlw.go.jp/stf/newpage_02334.html. [in Japanese]

JBRC (2019). n-Butyl methacrylate. Two-year inhalation studies in rats and mice. Available from: https://www.mhlw.go.jp/stf/newpage_02334.html.

JECFA (2013). Gentian violet, 78th meeting, Toxicological evaluation of certain veterinary drug residues in food. Available from: http://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=6189.

Jensen AØ, Thomsen HF, Engebjerg MC, Olesen AB, Friis S, Karagas MR, et al. (2009). Use of oral glucocorticoids and risk of skin cancer and non-Hodgkin's lymphoma: a population-based case-control study. Br J Cancer. 100(1):200–5. https://doi.org/10.1038/sj.bjc.6604796 PMID:19034275

Jeong KS, Zhou J, Griffin SC, Jacobs ET, Dearmon-Moore D, Zhai J, et al. (2018). MicroRNA changes in firefighters. J Occup Environ Med. 60(5):469–74. https://doi.org/10.1097/JOM.0000000000001307 PMID:29465512

Jin M, Kijima A, Hibi D, Ishii Y, Takasu S, Matsushita K, et al. (2013). In vivo genotoxicity of methyleugenol in *gpt* delta transgenic rats following medium-term exposure. Toxicol Sci. 131(2):387–94. https://doi.org/10.1093/toxsci/kfs294 PMID:23074021

Jin Y, Zhu Y, Yang X, Jiang H, Li C (2006). In situ synthesis of sulfide-coated polystyrene composites for the fabrication of photonic crystals. J Colloid Interface Sci. 301(1):130–6. https://doi.org/10.1016/j.jcis.2006.04.038 PMID:16737704

Jing Y, Wu K, Liu J, Ai Q, Ge P, Dai J, et al. (2015). Aminotriazole alleviates acetaminophen poisoning via downregulating P450 2E1 and suppressing inflammation. PLoS One. 10(4):e0122781. https://doi.org/10.1371/journal.pone.0122781 PMID:25884831

JMPR (1982). Pesticide residues in food. Data and recommendations of the joint meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. Rome, 23 November–2 December 1982. Available from: http://www.inchem.org/documents/jmpr/jmpmono/v82pr09.htm.

JMPR (1995). Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO Toxicological and Environmental Core Assessment. FAO Plant Production and Protection Paper, 133, 1996 - Pesticide residues in food - 1995. Available from: http://apps.who.int/pesticide-residues-jmpr-database/pesticide?name=VINCLOZOLIN.

JMPR (1996). IPCS INCHEM. Evaluation for carbaryl. Available from: http://www.inchem.org/documents/jmpr/jmpmono/v96pr02.htm.

Johannsen FR, Levinskas GJ (2002a). Comparative chronic toxicity and carcinogenicity of acrylonitrile by drinking water and oral intubation to Spartan Sprague-Dawley rats. Toxicol Lett. 132(3):197–219. https://doi.org/10.1016/S0378-4274(02)00073-5 PMID:12044704

Johannsen FR, Levinskas GJ (2002b). Chronic toxicity and oncogenic dose-response effects of lifetime oral acrylonitrile exposure to Fischer 344 rats. Toxicol Lett. 132(3):221–47. https://doi.org/10.1016/S0378-4274(02)00074-7 PMID:12044705

Johansson E, Reynolds S, Anderson M, Maronpot R (1997). Frequency of Ha-*ras*-1 gene mutations inversely correlated with furan dose in mouse liver tumors. Mol Carcinog. 18(4):199–205. https://doi.org/10.1002/(SICI)1098-2744(199704)18:4<199::AID-MC3>3.0.CO;2-9 PMID:9142214

Johnston L, Cunningham RM, Young JS, Fry CH, McMurray G, Eccles R, et al. (2012). Altered distribution of interstitial cells and innervation in the rat urinary bladder following spinal cord injury. J Cell Mol Med. 16(7):1533–43. https://doi.org/10.1111/j.1582-4934.2011.01410.x PMID:21883887

Jones CR, Liu YY, Sepai O, Yan H, Sabbioni G (2005a). Hemoglobin adducts in workers exposed to nitrotoluenes. Carcinogenesis. 26(1):133–43. https://doi.org/10.1093/carcin/bgh286 PMID:15471893

Jones CR, Sabbioni G (2003). Identification of DNA adducts using HPLC/MS/MS following in vitro and in vivo experiments with arylamines and nitroarenes. Chem Res Toxicol. 16(10):1251–63. https://doi.org/10.1021/tx020064i PMID:14565767

Jones CR, Sepai O, Liu YY, Yan H, Sabbioni G (2005b). Urinary metabolites of workers exposed to nitrotoluenes. Biomarkers. 10(1):10–28. https://doi.org/10.1080/13547500500079670 PMID:16097390

Jones ME, Schoemaker MJ, Wright LB, Ashworth A, Swerdlow AJ (2017b). 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, Barone-Adesi F, Koutros S, Lerro CC, Blair A, Lubin J, et al. (2015). Incidence of solid tumours among pesticide applicators exposed to the organophosphate insecticide diazinon in the Agricultural Health Study: an updated analysis. Occup Environ Med. 72(7):496–503. https://doi.org/10.1136/oemed-2014-102728 PMID:25907210

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, Weyer PJ, DellaValle CT, Robien K, Cantor KP, Krasner S, et al. (2017a). Ingested nitrate, disinfection by-products, and kidney cancer risk in older women. Epidemiology. 28(5):703–11. https://doi.org/10.1097/EDE.0000000000000647 PMID:28252454

Jones SR, Atkin P, Holroyd C, Lutman E, Batlle JV, Wakeford R, et al. (2007). Lung cancer mortality at a UK tin smelter. Occup Med (Lond). 57(4):238–45. https://doi.org/10.1093/occmed/kql153 PMID:17437956

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

Joshy G, Arora M, Korda RJ, Chalmers J, Banks E (2016). Is poor oral health a risk marker for incident cardiovascular disease hospitalisation and all-cause mortality? Findings from 172 630 participants from the prospective 45 and Up Study. BMJ Open. 6(8):e012386. https://doi.org/10.1136/bmjopen-2016-012386 PMID:27577588

Journy N, Rehel JL, Ducou Le Pointe H, Lee C, Brisse H, Chateil JF, et al. (2015). Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France. Br J Cancer. 112(1):185–93. https://doi.org/10.1038/bjc.2014.526 PMID:25314057

JPEC (2010). Carcinogenicity study of 2-ethoxy-2-methylpropane in F344 rats (inhalation study) (final report). Study No. 0686. Japan Petroleum Energy Center. Available from http://www.pecj.or.jp/english/news/pdf/H220513_etbe05.pdf, accessed 2 April 2019.

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

Kachuri L, Demers PA, Blair A, Spinelli JJ, Pahwa M, McLaughlin JR, et al. (2013). Multiple pesticide exposures and the risk of multiple myeloma in Canadian men. Int J Cancer. 133(8):1846–58. https://doi.org/10.1002/ijc.28191 PMID:23564249

Käfferlein HU, Broding HC, Bünger J, Jettkant B, Koslitz S, Lehnert M, et al. (2014). Human exposure to airborne aniline and formation of methemoglobin: a contribution to occupational exposure limits. Arch Toxicol. 88(7):1419–26. https://doi.org/10.1007/s00204-014-1266-y PMID:24899222

Kagawa M, Yamamoto A, Ogawa K, Shirai T, Fukushima S (1992). Uracil-induced urolithiasis in the urinary bladder of rats is irritation-dependent. Toxicol Lett. 61(1):21–6. https://doi.org/10.1016/0378-4274(92)90059-S PMID:1609435

Kalinich JF, Emond CA, Dalton TK, Mog SR, Coleman GD, Kordell JE, et al. (2005). Embedded weapons-grade tungsten alloy shrapnel rapidly induces metastatic high-grade rhabdomyosarcomas in F344 rats. Environ Health Perspect. 113(6):729–34. https://doi.org/10.1289/ehp.7791 PMID:15929896

Kalinich JF, Vergara VB, Emond CA (2008). Urinary and serum metal levels as indicators of embedded tungsten alloy fragments. Mil Med. 173(8):754–8. https://doi.org/10.7205/MILMED.173.8.754 PMID:18751592

Kalkman HO, Feuerbach D (2016). Antidepressant therapies inhibit inflammation and microglial M1-polarization. Pharmacol Ther. 163:82–93. https://doi.org/10.1016/j.pharmthera.2016.04.001 PMID:27101921

Kamenickova A, Pecova M, Bachleda P, Dvorak Z (2013). Effects of artificial sweeteners on the AhR- and GR-dependent CYP1A1 expression in primary human hepatocytes and human cancer cells. Toxicol In Vitro. 27(8):2283–8. https://doi.org/10.1016/j.tiv.2013.10.001 PMID:24120730

Kang M, Martin A (2017). Microbiome and colorectal cancer: Unraveling host-microbiota interactions in colitis-associated colorectal cancer development. Semin Immunol. 32:3–13. https://doi.org/10.1016/j.smim.2017.04.003 PMID:28465070

Kania N, Setiawan B, Widjadjanto E, Nurdiana N, Widodo MA, Kusuma HM, et al. (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

Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL (2015). Trends in prescription drug use among adults in the United States from 1999-2012. JAMA. 314(17):1818–31. https://doi.org/10.1001/jama.2015.13766 PMID:26529160

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

Karpuzoglu E, Holladay SD, Gogal RM Jr (2013). Parabens: potential impact of low-affinity estrogen receptor binding chemicals on human health. J Toxicol Environ Health B Crit Rev. 16(5):321–35. https://doi.org/10.1080/10937404.2013.809252 PMID:23909435

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

Kasai T, Umeda Y, Sasaki T, Fukushima S (2019). Thinking on occupational exposure assessment of multi-walled carbon nanotube carcinogenicity. J Occup Health. 61(2):208–10. https://doi.org/10.1002/1348-9585.12045 PMID:30801936

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

Katz E, Nisani S, Chamovitz DA (2018). Indole-3-carbinol: a plant hormone combatting cancer. F1000 Res. 7:7. https://doi.org/10.12688/f1000research.14127.1 PMID:29904587

Kauppinen T, Pukkala E, Saalo A, Sasco AJ (2003). Exposure to chemical carcinogens and risk of cancer among Finnish laboratory workers. Am J Ind Med. 44(4):343–50. https://doi.org/10.1002/ajim.10278 PMID:14502761

Kauppinen T, Toikkanen J, Pedersen D, Young R, Ahrens W, Boffetta P, et al. (2000). Occupational exposure to carcinogens in the European Union. Occup Environ Med. 57(1):10–8. https://doi.org/10.1136/oem.57.1.10 PMID:10711264

Kawamoto K, Oashi T, Oami K, Liu W, Jin Y, Saito N, et al. (2010). Perfluorooctanoic acid (PFOA) but not perfluorooctane sulfonate (PFOS) showed DNA damage in comet assay on *Paramecium caudatum*. J Toxicol Sci. 35(6):835–41. https://doi.org/10.2131/jts.35.835 PMID:21139333

Keir JLA, Akhtar US, Matschke DMJ, Kirkham TL, Chan HM, Ayotte P, et al. (2017). Elevated exposures to polycyclic aromatic hydrocarbons and other organic mutagens in Ottawa firefighters participating in emergency, on-shift fire suppression. Environ Sci Technol. 51(21):12745–55. https://doi.org/10.1021/acs.est.7b02850 PMID:29043785

Kelly CM, Juurlink DN, Gomes T, Duong-Hua M, Pritchard KI, Austin PC, et al. (2010). Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. BMJ. 340:c693. https://doi.org/10.1136/bmj.c693 PMID:20142325

Keskın N, Teksen YA, Ongun EG, Ozay Y, Saygili H (2009). Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study. Arch Gynecol Obstet. 280(6):925–31. https://doi.org/10.1007/s00404-009-1030-3 PMID:19301023

Khan R, Rehman MU, Khan AQ, Tahir M, Sultana S (2018). Glycyrrhizic acid suppresses 1,2-dimethylhydrazine-induced colon tumorigenesis in Wistar rats: alleviation of inflammatory, proliferation, angiogenic, and apoptotic markers. Environ Toxicol. 33(12):1272–83. https://doi.org/10.1002/tox.22635 PMID:30255981

Kieny A, Cribier B, Meyer N, Velten M, Jégu J, Lipsker D (2019). Epidemiology of Merkel cell carcinoma. A population-based study from 1985 to 2013, in northeastern of France. Int J Cancer. 144(4):741–5. https://doi.org/10.1002/ijc.31860 PMID:30194728

Kim I, Kim HJ, Lim SY, Kongyoo J (2012). Leukemia and non-Hodgkin lymphoma in semiconductor industry workers in Korea. Int J Occup Environ Health. 18(2):147–53. https://doi.org/10.1179/1077352512Z.00000000019 PMID:22762495

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 J-M, Kim J-Y, Jung EJ, Song EJ, Kim DC, Jeong C-Y, et al. (2017). Cooccurrence of metastatic papillary thyroid carcinoma and *Salmonella* induced neck abscess in a cervical lymph node. Case Rep Med. 2017:5670429. https://doi.org/10.1155/2017/5670429 PMID:28261270

Kim KH, Kabir E, Jahan SA (2016). Review of electronic cigarettes as tobacco cigarette substitutes: their potential human health impact. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 34(4):262–75. https://doi.org/10.1080/10590501.2016.1236604 PMID:27635466

Kim MH, Kim H, Paek D (2014). 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 SH, Hwang KA, Shim SM, Choi KC (2015). Growth and migration of LNCaP prostate cancer cells are promoted by triclosan and benzophenone-1 via an androgen receptor signaling pathway. Environ Toxicol Pharmacol. 39(2):568–76. https://doi.org/10.1016/j.etap.2015.01.003 PMID:25682003

Kimura M, Abe H, Mizukami S, Tanaka T, Itahashi M, Onda N, et al. (2016). Onset of hepatocarcinogen-specific cell proliferation and cell cycle aberration during the early stage of repeated hepatocarcinogen administration in rats. J Appl Toxicol. 36(2):223–37. https://doi.org/10.1002/jat.3163 PMID:26011634

Kirchhoff MG, de Gannes GC (2013). The health controversies of parabens. Skin Therapy Lett. 18(2):1–8. Available from: http://www.medscape.com/viewarticle/780590_7.

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

Kleinstreuer NC, Ceger P, Watt ED, Martin M, Houck K, Browne P, et al. (2017). Development and validation of a computational model for androgen receptor activity. Chem Res Toxicol. 30(4):946–64. https://doi.org/10.1021/acs.chemrestox.6b00347 PMID:27933809

Kligerman AD, Doerr CL, Tennant AH, Peng B (2000). Cytogenetic studies of three triazine herbicides. II. In vivo micronucleus studies in mouse bone marrow. Mutat Res. 471(1–2):107–12. https://doi.org/10.1016/S1383-5718(00)00124-8 PMID:11080666

Knips J, Czech-Sioli M, Spohn M, Heiland M, Moll I, Grundhoff A, et al. (2017). Spontaneous lung metastasis formation of human Merkel cell carcinoma cell lines transplanted into scid mice. Int J Cancer. 141(1):160–71. https://doi.org/10.1002/ijc.30723 PMID:28380668

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 N, Izumi H, Morimoto Y (2017). Review of toxicity studies of carbon nanotubes. J Occup Health. 59(5):394–407. https://doi.org/10.1539/joh.17-0089-RA PMID:28794394

Kocaman A, Altun G, Kaplan AA, Deniz ÖG, Yurt KK, Kaplan S (2018). Genotoxic and carcinogenic effects of non-ionizing electromagnetic fields. Environ Res. 163:71–9. https://doi.org/10.1016/j.envres.2018.01.034 PMID:29427953

Koczor CA, Jiao Z, Fields E, Russ R, Ludaway T, Lewis W (2015). AZT-induced mitochondrial toxicity: an epigenetic paradigm for dysregulation of gene expression through mitochondrial oxidative stress. Physiol Genomics. 47(10):447–54. https://doi.org/10.1152/physiolgenomics.00045.2015 PMID:26199398

Koda T, Umezu T, Kamata R, Morohoshi K, Ohta T, Morita M (2005). Uterotrophic effects of benzophenone derivatives and a *p*-hydroxybenzoate used in ultraviolet screens. Environ Res. 98(1):40–5. https://doi.org/10.1016/j.envres.2004.05.015 PMID:15721882

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

Koenig CM, Beevers C, Pant K, Young RR (2018). Assessment of the mutagenic potential of *para*-chloroaniline and aniline in the liver, spleen, and bone marrow of Big Blue® rats with micronuclei analysis in peripheral blood. Environ Mol Mutagen. 59(9):785–97. https://doi.org/10.1002/em.22241 PMID:30216547

Kogevinas M, Villanueva CM, Font-Ribera L, Liviac D, Bustamante M, Espinoza F, et al. (2010). Genotoxic effects in swimmers exposed to disinfection by-products in indoor swimming pools. Environ Health Perspect. 118(11):1531–7. https://doi.org/10.1289/ehp.1001959 PMID:20833606

Koliarakis I, Psaroulaki A, Nikolouzakis TK, Kokkinakis M, Sgantzos MN, Goulielmos G, et al. (2018). Intestinal microbiota and colorectal cancer: a new aspect of research. J BUON. 23(5):1216–34. PMID:30512251

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

Korea Crop Protection Association (2018). Pesticide handbook. Available from: http://www.koreacpa.org/.

Korinth G, Schaller KH, Bader M, Bartsch R, Göen T, Rossbach B, et al. (2012). Comparison of experimentally determined and mathematically predicted percutaneous penetration rates of chemicals. Arch Toxicol. 86(3):423–30. https://doi.org/10.1007/s00204-011-0777-z PMID:22076108

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

Kotemori A, Ishihara J, Zha L, Liu R, Sawada N, Iwasaki M, et al.; JPHC Study Group (2018). Dietary acrylamide intake and risk of breast cancer: the Japan Public Health Center-based Prospective Study. Cancer Sci. 109(3):843–53. https://doi.org/10.1111/cas.13496 PMID:29288560

Koutros S, Alavanja MCR, Lubin JH, Sandler DP, Hoppin JA, Lynch CF, et al. (2010). An update of cancer incidence in the Agricultural Health Study. J Occup Environ Med. 52(11):1098–105. https://doi.org/10.1097/JOM.0b013e3181f72b7c PMID:21063187

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, Silverman DT, Alavanja MC, Andreotti G, Lerro CC, Heltshe S, et al. (2016). Occupational exposure to pesticides and bladder cancer risk. Int J Epidemiol. 45(3):792–805. https://doi.org/10.1093/ije/dyv195 PMID:26411407

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

Kristal AR, Darke AK, Morris JS, Tangen CM, Goodman PJ, Thompson IM, et al. (2014). Baseline selenium status and effects of selenium and vitamin E supplementation on prostate cancer risk. J Natl Cancer Inst. 106(3):djt456. https://doi.org/10.1093/jnci/djt456 PMID:24563519

Kubale T, Hiratzka S, Henn S, Markey A, Daniels R, Utterback D, et al. (2008). A cohort mortality study of chemical laboratory workers at Department of Energy nuclear plants. Am J Ind Med. 51(9):656–67. https://doi.org/10.1002/ajim.20601 PMID:18609549

Kuempel ED, Jaurand MC, Møller P, Morimoto Y, Kobayashi N, Pinkerton KE, et al. (2017). Evaluating the mechanistic evidence and key data gaps in assessing the potential carcinogenicity of carbon nanotubes and nanofibers in humans. Crit Rev Toxicol. 47(1):1–58. https://doi.org/10.1080/10408444.2016.1206061 PMID:27537422

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

Kullberg C, Andersson T, Gustavsson P, Selander J, Tornling G, Gustavsson A, et al. (2018). Cancer incidence in Stockholm firefighters 1958-2012: an updated cohort study. Int Arch Occup Environ Health. 91(3):285–91. https://doi.org/10.1007/s00420-017-1276-1 PMID:29164319

Kütting B, Göen T, Schwegler U, Fromme H, Uter W, Angerer J, et al. (2009). Monoarylamines in the general population – a cross-sectional population-based study including 1004 Bavarian subjects. Int J Hyg Environ Health. 212(3):298–309. https://doi.org/10.1016/j.ijheh.2008.07.004 PMID:18789761

Kuugbee ED, Shang X, Gamallat Y, Bamba D, Awadasseid A, Suliman MA, et al. (2016). Structural change in microbiota by a probiotic cocktail enhances the gut barrier and reduces cancer via TLR2 signaling in a rat model of colon cancer. Dig Dis Sci. 61(10):2908–20. https://doi.org/10.1007/s10620-016-4238-7 PMID:27384052

Kuzu OF, Noory MA, Robertson GP (2016). The role of cholesterol in cancer. Cancer Res. 76(8):2063–70. https://doi.org/10.1158/0008-5472.CAN-15-2613 PMID:27197250

Kwon JY, Koedrith P, Seo YR (2014). Current investigations into the genotoxicity of zinc oxide and silica nanoparticles in mammalian models in vitro and in vivo: carcinogenic/genotoxic potential, relevant mechanisms and biomarkers, artifacts, and limitations. Int J Nanomedicine. 9(Suppl 2):271–86. PMID:25565845

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

Labine MA, Green C, Mak G, Xue L, Nowatzki J, Griffith J, et al. (2015). The geographic distribution of liver cancer in Canada does not associate with cyanobacterial toxin exposure. Int J Environ Res Public Health. 12(12):15143–53. https://doi.org/10.3390/ijerph121214969 PMID:26633441

Lachenmeier DW, Lima MC, Nóbrega IC, Pereira JA, Kerr-Corrêa F, Kanteres F, et al. (2010). Cancer risk assessment of ethyl carbamate in alcoholic beverages from Brazil with special consideration to the spirits cachaça and tiquira. BMC Cancer. 10(1):266. https://doi.org/10.1186/1471-2407-10-266 PMID:20529350

Lachenmeier DW, Salaspuro M (2017). ALDH2-deficiency as genetic epidemiologic and biochemical model for the carcinogenicity of acetaldehyde. Regul Toxicol Pharmacol. 86:128–36. https://doi.org/10.1016/j.yrtph.2017.02.024 PMID:28257851

Lagergren K, Wahlin K, Mattsson F, Alderson D, Lagergren J (2016). Haemochromatosis and gastrointestinal cancer. Int J Cancer. 139(8):1740–3. https://doi.org/10.1002/ijc.30229 PMID:27300578

Lal M, Caplan M (2011). Regulated intramembrane proteolysis: signaling pathways and biological functions. Physiology (Bethesda). 26(1):34–44. https://doi.org/10.1152/physiol.00028.2010 PMID:21357901

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

Landgren O, Kyle RA, Hoppin JA, Beane Freeman LE, Cerhan JR, Katzmann JA, et al. (2009). Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. Blood. 113(25):6386–91. https://doi.org/10.1182/blood-2009-02-203471 PMID:19387005

Lanes SF, Rothman KJ, Soden KJ, Amsel J, Dreyer NA (1994). Mortality among synthetic fiber workers exposed to glycerol polyglycidyl ether. Am J Ind Med. 25(5):689–96. https://doi.org/10.1002/ajim.4700250508 PMID:8030639

Lansdown ABG (2014). The carcinogenicity of metals. Human risk through occupational and environmental exposure. Issues in Toxicology No. 18. Cambridge, UK: RSC Publishing.

LaPlante CD, Bansal R, Dunphy KA, Jerry DJ, Vandenberg LN (2018). Oxybenzone alters mammary gland morphology in mice exposed during pregnancy and lactation. J Endocr Soc. 2(8):903–21. https://doi.org/10.1210/js.2018-00024 PMID:30057971

Larsson SC, Orsini N, Wolk A (2015). Urinary cadmium concentration and risk of breast cancer: a systematic review and dose-response meta-analysis. Am J Epidemiol. 182(5):375–80. https://doi.org/10.1093/aje/kwv085 PMID:26254432

Lassek E, Montag A (1990). Nucleic acid components in carbohydrate-rich food. Z Lebensm Unters Forsch. 190(1):17–21. https://doi.org/10.1007/BF01188257 PMID:1689090 [in German]

Lau SS, Monks TJ, Everitt JI, Kleymenova E, Walker CL (2001). Carcinogenicity of a nephrotoxic metabolite of the "nongenotoxic" carcinogen hydroquinone. Chem Res Toxicol. 14(1):25–33. https://doi.org/10.1021/tx000161g PMID:11170505

Laulicht F, Brocato J, Cartularo L, Vaughan J, Wu F, Kluz T, et al. (2015). Tungsten-induced carcinogenesis in human bronchial epithelial cells. Toxicol Appl Pharmacol. 288(1):33–9. https://doi.org/10.1016/j.taap.2015.07.003 PMID:26164860

Lavigne É, Bélair MA, Do MT, Stieb DM, Hystad P, van Donkelaar A, et al. (2017). Maternal exposure to ambient air pollution and risk of early childhood cancers: a population-based study in Ontario, Canada. Environ Int. 100:139–47. https://doi.org/10.1016/j.envint.2017.01.004 PMID:28108116

Laviolette LA, Garson K, Macdonald EA, Senterman MK, Courville K, Crane CA, et al. (2010). 17β-estradiol accelerates tumor onset and decreases survival in a transgenic mouse model of ovarian cancer. Endocrinology. 151(3):929–38. https://doi.org/10.1210/en.2009-0602 PMID:20056833

Lazzeroni M, Guerrieri-Gonzaga A, Gandini S, Johansson H, Serrano D, Cazzaniga M, et al. (2016). A presurgical study of oral silybin-phosphatidylcholine in patients with early breast cancer. Cancer Prev Res (Phila). 9(1):89–95. https://doi.org/10.1158/1940-6207.CAPR-15-0123 PMID:26526990

Lécuyer L, Victor Bala A, Deschasaux M, Bouchemal N, Nawfal Triba M, Vasson MP, et al. (2018). NMR metabolomic signatures reveal predictive plasma metabolites associated with long-term risk of developing breast cancer. Int J Epidemiol. 47(2):484–94. https://doi.org/10.1093/ije/dyx271 PMID:29365091

Lee DG, Burstyn I, Lai AS, Grundy A, Friesen MC, Aronson KJ, et al. (2019). Women's occupational exposure to polycyclic aromatic hydrocarbons and risk of breast cancer. Occup Environ Med. 76(1):22–9. https://doi.org/10.1136/oemed-2018-105261 PMID:30541747

Lee HE, Kim EA, Park J, Kang SK (2011). Cancer mortality and incidence in Korean semiconductor workers. Saf Health Work. 2(2):135–47. https://doi.org/10.5491/SHAW.2011.2.2.135 PMID:22953196

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 J, Scheri RC, Zhang Y, Curtis LR (2008). Chlordecone, a mixed pregnane X receptor (PXR) and estrogen receptor alpha (ERα) agonist, alters cholesterol homeostasis and lipoprotein metabolism in C57BL/6 mice. Toxicol Appl Pharmacol. 233(2):193–202. https://doi.org/10.1016/j.taap.2008.08.011 PMID:18789348

Lee JG, Park SK, Yoon HJ, Kang DH, Kim M (2016). Exposure assessment and risk characterisation of ethyl carbamate from Korean traditional fermented rice wine, *Takju* and *Yakju*. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 33(2):207–14. PMID:26794849

Lee JS, Choi YC, Shin JH, Lee JH, Lee Y, Park SY, et al. (2015b). Health surveillance study of workers who manufacture multi-walled carbon nanotubes. Nanotoxicology. 9(6):802–11. https://doi.org/10.3109/17435390.2014.978404 PMID:25395166

Lee K, Kim SG, Kim D (2015a). Potential risk factors for haematological cancers in semiconductor workers. Occup Med (Lond). 65(7):585–9. https://doi.org/10.1093/occmed/kqv112 PMID:26272382

Lee WJ, Blair A, Hoppin JA, Lubin JH, Rusiecki JA, Sandler DP, et al. (2004b). 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, Colt JS, Heineman EF, McComb R, Weisenburger DD, Lijinsky W, et al. (2005). Agricultural pesticide use and risk of glioma in Nebraska, United States. Occup Environ Med. 62(11):786–92. https://doi.org/10.1136/oem.2005.020230 PMID:16234405

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 WJ, Lijinsky W, Heineman EF, Markin RS, Weisenburger DD, Ward MH (2004c). Agricultural pesticide use and adenocarcinomas of the stomach and oesophagus. Occup Environ Med. 61(9):743–9. https://doi.org/10.1136/oem.2003.011858 PMID:15317914

Lee WJ, Sandler DP, Blair A, Samanic C, Cross AJ, Alavanja MC (2007). Pesticide use and colorectal cancer risk in the Agricultural Health Study. Int J Cancer. 121(2):339–46. https://doi.org/10.1002/ijc.22635 PMID:17390374

Lee WY, Sun LM, Lin CL, Liang JA, Chang YJ, Sung FC, et al. (2014). Risk of prostate and bladder cancers in patients with spinal cord injury: a population-based cohort study. Urol Oncol. 32(1):51.e1–7. https://doi.org/10.1016/j.urolonc.2013.07.019 PMID:24239459

Lee Y, Kim YJ, Choi YJ, Lee JW, Lee S, Cho YH, et al. (2015c). Radiation-induced changes in DNA methylation and their relationship to chromosome aberrations in nuclear power plant workers. Int J Radiat Biol. 91(2):142–9. https://doi.org/10.3109/09553002.2015.969847 PMID:25264146

Lehrer S (2012). Cytomegalovirus infection in early childhood may be protective against glioblastoma multiforme, while later infection is a risk factor. Med Hypotheses. 78(5):657–8. https://doi.org/10.1016/j.mehy.2012.02.003 PMID:22385772

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, 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. [Epub ahead of print] https://doi.org/10.1093/ije/dyz017 PMID:30880337

León-Mejía G, Machado MN, Okuro RT, Silva LFO, Telles C, Dias J, et al. (2018). Intratracheal instillation of coal and coal fly ash particles in mice induces DNA damage and translocation of metals to extrapulmonary tissues. Sci Total Environ. 625:589–99. https://doi.org/10.1016/j.scitotenv.2017.12.283 PMID:29291573

León-Mejía G, Silva LFO, Civeira MS, Oliveira MLS, Machado M, Villela IV, et al. (2016). Cytotoxicity and genotoxicity induced by coal and coal fly ash particles samples in V79 cells. Environ Sci Pollut Res Int. 23(23):24019–31. https://doi.org/10.1007/s11356-016-7623-z PMID:27638803

Leone AM, Crawshaw GJ, Garner MM, Frasca S Jr, Stasiak I, Rose K, et al. (2016). A retrospective study of the lesions associated with iron storage disease in captive Egyptian fruit bats (*Rousettus aegyptiacus*). J Zoo Wildl Med. 47(1):45–55. https://doi.org/10.1638/2015-0224.1 PMID:27010264

Lerro CC, Andreotti G, Koutros S, Lee WJ, Hofmann JN, Sandler DP, et al. (2018a). 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, Jones RR, Langseth H, Grimsrud TK, Engel LS, Sjödin A, et al. (2018b). A nested case-control study of polychlorinated biphenyls, organochlorine pesticides, and thyroid cancer in the Janus Serum Bank cohort. Environ Res. 165:125–32. https://doi.org/10.1016/j.envres.2018.04.012 PMID:29698872

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

Lerro CC, Koutros S, Andreotti G, Sandler DP, Lynch CF, Louis LM, et al. (2019). Cancer incidence in the Agricultural Health Study after 20 years of follow-up. Cancer Causes Control. 30(4):311–22. https://doi.org/10.1007/s10552-019-01140-y PMID:30805813

Leung AM (2017). Exposure to flame retardants is inconsistently associated with papillary thyroid cancer. Clin Thyroidol. 29(10):392–4. https://doi.org/10.1089/ct.2017;29.392-394

Leuraud K, Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, et al. (2015). Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. Lancet Haematol. 2(7):e276–81. https://doi.org/10.1016/S2352-3026(15)00094-0 PMID:26436129

Lewis-Mikhael AM, Olmedo-Requena R, Martínez-Ruiz V, Bueno-Cavanillas A, Jiménez-Moleón JJ (2015). Organochlorine pesticides and prostate cancer, is there an association? A meta-analysis of epidemiological evidence. Cancer Causes Control. 26(10):1375–92. https://doi.org/10.1007/s10552-015-0643-z PMID:26245248

Li B, Wang Y, Yin L, Huang G, Xu Y, Su J, et al. (2019). Glucocorticoids promote the development of azoxymethane and dextran sulfate sodium-induced colorectal carcinoma in mice. BMC Cancer. 19(1):94. https://doi.org/10.1186/s12885-019-5299-8 PMID:30665389

Li D, Yin D, Han X (2007). Methyl *tert*-butyl ether (MTBE)-induced cytotoxicity and oxidative stress in isolated rat spermatogenic cells. J Appl Toxicol. 27(1):10–7. https://doi.org/10.1002/jat.1178 PMID:17177168

Li FP, Fraumeni JF Jr, Mantel N, Miller RW (1969). Cancer mortality among chemists. J Natl Cancer Inst. 43(5):1159–64. PMID:5353243

Li J, Li B, Xu WW, Chan KW, Guan XY, Qin YR, et al. (2016). Role of AMPK signaling in mediating the anticancer effects of silibinin in esophageal squamous cell carcinoma. Expert Opin Ther Targets. 20(1):7–18. https://doi.org/10.1517/14728222.2016.1121236 PMID:26568207

Li J, Liu H, Yu J, Yu H (2015a). Chemoresistance to doxorubicin induces epithelial-mesenchymal transition via upregulation of transforming growth factor β signaling in HCT116 colon cancer cells. Mol Med Rep. 12(1):192–8. https://doi.org/10.3892/mmr.2015.3356 PMID:25684678

Li LY, Luo Y, Lu MD, Xu XW, Lin HD, Zheng ZQ (2015b). Cruciferous vegetable consumption and the risk of pancreatic cancer: a meta-analysis. World J Surg Oncol. 13(1):44. https://doi.org/10.1186/s12957-015-0454-4 PMID:25889229

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 WG, Wang HQ (2016). Inhibitory effects of silibinin combined with doxorubicin in hepatocellular carcinoma; an in vivo study. J BUON. 21(4):917–24. PMID:27685914

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, Zhang S, Safe S (2006). Activation of kinase pathways in MCF-7 cells by 17β-estradiol and structurally diverse estrogenic compounds. J Steroid Biochem Mol Biol. 98(2–3):122–32. https://doi.org/10.1016/j.jsbmb.2005.08.018 PMID:16413991

Li X, Zhang X, Xie W, Zhou C, Li Y, Zhang X (2017). Alterations in transcription and protein expressions of HCC-related genes in HepG2 cells caused by microcystin-LR. Toxicol In Vitro. 40(40):115–23. https://doi.org/10.1016/j.tiv.2016.12.016 PMID:28062358

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

Lichtner M, Cicconi P, Vita S, Cozzi-Lepri A, Galli M, Lo Caputo S, et al. (2014). Cytomegalovirus coinfection is associated with an increased risk of severe non-AIDS-defining events in a large cohort of HIV-infected patients. J Infect Dis. 211(2):178–86. https://doi.org/10.1093/infdis/jiu417 PMID:25081936

Liddell CM, Summers CJ (2004). Nonspherical ZnS colloidal building blocks for three-dimensional photonic crystals. J Colloid Interface Sci. 274(1):103–6. https://doi.org/10.1016/j.jcis.2003.12.012 PMID:15120283

Lietzen LW, Ahern T, Christiansen P, Jensen AB, Sørensen HT, Lash TL, et al. (2014). Glucocorticoid prescriptions and breast cancer recurrence: a Danish nationwide prospective cohort study. Ann Oncol. 25(12):2419–25. https://doi.org/10.1093/annonc/mdu453 PMID:25223486

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.3374 PMID:27581495

Lim IK (2002). Spectrum of molecular changes during hepatocarcinogenesis induced by DEN and other chemicals in Fischer 344 male rats. Mech Ageing Dev. 123(12):1665–80. https://doi.org/10.1016/S0047-6374(02)00087-8 PMID:12470904

Lim Y, Shin SH, Lee MH, Malakhova M, Kurinov I, Wu Q, et al. (2016). A natural small molecule, catechol, induces c-Myc degradation by directly targeting ERK2 in lung cancer. Oncotarget. 7(23):35001–14. https://doi.org/10.18632/oncotarget.9223 PMID:27167001

Lin H, Liu W, Zeng H, Pu C, Zhang R, Qiu Z, et al. (2016). Determination of environmental exposure to microcystin and aflatoxin as a risk for renal function based on 5493 rural people in Southwest China. Environ Sci Technol. 50(10):5346–56. https://doi.org/10.1021/acs.est.6b01062 PMID:27071036

Lin KH, Shibu MA, Kuo YH, Chen YC, Hsu HH, Bau DT, et al. (2017). Taiwanin C selectively inhibits arecoline and 4-NQO-induced oral cancer cell proliferation via ERK1/2 inactivation. Environ Toxicol. 32(1):62–9. https://doi.org/10.1002/tox.22212 PMID:26537528

Lin WC, Lin YP, Wang YC, Chang TK, Chiang LC (2014). Assessing and mapping spatial associations among oral cancer mortality rates, concentrations of heavy metals in soil, and land use types based on multiple scale data. Int J Environ Res Public Health. 11(2):2148–68. https://doi.org/10.3390/ijerph110202148 PMID:24566045

Linhart C, Talasz H, Morandi EM, Exley C, Lindner HH, Taucher S, et al. (2017). Use of underarm cosmetic products in relation to risk of breast cancer: a case-control study. EBioMedicine. 21:79–85. https://doi.org/10.1016/j.ebiom.2017.06.005 PMID:28629908

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

Lipfert FW (2018). Long-term associations of morbidity with air pollution: a catalog and synthesis. J Air Waste Manag Assoc. 68(1):12–28. https://doi.org/10.1080/10962247.2017.1349010 PMID:28679072

Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, et al. (2009). Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 301(1):39–51. https://doi.org/10.1001/jama.2008.864 PMID:19066370

Littlefield NA, Blackwell BN, Hewitt CC, Gaylor DW (1985). Chronic toxicity and carcinogenicity studies of gentian violet in mice. Fundam Appl Toxicol. 5(5):902–12. https://doi.org/10.1016/0272-0590(85)90172-1 PMID:4065463

Littlefield NA, Gaylor DW, Blackwell BN, Allen RR (1989). Chronic toxicity/carcinogenicity studies of gentian violet in Fischer 344 rats: two-generation exposure. Food Chem Toxicol. 27(4):239–47. https://doi.org/10.1016/0278-6915(89)90162-2 PMID:2731819

Liu B, Mao Q, Cao M, Xie L (2012). Cruciferous vegetables intake and risk of prostate cancer: a meta-analysis. Int J Urol. 19(2):134–41. https://doi.org/10.1111/j.1442-2042.2011.02906.x PMID:22121852

Liu B, Mao Q, Lin Y, Zhou F, Xie L (2013a). The association of cruciferous vegetables intake and risk of bladder cancer: a meta-analysis. World J Urol. 31(1):127–33. https://doi.org/10.1007/s00345-012-0850-0 PMID:22391648

Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. (2013c). A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 9(1):30. https://doi.org/10.1186/1710-1492-9-30 PMID:23947590

Liu J, Xu A, Lam KS, Wong NS, Chen J, Shepherd PR, et al. (2013b). Cholesterol-induced mammary tumorigenesis is enhanced by adiponectin deficiency: role of LDL receptor upregulation. Oncotarget. 4(10):1804–18. https://doi.org/10.18632/oncotarget.1364 PMID:24113220

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 R, Zhang L, McHale CM, Hammond SK (2011). Paternal smoking and risk of childhood acute lymphoblastic leukemia: systematic review and meta-analysis. J Oncol. 2011:854584. https://doi.org/10.1155/2011/854584 PMID:21765828

Liu W, Krump NA, MacDonald M, You J (2018). Merkel cell polyomavirus infection of animal dermal fibroblasts. J Virol. 92(4):e01610–7. https://doi.org/10.1128/JVI.00476-18 PMID:29167345

Liu W, Wang L, Yang X, Zeng H, Zhang R, Pu C, et al. (2017b). Environmental microcystin exposure increases liver injury risk induced by hepatitis B virus combined with aflatoxin: a cross-sectional study in southwest China. Environ Sci Technol. 51(11):6367–78. https://doi.org/10.1021/acs.est.6b05404 PMID:28467052

Liu X, Lv K (2013). Cruciferous vegetables intake is inversely associated with risk of breast cancer: a meta-analysis. Breast. 22(3):309–13. https://doi.org/10.1016/j.breast.2012.07.013 PMID:22877795

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 XY, Yang ZH, Pan XJ, Zhu MX, Xie JP (2010a). Crotonaldehyde induces oxidative stress and caspase-dependent apoptosis in human bronchial epithelial cells. Toxicol Lett. 195(1):90–8. https://doi.org/10.1016/j.toxlet.2010.02.004 PMID:20153411

Liu XY, Yang ZH, Pan XJ, Zhu MX, Xie JP (2010b). Gene expression profile and cytotoxicity of human bronchial epithelial cells exposed to crotonaldehyde. Toxicol Lett. 197(2):113–22. https://doi.org/10.1016/j.toxlet.2010.05.005 PMID:20471460

Liu Y, Qi Y, Bai ZH, Ni CX, Ren QH, Xu WH, et al. (2017a). A novel matrine derivate inhibits differentiated human hepatoma cells and hepatic cancer stem-like cells by suppressing PI3K/AKT signaling pathways. Acta Pharmacol Sin. 38(1):120–32. https://doi.org/10.1038/aps.2016.104 PMID:27773936

Liu Y, Xu Y, Ji W, Li X, Sun B, Gao Q, et al. (2014). Anti-tumor activities of matrine and oxymatrine: literature review. Tumour Biol. 35(6):5111–9. https://doi.org/10.1007/s13277-014-1680-z PMID:24526416

Liu YJ, Peng W, Hu MB, Xu M, Wu CJ (2016). The pharmacology, toxicology and potential applications of arecoline: a review. Pharm Biol. 54(11):2753–60. https://doi.org/10.3109/13880209.2016.1160251 PMID:27046150

Livingstone MC, Johnson NM, Roebuck BD, Kensler TW, Groopman JD (2017). Profound changes in miRNA expression during cancer initiation by aflatoxin B_1 and their abrogation by the chemopreventive triterpenoid CDDO-Im. Mol Carcinog. 56(11):2382–90. https://doi.org/10.1002/mc.22635 PMID:28218475

Llaverias G, Danilo C, Mercier I, Daumer K, Capozza F, Williams TM, et al. (2011). Role of cholesterol in the development and progression of breast cancer. Am J Pathol. 178(1):402–12. https://doi.org/10.1016/j.ajpath.2010.11.005 PMID:21224077

Löfstedt Gilljam J, Leonel J, Cousins IT, Benskin JP (2016). Is ongoing sulfluramid use in South America a significant source of perfluorooctanesulfonate (PFOS)? Production inventories, environmental fate, and local occurrence. Environ Sci Technol. 50(2):653–9. https://doi.org/10.1021/acs.est.5b04544 PMID:26653085

Loh JT, Beckett AC, Scholz MB, Cover TL (2018). High-salt conditions alter transcription of *Helicobacter pylori* genes encoding outer membrane proteins. Infect Immun. 86(3):e00626–17. 10.1128/IAI.00626-17 PMID:29229727

Lokhov PG, Trifonova OP, Maslov DL, Archakov AI (2013). Blood plasma metabolites and the risk of developing lung cancer in Russia. Eur J Cancer Prev. 22(4):335–41. https://doi.org/10.1097/CEJ.0b013e32835b3898 PMID:23212094

Lone Y, Bhide M, Koiri RK (2016). Microcystin-LR induced immunotoxicity in mammals. J Toxicol. 2016:8048125. https://doi.org/10.1155/2016/8048125 PMID:26925102

López-Carrillo L, López-Cervantes M, Torres-Sánchez L, Blair A, Cebrián ME, García RM (2002). Serum levels of beta-hexachlorocyclohexane, hexachlorobenzene and polychlorinated biphenyls and breast cancer in Mexican women. Eur J Cancer Prev. 11(2):129–35. https://doi.org/10.1097/00008469-200204000-00004 PMID:11984130

Louis LM, Lerro CC, Friesen MC, Andreotti G, Koutros S, Sandler DP, et al. (2017). A prospective study of cancer risk among Agricultural Health Study farm spouses associated with personal use of organochlorine insecticides. Environ Health. 16(1):95. https://doi.org/10.1186/s12940-017-0298-1 PMID:28874165

Lu C, Sun H, Huang J, Yin S, Hou W, Zhang J, et al. (2017a). Long-term sleep duration as a risk factor for breast cancer: evidence from a systematic review and dose-response meta-analysis. BioMed Res Int. 2017:4845059. https://doi.org/10.1155/2017/4845059 PMID:29130041

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 K, Gul H, Upton PB, Moeller BC, Swenberg JA (2012). Formation of hydroxymethyl DNA adducts in rats orally exposed to stable isotope labeled methanol. Toxicol Sci. 126(1):28–38. https://doi.org/10.1093/toxsci/kfr328 PMID:22157354

Lu SS, Grigoryan H, Edmands WM, Hu W, Iavarone AT, Hubbard A, et al. (2017b). Profiling the serum albumin Cys34 adductome of solid fuel users in Xuanwei and Fuyuan, China. Environ Sci Technol. 51(1):46–57. https://doi.org/10.1021/acs.est.6b03955 PMID:27936627

Luanpitpong S, Wang L, Davidson DC, Riedel H, Rojanasakul Y (2016). Carcinogenic potential of high aspect ratio carbon nanomaterials. Environ Sci Nano. 3(3):483–93. https://doi.org/10.1039/C5EN00238A PMID:27570625

Lucas C, Barnich N, Nguyen HTT (2017). Microbiota, inflammation and colorectal cancer. Int J Mol Sci. 18(6):E1310. https://doi.org/10.3390/ijms18061310 PMID:28632155

Lundin JI, Checkoway H (2009). Endotoxin and cancer. Environ Health Perspect. 117(9):1344–50. https://doi.org/10.1289/ehp.0800439 PMID:19750096

Luo JC, Shih TS, Chang CP, Huang CC (2011). Blood oxidative stress in Taiwan workers exposed to carbon disulfide. Am J Ind Med. 54(8):637–45. https://doi.org/10.1002/ajim.20971 PMID:21630299

Luzy AP, Orsini N, Linget JM, Bouvier G (2013). Evaluation of the GADD45α-GFP GreenScreen HC assay for rapid and reliable in vitro early genotoxicity screening. J Appl Toxicol. 33(11):1303–15. PMID:22806210

Lv YF, Chang X, Hua RX, Yan GN, Meng G, Liao XY, et al. (2016). The risk of new-onset cancer associated with HFE C282Y and H63D mutations: evidence from 87,028 participants. J Cell Mol Med. 20(7):1219–33. https://doi.org/10.1111/jcmm.12764 PMID:26893171

Lynch J (2001). Occupational exposure to butadiene, isoprene and chloroprene. Chem Biol Interact. 135-136:207–14. https://doi.org/10.1016/S0009-2797(01)00191-0 PMID:11397391

Lynge E, Andersen A, Nilsson R, Barlow L, Pukkala E, Nordlinder R, et al. (1997). Risk of cancer and exposure to gasoline vapors. Am J Epidemiol. 145(5):449–58. https://doi.org/10.1093/oxfordjournals.aje.a009127 PMID:9048519

Lynge E, Andersen A, Rylander L, Tinnerberg H, Lindbohm ML, Pukkala E, et al. (2006). Cancer in persons working in dry cleaning in the Nordic countries. Environ Health Perspect. 114(2):213–9. https://doi.org/10.1289/ehp.8425 PMID:16451857

Lynge E, Carstensen B, Andersen O (1995). Primary liver cancer and renal cell carcinoma in laundry and dry-cleaning workers in Denmark. Scand J Work Environ Health. 21(4):293–5. https://doi.org/10.5271/sjweh.41 PMID:8553005

Lynge E, Thygesen L (1990). Primary liver cancer among women in laundry and dry-cleaning work in Denmark. Scand J Work Environ Health. 16(2):108–12. https://doi.org/10.5271/sjweh.1810 PMID:2353193

M Vidal L, Pimentel E, Cruces MP, Hernández S, Ruiz-Azuara L (2017). Cytotoxic and genotoxic actions of Casiopeina III-Ea (Cas III-Ea) in somatic and germ cells of *Drosophila melanogaster*. J Toxicol Environ Health A. 80(6):365–73. https://doi.org/10.1080/15287394.2017.1326072 PMID:28644726

Ma J, Lessner L, Schreiber J, Carpenter DO (2009). Association between residential proximity to PERC dry cleaning establishments and kidney cancer in New York City. J Environ Public Health. 2009:183920. https://doi.org/10.1155/2009/183920 PMID:20169137

Ma J, Li Y, Duan H, Sivakumar R, Li X (2018). Chronic exposure of nanomolar MC-LR caused oxidative stress and inflammatory responses in HepG2 cells. Chemosphere. 192:305–17. https://doi.org/10.1016/j.chemosphere.2017.10.158 PMID:29117589

Ma X, Li RS, Wang J, Huang YQ, Li PY, Wang J, et al. (2016). The therapeutic efficacy and safety of Compound Kushen Injection combined with transarterial chemoembolization in unresectable hepatocellular carcinoma: an update systematic review and meta-analysis. Front Pharmacol. 7:70. https://doi.org/10.3389/fphar.2016.00070 PMID:27065861

Mackevica A, Foss Hansen S (2016). Release of nanomaterials from solid nanocomposites and consumer exposure assessment - a forward-looking review. Nanotoxicology. 10(6):641–53. https://doi.org/10.3109/17435390.2015.1132346 PMID:26667577

MacLennan PA, Delzell E, Sathiakumar N, Myers SL, Cheng H, Grizzle W, et al. (2002). Cancer incidence among triazine herbicide manufacturing workers. J Occup Environ Med. 44(11):1048–58. https://doi.org/10.1097/00043764-200211000-00011 PMID:12448356

Mager DL (2006). Bacteria and cancer: cause, coincidence or cure? A review. J Transl Med. 4(1):14. https://doi.org/10.1186/1479-5876-4-14 PMID:16566840

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

Mahale P, Aka P, Chen X, Pfeiffer RM, Liu P, Groover S, et al. (2019). Hepatitis D virus infection, cirrhosis and hepatocellular carcinoma in The Gambia. J Viral Hepat. 26(6):738–49. https://doi.org/10.1111/jvh.13065 PMID:30661282

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/dyx137 PMID:29025130

MAK (1999). MAK value documentation: ethanol. Available from: https://onlinelibrary.wiley.com/browse/book/10.1002/3527600418/topic?ConceptID=206919&seriesKey=mrwseries&tagCode=&startPage=0&pageSize=20.

MAK (2007). n-Butyltin compounds. The MAK Collection, Part I. Deutsche Forschungsgemeinschaft, Wiley-VCH Verlag.

Makris KC, Voniatis M (2018). Brain cancer cluster investigation around a factory emitting dichloromethane. Eur J Public Health. 28(2):338–43. https://doi.org/10.1093/eurpub/ckx170 PMID:29036600

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 PMID:26453019

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

Mallozzi M, Leone C, Manurita F, Bellati F, Caserta D (2017). Endocrine disrupting chemicals and endometrial cancer: an overview of recent laboratory evidence and epidemiological studies. Int J Environ Res Public Health. 14(3):E334. https://doi.org/10.3390/ijerph14030334 PMID:28327540

Maltoni C, Belpoggi F, Soffritti M, Minardi F (1999). Comprehensive long-term experimental project of carcinogenicity bioassays on gasoline oxygenated additives: plan and first report of results from the study on ethyl-tertiary-butyl ether (ETBE). Eur J Oncol. 4(5):493–508.

Maltoni C, Ciliberti A, Pinto C, Soffritti M, Belpoggi F, Menarini L (1997). Results of long-term experimental carcinogenicity studies of the effects of gasoline, correlated fuels, and major gasoline aromatics on rats. Ann N Y Acad Sci. 837(1):15–52. https://doi.org/10.1111/j.1749-6632.1997.tb56863.x PMID:9472329

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

Mamtani R, Cheema S, Sheikh J, Al Mulla A, Lowenfels A, Maisonneuve P (2017). Cancer risk in waterpipe smokers: a meta-analysis. Int J Public Health. 62(1):73–83. https://doi.org/10.1007/s00038-016-0856-2 PMID:27421466

Mandel JS, McLaughlin JK, Schlehofer B, Mellemgaard A, Helmert U, Lindblad P, et al. (1995). International renal-cell cancer study. IV. Occupation. Int J Cancer. 61(5):601–5. https://doi.org/10.1002/ijc.2910610503 PMID:7768630

Mandriota SJ (2017). A case-control study adds a new piece to the aluminium/breast cancer puzzle. EBioMedicine. 22:22–3. https://doi.org/10.1016/j.ebiom.2017.06.025 PMID:28693981

Manjanatha MG, Shelton SD, Bishop M, Shaddock JG, Dobrovolsky VN, Heflich RH, et al. (2004). Analysis of mutations and bone marrow micronuclei in Big Blue rats fed leucomalachite green. Mutat Res. 547(1–2):5–18. https://doi.org/10.1016/j.mrfmmm.2003.11.009 PMID:15013694

Manju V, Nalini N (2005). Chemopreventive efficacy of ginger, a naturally occurring anticarcinogen during the initiation, post-initiation stages of 1,2 dimethylhydrazine-induced colon cancer. Clin Chim Acta. 358(1–2):60–7. https://doi.org/10.1016/j.cccn.2005.02.018 PMID:16018877

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

Mansourian M, Haghjooy-Javanmard S, Eshraghi A, Vaseghi G, Hayatshahi A, Thomas J (2016). Statins use and risk of breast cancer recurrence and death: a systematic review and meta-analysis of observational studies. J Pharm Pharm Sci. 19(1):72–81. https://doi.org/10.18433/J3202B PMID:27096694

Manz DH, Blanchette NL, Paul BT, Torti FM, Torti SV (2016). Iron and cancer: recent insights. Ann N Y Acad Sci. 1368(1):149–61. https://doi.org/10.1111/nyas.13008 PMID:26890363

Marano DE, Boice JD Jr, Munro HM, Chadda BK, Williams ME, McCarthy CM, et al. (2010). Exposure assessment among US workers employed in semiconductor wafer fabrication. J Occup Environ Med. 52(11):1075–81. https://doi.org/10.1097/JOM.0b013e3181f6ee1d PMID:21063185

Marchese S, Polo A, Ariano A, Velotto S, Costantini S, Severino L (2018). Aflatoxin B_1 and M_1: biological properties and their involvement in cancer development. Toxins (Basel). 10(6):E214. https://doi.org/10.3390/toxins10060214 PMID:29794965

Maronpot RR, Mitsumori K, Mann P, Takaoka M, Yamamoto S, Usui T, et al. (2000). Interlaboratory comparison of the CB6F_1-Tg rasH2 rapid carcinogenicity testing model. Toxicology. 146(2–3):149–59. https://doi.org/10.1016/S0300-483X(00)00168-2 PMID:10814847

Marouf BH (2018). Association between serum heavy metals level and cancer incidence in Darbandikhan and Kalar Area, Kurdistan Region, Iraq. Niger J Clin Pract. 21(6):766–71. https://doi.org/10.4103/njcp.njcp_384_16 PMID:29888725

Marsà A, Cortés C, Hernández A, Marcos R (2018). Hazard assessment of three haloacetic acids, as byproducts of water disinfection, in human urothelial cells. Toxicol Appl Pharmacol. 347:70–8. https://doi.org/10.1016/j.taap.2018.04.004 PMID:29634955

Marsh GM, Buchanich JM, Zimmerman S, Liu Y, Balmert LC, Graves J, et al. (2017). Mortality among hardmetal production workers: pooled analysis of cohort data from an international investigation. J Occup Environ Med. 59(12):e342–64. https://doi.org/10.1097/JOM.0000000000001151 PMID:29215487

Marsh GM, Youk AO, Collins JJ (2001). Reevaluation of lung cancer risk in the acrylonitrile cohort study of the National Cancer Institute and the National Institute for Occupational Safety and Health. Scand J Work Environ Health. 27(1):5–13. https://doi.org/10.5271/sjweh.581 PMID:11266147

Martel-Jantin C, Pedergnana V, Nicol JT, Leblond V, Trégouët DA, Tortevoye P, et al. (2013). Merkel cell polyomavirus infection occurs during early childhood and is transmitted between siblings. J Clin Virol. 58(1):288–91. https://doi.org/10.1016/j.jcv.2013.06.004 PMID:23829968

Martinez-Valenzuela C, Soto FB, Waliszewski SM, Meza E, Arroyo SG, Martínez LD, et al. (2017). Induced cytotoxic damage by exposure to gasoline vapors: a study in Sinaloa, Mexico. Environ Sci Pollut Res Int. 24(1):539–46. https://doi.org/10.1007/s11356-016-7821-8 PMID:27734313

Massey IY, Yang F, Ding Z, Yang S, Guo J, Tezi C, et al. (2018). Exposure routes and health effects of microcystins on animals and humans: a mini-review. Toxicon. 151:156–62. https://doi.org/10.1016/j.toxicon.2018.07.010 PMID:30003917

Masui T, Mann AM, Garland EM, Cohen SM (1989). Strong promoting activity by uracil on urinary bladder carcinogenesis and a possible inhibitory effect on thyroid tumorigenesis in rats initiated with *N*-methyl-*N*-nitrosourea. Carcinogenesis. 10(8):1471–4. https://doi.org/10.1093/carcin/10.8.1471 PMID:2752521

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/jf103251w PMID:21077678

Matthews GA (2000). Pesticide application methods. 3rd ed. Oxford, UK: Blackwell Science Ltd. https://doi.org/10.1002/9780470760130

Matzenbacher CA, Garcia AL, Dos Santos MS, Nicolau CC, Premoli S, Corrêa DS, et al. (2017). DNA damage induced by coal dust, fly and bottom ash from coal combustion evaluated using the micronucleus test and comet assay in vitro. J Hazard Mater. 324(Pt B):781–8. https://doi.org/10.1016/j.jhazmat.2016.11.062 PMID:27894755

Mazigo HD, Waihenya R, Lwambo NJ, Mnyone LL, Mahande AM, Seni J, et al. (2010). Co-infections with *Plasmodium falciparum*, *Schistosoma mansoni* and intestinal helminths among schoolchildren in endemic areas of northwestern Tanzania. Parasit Vectors. 3(1):44. https://doi.org/10.1186/1756-3305-3-44 PMID:20482866

McBride JM, Sheinson D, Jiang J, Lewin-Koh N, Werner BG, Chow JKL, et al. (2019). Correlation of cytomegalovirus (CMV) disease severity and mortality with CMV viral burden in CMV-seropositive donor and CMV-seronegative solid organ transplant recipients. Open Forum Infect Dis. 6(2):ofz003. https://doi.org/10.1093/ofid/ofz003 PMID:30775403

McCredie M, Stewart JH (1993). Risk factors for kidney cancer in New South Wales. IV. Occupation. Br J Ind Med. 50(4):349–54. https://doi.org/10.1136/oem.50.4.349 PMID:8494775

McElvenny DM, Darnton AJ, Hodgson JT, Clarke SD, Elliott RC, Osman J (2003). Investigation of cancer incidence and mortality at a Scottish semiconductor manufacturing facility. Occup Med (Lond). 53(7):419–30. https://doi.org/10.1093/occmed/kqg111 PMID:14581638

McGlynn AP, Wasson GR, O'Reilly SL, McNulty H, Downes CS, Chang CK, et al. (2013). Low colonocyte folate is associated with uracil misincorporation and global DNA hypomethylation in human colorectum. J Nutr. 143(1):27–33. https://doi.org/10.3945/jn.112.167148 PMID:23190761

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

McGrath KG (2003). An earlier age of breast cancer diagnosis related to more frequent use of antiperspirants/deodorants and underarm shaving. Eur J Cancer Prev. 12(6):479–85. https://doi.org/10.1097/00008469-200312000-00006 PMID:14639125

McGregor D (2006). Methyl tertiary-butyl ether: studies for potential human health hazards. Crit Rev Toxicol. 36(4):319–58. https://doi.org/10.1080/10408440600569938 PMID:16809102

McGregor D (2007). Hydroquinone: an evaluation of the human risks from its carcinogenic and mutagenic properties. Crit Rev Toxicol. 37(10):887–914. https://doi.org/10.1080/10408440701638970 PMID:18027166

McGregor DB, Heseltine E, Møller H (1995). Dry cleaning, some solvents used in dry cleaning and other industrial chemicals. IARC meeting, Lyon, 7-14 February 1995. Scand J Work Environ Health. 21(4):310–2. https://doi.org/10.5271/sjweh.1078 PMID:8553008

McKelvey SM, Horgan KA, Murphy RA (2015). Chemical form of selenium differentially influences DNA repair pathways following exposure to lead nitrate. J Trace Elem Med Biol. 29:151–69. https://doi.org/10.1016/j.jtemb.2014.06.005 PMID:25023848

Megna BW, Carney PR, Nukaya M, Geiger P, Kennedy GD (2016). Indole-3-carbinol induces tumor cell death: function follows form. J Surg Res. 204(1):47–54. https://doi.org/10.1016/j.jss.2016.04.021 PMID:27451867

Meier C, Boche G (1991). The modification of guanine nucleosides and nucleotides by the borderline arylamine carcinogens 4-methyl- and 4-methoxyaniline: chemistry and structural characterization. Carcinogenesis. 12(9):1633–40. https://doi.org/10.1093/carcin/12.9.1633 PMID:1893521

Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH (1994). Occupational risk factors for renal-cell carcinoma in Denmark. Scand J Work Environ Health. 20(3):160–5. https://doi.org/10.5271/sjweh.1413 PMID:7973487

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

Melnick RL, Sills RC (2001). Comparative carcinogenicity of 1,3-butadiene, isoprene, and chloroprene in rats and mice. Chem Biol Interact. 135-136:27–42. https://doi.org/10.1016/S0009-2797(01)00213-7 PMID:11397379

Melnick RL, Sills RC, Roycroft JH, Chou BJ, Ragan HA, Miller RA (1994). Isoprene, an endogenous hydrocarbon and industrial chemical, induces multiple organ neoplasia in rodents after 26 weeks of inhalation exposure. Cancer Res. 54(20):5333–9. PMID:7923161

Mena M, Taberna M, Monfil L, Arbyn M, de Sanjose S, Bosch FX, et al. (2018). May oral HPV in healthy individuals explain differences in HPV-attributable fractions in oropharyngeal cancer? A systematic review and meta-analysis. J Infect Dis. PMID:30590684

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

Meng J, Wang T, Song S, Wang P, Li Q, Zhou Y, et al. (2018). Tracing perfluoroalkyl substances (PFASs) in soils along the urbanizing coastal area of Bohai and Yellow Seas, China. Environ Pollut. 238:404–12. https://doi.org/10.1016/j.envpol.2018.03.056 PMID:29587211

Menya D, Maina SK, Kibosia C, Kigen N, Oduor M, Some F, et al. (2018). Dental fluorosis and oral health in the African esophageal cancer corridor: findings from the Kenya ESCCAPE case-control study and a pan-African perspective. IJC. 145(1):99–109. https://doi.org/10.1002/ijc.32086 PMID:30582155

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

Metayer C, Petridou E, Aranguré JM, Roman E, Schüz J, Magnani C, et al.; MIGICCL Group (2016a). Parental tobacco smoking and acute myeloid leukemia: the Childhood Leukemia International Consortium. Am J Epidemiol. 184(4):261–73. https://doi.org/10.1093/aje/kww018 PMID:27492895

Metayer C, Scelo G, Kang AY, Gunier RB, Reinier K, Lea S, et al. (2016b). A task-based assessment of parental occupational exposure to organic solvents and other compounds and the risk of childhood leukemia in California. Environ Res. 151:174–83. https://doi.org/10.1016/j.envres.2016.06.047 PMID:27494537

Meulepas JM, Ronckers CM, Merks J, Weijerman ME, Lubin JH, Hauptmann M (2016). Confounding of the association between radiation exposure from CT scans and risk of leukemia and brain tumors by cancer susceptibility syndromes. J Radiol Prot. 36(4):953–74. https://doi.org/10.1088/0952-4746/36/4/953 PMID:27893452

Meulepas JM, Ronckers CM, Smets AMJB, Nievelstein RAJ, Gradowska P, Lee C, et al. (2019). Radiation exposure from pediatric CT scans and subsequent cancer risk in the Netherlands. J Natl Cancer Inst. 111(3):256–63. https://doi.org/10.1093/jnci/djy104 PMID:30020493

Miao C, Ren Y, Chen M, Wang Z, Wang T (2016). Microcystin-LR promotes migration and invasion of colorectal cancer through matrix metalloproteinase-13 up-regulation. Mol Carcinog. 55(5):514–24. https://doi.org/10.1002/mc.22298 PMID:25789966

Middha P, Weinstein SJ, Männistö S, Albanes D, Mondul AM (2018). β-Carotene supplementation and lung cancer incidence in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study: the role of tar and nicotine. Nicotine Tob Res. 21(8):1045–50. https://doi.org/10.1093/ntr/nty115 PMID:29889248

Miller AC, Blakely WF, Livengood D, Whittaker T, Xu J, Ejnik JW, et al. (1998). Transformation of human osteoblast cells to the tumorigenic phenotype by depleted uranium-uranyl chloride. Environ Health Perspect. 106(8):465–71. https://doi.org/10.1289/ehp.98106465 PMID:9681973

Miller AC, Bonait-Pellie C, Merlot RF, Michel J, Stewart M, Lison PD (2005). Leukemic transformation of hematopoietic cells in mice internally exposed to depleted uranium. Mol Cell Biochem. 279(1–2):97–104. https://doi.org/10.1007/s11010-005-8226-z PMID:16283518

Miller AC, Brooks K, Smith J, Page N (2004). Effect of the militarily-relevant heavy metals, depleted uranium and heavy metal tungsten-alloy on gene expression in human liver carcinoma cells (HepG2). Mol Cell Biochem.

255(1–2):247–56. https://doi.org/10.1023/B:MCBI.0000007280.72510.96 PMID:14971665

Miller AC, Mog S, McKinney L, Luo L, Allen J, Xu J, et al. (2001a). Neoplastic transformation of human osteoblast cells to the tumorigenic phenotype by heavy metal-tungsten alloy particles: induction of genotoxic effects. Carcinogenesis. 22(1):115–25. https://doi.org/10.1093/carcin/22.1.115 PMID:11159749

Miller AC, Rivas R, Tesoro L, Kovalenko G, Kovaric N, Pavlovic P, et al. (2017). Radiation exposure from depleted uranium: the radiation bystander effect. Toxicol Appl Pharmacol. 331:135–41. https://doi.org/10.1016/j.taap.2017.06.004 PMID:28602947

Miller AC, Stewart M, Rivas R (2009). DNA methylation during depleted uranium-induced leukemia. Biochimie. 91(10):1328–30. https://doi.org/10.1016/j.biochi.2009.03.010 PMID:19324073

Miller AC, Xu J, Stewart M, Brooks K, Hodge S, Shi L, et al. (2002a). Observation of radiation-specific damage in human cells exposed to depleted uranium: dicentric frequency and neoplastic transformation as endpoints. Radiat Prot Dosimetry. 99(1–4):275–8. https://doi.org/10.1093/oxfordjournals.rpd.a006783 PMID:12194305

Miller AC, Xu J, Stewart M, McClain D (2001b). Suppression of depleted uranium-induced neoplastic transformation of human cells by the phenyl fatty acid, phenyl acetate: chemoprevention by targeting the p21RAS protein pathway. Radiat Res. 155(1 Pt 2):163–70. https://doi.org/10.1667/0033-7587(2001)155[0163:SODUIN]2.0.CO;2 PMID:11121229

Miller AC, Xu J, Stewart M, Prasanna PG, Page N (2002b). Potential late health effects of depleted uranium and tungsten used in armor-piercing munitions: comparison of neoplastic transformation and genotoxicity with the known carcinogen nickel. Mil Med. 167(2 Suppl):120–2. https://doi.org/10.1093/milmed/167.suppl_1.120 PMID:11873492

Milne E, Greenop KR, Scott RJ, Bailey HD, Attia J, Dalla-Pozza L, et al. (2012). Parental prenatal smoking and risk of childhood acute lymphoblastic leukemia. Am J Epidemiol. 175(1):43–53. https://doi.org/10.1093/aje/kwr275 PMID:22143821

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

Mirick DK, Davis S, Thomas DB (2002). Antiperspirant use and the risk of breast cancer. J Natl Cancer Inst. 94(20):1578–80. https://doi.org/10.1093/jnci/94.20.1578 PMID:12381712

Mittal V, Kumar S, Pandey A, Singh S (2018). Is *Salmonella enterica* serovar Typhi associated with carcinoma gall bladder? Biomedical Research. 29(8):1617–1620. https://doi.org/10.4066/biomedicalresearch.29-17-263

Mittelstaedt RA, Mei N, Webb PJ, Shaddock JG, Dobrovolsky VN, McGarrity LJ, et al. (2004). Genotoxicity of malachite green and leucomalachite green in female Big Blue B6C3F$_1$ mice. Mutat Res. 561(1–2):127–38. https://doi.org/10.1016/j.mrgentox.2004.04.003 PMID:15238237

Mizumoto A, Ohashi S, Hirohashi K, Amanuma Y, Matsuda T, Muto M (2017). Molecular mechanisms of acetaldehyde-mediated carcinogenesis in squamous epithelium. Int J Mol Sci. 18(9):1943. https://doi.org/10.3390/ijms18091943 PMID:28891965

Mohapatra P, Preet R, Das D, Satapathy SR, Siddharth S, Choudhuri T, et al. (2014). The contribution of heavy metals in cigarette smoke condensate to malignant transformation of breast epithelial cells and in vivo initiation of neoplasia through induction of a PI3K-AKT-NFκB cascade. Toxicol Appl Pharmacol. 274(1):168–79. https://doi.org/10.1016/j.taap.2013.09.028 PMID:24099783

Mona GG, Chimbari MJ, Hongoro C (2019). A systematic review on occupational hazards, injuries and diseases among police officers worldwide: policy implications for the South African Police Service. J Occup Med Toxicol. 14(1):2. https://doi.org/10.1186/s12995-018-0221-x PMID:30679940

Monakhova YB, Lachenmeier DW (2012). The margin of exposure of 5-hydroxymethylfurfural (HMF) in alcoholic beverages. Environ Health Toxicol. 27:e2012016. https://doi.org/10.5620/eht.2012.27.e2012016 PMID:23106038

Mondul AM, Moore SC, Weinstein SJ, Karoly ED, Sampson JN, Albanes D (2015). Metabolomic analysis of prostate cancer risk in a prospective cohort: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study. Int J Cancer. 137(9):2124–32. https://doi.org/10.1002/ijc.29576 PMID:25904191

Monien BH, Schumacher F, Herrmann K, Glatt H, Turesky RJ, Chesné C (2015). Simultaneous detection of multiple DNA adducts in human lung samples by isotope-dilution UPLC-MS/MS. Anal Chem. 87(1):641–8. https://doi.org/10.1021/ac503803m PMID:25423194

Montazeri Z, Nyiraneza C, El-Katerji H, Little J (2017). Waterpipe smoking and cancer: systematic review and meta-analysis. Tob Control. 26(1):92–7. https://doi.org/10.1136/tobaccocontrol-2015-052758 PMID:27165994

Montero J, Morales A, Llacuna L, Lluis JM, Terrones O, Basañez G, et al. (2008). Mitochondrial cholesterol contributes to chemotherapy resistance in hepatocellular carcinoma. Cancer Res. 68(13):5246–56. https://doi.org/10.1158/0008-5472.CAN-07-6161 PMID:18593925

Moolenaar RL, Hefflin BJ, Ashley DL, Middaugh JP, Etzel RA (1994). Methyl tertiary butyl ether in human blood after exposure to oxygenated fuel in Fairbanks, Alaska. Arch Environ Health. 49(5):402–9. https://doi.org/10.1080/00039896.1994.9954993 PMID:7524452

Moorthy B, Chu C, Carlin DJ (2015). Polycyclic aromatic hydrocarbons: from metabolism to lung cancer. Toxicol Sci. 145(1):5–15. https://doi.org/10.1093/toxsci/kfv040 PMID:25911656

Morais ARC, Dworakowska S, Reis A, Gouveia L, Matos CT, Bogdal D, et al. (2015). Chemical and biological-based isoprene production: green metrics. Catal Today. 239:38–43. https://doi.org/10.1016/j.cattod.2014.05.033

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

Moro AM, Brucker N, Charão MF, Baierle M, Sauer E, Goethel G, et al. (2017). Biomonitoring of gasoline station attendants exposed to benzene: effect of gender. Mutat Res. 813:1–9. https://doi.org/10.1016/j.mrgentox.2016.11.002 PMID:28010923

Moro AM, Brucker N, Charão MF, Sauer E, Freitas F, Durgante J, et al. (2015). Early hematological and immunological alterations in gasoline station attendants exposed to benzene. Environ Res. 137:349–56. https://doi.org/10.1016/j.envres.2014.11.003 PMID:25601738

Moser GJ, Foley J, Burnett M, Goldsworthy TL, Maronpot R (2009). Furan-induced dose-response relationships for liver cytotoxicity, cell proliferation, and tumorigenicity (furan-induced liver tumorigenicity). Exp Toxicol Pathol. 61(2):101–11. https://doi.org/10.1016/j.etp.2008.06.006 PMID:18809303

Muegge CM, Zollinger TW, Song Y, Wessel J, Monahan PO, Moffatt SM (2018). Excess mortality among Indiana firefighters, 1985-2013. Am J Ind Med. 61(12):961–7. https://doi.org/10.1002/ajim.22918 PMID:30421827

Mughal BB, Demeneix BA (2017). Endocrine disruptors: flame retardants and increased risk of thyroid cancer. Nat Rev Endocrinol. 13(11):627–8. https://doi.org/10.1038/nrendo.2017.123 PMID:28937689

Mulder JE, Turner PV, Massey TE (2015). Effect of 8-oxoguanine glycosylase deficiency on aflatoxin B_1 tumourigenicity in mice. Mutagenesis. 30(3):401–9. https://doi.org/10.1093/mutage/geu087 PMID:25583175

Multigner L, Kadhel P, Rouget F, Blanchet P, Cordier S (2016). Chlordecone exposure and adverse effects in French West Indies populations. Environ Sci Pollut Res Int. 23(1):3–8. https://doi.org/10.1007/s11356-015-4621-5 PMID:25940496

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

Murai T (2015). Cholesterol lowering: role in cancer prevention and treatment. Biol Chem. 396(1):1–11. https://doi.org/10.1515/hsz-2014-0194 PMID:25205720

Murphy CL, O'Toole PW, Shanahan F (2019). The gut microbiota in causation, detection, and treatment of cancer. Am J Gastroenterol. 114(7):1036–42. https://doi.org/10.14309/ajg.0000000000000075 PMID:30848738

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

Nagaraja V, Eslick GD (2014a). Letter: chronic *Salmonella typhi* carrier status and gall-bladder cancer - authors' reply. Aliment Pharmacol Ther. 39(12):1440. https://doi.org/10.1111/apt.12792 PMID:24849164

Nagaraja V, Eslick GD (2014b). 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

Nahm LS, Chen Y, DeVivo MJ, Lloyd LK (2015). Bladder cancer mortality after spinal cord injury over 4 decades. J Urol. 193(6):1923–8. https://doi.org/10.1016/j.juro.2015.01.070 PMID:25615534

Naiman K, Dracínská H, Martínková M, Sulc M, Dracínský M, Kejíková L, et al. (2008). Redox cycling in the metabolism of the environmental pollutant and suspected human carcinogen *o*-anisidine by rat and rabbit hepatic microsomes. Chem Res Toxicol. 21(8):1610–21. https://doi.org/10.1021/tx8001127 PMID:18624415

Naiman K, Dracínský M, Hodek P, Martínková M, Schmeiser HH, Frei E, et al. (2012). Formation, persistence, and identification of DNA adducts formed by the carcinogenic environmental pollutant *o*-anisidine in rats. Toxicol Sci. 127(2):348–59. https://doi.org/10.1093/toxsci/kfs104 PMID:22403159

Naiman K, Frei E, Stiborova M (2010). Identification of rat cytochromes P450 metabolizing *N*-(2-methoxyphenyl)hydroxylamine, a human metabolite of the environmental pollutants and carcinogens *o*-anisidine and *o*-nitroanisole. Neuro Endocrinol Lett. 31(Suppl 2):36–45. PMID:21187827

Naiman K, Martínková M, Schmeiser HH, Frei E, Stiborová M (2011). Human cytochrome-P450 enzymes metabolize *N*-(2-methoxyphenyl)hydroxylamine, a metabolite of the carcinogens *o*-anisidine and *o*-nitroanisole, thereby dictating its genotoxicity. Mutat Res. 726(2):160–8. https://doi.org/10.1016/j.mrgentox.2011.09.010 PMID:21946300

Nakamura H, Wang Y, Kurita T, Adomat H, Cunha GR, Wang Y (2011). Genistein increases epidermal growth factor receptor signaling and promotes tumor progression in advanced human prostate cancer. PLoS One. 6(5):e20034. https://doi.org/10.1371/journal.pone.0020034 PMID:21603581

Nakanishi T (2008). Endocrine disruption induced by organotin compounds; organotins function as a powerful agonist for nuclear receptors rather than an aromatase inhibitor. J Toxicol Sci. 33(3):269–76. https://doi.org/10.2131/jts.33.269 PMID:18670157

Nakano M, Omae K, Takebayashi T, Tanaka S, Koda S (2018). An epidemic of bladder cancer: ten cases of bladder cancer in male Japanese workers exposed to *ortho*-toluidine. J Occup Health. 60(4):307–11. https://doi.org/10.1539/joh.2017-0220-OA PMID:29743389

Nalwoga A, Cose S, Nash S, Miley W, Asiki G, Kusemererwa S, et al. (2018). Relationship between anaemia, malaria co-infection and Kaposi's sarcoma-associated herpesvirus (KSHV) seropositivity in a population-based study in rural Uganda. J Infect Dis. 218(7):1061–5. https://doi.org/10.1093/infdis/jiy274 PMID:29741631

Nalwoga A, Cose S, Wakeham K, Miley W, Ndibazza J, Drakeley C, et al. (2015). Association between malaria exposure and Kaposi's sarcoma-associated herpes virus seropositivity in Uganda. Trop Med Int Health. 20(5):665–72. https://doi.org/10.1111/tmi.12464 PMID:25611008

Nambiar DK, Rajamani P, Deep G, Jain AK, Agarwal R, Singh RP (2015). Silibinin preferentially radiosensitizes prostate cancer by inhibiting DNA repair signaling. Mol Cancer Ther. 14(12):2722–34. https://doi.org/10.1158/1535-7163.MCT-15-0348 PMID:26516160

Nardone B, Majewski S, Kim AS, Kiguradze T, Martinez-Escala EM, Friedland R, et al. (2017). Melanoma and non-melanoma skin cancer associated with angiotensin-converting-enzyme inhibitors, angiotensin-receptor

blockers and thiazides: a matched cohort study. Drug Saf. 40(3):249–55. https://doi.org/10.1007/s40264-016-0487-9 PMID:27943160

Nath G, Gulati AK, Shukla VK (2010). Role of bacteria in carcinogenesis, with special reference to carcinoma of the gallbladder. World J Gastroenterol. 16(43):5395–404. https://doi.org/10.3748/wjg.v16.i43.5395 PMID:21086555

Nath G, Singh H, Shukla VK (1997). Chronic typhoid carriage and carcinoma of the gallbladder. Eur J Cancer Prev. 6(6):557–9. https://doi.org/10.1097/00008469-199712000-00011 PMID:9496458

National Clinical Guideline Centre UK (2014). Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. PMID:25340243.

National Research Council (2010). Review of the Environmental Protection Agency's draft IRIS assessment of tetrachloroethylene. Washington (DC), USA: National Academies Press. Available from: https://doi.org/10.17226/12863.

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

NCI (1978a). Bioassay for aniline hydrochloride for possible carcinogenicity (CAS No. 142-04-1). Natl Cancer Inst Carcinog Tech Rep Ser. 130:1–115. PMID:12799662

NCI (1978b). Bioassay of *o*-anisidine hydrochloride for possible carcinogenicity (CAS No. 134-29-2). Natl Cancer Inst Carcinog Tech Rep Ser. 89:1–149. PMID:12806402

NCI (2017). Acrylamide and cancer risk. Available from: https://www.cancer.gov/about-cancer/causes-prevention/risk/diet/acrylamide-fact-sheet.

NCI (2019). Anthracycline. NCI dictionary of cancer terms. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/anthracycline.

NCTR (2015). Technical Report for NCTR Experiment No. E2168.01 (Test No. E2168.02) Two-year carcinogenicity bioassay of furan in F344 rats. Washington (DC), USA: National Centre for Toxicological Research.

Ndeffo Mbah ML, Skrip L, Greenhalgh S, Hotez P, Galvani AP (2014). Impact of *Schistosoma mansoni* on malaria transmission in sub-Saharan Africa. PLoS Negl Trop Dis. 8(10):e3234. https://doi.org/10.1371/journal.pntd.0003234 PMID:25329403

Negro F (2014). Hepatitis D virus coinfection and superinfection. Cold Spring Harb Perspect Med. 4(11):a021550. https://doi.org/10.1101/cshperspect.a021550 PMID:25368018

Nelson ER, Wardell SE, Jasper JS, Park S, Suchindran S, Howe MK, et al. (2013). 27-Hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology. Science. 342(6162):1094–8. https://doi.org/10.1126/science.1241908 PMID:24288332

Neuhouser ML, Barnett MJ, Kristal AR, Ambrosone CB, King IB, Thornquist M, et al. (2009). Dietary supplement use and prostate cancer risk in the Carotene and Retinol Efficacy Trial. Cancer Epidemiol Biomarkers Prev. 18(8):2202–6. https://doi.org/10.1158/1055-9965.EPI-09-0013 PMID:19661078

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

Newton R, Labo N, Wakeham K, Marshall V, Roshan R, Nalwoga A, et al. (2018b). Determinants of gamma-herpesvirus shedding in saliva among Ugandan children and their mothers. J Infect Dis. 218(6):892–900. https://doi.org/10.1093/infdis/jiy262 PMID:29762709

Newton R, Labo N, Wakeham K, Miley W, Asiki G, Johnston WT, et al. (2018a). Kaposi sarcoma-associated herpesvirus in a rural Ugandan cohort, 1992-2008. J Infect Dis. 217(2):263–9. https://doi.org/10.1093/infdis/jix569 PMID:29099933

NHS Digital (2018). Breast and Cosmetic Implant Registry: October 2016 to June 2018 data summary. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/mi-breast-and-cosmetic-implant-registry/first-data-report-from-the-breast-and-cosmetic-implant-registry.

Nichols L, Sorahan T (2005). Cancer incidence and cancer mortality in a cohort of UK semiconductor workers, 1970-2002. Occup Med (Lond). 55(8):625–30. https://doi.org/10.1093/occmed/kqi156 PMID:16234257

Nickerson KP, Senger S, Zhang Y, Lima R, Patel S, Ingano L, et al. (2018). *Salmonella* Typhi colonization provokes extensive transcriptional changes aimed at evading host mucosal immune defense during early infection of human intestinal tissue. EBioMedicine. 31:92–109. https://doi.org/10.1016/j.ebiom.2018.04.005 PMID:29735417

NIOSH (1983). National Occupational Exposure Survey (1981–1983). Estimated numbers of employees potentially exposed to specific agents by 2-digit Standard Industrial Classification (SIC): glycerol. Available from: https://web.archive.org/web/20111026171131/http://www.cdc.gov/noes/noes1/35085sic.html.

NIOSH (2006). International safety cards. o-Benzyl-p-chlorophenol. CAS No. 120-32-4. Available from: http://www.cdc.gov/noes/, accessed 21 February 2019.

NIOSH (2007). NIOSH pocket guide to chemical hazards. DHHS (NIOSH) Publication No. 2005-149. Cincinnati (OH), USA: National Institute for Occupational Safety and Health. Available from: https://www.cdc.gov/niosh/docs/2005-149/pdfs/2005-149.pdf.

NIOSH (2011). Aniline (and HO. Cincinnati (OH), USA: National Institute for Occupational Safety and Health. Available from: https://www.cdc.gov/niosh/pel88/62-53.html, accessed 15 March 2019.

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

Nordlinder R, Järvholm B (1997). Environmental exposure to gasoline and leukemia in children and young adults – an ecology study. Int Arch Occup Environ Health. 70(1):57–60. https://doi.org/10.1007/s004200050186 PMID:9258708

Noto JM, Chopra A, Loh JT, Romero-Gallo J, Piazuelo MB, Watson M, et al. (2018). Pan-genomic analyses identify key *Helicobacter pylori* pathogenic loci modified by carcinogenic host microenvironments. Gut. 67(10):1793–804. https://doi.org/10.1136/gutjnl-2017-313863 PMID:28924022

Nowak A, Giger RS, Krayenbuehl PA (2018). Higher age at diagnosis of hemochromatosis is the strongest predictor of the occurrence of hepatocellular carcinoma in the Swiss hemochromatosis cohort: a prospective longitudinal observational study. Medicine (Baltimore). 97(42):e12886. https://doi.org/10.1097/MD.0000000000012886 PMID:30335010

NTP (1978a). Bioassay of cupferron for possible carcinogenicity (CAS No. 135-20-6). Natl Cancer Inst Carcinog Tech Rep Ser. 100:1–131. PMID:12806391

NTP (1978b). Bioassay of hydrazobenzene for possible carcinogenicity. Natl Cancer Inst Carcinog Tech Rep Ser. 92:1–123. PMID:12806399

NTP (1978c). Bioassay of *p*-anisidine hydrochloride for possible carcinogenicity (CAS No. 20265-97-8). Natl Cancer Inst Carcinog Tech Rep Ser. 116:1–115. PMID:12799675

NTP (1980). Bioassay of selenium sulfide for possible carcinogenicity. Natl Cancer Inst Carcinog Tech Rep Ser. 194:1–122. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr194.pdf.

NTP (1985). NTP toxicology and carcinogenesis studies of dimethyl hydrogen phosphite (CAS No. 868-85-9) in F344/N rats and B6C3F$_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 287:1–180. PMID:12748716

NTP (1986a). NTP toxicology and carcinogenesis studies of chlorinated paraffins (C23, 43% Chlorine) in F344/N rats and B6C3F$_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 305:1–202. PMID:12748724

NTP (1986b). NTP toxicology and carcinogenesis studies of dimethyl morpholinophosphoramidate (CAS No. 597-25-1) in F344/N rats and B6C3F$_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 298:1–186. PMID:12748708

NTP (1986c). NTP toxicology and carcinogenesis studies of isophorone (CAS No. 78-59-1) in F344/N rats and B6C3F$_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 291:1–198. PMID:12748713

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. PMID:12724781

NTP (1989b). NTP toxicology and carcinogenesis study of *N*-methylolacrylamide in F344/N rats and B6C3F$_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 352:1–204. PMID:12704432

NTP (1990). Toxicology and carcinogenesis studies of furfural (CAS No. 98-01-1) in Fischer 344/N rats and B6C3F$_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 382:1–201. PMID:12692654.

NTP (1991). NTP toxicology and carcinogenesis studies of tris(2-chloroethyl) phosphate (CAS No. 115-96-8) in F344/N rats and B6C3F$_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 391:1–233. PMID:12637968

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. PMID:12616287

NTP (1994b). NTP toxicology and carcinogenesis studies of C.I. Direct Blue 218 (CAS No. 28407-37-6) in F344/N rats and B6C3F$_1$ mice (feed studies). Natl Toxicol Program Tech Rep Ser. 430:1–280. PMID:12616301

NTP (1994c). 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. PMID:12595923

NTP (1995a). 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. PMID:12595919

NTP (1995b). 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. PMID:12595927

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. PMID:12571678

NTP (1999b). NTP toxicology and carcinogenesis studies of isoprene (CAS No. 78-79-5) in F344/N rats (inhalation studies). Natl Toxicol Program Tech Rep Ser. 486:1–176. PMID:12571689

NTP (1999c). Toxicology and carcinogenesis studies of AZT (CAS No. 30516-87-1) and AZT/α-interferon A/D in B6C3F$_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 469:1–361. PMID:12579204

NTP (2001). Toxicology and carcinogenesis studies of acrylonitrile (CAS No. 107-13-1) in B3C3F$_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 506:1–201. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr506.pdf PMID: 11803701.

NTP (2002a). Toxicology and carcinogenesis studies of o-nitrotoluene sulfone (CAS No. 88-72-2) in F344/N rats and B6C3F$_1$ mice (feed studies). Natl Toxicol Program Tech Rep Ser. 504:1–357. Available from: https://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr500580/listedreports/tr504/index.html PMID:12087420

NTP (2002b). Toxicology and carcinogenesis studies of p-nitrotoluene in F344/N rats and B6C3F$_1$ mice (feed studies). Natl Toxicol Program Tech Rep Ser. 498:1–277. Available from: https://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr400499/abstracts/tr498/index.html PMID:12118261

NTP (2002c). NTP technical report on the toxicity studies of p-*tert*-butylcatechol (CAS No. 98-29-3) administered in feed to F344/N rats and B6C3F$_1$ mice. Toxic Rep Ser. (70):5–51. PMID:12592414

NTP (2003). Toxicology and carcinogenesis studies of riddelliine (CAS No. 23246-96-0) in F344/N rats and B6C3F$_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. (508):1–280. PMID:12844193

NTP (2005a). Studies of malachite green chloride and leucomalachite green. Natl Toxicol Program Tech Rep Ser. 527. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr527.pdf.

NTP (2005b). NTP report on the toxicology studies of aspartame in genetically modified (FVB Tg.AC HEMIZYGOUS) and B6.129-Cdkn2atm1Rdp (N2) deficient mice and carcinogenicity studies of aspartame in genetically modified [B6.129-Trp53tm1Brd (N5) haploinsufficient] mice (feed studies). NTP GMM 1, NIH Publication No. 06–4459. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/gmm_rpts/gmm1.pdf.

NTP (2005c). Butylparaben [CAS No. 94-26-8]: review of toxicological literature. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/chem_background/exsumpdf/butylparaben_508.pdf.

NTP (2007a). Toxicology and carcinogenesis study of genistein in Sprague-Dawley rats (feed study). Natl Toxicol Program Tech Rep Ser. 545. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr545.pdf.

NTP (2007b). Toxicology and carcinogenesis studies of methyl isobutyl ketone in F344/N rats and B6C3F$_1$ mice (inhalation studies). Natl Toxicol Program Tech Rep Ser. 538. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr538.pdf.

NTP (2008). Final report on carcinogens background document for *o*-nitrotoluene. Rep Carcinog Backgr Doc. (8-5975):i–xviii, 1–102. PMID:20737007

NTP (2010a). 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. 1(560):1, 7–31, 33–171 passim. PMID:21037592

NTP (2010b). NTP toxicology and carcinogenesis studies of 5-(hydroxymethyl)-2-furfural (CAS No. 67-47-0) in F344/N rats and B6C3F$_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. (554):7–13, 15–9, 21–31 passim. Available from: http://ntp.niehs.nih.gov/?objectid=793A39F7-F1F6-975E-761D9DAC33E41B3F PMID:20725154

NTP (2010c). NTP toxicology and carcinogenesis studies of isoeugenol (CAS NO. 97-54-1) in F344/N rats and B6C3F$_1$ mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 551:1–178. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr551.pdf.

NTP (2010d). Toxicology and carcinogenesis studies of goldenseal root powder (*Hydrastis canadensis*) in F344/N rats and B6C3F$_1$ mice (feed studies). Natl Toxicol Program Tech Rep Ser. 562:1–188. PMID:21372858

NTP (2011a). NTP toxicology and carcinogenesis studies of milk thistle extract (CAS No. 84604-20-6) in F344/N rats and B6C3F$_1$ mice (feed studies). Natl Toxicol Program Tech Rep Ser. 565:1–178. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr565.pdf.

NTP (2011b). Amitrole. NTP 12th report on carcinogens. Rep Carcinog. 12:42–3. PMID:21829250

NTP (2011c). o-Nitrotoluene. NTP 12th report on carcinogens. Available from: https://ntp.niehs.nih.gov/ntp/roc/twelfth/2010/finalbds/o-nt-final_508.pdf.

NTP (2011d). Isoprene. NTP 12th report on carcinogens. Rep Carcinog. 12:247–50. PMID:21852856

NTP (2011e). Kepone. NTP 12th report on carcinogens. 14th ed. Rep Carcinog. 12:250–1.

NTP (2012a). Testing status of tris(chloropropyl)phosphate M20263. Available from: https://ntp.niehs.nih.gov/testing/status/agents/ts-m20263.html.

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. PMID:22837102

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. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr588_508.pdf.

NTP (2015a). NTP toxicology studies of bromodichloroacetic acid in F344/N rats and B6C3F$_1$/N mice and toxicology and carcinogenesis studies of bromodichloroacetic acid in F344/NTac rats and B6C3F$_1$/N mice (drinking water studies). Natl Toxicol Program Tech Rep Ser. 583. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr583_508.pdf.

NTP (2015b). NTP toxicology and carcinogenesis 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). Natl Toxicol Program Tech Rep Ser. 586.

NTP (2016a). Cupferron. Report on carcinogens. 14th ed. Research Triangle Park (NC), USA: United States Department of Health and Human Services, Public Health Service. Available from: https://ntp.niehs.nih.gov/go/roc14.

NTP (2016b). Hydrazobenzene. Report on carcinogens. 14th ed. Research Triangle Park (NC), USA: United States Department of Health and Human Services, Public Health Service. Available from: https://ntp.niehs.nih.gov/go/roc14.

NTP (2016c). Toxicology studies of a pentabromodiphenyl ether mixture [DE-71 (technical grade)] 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 B6C3F$_1$/N mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 589. Available from: https://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr500580/listedreports/tr589/index.html.

NTP (2016d). Oxymetholone. Report on carcinogens. 14th ed. Research Triangle Park (NC), USA: US Department of Health and Human Services, Public Health Service. Available from: http://ntp.niehs.nih.gov/ntp/roc/content/profiles/tetrachlorodibenzodioxin.pdf.

NTP (2016e). Research report on organotin and total tin levels in Danish women of reproductive age. National Toxicology Program National Institute of Environmental Health Sciences. https://ntp.niehs.nih.gov/ntp/results/pubs/rr/reports/rr02_508.pdf

NTP (2016f). 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). Natl Toxicol Program Tech Rep Ser. 591. Available from: https://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2016/february/tr591_peerdraft.pdf.

NTP (2016g). Profile: acrylonitrile. Report on carcinogens. 14th ed. Research Triangle Park (NC), USA: United States Department of Health and Human Services, Public Health Service. Available from: https://ntp.niehs.nih.gov/ntp/roc/content/profiles/acrylonitrile.pdf.

NTP (2016h). Cumene. Report on carcinogens. 14th ed. Research Triangle Park (NC), USA: US Department of Health and Human Services, Public Health Service. Available from: https://ntp.niehs.nih.gov/go/roc14.

NTP (2016i). Riddelliine. Report on carcinogens. 14th ed. Research Triangle Park (NC), USA: US Department of Health and Human Services, Public Health Service. Available from: https://ntp.niehs.nih.gov/go/roc14.

NTP (2016j). Cobalt and cobalt compounds that release cobalt ions in vivo. Report on carcinogens. 14th ed. Research Triangle Park (NC), USA: US Department of Health and Human Services, Public Health Service. Available from: http://ntp.niehs.nih.gov/go/roc.

NTP (2016k). Nickel compounds and metallic nickel. Report on carcinogens. 14th ed. Research Triangle Park (NC), USA: US Department of Health and Human Services, Public Health Service; 4 pp.

NTP (2016l). 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 B6C3F$_1$/N mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 589. Available from: http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr589_508.pdf.

NTP (2016m). Review of Merkel cell polyomavirus (MCV). Report on carcinogens. 14th ed. Research Triangle Park (NC), USA: US Department of Health and Human Services, Public Health Service. Available from: https://ntp.niehs.nih.gov/pubhealth/roc/listings/mcv/.

NTP (2016n). Cobalt. Report on carcinogens. 14th ed. Research Triangle Park (NC), USA: US Department of Health and Human Services, Public Health Service. Available from: https://ntp.niehs.nih.gov/ntp/roc/content/profiles/cobalt.pdf.

NTP (2017). Toxicology studies of indole-3-carbinol in F344/N rats and B6C3F$_1$/N mice and toxicology and carcinogenesis studies of indole-3-carbinol in Harlan Sprague Dawley rats and B6C3F$_1$/N mice (gavage studies). Natl Toxicol Program Tech Rep Ser. 584. Available from: https://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr500580/listedreports/tr584/index.html.

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: US Department of Health and Human Services, Public Health Service. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr596_508.pdf.

NTP (2018b). Toxicology and carcinogenesis studies in Hsd:Sprague Dawley SD rats exposed to whole-body radiofrequency radiation at a frequency (900MHz) and modulations (GSM and CDMA) used by cellphones. Natl

Toxicol Program Tech Rep Ser. 595. Research Triangle Park (NC), USA: US Department of Health and Human Services, Public Health Service. Available from: https://www.niehs.nih.gov/ntp-temp/tr595_508.pdf.

NTP (2018c). NTP toxicology and carcinogenesis studies of 2,3-butanedione (CAS No. 431-03-8) in Wistar Han [Crl:WI (Han)] rats and B6C3F$_1$/N mice (inhalation studies). Natl Toxicol Program Tech Rep Ser, 593:1–198. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr593_508.pdf.

NTP (2018d). NTP research report on the CLARITY-BPA core study: a perinatal and chronic extended-dose-range study of bisphenol A in rats. Research Triangle Park (NC), USA: National Toxicology Program; pp. 1–221. Available from: https://ntp.niehs.nih.gov/results/pubs/rr/reports/abstracts/rr09/index.html.

NTP (2018e). Monograph on haloacetic acids found as water disinfection by-products. Report on carcinogens. Research Triangle Park (NC), USA: US Department of Health and Human Services, Public Health Service. Available from: https://ntp.niehs.nih.gov/ntp/roc/monographs/haafinal_508.pdf, accessed 18 March 2019.

NTP (2018f). Genetic toxicity evaluation of 1,1,1-trichloroethane (71-55-6) in micronucleus study B09633 in B6C3F$_1$ mice. Research Triangle Park (NC), USA: US Department of Health and Human Services, Public Health Service. Available from: https://tools.niehs.nih.gov/cebs3/views/index.cfm?action=main.dataReview&bin_id=10491.

NTP (2018g). Monograph on antimony trioxide. Report on carcinogens. Research Triangle Park (NC), USA: US Department of Health and Human Services, Public Health Service. Available from: https://ntp.niehs.nih.gov/ntp/roc/monographs/antimony_final20181019_508.pdf.

NTP (2019a). Testing status of butyl paraben M88007. Available from: https://ntp.niehs.nih.gov/testing/status/agents/ts-m88007.html.

NTP (2019b). Testing status of silymarin. Available from: https://ntp.niehs.nih.gov/testing/status/agents/ts-m990027.html.

NTP (2019c). Testing status of 1020 long multiwalled carbon nanotube M070062. Research Triangle Park (NC), USA: US Department of Health and Human Services. Available from: https://ntp.niehs.nih.gov/testing/status/agents/ts-m070062.html.

NTP (2019d). Testing status of perfluorooctanoic acid M910070. Available from: https://ntp.niehs.nih.gov/testing/status/agents/ts-m910070.html.

NTP (2019e). Testing status of tris(chloropropyl) phosphate (TCPP) M20263. Available from: https://ntp.niehs.nih.gov/testing/status/agents/ts-m20263.html.

NTP (2019f). Ongoing tungsten bioassay at NTP. Available from: https://ntp.niehs.nih.gov/testing/status/agents/ts-m030038.html.

NTP (2019g). TR-597: 2-Hydroxy-4-methoxybenzophenone. Available from: https://tools.niehs.nih.gov/cebs3/views/index.cfm?action=main.dataReview&bin_id=3114. 77

Núñez O, Fernández-Navarro P, Martín-Méndez I, Bel-Lan A, Locutura Rupérez JF, López-Abente G (2017). Association between heavy metal and metalloid levels in topsoil and cancer mortality in Spain. Environ Sci Pollut Res Int. 24(8):7413–21. https://doi.org/10.1007/s11356-017-8418-6 PMID:28108922

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 PMID:6726483

Nwogu N, Boyne JR, Dobson SJ, Poterlowicz K, Blair GE, Macdonald A, et al. (2018). Cellular sheddases are induced by Merkel cell polyomavirus small tumour antigen to mediate cell dissociation and invasiveness. PLoS Pathog. 14(9):e1007276. https://doi.org/10.1371/journal.ppat.1007276 PMID:30188954

O'Callaghan JP, Daughtrey WC, Clark CR, Schreiner CA, White R (2014). Health assessment of gasoline and fuel oxygenate vapors: neurotoxicity evaluation. Regul Toxicol Pharmacol. 70(2 Suppl):S35–42. https://doi.org/10.1016/j.yrtph.2014.05.002 PMID:24879970

Oberg M, Jaakkola MS, Woodward A, Peruga A, Prüss-Ustün A (2011). Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. Lancet. 377(9760):139–46. https://doi.org/10.1016/S0140-6736(10)61388-8 PMID:21112082

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 PMID:26376083

Odashima S (1980). Cooperative programme on long-term assays for carcinogenicity in Japan. In: Montesano R, Bartsch H, Tomatis L. Molecular and cellular aspects of carcinogen screening tests (IARC Scientific Publications, No. 27). Lyon, France: International Agency for Research on Cancer; pp. 315–22.

OECD (2002). Co-operation on existing chemicals. Hazard assessment of perfluorooctane sulfonate (PFOS) and its salts. Joint meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. Paris, France: Environment Directorate, Organisation for Economic Co-operation and Development. Available from: http://www.oecd.org/dataoecd/23/18/2382880.pdf.

OECD (2004a). *n*-Butyl methacrylate. CAS No. 97-88-1. Summary conclusions of the SIAR. SIDS initial assessment profile, SIAM. 18:20–3.

OECD (2004b). Screening information dataset. Dimethyl phosphonate, CAS No. 868-85-9. SIDS Initial Assessment Report for SIAM 18. Paris, France: Organisation for Economic Co-operation and Development. Available from: https://hpvchemicals.oecd.org/ui/handler.axd?id=c015122a-4f95-4619-b643-55e4fbd5e38e.

OECD (2009). The 2007 OECD list of high production volume chemicals. Environment Directorate, Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. OECD Environment, Health and Safety Publications Series on Testing and Assessment No. 112. Report No. ENV/JM/MONO(2009)40. Paris, France: Environment Directorate, Organisation for Economic Co-operation and Development.

OECD (2011). Screening information dataset. SIDS initial assessment profile. Dichloromethane. Paris, France: Organisation for Economic Co-operation and Development. Available from: https://hpvchemicals.oecd.org/ui/handler.axd?id=B8EA971C-0C2C-4976-8706-A9A68033DAA0, accessed 17 March 2019.

OEHHA (1999). Health effects of exposure to methyl tertiary butyl ether (MTBE). California Office of Environmental Health Hazard Assessment. Available from: https://oehha.ca.gov/media/downloads/air/document/mtbeta1.pdf, accessed 18 March 2019.

OEHHA (2009). Bromate. California Office of Environmental Health Hazard Assessment. Available from: https://oehha.ca.gov/chemicals/bromate.

OEHHA (2019a). Aniline. California Office of Environmental Health Hazard Assessment. Available from: https://oehha.ca.gov/chemicals/aniline.

OEHHA (2019b). Furmecyclox. California Office of Environmental Health Hazard Assessment. Available from: https://oehha.ca.gov/chemicals/furmecyclox.

Offermans NSM, Ketcham SM, van den Brandt PA, Weijenberg MP, Simons CCJM (2018). Alcohol intake, *ADH1B* and *ADH1C* genotypes, and the risk of colorectal cancer by sex and subsite in the Netherlands Cohort Study. Carcinogenesis. 39(3):375–88. https://doi.org/10.1093/carcin/bgy011 PMID:29390059

Ohnishi M, Umeda Y, Katagiri T, Kasai T, Ikawa N, Nishizawa T, et al. (2013). Inhalation carcinogenicity of 1,1,1-trichloroethane in rats and mice. Inhal Toxicol. 25(5):298–306. https://doi.org/10.3109/08958378.2013.780116 PMID:23614731

Ohno S, Nakajima Y, Inoue K, Nakazawa H, Nakajin S (2003). Genistein administration decreases serum corticosterone and testosterone levels in rats. Life Sci. 74(6):733–42. https://doi.org/10.1016/j.lfs.2003.04.006 PMID:14654166

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 PMID:11470755

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 PMID:24468856

Oji C, Chukwuneke F (2012). Poor oral hygiene may be the sole cause of oral cancer. J Maxillofac Oral Surg. 11(4):379–83. https://doi.org/10.1007/s12663-012-0359-5 PMID:24293926

Okubo T, Yokoyama Y, Kano K, Soya Y, Kano I (2004). Estimation of estrogenic and antiestrogenic activities of selected pesticides by MCF-7 cell proliferation assay. Arch Environ Contam Toxicol. 46(4):445–53. https://doi.org/10.1007/s00244-003-3017-6 PMID:15253041

Olin GR (1978). The hazards of a chemical laboratory environment – a study of the mortality in two cohorts of Swedish chemists. Am Ind Hyg Assoc J. 39(7):557–62. https://doi.org/10.1080/0002889778507808 PMID:567938

Olin GR, Ahlbom A (1980). The cancer mortality among Swedish chemists graduated during three decades. A comparison with the general population and with a cohort of architects. Environ Res. 22(1):154–61. https://doi.org/10.1016/0013-9351(80)90127-9 PMID:7418674

Olin GR, Ahlbom A (1982). Cancer mortality among three Swedish male academic cohorts: chemists, architects, and mining engineers/metallurgists. Ann N Y Acad Sci. 381(1):197–201. https://doi.org/10.1111/j.1749-6632.1982.tb50385.x PMID:6953790

Oliveira M, Delerue-Matos C, Morais S, Slezakova K, Pereira MC, Fernandes A, et al. (2018). Levels of urinary biomarkers of exposure and potential genotoxic risks in firefighters. Occupational Safety and Hygiene VI - Selected contributions from the International Symposium Occupational Safety and Hygiene, SHO 2018.

Olivero OA (2007). Mechanisms of genotoxicity of nucleoside reverse transcriptase inhibitors. Environ Mol Mutagen. 48(3–4):215–23. https://doi.org/10.1002/em.20195 PMID:16395695

Ollberding NJ, Lim U, Wilkens LR, Setiawan VW, Shvetsov YB, Henderson BE, et al. (2012). Legume, soy, tofu, and isoflavone intake and endometrial cancer risk in postmenopausal women in the Multiethnic Cohort Study. J Natl Cancer Inst. 104(1):67–76. https://doi.org/10.1093/jnci/djr475 PMID:22158125

Olsson AC, Fevotte J, Fletcher T, Cassidy A, 't Mannetje A, Zaridze D, et al. (2010). Occupational exposure to polycyclic aromatic hydrocarbons and lung cancer risk: a multicenter study in Europe. Occup Environ Med. 67(2):98–103. https://doi.org/10.1136/oem.2009.046680 PMID:19773276

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. PMID:18225543

Omar HH, Taha SA, Hassan WH, Omar HH (2017). Impact of schistosomiasis on increase incidence of occult hepatitis B in chronic hepatitis C patients in Egypt. J Infect Public Health. 10(6):761–5. https://doi.org/10.1016/j.jiph.2016.11.010 PMID:28196636

Onoda A, Umezawa M, Takeda K, Ihara T, Sugamata M (2014). Effects of maternal exposure to ultrafine carbon black on brain perivascular macrophages and surrounding astrocytes in offspring mice. PLoS One. 9(4):e94336. https://doi.org/10.1371/journal.pone.0094336 PMID:24722459

Ose J, Fortner RT, Rinaldi S, Schock H, Overvad K, Tjonneland A, et al. (2015). Endogenous androgens and risk of epithelial invasive ovarian cancer by tumor characteristics in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 136(2):399–410. https://doi.org/10.1002/ijc.29000 PMID:24890047

Osimitz TG, Lake BG (2009). Mode-of-action analysis for induction of rat liver tumors by pyrethrins: relevance to human cancer risk. Crit Rev Toxicol. 39(6):501–11. https://doi.org/10.1080/10408440902914014 PMID:19463055

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 PMID:23116185

Palumbo E (2007). Association between schistosomiasis and cancer. Infect Dis Clin Pract. 15(3):145–8. https://doi.org/10.1097/01.idc.0000269904.90155.ce

Pan WC, Wu CD, Chen MJ, Huang YT, Chen CJ, Su HJ, et al. (2015). Fine particle pollution, alanine transaminase, and liver cancer: a Taiwanese prospective cohort study (REVEAL-HBV). J Natl Cancer Inst. 108(3): https://doi.org/10.1093/jnci/djv341 PMID:26561636

Pandey M, Shukla VK (2003). Lifestyle, parity, menstrual and reproductive factors and risk of gallbladder cancer. Eur J Cancer Prev. 12(4):269–72. https://doi.org/10.1097/00008469-200308000-00005 PMID:12883378

Pang B, Qiao X, Janssen L, Velds A, Groothuis T, Kerkhoven R, et al. (2013). Drug-induced histone eviction from open chromatin contributes to the chemotherapeutic effects of doxorubicin. Nat Commun. 4(1):1908. https://doi.org/10.1038/ncomms2921 PMID:23715267

Park AS, Ritz B, Ling C, Cockburn M, Heck JE (2017). Exposure to ambient dichloromethane in pregnancy and infancy from industrial sources and childhood cancers in California. Int J Hyg Environ Health. 220(7):1133–40. https://doi.org/10.1016/j.ijheh.2017.06.006 PMID:28720343

Park D (2018). 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 PMID:30370156

Park DE, Cheng J, Berrios C, Montero J, Cortés-Cros M, Ferretti S, et al. (2019). Dual inhibition of MDM2 and MDM4 in virus-positive Merkel cell carcinoma enhances the p53 response. Proc Natl Acad Sci USA. 116(3):1027–32. https://doi.org/10.1073/pnas.1818798116 PMID:30598450

Park MA, Hwang KA, Lee HR, Yi BR, Jeung EB, Choi KC (2013). Benzophenone-1 stimulated the growth of BG-1 ovarian cancer cells by cell cycle regulation via an estrogen receptor alpha-mediated signaling pathway in cellular and xenograft mouse models. Toxicology. 305:41–8. https://doi.org/10.1016/j.tox.2012.12.021 PMID:23328252

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 PMID:11301474

Parodi S, Pala M, Russo P, Zunino A, Balbi C, Albini A, et al. (1982). DNA damage in liver, kidney, bone marrow, and spleen of rats and mice treated with commercial and purified aniline as determined by alkaline elution assay and sister chromatid exchange induction. Cancer Res. 42(6):2277–83. PMID:7074610

Partanen T, Heikkilä P, Hernberg S, Kauppinen T, Moneta G, Ojajärvi A (1991). Renal cell cancer and occupational exposure to chemical agents. Scand J Work Environ Health. 17(4):231–9. https://doi.org/10.5271/sjweh.1708 PMID:1925434

Pasquereau S, Al Moussawi F, Karam W, Diab Assaf M, Kumar A, Herbein G (2017). Cytomegalovirus, macrophages and breast cancer. Open Virol J. 11(1):15–27. https://doi.org/10.2174/1874357901711010015 PMID:28567162

Patel AS, Talbott EO, Zborowski JV, Rycheck JA, Dell D, Xu X, et al. (2004). Risk of cancer as a result of community exposure to gasoline vapors. Arch Environ Health. 59(10):497–503. https://doi.org/10.1080/00039890409605165 PMID:16425659

Patel S (2017). Fragrance compounds: the wolves in sheep's clothings. Med Hypotheses. 102:106–11. https://doi.org/10.1016/j.mehy.2017.03.025 PMID:28478814

Patlewicz G, Richard AM, Williams AJ, Grulke CM, Sams R, Lambert J, et al. (2019). A chemical category-based prioritization approach for selecting 75 per- and polyfluoroalkyl substances (PFAS) for tiered toxicity and toxicokinetic testing. Environ Health Perspect. 127(1):14501. https://doi.org/10.1289/EHP4555 PMID:30632786

Paton GR, Allison AC (1972). Chromosome damage in human cell cultures induced by metal salts. Mutat Res. 16(3):332–6. https://doi.org/10.1016/0027-5107(72)90166-2 PMID:5078138

Patra AK, Gautam PS, Kumar P (2016). Emissions and human health impact of particulate matter from surface mining operation – a review. Environmental Technology & Innovation. 5:233–49. https://doi.org/10.1016/j.eti.2016.04.002

Pavlatos AM, Fultz O, Monberg MJ, Vootkur A, Pharmd (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 PMID:11440282

Pavuk M, Cerhan JR, Lynch CF, Kocan A, Petrik J, Chovancova J (2003). Case-control study of PCBs, other organochlorines and breast cancer in Eastern Slovakia. J Expo Anal Environ Epidemiol. 13(4):267–75. https://doi.org/10.1038/sj.jea.7500277 PMID:12923553

Pedersen C, Poulsen AH, Rod NH, Frei P, Hansen J, Grell K, et al. (2017). Occupational exposure to extremely low-frequency magnetic fields and risk for central nervous system disease: an update of a Danish cohort study among utility workers. Int Arch Occup Environ Health. 90(7):619–28. https://doi.org/10.1007/s00420-017-1224-0 PMID:28429106

Pedersen M, Stafoggia M, Weinmayr G, Andersen ZJ, Galassi C, Sommar J, et al. (2018b). 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 PMID:28753823

Pedersen SA, Gaist D, Schmidt SAJ, Hölmich LR, Friis S, Pottegård A (2018a). Hydrochlorothiazide use and risk of nonmelanoma skin cancer: a nationwide case-control study from Denmark. J Am Acad Dermatol. 78(4):673–681.e9. https://doi.org/10.1016/j.jaad.2017.11.042 PMID:29217346

Pedersen SA, Johannesdottir Schmidt SA, Hölmich LR, Friis S, Pottegård A, Gaist D (2019). Hydrochlorothiazide use and risk for Merkel cell carcinoma and malignant adnexal skin tumors: a nationwide case-control study. J Am Acad Dermatol. 80(2):460–465.e9. https://doi.org/10.1016/j.jaad.2018.06.014 PMID:29913261

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 PMID:9169083

Pelton K, Coticchia CM, Curatolo AS, Schaffner CP, Zurakowski D, Solomon KR, et al. (2014). Hypercholesterolemia induces angiogenesis and accelerates growth of breast tumors in vivo. Am J Pathol. 184(7):2099–110. https://doi.org/10.1016/j.ajpath.2014.03.006 PMID:24952430

Peng W, Liu YJ, Hu MB, Yan D, Gao YX, Wu CJ (2017). Using the "target constituent removal combined with bioactivity assay" strategy to investigate the optimum arecoline content in charred areca nut. Sci Rep. 7(1):40278. https://doi.org/10.1038/srep40278 PMID:28054652

Penninkilampi R, Eslick GD (2018). Perineal talc use and ovarian cancer: a systematic review and meta-analysis. Epidemiology. 29(1):41–9. https://doi.org/10.1097/EDE.0000000000000745 PMID:28863045

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. PMID:11764856

Pérez del Villar L, Vicente B, Galindo-Villardón P, Castellanos A, Pérez-Losada J, Muro A (2013). *Schistosoma mansoni* experimental infection in *Mus spretus* (SPRET/EiJ strain) mice. Parasite. 20:27. https://doi.org/10.1051/parasite/2013027 PMID:23985166

Pesatori AC, Sontag JM, Lubin JH, Consonni D, Blair A (1994). Cohort mortality and nested case-control study of lung cancer among structural pest control workers in Florida (United States). Cancer Causes Control. 5(4):310–8. https://doi.org/10.1007/BF01804981 PMID:8080942

Peters KM, Carlson BA, Gladyshev VN, Tsuji PA (2018). Selenoproteins in colon cancer. Free Radic Biol Med. 127:14–25. https://doi.org/10.1016/j.freeradbiomed.2018.05.075 PMID:29793041

Petersen KU, Pedersen JE, Bonde JP, Ebbehoej NE, Hansen J (2018a). Long-term follow-up for cancer incidence in a cohort of Danish firefighters. Occup Environ Med. 75(4):263–9. https://doi.org/10.1136/oemed-2017-104660 PMID:29055884

Petersen KU, Pedersen JE, Bonde JP, Ebbehøj NE, Hansen J (2018b). Mortality in a cohort of Danish firefighters; 1970-2014. Int Arch Occup Environ Health. 91(6):759–66. https://doi.org/10.1007/s00420-018-1323-6 PMID:29808435

Petit P, Maître A, Persoons R, Bicout DJ (2019). Lung cancer risk assessment for workers exposed to polycyclic aromatic hydrocarbons in various industries. Environ Int. 124:109–20. https://doi.org/10.1016/j.envint.2018.12.058 PMID:30641254

Pettersson D, Mathiesen T, Prochazka M, Bergenheim T, Florentzson R, Harder H, et al. (2014). Long-term mobile phone use and acoustic neuroma risk. Epidemiology. 25(2):233–41. https://doi.org/10.1097/EDE.0000000000000058 PMID:24434752

Pew Research Center (2018). Social media use continues to rise in developing countries, but plateaus across developed ones. Available from: https://www.pewglobal.org/2018/06/19/social-media-use-continues-to-rise-in-developing-countries-but-plateaus-across-developed-ones/.

Pflaum T, Hausler T, Baumung C, Ackermann S, Kuballa T, Rehm J, et al. (2016). Carcinogenic compounds in alcoholic beverages: an update. Arch Toxicol. 90(10):2349–67. https://doi.org/10.1007/s00204-016-1770-3 PMID:27353523

Phiboonchaiyanan PP, Busaranon K, Ninsontia C, Chanvorachote P (2017). Benzophenone-3 increases metastasis potential in lung cancer cells via epithelial to mesenchymal transition. Cell Biol Toxicol. 33(3):251–61. https://doi.org/10.1007/s10565-016-9368-3 PMID:27796700

Phillips S, Palmer RB, Brody A (2008). Epidemiology, toxicokinetics, and health effects of methyl *tert*-butyl ether (MTBE). J Med Toxicol. 4(2):115–26. https://doi.org/10.1007/BF03160966 PMID:18570173

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 PMID:26498098

Piel C, Pouchieu C, Migault L, Béziat B, Boulanger M, Bureau M, et al.; AGRICAN group (2018). Increased risk of central nervous system tumours with carbamate insecticide use in the prospective cohort AGRICAN. Int J Epidemiol. PMID:30476073

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. [Epub ahead of print] https://doi.org/10.1002/wnan.1513 PMID:29473695

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 PMID:29535025

Pinto I, Bogi A, Picciolo F, Stacchini N, Buonocore G, Bellieni CV (2015). Blue light and ultraviolet radiation exposure from infant phototherapy equipment. J Occup Environ Hyg. 12(9):603–10. https://doi.org/10.1080/15459624.2015.1029611 PMID:25894632

Piotrowski J (1957). Quantitative estimation of aniline absorption through the skin in man. J Hyg Epidemiol Microbiol Immunol. 1(1):23–32. PMID:13475789

Pisinger C (2015). A systematic review of health effects of electronic cigarettes. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/tobacco/industry/product_regulation/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 PMID:25456810

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 PMID:15680779

Placke ME, Griffis L, Bird M, Bus J, Persing RL, Cox LA Jr (1996). Chronic inhalation oncogenicity study of isoprene in B6C3F_1 mice. Toxicology. 113(1–3):253–62. https://doi.org/10.1016/0300-483X(96)03454-3 PMID:8901906

Platel A, Gervais V, Sajot N, Nesslany F, Marzin D, Claude N (2010). Study of gene expression profiles in TK6 human cells exposed to DNA-oxidizing agents. Mutat Res. 689(1–2):21–49. https://doi.org/10.1016/j.mrfmmm.2010.04.004 PMID:20466008

Platel A, Nesslany F, Gervais V, Marzin D (2009). Study of oxidative DNA damage in TK6 human lymphoblastoid cells by use of the in vitro micronucleus test: determination of No-Observed-Effect Levels. Mutat Res. 678(1):30–7. https://doi.org/10.1016/j.mrgentox.2009.06.006 PMID:19559100

Poirier MC, Olivero OA, Walker DM, Walker VE (2004). Perinatal genotoxicity and carcinogenicity of anti-retroviral nucleoside analog drugs. Toxicol Appl Pharmacol. 199(2):151–61. https://doi.org/10.1016/j.taap.2003.11.034 PMID:15313587

Pottegård A, Hallas J, Olesen M, Svendsen MT, Habel LA, Friedman GD, et al. (2017). Hydrochlorothiazide use is strongly associated with risk of lip cancer. J Intern Med. 282(4):322–31. https://doi.org/10.1111/joim.12629 PMID:28480532

Pottegård A, Pedersen SA, Schmidt SAJ, Hölmich LR, Friis S, Gaist D (2018). Association of hydrochlorothiazide use and risk of malignant melanoma. JAMA Intern Med. 178(8):1120–2. https://doi.org/10.1001/jamainternmed.2018.1652 PMID:29813157

Prah J, Ashley D, Blount B, Case M, Leavens T, Pleil J, et al. (2004). Dermal, oral, and inhalation pharmacokinetics of methyl tertiary butyl ether (MTBE) in human volunteers. Toxicol Sci. 77(2):195–205. https://doi.org/10.1093/toxsci/kfh009 PMID:14600279

Pratap CB, Scanu T, Spaapen RM, Bakker JM, Wu L-E, Hofland I, et al. (2016). *Salmonella* manipulation of host signalling pathways promotes cellular transformation and cancer of infected tissues. Int J Infect Dis. 45:145. https://doi.org/10.1016/j.ijid.2016.02.353

Pratt LA, Brody DJ, Gu Q (2017). Antidepressant use among persons aged 12 and over: United States, 2011–2014. NCHS Data Brief No. 283, August 2017.

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 PMID:27261772

Preziosi ME, Singh S, Valore EV, Jung G, Popovic B, Poddar M, et al. (2017). Mice lacking liver-specific β-catenin develop steatohepatitis and fibrosis after iron overload. J Hepatol. 67(2):360–9. https://doi.org/10.1016/j.jhep.2017.03.012 PMID:28341391

Pritchard JB, French JE, Davis BJ, Haseman JK (2003). The role of transgenic mouse models in carcinogen identification. Environ Health Perspect. 111(4):444–54. https://doi.org/10.1289/ehp.5778 PMID:12676597

Pukkala E, Martinsen JI, Weiderpass E, Kjaerheim K, Lynge E, Tryggvadottir L, et al. (2014). Cancer incidence among firefighters: 45 years of follow-up in five Nordic countries. Occup Environ Med. 71(6):398–404. https://doi.org/10.1136/oemed-2013-101803 PMID:24510539

Purdue MP, Stewart PA, Friesen MC, Colt JS, Locke SJ, Hein MJ, et al. (2017). Occupational exposure to chlorinated solvents and kidney cancer: a case-control study. Occup Environ Med. 74(4):268–74. https://doi.org/10.1136/oemed-2016-103849 PMID:27803178

Qian G, Tang L, Lin S, Xue KS, Mitchell NJ, Su J, et al. (2016). Sequential dietary exposure to aflatoxin B_1 and fumonisin B_1 in F344 rats increases liver preneoplastic changes indicative of a synergistic interaction. Food Chem Toxicol. 95:188–95. https://doi.org/10.1016/j.fct.2016.07.017 PMID:27430420

Quarles JM, Tennant RW (1975). Effects of nitrosocarbaryl on BALB/3T3 cells. Cancer Res. 35(10):2637–43. PMID:50878

Quast JF (2002). Two-year toxicity and oncogenicity study with acrylonitrile incorporated in the drinking water of rats. Toxicol Lett. 132(3):153–96. https://doi.org/10.1016/S0378-4274(02)00072-3 PMID:12044703

Quast JF, Schuetz DJ, Balmer MF, Gushow TS, Park CH, McKenna MJ (1980). A two-year toxicity and oncogenicity study with acrylonitrile following inhalation exposure of rats, prepared by the Toxicology Research Laboratory, Dow Chemical, Midland MI for the Chemical Manufacturing Association, as cited in US Environmental Protection Agency, Health Assessment Document for Acrylonitrile, Office of Health and Environmental Assessment, Washington (DC), EPA-600/8-82-007F, October 1983.

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.31055 PMID:28921575

Rahbar A, Stragliotto G, Orrego A, Peredo I, Taher C, Willems J, et al. (2012). Low levels of human cytomegalovirus infection in glioblastoma multiforme associates with patient survival; -a case-control study. Herpesviridae. 3(1):3. https://doi.org/10.1186/2042-4280-3-3 PMID:22424569

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 PMID:11943619

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 PMID:17164378

Ramanakumar AV, Parent ME, Latreille B, Siemiatycki J (2008). Risk of lung cancer following exposure to carbon black, titanium dioxide and talc: results from two case-control studies in Montreal. Int J Cancer. 122(1):183–9. https://doi.org/10.1002/ijc.23021 PMID:17722096

Ramaswamy BR, Kim JW, Isobe T, Chang KH, Amano A, Miller TW, et al. (2011). Determination of preservative and antimicrobial compounds in fish from Manila Bay, Philippines using ultra high performance liquid

chromatography tandem mass spectrometry, and assessment of human dietary exposure. J Hazard Mater. 192(3):1739–45. https://doi.org/10.1016/j.jhazmat.2011.07.006 PMID:21798664

Rantakokko P, Main KM, Wohlfart-Veje C, Kiviranta H, Airaksinen R, Vartiainen T, et al. (2014). Association of placenta organotin concentrations with growth and ponderal index in 110 newborn boys from Finland during the first 18 months of life: a cohort study. Environ Health. 13(1):45. https://doi.org/10.1186/1476-069X-13-45 PMID:24899383

Rashid HU, Xu Y, Muhammad Y, Wang L, Jiang J (2019). Research advances on anticancer activities of matrine and its derivatives: an updated overview. Eur J Med Chem. 161:205–38. https://doi.org/10.1016/j.ejmech.2018.10.037 PMID:30359819

Rauert C, Harner T, Schuster JK, Eng A, Fillmann G, Castillo LE, et al. (2018). Atmospheric concentrations of new persistent organic pollutants and emerging chemicals of concern in the Group of Latin America and Caribbean (GRULAC) region. Environ Sci Technol. 52(13):7240–9. https://doi.org/10.1021/acs.est.8b00995 PMID:29846065

Ray S, Xu F, Li P, Sanchez NS, Wang H, Das SK (2007). Increased level of cellular Bip critically determines estrogenic potency for a xenoestrogen kepone in the mouse uterus. Endocrinology. 148(10):4774–85. https://doi.org/10.1210/en.2007-0537 PMID:17640991

Reger MK, Zollinger TW, Liu Z, Jones JF, Zhang J (2018). Dietary intake of isoflavones and coumestrol and the risk of prostate cancer in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Int J Cancer. 142(4):719–28. https://doi.org/10.1002/ijc.31095 PMID:29114854

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 PMID:16507460

Reigstad MM, Oldereid NB, Omland AK, Storeng R (2017). Literature review on cancer risk in children born after fertility treatment suggests increased risk of haematological cancers. Acta Paediatr. 106(5):698–709. https://doi.org/10.1111/apa.13755 PMID:28128867

Rekhadevi PV, Mahboob M, Rahman MF, Grover P (2011). Determination of genetic damage and urinary metabolites in fuel filling station attendants. Environ Mol Mutagen. 52(4):310–8. https://doi.org/10.1002/em.20622 PMID:20872828

Ren Y, Yang M, Chen M, Zhu Q, Zhou L, Qin W, et al. (2017). Microcystin-LR promotes epithelial-mesenchymal transition in colorectal cancer cells through PI3-K/AKT and SMAD2. Toxicol Lett. 265:53–60. https://doi.org/10.1016/j.toxlet.2016.11.004 PMID:27856280

Rho JK, Choi YJ, Jeon BS, Choi SJ, Cheon GJ, Woo SK, et al. (2010). Combined treatment with silibinin and epidermal growth factor receptor tyrosine kinase inhibitors overcomes drug resistance caused by T790M mutation. Mol Cancer Ther. 9(12):3233–43. https://doi.org/10.1158/1535-7163.MCT-10-0625 PMID:21159609

Richards C, Pantanowitz L, Dezube BJ (2011). Antimicrobial and non-antimicrobial tetracyclines in human cancer trials. Pharmacol Res. 63(2):151–6. https://doi.org/10.1016/j.phrs.2010.10.008 PMID:20951804

Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, Hamra GB, et al. (2015). Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS). BMJ. 351:h5359. https://doi.org/10.1136/bmj.h5359 PMID:26487649

Richardson SD, Plewa MJ, Wagner ED, Schoeny R, Demarini DM (2007). Occurrence, genotoxicity, and carcinogenicity of regulated and emerging disinfection by-products in drinking water: a review and roadmap for research. Mutat Res. 636(1–3):178–242. https://doi.org/10.1016/j.mrrev.2007.09.001 PMID:17980649

Richter E, Rösler S, Scherer G, Gostomzyk JG, Grübl A, Krämer U, et al. (2001). Haemoglobin adducts from aromatic amines in children in relation to area of residence and exposure to environmental tobacco smoke. Int Arch Occup Environ Health. 74(6):421–8. https://doi.org/10.1007/s004200100243 PMID:11563605

Rienks J, Barbaresko J, Nöthlings U (2017). Association of isoflavone biomarkers with risk of chronic disease and mortality: a systematic review and meta-analysis of observational studies. Nutr Rev. 75(8):616–41. https://doi.org/10.1093/nutrit/nux021 PMID:28969363

Riethdorf S, Hildebrandt L, Heinzerling L, Heitzer E, Fischer N, Bergmann S, et al. (2019). Detection and characterization of circulating tumor cells in patients with Merkel cell carcinoma. Clin Chem. 65(3):462–72. https://doi.org/10.1373/clinchem.2018.297028 PMID:30626636

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 PMID:26264677

Ríos-León K, Fuertes-Ruiton C, Arroyo J, Ruiz J (2017). Chemoprotective effect of the alkaloid extract of *Melocactus bellavistensis* against colon cancer induced in rats using 1,2-dimethylhydrazine. Rev Peru Med Exp Salud Publica. 34(1):70–5. https://doi.org/10.17843/rpmesp.2017.341.2768 PMID:28538848 [in Spanish]

Rittinghausen S, Hackbarth A, Creutzenberg O, Ernst H, Heinrich U, Leonhardt A, et al. (2014). The carcinogenic effect of various multi-walled carbon nanotubes (MWCNTs) after intraperitoneal injection in rats. Part Fibre Toxicol. 11(1):59. https://doi.org/10.1186/s12989-014-0059-z PMID:25410479

Rizzuto I, Behrens RF, Smith LA (2013). Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility. Cochrane Database Syst Rev. (8):CD008215. https://doi.org/10.1002/14651858.CD008215.pub2 PMID:23943232

Roa I, Ibacache G, Carvallo J, Melo A, Araya J, De Aretxabala X, et al. (1999). Microbiological study of gallbladder bile in a high risk zone for gallbladder cancer. Rev Med Chil. 127(9):1049–55. PMID:10752267 [in Spanish]

Robbiani DF, Bothmer A, Callen E, Reina-San-Martin B, Dorsett Y, Difilippantonio S, et al. (2008). AID is required for the chromosomal breaks in *c-myc* that lead to *c-myc/IgH* translocations. Cell. 135(6):1028–38. https://doi.org/10.1016/j.cell.2008.09.062 PMID:19070574

Robbiani DF, Deroubaix S, Feldhahn N, Oliveira TY, Callen E, Wang Q, et al. (2015). Plasmodium infection promotes genomic instability and AID-dependent B cell lymphoma. Cell. 162(4):727–37. https://doi.org/10.1016/j.cell.2015.07.019 PMID:26276629

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 PMID:23344461

Rockfield S, Raffel J, Mehta R, Rehman N, Nanjundan M (2017). Iron overload and altered iron metabolism in ovarian cancer. Biol Chem. 398(9):995–1007. https://doi.org/10.1515/hsz-2016-0336 PMID:28095368

Roderfeld M, Padem S, Lichtenberger J, Quack T, Weiskirchen R, Longerich T, et al. (2018). *Schistosoma mansoni* egg-secreted antigens activate hepatocellular carcinoma-associated transcription factors c-Jun and STAT3 in hamster and human hepatocytes. Hepatology. [Epub ahead of print] https://doi.org/10.1002/hep.30192 PMID:30053321

Rodgers KM, Udesky JO, Rudel RA, Brody JG (2018). Environmental chemicals and breast cancer: an updated review of epidemiological literature informed by biological mechanisms. Environ Res. 160:152–82. https://doi.org/10.1016/j.envres.2017.08.045 PMID:28987728

Rodgman A, Perfetti TA (2013). The chemical components of tobacco and tobacco smoke. 2nd ed. Boca Raton (FL), USA: CRC Press.

Rodríguez T, van Wendel de Joode B, Lindh CH, Rojas M, Lundberg I, Wesseling C (2012). Assessment of long-term and recent pesticide exposure among rural school children in Nicaragua. Occup Environ Med. 69(2):119–25. https://doi.org/10.1136/oem.2010.062539 PMID:21725072

Rodríguez-Mercado JJ, Florín-Ramírez D, Álvarez-Barrera L, Altamirano-Lozano MA (2017). In vitro DNA damage by Casiopeina II-gly in human blood cells. Drug Chem Toxicol. 40(2):164–70. https://doi.org/10.1080/01480545.2016.1190738 PMID:27309204

Roedel EQ, Cafasso DE, Lee KW, Pierce LM (2012). Pulmonary toxicity after exposure to military-relevant heavy metal tungsten alloy particles. Toxicol Appl Pharmacol. 259(1):74–86. https://doi.org/10.1016/j.taap.2011.12.008 PMID:22198552

Rohr P, Kvitko K, da Silva FR, Menezes APS, Porto C, Sarmento M, et al. (2013). Genetic and oxidative damage of peripheral blood lymphocytes in workers with occupational exposure to coal. Mutat Res. 758(1–2):23–8. https://doi.org/10.1016/j.mrgentox.2013.08.006 PMID:24004879

Romaniuk A, Lyndin M, Sikora V, Lyndina Y, Romaniuk S, Sikora K (2017). Heavy metals effect on breast cancer progression. J Occup Med Toxicol. 12(1):32. https://doi.org/10.1186/s12995-017-0178-1 PMID:29209407

Romaniuk A, Lyndin M, Moskalenko R, Kuzenko Y, Gladchenko O, Lyndina Y (2015). Pathogenetic mechanisms of heavy metals effect on proapoptotic and proliferative potential of breast cancer. Interv Med Appl Sci. 7(2):63–8. https://doi.org/10.1556/1646.7.2015.2.4 PMID:26120478

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 PMID:30633716

Rosenquist K (2005). Risk factors in oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden. Swed Dent J Suppl. 2005(179):1–66. PMID:16335030

Roth-Walter F, Bergmayr C, Meitz S, Buchleitner S, Stremnitzer C, Fazekas J, et al. (2017). Janus-faced Acrolein prevents allergy but accelerates tumor growth by promoting immunoregulatory Foxp3+ cells: mouse model for passive respiratory exposure. Sci Rep. 7(1):45067. https://doi.org/10.1038/srep45067 PMID:28332605

Rotterdam-Convention (2011a). Decision Guidance Document: alachlor, in Annex 3: Operation of the prior informed consent procedure for banned or severely restricted chemicals. Available from: from http://www.pic.int/TheConvention/Chemicals/AnnexIIIChemicals/tabid/1132/language/en-US/Default.aspx.

Rotterdam-Convention (2011b). Decision Guidance Document: hexachlorobenzene, in: Annex 3: Operation of the prior informed consent procedure for banned or severely restricted chemicals in international trade. Available from:
http://www.pic.int/TheConvention/Chemicals/AnnexIIIChemicals/tabid/1132/language/en-US/Default.aspx.

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 PMID:30181710

Ruder AM, Ward EM, Brown DP (1994). Cancer mortality in female and male dry-cleaning workers. J Occup Med. 36(8):867–74. PMID:7807267

Ruder AM, Ward EM, Brown DP (2001). Mortality in dry-cleaning workers: an update. Am J Ind Med. 39(2):121–32. https://doi.org/10.1002/1097-0274(200102)39:2<121::AID-AJIM1000>3.0.CO;2-H PMID:11170155

Ruiz-Azuara L, Bastian G, Bravo-Gómez ME, Cañas RC, Flores-Alamo M, Fuentes I, et al. (2014). Phase I study of one mixed chelates copper(II) compound, Casiopeína CasIIIia with antitumor activity and its mechanism of action. Cancer Res. 74(19):CT408. https://doi.org/10.1158/1538-7445.AM2014-CT408

Ruiz-Azuara L, Bravo-Gómez ME (2010). Copper compounds in cancer chemotherapy. Curr Med Chem. 17(31):3606–15. https://doi.org/10.2174/092986710793213751 PMID:20846116

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 PMID:28718417

Ruiz-Ojeda FJ, Gomez-Llorente C, Aguilera CM, Gil A, Rupérez AI (2016). Impact of 3-amino-1,2,4-triazole (3-AT)-derived increase in hydrogen peroxide levels on inflammation and metabolism in human differentiated adipocytes. PLoS One. 11(3):e0152550. https://doi.org/10.1371/journal.pone.0152550 PMID:27023799

Rujeni N, Morona D, Ruberanziza E, Mazigo HD (2017). Schistosomiasis and soil-transmitted helminthiasis in Rwanda: an update on their epidemiology and control. Infect Dis Poverty. 6(1):8. https://doi.org/10.1186/s40249-016-0212-z PMID:28245883

Rushing BR, Selim MI (2019). Aflatoxin B_1: a review on metabolism, toxicity, occurrence in food, occupational exposure, and detoxification methods. Food Chem Toxicol. 124:81–100. https://doi.org/10.1016/j.fct.2018.11.047 PMID:30468841

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 PMID:19440497

Russo J, Russo IH (2006). The role of estrogen in the initiation of breast cancer. J Steroid Biochem Mol Biol. 102(1–5):89–96. https://doi.org/10.1016/j.jsbmb.2006.09.004 PMID:17113977

Safaeian M, Gao Y-T, Sakoda LC, Quraishi SM, Rashid A, Wang B-S, et al. (2011). Chronic typhoid infection and the risk of biliary tract cancer and stones in Shanghai, China. Infect Agent Cancer. 6(1):6. https://doi.org/10.1186/1750-9378-6-6 PMID:21535882

Saito A, Sasaki T, Kasai T, Katagiri T, Nishizawa T, Noguchi T, et al. (2013). Hepatotumorigenicity of ethyl tertiary-butyl ether with 2-year inhalation exposure in F344 rats. Arch Toxicol. 87(5):905–14. https://doi.org/10.1007/s00204-012-0997-x PMID:23389738

Saleem TH, Attya AM, Ahmed EA, Ragab SM, Ali Abdallah MA, Omar HM (2015). Possible protective effects of quercetin and sodium gluconate against colon cancer induction by dimethylhydrazine in mice. Asian Pac J Cancer Prev. 16(14):5823–8. https://doi.org/10.7314/APJCP.2015.16.14.5823 PMID:26320457

Salem E, El-Garawani I, Allam H, El-Aal BA, Hegazy M (2018). Genotoxic effects of occupational exposure to benzene in gasoline station workers. Ind Health. 56(2):132–40. https://doi.org/10.2486/indhealth.2017-0126 PMID:29070767

Samavat H, Kurzer MS (2015). Estrogen metabolism and breast cancer. Cancer Lett. 356(2 Pt A):231–43. https://doi.org/10.1016/j.canlet.2014.04.018 PMID:24784887

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 PMID:23535402

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 PMID:30324367

Sarıgöl Kılıç Z, Aydın S, Ündeğer Bucurgat Ü, Başaran N (2018). In vitro genotoxicity assessment of dinitroaniline herbicides pendimethalin and trifluralin. Food Chem Toxicol. 113:90–8. https://doi.org/10.1016/j.fct.2018.01.034 PMID:29374591

Sarkar P (2019). Response of DNA damage genes in acrolein-treated lung adenocarcinoma cells. Mol Cell Biochem. 450(1–2):187–98. https://doi.org/10.1007/s11010-018-3385-x PMID:29968166

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)00183-6 PMID:9539969

Sathiakumar N, Delzell E, Rodu B, Beall C, Myers S (2001). Cancer incidence among employees at a petrochemical research facility. J Occup Environ Med. 43(2):166–74. https://doi.org/10.1097/00043764-200102000-00017 PMID:11227635

Saunders FJ, Pautsch WF, Nutting EF (1980). The biological properties of aspartame. III. Examination for endocrine-like activities. J Environ Pathol Toxicol. 3(5–6):363–73. PMID:7441091

Sauni R, Oksa P, Uitti J, Linna A, Kerttula R, Pukkala E (2017). Cancer incidence among Finnish male cobalt production workers in 1969-2013: a cohort study. BMC Cancer. 17(1):340. https://doi.org/10.1186/s12885-017-3333-2 PMID:28521771

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 PMID:23442093

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 PMID:26028364

Scélo G, Constantinescu V, Csiki I, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, et al. (2004). Occupational exposure to vinyl chloride, acrylonitrile and styrene and lung cancer risk (Europe). Cancer Causes Control. 15(5):445–52. https://doi.org/10.1023/B:CACO.0000036444.11655.be PMID:15286464

Schernhammer ES, Bertrand KA, Birmann BM, Sampson L, Willett WC, Feskanich D (2012). Consumption of artificial sweetener- and sugar-containing soda and risk of lymphoma and leukemia in men and women. Am J Clin Nutr. 96(6):1419–28. https://doi.org/10.3945/ajcn.111.030833 PMID:23097267

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 PMID:24935969

Schröder FH, Roobol MJ, Boevé ER, de Mutsert R, Zuijdgeest-van Leeuwen SD, Kersten I, et al. (2005). Randomized, double-blind, placebo-controlled crossover study in men with prostate cancer and rising PSA: effectiveness of a dietary supplement. Eur Urol. 48(6):922–30, discussion 930–1. https://doi.org/10.1016/j.eururo.2005.08.005 PMID:16263208

Schubauer-Berigan MK, Daniels RD, Bertke SJ, Tseng CY, Richardson DB (2015). Cancer mortality through 2005 among a pooled cohort of U.S. nuclear workers exposed to external ionizing radiation. Radiat Res. 183(6):620–31. https://doi.org/10.1667/RR13988.1 PMID:26010709

Schuster BE, Roszell LE, Murr LE, Ramirez DA, Demaree JD, Klotz BR, et al. (2012). In vivo corrosion, tumor outcome, and microarray gene expression for two types of muscle-implanted tungsten alloys. Toxicol Appl Pharmacol. 265(1):128–38. https://doi.org/10.1016/j.taap.2012.08.025 PMID:22982072

Schüz J, Steding-Jessen M, Hansen S, Stangerup SE, Cayé-Thomasen P, Poulsen AH, et al. (2011). Long-term mobile phone use and the risk of vestibular schwannoma: a Danish nationwide cohort study. Am J Epidemiol. 174(4):416–22. https://doi.org/10.1093/aje/kwr112 PMID:21712479

Schwingshackl L, Hoffmann G (2016). Does a Mediterranean-type diet reduce cancer risk? Curr Nutr Rep. 5(1):9–17. https://doi.org/10.1007/s13668-015-0141-7 PMID:27014505

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 PMID:28701164

Sedgwick B (1992). Oxidation of methylhydrazines to mutagenic methylating derivatives and inducers of the adaptive response of *Escherichia coli* to alkylation damage. Cancer Res. 52(13):3693–7. PMID:1617641

Seldén AI, Ahlborg G Jr (2011). Cancer morbidity in Swedish dry-cleaners and laundry workers: historically prospective cohort study. Int Arch Occup Environ Health. 84(4):435–43. https://doi.org/10.1007/s00420-010-0582-7 PMID:20886350

Seldén AI, Westberg HB, Axelson O (1997). Cancer morbidity in workers at aluminum foundries and secondary aluminum smelters. Am J Ind Med. 32(5):467–77. https://doi.org/10.1002/(SICI)1097-0274(199711)32:5<467::AID-AJIM6>3.0.CO;2-P PMID:9327070

Sellappa S, Sadhanandhan B, Francis A, Vasudevan SG (2010). Evaluation of genotoxicity in petrol station workers in South India using micronucleus assay. Ind Health. 48(6):852–6. https://doi.org/10.2486/indhealth.MS1055 PMID:20616461

Senedese JM, Rinaldi-Neto F, Furtado RA, Nicollela HD, de Souza LDR, Ribeiro AB, et al. (2019). Chemopreventive role of *Copaifera reticulata* Ducke oleoresin in colon carcinogenesis. Biomed Pharmacother. 111:331–7. https://doi.org/10.1016/j.biopha.2018.12.091 PMID:30590321

Senthong P, Boriboon U (2017). Evaluation of occupational exposure to nitrosamine, carbon black and dust in rubber processing industry. Int J Occup Environ Med. 8(3):181–3. https://doi.org/10.15171/ijoem.2017.1098 PMID:28689215

Serra I, Yamamoto M, Calvo A, Cavada G, Báez S, Endoh K, et al. (2002). Association of chili pepper consumption, low socioeconomic status and longstanding gallstones with gallbladder cancer in a Chilean population. Int J Cancer. 102(4):407–11. https://doi.org/10.1002/ijc.10716 PMID:12402311

Severi G, Baglietto L, Muller DC, English DR, Jenkins MA, Abramson MJ, et al. (2010). Asthma, asthma medications, and prostate cancer risk. Cancer Epidemiol Biomarkers Prev. 19(9):2318–24. https://doi.org/10.1158/1055-9965.EPI-10-0381 PMID:20671137

Shafei A, Ramzy MM, Hegazy AI, Husseny AK, El-Hadary UG, Taha MM, et al. (2018). The molecular mechanisms of action of the endocrine disrupting chemical bisphenol A in the development of cancer. Gene. 647:235–43. https://doi.org/10.1016/j.gene.2018.01.016 PMID:29317319

Shafique K, McLoone P, Qureshi K, Leung H, Hart C, Morrison DS (2012). Cholesterol and the risk of grade-specific prostate cancer incidence: evidence from two large prospective cohort studies with up to 37 years' follow up. BMC Cancer. 12(1):25. https://doi.org/10.1186/1471-2407-12-25 PMID:22260413

Shaham J, Gurvich R, Kneshet Y (2003a). Cancer incidence among laboratory workers in biomedical research and routine laboratories in Israel: part I - the cohort study. Am J Ind Med. 44(6):600–10. https://doi.org/10.1002/ajim.10311 PMID:14635237

Shaham J, Gurvich R, Kneshet Y (2003b). Cancer incidence among laboratory workers in biomedical research and routine laboratories in Israel: part II - nested case-control study. Am J Ind Med. 44(6):611–26. https://doi.org/10.1002/ajim.10312 PMID:14635238

Shahbazi F, Sadighi S, Dashti-Khavidaki S, Shahi F, Mirzania M, Abdollahi A, et al. (2015). Effect of silymarin administration on cisplatin nephrotoxicity: report from a pilot, randomized, double-blinded, placebo-controlled clinical trial. Phytother Res. 29(7):1046–53. https://doi.org/10.1002/ptr.5345 PMID:25857366

Shaikh A, Barot D, Chandel D (2018). Genotoxic effects of exposure to gasoline fumes on petrol pump workers. Int J Occup Environ Med. 9(2):79–87. https://doi.org/10.15171/ijoem.2018.1159 PMID:29667645

Sharma V, Chauhan VS, Nath G, Kumar A, Shukla VK (2007). Role of bile bacteria in gallbladder carcinoma. Hepatogastroenterology. 54(78):1622–5. PMID:18019679

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.0105709 PMID:25153314

Shen J, Liao Y, Hopper JL, Goldberg M, Santella RM, Terry MB (2017). Dependence of cancer risk from environmental exposures on underlying genetic susceptibility: an illustration with polycyclic aromatic hydrocarbons and breast cancer. Br J Cancer. 116(9):1229–33. https://doi.org/10.1038/bjc.2017.81 PMID:28350789

Shi S, Tang A, Yin S, Wang L, Xie M, Yi X (2014). Inhibitive effect of matrine modification X on the growth of human nasopharyngeal carcinoma CNE2 cell xenografts in nude mice. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 28(21):1697–700. PMID:25735106 [in Chinese]

Shin S, Go RE, Kim CW, Hwang KA, Nam KH, Choi KC (2016). Effect of benzophenone-1 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 PMID:27145024

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 PMID:24854250

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 PMID:27484955

Shukla VK, Singh H, Pandey M, Upadhyay SK, Nath G (2000). Carcinoma of the gallbladder – is it a sequel of typhoid? Dig Dis Sci. 45(5):900–3. https://doi.org/10.1023/A:1005564822630 PMID:10795752

Shukla Y, Antony M, Mehrotra NK (1992). Carcinogenic and cocarcinogenic studies with carbaryl following topical exposure in mice. Cancer Lett. 62(2):133–40. https://doi.org/10.1016/0304-3835(92)90183-V PMID:1540940

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.i2.70 PMID:11394711

Shukla Y, Arora A, Singh A (2001). Tumourigenic studies on deltamethrin in Swiss albino mice. Toxicology. 163(1):1–9. https://doi.org/10.1016/S0300-483X(00)00416-9 PMID:11376860

Shwe TT, Yamamoto S, Kakeyama M, Kobayashi T, Fujimaki H (2005). Effect of intratracheal instillation of ultrafine carbon black on proinflammatory cytokine and chemokine release and mRNA expression in lung and lymph nodes of mice. Toxicol Appl Pharmacol. 209(1):51–61. https://doi.org/10.1016/j.taap.2005.03.014 PMID:16331831

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 PMID:30673666

Siegel AB, Narayan R, Rodriguez R, Goyal A, Jacobson JS, Kelly K, et al. (2014). A phase I dose-finding study of silybin phosphatidylcholine (milk thistle) in patients with advanced hepatocellular carcinoma. Integr Cancer Ther. 13(1):46–53. https://doi.org/10.1177/1534735413490798 PMID:23757319

Sillah A, Watson NF, Schwartz SM, Gozal D, Phipps AI (2018). Sleep apnea and subsequent cancer incidence. Cancer Causes Control. 29(10):987–94. https://doi.org/10.1007/s10552-018-1073-5 PMID:30120643

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 PMID:11397402

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 PMID:16760381

Singh H, Pandey M, Shukla VK (1996). *Salmonella* carrier state, chronic bacterial infection and gallbladder carcinogenesis. Eur J Cancer Prev. 5(2):144. https://doi.org/10.1097/00008469-199604000-00010 PMID:8736080

Singh RP, Mallikarjuna GU, Sharma G, Dhanalakshmi S, Tyagi AK, Chan DC, et al. (2004). Oral silibinin inhibits lung tumor growth in athymic nude mice and forms a novel chemocombination with doxorubicin targeting nuclear factor kappaB-mediated inducible chemoresistance. Clin Cancer Res. 10(24):8641–7. https://doi.org/10.1158/1078-0432.CCR-04-1435 PMID:15623648

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 PMID:27530330

Skalkidou A, Sergentanis TN, Gialamas SP, Georgakis MK, Psaltopoulou T, Trivella M, et al. (2017). Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility. Cochrane Database Syst Rev. 3:CD010931. https://doi.org/10.1002/14651858.CD010931.pub2 PMID:28349511

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 PMID:26585656

Skorupski KA, Hammond GM, Irish AM, Kent MS, Guerrero TA, Rodriguez CO, et al. (2011). Prospective randomized clinical trial assessing the efficacy of Denamarin for prevention of CCNU-induced hepatopathy in tumor-bearing dogs. J Vet Intern Med. 25(4):838–45. https://doi.org/10.1111/j.1939-1676.2011.0743.x PMID:21689156

Slamon ND, Pentreath VW (2000). Antioxidant defense against antidepressants in C6 and 1321N1 cells. Chem Biol Interact. 127(3):181–99. https://doi.org/10.1016/S0009-2797(00)00172-1 PMID:10967317

Sleiman M, Logue JM, Luo W, Pankow JF, Gundel LA, Destaillats H (2014). Inhalable constituents of thirdhand tobacco smoke: chemical characterization and health impact considerations. Environ Sci Technol. 48(22):13093–101. https://doi.org/10.1021/es5036333 PMID:25317906

Smith AG, Carthew P, Francis JE, Cabral JR, Manson MM (1993). Enhancement by iron of hepatic neoplasia in rats caused by hexachlorobenzene. Carcinogenesis. 14(7):1381–7. https://doi.org/10.1093/carcin/14.7.1381 PMID:8330354

Smith KR, Bruce N, Balakrishnan K, Adair-Rohani H, Balmes J, Chafe Z, et al.; HAP CRA Risk Expert Group (2014). Millions dead: how do we know and what does it mean? Methods used in the comparative risk assessment of household air pollution. Annu Rev Public Health. 35(1):185–206. https://doi.org/10.1146/annurev-publhealth-032013-182356 PMID:24641558

Sobel ES, Gianini J, Butfiloski EJ, Croker BP, Schiffenbauer J, Roberts SM (2005). Acceleration of autoimmunity by organochlorine pesticides in (NZB × NZW)F$_1$ mice. Environ Health Perspect. 113(3):323–8. https://doi.org/10.1289/ehp.7347 PMID:15743722

Sobel ES, Wang F, Butfiloski E, Croker B, Roberts SM (2006). Comparison of chlordecone effects on autoimmunity in (NZB×NZW) F$_1$ and BALB/c mice. Toxicology. 218(2–3):81–9. https://doi.org/10.1016/j.tox.2005.03.018 PMID:16309813

Sobue T, Utada M, Makiuchi T, Ohno Y, Uehara S, Hayashi T, et al. (2015). Risk of bile duct cancer among printing workers exposed to 1,2-dichloropropane and/or dichloromethane. J Occup Health. 57(3):230–6. https://doi.org/10.1539/joh.14-0116-OA PMID:25739336

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 PMID:15849280

Sodhi-Berry N, Reid A, Fritschi L, Musk AB, Vermeulen R, de Klerk N, et al. (2017). Cancer incidence in the Western Australian mining industry (1996-2013). Cancer Epidemiol. 49:8–18. https://doi.org/10.1016/j.canep.2017.05.001 PMID:28528292

Soffritti M, Belpoggi F, Cevolani D, Guarino M, Padovani M, Maltoni C (2002). 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 PMID:12562628

Soffritti M, Padovani M, Tibaldi E, Falcioni L, Manservisi F, Belpoggi F (2014). The carcinogenic effects of aspartame: the urgent need for regulatory re-evaluation. Am J Ind Med. 57(4):383–97. https://doi.org/10.1002/ajim.22296 PMID:24436139

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 PMID:27078173

Song JH, Kim YS, Heo NJ, Lim JH, Yang SY, Chung GE, et al. (2017). High salt intake is associated with atrophic gastritis with intestinal metaplasia. Cancer Epidemiol Biomarkers Prev. 26(7):1133–8. https://doi.org/10.1158/1055-9965.EPI-16-1024 PMID:28341758

Sorahan T (2008). Bladder cancer risks in workers manufacturing chemicals for the rubber industry. Occup Med (Lond). 58(7):496–501. https://doi.org/10.1093/occmed/kqn104 PMID:18725381

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 PMID:17516558

Sørensen GV, Cronin-Fenton DP, Sørensen HT, Ulrichsen SP, Pedersen L, Lash TL (2012). Use of glucocorticoids and risk of breast cancer: a Danish population-based case-control study. Breast Cancer Res. 14(1):R21. https://doi.org/10.1186/bcr3106 PMID:22305057

Sørensen HT, Mellemkjaer L, Nielsen GL, Baron JA, Olsen JH, Karagas MR (2004). Skin cancers and non-Hodgkin lymphoma among users of systemic glucocorticoids: a population-based cohort study. J Natl Cancer Inst. 96(9):709–11. https://doi.org/10.1093/jnci/djh118 PMID:15126608

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. 8:14073. https://doi.org/10.1038/ncomms14073 PMID:28102225

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 PMID:23893659

Soward TE (2011). Evaluation of cancer from exposure to cyanotoxins in drinking water at Grand Lake Saint Marys [master thesis]. Dayton (OH), USA: Wright State University.

Spaan M, van den Belt-Dusebout AW, van den Heuvel-Eibrink MM, Hauptmann M, Lambalk CB, Burger CW, et al.; OMEGA-steering group (2019). Risk of cancer in children and young adults conceived by assisted reproductive technology. Hum Reprod. 34(4):740–50. https://doi.org/10.1093/humrep/dey394 PMID:30715305

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 PMID:26178025

Spinelli JJ, Ng CH, Weber JP, Connors JM, Gascoyne RD, Lai AS, et al. (2007). Organochlorines and risk of non-Hodgkin lymphoma. Int J Cancer. 121(12):2767–75. https://doi.org/10.1002/ijc.23005 PMID:17722095

Sponsiello-Wang Z, Sanders E, Weitkunat R (2006). Occupational acrylonitrile exposure and lung cancer: a meta-analysis. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 24(2):257–84. https://doi.org/10.1080/10590500601006715 PMID:17114112

Spurgeon ME, Lambert PF (2013). Merkel cell polyomavirus: a newly discovered human virus with oncogenic potential. Virology. 435(1):118–30. https://doi.org/10.1016/j.virol.2012.09.029 PMID:23217622

Srivastava AK, Ali W, Singh R, Bhui K, Tyagi S, Al-Khedhairy AA, et al. (2012). Mancozeb-induced genotoxicity and apoptosis in cultured human lymphocytes. Life Sci. 90(21-22):815–24. https://doi.org/10.1016/j.lfs.2011.12.013 PMID:22289270

Staňková P, Kučera O, Lotková H, Roušar T, Endlicher R, Cervinková Z (2010). The toxic effect of thioacetamide on rat liver in vitro. Toxicol In Vitro. 24(8):2097–103. https://doi.org/10.1016/j.tiv.2010.06.011 PMID:20600801

Starek-Świechowicz B, Budziszewska B, Starek A (2017). Hexachlorobenzene as a persistent organic pollutant: toxicity and molecular mechanism of action. Pharmacol Rep. 69(6):1232–9. https://doi.org/10.1016/j.pharep.2017.06.013 PMID:29128804

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 PMID:28546320

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 PMID:31296664

Steenland K, Zhao L, Winquist A (2015). A cohort incidence study of workers exposed to perfluorooctanoic acid (PFOA). Occup Environ Med. 72(5):373–80. https://doi.org/10.1136/oemed-2014-102364 PMID:25601914

Stiborová M, Miksanová M, Havlícek V, Schmeiser HH, Frei E (2002). Mechanism of peroxidase-mediated oxidation of carcinogenic *o*-anisidine and its binding to DNA. Mutat Res. 500(1–2):49–66. https://doi.org/10.1016/S0027-5107(01)00295-0 PMID:11890934

Stiborová M, Miksanová M, Sulc M, Rýdlová H, Schmeiser HH, Frei E (2005). Identification of a genotoxic mechanism for the carcinogenicity of the environmental pollutant and suspected human carcinogen *o*-anisidine. Int J Cancer. 116(5):667–78. https://doi.org/10.1002/ijc.21122 PMID:15828049

Stockdale AJ, Chaponda M, Beloukas A, Phillips RO, Matthews PC, Papadimitropoulos A, et al. (2017). Prevalence of hepatitis D virus infection in sub-Saharan Africa: a systematic review and meta-analysis. Lancet Glob Health. 5(10):e992–1003. https://doi.org/10.1016/S2214-109X(17)30298-X PMID:28911765

Stockholm Convention (2004a). Perfluorooctanoic acid (PFOA). Available from: http://www.pops.int/TheConvention/ThePOPs/AllPOPs/tabid/2510/Default.aspx.

Stockholm Convention (2004b). Chlordecone. Annex A (elimination). Available from: http://www.pops.int/TheConvention/ThePOPs/AllPOPs/tabid/2509/Default.aspx.

Stolka K, Ndom P, Hemingway-Foday J, Iriondo-Perez J, Miley W, Labo N, et al. (2014). Risk factors for Kaposi's sarcoma among HIV-positive individuals in a case control study in Cameroon. Cancer Epidemiol. 38(2):137–43. https://doi.org/10.1016/j.canep.2014.02.006 PMID:24631417

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 PMID:10528630

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. PMID:4202501

Stragliotto G, Rahbar A, Solberg NW, Lilja A, Taher C, Orrego A, et al. (2013). Effects of valganciclovir as an add-on therapy in patients with cytomegalovirus-positive glioblastoma: a randomized, double-blind, hypothesis-generating study. Int J Cancer. 133(5):1204–13. https://doi.org/10.1002/ijc.28111 PMID:23404447

Straif K, Loomis D, Guyton K, Grosse Y, Lauby-Secretan B, El Ghissassi F, et al. (2014). Future priorities for the IARC Monographs. Lancet Oncol. 15(7):683–4. https://doi.org/10.1016/S1470-2045(14)70168-8

Strohmaier S, Edlinger M, Manjer J, Stocks T, Bjørge T, Borena W, et al. (2013). Total serum cholesterol and cancer incidence in the Metabolic syndrome and Cancer Project (Me-Can). PLoS One. 8(1):e54242. https://doi.org/10.1371/journal.pone.0054242 PMID:23372693

Strom BL, Soloway RD, Rios-Dalenz JL, Rodriguez-Martinez HA, West SL, Kinman JL, et al. (1995). Risk factors for gallbladder cancer. An international collaborative case-control study. Cancer. 76(10):1747–56. https://doi.org/10.1002/1097-0142(19951115)76:10<1747::AID-CNCR2820761011>3.0.CO;2-L PMID:8625043

Su CC, Tsai KY, Hsu YY, Lin YY, Lian IeB (2010). Chronic exposure to heavy metals and risk of oral cancer in Taiwanese males. Oral Oncol. 46(8):586–90. https://doi.org/10.1016/j.oraloncology.2010.05.001 PMID:20619722

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 Shaik A, Shaik AP, Jamil K, Alsaeed AH (2016). Evaluation of cytotoxicity and genotoxicity of pesticide mixtures on lymphocytes. Toxicol Mech Methods. 26(8):588–94. https://doi.org/10.1080/15376516.2016.1218577 PMID:27603568

Sun B, Xu M (2015). Matrine inhibits the migratory and invasive properties of nasopharyngeal carcinoma cells. Mol Med Rep. 11(6):4158–64. https://doi.org/10.3892/mmr.2015.3276 PMID:25633440

Sun Q, Ma W, Gao Y, Zheng W, Zhang B, Peng Y (2011). Meta-analysis: therapeutic effect of transcatheter arterial chemoembolization combined with Compound Kushen Injection in hepatocellular carcinoma. Afr J Tradit Complement Altern Med. 9(2):178–88. PMID:23983333

Sun T, Liu S, Zhou Y, Yao Z, Zhang D, Cao S, et al. (2017). Evolutionary biologic changes of gut microbiota in an 'adenoma-carcinoma sequence' mouse colorectal cancer model induced by 1, 2-dimethylhydrazine. Oncotarget. 8(1):444–57. https://doi.org/10.18632/oncotarget.13443 PMID:27880935

Surh YJ, Liem A, Miller JA, Tannenbaum SR (1994). 5-Sulfooxymethylfurfural as a possible ultimate mutagenic and carcinogenic metabolite of the Maillard reaction product, 5-hydroxymethylfurfural. Carcinogenesis. 15(10):2375–7. https://doi.org/10.1093/carcin/15.10.2375 PMID:7955080

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 M, Yamazaki K, Kano H, Aiso S, Nagano K, Fukushima S (2012). No carcinogenicity of ethyl tertiary-butyl ether by 2-year oral administration in rats. J Toxicol Sci. 37(6):1239–46. https://doi.org/10.2131/jts.37.1239 PMID:23208438

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

Svensson RU, Bannick NL, Marin MJ, Robertson LW, Lynch CF, Henry MD (2013). Chronic chlorpyrifos exposure does not promote prostate cancer in prostate specific PTEN mutant mice. J Environ Pathol Toxicol Oncol. 32(1):29–39. https://doi.org/10.1615/JEnvironPatholToxicolOncol.2013006778 PMID:23758150

Svirčev Z, Drobac D, Tokodi N, Mijović B, Codd GA, Meriluoto J (2017). Toxicology of microcystins with reference to cases of human intoxications and epidemiological investigations of exposures to cyanobacteria and cyanotoxins. Arch Toxicol. 91(2):621–50. https://doi.org/10.1007/s00204-016-1921-6 PMID:28042640

Svirčev Z, Drobac D, Tokodi N, Vidović M, Simeunović J, Miladinov-Mikov M, et al. (2013). Epidemiology of primary liver cancer in Serbia and possible connection with cyanobacterial blooms. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 31(3):181–200. https://doi.org/10.1080/10590501.2013.824187 PMID:24024518

Svirčev Z, Tokodi N, Drobac D, Codd GA (2014). Cyanobacteria in aquatic ecosystems in Serbia: effects on water quality, human health and biodiversity. Syst Biodivers. 12(3):261–70. https://doi.org/10.1080/14772000.2014.921254

Symanski E, Tee Lewis PG, Chen TY, Chan W, Lai D, Ma X (2016). Air toxics and early childhood acute lymphocytic leukemia in Texas, a population based case control study. Environ Health. 15(1):70. https://doi.org/10.1186/s12940-016-0154-8 PMID:27301866

Symons JM, Kreckmann KH, Sakr CJ, Kaplan AM, Leonard RC (2008). Mortality among workers exposed to acrylonitrile in fiber production: an update. J Occup Environ Med. 50(5):550–60. https://doi.org/10.1097/JOM.0b013e318162f640 PMID:18469624

Tabet E, Gelu-Simeon M, Genet V, Lamontagne L, Piquet-Pellorce C, Samson M (2018). Chlordecone potentiates auto-immune hepatitis and promotes brain entry of MHV3 during viral hepatitis in mouse models. Toxicol Lett. 299:129–36. https://doi.org/10.1016/j.toxlet.2018.09.014 PMID:30287270

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 W-P, 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

Taieb F, Petit C, Nougayrède J-P, Oswald E (2016). The enterobacterial genotoxins: cytolethal distending toxin and colibactin. Ecosal Plus. 7(1): https://doi.org/10.1128/ecosalplus.ESP-0008-2016 PMID:27419387

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

Takasawa H, Takashima R, Narumi K, Kawasako K, Hattori A, Kawabata M, et al. (2015). Results of the International Validation of the *in vivo* rodent alkaline comet assay for the detection of genotoxic carcinogens: individual data for 1,2-dibromoethane, *p*-anisidine, and *o*-anthranilic acid in the 2nd step of the 4th phase Validation Study under the JaCVAM initiative. Mutat Res Genet Toxicol Environ Mutagen. 786-788:144–50. https://doi.org/10.1016/j.mrgentox.2015.03.002 PMID:26212305

Takashi M, Sakata T, Nakano Y, Takagi Y, Yamada Y, Hibi H, et al. (1994). Initiation-stage enhancement by uracil of *N*-ethyl-*N*-hydroxyethylnitrosamine-induction of kidney carcinogenesis in rats. Cancer Lett. 87(2):151–7. https://doi.org/10.1016/0304-3835(94)90216-X PMID:7812934

Talbott EO, Xu X, Youk AO, Rager JR, Stragand JA, Malek AM (2011). Risk of leukemia as a result of community exposure to gasoline vapors: a follow-up study. Environ Res. 111(4):597–602. https://doi.org/10.1016/j.envres.2011.03.009 PMID:21453914

Talibov M, Auvinen A, Weiderpass E, Hansen J, Martinsen JI, Kjaerheim K, et al. (2017). Occupational solvent exposure and adult chronic lymphocytic leukemia: no risk in a population-based case-control study in four Nordic countries. Int J Cancer. 141(6):1140–7. https://doi.org/10.1002/ijc.30814 PMID:28571111

Tang MS, Wang HT, Hu Y, Chen WS, Akao M, Feng Z, et al. (2011). Acrolein induced DNA damage, mutagenicity and effect on DNA repair. Mol Nutr Food Res. 55(9):1291–300. https://doi.org/10.1002/mnfr.201100148 PMID:21714128

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. J Toxicol Sci. 37(6):1113–26. https://doi.org/10.2131/jts.37.1113 PMID:23208427

Tarapore P, Ying J, Ouyang B, Burke B, Bracken B, Ho SM (2014). Exposure to bisphenol A correlates with early-onset prostate cancer and promotes centrosome amplification and anchorage-independent growth in vitro. PLoS One. 9(3):e90332. https://doi.org/10.1371/journal.pone.0090332 PMID:24594937

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

Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. (2013). Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. (1):CD004816. https://doi.org/10.1002/14651858.CD004816.pub5 PMID:23440795

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 M, Pryce C, Meinlschmidt G (2009). Effects of intrauterine exposure to synthetic glucocorticoids on fetal, newborn, and infant hypothalamic-pituitary-adrenal axis function in humans: a systematic review. Endocr Rev. 30(7):753–89. https://doi.org/10.1210/er.2008-0014 PMID:19837868

Tennant AH, Peng B, Kligerman AD (2001). Genotoxicity studies of three triazine herbicides: in vivo studies using the alkaline single cell gel (SCG) assay. Mutat Res. 493(1–2):1–10. https://doi.org/10.1016/S1383-5718(01)00145-0 PMID:11516710

Tennant RW, French JE, Spalding JW (1995). Identifying chemical carcinogens and assessing potential risk in short-term bioassays using transgenic mouse models. Environ Health Perspect. 103(10):942–50. https://doi.org/10.1289/ehp.95103942 PMID:8529591

Terrell ML, Rosenblatt KA, Wirth J, Cameron LL, Marcus M (2016). Breast cancer among women in Michigan following exposure to brominated flame retardants. Occup Environ Med. 73(8):564–7. https://doi.org/10.1136/oemed-2015-103458 PMID:27312402

Tewari M, Mishra RR, Shukla HS (2010). *Salmonella typhi* and gallbladder cancer: report from an endemic region. Hepatobiliary Pancreat Dis Int. 9(5):524–30. PMID:20943463

Thistle JE, Yang B, Petrick JL, Fan JH, Qiao YL, Abnet CC, et al. (2018). Association of tooth loss with liver cancer incidence and chronic liver disease mortality in a rural Chinese population. PLoS One. 13(9):e0203926. https://doi.org/10.1371/journal.pone.0203926 PMID:30222759

Thomas JO, Ribelin WE, Wilson RH, Keppler DC, DeEds F (1967a). Chronic toxicity of diphenylamine to albino rats. Toxicol Appl Pharmacol. 10(2):362–74. https://doi.org/10.1016/0041-008X(67)90118-4 PMID:6034619

Thomas JO, Ribelin WE, Woodward JR, DeEds F (1967b). The chronic toxicity of diphenylamine for dogs. Toxicol Appl Pharmacol. 11(1):184–94. https://doi.org/10.1016/0041-008X(67)90037-3 PMID:6056151

Thomas P, Dong J (2006). Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: a potential novel mechanism of endocrine disruption. J Steroid Biochem Mol Biol. 102(1–5):175–9. https://doi.org/10.1016/j.jsbmb.2006.09.017 PMID:17088055

Thomford PJ (2002). 104-week dietary chronic toxicity and carcinogenicity study with perfluorooctane sulfonic acid potassium salt (PFOS; T-6295) in rats. Princeton (NJ), USA: Covance Laboratories Inc.; pp. 6329–83.

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 DC, Eling TE (1991). Reactive intermediates formed during the peroxidative oxidation of anisidine isomers. Chem Res Toxicol. 4(4):474–81. https://doi.org/10.1021/tx00022a012 PMID:1912336

Thompson DC, Josephy PD, Chu JW, Eling TE (1992). Enhanced mutagenicity of anisidine isomers in bacterial strains containing elevated *N*-acetyltransferase activity. Mutat Res. 279(2):83–9. https://doi.org/10.1016/0165-1218(92)90249-Y PMID:1375342

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

Tin Tin Win S, Yamamoto S, Ahmed S, Kakeyama M, Kobayashi T, Fujimaki H (2006). Brain cytokine and chemokine mRNA expression in mice induced by intranasal instillation with ultrafine carbon black. Toxicol Lett. 163(2):153–60. https://doi.org/10.1016/j.toxlet.2005.10.006 PMID:16293374

Tirnitz-Parker JE, Glanfield A, Olynyk JK, Ramm GA (2013). Iron and hepatic carcinogenesis. Crit Rev Oncog. 18(5):391–407. https://doi.org/10.1615/CritRevOncog.2013007759 PMID:23879586

Toda KS, Kikuchi L, Chagas AL, Tanigawa RY, Paranaguá-Vezozzo DC, Pfiffer T, et al. (2015). Hepatocellular carcinoma related to *Schistosoma mansoni* infection: case series and literature review. J Clin Transl Hepatol. 3(4):260–4. https://doi.org/10.14218/JCTH.2015.00027 PMID:26807381

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):E269. https://doi.org/10.3390/ijerph14030269 PMID:28272360

Torgbor C, Awuah P, Deitsch K, Kalantari P, Duca KA, Thorley-Lawson DA (2014). A multifactorial role for *P. falciparum* malaria in endemic Burkitt's lymphoma pathogenesis. PLoS Pathog. 10(5):e1004170. https://doi.org/10.1371/journal.ppat.1004170 PMID:24874410

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

Torti SV, Torti FM (2013). Iron and cancer: more ore to be mined. Nat Rev Cancer. 13(5):342–55. https://doi.org/10.1038/nrc3495 PMID:23594855

Toth B (1977). The large bowel carcinogenic effects of hydrazines and related compounds occurring in nature and in the environment. Cancer. 40(5 Suppl):2427–31. https://doi.org/10.1002/1097-0142(197711)40:5+<2427::AID-CNCR2820400906>3.0.CO;2-Y PMID:922685

Trabert B, Falk RT, Figueroa JD, Graubard BI, Garcia-Closas M, Lissowska J, et al. (2014). Urinary bisphenol A-glucuronide and postmenopausal breast cancer in Poland. Cancer Causes Control. 25(12):1587–93. https://doi.org/10.1007/s10552-014-0461-8 PMID:25189422

Travier N, Gridley G, De Roos AJ, Plato N, Moradi T, Boffetta P (2002). Cancer incidence of dry cleaning, laundry and ironing workers in Sweden. Scand J Work Environ Health. 28(5):341–8. https://doi.org/10.5271/sjweh.684 PMID:12432988

Travis RC, Allen NE, Appleby PN, Price A, Kaaks R, Chang-Claude J, et al. (2012). Prediagnostic concentrations of plasma genistein and prostate cancer risk in 1,605 men with prostate cancer and 1,697 matched control participants in EPIC. Cancer Causes Control. 23(7):1163–71. https://doi.org/10.1007/s10552-012-9985-y PMID:22674291

Tremmel R, Herrmann K, Engst W, Meinl W, Klein K, Glatt H, et al. (2017). Methyleugenol DNA adducts in human liver are associated with *SULT1A1* copy number variations and expression levels. Arch Toxicol. 91(10):3329–39. https://doi.org/10.1007/s00204-017-1955-4 PMID:28326452

Troche JR, Ferrucci LM, Cartmel B, Leffell DJ, Bale AE, Mayne ST (2014). Systemic glucocorticoid use and early-onset basal cell carcinoma. Ann Epidemiol. 24(8):625–7. https://doi.org/10.1016/j.annepidem.2014.05.009 PMID:24958637

Trompet S, Jukema JW, Katan MB, Blauw GJ, Sattar N, Buckley B, et al. (2009). Apolipoprotein E genotype, plasma cholesterol, and cancer: a Mendelian randomization study. Am J Epidemiol. 170(11):1415–21. https://doi.org/10.1093/aje/kwp294 PMID:19889709

Tsai MK, Lin YL, Huang YT (2010). Effects of salvianolic acids on oxidative stress and hepatic fibrosis in rats. Toxicol Appl Pharmacol. 242(2):155–64. https://doi.org/10.1016/j.taap.2009.10.002 PMID:19822164

Tsai RJ, Luckhaupt SE, Schumacher P, Cress RD, Deapen DM, Calvert GM (2015). Risk of cancer among firefighters in California, 1988-2007. Am J Ind Med. 58(7):715–29. https://doi.org/10.1002/ajim.22466 PMID:25943908

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.2017.06.012 PMID:28644961

Tsuchiya Y, Loza E, Villa-Gomez G, Trujillo CC, Baez S, Asai T, et al. (2018). Metagenomics of microbial communities in gallbladder bile from patients with gallbladder cancer or cholelithiasis. Asian Pac J Cancer Prev. 19(4):961–7. https://doi.org/10.22034/APJCP.2018.19.4.961 PMID:29693356

Tsugane S, Sasazuki S (2007). Diet and the risk of gastric cancer: review of epidemiological evidence. Gastric Cancer. 10(2):75–83. https://doi.org/10.1007/s10120-007-0420-0 PMID:17577615

Tual S, Silverman DT, Koutros S, Blair A, Sandler DP, Lebailly P, et al. (2016). Use of dieselized farm equipment and incident lung cancer: findings from the Agricultural Health Study cohort. Environ Health Perspect. 124(5):611–8. https://doi.org/10.1289/ehp.1409238 PMID:26452295

Tunsaringkarn T, Suwansaksri J, Soogarun S, Siriwong W, Rungsiyothin A, Zapuang K, et al. (2011). Genotoxic monitoring and benzene exposure assessment of gasoline station workers in metropolitan Bangkok: sister chromatid exchange (SCE) and urinary trans, trans-muconic acid (t,t-MA). Asian Pac J Cancer Prev. 12(1):223–7. PMID:21517262

Türker Y, Nazıroğlu M, Gümral N, Celik O, Saygın M, Cömlekçi S, et al. (2011). Selenium and L-carnitine reduce oxidative stress in the heart of rat induced by 2.45-GHz radiation from wireless devices. Biol Trace Elem Res. 143(3):1640–50. https://doi.org/10.1007/s12011-011-8994-0 PMID:21360060

Turner MC, Krewski D, Diver WR, Pope CA 3rd, Burnett RT, Jerrett M, et al. (2017). Ambient air pollution and cancer mortality in the Cancer Prevention Study-II. Environ Health Perspect. 125(8):087013. https://doi.org/10.1289/EHP1249 PMID:28886601

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.2010.0076 PMID:21375462

Ulger H, Ertekin T, Karaca O, Canoz O, Nisari M, Unur E, et al. (2013). Influence of gilaburu (*Viburnum opulus*) juice on 1,2-dimethylhydrazine (DMH)-induced colon cancer. Toxicol Ind Health. 29(9):824–9. https://doi.org/10.1177/0748233712445049 PMID:22546843

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

USDA Foreign Agricultural Service (2012). Global Agricultural Information Network (GAIN). Japan: Biofuels Annual: Japan focuses on next generation biofuels. Washington (DC), USA: United States Department of Agriculture Foreign Agricultural Service. Available from: https://gain.fas.usda.gov/Recent%20GAIN%20Publications/Biofuels%20Annual_Tokyo_Japan_7-2-2012.pdf.

Vaishnavi C, Kochhar R, Singh G, Kumar S, Singh S, Singh K (2005). Epidemiology of typhoid carriers among blood donors and patients with biliary, gastrointestinal and other related diseases. Microbiol Immunol. 49(2):107–12. https://doi.org/10.1111/j.1348-0421.2005.tb03709.x PMID:15722595

Valberg PA, Long CM, Sax SN (2006). Integrating studies on carcinogenic risk of carbon black: epidemiology, animal exposures, and mechanism of action. J Occup Environ Med. 48(12):1291–307. https://doi.org/10.1097/01.jom.0000215342.52699.2a PMID:17159645

van Barneveld TA, Sasco AJ, van Leeuwen FE (2004). A cohort study of cancer mortality among Biology Research Laboratory workers in The Netherlands. Cancer Causes Control. 15(1):55–66. https://doi.org/10.1023/B:CACO.0000016607.70457.47 PMID:14970735

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 den Belt-Dusebout AW, Spaan M, Lambalk CB, Kortman M, Laven JS, van Santbrink EJ, et al. (2016). Ovarian stimulation for in vitro fertilization and long-term risk of breast cancer. JAMA. 316(3):300–12. https://doi.org/10.1001/jama.2016.9389 PMID:27434442

van der Plaat DA, de Jong K, de Vries M, van Diemen CC, Nedeljković I, Amin N, et al.; Biobank-based Integrative Omics Study Consortium (2018). Occupational exposure to pesticides is associated with differential DNA methylation. Occup Environ Med. 75(6):427–35. https://doi.org/10.1136/oemed-2017-104787 PMID:29459480

Van Maele-Fabry G, Lombaert N, Lison D (2016). Dietary exposure to cadmium and risk of breast cancer in postmenopausal women: a systematic review and meta-analysis. Environ Int. 86:1–13. https://doi.org/10.1016/j.envint.2015.10.003 PMID:26479829

van Tong H, Brindley PJ, Meyer CG, Velavan TP (2017). Parasite infection, carcinogenesis and human malignancy. EBioMedicine. 15:12–23. https://doi.org/10.1016/j.ebiom.2016.11.034 PMID:27956028

van Veldhoven K, Keski-Rahkonen P, Barupal DK, Villanueva CM, Font-Ribera L, Scalbert A, et al. (2018). Effects of exposure to water disinfection by-products in a swimming pool: a metabolome-wide association study. Environ Int. 111:60–70. https://doi.org/10.1016/j.envint.2017.11.017 PMID:29179034

van Wendel de Joode B, Barraza D, Ruepert C, Mora AM, Córdoba L, Oberg M, et al. (2012). Indigenous children living nearby plantations with chlorpyrifos-treated bags have elevated 3,5,6-trichloro-2-pyridinol (TCPy) urinary concentrations. Environ Res. 117:17–26. https://doi.org/10.1016/j.envres.2012.04.006 PMID:22749112

Varela-Ramirez A, Costanzo M, Carrasco YP, Pannell KH, Aguilera RJ (2011). Cytotoxic effects of two organotin compounds and their mode of inflicting cell death on four mammalian cancer cells. Cell Biol Toxicol. 27(3):159–68. https://doi.org/10.1007/s10565-010-9178-y PMID:21069563

Vaughan TL, Stewart PA, Davis S, Thomas DB (1997). Work in dry cleaning and the incidence of cancer of the oral cavity, larynx, and oesophagus. Occup Environ Med. 54(9):692–5. https://doi.org/10.1136/oem.54.9.692 PMID:9423585

Velazquez I, Alter BP (2004). Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. Am J Hematol. 77(3):257–67. https://doi.org/10.1002/ajh.20183 PMID:15495253

Verhaegen ME, Mangelberger D, Harms PW, Eberl M, Wilbert DM, Meireles J, et al. (2017). Merkel cell polyomavirus small T antigen initiates Merkel cell carcinoma-like tumor development in mice. Cancer Res. 77(12):3151–7. https://doi.org/10.1158/0008-5472.CAN-17-0035 PMID:28512245

Verhoeven DT, Goldbohm RA, van Poppel G, Verhagen H, van den Brandt PA (1996). Epidemiological studies on brassica vegetables and cancer risk. Cancer Epidemiol Biomarkers Prev. 5(9):733–48. PMID:8877066

Verma R, Xu X, Jaiswal MK, Olsen C, Mears D, Caretti G, et al. (2011). In vitro profiling of epigenetic modifications underlying heavy metal toxicity of tungsten-alloy and its components. Toxicol Appl Pharmacol. 253(3):178–87. https://doi.org/10.1016/j.taap.2011.04.002 PMID:21513724

Vermeulen R, Coble JB, Lubin JH, Portengen L, Blair A, Attfield MD, et al. (2010). The Diesel Exhaust in Miners Study: IV. Estimating historical exposures to diesel exhaust in underground non-metal mining facilities. Ann Occup Hyg. 54(7):774–88. PMID:20876235

Viau M, Genot C, Ribourg L, Meynier A (2016). Amounts of the reactive aldehydes, malonaldehyde, 4-hydroxy-2-hexenal, and 4-hydroxy-2-nonenal in fresh and oxidized edible oils do not necessary reflect their peroxide and anisidine values. Eur J Lipid Sci Technol. 118(3):435–44. https://doi.org/10.1002/ejlt.201500103

Vicentino ARR, Carneiro VC, Allonso D, Guilherme RF, Benjamim CF, Dos Santos HAM, et al. (2018). Emerging role of HMGB1 in the pathogenesis of schistosomiasis liver fibrosis. Front Immunol. 9:1979. https://doi.org/10.3389/fimmu.2018.01979 PMID:30258438

Vidlar A, Vostalova J, Ulrichova J, Student V, Krajicek M, Vrbkova J, et al. (2010). The safety and efficacy of a silymarin and selenium combination in men after radical prostatectomy - a six month placebo-controlled double-blind clinical trial. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 154(3):239–44. https://doi.org/10.5507/bp.2010.036 PMID:21048810

Vigneri R, Malandrino P, Gianì F, Russo M, Vigneri P (2017). Heavy metals in the volcanic environment and thyroid cancer. Mol Cell Endocrinol. 457:73–80. https://doi.org/10.1016/j.mce.2016.10.027 PMID:27794445

Vinceti M, Filippini T, Cilloni S, Crespi CM (2017). The epidemiology of selenium and human cancer. Adv Cancer Res. 136:1–48. https://doi.org/10.1016/bs.acr.2017.07.001 PMID:29054414

Vinceti M, Filippini T, Wise LA (2018). Environmental selenium and human health: an update. Curr Environ Health Rep. 5(4):464–85. https://doi.org/10.1007/s40572-018-0213-0 PMID:30280317

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. PMID:17361554 [in Spanish]

Virtamo J, Taylor PR, Kontto J, Männistö S, Utriainen M, Weinstein SJ, et al. (2014). Effects of α-tocopherol and β-carotene supplementation on cancer incidence and mortality: 18-year postintervention follow-up of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Int J Cancer. 135(1):178–85. https://doi.org/10.1002/ijc.28641 PMID:24338499

Vlaanderen J, Straif K, Pukkala E, Kauppinen T, Kyyrönen P, Martinsen JI, et al. (2013). Occupational exposure to trichloroethylene and perchloroethylene and the risk of lymphoma, liver, and kidney cancer in four Nordic countries. Occup Environ Med. 70(6):393–401. https://doi.org/10.1136/oemed-2012-101188 PMID:23447073

Vlaanderen J, Straif K, Ruder A, Blair A, Hansen J, Lynge E, et al. (2014). Tetrachloroethylene exposure and bladder cancer risk: a meta-analysis of dry-cleaning-worker studies. Environ Health Perspect. 122(7):661–6. https://doi.org/10.1289/ehp.1307055 PMID:24659585

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

Von Tungeln LS, Walker NJ, Olson GR, Mendoza MC, Felton RP, Thorn BT, et al. (2017). Low dose assessment of the carcinogenicity of furan in male F344/N Nctr rats in a 2-year gavage study. Food Chem Toxicol. 99:170–81. https://doi.org/10.1016/j.fct.2016.11.015 PMID:27871980

Voss KA, Riley RT (2013). Fumonisin toxicity and mechanism of action: overview and current perspectives. Food Safety. 1(1):49–69. https://doi.org/10.14252/foodsafetyfscj.2013006

Waddell BL, Zahm SH, Baris D, Weisenburger DD, Holmes F, Burmeister LF, et al. (2001). Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). Cancer Causes Control. 12(6):509–17. https://doi.org/10.1023/A:1011293208949 PMID:11519759

Wagner M, Bolm-Audorff U, Hegewald J, Fishta A, Schlattmann P, Schmitt J, et al. (2015). Occupational polycyclic aromatic hydrocarbon exposure and risk of larynx cancer: a systematic review and meta-analysis. Occup Environ Med. 72(3):226–33. https://doi.org/10.1136/oemed-2014-102317 PMID:25398415

Wakeham K, Webb EL, Sebina I, Nalwoga A, Muhangi L, Miley W, et al. (2013). Risk factors for seropositivity to Kaposi sarcoma-associated herpesvirus among children in Uganda. J Acquir Immune Defic Syndr. 63(2):228–33. https://doi.org/10.1097/QAI.0b013e31828a7056 PMID:23403859

Walawalkar YD, Vaidya Y, Nayak V (2016a). Alteration in transforming growth factor-β receptor expression in gallbladder disease: implications of chronic cholelithiasis and chronic *Salmonella typhi* infection. Gastroenterology Insights. 1(1):1–10. https://doi.org/10.4081/gi.2016.6623

Walawalkar YD, Vaidya Y, Nayak V (2016b). Response of *Salmonella* Typhi to bile-generated oxidative stress: implication of quorum sensing and persister cell populations. Pathog Dis. 74(8):1–7. https://doi.org/10.1093/femspd/ftw090 PMID:27609462

Walker DM, Malarkey DE, Seilkop SK, Ruecker FA, Funk KA, Wolfe MJ, et al. (2007). Transplacental carcinogenicity of 3′-azido-3′-deoxythymidine in B6C3F_1 mice and F344 rats. Environ Mol Mutagen. 48(3–4):283–98. https://doi.org/10.1002/em.20297 PMID:17358026

Walker NJ, Crockett PW, Nyska A, Brix AE, Jokinen MP, Sells DM, et al. (2005). Dose-additive carcinogenicity of a defined mixture of "dioxin-like compounds". Environ Health Perspect. 113(1):43–8. https://doi.org/10.1289/ehp.7351 PMID:15626646

Wallace MC, Hamesch K, Lunova M, Kim Y, Weiskirchen R, Strnad P, et al. (2015). Standard operating procedures in experimental liver research: thioacetamide model in mice and rats. Lab Anim. 49(1 Suppl):21–9. https://doi.org/10.1177/0023677215573040 PMID:25835735

Walrath J, Li FP, Hoar SK, Mead MW, Fraumeni JF Jr (1985). Causes of death among female chemists. Am J Public Health. 75(8):883–5. https://doi.org/10.2105/AJPH.75.8.883 PMID:4025649

Walther T, Menrad A, Orzechowski H-D, Siemeister G, Paul M, Schirner M (2003). Differential regulation of in vivo angiogenesis by angiotensin II receptors. FASEB J. 17(14):2061–7. https://doi.org/10.1096/fj.03-0129com PMID:14597675

Wang C, Gu S, Yin X, Yuan M, Xiang Z, Li Z, et al. (2016c). The toxic effects of microcystin-LR on mouse lungs and alveolar type II epithelial cells. Toxicon. 115:81–8. https://doi.org/10.1016/j.toxicon.2016.03.007 PMID:26995211

Wang C, Li P, Xuan J, Zhu C, Liu J, Shan L, et al. (2017c). Cholesterol enhances colorectal cancer progression via ROS elevation and MAPK signaling pathway activation. Cell Physiol Biochem. 42(2):729–42. https://doi.org/10.1159/000477890 PMID:28618417

Wang F, Roberts SM, Butfiloski EJ, Morel L, Sobel ES (2007). Acceleration of autoimmunity by organochlorine pesticides: a comparison of splenic B-cell effects of chlordecone and estradiol in (NZBxNZW)F_1 mice. Toxicol Sci. 99(1):141–52. https://doi.org/10.1093/toxsci/kfm137 PMID:17578864

Wang F, Sobel ES, Butfiloski EJ, Roberts SM (2008b). Comparison of chlordecone and estradiol effects on splenic T-cells in (NZB×NZW)F_1 mice. Toxicol Lett. 183(1–3):1–9. https://doi.org/10.1016/j.toxlet.2008.08.020 PMID:18951962

Wang G, Fowler BA (2008). Roles of biomarkers in evaluating interactions among mixtures of lead, cadmium and arsenic. Toxicol Appl Pharmacol. 233(1):92–9. https://doi.org/10.1016/j.taap.2008.01.017 PMID:18325558

Wang H, Wu X, Lezmi S, Li Q, Helferich WG, Xu Y, et al. (2017a). Extract of *Ginkgo biloba* exacerbates liver metastasis in a mouse colon cancer xenograft model. BMC Complement Altern Med. 17(1):516. https://doi.org/10.1186/s12906-017-2014-7 PMID:29197355

Wang HT, Hu Y, Tong D, Huang J, Gu L, Wu XR, et al. (2012b). Effect of carcinogenic acrolein on DNA repair and mutagenic susceptibility. J Biol Chem. 287(15):12379–86. https://doi.org/10.1074/jbc.M111.329623 PMID:22275365

Wang J, Chen S, Tian M, Zheng X, Gonzales L, Ohura T, et al. (2012a). Inhalation cancer risk associated with exposure to complex polycyclic aromatic hydrocarbon mixtures in an electronic waste and urban area in South China. Environ Sci Technol. 46(17):9745–52. https://doi.org/10.1021/es302272a PMID:22913732

Wang L, Li X, Yang Z, Pan X, Liu X, Zhu M, et al. (2017b). Crotonaldehyde induces autophagy-mediated cytotoxicity in human bronchial epithelial cells via PI3K, AMPK and MAPK pathways. Environ Pollut. 228:287–96. https://doi.org/10.1016/j.envpol.2017.03.083 PMID:28551559

Wang M, Cheng G, Khariwala SS, Bandyopadhyay D, Villalta PW, Balbo S, et al. (2013). Evidence for endogenous formation of the hepatocarcinogen *N*-nitrosodihydrouracil in rats treated with dihydrouracil and sodium nitrite: a potential source of human hepatic DNA carboxyethylation. Chem Biol Interact. 206(1):83–9. https://doi.org/10.1016/j.cbi.2013.07.010 PMID:23911671

Wang Q, Du H, Geng G, Zhou H, Xu M, Cao H, et al. (2014). Matrine inhibits proliferation and induces apoptosis via BID-mediated mitochondrial pathway in esophageal cancer cells. Mol Biol Rep. 41(5):3009–20. https://doi.org/10.1007/s11033-014-3160-3 PMID:24510386

Wang T, Chen L, Yang T, Wang L, Zhao L, Zhang S, et al. (2018a). Cancer risk among children conceived by fertility treatment. Int J Cancer. ijc.32062. PMID:30548591

Wang T, Liu Y, Yuan W, Zhang L, Zhang Y, Wang Z, et al. (2015a). Identification of microRNAome in rat bladder reveals miR-1949 as a potential inducer of bladder cancer following spinal cord injury. Mol Med Rep. 12(2):2849–57. https://doi.org/10.3892/mmr.2015.3769 PMID:25962430

Wang TY, Peng CY, Lee SS, Chou MY, Yu CC, Chang YC (2016a). Acquisition cancer stemness, mesenchymal transdifferentiation, and chemoresistance properties by chronic exposure of oral epithelial cells to arecoline. Oncotarget. 7(51):84072–81. https://doi.org/10.18632/oncotarget.11432 PMID:27557511

Wang WH, Zhou R-Y, Yan Z-P (2008a). Regulatory effect of bushen jianpi recipe on cellular immunity of patients with primary liver cancer after intervention therapy. Zhongguo Zhong Xi Yi Jie He Za Zhi. 28(7):583–7. PMID:18822903 [in Chinese]

Wang X, Huang P, Liu Y, Du H, Wang X, Wang M, et al. (2015b). Role of nitric oxide in the genotoxic response to chronic microcystin-LR exposure in human-hamster hybrid cells. J Environ Sci (China). 29(29):210–8. https://doi.org/10.1016/j.jes.2014.07.036 PMID:25766030

Wang Y, Gao H, Na XL, Dong SY, Dong HW, Yu J, et al. (2016b). Aniline induces oxidative stress and apoptosis of primary cultured hepatocytes. Int J Environ Res Public Health. 13(12):E1188. https://doi.org/10.3390/ijerph13121188 PMID:27916916

Wang Y, Jiang L, He J, Hu M, Zeng F, Li Y, et al. (2018b). The adverse effects of Se toxicity on inflammatory and immune responses in chicken spleens. Biol Trace Elem Res. 185(1):170–6. https://doi.org/10.1007/s12011-017-1224-7 PMID:29302868

Ward MH, Cross AJ, Abnet CC, Sinha R, Markin RS, Weisenburger DD (2012). Heme iron from meat and risk of adenocarcinoma of the esophagus and stomach. Eur J Cancer Prev. 21(2):134–8. https://doi.org/10.1097/CEJ.0b013e32834c9b6c PMID:22044848

Warner SD, Gerbig CG, Strebing RJ, Molello JA (1980). Results of a two-year toxicity and oncogenic study of chlorpyrifos administered to CD-1 mice in the diet. Indianapolis (IN), USA: Dow Chemical Co. [Unpublished]

Watanabe C, Egami T, Midorikawa K, Hiraku Y, Oikawa S, Kawanishi S, et al. (2010). DNA damage and estrogenic activity induced by the environmental pollutant 2-nitrotoluene and its metabolite. Environ Health Prev Med. 15(5):319–26. https://doi.org/10.1007/s12199-010-0146-1 PMID:21432561

Watkins DJ, Ferguson KK, Anzalota Del Toro LV, Alshawabkeh AN, Cordero JF, Meeker JD (2015). Associations between urinary phenol and paraben concentrations and markers of oxidative stress and inflammation among pregnant women in Puerto Rico. Int J Hyg Environ Health. 218(2):212–9. https://doi.org/10.1016/j.ijheh.2014.11.001 PMID:25435060

Watkins DK, Chiazze L Jr, Fryar CD, Amsel J (2001). An historical cohort mortality study of synthetic fiber workers potentially exposed to glycerol polyglycidyl ether. J Occup Environ Med. 43(11):984–8. https://doi.org/10.1097/00043764-200111000-00009 PMID:11725339

Waziry R, Jawad M, Ballout RA, Al Akel M, Akl EA (2017). The effects of waterpipe tobacco smoking on health outcomes: an updated systematic review and meta-analysis. Int J Epidemiol. 46(1):32–43. PMID:27075769

WCRF/AICR (2018). Diet, nutrition, physical activity and cancer: a global perspective. Third expert report. Available from: https://www.wcrf.org/sites/default/files/stomach-cancer-slr.pdf.

Weichenthal S, Moase C, Chan P (2010). A review of pesticide exposure and cancer incidence in the Agricultural Health Study cohort. Environ Health Perspect. 118(8):1117–25. https://doi.org/10.1289/ehp.0901731 PMID:20444670

Weinstein JR, Asteria-Peñaloza R, Diaz-Artiga A, Davila G, Hammond SK, Ryde IT, et al. (2017). Exposure to polycyclic aromatic hydrocarbons and volatile organic compounds among recently pregnant rural Guatemalan women cooking and heating with solid fuels. Int J Hyg Environ Health. 220(4):726–35. https://doi.org/10.1016/j.ijheh.2017.03.002 PMID:28320639

Weiskirchen R, Irungbam K, Longerich T, Roeb E, Padem S, Windhorst A, et al. (2018). *Schistosoma mansoni* egg secreted antigens activate HCC-associated transcription factors c-Jun and STAT3 in hamster and human hepatocytes. Hepatology. 0–3: https://doi.org/10.1002/hep.30192

Weiss J, Sauer A, Divac N, Herzog M, Schwedhelm E, Böger RH, et al. (2010). Interaction of angiotensin receptor type 1 blockers with ATP-binding cassette transporters. Biopharm Drug Dispos. 31(2–3):150–61. https://doi.org/10.1002/bdd.699 PMID:20222053

Weiss T, Angerer J (2002). Simultaneous determination of various aromatic amines and metabolites of aromatic nitro compounds in urine for low level exposure using gas chromatography-mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 778(1–2):179–92. https://doi.org/10.1016/S0378-4347(01)00542-4 PMID:12376125

Welton JC, Marr JS, Friedman SM (1979). Association between hepatobiliary cancer and typhoid carrier state. Lancet. 1(8120):791–4. https://doi.org/10.1016/S0140-6736(79)91315-1 PMID:86039

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 Pt 1):L921–9. PMID:9374718

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 MW, Lee HW, Choi B, Wang HT, Hu Y, Mehta M, et al. (2017). AFB_1 hepatocarcinogenesis is via lipid peroxidation that inhibits DNA repair, sensitizes mutation susceptibility and induces aldehyde-DNA adducts at p53 mutational hotspot codon 249. Oncotarget. 8(11):18213–26. https://doi.org/10.18632/oncotarget.15313 PMID:28212554

Wennborg H, Yuen J, Axelsson G, Ahlbom A, Gustavsson P, Sasco AJ (1999). Mortality and cancer incidence in biomedical laboratory personnel in Sweden. Am J Ind Med. 35(4):382–9. https://doi.org/10.1002/(SICI)1097-0274(199904)35:4<382::AID-AJIM9>3.0.CO;2-F PMID:10086198

Wennborg H, Yuen J, Nise G, Sasco AJ, Vainio H, Gustavsson P (2001). Cancer incidence and work place exposure among Swedish biomedical research personnel. Int Arch Occup Environ Health. 74(8):558–64. https://doi.org/10.1007/s004200100267 PMID:11768044

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, Bradshaw PT, Herring AH, Teitelbaum SL, Beyea J, Stellman SD, et al. (2016). Exposure to multiple sources of polycyclic aromatic hydrocarbons and breast cancer incidence. Environ Int. 89-90:185–92. https://doi.org/10.1016/j.envint.2016.02.009 PMID:26878284

White AJ, Chen J, McCullough LE, Xu X, Cho YH, Teitelbaum SL, et al. (2015). Polycyclic aromatic hydrocarbon (PAH)-DNA adducts and breast cancer: modification by gene promoter methylation in a population-based study. Cancer Causes Control. 26(12):1791–802. https://doi.org/10.1007/s10552-015-0672-7 PMID:26407953

White AJ, O'Brien KM, Niehoff NM, Carroll R, Sandler DP (2019). Metallic air pollutants and breast cancer risk in a nationwide cohort study. Epidemiology. 30(1):20–8. https://doi.org/10.1097/EDE.0000000000000917 PMID:30198937

White MC, Johnson CA, Ashley DL, Buchta TM, Pelletier DJ (1995). Exposure to methyl tertiary-butyl ether from oxygenated gasoline in Stamford, Connecticut. Arch Environ Health. 50(3):183–9. https://doi.org/10.1080/00039896.1995.9940385 PMID:7618951

Whitehead TP, Metayer C, Wiemels JL, Singer AW, Miller MD (2016). Childhood leukemia and primary prevention. Curr Probl Pediatr Adolesc Health Care. 46(10):317–52. https://doi.org/10.1016/j.cppeds.2016.08.004 PMID:27968954

Whitlock G, Clark T, Vander Hoorn S, Rodgers A, Jackson R, Norton R, et al. (2001). Random errors in the measurement of 10 cardiovascular risk factors. Eur J Epidemiol. 17(10):907–9. https://doi.org/10.1023/A:1016228410194 PMID:12188008

WHO (2000a). Air quality guidelines for Europe, second edition. WHO Regional Publications, European Series, No. 91. Copenhagen, Denmark: WHO Regional Office for Europe. Available from: http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/pre2009/air-quality-guidelines-for-europe.

WHO (2000b). WHO Food Additives Series 46: furfural (addendum). Available from: http://www.inchem.org/documents/jecfa/jecmono/v46je02.htm.

WHO (2004). Brominated acetic acids in drinking-water. Report WHO/SDE/WSH/03.04/79. Geneva, Switzerland: World Health Organization.

WHO (2006). International Programme on Chemical Safety (IPCS). Concise Int Chem Assess Doc. 73:1–65. Mono- and disubstituted methyltin, butyltin, and octyltin compounds. Available from: http://www.inchem.org/documents/cicads/cicads/cicad73.pdf.

WHO (2008). Concise International Chemical Assessment Document 74. 2-Butenal. Available from: http://www.inchem.org/documents/cicads/cicads/cicad74.pdf.

WHO (2009). Toxicological evaluation of certain veterinary drug residues in food prepared by the Seventieth meeting of JECFA. Malachite green. WHO Food Additives Series 61: 37.69.

WHO (2017). WHO Model List of Essential Medicines. 20th ed. Available from: https://www.who.int/medicines/publications/essentialmedicines/en/.

WHO (2018). Food safety digest: aflatoxins. Available from: https://www.who.int/foodsafety/FSDigest_Aflatoxins_EN.pdf.

WHO (2019a). Global Health Observatory (GHO) data. Prevalence of tobacco smoking. Available from: https://www.who.int/gho/tobacco/use/en/, accessed 15 March 2019.

WHO (2019b). Global Health Observatory (GHO) data. Raised cholesterol. Available from: https://www.who.int/gho/ncd/risk_factors/cholesterol_text/en/, accessed 15 March 2019.

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

Wielsøe M, Kern P, Bonefeld-Jørgensen EC (2017). Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit: a case control study. Environ Health. 16(1):56. https://doi.org/10.1186/s12940-017-0269-6 PMID:28610584

Williams CL, Jones ME, Swerdlow AJ, Botting BJ, Davies MC, Jacobs I, et al. (2018). Risks of ovarian, breast, and corpus uteri cancer in women treated with assisted reproductive technology in Great Britain, 1991-2010: data

linkage study including 2.2 million person years of observation. BMJ. 362:k2644. https://doi.org/10.1136/bmj.k2644 PMID:29997145

Williams DE (2012). The rainbow trout liver cancer model: response to environmental chemicals and studies on promotion and chemoprevention. Comp Biochem Physiol C Toxicol Pharmacol. 155(1):121–7. https://doi.org/10.1016/j.cbpc.2011.05.013 PMID:21704190

Williams GM, Iatropoulos MJ, Jeffrey AM, Duan JD (2013). Methyleugenol hepatocellular cancer initiating effects in rat liver. Food Chem Toxicol. 53:187–96. https://doi.org/10.1016/j.fct.2012.11.050 PMID:23220513

Williams TM, Cattley RC, Borghoff SJ (2000). Alterations in endocrine responses in male Sprague-Dawley rats following oral administration of methyl *tert*-butyl ether. Toxicol Sci. 54(1):168–76. https://doi.org/10.1093/toxsci/54.1.168 PMID:10746943

Wilmore JR, Asito AS, Wei C, Piriou E, Sumba PO, Sanz I, et al. (2015). AID expression in peripheral blood of children living in a malaria holoendemic region is associated with changes in B cell subsets and Epstein-Barr virus. Int J Cancer. 136(6):1371–80. https://doi.org/10.1002/ijc.29127 PMID:25099163

Wilmore JR, Maue AC, Rochford R (2016). *Plasmodium chabaudi* infection induces AID expression in transitional and marginal zone B cells. Immun Inflamm Dis. 4(4):497–505. https://doi.org/10.1002/iid3.134 PMID:27980783

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

Wiréhn AB, Törnberg S, Carstensen J (2005). Serum cholesterol and testicular cancer incidence in 45,000 men followed for 25 years. Br J Cancer. 92(9):1785–6. https://doi.org/10.1038/sj.bjc.6602539 PMID:15827555

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

Wong CM, Tsang H, Lai HK, Thomas GN, Lam KB, Chan KP, et al. (2016). Cancer mortality risks from long-term exposure to ambient fine particle. Cancer Epidemiol Biomarkers Prev. 25(5):839–45. https://doi.org/10.1158/1055-9965.EPI-15-0626 PMID:27197138

Woutersen RA, Appelman LM, Van Garderen-Hoetmer A, Feron VJ (1986). Inhalation toxicity of acetaldehyde in rats. III. Carcinogenicity study. Toxicology. 41(2):213–31. https://doi.org/10.1016/0300-483X(86)90201-5 PMID:3764943

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 assessement. Food Chem Toxicol. 120:510–22. https://doi.org/10.1016/j.fct.2018.07.035 PMID:30055318

Wróbel A, Gregoraszczuk EL (2013). Effects of single and repeated in vitro exposure of three forms of parabens, methyl-, butyl- and propylparabens on the proliferation and estradiol secretion in MCF-7 and MCF-10A cells. Pharmacol Rep. 65(2):484–93. https://doi.org/10.1016/S1734-1140(13)71024-7 PMID:23744433

Wróbel AM, Gregoraszczuk EŁ (2014). Actions of methyl-, propyl- and butylparaben on estrogen receptor-α and -β and the progesterone receptor in MCF-7 cancer cells and non-cancerous MCF-10A cells. Toxicol Lett. 230(3):375–81. https://doi.org/10.1016/j.toxlet.2014.08.012 PMID:25128701

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 signaling 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.2015.08.001 PMID:26253279

Wu F, Khan S, Wu Q, Barhoumi R, Burghardt R, Safe S (2008). Ligand structure-dependent activation of estrogen receptor alpha/Sp by estrogens and xenoestrogens. J Steroid Biochem Mol Biol. 110(1–2):104–15. https://doi.org/10.1016/j.jsbmb.2008.02.008 PMID:18400491

Wu QJ, Yang Y, Vogtmann E, Wang J, Han LH, Li HL, et al. (2013a). Cruciferous vegetables intake and the risk of colorectal cancer: a meta-analysis of observational studies. Ann Oncol. 24(4):1079–87. https://doi.org/10.1093/annonc/mds601 PMID:23211939

Wu QJ, Yang Y, Wang J, Han LH, Xiang YB (2013b). Cruciferous vegetable consumption and gastric cancer risk: a meta-analysis of epidemiological studies. Cancer Sci. 104(8):1067–73. https://doi.org/10.1111/cas.12195 PMID:23679348

Wu X, Cobbina SJ, Mao G, Xu H, Zhang Z, Yang L (2016). A review of toxicity and mechanisms of individual and mixtures of heavy metals in the environment. Environ Sci Pollut Res Int. 23(9):8244–59. https://doi.org/10.1007/s11356-016-6333-x PMID:26965280

Wu Y, Li RW, Huang H, Fletcher A, Yu L, Pham Q, et al. (2019). Inhibition of tumor growth by dietary indole-3-carbinol in a prostate cancer xenograft model may be associated with disrupted gut microbial interactions. Nutrients. 11(2):467. https://doi.org/10.3390/nu11020467 PMID:30813350

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

Xie H, LaCerte C, Thompson WD, Wise JP Sr (2010). Depleted uranium induces neoplastic transformation in human lung epithelial cells. Chem Res Toxicol. 23(2):373–8. https://doi.org/10.1021/tx9003598 PMID:20000475

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 W-Z, Jin Y-H, Leng W-D, Wang X-H, Zeng X-T; BPSC investigators (2018). Periodontal disease and risk of bladder cancer: a meta-analysis of 298476 participants. Front Physiol. 9:979. https://doi.org/10.3389/fphys.2018.00979 PMID:30083109

Xing Y, Wang Y, Wang S, Wang X, Fan D, Zhou D, et al. (2016). Human cytomegalovirus infection contributes to glioma disease progression via upregulating endocan expression. Transl Res. 177:113–26. https://doi.org/10.1016/j.trsl.2016.06.008 PMID:27474433

Xu L, Li T, Ding W, Cao Y, Ge X, Wang Y (2018). Combined seven miRNAs for early hepatocellular carcinoma detection with chronic low-dose exposure to microcystin-LR in mice. Sci Total Environ. 628–629:271–81. https://doi.org/10.1016/j.scitotenv.2018.02.021 PMID:29438936

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. Exp Toxicol Pathol. 66(1):1–11. https://doi.org/10.1016/j.etp.2013.07.001 PMID:23890812

Yagyu K, Lin Y, Obata Y, Kikuchi S, Ishibashi T, Kurosawa M, et al. (2004). Bowel movement frequency, medical history and the risk of gallbladder cancer death: a cohort study in Japan. Cancer Sci. https://doi.org/10.1111/j.1349-7006.2004.tb03328.x

Yamada Y, Takashi M, Sakata T, Nakano Y, Takagi Y, Hibi H, et al. (1995). Strain and sex differences in kidney carcinogenesis in rats treated with N-ethyl-N-hydroxyethylnitrosamine and uracil. Hinyokika Kiyo. 41(10):781–7. PMID:8533674

Yamamoto S, Tin-Tin-Win-Shwe, Ahmed S, Kobayashi T, Fujimaki H (2006). Effect of ultrafine carbon black particles on lipoteichoic acid-induced early pulmonary inflammation in BALB/c mice. Toxicol Appl Pharmacol. 213(3):256–66. https://doi.org/10.1016/j.taap.2005.11.007 PMID:16387335

Yang B, Petrick JL, Abnet CC, Graubard BI, Murphy G, Weinstein SJ, et al. (2017b). Tooth loss and liver cancer incidence in a Finnish cohort. Cancer Causes Control. 28(8):899–904. https://doi.org/10.1007/s10552-017-0906-y PMID:28534090

Yang C-F, Ho H-L, Lin S-C, Hsu C-Y, Ho DM-T (2017a). Detection of human cytomegalovirus in glioblastoma among Taiwanese subjects. PLoS One. 12(6):e0179366. https://doi.org/10.1371/journal.pone.0179366 PMID: 28594901

Yang L, Zhang B, Yuan Y, Li C, Wang Z (2014). Oxidative stress and DNA damage in utero and embryo implantation of mice exposed to carbon disulfide at peri-implantation. Hum Exp Toxicol. 33(4):424–34. https://doi.org/10.1177/0960327112474849 PMID:23739845

Yang WS, Zhao H, Wang X, Deng Q, Fan WY, Wang L (2016). An evidence-based assessment for the association between long-term exposure to outdoor air pollution and the risk of lung cancer. Eur J Cancer Prev. 25(3):163–72.

https://doi.org/10.1097/CEJ.0000000000000158 PMID:25757194

Yang Z-H, Fan B-X, Lu Y, Cao Z-S, Yu S, Fan F-Y, et al. (2002). Malignant transformation of human bronchial epithelial cell (BEAS-2B) induced by depleted uranium. Chin J Cancer. 21(9):944–8. [in Chinese]

Yanju B, Yang L, Hua B, Hou W, Shi Z, Li W, et al. (2014). A systematic review and meta-analysis on the use of traditional Chinese medicine compound kushen injection for bone cancer pain. Support Care Cancer. 22(3):825–36. https://doi.org/10.1007/s00520-013-2063-5 PMID:24276956

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 H, Peng Y, Zheng J (2016). Identification of glutathione and related cysteine conjugates derived from reactive metabolites of methyleugenol in rats. Chem Biol Interact. 253:143–52. https://doi.org/10.1016/j.cbi.2016.05.006 PMID:27154494

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

Yasokawa D, Murata S, Iwahashi Y, Kitagawa E, Nakagawa R, Hashido T, et al. (2010). Toxicity of methanol and formaldehyde towards *Saccharomyces cerevisiae* as assessed by DNA microarray analysis. Appl Biochem Biotechnol. 160(6):1685–98. https://doi.org/10.1007/s12010-009-8684-y PMID:19499198

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

Yoon S, Choi J-W, Lee E, An H, Choi HD, Kim N (2015). Mobile phone use and risk of glioma: a case-control study in Korea for 2002-2007. Environ Health Toxicol. 30:e2015015. https://doi.org/10.5620/eht.e2015015 PMID:26726040

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

Yu C, Guo Y, Bian Z, Yang L, Millwood IY, Walters RG, et al.; China Kadoorie Biobank Collaborative Group (2018). Association of low-activity ALDH2 and alcohol consumption with risk of esophageal cancer in Chinese adults: a population-based cohort study. Int J Cancer. 143(7):1652–61. https://doi.org/10.1002/ijc.31566 PMID:29707772

Yu FL (2002). 17β-estradiol epoxidation as the molecular basis for breast cancer initiation and prevention. Asia Pac J Clin Nutr. 11(Suppl 7):S460–6. https://doi.org/10.1046/j.1440-6047.11.s.7.4.x PMID:12492635

Yu X, Yin H, Peng H, Lu G, Liu Z, Dang Z (2019). 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

Yuan JM, Butler LM, Gao YT, Murphy SE, Carmella SG, Wang R, et al. (2014). Urinary metabolites of a polycyclic aromatic hydrocarbon and volatile organic compounds in relation to lung cancer development in lifelong never smokers in the Shanghai Cohort Study. Carcinogenesis. 35(2):339–45. https://doi.org/10.1093/carcin/bgt352 PMID:24148823

Yue YC, Li MH, Wang HB, Zhang BL, He W (2018). The toxicological mechanisms and detoxification of depleted uranium exposure. Environ Health Prev Med. 23(1):18. https://doi.org/10.1186/s12199-018-0706-3 PMID:29769021

Yumrutas O, Kara M, Atilgan R, Kavak SB, Bozgeyik I, Sapmaz E (2015). Application of talcum powder, trichloroacetic acid and silver nitrate in female rats for non-surgical sterilization: evaluation of the apoptotic pathway mRNA and miRNA genes. Int J Exp Pathol. 96(2):111–5. https://doi.org/10.1111/iep.12123 PMID:25885949

Zacharski LR, Chow BK, Howes PS, Shamayeva G, Baron JA, Dalman RL, et al. (2008). Decreased cancer risk after iron reduction in patients with peripheral arterial disease: results from a randomized trial. J Natl Cancer Inst. 100(14):996–1002. https://doi.org/10.1093/jnci/djn209 PMID:18612130

Zafiropoulos A, Tsarouhas K, Tsitsimpikou C, Fragkiadaki P, Germanakis I, Tsardi M, et al. (2014). Cardiotoxicity in rabbits after a low-level exposure to diazinon, propoxur, and chlorpyrifos. Hum Exp Toxicol. 33(12):1241–52. https://doi.org/10.1177/0960327114532384 PMID:24818614

Zane M, Parello C, Pennelli G, Townsend DM, Merigliano S, Boscaro M, et al. (2017). Estrogen and thyroid cancer is a stem affair: a preliminary study. Biomed Pharmacother. 85:399–411. https://doi.org/10.1016/j.biopha.2016.11.043 PMID:27899250

Zanetti I, Coati I, Alaibac M (2017). Interaction between Merkel cell carcinoma and the immune system: pathogenetic and therapeutic implications. Mol Clin Oncol. 7(5):729–32. https://doi.org/10.3892/mco.2017.1406 PMID:29142746

Zeidler-Erdely PC, Meighan TG, Erdely A, Battelli LA, Kashon ML, Keane M, et al. (2013). Lung tumor promotion by chromium-containing welding particulate matter in a mouse model. Part Fibre Toxicol. 10(1):45. https://doi.org/10.1186/1743-8977-10-45 PMID:24107379

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(S21):2–141. https://doi.org/10.1002/em.2850190603 PMID:1541260

Zeljezic D, Garaj-Vrhovac V, Perkovic P (2006). Evaluation of DNA damage induced by atrazine and atrazine-based herbicide in human lymphocytes in vitro using a comet and DNA diffusion assay. Toxicol In Vitro. 20(6):923–35. https://doi.org/10.1016/j.tiv.2006.01.017 PMID:16527446

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

Zhang B, Li SS, Li L, Han R, Zhang ZH (2018a). Effect of crotonaldehyde long-term exposure induced kidney inflammatory and oxidative injury in male rats. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 36(8):580–4. PMID:30317805 [in Chinese]

Zhang B, Shen C, Yang L, Li C, Yi A, Wang Z (2013a). DNA damage and apoptosis of endometrial cells cause loss of the early embryo in mice exposed to carbon disulfide. Toxicol Appl Pharmacol. 273(2):381–9. https://doi.org/10.1016/j.taap.2013.09.013 PMID:24080331

Zhang C, Liu F, He Z, Deng Q, Pan Y, Liu Y, et al. (2014). Seroprevalence of Merkel cell polyomavirus in the general rural population of Anyang, China. PLoS One. 9(9):e106430. https://doi.org/10.1371/journal.pone.0106430 PMID:25184447

Zhang D, Ni M, Wu J, Liu S, Meng Z, Tian J, et al. (2019b). The optimal Chinese herbal injections for use with radiotherapy to treat esophageal cancer: a systematic review and Bayesian network meta-analysis. Front Pharmacol. 9:1470. https://doi.org/10.3389/fphar.2018.01470 PMID:30662402

Zhang D, Wu J, Liu S, Zhang X, Zhang B (2017b). Network meta-analysis of Chinese herbal injections combined with the chemotherapy for the treatment of pancreatic cancer. Medicine (Baltimore). 96(21):e7005. https://doi.org/10.1097/MD.0000000000007005 PMID:28538415

Zhang D, Wu J, Wang K, Duan X, Liu S, Zhang B (2018b). Which are the best Chinese herbal injections combined with XELOX regimen for gastric cancer?: a PRISMA-compliant network meta-analysis. Medicine (Baltimore). 97(12):e0127. https://doi.org/10.1097/MD.0000000000010127 PMID:29561411

Zhang G-L, Jiang L, Yan Q, Liu RH, Zhang L (2015a). Anti-tumor effect of matrine combined with cisplatin on rat models of cervical cancer. Asian Pac J Trop Med. 8(12):1055–9. https://doi.org/10.1016/j.apjtm.2015.11.005 PMID:26706679

Zhang J, Li Y, Chen X, Liu T, Chen Y, He W, et al. (2011). Autophagy is involved in anticancer effects of matrine on SGC-7901 human gastric cancer cells. Oncol Rep. 26(1):115–24. https://doi.org/10.3892/or.2014.3173 PMID:21519796

Zhang K, Hornef M, Fulde M (2015b). The deadly bite of *Salmonella* Typhi. EMBO Rep. 16(8):887–8. https://doi.org/10.15252/embr.201540748 PMID:26101373

Zhang L, Qin J, Zhang Z, Li Q, Huang J, Peng X, et al. (2016c). Concentrations and potential health risks of methyl tertiary-butyl ether (MTBE) in air and drinking water from Nanning, South China. Sci Total Environ. 541:1348–54. https://doi.org/10.1016/j.scitotenv.2015.10.038 PMID:26479908

Zhang L, Rana I, Shaffer RM, Taioli E, Sheppard L (2019a). Exposure to glyphosate-based herbicides and risk for non-Hodgkin lymphoma: a meta-analysis and supporting evidence. Mutat Res. 781:186–206. https://doi.org/10.1016/j.mrrev.2019.02.001 PMID:31342895

Zhang M, Teng XD, Guo XX, Li ZG, Han JG, Yao L (2013b). Expression of tissue levels of matrix metalloproteinases and their inhibitors in breast cancer. Breast. 22(3):330–4. https://doi.org/10.1016/j.breast.2012.08.002 PMID:22995648

Zhang M, Wang K, Chen L, Yin B, Song Y (2016a). Is phytoestrogen intake associated with decreased risk of prostate cancer? A systematic review of epidemiological studies based on 17,546 cases. Andrology. 4(4):745–56. https://doi.org/10.1111/andr.12196 PMID:27260185

Zhang Q, Feng H, Qluwakemi B, Wang J, Yao S, Cheng G, et al. (2017a). Phytoestrogens and risk of prostate cancer: an updated meta-analysis of epidemiologic studies. Int J Food Sci Nutr. 68(1):28–42. https://doi.org/10.1080/09637486.2016.1216525 PMID:27687296

Zhang Q-S, Tang W, Deater M, Phan N, Marcogliese AN, Li H, et al. (2016b). Metformin improves defective hematopoiesis and delays tumor formation in Fanconi anemia mice. Blood. 128(24):2774–84. https://doi.org/10.1182/blood-2015-11-683490 PMID:27756748

Zhang R-K, Wang C (2018). Effect of matrine on tumor growth and inflammatory factors and immune function in Wistar rat with breast cancer. Zhongguo Ying Yong Sheng Li Xue Za Zhi. 34(4):375–8. https://doi.org/10.12047/j.cjap.5657.2018.086 PMID:30788949 [in Chinese]

Zhang W, Zhang Y, Hou J, Xu T, Yin W, Xiong W, et al. (2017d). Tris (2-chloroethyl) phosphate induces senescence-like phenotype of hepatocytes via the $p21^{Waf1/Cip1}$-Rb pathway in a p53-independent manner. Environ Toxicol Pharmacol. 56:68–75. https://doi.org/10.1016/j.etap.2017.08.028 PMID:28886428

Zhang XL, Xu HR, Chen WL, Chu NN, Li XN, Liu GY, et al. (2009). Matrine determination and pharmacokinetics in human plasma using LC/MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci. 877(27):3253–6. https://doi.org/10.1016/j.jchromb.2009.08.026 PMID:19726245

Zhang Y, Hui F, Yang Y, Chu H, Qin X, Zhao M, et al. (2017c). Can Kushen injection combined with TACE improve therapeutic efficacy and safety in patients with advanced HCC? A systematic review and network meta-analysis. Oncotarget. 8(63):107258–72. https://doi.org/10.18632/oncotarget.20921 PMID:29291026

Zhang Z, Zhang XX, Qin W, Xu L, Wang T, Cheng S, et al. (2012). Effects of microcystin-LR exposure on matrix metalloproteinase-2/-9 expression and cancer cell migration. Ecotoxicol Environ Saf. 77:88–93. https://doi.org/10.1016/j.ecoenv.2011.10.022 PMID:22088328

Zhao G, Wang Z, Zhou H, Zhao Q (2009). Burdens of PBBs, PBDEs, and PCBs in tissues of the cancer patients in the e-waste disassembly sites in Zhejiang, China. Sci Total Environ. 407(17):4831–7. https://doi.org/10.1016/j.scitotenv.2009.05.031 PMID:19539352

Zhao G, Wu X, Chen P, Zhang L, Yang CS, Zhang J (2018). Selenium nanoparticles are more efficient than sodium selenite in producing reactive oxygen species and hyper-accumulation of selenium nanoparticles in cancer cells generates potent therapeutic effects. Free Radic Biol Med. 126:55–66. https://doi.org/10.1016/j.freeradbiomed.2018.07.017 PMID:30056082

Zhao J, Zhao L (2013). Cruciferous vegetables intake is associated with lower risk of renal cell carcinoma: evidence from a meta-analysis of observational studies. PLoS One. 8(10):e75732. https://doi.org/10.1371/journal.pone.0075732 PMID:24204579

Zhao L, Mao L, Hong G, Yang X, Liu T (2015). Design, synthesis and anticancer activity of matrine-1*H*-1,2,3-triazole-chalcone conjugates. Bioorg Med Chem Lett. 25(12):2540–4. https://doi.org/10.1016/j.bmcl.2015.04.051 PMID:25959813

Zhao Q, Wang Y, Cao Y, Chen A, Ren M, Ge Y, et al. (2014). Potential health risks of heavy metals in cultivated topsoil and grain, including correlations with human primary liver, lung and gastric cancer, in Anhui province, Eastern China. Sci Total Environ. 470-471:340–7. https://doi.org/10.1016/j.scitotenv.2013.09.086 PMID:24144938

Zhao Z, Yu P, Feng X, Yin Z, Wang S, Qiu Z, et al. (2017). No associations between fruit and vegetable consumption and pancreatic cancer risk: a meta-analysis of prospective studies. Oncotarget. 9(63):32250–61. 10.18632/oncotarget.23128 PMID:30181814

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 J, Chen KH, Yan X, Chen SJ, Hu GC, Peng XW, et al. (2013). Heavy metals in food, house dust, and water from an e-waste recycling area in South China and the potential risk to human health. Ecotoxicol Environ Saf. 96:205–12. https://doi.org/10.1016/j.ecoenv.2013.06.017 PMID:23849468

Zheng T, Zahm SH, Cantor KP, Weisenburger DD, Zhang Y, Blair A (2001). Agricultural exposure to carbamate pesticides and risk of non-Hodgkin lymphoma. J Occup Environ Med. 43(7):641–9. https://doi.org/10.1097/00043764-200107000-00012 PMID:11464396

Zheng TZ, Boyle P, Hu HF, Duan J, Jian PJ, Ma DQ, et al. (1990). Dentition, oral hygiene, and risk of oral cancer: a case-control study in Beijing, People's Republic of China. Cancer Causes Control. 1(3):235–41. https://doi.org/10.1007/BF00117475 PMID:2102296

Zheng X, Xu X, Yekeen TA, Chen A, Kim SS, Dietrich KN, et al. (2016). Ambient air heavy metals in $PM_{2.5}$ and potential human health risk assessment in an informal electronic waste recycling site of China. Aerosol Air Qual Res. 16:388–97. https://doi.org/10.4209/aaqr.2014.11.0292

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

Zhou M, Tu WW, Xu J (2015b). Mechanisms of microcystin-LR-induced cytoskeletal disruption in animal cells. Toxicon. 101:92–100. https://doi.org/10.1016/j.toxicon.2015.05.005 PMID:25981867

Zhou Y, Zhao H, Peng C (2015a). 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 Q, Wang Z, Zhou L, Ren Y, Gong Y, Qin W, et al. (2018). The role of cadherin-11 in microcystin-LR-induced migration and invasion in colorectal carcinoma cells. Oncol Lett. 15(2):1417–22. PMID:29399188

Zhu Y, Wang PP, Zhao J, Green R, Sun Z, Roebothan B, et al. (2014). Dietary *N*-nitroso compounds and risk of colorectal cancer: a case-control study in Newfoundland and Labrador and Ontario, Canada. Br J Nutr. 111(6):1109–17. https://doi.org/10.1017/S0007114513003462 PMID:24160559

Ziegler RG, Fuhrman BJ, Moore SC, Matthews CE (2015). Epidemiologic studies of estrogen metabolism and breast cancer. Steroids. 99(Pt A):67–75. https://doi.org/10.1016/j.steroids.2015.02.015 PMID:25725255

Annex 1

List of Participants

IARC requests that you do not contact or lobby meeting participants, 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.

Working Group Members and Invited Specialists 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.

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Jiri Zavadil, Molecular Mechanisms and Biomarkers Group (Group Head)

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 interests.

Official invitations were extended after careful assessment of any declared interests that might constitute a real or perceived 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 Monographs Programme at imo@iarc.fr.

Participants identified as Invited Specialists will not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or draft text that pertains to the description or interpretation of cancer data. The Declarations will be updated and reviewed again at the opening of the meeting.

Posted on 14 February 2019, updated on 30 October 2019

[1]Susan Borghoff is employed by ToxStrategies, a consulting firm that has provided research services to the American Beverage Association.

Annex 2

MEETING AGENDA

Monday 25 March 2019

09:00–09:30	Registration, lobby
09:30–10:30	Plenary session: introductions and discussion of prioritization criteria
10:30–11:00	Group photo, lobby
11:00–13:00	Subgroup sessions: exposure, human cancer, cancer bioassays, mechanisms
14:00–16:00	Subgroup sessions: exposure, human cancer, cancer bioassays, mechanisms
16:30–17:30	Subgroup sessions: exposure, human cancer, cancer bioassays, mechanisms
17:30–18:00	Remote presentation from Dr Dinesh K. Barupal, University of California Davis, USA
18:00–19:00	Chairs' coordination meeting

Tuesday 26 March 2019

09:00–10:30	Plenary session: subgroup presentations
11:00–13:00	Subgroup sessions: agent type categories
14:00–15:45	Subgroup sessions: agent type categories
16:15–17:00	Subgroup sessions: agent type categories
17:00–18:00	Chairs' coordination meeting
20:00	Group dinner

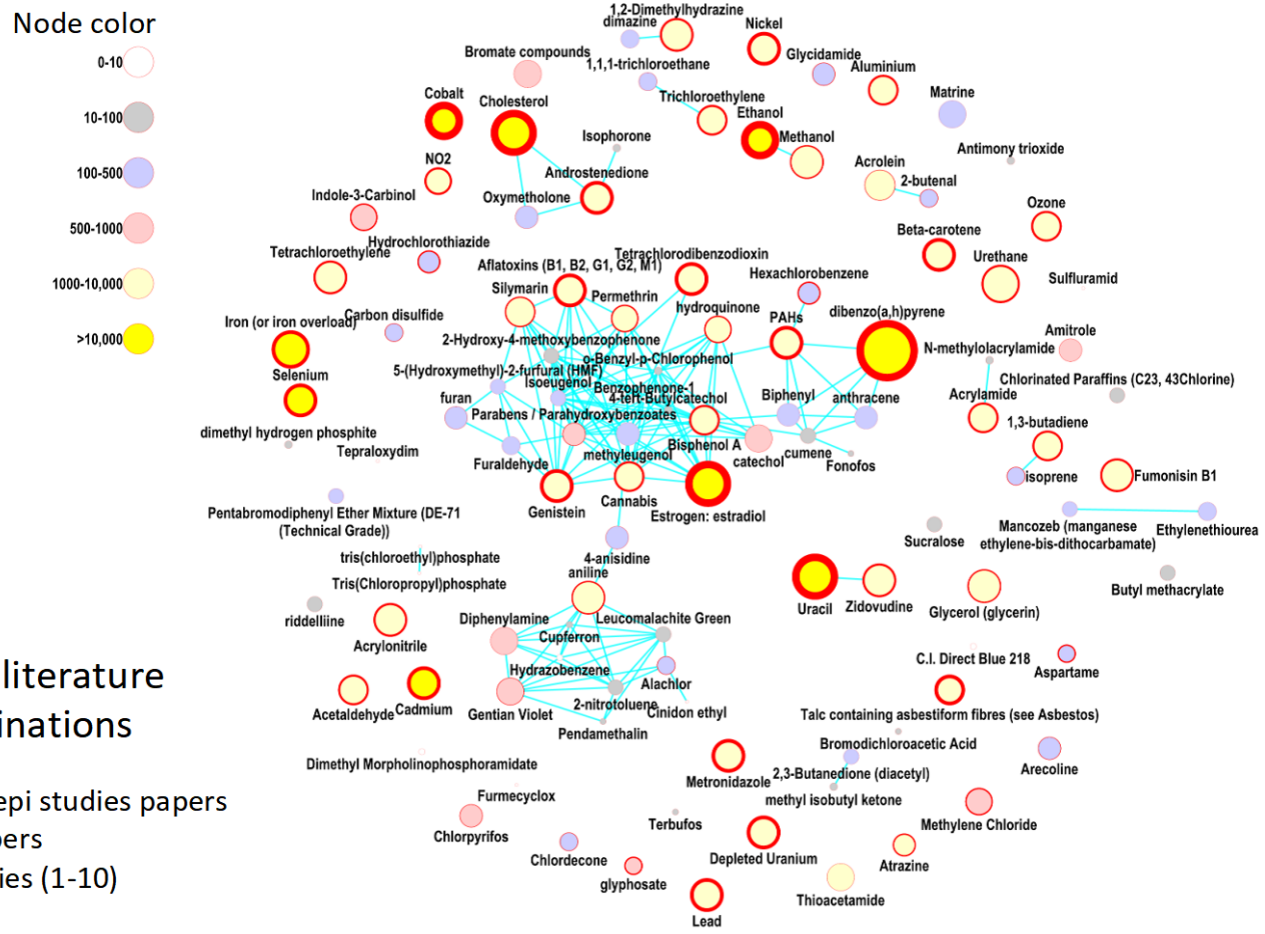
Wednesday 27 March 2019

09:00–10:30	Plenary session
11:00–13:00	Report revision and finalisation
14:00–15:45	Plenary session
16:15–18:00	Plenary session and closing remarks
18:00	Closing reception

Annex 3

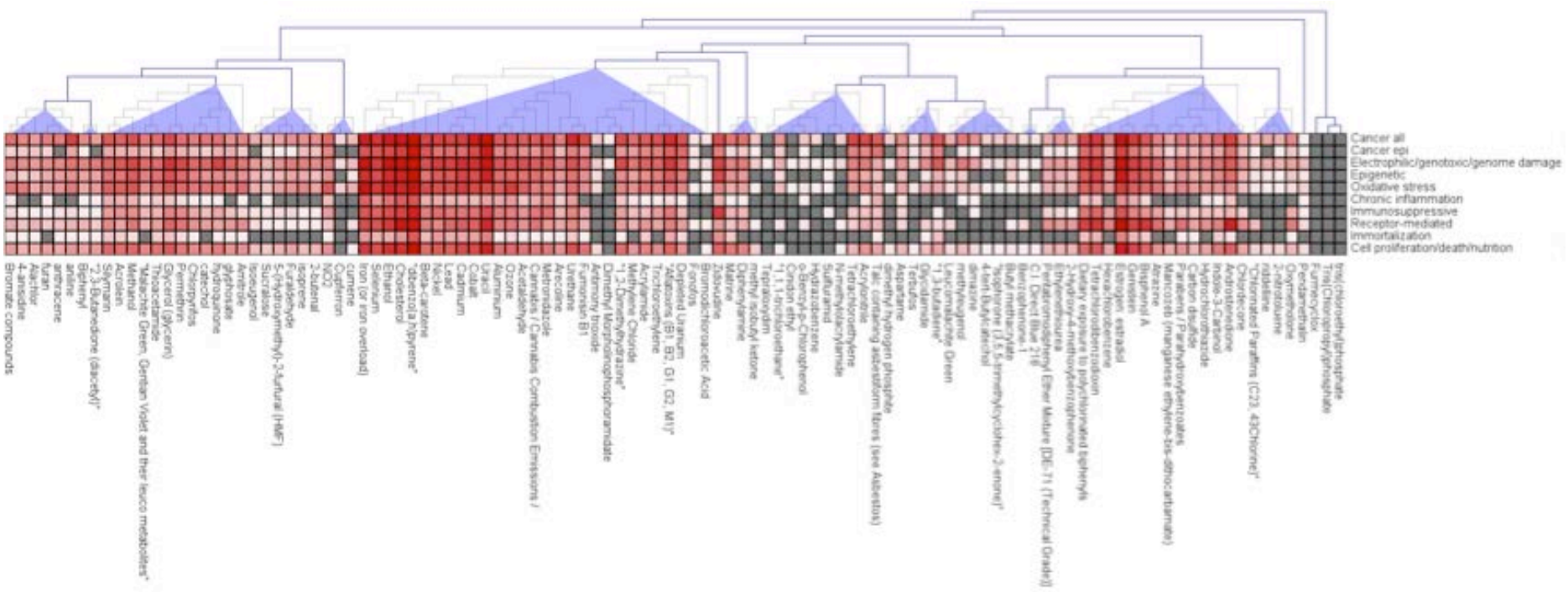
Topic	Search terms
Cancer all	(neoplasm* OR carcinogen* OR malignan* OR tumor OR tumors OR tumour OR tumours OR cancer OR cancers)
Cancer epi	(neoplasm* OR carcinogen* OR malignan* OR tumor OR tumors OR tumour OR tumours OR cancer OR cancers) AND (“Epidemiology”[Mesh] OR “Epidemiologic Studies”[Mesh] OR epidemiolog* OR case-control OR case-referent OR cohort)
Key characteristics of carcinogens	
1- Is electrophilic; 2- is genotoxic; 3- Alters DNA repair or genomic instability	(“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")
4- induces epigenetic alterations	("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)
5- induces oxidative stress	("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])
6- induces chronic inflammation	((chronic[All Fields] AND "inflammation"[MeSH Terms]) OR (chronic inflamm*))
7- is immunosuppressive	(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

Topic	**Search terms**
	T4 Lymphocyte[tw])
8- modulates receptor-mediated effects	(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])
9- causes immortalization	(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])
10- alters cell proliferation, cell death, or nutrient supply	(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])



Chemical map and literature data for 2019 nominations

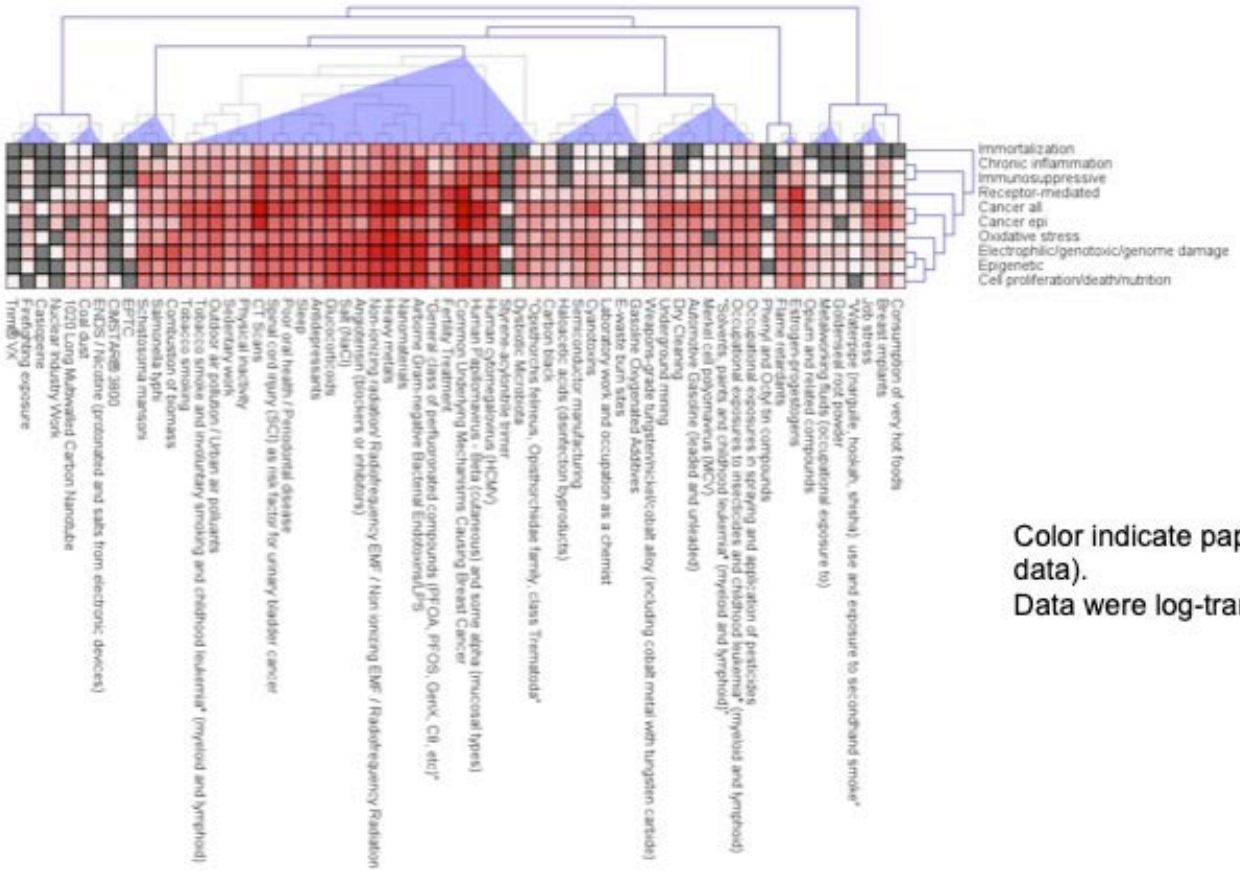
Node border thickness – epi studies papers
Node size – cancer all papers
Node color – sum of queries (1-10)



Clustering of chemical agents using literature data

Color indicate paper count : pink (min) red (max) and grey (no data).
Data were log-transformed before the clustering analysis.

Clustering of non chemical agents using literature data



Color indicate paper count : pink (min) red (max) and grey (no data).
Data were log-transformed before the clustering analysis.

Annex 4

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

Agent name	Rationale
Agents not previously evaluated by the *IARC Monographs*	
Haloacetic acids (and other disinfection by-products)	Relevant human cancer, bioassay, and mechanistic evidence
Metalworking fluids	Relevant human cancer and bioassay evidence
Cannabis smoking, Fertility treatment, Glucocorticoids, *Salmonella typhi*, Sedentary behaviour*, Tetracyclines and other photosensitizing drugs	Relevant human cancer and mechanistic evidence
Cupferron, Gasoline oxygenated additives, Gentian violet, Glycidamide, Malachite green and Leucomalachite green, Oxymetholone, Pentabromodiphenyl ethers, Vinclozolin	Relevant bioassay and mechanistic evidence
Breast implants, Dietary salt intake*, Neonatal phototherapy*, Poor oral hygiene*	Relevant human cancer evidence
Aspartame	Relevant bioassay evidence
Arecoline, Carbon disulfide, Electronic nicotine delivery systems and Nicotine*, Human cytomegalovirus, Parabens	Relevant mechanistic evidence
Agents previously evaluated by the *IARC Monographs*[2]	
Automotive gasoline (leaded and unleaded), Carbaryl, Malaria	New human cancer, bioassay, and mechanistic evidence to warrant re-evaluation of the classification

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

Agent name	Rationale
Acrylamide*, Acrylonitrile, Some anthracyclines, Coal dust, Combustion of biomass, Domestic talc products, Firefighting exposure, Metallic nickel, Some pyrethroids (i.e. permethrin, cypermethrin, deltamethrin)	New human cancer and mechanistic evidence to warrant re-evaluation of the classification
Aniline, Acrolein, Methyl eugenol and isoeugenol*, Multi-walled carbon nanotubes*, Non-ionizing radiation (radiofrequency)*, Some perfluorinated compounds (e.g. perfluorooctanoic acid)	New bioassay and mechanistic evidence to warrant re-evaluation of the classification
Estrogen: estradiol and estrogen–progestogens[3], Hydrochlorothiazide, Merkel cell polyomavirus, Perchloroethylene, Very hot foods and beverages	New human cancer evidence to warrant re-evaluation of the classification
1,1,1-Trichloroethane, Weapons-grade tungsten/nickel/cobalt alloy	New bioassay evidence to warrant re-evaluation of the classification
Acetaldehyde, Bisphenol A*, Cobalt and cobalt compounds, Crotonaldehyde, Cyclopeptide cyanotoxins, Fumonisin B_1, Inorganic lead compounds, Isoprene, *o*-Anisidine	New mechanistic evidence to warrant re-evaluation of the classification

[1] Evidence of human exposure was identified for all agents.

[2] See https://monographs.iarc.fr/list-of-classifications for list of current classifications.

[3] Group 1 carcinogen; new evidence of cancer in humans indicates possible causal association(s) for additional tumour site(s) (see Section 3 of the Preamble to the *IARC Monographs*).

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

Table 2. Agents recommended for evaluation by the *IARC Monographs* with medium and low priority[1]

Agent name	Previous evaluation status
Medium-priority agents	
2,3-Butanedione (diacetyl), Alachlor, Biphenyl, Chlorinated paraffins, Chlorpyrifos, C.I. Direct Blue 218, Diphenylamine, Hydrazobenzene, Indole-3-carbinol, Mancozeb, Nanomaterials (e.g. titanium dioxide or nanosilica), Nitrogen dioxide, *o*-Benzyl-*p*-chlorophenol, Ozone, Pendimethalin, Sleep, Styrene-acrylonitrile trimer, Terbufos, Tris(chloropropyl) phosphate	Agents not previously evaluated by the *IARC Monographs*
Aflatoxins[3], Anthracene, Antimony trioxide, Atrazine, Bromate compounds, Dimethyl hydrogen phosphite, Furan, *N*-Methylolacrylamide, *p*-Nitrotoluene, *Schistosoma mansoni*, Tris(2-chloroethyl) phosphate, Tobacco smoking (including second-hand)[3]	Agents previously evaluated by the *IARC Monographs*[2]
Low-priority agents	
2-Hydroxy-4-methoxybenzophenone, Aluminium, Androstenedione, Butyl methacrylate, Cinidon ethyl, Dysbiotic microbiota, Fonofos, Furmecyclox, Isoflavones, Isophorone, Laboratory work and occupation as a chemist, Methanol, *S*-Ethyl-*N*,*N*-dipropylthiocarbamate, Semiconductor manufacturing, Sucralose	Agents not previously evaluated by the *IARC Monographs*
1,1-Dimethylhydrazine, Benzophenone-1, Carbon black, Catechol, Chlordecone, Cumene, Dichloromethane, Hepatitis D virus, Human papillomavirus – Beta (cutaneous) and some alpha (mucosal) type), *Opisthorchis felineus*, Outdoor air pollution[3], Pyrrolizidine alkaloids, Selenium and selenium compounds	Agents previously evaluated by the *IARC Monographs*[2]

[1] Evidence of human exposure was identified for all agents.

[2] See https://monographs.iarc.fr/list-of-classifications for list of current classifications.

[3] Group 1 carcinogen; new evidence of cancer in humans indicates possible causal association(s) for additional tumour site(s) (see Section 3 of the Preamble to the *IARC Monographs*).

Exhibit B

EXECUTIVE SUMMARY[1]

PRELIMINARY RECOMMENDATIONS ON TESTING METHODS FOR ASBESTOS IN TALC AND CONSUMER PRODUCTS CONTAINING TALC

January 6, 2020

In the fall of 2018, the United States Food and Drug Administration (US FDA) formed the Interagency Working Group on Asbestos in Consumer Products (IWGACP), with representatives from eight federal agencies[2], to support the development of standardized testing methods for asbestos and other mineral particles of health concern in talc that could potentially affect consumer product safety.[3] The IWGACP was formed in response to reports of the presence of asbestos in talc-containing cosmetic products, with talc being the presumptive source of asbestos. Since 2017, there have been several voluntary recalls of cosmetic products by retailers in the US and globally (Canada, Netherlands, Taiwan) due to the presence of asbestos.

Talc is a hydrated magnesium silicate mineral that is used in a wide variety of consumer products including cosmetics, foods, dietary supplements, drugs, medical devices, ceramics, and art materials. Raw material talc is obtained from mines that may also contain asbestos and related minerals. Removal of asbestos by purification of talc ores is extremely difficult. Thus, judicious selection of talc deposits and mining locations within the deposits is necessary to avoid contamination with asbestos and similar biologically active mineral particles. It is imperative that appropriate monitoring methods are available to detect asbestos in talc to ensure its suitability as a raw material for use as an ingredient in consumer products.

The health hazards associated with asbestos are well documented. There is general agreement among US federal agencies, most developed nations, and the World Health Organization (WHO) that there is no known safe level of asbestos exposure. Inhalation of asbestos, from any source, is a safety concern because it can cause the formation of scar-like tissue in the lung, resulting in

[1] The recommendations and opinions expressed in this document are based on discussions on matters of "scientific debate" (contentious issues that have not been completely resolved or finalized in the ongoing debate) among subject matter experts on the IWGACP and do not necessarily reflect the opinions or policies of their agencies. These recommendations do not represent proposed changes to any regulations of the U.S. Government. The use of the terms "IWGACP" or "we" refers to the consensus opinion of the working group scientists and not the individual experts or the agencies they represent.

[2] Food and Drug Administration (FDA), National Institutes for Occupational Safety and Health (NIOSH), National Institute of Health (NIH)/ National Institute of Environmental Health Sciences (NIEHS), Occupational Safety and Health Administration (OSHA), Environmental Protection Agency (EPA), Consumer Product Safety Commission (CPSC), the National Institute of Standards & Technology (NIST), and the Department of Interior's U.S. Geological Survey (USGS). The participating federal agencies have expertise in asbestos-testing and/or asbestos-related issues (e.g., from a health perspective), or because they regulate some of the consumer products that contain talc as an ingredient.

[3] By "consumer products", we are referring to products used by consumers, which are regulated by a variety of federal agencies. This includes, but is not limited to, "consumer products" as defined under the Consumer Product Safety Act.

asbestosis or pleural plaques, or it may lead to the development of lung cancers and mesothelioma. Exposure to asbestos may also lead to the development of other cancers.[4]

Concern about the purity of talc used as a raw material was heightened in the early 1970s when numerous cosmetic products tested positive for asbestos. However, at that time the development of asbestos testing methods was still in its infancy. In 1976, the cosmetics industry implemented voluntary asbestos testing of talc raw materials using the Cosmetic, Toiletry, and Fragrance Association (CTFA) J4-1 method. Talc suppliers to the pharmaceutical industry use a similar method to certify that talc meets the United States Pharmacopeia's (USP's) requirement for "Absence of Asbestos." To date, both methods rely on the use of X-ray diffraction (XRD) or infrared (IR) spectroscopy followed by polarized light microscopy (PLM) only if XRD or IR is positive for amphibole or serpentine minerals in talc. The CTFA J4-1 and USP methods remain standard test methods despite long-recognized shortcomings in specificity and sensitivity compared with electron microscopy-based methods.

In 2010, FDA asked the USP to consider revising the current tests for asbestos in talc to ensure adequate specificity, and in 2014 the Talc USP expert panel recommended an update of the Talc USP monograph to require an electron microscopy method for the measurement of asbestos in talc (Woodcock, 2010[5]; Block et al. 2014[6]). Recent reports from testing of cosmetic products indicate that because of shortcomings in sensitivity, light microscopy (polarized light microscopy; PLM) sometimes fails to detect finely-sized particles of asbestos and similar minerals even when they are present in talc. Moreover, modern laboratories with expertise in asbestos testing, when asked to test talc-containing consumer products, routinely perform electron microscopy and do not rely solely on PLM. These findings provide support to recommendations from many scientific experts, including those on this Working Group, that transmission electron microscopy (TEM) should be used for asbestos-testing of talc, even if the findings of PLM are negative. (See, for example, Rohl and Langer, 1974[7], Millette 2015[8], Block et al. 2014[5]).

There are many definitions of "asbestos" used in the commercial, geological, and legal domains. As a commercial term, asbestos refers to a group of six mined minerals that have commercially useful properties including flexibility, durability, and heat-resistance. Mineralogists define "asbestos" as those silicate minerals belonging to the serpentine and amphibole groups which have an unusual fibrous (asbestiform) crystal growth habit as opposed to non-asbestiform crystal

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[4] *Asbestos: Selected Cancers*, 2006, Institute of Medicine of the National Academy, Committee on Asbestos; International Agency for Research on Cancer (IARC), 2012, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Monograph 100C. A Review of Human Carcinogens: Arsenic, Metals, Fibres, and Dusts.

[5]Woodcock, J. (2010) Letter to Roger L. Williams, CEO of USP (October 12, 2010). See https://www.usp.org/sites/default/files/usp/document/get-involved/monograph-modernization/2010-10-12-letter-from-dr-janet-woodcock.pdf

[6] Block LH, Beckers D, Ferret J, Meeker GP, Miller A, Osterberg RE, Patil DM, Pier JW, Riseman S, Rutstein MS, Tomaino GP, Van Orden DR, Webber JS, Medwid J, Wolfgang S, and Moore K (2014) Stimuli to the Revision Process, Modernization of Asbestos Testing in USP Talc USP-PF 40(4) https://www.fairwarning.org/wp-content/uploads/2017/12/11TalcDoc.pdf

6 Rohl AN and Langer AM. (1974) Identification and quantitation of asbestos in talc. Environ Health Perspect. 9: 95-109.

[8] Millette JR (2015) Procedure for the Analysis of Talc for Asbestos. The Microscope 63(1): 11-20.

growth. US asbestos regulations and the test methods required to establish regulatory compliance specify each regulated type of asbestos using mineral and commercial nomenclature. Most US regulations specify the six asbestos minerals historically used commercially: chrysotile (a member of the serpentine group) and asbestiform riebeckite (commercially called "crocidolite"), asbestiform grunerite-cummingtonite (commercially called "amosite"), tremolite asbestos, anthophyllite asbestos, and actinolite asbestos (with the latter five being members of the amphibole group).

Asbestos regulations and standard methods for analysis contain a wide variety of "counting rules" designating how to quantify asbestos in occupational or environmental settings using various microscopic methods. Rules were tailored to simplify counting, to improve statistical analysis, and to provide a threshold for mitigating risk when asbestos is known to be present. To date, counting rules have not specifically considered biological activity, overt toxicity, or epidemiology of the kinds of chrysotile and amphibole particles being detected and counted. That is, all mineral particles meeting specified criteria for mineral type and dimensions are expected to be reported and counted.

Importantly, testing methods pertaining to asbestos in articles of commerce were developed for analyzing "bulk materials" containing at least 1% asbestos as an intentional ingredient by weight or in settings where asbestos was known to be present (*e.g.* mines, mills, factories, schools, and other settings). Published methods for analysis of bulk materials were not intended to determine the presence of asbestos in products at less than 1% concentration. In contrast, the likely amount present when asbestos is a contaminant or impurity in talc or talc-containing consumer products might be orders of magnitude below 1%.

Because no single published testing method can be followed, as written, for the analysis of asbestos in talc and talc-containing consumer products, analytical laboratories appear to be adapting published testing methods that were intended for analysis of asbestos in air or building materials. Thus, to help reconcile potential discrepancies in reports of analysis, IWGACP recommends the development of a standardized method specifically for the analysis of asbestos and other biologically active EMPs in talc and talc-containing consumer products for use by government regulatory authorities, industry, and contracting laboratories. Rigorous training requirements, quality assurance, and quality control would need to accompany the implementation of these methods to maintain consistency of results across the field.

The difficulty of identifying and quantifying individual asbestos or other mineral particles present at low concentrations in talc is compounded by the presence of non-asbestiform analogs with the same elemental composition and crystal structure, but different growth habit. Using TEM, differentiation of chrysotile from non-asbestiform serpentine analogs is relatively straightforward; however, each of the non-asbestiform amphiboles can disaggregate into particles resembling asbestiform fibers, giving rise to disputes between laboratories over whether elongate amphibole particles are truly asbestos, or are particles resulting from attrition of larger particles of a non-asbestiform analog. Because both types of elongate minerals are suspected of having biological activity with similar pathological outcomes, the distinction is irrelevant. Lack of consensus concerning what should be called "asbestos" has persisted since the first reports indicating that asbestos might be present in talc used in cosmetics and has inhibited thorough toxicological and epidemiological investigations of disease attributable to talc that contains asbestos.

In light of this lack of consensus, the IWGACP considered applicable published asbestos test methods[9] and other published documents in developing recommendations for terminology, analytical techniques, and criteria for qualitative and quantitative measurement of asbestos in talc and talc-containing consumer products. Based on its review, the IWGACP agrees with the recommendations and rationale provided in the peer reviewed NIOSH Bulletin 62[10] regarding adopting the term "elongate mineral particle" or "EMP" that is defined as "*any mineral particle with a minimum aspect ratio* [*i.e.*, length: width ratio] *of 3:1.*" Thus, an EMP encompasses both asbestiform and non-asbestiform particles that have dimensions that enable them to be respirable. NIOSH Bulletin 62 also introduced two terms "covered mineral" and "countable EMP," that appear to be applicable to the analysis of talc and talc-containing products. A "covered mineral" is defined as "*a mineral encompassed by a specified regulation or recommended standard*" and a "countable EMP" as "*a particle that meets specified dimensional criteria and is to be counted according to an established protocol*." However, for talc and talc-containing products, the recommendations for covered minerals and countable EMP dimensions differ from those discussed in Bulletin 62 for the NIOSH recommended exposure limit (REL). For talc and talc-containing products:

- Covered minerals include chrysotile (but not other serpentine minerals) and members of the amphibole group (inclusive; not restricted to the five amphiboles used commercially).
- Countable EMPs have an aspect ratio (AR) of $\geq$3:1 and a length of > 0.5 µm using the most inclusive criteria for length and AR from among the "asbestos" counting rules in established testing protocols. The specified minimum length of 0.5 µm is consistent with the counting rules for fibers established by the global standard for TEM sampling and analysis, ISO 10312:2019 (Appendix C) and is supported by studies that indicate asbestos particles and EMPs of these dimensions could pose a health concern.[11]

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[9] The Cosmetic, Toiletry, and Fragrance Association (CTFA) J4-1 Method (1976): http://www.asbestosandtalc.com/EMP%20Detection%20Limits%20ASTM/PCPC000960.pdf ; United States Pharmacopeia (USP) standard for talc (2011): http://ftp.uspbpep.com/v29240/usp29nf24s0_m80360.html; https://www.astm.org/Standard/standards-and-publications.html; USP Food Chemicals Codex (2019): https://www.foodchemicalscodex.org/ ; various ASTM, ISO, EPA, and NIOSH standards: https://www.astm.org/Standard/standards-and-publications.html; https://www.iso.org/standards.html; https://www.epa.gov/asbestos/asbestos-laws-and-regulations; https://www.cdc.gov/niosh/pubs/all_date_desc_nopubnumbers.html

[10] NIOSH (2011) "Asbestos Fibers and Other Elongate Mineral Particles: State of the Science and Roadmap for Research" *Current Intelligence Bulletin 62*. Department of Health and Human Services. Centers for Disease Control and Prevention. National Institute for Occupational Safety and Health. Publication No. 2011-159 (March 2011). http://www.cdc.gov/niosh/docs/2011-159/pdfs/2011-159.pdf.

[11] For example, see Suzuki and Yuen (2002) Asbestos fibers contributing to the induction of human malignant mesothelioma. Ann NY Acad Sci 982: 160-176: https://www.ncbi.nlm.nih.gov/pubmed/12562635; Dodson et al. (2003) Asbestos fiber length as related to potential pathogenicity: a critical review. Am J. Ind. Med. 44: 291-297: https://www.ncbi.nlm.nih.gov/pubmed/12929149; Suzuki et al. (2005) Short, thin, asbestos fibers contribute to the development of human malignant mesothelioma: pathological evidence. Int. J. Hyg. Environ. Health 208(3): 201-210: https://www.ncbi.nlm.nih.gov/pubmed/15971859; Boulanger et al. (2014) Quantification of short and long asbestos fibers to assess asbestos exposure: a review of fiber size toxicity. Environmental Health 13:59: https://www.ncbi.nlm.nih.gov/pubmed/25043725; ANSES (2015) Opinion of the French Agency for Food, Environmental and Occupational Health and Safety on "Health effects and the identification of cleavage fragments of amphiboles from quarried minerals": https://www.anses.fr/en/system/files/AIR2014sa0196RaEN.pdf .

The optimal analytical approach should address potential interference by sample matrices and thereby ensure sensitivity at levels or concentrations that are protective of public health. In addition, multiple sampling and analysis methods will be required to provide all the information that is needed to make health protective identification and classification of asbestos and other EMPs of potential concern. To improve agreement in data interpretation among stakeholders and resolve inconsistencies in applying published methods and counting criteria, IWGACP recommends minimum content and format for analytical reports. IWGACP also suggests written protocols that specify appropriate instruments, methods, and counting rules for the detection, quantification, and classification of EMPs. In conclusion, the IWGACP recommends:

1. Adoption of the term EMP as *"any mineral particle with a minimum aspect ratio of 3:1"*, consistent with how this term is defined in the NIOSH Bulletin 62, to resolve ambiguity and disagreement in mineral (asbestos versus non-asbestos) identification.

2. Testing laboratories report all EMPs having length ≥ 0.5 µm (500 nm).

3. That test methods specify reportable EMPs identified as amphibole or chrysotile particles as covered minerals.

4. Test methods require the counting and reporting of covered EMPs as a function of sample mass. When counting, IWGACP recommends referring to guidelines such as ISO 10312 to classify primary and secondary structures. Individual fibers in secondary structures can be counted recording the dimensions of each fiber.

5. Use of TEM at nominally 20,000x magnification, in addition to PLM, to resolve the issues of sensitivity that cause reporting of false negatives for covered EMPs. IWGACP strongly recommends using TEM with energy dispersive X-ray spectroscopy (EDS) and selected area electron diffraction (SAED) analyses to reliably detect and identify chrysotile and asbestiform and non-asbestiform amphibole minerals, including EMPs whose narrowest width is <200 nm (the limit of resolution for light microscopy). SEM might be useful as a complementary method but has significant shortcomings for identification of chrysotile and visualization of the narrowest particles in the population that can only be overcome by using TEM.

6. That "mass percent," a unit that is frequently used to express content of asbestos in commercial bulk materials, is not appropriate for measurement of EMPs in talc and consumer products containing talc because weight percent does not correlate with the number of fibers, and one large fiber could dominate the mass percent value.

7. Although IWGACP concludes that criteria for differential counting and classification of EMPs meeting criteria in #2 would be beneficial, no specific recommendations were agreed upon during deliberations. Therefore, at this time the IWGACP recommends reporting and counting all EMPs of covered minerals under a single classification with additional information that would allow further classification based on measurements such as mineral type and dimensions in the future.

In addition, the IWGACP has identified the following as areas for directing efforts to promote reliability of the analytical methods for asbestos and other EMPs of health concern in talc and talc-containing consumer products:

- Validation of analytical methods (XRD, PLM, TEM) specific to talc and consumer products containing talc that minimize false positive and false negative results.
- Research and validation of methods of sampling that maximize sample representativeness and minimize error and false positives and false negatives.
- Research on methods for sample preparation, in particular, treatments (e.g. “concentration methods”) that improve sensitivity while leaving covered minerals unchanged with respect to identity and dimensions.
- Development of talc-specific reference standards with known concentrations of specific EMPs that can be used to assess laboratory and analyst proficiency, increase inter-laboratory concurrence in method validation, minimize reporting errors, and potentially provide for improved reliability of quantitative analysis.

Exhibit C

OPEN

Serous Ovarian Cancer Caused by Exposure to Asbestos and Fibrous Talc in Cosmetic Talc Powders—A Case Series

Joan E. Steffen, BA, Triet Tran, BA, BS, Muna Yimam, BS, Kate M. Clancy, Tess B. Bird, DPhil, Mark Rigler, PhD, William Longo, PhD, and David S. Egilman, MD, MPH

Objective: Asbestos is a known cause of ovarian cancer. We report 10 cases of serous ovarian cancer among users of Johnson & Johnson (J&J) asbestos-containing "cosmetic" talc products. **Methods:** We conducted an asbestos exposure assessment during talc application and analyzed surgical tissues and talc containers for asbestos and talc. **Results:** Talc was found in all cases and tremolite and/or anthophyllite asbestos was found in 8/10 cases. The asbestos fibers found in the "cosmetic" talc containers matched those found in tissues. We estimated inhaled asbestos dose ranged from 0.38 to 5.18 fiber years. **Conclusion:** We provide evidence that the inhaled dose of asbestos/fibrous talc from "cosmetic" talc use causes ovarian cancer. The unique combination of the types of asbestiform minerals detected in cancerous tissue and "cosmetic" talc is a fingerprint for exposure to asbestos-containing talc.

Keywords: asbestos, baby powder, cosmetics, Johnson & Johnson, ovarian cancer, talc

Known amongst oncologists as a "silent killer," ovarian cancer is the leading cause of death from all gynecologic cancers and the fifth leading cause of cancer-related deaths among women in the United States.[1] The American Cancer Society estimates that about 22,000 American women will be diagnosed and 13,850 will die of the disease in 2019.[2] In 2010, the agency determined that perineal talc powder use is possibly carcinogenic to humans (group 2b).[3]

Epidemiological studies have examined the relationship between perineal talc use and ovarian cancer. In a 1982 case–control study, Cramer et al[4] first reported an association between genital talc use and ovarian cancer. At least 32 subsequent epidemiologic studies have examined the association between talc powder use and ovarian cancer.[5–36] High-grade serous carcinoma (HGSC) is the most common form of ovarian cancer and the type of ovarian cancer that has been most consistently associated with perineal use of cosmetic talc products.[6–8,10,12,14,15,24,27,29,32,33,36,37] Meta-analyses have consistently shown an increased risk of HGSC of about 1.3 for perineal talc use.[18,38–40]

Asbestos exposure by inhalation occurs during cosmetic talc use.[41,42] International Agency for Research on Cancer (IARC) concluded in 2009 that asbestos was a group 1 ovarian carcinogen.[43,44] Dr Wyers' first reported a case of ovarian cancer in a woman with asbestosis in 1949.[45] Twenty-seven epidemiologic studies have since examined the relationship between asbestos exposure and ovarian cancer.[46–72] Nine of these 27 studies report a statistically significant elevation in ovarian cancer risk.[46–48,51,61,62,68,69,71] Epidemiologic findings have demonstrated consistency in different populations: studies of asbestos and ovarian cancer have shown a statistically-significant association among women in different countries with exposures to different types of asbestos fibers and in various occupational and environmental settings.[46–48,51,61,62,68,69,71] Epidemiologic research also suggests a dose–response relationship for asbestos and ovarian cancer when comparing low-exposure and high-exposure subgroups.[47,72] Camargo et al[73] performed a meta-analysis of 18 cohort studies of occupational asbestos exposure and reported a pooled standardized mortality ratio (SMR) for ovarian cancer of 1.77 (95% confidence interval [CI], 1.37–2.28).

Epidemiologic studies of talc and ovarian cancer have generally accepted representations by talc mining and manufacturing companies that consumer talc has been asbestos-free since 1976.[6–8,10,12,14,15,24,25,27,29,32,36] However, studies show that

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Institution and Ethics approval and informed consent: There was no requirement for ethics review or institutional review board approval because this research was not experimental and was originally conducted pursuant to a lawsuit. Informed consent was obtained from all living patients. For one deceased patient (Case No. 8), consent was obtained from the surviving spouse. For the remaining two deceased patients (Case No. 4 and Case No. 9), authors relied only on public information revealed during court proceedings.

Disclosure (Authors): T.T., J.S., K.C., M.Y. and T.B. work for Dr Egilman, who served as an expert witness in litigation at the request of people who were injured as the result of using talcum powders. Mr Tran, Ms Steffen, Ms Clancy, Ms Yimam, and Dr Bird were not compensated by law firms for work on this paper and the lawyers for the injured plaintiffs did not review this paper and had no input into the content of the paper.

Dr Egilman, Dr Rigler and Dr Longo report payments from lawyers related to the submitted work. All serve as expert witnesses in litigation at the request of people who were injured as the result of using talcum powders; plaintiffs' lawyers paid for the patient examinations taken by Dr Egilman as part of his expert witness work.

Dr Rigler and Dr Longo originally performed the tissue analysis for talc and asbestos as part of their expert witness work and were paid by plaintiffs' lawyers for their work. Dr Egilman has also served as an expert witness at the request of companies who have been sued for exposure to asbestos from their mines or products. They were not compensated for work on this paper and the lawyers for the injured plaintiffs did not review this paper and had no input into the content of the article.

Disclaimer: Historic testing of talc for asbestos is limited in methodology and scope. Courts and plaintiff lawyers have agreed, without the knowledge or permission of their clients, to keep secret some of the documents reported here; these documents became public during court proceedings over the objections of J&J and Imerys. Many documents remain sealed.

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Clinical significance: We provide evidence that asbestiform minerals present in "cosmetic" talc causes ovarian cancer. We provide an estimate of asbestiform minerals inhaled per talc application and cumulative lifetime exposure. The unique combination of asbestiform minerals detected in cancerous tissue and "cosmetic" talc is a fingerprint for exposure to asbestos-containing talc.

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consumer talc contains asbestos and a review of the world's largest talc producers records indicated that talc mines contained asbestos, that asbestos cannot be removed from talc, and that talc used in cosmetics was not asbestos-free.[41,74–82] Case control and cohort studies of talc use and ovarian cancer have not differentiated inhalation and perineal talc exposures, and have not considered inhalation exposures in their analyses; this has contributed to misclassification of exposed cases and inaccurate dose–response assessments.[42] In addition, industry marketing studies from the 1970s indicate that up to 85% of women used talc powders thus many ''controls'' were probably exposed to asbestos containing talcs.[42,83]

We report 10 cases of serous ovarian cancer among users of asbestos-containing Johnson & Johnson (J&J) cosmetic talc products. Unlike most previous studies on talc and ovarian cancer, we focused on inhalation exposures to asbestos during various talc uses and not perineal exposure.[4,6,12,40] We measured inhalation exposures during perineal application of asbestos-containing cosmetic talc. Based on exposure histories, we estimate the dose of inhaled asbestos and the increase in ovarian cancer risk for each case. Our case series also includes tissue analysis for talc and asbestos in both product and cancer tissue. By synthesizing current knowledge of asbestos carcinogenicity and evidence of asbestos in consumer talc products, our case series provides novel insight into the link between cosmetic talc use and ovarian cancer.

MATERIALS AND METHODS

We report 10 cases of serous ovarian cancer in women who primarily or exclusively used a variety of J&J cosmetic talc products including Johnson's Baby Powder (JBP), Shower to Shower (STS), and STS Shimmer.[84] These cases were identified among a group of 22 plaintiffs in Ingham et al versus Johnson & Johnson et al. All plaintiffs were diagnosed with ovarian cancer after exposure to J&J cosmetic talc products and transmission electron microscope (TEM) tissue analysis for talc and asbestos was performed for 10 of these plaintiffs. We only report on the 10 plaintiffs for whom TEM tissue analysis was completed.

There was no requirement for ethics review or institutional review board approval because this research was not experimental and patients participated voluntarily in conjunction with a lawsuit. Informed consent for publication was obtained from all living patients. One patient (Case No. 8) passed away after her exposure history was collected but before consent for publication was obtained. In this case, consent was obtained from the surviving spouse. For the remaining two deceased patients (Case No. 4 and Case No. 9), authors relied only on public information revealed during court proceedings. For the exposure assessment, the researcher wore a respirator and was decontaminated post-assessment. The researcher was not exposed to any risk, required to reveal personal information or subjected to specimen collection. The assessment did not meet the requirements to necessitate Institutional Review Board (IRB) approval.[85]

Patient Histories

Medical histories, exposure histories (history questionnaire attached as Appendix 1, http://links.lww.com/JOM/A685), and physical examinations were collected for all living patients (8/10 cases). Exposure histories included questions about talc powder use and other sources of asbestos exposure. We analyzed the frequency and duration of talc uses for each case. For the two deceased patients (Case No. 4 and Case No. 9), a rough exposure history was compiled from the testimony of relatives who were familiar with each patient. Available medical records were also reviewed for all cases.

Exposure Assessment—Perineal Application

The exposure assessment was completed in a $15'' \times 15'' \times 8''$ room with appropriate negative asbestos airflow technology. The experiment was videotaped using two Sony Model HDR-CX900 cameras with alternating Tyndall and standard lighting. (See Appendix 2, http://links.lww.com/JOM/A686.) Area and background samples were collected using four high-volume area sampling pump stations set up 5″ to 6″ from the talc user; these pump stations used 25 mm air cassettes containing 0.8 μm pore size mixed cellulose ester (MCE) filters with 5.0 μm backing pads and were calibrated to run at 10 L/min. Personal samples were collected using four low-volume pumps affixed to the talc user with the cassettes adjusted to be in the breathing zone of the investigator; the ''personal'' pumps were calibrated to 2.5 L/min. During the experiment, air samples were collected for 5 minutes from all sources.

A researcher wearing personal protective equipment and ''personal'' air pumps used a metal container of JBP for the experiment. Based on JBP advertisements featuring product images, we estimated that the JBP used in this test had been manufactured sometime in the 1950s and sourced from the Val Chisone mine.[86,87] (See Appendix 3, http://links.lww.com/JOM/A688 for images of JBP product tested and for full written report on exposure assessment.) J&J used this mine source from 1946 until 1968 and 1980 to 1981.[86–88] From 1969 to 2003, J&J used Vermont talc in their powder products and later switched to Chinese talc.[42,89] Using *t* test analysis, the asbestos content (fibers per gram) in all the bottles tested were statistically comparable across these three talc sources. (See Appendix 4, http://links.lww.com/JOM/A689)

The JBP can was weighed before the experiment using a Fisher Scientific balance. The researcher wore a bikini bottom over an inner pair of boxer briefs and sat on a chair in the middle of the room for the experiment. To simulate perineal talc application, the researcher shook the talc powder into his hand twice and then rubber the powder into the upper leg area. This was repeated for the other leg. Then, the researcher stood, pulled the bikini bottom down and away from the body, and applied two squeezes of talc powder into the bikini bottom. The researcher released the briefs and sat down on the chair for the remainder of the study. The metal container of JBP was weighed again following the study. After the study, two field blanks were opened inside the study room.

A total of four background samples, four personal samples, and four area samples were collected along with two field blanks. All 12 air samples were analyzed for asbestos by the National Institute Occupational Safety and Health (NIOSH) 7400 phase contrast microscopy method using ''A'' counting rules and by the NIOSH 7402 TEM method.[90,91] For TEM analysis, amphibole asbestos fibers or bundles with substantially parallel sides and an aspect ratio of 3:1 or greater, at least longer than 5.0 μm in length and greater than 0.25 μm were counted as per NIOSH 7402 asbestos structure sizing rules.[91] The four personal air samples were also analyzed by the NIOSH 7402 method for fibrous talc particles.[91] The two field blanks were analyzed for asbestos by phase contrast microscopy and TEM in accordance with NIOSH 7400 and NIOSH 7402.[90,91]

Dose Calculations

For each case, we calculated asbestos dose in environmental fiber years (for consistency with the Environmental Protection Agency (EPA) risk assessment model) and in total fibers inhaled (to account for changes in respiratory intake in infancy vs. adulthood).[92] We used the asbestos dose in environmental fiber years to calculate the excess risk. (See section on Dose–Response Risk Assessment.)

We calculated total asbestos dose based on the four most common usages of J&J talc powder reported among the 10 cases: perineal application (10/10), upper body powdering (9/10), exposure as an adult during diapering (8/10), and exposures as an infant during diapering (7/10). For each of these scenarios, we incorporated the intensity of the exposure (f/cc), duration of each exposure (minutes), and total number of applications (from exposure

histories) to calculate the dose. Although we did not adjust for latency, we excluded exposures that occurred after ovarian cancer diagnosis. Fibrous talc exposures from powdering were excluded from our calculations except exposure from baby diapering.[41] Dement et al[93] did not differentiate type of fiber detected.

For perineal powdering exposures, we relied on measurements from our exposure assessment. (See above.) Air samples were collected over the course of 5 minutes in this test.

For upper body powdering, we used Gordon's et al[41] measurements for shaker application of cosmetic talc powder to the underarm, shoulder, and upper arm area. Gordon et al[41] used Cashmere Bouquet, which used the same Italian mine source as J&J (Val Chisone) from 1940 until 1992.[94,95] Gordon et al[41] found that users were exposed to 1.9 f/cc of asbestos fibers over the course of 5 minutes.[41]

For exposures during diapering, Dement et al[93] from NIOSH found that an adult is exposed to 2.2 f/cc of fibrous material and that a baby is exposed to 1.8 f/cc over the course of two minutes. When subjects reported that their parents had used talc on them during diaper changes as an infant, we relied on diaper changing norms to estimate infant exposures. United States market research and survey data show that diaper changes typically occur 8 to 10 times per day for infants (0 to 6 months) and 4 to 6 times per day for toddlers (6 to 24 months).[96–98] Diaper changing frequency in the U.S. also changed over time: the average number of diaper changes per day over the first two years of life dropped from eight times per day in the 1960s to 5 to 6 times per day by the 1980s due to improvements in disposable diapers and reduction in cloth diaper use.[97,99] Since all of the women in our series were born prior to 1975, we assumed that diaper changes occurred eight times per day for two years.

We calculated the dose for each case in fiber years $\left(\frac{f}{cc} \times year\right)$ using the same conversions as Anderson et al.[100] For consistency with the EPA dose–response curve used for our risk assessment, we calculated the total duration of exposure based on a continuous, 24-hour exposure period (525,600 min/yr) until date of diagnosis.[92]

Formula 1:

Formula to estimate inhalation exposure from talc application:

$$\text{Asbestos exposure in } \frac{f}{cc} \times \frac{\text{duration of each exposure} \times \text{total number of applications}}{525,600 \text{ min per year}} = \text{total dose in } \frac{f}{cc} \cdot \text{years}$$

We also calculated the total number of asbestos fibers inhaled in each case. For adults, we used the National Research Council (NRC)'s estimate of "an annual inhaled air volume of 7,300 m^3" and formula to convert the dose from fiber years to total fibers.[101] We relied on measurements of infant lung volume from Hall[102] and on median infant respiratory rates calculated by Fleming et al[103] to estimate the total inhaled air volume for infants from age 0 to 2. Using time-weighted averages for tidal volume and respiratory rate, we calculated that infants breathed 11,025,072,000 ccs in the first 2 years of life, or 5,512,536,000 ccs per year on average.

Formula 2:

Formula to convert adult exposures to total fibers based on NRC (1984):

$$\left[\text{total does in } \frac{f}{cc} \times \text{years}\right] \times \frac{7,300,000,000 \ cc}{\text{year}} = \text{Total number of asbestos fibers}$$

Formula 3:

Formula to convert infant exposures to total fibers based on Hall[102] and Fleming et al[103]:

$$\left[\text{total does in } \frac{f}{cc} \times \text{years}\right] \times \frac{5,512,536,000 \ cc}{\text{year}} = \text{Total number of asbestos fibers}$$

We added together adult and infant exposures to calculate the exposures in total number of asbestos fibers. See Appendix 5, http://links.lww.com/JOM/A690 for the full dose calculations for each case.

Dose–Response Risk Assessment

We developed a method to apply the EPA dose–response curves for inhaled asbestos and mesothelioma risk to ovarian cancer risk.[92] First, we examined the EPA dose–response table for mesothelioma from environmental asbestos exposure (24-hours, 365 days per year).[92] Utilizing the EPA dose–response estimates, we extrapolated a formula for the line of best fit for mesothelioma risk.

We then identified studies that reported mesothelioma and ovarian cancer rates in the same cohort and calculated comparative risk of mesothelioma versus ovarian cancer for each study.[58,62,63,68,71] (See Table 1.)

Using these studies, we calculated the geometric mean comparative risk of contracting mesothelioma versus ovarian cancer from the same asbestos exposures. We applied this comparative risk to the line of best fit for mesothelioma based on the EPA dose–response data to determine a formula for risk of ovarian cancer.

The subjects of the EPA occupational exposure study were entirely men.[92] Since women are more susceptible to cancer from asbestos exposure, we used Lacourt's[104] findings comparing the mesothelioma odds ratio (OR) in men versus women with the same exposures to adjust the formula for the increase in cancer risk for women. At total doses more than 0 to 0.1 fiber years, women were 1.725 times more likely to have mesothelioma than men.[104] At total doses more than 0.1 to 1 fiber years, women were 2.855 times more likely to have mesothelioma than men.[104] We applied these ratios to the EPA dose curve calculated to obtain a better estimate of the ovarian cancer dose–response in women.

The resulting dose–response curve for inhaled asbestos and ovarian cancer is shown in Fig. 1. We used each case's asbestos dose estimate in fiber years to identify their relative lifetime risk of developing ovarian cancer along the dose–response curve. We then compared each case's risk of contracting ovarian cancer due to inhaled asbestos exposure to the expected incidence of ovarian cancer for those without asbestos exposure: 11.4 per 100,000 from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program.[105]

Tissue Analysis for Asbestos and Talc

Samples from a combination of the left and right ovaries, left and right fallopian tubes, and left and right pelvic lymph nodes were obtained from the hospital for each of the 10 patients. Tissues were analyzed to identify and quantify talc and asbestos content in the tissue.

For tissue analysis, a small portion of the tissue in each block was removed with a clean razor blade and placed in a pre-weighed 20 to 30 mL borosilicate glass vial. The vial was filled with 10 mL of filtered extraction solvent (hexane) and placed in a 60 °C water bath. The filtered extraction solvent was replaced every 20 minutes for a total of three changes. After the last extraction solvent change, two changes of filtered ethanol (10 mL, each) 10 minutes each were performed, then the tissue piece(s) were dried at 110 to 120 °C.

TABLE 1. Studies with Both Mesothelioma and Ovarian Cancer Rates in the Same Cohort and Calculated Comparative Risk of Mesothelioma to Ovarian Cancer in Female-Only Cohorts

Study	Mesothelioma Risk (SMR)	Ovarian Cancer Risk (SMR)	Comparative Risk M/OC
Loomis 2009	10.92	1.23	8.88
Magnani 2008	51.49	2.27	22.68
Pira 2016	51.3	3.03	16.93
Wang 2013	166.67	7.69	21.67
Wilczyńska 2005	22.67	1.76	12.88
Geometric mean of comparative risk			15.69

Tissue samples were digested with 15 to 30 mL of filtered sodium hypochlorite (appx. 8.0% bleach). After digestion, the remaining digested material was filtered through a 25 mm, 0.4 μm polycarbonate (PC) filter. The filter containing the tissue residue was dried and subsequently prepared for TEM examination.

A paraffin control sample (wax blank) was obtained by dissolving a known quantity of the paraffin blocks (devoid of tissue) in 10 mL of filtered extraction solvent and the dissolved solvent/wax solution was then filtered onto a 25 mm, 0.4 μm PC filter. The filter was allowed to dry and then prepared for TEM analysis. A process blank (sample vial) was prepared in the same manner and followed the wax blank and tissue sample vials through all steps.

For TEM analysis, 100 to 300 grid openings were analyzed for all asbestos and talc structures at a magnification of between 4000 and 20,000×. As per standard TEM analysis protocols, asbestos fiber/bundle identification was done by morphology (substantially parallel sides and length to width ratio of at least 5:1), length (greater than 0.5 μm in length), selected area electron diffraction (SAED), and energy dispersive X-ray spectroscopy (EDS).[106–112] Talc structures (platy and fibrous) were identified morphologically, by selected area diffraction (SAED), and energy dispersive spectroscopy (EDS).

RESULTS

Exposure Assessment

Total weight used during the application process was 4.05 g of talc powder. For the five minute sampling time, the average total fiber exposure was 4.52 f/cc (5.86, 4.38, 3.85, and 3.98 f/cc), the average asbestos exposure was 2.57 f/cc (4.51, 1.88, 2.07, and 1.81 f/cc), and the average talc exposure was 1.95 f/cc (1.35, 2.50, 1.78, and 2.16 f/cc) for the talc user personal samples. For area samples, the average total fiber exposure was 0.41 f/cc (0.52, 0.28, 0.42, 0.40 f/cc), the average asbestos exposure was 0.2 f/cc (0.31, 0.20, 0.13, and 0.16 f/cc) and the average fibrous talc exposure was 0.19 f/cc (0.13, 0.08, 0.29, and 0.24 f/cc). The type of asbestos fiber identified in all samples was tremolite asbestos. No fibers were detected in the background samples or field blanks. The complete exposure assessment report, including count sheets and fiber images, is available as Appendix 3, http://links.lww.com/JOM/A688.

Dose Calculations and Risk Assessment

Results for dose calculations, risk assessment, and tissue analysis are summarized in Table 2. See Appendix 5, http://links.lww.com/JOM/A690 for complete past medical history, history of present illness, other ovarian risk factors, exposure history, and dose calculations for each case.

STS was comprised of talcum powder mixed with cornstarch. The STS products contained between 80% and 100% talc sourced from the same mines as JBP.[84] Only four cases used these products for brief or unknown periods of time. Case No. 3 reported infrequent use of unidentified facial make-up powder, and Case No. 6 reported infrequent use of generic store-brand talcum powder. We could not calculate exposures for the brief use of these unknown products.

All cases had pathologically confirmed serous ovarian cancer. Age at diagnosis ranged from 41 to 78 years, with a mean age at diagnosis of 51.1 years and median age at diagnosis of 50 years. By contrast, the median age of ovarian cancer diagnosis in the United States is 63 with most cases occurring in women aged 55 to 64. Seven of 10 cases tested negative for BRCA mutations; two cases were never tested (No. 2 and No. 5), and one case (No. 8) tested positive for BRCA2 variant L771 V.

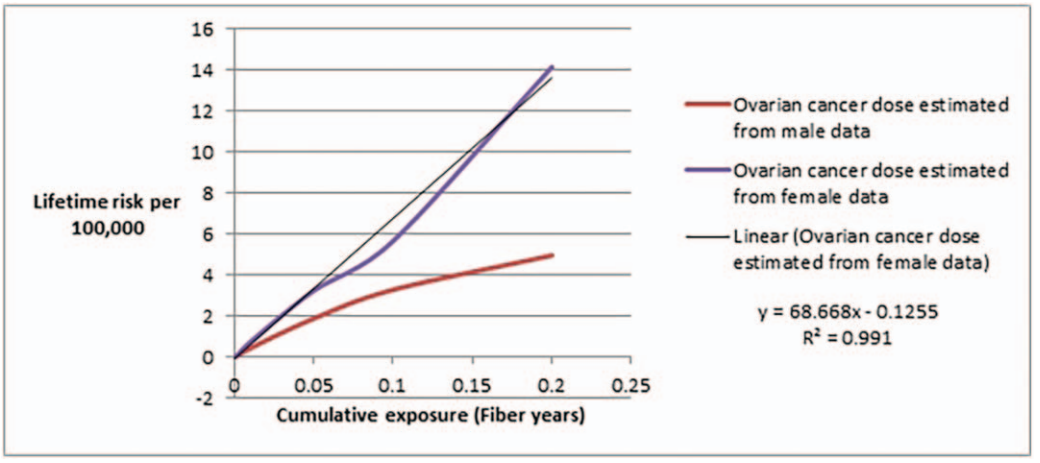

FIGURE 1. Ovarian cancer dose response (adjusted for difference in female mesothelioma risk).

All cases reported perineal talc application; the frequency of perineal powdering with talc ranged from once per day to 10 times per day and the duration ranged from 24 years to 47 years. Nine of 10 cases reported upper body powdering with talc ranging from 1 to 5 times per day and lasting from 20 to 47 years. Seven of 10 cases reported that their parents used talc powder on them during diaper changes and eight of 10 cases used talc powder during diapering. The total asbestos dose from talc powder use ranged from 2,774,000,000 to 37,742,501,440 asbestos fibers (0.38 to 5.18 fiber years) and the average dose was 9,308,551,008 asbestos fibers (1.28 fiber years). No other known asbestos exposure was identified for any of the cases. Based on EPA dose–response estimates, the risk of developing ovarian cancer due to inhaled asbestos exposure was calculated to be 2.3 to 31.1 times greater in these cases compared with baseline risk for ovarian cancer.[105] On average, the risk of ovarian cancer increased 7.7-fold among these cases.

Tissue Analysis

Talc and/or asbestos was identified in the tissue from all cases. Platy talc was found in 9/10 cases (90%) with an average concentration of 264,487 structures per gram (s/g) (range, 0 to 2,057,640 s/g). Fibrous talc was found in 8/10 cases (80%) with an average concentration of 5878 s/g (range, 0 to 21,545 s/g). Tremolite asbestos was found in 6/10 cases (60%) with an average concentration of 6488 s/g (range, 0 to 22,000 s/g). Anthophyllite asbestos was found in 4/10 cases (40%) with an average concentration of 2393 s/g (range: 0 to 12,000 s/g). Ferro-anthophyllite asbestos was also identified in two cases (20%), winchite and richterite asbestos were identified in one case (10%), and crocidolite asbestos was identified in one case (10%). Two tremolite structures with aspect ratios less than 5:1 were observed in one case, but were not counted as asbestos.

In the ''possible fallopian tube B'' tissue of Case No. 2, a cluster measuring $20.0 \times 16.0\,\mu m$ was identified composed of 36 counted talc plates, two fibrous talc structures, and one tremolite fiber. (See Fig. 2.)

DISCUSSION

This case series identified asbestos and/or talc in the tissue of 10 women diagnosed with serous ovarian cancer and exposed to J&J cosmetic talc products. Prior to their ovarian cancer diagnosis, these women were exposed to as much as 2,774,000,000 to 37,742,501,440 asbestos fibers (0.38 to 5.18 fiber years) due to their use of J&J cosmetic talc products. In all reported cases, asbestos exposures due to J&J talc use resulted in a substantial increase in ovarian cancer risk (2.3 to 31.1) based on our model. Early median age of diagnosis (50 in this case series vs. 63 nationally), and the EPA dose response table, indicates that asbestos exposure in infancy may cause ovarian cancer to occur sooner than it would have occurred absent this exposure.[92,105]

The asbestos type found in the perineal talc use inhalation exposure assessment (tremolite asbestos) and the predominant asbestos types identified in these tissue samples (tremolite and anthophyllite asbestos) matched the fiber types previously identified in cosmetic talc products and in talc mines.[41,74,75,77–81] (See Table 3.) Researchers have previously identified anthophyllite asbestos in Johnson's Baby Powder (by TEM analysis),[79] amphibole needles and fibers in baby powder sourced from Vermont,[76,77] and tremolite asbestos fibers in commercial talc produced prior to 1975 from J&J's talc source in Val Chisone, Italy.[81,89]

In 2017, a bundle of tremolite asbestos fibers was found in a bottle of JBP purchased by Case No. 3 in 2014. (See Appendix 6, http://links.lww.com/JOM/A691 for full purchase report.) Tremolite asbestos was also identified in Case No. 3's right pelvic lymph node. (See Fig. 3.) Winchite and richterite asbestos were found in the tissue in one case. However, richterite was called sodium tremolite prior to 1978.[113] Winchite is found in talc from the Allamoore, Texas mine, and may have contaminated J&J Italian talc processed at the same plant in the 1970s.[114–118] Similarly, Transite pipes present in Royston Plant for J&J baby products may have contaminated J&J talc with crocidolite.[119,120] Furthermore, Colgate acknowledges that there is crocidolite in some talc.[121]

The most common structures identified by tissue analysis (platy talc, fibrous talc, tremolite and anthophyllite asbestos) strongly indicate talc powder as the source of asbestos exposure in these cases. Tremolite asbestos has had minor commercial production in India and Italy and is mainly found as an accessory mineral in talc, vermiculite, and chrysotile.[122–124] Anthophyllite asbestos, which occurs as an accessory mineral in talc and chrysotile, has also had limited commercial use.[123–125] Anthophyllite and tremolite together account for less than 1% of asbestos production and consumption worldwide.[124]

None of the cases reported in this series had any known history of alternative asbestos or vermiculite exposure and no chrysotile or vermiculite was found in any of the tissue samples. Churg and Warnock[126] performed a population study of lung asbestos and noted that ''. . . in women a major source [of asbestos fibers] may be cosmetic talc, which is often contaminated with anthophyllite and tremolite.'' Finkelstein's[127] analysis of mesothelial tissue found a statistically significant association for tremolite detected with talc in tissue. This association was higher for women, 82% of whom had talc in their tissue compared with 68% of men.[127] The increased use of talcum-based cosmetics by women, and the similar fiber type combination is a fingerprint of cosmetic talc migrating to the pelvic organs. The combination of talc with tremolite and/or anthophyllite asbestos, as identified by Finkelstein[127] and the 10 cases reported here, are a fingerprint for exposure to asbestos-containing talc.[128–130] (Appendix 7, http://links.lww.com/JOM/A692: a chart of fibers detected in J&J compared with fibers in tissue). These results indicate that perineal use can result in important inhalation exposure to asbestos, which is an accepted route of transmigration to the peritoneum and ovary.[131]

Our exposure assessment found that cosmetic talc users can be exposed to 2.57 f/cc asbestos in the breathing zone during perineal talc application; this finding was generally in agreement with previous studies of asbestos exposures during talc use.[41,93] The bottle of JBP used in this exposure assessment was tested by TEM which detected 15 million fibers per gram. Further analysis found asbestos in 56/90 JBP bottles with a range of 4400 to 15,100,000 asbestos fibers per gram (appendix 4, http://links.lww.com/JOM/A689). For comparison, Gordon et al[41] conducted examination on 50 samples of a single brand of cosmetic talc, sourced from either Montana, North Carolina or Val Chisone. Gordon et al[41] found a range of 1840 to 200 million asbestos fibers per gram. Asbestos is not evenly distributed in talc ores and sampling cannot be completely representative of exposure.[88,132]

Gordon et al[41] selected a bottle with 18 million asbestos fibers per gram for the inhalation study. The results for Gordon's et al.'s[41] simulation of body powdering, 1.9 f/cc, is comparable to our findings of 2.57 f/cc asbestos exposure per application. Application of cosmetic talc varies greatly, including differences in product, application time, grams per use, and location of application. In addition, talc is mined and milled prior to sale, potentially modifying fiber size or dispersing asbestos unequally in finished cosmetic talc product.[133] Talc was sourced from various mines and processing methods changed over time, adding to the variability of asbestos content in talc-containing cosmetic products. However, our findings of an asbestos fingerprint in the tissue reveal that regardless of the dose, exposure to talc-containing cosmetic products is sufficient to cause ovarian cancer.

We relied on NIOSH measurements by Dement et al[93] to calculate exposures during diapering, however these measurements did not account for airborne asbestos exposures that continued after

TABLE 2. Summary of Cases

Case Number	Diagnosis	Age at Diagnosis	Talc Exposure History				Calculated Asbestos Dose	Relative Increase in Ovarian Cancer Risk	Pathological Examination	
			Perineal Powdering	Upper body Powdering	Infant Exposure During Diapering	Adult Exposure During Diapering			Tissue Examined	Findings (Structures Per Gram of Tissue)
1	Metastatic high grade papillary serous carcinoma	45	10x/d, 40yrs	5x/d, 40yrs	8x/d, 2yrs	10x/d, 8yrs	37,742,501,440 fibers, (5.18 fiber years)	31.1	Ovary (R)	Platy talc (333 s/g), Fibrous talc (4,000 s/g), Ferro-anthophyllite (3,667 s/g)
									Ovary (L)	Fibrous talc (1,200 s/g), ferro-anthophyllite (399 s/g)
									Fallopian tube (R)	NSD*
									Fallopian tube (L)	——†
									Pelvic Lymph Node (R)	——†
									Pelvic Lymph Node (L)	NSD*
2	Poorly differentiated high grade serous ovarian carcinoma	53	1x/d, 36yrs	1x/d, 23yrs	8x/d, 2yrs	7.5x/d, 7.5yrs	4,892,501,440 fibers, (0.68 fiber years)	4.1	Ovary A	NSD*
									Ovary B	Platy talc (323 s/g)
									Possible fallopian tube A	NSD*
									Possible fallopian tube B	Platy talc (56,700 s/g), Fibrous talc (4,720 s/g), Tremolite (22,000 s/g)
3	High grade serous carcinoma	49	3x/d, 39yrs	3x/d, 20yrs	8x/d, 2yrs	7x/d, 5yrs	11,535,501,440 fibers, (1.59 fiber years)	9.6	Ovary, fallopian tube (R)	Platy talc (2,001,503 s/g), Fibrous talc (13,343 s/g)
									Adnexa, fallopian tube (L)	Platy talc (12,308 s/g), Fibrous talc (8,202 s/g)
									Pelvic lymph node (R)	Tremolite (15,670 s/g), Winchite (15,670 s/g),‡ Richterite (15,670 s/g)‡
									Pelvic lymph node (L)	Platy talc (43,829 s/g)
4	Poorly differentiated serous adenocarcinoma	78	1x/day, 43yrs§	unknown§	unknown§	unknown§	2,774,000,000 fibers, (0.38 fiber years)	2.3	Ovary (R)	Platy talc (2,860 s/g), Anthophyllite (952 s/g)
									Ovary (L)	Tremolite (604 s/g)
									Fallopian tube (R)	Platy talc (30,000 s/g)
									Fallopian tube (L)	Fibrous talc (868 s/g)
									Pelvic Lymph Node (R)	Platy talc (12,600 s/g)
									Pelvic Lymph Node (L)	Platy talc (17,600 s/g), Tremolite (2,510 s/g)
5	Low grade serous carcinoma	52	1x/d, 47yrs	1x/d, 47yrs	8x/d, 2yrs	10x/d, 10yrs	7,812,501,440 fibers, (1.08 fiber years)	6.5	Ovary (R)	Platy talc (10,900 s/g), Fibrous talc (1,810 s/g)
									Ovary (L)	Platy talc (25,000 s/g), Fibrous talc (5,000 s/g), Tremolite (5,000 s/g)
									Int. Iliac lymph node (R)	Platy talc (77,200 s/g), Fibrous talc (7,720 s/g), Tremolite (3,860 s/g), Anthophyllite (3,860 s/g)
									Comm. Iliac lymph node (R)	Platy talc (50,600 s/g)

(*continues*)

TABLE 2. (*Continued*)

Case Number	Diagnosis	Age at Diagnosis	Talc Exposure History				Calculated Asbestos Dose	Relative Increase in Ovarian Cancer Risk	Pathological Examination	
			Perineal Powdering	Upper body Powdering	Infant Exposure During Diapering	Adult Exposure During Diapering			Tissue Examined	Findings (Structures Per Gram of Tissue)
6	High grade serous papillary carcinoma	51	1x/d, 40yrs	1x/d, 40yrs	8x/d, 2yrs	10x/d, 10yrs	7,009,501,440 fibers, (0.97 fiber years)	5.8	Adnexa, tumor/ovary (R)	Platy talc (21,300 s/g)
									Adnexa, tumor/ovary (L)	Platy talc (4,720 s/g)
									Adnexa, fallopian tube (R)	Platy talc (12,000 s/g), Tremolite (12,000 s/g), Anthophyllite (12,000 s/g)
									Adnexa, fallopian tube (L)	Platy talc (13,700 s/g)
									Pelvic lymph node (L)	Platy talc (11,500 s/g)
7	Serous adenocarcinoma	56	1x/d, 37yrs	1x/d, 37yrs	Unknown	7.5x/d, 6yrs	5,183,000,000 fibers, (0.71 fiber years)	4.3	Ovary (R)	Platy talc (8,740 s/g), fibrous talc (1,090 s/g)
									Ovary (L)	Platy talc (10,500 s/g)
									Fallopian tube (R)	Platy talc (8,500 s/g)
									Fallopian tube (L)	Platy talc (10,900 s/g)
8	High grade ovarian serous carcinoma	44	1x/d, 24yrs	1x/d, 24yrs	Unknown	3.5x/d, 4yrs	2,993,000,000 fibers, (0.41 fiber years)	2.5	Ovary (R)	Platy talc (3,340 s/g), Ferro-anthophyllite (1,670 s/g), Crocidolite (1,670 s/g)
									Ovary (L)	Platy talc (799 s/g)
									Fallopian tube (R)	Platy talc (9,690 s/g), Fibrous talc (1,380 s/g), Tremolite (1,385 s/g), Anthophyllite (1,385 s/g)
									Fallopian tube (L)	Platy talc (7,400 s/g), Tremolite (1,850 s/g)
9	Poorly differentiated serous papillary adenocarcinoma[‖]	41	1x/d, 42yrs[§]	1x/d, 42yrs[§]	8x/d, 2yrs[§]	n/a[§]	4,965,501,440 fibers, (0.69 fiber years)	4.1	Ovary (R)	NSD[*]
									Ovary (L)	NSD[*]
									Fallopian tube (R)	NSD[*]
									Fallopian tube (L)	NSD[*]
									Pelvic Lymph Node (L)	Fibrous talc (8,770 s/g)
10	High-grade ovarian papillary serous carcinoma	42	2x/d, 32yrs	2x/d, 32yrs	8x/d, 2yrs	8x/d, 4yrs	8,177,501,440 fibers, (1.13 fiber years)	6.8	Ovary, fallopian tube (R)	Platy talc (10,800 s/g)[¶]
									Ovary, fallopian tube (L)	Platy talc (5,520 s/g)
									Pelvic lymph node (R)	Platy talc (79,300 s/g)
									Pelvic lymph node (L)	Platy talc (84,400 s/g)

[*]No asbestos or talc structures detected.
[†]Tissue received, but not analyzed.
[‡]Richterite asbestos were known as sodium tremolite.
[§]Patient deceased; exposure history based on recollections of family and friends.
[‖]The final pathology report also noted minor components of transitional cell and mucinous carcinoma.
[¶]Two tremolite structures were reported with an aspect ratio of less that 5:1 that were not counted.

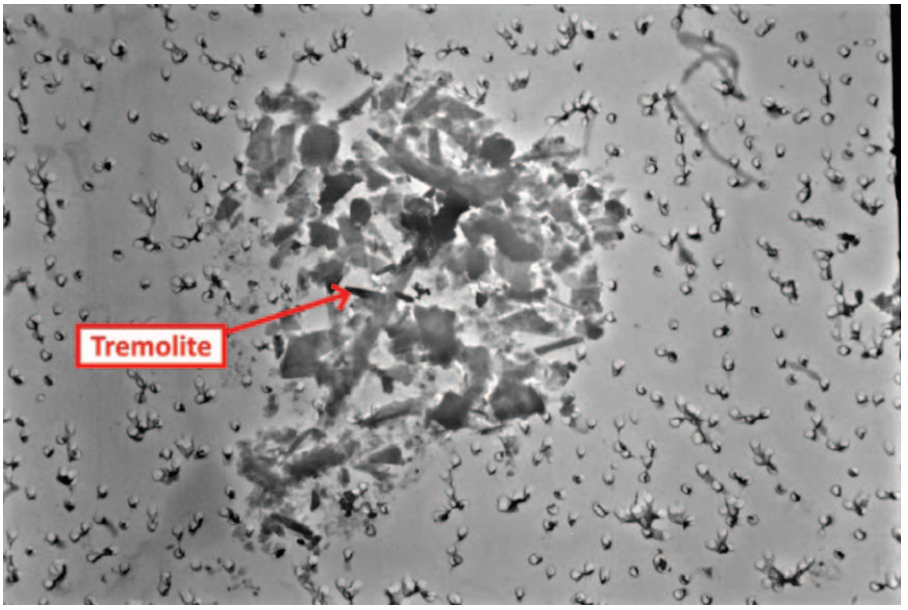

FIGURE 2. TEM image of cluster measuring 20.0 × 16.0 μm composed of 36 counted talc plates, two fibrous talc structures, and one tremolite fiber identified in ''possible fallopian tube B'' tissue of Case No. 2.

the sampling time.[93] Dement et al[93] collected air samples for 2 minutes during a simulated diaper change with JBP, but another experiment in the same study indicated that exposures continued for at least 3 minutes and likely persisted for even longer. Dement et al[93] used phase contrast microscopy and did not differentiate between asbestos and fibrous talc. However, in 1968, NIOSH injected asbestos containing ''cosmetic'' talc into hamsters and detected tremolite asbestos bodies but no fibrous talc in the animal lungs.[134] Anderson et al[100] reported much lower levels during body dusting with talc (0 to 0.0039 f/cc). However, the microscopist in the Anderson et al[100,135] study originally identified four anthophyllite asbestos fibers in the air samples by TEM, but changed the result to transition fibers at the request of the project supervisor due to concern that the results would be used in litigation.[135]

Both our study and Gordon's et al [41] exposures assessment used less talc powder than the average user: these experiments used 4.05 and 0.37 g of talc respectively, but J&J's unpublished studies found that women used 8.16 g and men used 13.02 g of talc powder on average during body powdering.[41,136] Anderson et al[100] reported that subjects used 11.6 g of talc on average to powder their bodies after showering. Therefore, our use estimates were 3 to 20 times lower than Anderson et al[100] and J&J's.

We also excluded many reported talc uses from our dose calculations due to a lack of exposure data. For instance, three cases (No. 1, No. 3, and No. 5) regularly used talc powder on their sheets and pillows; several other cases also reported seeing and smelling dust in the air while cleaning the room where they regularly applied talc. (See Appendix 5, http://links.lww.com/JOM/A690 for complete exposure

TABLE 3. Summary of Studies Reporting Asbestos in Consumer Talc Products

Study	Test Method	Summary of Findings
Rohl et al (1976)	XRD, PLM, TEM, SEM	0.1–14% tremolite and anthophyllite (mostly fibrous) by weight in 10 of 20 consumer talc products tested
Paoletti et al (1984)	TEM	0.5–1.6% tremolite asbestos in two of six Italian cosmetic talc powders tested Trace to 0.15% chrysotile in 3 of 14, 18.7–21.7% anthophyllite asbestos and tremolite asbestos in 2 of 14, and 0.13% tremolite asbestos & chrysotile in 2 of 10 samples provided by the European Pharmacopeia
Blount (1991)	PLM	10 to 341 structures per mg amphibole fibers, needles, cleavages and ''prismatic pieces'' in 9 of 14 samples of pharmaceutical and cosmetic-grade talc powders tested
Jehan (2004)	PLM	Qualitative identification of tremolite asbestos in 13 of 28, chrysotile in 12 of 28, anthophyllite asbestos in 3 of 28, and a mixture of asbestos fibers in 4 of 28 cosmetic talc powder products used in Pakistan
Floyd (2004)	TEM	0.20% anthophyllite asbestos by weight in Johnson's Baby Powder
Mattenklott (2009)	SEM	0.001–0.0073% asbestos by weight in 13 of 57 samples of talc powders sold on the German market from 1996 to 2005
Gordon et al (2014)	PLM	1,840–1,104,000 fibers per gram asbestos in 50 of 50 historical samples of one brand of cosmetic talc powder tested (40 of 50 contained anthophyllite asbestos only, four contained tremolite asbestos only, four contained tremolite and anthophyllite asbestos, two contained tremolite, anthophyllite, and chrysotile asbestos)
	TEM	0.004–0.9% amphibole asbestos by weight in nine of nine samples of the same cosmetic talc product
Ilgren et al (2017)	TEM	3.687×10^6 tremolite asbestos fibers/g in an authentic sample of commercial talc produced prior to 1975 from the talc mine in Val Chisone, Italy

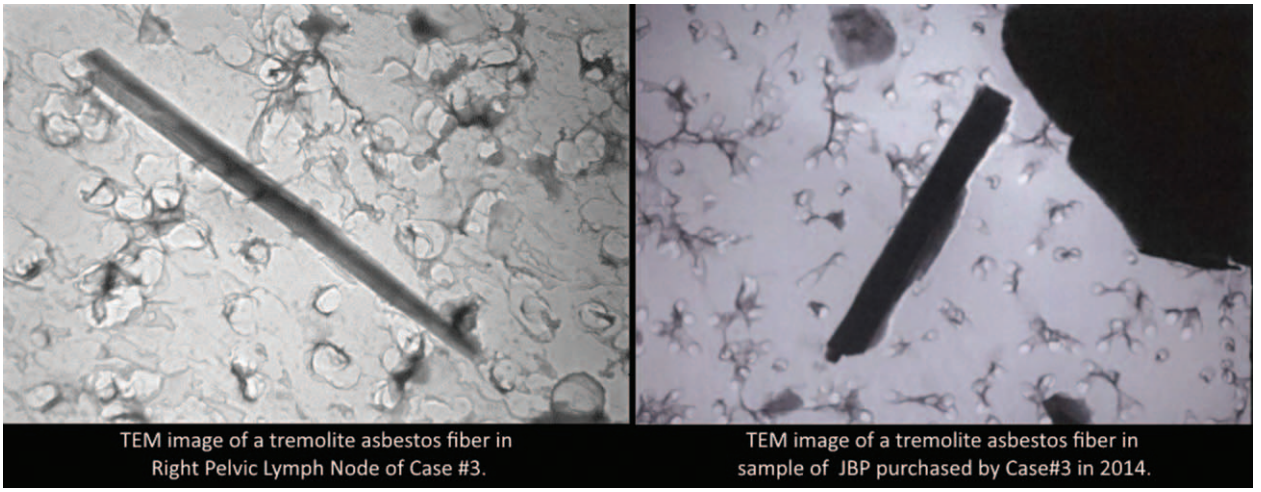

FIGURE 3. TEM images of a tremolite asbestos fibers in Case No. 3 right pelvic lymph node tissue (left) and in sample of JBP purchased by Case No. 3 in 2014 (right).

histories.) Although our findings indicate that asbestos is present in consumer talc products at a level sufficient to cause disease, our dose estimates may under or over estimate the total exposure to asbestos in talc in these cases.

Burns et al[137] created a dose estimation-model for cosmetic talc, relying on previous assessments to predict asbestos exposure, including Moon et al[138], Gordon et al[41], Russell et al[136], and Anderson et. al.[100] Burns's et al[137] assessment was based on an assumption of 0.1% level of asbestos in talc mathematical model that incorrectly reduced the exposure estimate by 1000. For example, Gordon et al[41] reported, 4.8 f/cc, however, Burns's et al[137] math model reduces this figure to 0.0048 f/cc. In comparison, Addison et al (1988)[139] reported that dusts containing 0.1% asbestos may release 1.17 to 2.79 asbestos fibers/cc into the air, consistent with our measurements.

Our tissue analysis results were consistent with previous reports of asbestos and/or talc in ovarian tissue.[136,140–144] (See Table 4.) The number of asbestos structures per gram, however, was approximately one order of magnitude lower in our study than in previous quantitative studies of asbestos in ovarian tissue.[143] This discrepancy may be due to differences in tissue preparation and analytical procedures. Other quantitative studies relied on wet tissue weight for their analysis whereas we used a dry weight procedure.[143] Additionally, we counted 100 to 300 grid openings in our study while other studies appear to have counted the entire grid area.[143] We also found that some tissue samples contained "hot spots" with very high concentrations of asbestos and/or talc compared with the surrounding tissue. (See Fig. 2.) The occurrence or absence of "hot spots" may also account for variability in reported asbestos concentrations in tissue. The predominant types of asbestos identified in our series (tremolite and anthophyllite asbestos) are the same as those most commonly reported in past studies.[140,143,144]

We did not consider latency in our risk estimate because our calculations followed the EPA risk assessment, which did not consider latency.[92] In addition, Pira et al[68] found that for asbestos-caused ovarian cancer "…the SMRs increased monotonically with time since first employment, although the number of deaths was small in several categories..." Our omission of latency from this study is to remain consistent with the EPA assessment and reflect the lack of effect demonstrated by Pira's et al analysis.

We omitted fibrous talc from our risk assessment due to a lack of dose–response data in the published literature. IARC has previously classified fibrous talc as a Group 1 carcinogen and OSHA regulates fibrous talc per the asbestos standard.[3,43,145–147] Further research on the relationship between talc powder use and ovarian cancer should include studies of fibrous talc toxicity.

CONCLUSION

Of the 10 reported cases of serous ovarian cancer, all were found to have talc and eight were found to have asbestos in their tissue samples. The main types of asbestos identified in tissue, tremolite and anthophyllite, constitute a fingerprint for talc containing asbestos and indicate that "cosmetic" talc powder as the source of asbestos exposure in these cases. IARC has concluded that asbestos is an ovarian carcinogen.[43] IARC has likewise classified talc containing asbestiform fibers (including both asbestos and fibrous talc) as a carcinogen.[3,43,148] These cases provide more evidence of the causal link between asbestos, talc, and ovarian cancer and indicate that asbestos is present in consumer talc products at a level sufficient to cause disease.

In 1973, J&J told the Food and Drug Administration (FDA) that "Johnson & Johnson's policy of full cooperation with FDA and that if the results of any scientific studies show any question of safety of talc, Johnson & Johnson will not hesitate to take it off the market" and their corporate position is that there is no known safe level of exposure to asbestos.[149] J&J's studies have shown that asbestos has been present in its cosmetic talc ores since the 1950s. In 2019, the FDA has found asbestos in JBP sourced from China and Claire's cosmetics.[150,151] At least three retailers of cosmetic talc accept the causal relationship between talc use and ovarian cancer: Angel of Mine, Perfect Purity, and Assured Body and Foot Powders warn that "frequent application of talcum powder in the female genital area may increase the risk of ovarian cancer."[152] In addition, J&J's talc supplier Rio Tinto Minerals has warned its customers since 2006 of this risk in Material Safety Data Sheets (MSDS) for talc: "perineal use of talc-based body powder is possibly carcinogenic to humans."[153,154] J&J removes this warning from its talc MSDS and cosmetic talc products.[155] Because talc powder is a cosmetic product with no medical benefit, these warnings still do not warrant the sale of a products when the benefits cannot outweigh the risks, especially when there is a safer substitute.[156–158]

TABLE 4. Summary of Studies Finding Asbestos and/or Talc in Ovarian Tissue From Cosmetic Talc Use

Study	Tissue Weight Type	Test Method	Summary of Findings
Henderson et al (1971)	n/a	TEM	Qualitative identification of talc in 10/13 ovarian tumors Qualitative identification of talc in 12/21 cervical tumors
Langer (1971)	n/a	Unknown	Qualitative identification of talc and chrysotile asbestos in Henderson et al (1971) samples
Heller, Westhoff et al (1996)	Wet weight	PLM	26–464 talc particles per gram in 12/12 samples of benign ovarian neoplasms from 12 women with history of adult perineal talc use 69–420 talc particles per gram in 11/11 samples of benign ovarian neoplasms from 12 women with history of talc diapering during infancy 6–2,200 talc particles per gram in 6/7 samples of benign ovarian neoplasms from 12 women with no history of adult perineal talc use and an unknown history of other talc uses
		TEM	151,300–7,565,000 talc particles per gram in 5/12 samples of benign ovarian neoplasms from 12 women with history of adult perineal talc use 151,300–1,600,288 talc particles per gram in 6/11 samples of benign ovarian neoplasms from 12 women with history of talc diapering during infancy 63,042–1,669,000 talc particles per gram in 3/7 samples of benign ovarian neoplasms from 12 women with no history of adult perineal talc use and an unknown history of other talc uses
Cramer et al (2007)	n/a	PLM and SEM	Qualitative identification of birefringent particles consistent with talc in pelvic lymph nodes of a 68-year-old woman with stage III ovarian papillary serous carcinoma and a 30-year history of perineal talc use

J&J should comply with its self-proclaimed obligation to take talc-containing cosmetic products off the market ''if the results of any scientific studies show any question of safety of talc, Johnson & Johnson will not hesitate to take it off the market.''[149]

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REFERENCES

1. Gajjar K, Ogden G, Mujahid MI, Razvi K. Symptoms and risk factors of ovarian cancer: a survey in primary care. *ISRN Obstet Gynecol*. 2012;2012:754197.
2. Society AC. Key Statistics for Ovarian Cancer; 2019. Available at: https://www.cancer.org/cancer/ovarian-cancer/about/key-statistics.html. Accessed May 14, 2019.
3. International Agency for Research on Cancer (IARC). Carbon black, titanium dioxide, and talc. *IARC Monogr Eval Carcinog Risks Hum*. 2010;93:1–413.
4. Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc: a case-control study. *Cancer*. 1982;50:372–376.
5. Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. *Br J Cancer*. 1989;60:592–598.
6. Chang S, Risch HA. Perineal talc exposure and risk of ovarian carcinoma. *Cancer*. 1997;79:2396–2401.
7. Cook LS, Kamb ML, Weiss NS. Perineal powder exposure and the risk of ovarian cancer. *Am J Epidemiol*. 1997;145:459–465.
8. Cramer DW, Vitonis AF, Terry KL, Welch WR, Titus LJ. The association between talc use and ovarian cancer: a retrospective case-control study in two US States. *Epidemiology*. 2016;27:334–346.
9. Cramer DW, Xu H. Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. *Ann Epidemiol*. 1995;5:310–314.
10. Gates MA, Tworoger SS, Terry KL, et al. Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2008;17:2436–2444.
11. Godard B, Foulkes WD, Provencher D, et al. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *Am J Obstet Gynecol*. 1998;179:403–410.
12. Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. *Obstet Gynecol*. 1992;80:19–26.
13. Kurta ML, Moysich KB, Weissfeld JL, et al. Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 2012;21:1282–1292.
14. Merritt MA, Green AC, Nagle CM, Webb PM, Australian Cancer S, Australian Ovarian Cancer Study G. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int J Cancer*. 2008;122:170–176.
15. Mills PK, Riordan DG, Cress RD, Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *Int J Cancer*. 2004;112:458–464.
16. Ness RB, Grisso JA, Cottreau C, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology*. 2000;11:111–117.
17. Purdie D, Green A, Bain C, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. *Int J Cancer*. 1995;62:678–684.
18. Terry KL, Karageorgi S, Shvetsov YB, et al. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev Res (Phila)*. 2013;6:811–821.
19. Vitonis AF, Titus-Ernstoff L, Cramer DW. Assessing ovarian cancer risk when considering elective oophorectomy at the time of hysterectomy. *Obstet Gynecol*. 2011;117:1042–1050.
20. Wu AH, Pearce CL, Tseng CC, Pike MC. African Americans and Hispanics remain at lower risk of ovarian cancer than non-hispanic whites after considering nongenetic risk factors and oophorectomy rates. *Cancer Epidemiol Biomarkers Prev*. 2015;24:1094–1100.
21. Pike MC. Hormonal factors and the risk of invasive ovarian cancer: a population-based casecontrol study. *Fertil Steril*. 2004;82:186–195.
22. Chen Y, Wu PC, Lang JH, Ge WJ, Hartge P, Brinton LA. Risk factors for epithelial ovarian cancer in Beijing, China. *Int J Epidemiol*. 1992;21:23–29.
23. The Cosmetics Fragrance and Toiletry Association (CTFA). The Cosmetics, Fragrance and Toiletry Association (CTFA) Specifications - Talc & Cosmetic Talc; 1976.

24. Gertig DM, Hunter DJ, Cramer DW, et al. Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst*. 2000;92:249–252.
25. Harlow BL, Weiss NS. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *Am J Epidemiol*. 1989;130: 390–394.
26. Hartge P, Hoover R, Lesher LP, McGowan L. Talc and ovarian cancer. *JAMA*. 1983;250:1844.
27. Houghton SC, Reeves KW, Hankinson SE, et al. Perineal powder use and risk of ovarian cancer. *J Natl Cancer Inst*. 2014;106:dju208.
28. Moorman PG, Palmieri RT, Akushevich L, et al. Ovarian cancer risk factors in African-American and White Women. *Am J Epidemiol*. 2009;170: 598–606.
29. Rosenblatt KA, Weiss NS, Cushing-Haugen KL, Wicklund KG, Rossing MA. Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes Control*. 2011;22:737–742.
30. Tzonou A, Polychronopoulou A, Hsieh CC, Rebelakos A, Karakatsani A, Trichopoulos D. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *Int J Cancer*. 1993; 55:408–410.
31. Whittemore AS, Wu ML, Paffenbarger Jr RS, et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am J Epidemiol*. 1988; 128:1228–1240.
32. Gates MA, Rosner BA, Hecht JL, Tworoger SS. Risk factors for epithelial ovarian cancer by histologic subtype. *Am J Epidemiol*. 2010;171:45–53.
33. Wong C, Hempling RE, Piver MS, Natarajan N, Mettlin CJ. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstet Gynecol*. 1999;93:372–376.
34. Rosenblatt KA, Szklo M, Rosenshein NB. Mineral fiber exposure and the development of ovarian cancer. *Gynecol Oncol*. 1992;45:20–25.
35. Gonzalez NL, O'Brien KM, D'Aloisio AA, Sandler DP, Weinberg CR. Douching, talc use, and risk of ovarian cancer. *Epidemiology*. 2016;27: 797–802.
36. Schildkraut J, Abbott S, Alberg A, et al. Association between body powder use and ovarian cancer: The African American Cancer Epidemiology Studies (AACES). *Cancer Epidemiol Biomarkers Prev*. 2016;25:1411–1417.
37. Kim J, Park E, Kim O, et al. Cell origins of high-grade serous ovarian cancer. *Cancers*. 2018;10:433.
38. Huncharek M, Geschwind JF, Kupelnick B. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. *Anticancer Res*. 2003;23:1955–1960.
39. Muscat JE, Huncharek MS. Perineal talc use and ovarian cancer: a critical review. *Eur J Cancer Prev*. 2008;17:139–146.
40. Penninkilampi R, Eslick GD. Perineal talc use and ovarian cancer: a systematic review and meta-analysis. *Epidemiology*. 2018;29:41–49.
41. Gordon RE, Fitzgerald S, Millette J. Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women. *Int J Occup Environ Health*. 2014;20:318–332.
42. Tran T, Steffen J, Clancy K, Bird T, Egilman D. Talc, Asbestos, and Epidemiology: Corporate Influence and Scientific Incognizance. Epidemiology; 2019; 30:783–788.
43. IARC. Arsenic, Metals, Fibres, and Dusts - A Review of Human Carcinogens. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans; 2012: 100C.
44. Straif K, Benbrahim-Tallaa L, Baan R, et al. Special Report: Policy. A review of human carcinogens—Part C: metals, arsenic, dusts, and fibres. *Lancet*. 2009;10:453–454.
45. Wyers H. Asbestosis. *Postgrad Med J*. 1949;25:631–638. illust.
46. Acheson ED, Gardner MJ, Pippard EC, Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. *Br J Ind Med*. 1982;39:344–348.
47. Berry G, Newhouse ML, Wagner JC. Mortality from all cancers of asbestos factory workers in east London. *Occup Environ Med*. 2000; 57:782–785.
48. Bulbulyan MA, Ilychova SA, Zahm SH, Astashevsky SV, Zaridze DG. Cancer mortality among women in the Russian printing industry. *Am J Ind Med*. 1999;36:166–171.
49. Ferrante D, Bertolotti M, Todesco A, Mirabelli D, Terracini B, Magnani C. Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. *Environ Health Perspect*. 2007;115:1401–1405.
50. Gardner MJ, Winter PD, Pannett B, Powell CA. Follow up study of workers manufacturing chrysotile asbestos cement products. *Br J Ind Med*. 1986;43:726–732.
51. Germani D, Belli S, Bruno C, et al. Cohort mortality study of women compensated for asbestosis in Italy. *Am J Ind Med*. 1999;36:129–134.
52. Clin B, Morlais F, Dubois B, et al. Occupational asbestos exposure and digestive cancers - a cohort study. *Aliment Pharmacol Ther*. 2009;30: 364–374.
53. Newhouse ML, Sullivan KR. A mortality study of workers manufacturing friction materials. *Br J Ind Med*. 1989;46:176–179.
54. Rosler JA, Woitowitz HJ, Lange HJ, Woitowitz RH, Ulm K, Rodelsperger K. Mortality rates in a female cohort following asbestos exposure in Germany. *J Occup Med*. 1994;36:889–893.
55. Tarchi M, Orsi D, Comba P, et al. Cohort mortality study of rock salt workers in Italy. *Am J Ind Med*. 1994;25:251–256.
56. Szeszenia-Dabrowska N, Urszula W, Szymczak W, Strzelecka A. Mortality study of workers compensated for asbestosis in Poland. *Int J Occup Med Environ Health*. 2002;15:267–278.
57. Mamo C, Costa G. Mortality Experience in an Historical Cohort of Chrysotile Asbestos Textile Workers. Proceedings from the Global Asbestos Congress; November 19-21, 2004; Waseda University, Tokyo, Japan.
58. Wilczynska U, Szymczak W, Szeszenia-Dabrowska N. Mortality from malignant neoplasms among workers of an asbestos processing plant in Poland: results of prolonged observation. *Int J Occup Med Environ Health*. 2005;18:313–326.
59. McDonald JC, Harris JM, Berry G. Sixty years on: the price of assembling military gas masks in. *Occup Environ Med*. 2006;63:852–855.
60. Hein MJ, Stayner LT, Lehman E, Dement JM. Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. *Occup Environ Med*. 2007;64:616–625.
61. Pira E, Pelucchi C, Piolatto PG, Negri E, Discalzi G, La Vecchia C. First and subsequent asbestos exposures in relation to mesothelioma and lung cancer mortality. *Br J Cancer*. 2007;97:1300–1304.
62. Magnani C, Barone-Adesi FDF. Cancer risk after cessation of asbestos exposure: a cohort study of Italian Asbestos Cement Workers. *Occup Environ Med*. 2008;65:164–170.
63. Loomis D, Dement J, Wolf S, RIcherdson D. Lung cancer mortality and fibre exposures among North Carolina asbestos textile workers. *Occup Environ Med*. 2009;66:353–542.
64. Reid A, Segal A, Heyworth JS, de Klerk NH, Musk AW. Gynecologic and breast cancers in women after exposure to blue asbestos at Wittenoom. *Cancer Epidemiol Biomarkers Prev*. 2009;18:140–147.
65. Harding A-H, Darnton A, Wegerdt J, McElvenny D. Mortality among British asbestos workers undergoing regular medical examinations (1971–2005). *Occup Environ Med*. 2009;66:487–495.
66. Langseth H, Kjaerheim K. Ovarian cancer and occupational exposure among pulp and paper employees in Norway. *Scan J Work Environ Health*. 2004;30:356–361.
67. Pira E, Pelucchi C, Buffoni L, et al. Cancer mortality in a cohort of asbestos textile workers. *Br J Cancer*. 2005;92:580–586.
68. Pira ERC, Violante FS. Updated mortality study of a Cohort of asbestos textile workers. *Cancer Med*. 2016;5:2623–2628.
69. Reid A, Franklin P, Olsen N, et al. All-cause mortality and cancer incidence among adults exposed to blue asbestos during childhood. *Am J Ind Med*. 2013;56:133–145.
70. Vasama-Neuvonen K, Pukkala E, Paakkulainen H, et al. Ovarian cancer and occupational exposures in Finland. *Am J Ind Med*. 1999;36:83–89.
71. Wang X, Lin S, Yu I, Qiu H, Lan Y, Yano E. Cause-specific mortality in a Chinese chrysotile textile worker cohort. *Cancer Sci*. 2013;104:245–249.
72. Wignall BK, Fox AJ. Mortality of female gas mask assemblers. *Br J Ind Med*. 1982;39:34–38.
73. Camargo MC, Stayner LT, Straif K, et al. Occupational exposure to asbestos and ovarian cancer: a meta-analysis. *Environ Health Perspect*. 2011;119:1211–1217.
74. Rohl A, Langer A, Selikoff I, et al. Consumer talcums and powders: mineral and chemical characterization. *J Toxicol Environ Health*. 1976;2:255–284.
75. Paoletti L, Caiazza S, Donelli G, Pocchiari F. Evaluation by electron microscopy techniques of asbestos contamination in industrial, cosmetic, and pharmaceutical talcs. *Regul Toxicol Pharmacol*. 1984;4:222–235.
76. Blount A. "Amphibole Content of Cosmetic and Pharmaceutical Talcs" with attached letters and sample key; 1991:IMERY211157-211165.
77. Blount AM. Amphibole content of cosmetic and pharmaceutical talcs. *Environ Health Perspect*. 1991;94:225–230.

78. Jehan N. *Sustainable Management of Mineral Resources with Special Reference to Asbestos and Silica in Northern Pakistan.* National Centre of Excellence in Geology, University of Peshawar; 2004.
79. Floyd M. Exhibit PLT-00002-0001: Quantitative Analysis Report for Asbestos in Bulk Material TEM; 2004.
80. Mattenklott M. Asbestos in talc powders and soapstone- the present state. *Gefahrstoffe - Reinhalt der Luft*. 2007;67:287–291.
81. Ilgren E, Sartorio Carlo, Hoskins J. Analysis of an authentic historical Italian Cosmetic Talc sample – further evidence for the lack of cancer Risk. *Environ Pollut*. 2017;6.
82. Steffen JE, Tran T, Fassler EA, Egilman DS. Presence of Asbestos in Consumer Talc Products: Evaluating a ''zero tolerance'' Policy; 2017. Atlanta, GA: APHA.
83. Wells P. Memo: Johnson and Johnson Baby Powder- Review of Consumer Research; 1973. Available at: https://repository.library.brown.edu/studio/item/bdr:967137/. Accessed October 8, 2019.
84. Johnson Ja. 1969 & 1991 Shower to Shower and Specification. 1969; JNJ000280197 & JNJTALC000023772. Available at: https://repository.library.brown.edu/studio/item/bdr:958143/. Accessed October 8, 2019.
85. E-CFR. Electronic Code of Federal Regulations- Title 45- PART 46—Protection of Human Research Subjects; 2018. Available at: https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=83cd09e1c0f5c6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML#se45.1.46_1104. Accessed October 8, 2019.
86. Johnson & Johnson. Happy Mother's Day: Mothers and Children in Our Ads Through the Years; 2012. Available at: https://web.archive.org/web/20170511033452/https://www.kilmerhouse.com/2012/05/happy-mothers-day-mothers-and-children-in-our-ads-through-the-years. Accessed June 6, 2017.
87. Johnson & Johnson. Johnson & Johnson and The Adventures of Robin Hood; 2013. Available at: https://web.archive.org/web/20161218073707/http://www.kilmerhouse.com/2013/10/johnson-johnson-and-the-adventures-of-robin-hood/. Accessed December 18, 2016.
88. Minnitt RCA, Rice PM, Spangenberg C. Part 1: Understanding the components of the fundamental sampling error: a key to good sampling practice. *J Southern Afr Instit Mining Metall*. 2007;107:107–511.
89. Johnson & Johnson (J&J). Johnson & Johnson and Johnson & Johnson Consumer Inc.'s Supplemental Answer to Interrogatory No. 3 of Plaintiff's First Set of Interrogatories. In. Jody E Ratcliff v American Honda Motor Co. Inc., et al.: Superior Court for Washington for King County; 2017.
90. National Institute for Occupational Safety and Health (NIOSH). Method 7400, Issue 2: ASBESTOS and OTHER FIBERS by PCM. In: 1994.
91. National Institute for Occupational Safety and Health (NIOSH). Method 7402, Issue 2: ASBESTOS by TEM. In: 1994.
92. EPA. Airborne Asbestos Health Assessment Update. In: EPA Office of Health and Environmental Assessment; 1986.
93. Dement J, Shuler P, Zumwalde R. Preliminary Report: Fiber Exposure During Use of Baby Powders. NIOSH Environmental Investigations Branch; 1972.
94. Company CP. Defendant Colgate-Palmolive Company's Supplemental Responses And Objections To Plaintiff's Interrogatories 2-5, 7-12, 14-16, 19-22, 24-26, 32-37, and 39-42. In Re: Personal Injury And Wrongful Death Asbestos Litigation; 2013.
95. Palmolive C. *Formula for Cashmere Bouquet;* 1992, Available at: https://repository.library.brown.edu/studio/item/bdr:958148/. Accessed October 8, 2019.
96. DeVito M, Schecter A. Exposure assessment to dioxins from the use of tampons and diapers. *Environ Health Perspect*. 2002;110:23–28.
97. Sauer B, Hildebrandt C, Franklin W, Hunt R. Resource and environmental profile analysis of children's diaper systems. *Environ Toxicol Chem*. 1994;13:1003–1009.
98. Thaman L, Eichenfield L. Diapering: a global perspective. *Pediatric Dermatol*. 2014;31:15–18.
99. Elzinga K, Mills D. Innovation and entry in the US disposable diaper industry. *Ind Corporate Change*. 1996;5:791–812.
100. Anderson EL, Sheehan PJ, Kalmes RM, Griffin JR. Assessment of health risk from historical use of cosmetic talcum powder. *Risk Anal*. 2017; 37:918–929.
101. NRC. Asbestiform Fibers: Nonoccupational Health Risks. Committee on Nonoccupational Health Risks of Asbestiform Fibers, Board on Toxicology and Environmental Health Hazards, National Research Council; 1984.
102. Hall JE. The physiology of respiration in infants and young children. *Proc R Soc Med*. 1955;48:761–764.
103. Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet*. 2011;377:1011–1018.
104. Lacourt A, Gramond C, Rolland P, et al. Occupational and non-occupational attributable risk of asbestos exposure for malignant pleural mesothelioma. *Thorax*. 2014;69:532–539.
105. Surveillance E, and End Results Program. Cancer Stat Facts: Ovarian Cancer; 2016. Available at: https://seer.cancer.gov/statfacts/html/ovary.html. Accessed May 14, 2019.
106. ISO 10312:1995 Ambient air—Determination of asbestos fibres—Direct transfer transmission electron microscopy method. International Organization for Standardization; 1995.
107. ISO 13794:1999 Ambient air—Determination of asbestos fibres—Indirect-transfer transmission electron microscopy method. International Organization for Standardization; 1999.
108. ISO 22262-2:2014 Air quality—Bulk materials—Part 2: Quantitative determination of asbestos by gravimetric and microscopical methods. International Organization for Standardization; 2014.
109. EPA. *Asbestos Hazard Emergency Response Act. 40 CFR Part 763, Subpart E – Asbestos Containing Materials in Schools.* Washington, DC: U.S. Environmental Protection Agency; 1987.
110. ASTM D5756-02(2008), Standard Test Method for Microvacuum Sampling and Indirect Analysis of Dust by Transmission Electron Microscopy for Asbestos Mass Surface Loading (Withdrawn 2017). West Conshohocken, PA: ASTM International; 2008.
111. ASTM D5755-09(2014)e1, Standard Test Method for Microvacuum Sampling and Indirect Analysis of Dust by Transmission Electron Microscopy for Asbestos Structure Number Surface Loading. West Conshohocken, PA: ASTM International; 2014.
112. ASTM D7712-18, Standard Terminology for Sampling and Analysis of Asbestos. West Conshohocken. PA: ASTM International; 2018.
113. National Institute for Occupational Safety and Health (NIOSH). Asbestos Fibers and Other Elongate Mineral Particles: State of the Science and Roadmap for Research. In: Department of Health, Human Services - Centers for Disease Control, Prevention, ed., Vol, 62, Current Intelligence, Bulletin; 2011.
114. Whittaker Clark & Daniels. Review of Talc Meeting Held at South Kearny. In:1970:WCD002843-002844.
115. Whittaker Clark & Daniels. Inter-Office Correspondence. In:1970:FM-WCD-MOR-KAN 0002325.
116. Ferry DR. Letter to Mr. Robert G. Smith, President, Whittaker Clark & Daniels. In:1970:CAM-163.
117. Rohrbacher RG. Asbestos in the Allamoore Talc District, Hudspeth and Culberson Counties, Texas. Geological Circular: Bureau of Economic Geology, University of Texas at Austin; 1973.
118. Wylie AG, Huggins CW. Characteristics of a Potassium Winchite-Asbestos from the Allamoore Talc District, Texas. *Canadian Mineraol*. 1980; 18:101–107.
119. Ingham Vs. Johnson and Johnson. Videotaped Deposition of Mathew Sanchez- Tuesday May 8, 2018; 2018. Available at: https://web.archive.org/web/20191211212735/https://repository.library.brown.edu/studio/item/bdr:1047843/. Accessed November 31, 2019.
120. ENSR Corporation. Phase I Environmental Site Assessment and Environmental Compliance Assessment of the Johnson & Johnson Consumer Products Facility, Royston, Georgia; 2004. Available at: https://web.archive.org/save/; https://repository.library.brown.edu/studio/item/bdr:1047828//. Accessed November 31, 2019.
121. Cynthia Hayes VS. Colgate Palmolive et al. Videotaped Deposition of Michael Burke Colgate Palmolive- July 10, 2018; 2019. Available at: https://web.archive.org/save/https://repository.library.brown.edu/studio/item/bdr:1053202/. Accessed November 31, 2019.
122. Finley B, Pierce J, Phelka A, et al. Evaluation of tremolite asbestos exposures associated with the use of commercial products. *Crit Rev Toxicol*. 2012;42:119–146.
123. Alleman J, Mossman B. Asbestos revisited. *Scientific Am*. 1997;227:70–75.
124. Virta R. Mineral Commodity Profiles—Asbestos. In: Interior UDot, ed. Reston, Virginia: US Geological Survey (USGS); 2005.
125. Dodson R, Levin J. An Unusual Case of Mixed-Dust Exposure Involving a ''Noncommercial'' Asbestos. *Environ Health Perspect*. 2001;109:199–203.
126. Churg A, Warnock M. Analysis of the cores of ferruginous (asbestos) bodies from the general populations. *Lab Investig*. 1979;40:622–626.
127. Finkelstein M. Malignant Mesothelioma and its nonasbestos causes. *Arch Pathol Lab Med*. 2018;143:659–660.

128. Henderson DW, Silkin, Langlois SLP, Whitaker D. Malignant mesothelioma. In: *The Cancer Series*. New York, NY: Hemisphere Publishing; 1992
129. Roggli VL. Asbestos bodies and nonasbestos ferruginous bodies. In: Roggli VL, Sporn TA, Oury TD, editors. *Pathology of Asbestos-Associated Diseases*. New York, NY: Springer New York; 2004. p. 34–70.
130. Glickman L, Domanski L, Maguire T, Dubielzig R, Churg A. Mesothelioma in pet dogs associated with exposure of their owners to asbestos. *Environ Res*. 1983;32:305–313.
131. Attanoos RL, Gibbs AR. Primary malignant gonadal mesotheliomas and asbestos. *Histopathology*. 2000;37:150–159.
132. British Columbia: Ministry of Environment. Technical guidance on Contaiminated Site: Chapter 12 Composite Sample; 2005: 10–12.
133. Egilman D. Health Effects of Censored Elongated Mineral Particles: A Critical Review. In: Brisson M, ed. Detection Limits in Air Quality and Environmental Measurements - STP 1618. Vol Detection Limits in Air Quality And Environmental Measurements; 2019.
134. Cralley L. Fibrous and mineral content of cosmetic talcum products. *Am Ind Hyg Assoc J*. 1968;29:350–354.
135. Egilman D, Steffen J. Commentary on ''Assessment of Health Risk from Historical Use of Cosmetic Talcum Powder''. *New Solut*. 2018;28:400–409.
136. Russell R. Special Talc Studies - JBP, Respirable Particle Measurements During Adult Usage, Project #0503.01. In:1977:JNJ000886943-000886945.
137. Burns A, Barlow C, Banducci A, Unice K, Sahmel J. Potential airborne asbestos exposure and risk associated with the historical use of cosmetic talcum powder products. *Risk Anal*. 2019;39:2272–2294.
138. Moon MC, Park JD, Choi BS, et al. Risk assessment of baby powder exposure through inhalation. *Toxicol Res*. 2011;27:137–141.
139. Addison J, JMG. D. A comparison of the carcinogenicity of six tremolites using the intraperitoneal injection assay in rats. In: Proceedings of the VIIth International Pneumoconiosis Conference. Pittsburgh: NIOSH-ILO; 1998.
140. Langer AM. Letter to Dr. Gavin Hildick-Smith, Director of Clinical Research, Johnson & Johnson. In:1971:JNJ000288077-000288078.
141. Graham J, Graham R. Ovarian cancer and asbestos. *Environ Res*. 1967; 1:115–128.
142. Cramer DW, Welch WR, Berkowitz RS, Godleski JJ. Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. *Obstet Gynecol*. 2007;110(2 pt 2):498–501.
143. Langseth H, Johansen BV, Nesland JM, Kjaerheim K. Asbestos fibers in ovarian tissue from Norwegian pulp and paper workers. *Int J Gynecol Cancer*. 2007;17:44–49.
144. Musti M, Massaro T, Cavone D, et al. Exposure to asbestos and risk of occurrence of primary ovarian mesothelioma. Note II: Description of two case studies. *Conference Paper*. 2009.
145. Occupational Safety and Health Administration. OSHA Standard 1915.1000 - Air contaminants. Occup. Safety and Health Standards for Shipyard Employment, Toxic and Hazardous Substances - Air Contaminants; 2017. Available at: http://web.archive.org/web/20190401215023/https://www.osha.gov/laws-regs/regulations/standardnumber/1915/1915.1000. Accessed April 1, 2019.
146. Occupational Safety and Health Administration. Part 57-Health and Safety Standards - Metal and Nonmetallic Underground Mines, Miscellaneous Amendments. *Federal Reg*. 1974;39:24319.
147. Occupational Safety and Health Administration. Part 1910 - occupational safety and health standards, subpart g - occupational health and environmental control. *Federal Reg*. 1972;37:22139–22163.
148. International Agency for Research on Cancer (IARC). Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. In. Vol Supplement No. 71987.
149. Hildick-Smith G. Nashed W. Memo: Johnson & Johnson Meeting with the Commisioner: Substantial Asbestos Can be Allowed Safely in a Baby Powder. 1974; JNJ 000307413. Available at: https://repository.library.brown.edu/studio/item/bdr:841462/. Accessed November 31, 2019.
150. Food and Drug Administration (FDA). AMA Analytical Services, Inc. Summary of Asbestos and Talc Analysis – Claire's 2019. Available at: https://www.fda.gov/media/127825/download. Accessed November 31, 2019.
151. Food and Drug Administration (FDA). AMA Analytical Services, Inc. Summary of Asbestos and Talc Analysis – Johnson & Johnson – Baby Powder Lot #22318RB; 2019. Available at: https://www.fda.gov/media/131989/download. Accessed November 31, 2019.
152. Images of labels for Angel of Mine and Perfect Purity talc powder products; 2018.
153. Imerys. Rio Tinto Minerals Talc MSDS; 2009.
154. Rio Tinto Minerals. Material Data Safety Sheet - Talc, Version 1.0. In:2006:IMERYS042245-042249.
155. Johnson & Johnson. Safety Data Sheet - Johnson's Baby Powder; 2015:1–7.
156. Johnson & Johnson (J&J). Technological Forecast - Powders. In:1986:JNJ000000523-JNJ000000536.
157. Johnson & Johnson (J&J). Introducing Johnson & Johnson Baby Cornstarch - Advertisement. In:1984:JNJ000060260.
158. Nicholson S. Email to J. James and I. Ahmed, FW: Cornstarch containing JBP (with attachments). In:2016:JNJ000526749-JNJ000526754.

