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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

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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 $\geq 0.5 \mu$." *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

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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



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

Report of the Advisory Group to Recommend Priorities
for the *IARC Monographs* during 2020–2024

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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.

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(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 & Salaspuuro (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 (Besaratnia & 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 F₁ generation and of the Zymbal gland in the F₁ and F₂ 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; Korinith 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-1 β , 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 (Sb₂O₃) 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 & Järholm, 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 B6C3F₁ 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 B6C3F₁ mice that received 120, 240, or 480 mg/kg body weight for 2 years (NTP, 1994a). In male B6C3F₁ 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 B6C3F₁/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 B6C3F₁/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 B6C3F₁ 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 ranged 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, protham, 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); Ferruccio 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; Pepłowska 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); Neuhouwer 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 ER α (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 B6C3F₁ 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- κ B, 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 B6C3F₁ 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 CO₂. 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 (Keskin 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 (Keskin 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 O⁶-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 O⁶-methyldeoxyguanosine and an acrolein-derived DNA adduct in DNA isolated from lung, bladder, heart, and liver tissue, as assessed by immunoassays and ³²P-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 Bommel 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

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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 B₁ (CAS No. 116355-83-0)

Fumonisin B₁ 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 B₁ is a mycotoxin that is produced primarily by *Fusarium verticillioides* and *Fusarium proliferatum*. Fumonisins, primarily fumonisin B₁ and to a lesser extent fumonisin B₂, are widespread natural contaminants of corn (maize) and corn-based foods and animal feeds. Although more than 30 fumonisin analogues have been characterized, fumonisin B₁ 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 B₁, 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 B₁ (Voss & Riley, 2013).

Cancer in Experimental Animals

The carcinogenicity of fumonisin B₁ 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 B6C3F₁ 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 B₁.

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 B₁ 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 B₁ is due to a non-genotoxic mode of action (Bondy et al., 2012).

Mechanistic Evidence

There is little support for the view that fumonisin B₁ interacts directly with DNA or is metabolized to a metabolite that interacts with DNA. Fumonisin B₁ is inactive in bacterial mutagenesis assays but induces DNA damage in vitro and in vivo, perhaps as a consequence of oxidative damage.

Fumonisin B₁ 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 B₁ 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 B₁ 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 B₁ (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 B₁ (Torres et al., 2015).

Recent evidence demonstrates that urinary fumonisin B₁ may be used to assess continuing exposure to fumonisin B₁ in population-based studies. The use of this biomarker may increase the power of current and

future epidemiological studies to uncover relationships between fumonisin B₁ exposure and the development of preneoplastic lesions and/or cancer (Riley et al., 2015; Torres et al., 2015)

Rats treated sequentially with aflatoxin B₁ and fumonisin B₁ 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 B6C3F₁ mice treated orally with furan for 2 years had a dose-dependent increase in hepatocellular tumours (Moser et al., 2009). Infant male B6C3F₁ 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, furmecyclohexane 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. Furmecyclohexane 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 B6C3F₁ 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; Ostensfeld 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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ 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 Tgf β 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 β 1-HPV5 and β 2-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 (Pottg rd 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 (Pottg rd 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-1 α , 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 B6C3F₁/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'-diindolymethane 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); Coggs 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 B6C3F₁ 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 B6C3F₁ 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 Eppléy 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 α 2u 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 α 2u 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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ 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 (TiO₂) with cancer of the lung, but not on nano-TiO₂. 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-TiO₂ (Becker et al., 2011) and carbon nanotubes (Kobayashi et al., 2017) has been reviewed. Recently, long-term exposure to cerium oxide (CeO₂) and barium sulfate (BaSO₄) 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 (NO₂) (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 (NO₂), 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 NO₂ and cancer, and the findings in those studies were ambiguous.

Exposure Data

NO₂ is emitted from fossil fuel combustion, microbial activity, biomass burning, and oxidation of nitrous oxide. Globally, NO₂ 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 NO₂ 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 µg/m³ increment in NO₂ (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 NO₂ 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 NO₂.

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 NO₂ on cancer development.

Mechanistic Evidence

A substantial number of studies relevant to several key characteristics of carcinogens are available. Some studies evaluated whether NO₂ is genotoxic (Koehler et al., 2010), and others indicated that NO₂ 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). Rösli 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

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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 $10 \mu\text{g}/\text{m}^3$ for particulate matter with particles of aerodynamic diameter less than $2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) (Brauer et al., 2016). Trends vary by pollutant and by region. Large increases in global population-weighted $\text{PM}_{2.5}$ 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 17 α -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 (O₃) (CAS No. 10028-15-6)

Ozone (O₃) 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 µg/m³. 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 µg/m³, 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 uterotrophic 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 & Gregoraszcuk, 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 & Gregoraszcuk (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 (PPAR γ) 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-harboured 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 & Chukwunke, 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); Mellemegaard & 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 ($P_{\text{trend}} < 0.001$) and breast cancer ($P_{\text{trend}} < 0.001$). 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

Tepraloxymid 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 (ECSC, 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) B6C3F₁ 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 B6C3F₁ 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

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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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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

¹Susan 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

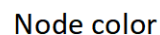
- | | |
|-------------|-------------------------------------|
| 09:00–10:30 | Plenary session |
| 11:00–13:00 | Report revision and finalisation |
| 14:00–15:45 | Plenary session |
| 16:15–18:00 | Plenary session and closing remarks |
| 18:00 | Closing reception |

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

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for the *IARC Monographs* during 2020–2024

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

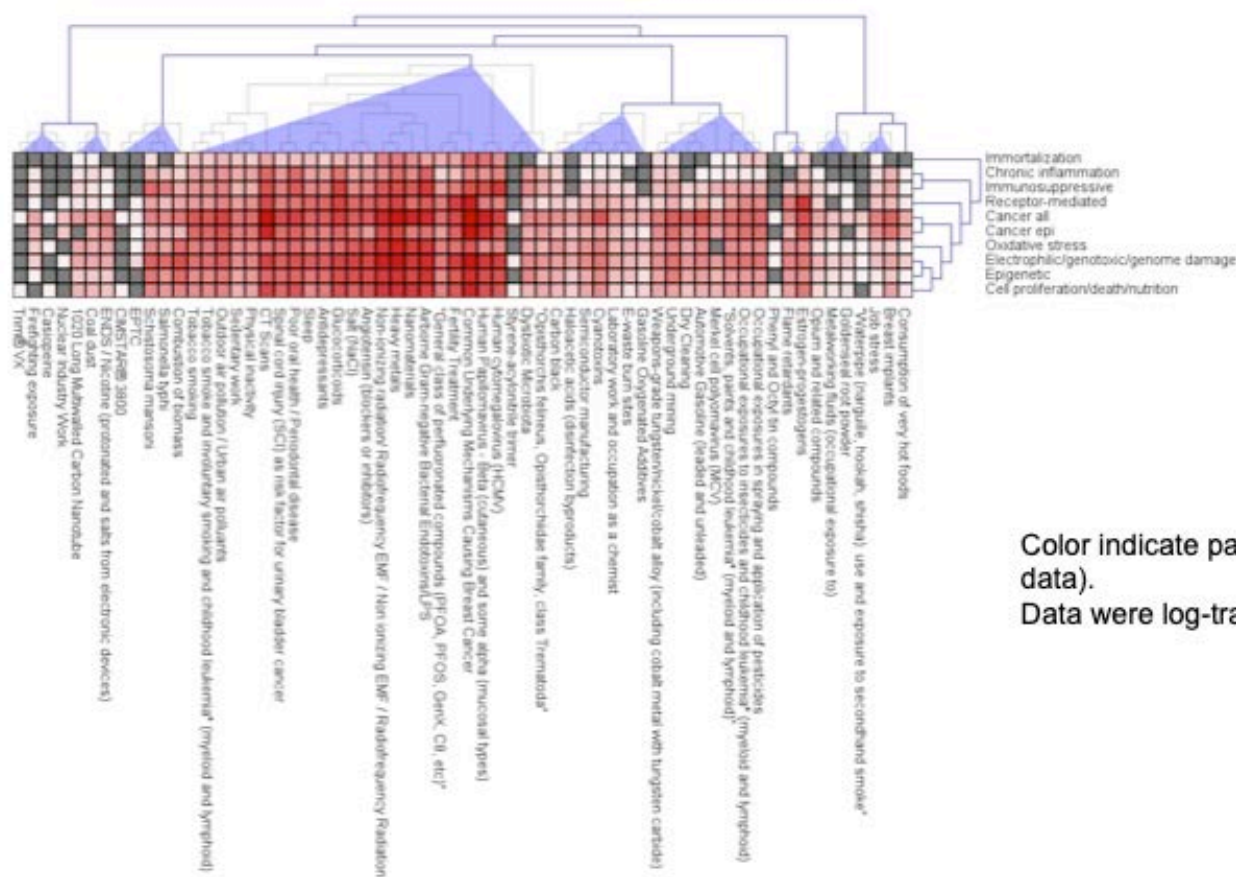
Node size – cancer all papers

Node color – sum of queries (1-10)



305

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 priority¹**

Agent name	Rationale
<u>Agents not previously evaluated by the <i>IARC Monographs</i></u>	
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, <i>Salmonella typhi</i> , 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
<u>Agents previously evaluated by the <i>IARC Monographs</i>²</u>	
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 priority¹

Agent name	Rationale
Acrylamide*, Acrylonitrile, Some anthracyclines, Coal dust, Combustion New human cancer and mechanistic evidence to warrant re-evaluation of the of biomass, Domestic talc products, Firefighting exposure, Metallic nickel,classification Some pyrethroids (i.e. permethrin, cypermethrin, deltamethrin)	
Aniline, Acrolein, Methyl eugenol and isoeugenol*, Multi-walled carbon New bioassay and mechanistic evidence to warrant re-evaluation of the classification nanotubes*, Non-ionizing radiation (radiofrequency)*, Some perfluorinated compounds (e.g. perfluorooctanoic acid)	
Estrogen: estradiol and estrogen–progestogens ³ , Hydrochlorothiazide, New human cancer evidence to warrant re-evaluation of the classification Merkel cell polyomavirus, Perchloroethylene, Very hot foods and beverages	
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, New mechanistic evidence to warrant re-evaluation of the classification Crotonaldehyde, Cyclopeptide cyanotoxins, Fumonisin B ₁ , Inorganic lead compounds, Isoprene, <i>o</i> -Anisidine	

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 priority¹

Agent name	Previous evaluation status
<u>Medium-priority agents</u>	
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, <i>o</i> -Benzyl- <i>p</i> -chlorophenol, Ozone, Pendimethalin, Sleep, Styrene-acrylonitrile trimer, Terbufos, Tris(chloropropyl) phosphate	Agents not previously evaluated by the <i>IARC Monographs</i>
Aflatoxins ³ , Anthracene, Antimony trioxide, Atrazine, Bromate compounds, Dimethyl hydrogen phosphite, Furan, <i>N</i> -Methylolacrylamide, <i>p</i> -Nitrotoluene, <i>Schistosoma mansoni</i> , Tris(2-chloroethyl) phosphate, Tobacco smoking (including second-hand) ³	Agents previously evaluated by the <i>IARC Monographs</i> ²
<u>Low-priority agents</u>	
2-Hydroxy-4-methoxybenzophenone, Aluminium, Androstenedione, Butyl methacrylate, Cinidon ethyl, Dysbiotic microbiota, Fonofos, Furmecyclox, Isoflavones, Isophorone, Laboratory work and occupation as a chemist, Methanol, <i>S</i> -Ethyl- <i>N,N</i> -dipropylthiocarbamate, Semiconductor manufacturing, Sucralose	Agents not previously evaluated by the <i>IARC Monographs</i>
1,1-Dimethylhydrazine, Benzophenone-1, Carbon black, Catechol, Chlordecone, Cumene, Dichloromethane, Hepatitis D virus, Human papillomavirus – Beta (cutaneous) and some alpha (mucosal) type), <i>Opisthorchis felineus</i> , Outdoor air pollution ³ , Pyrrolizidine alkaloids, Selenium and selenium compounds	Agents previously evaluated by the <i>IARC Monographs</i> 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 SUMMARY¹

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 agencies², 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, 2010⁵; Block et al. 2014⁶). 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, 1974⁷, Millette 2015⁸, Block et al. 2014⁵).

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

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>

⁷ 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 methods⁹ 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 62¹⁰ 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 $> 0.5 \mu\text{m}$ using the most inclusive criteria for length and AR from among the “asbestos” counting rules in established testing protocols. The specified minimum length of $0.5 \mu\text{m}$ 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

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 $\geq 0.5 \mu\text{m}$ (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 $<200 \text{ nm}$ (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

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 al⁴ 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 al⁷³ 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

From the Never Again Consulting, Attleboro, Massachusetts (Ms Steffen, Mr Tran, Ms Yimam, Ms Clancy, Dr Bird, Dr Egilman); College of Engineering and Mines (student), University of Alaska – Fairbanks, Fairbanks, Alaska (Ms Clancy); Mellon Postdoctoral Fellow, Wesleyan University, Middletown, Connecticut (Dr Bird); Materials Analytical Services LLC, Suwanee, Georgia (Dr Rigler, Dr Longo); Department of Family Medicine, Warren Alpert Medical School, Brown University, Providence, Rhode Island (Dr Egilman).

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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/JOEM/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" × 15" × 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/JOEM/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/JOEM/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/JOEM/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 rubbed 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 al⁹³ 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 et al⁴¹ measurements for shaker application of cosmetic talc powder to the underarm, shoulder, and upper arm area. Gordon et al⁴¹ used Cashmere Bouquet, which used the same Italian mine source as J&J (Val Chisone) from 1940 until 1992.^{94,95} Gordon et al⁴¹ 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 al⁹³ 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 ($\frac{f}{cc} \times \text{year}$) 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:

$$\begin{aligned} &\text{Asbestos exposure in } \frac{f}{cc} \\ &\quad \times \frac{\text{duration of each exposure} \times \text{total number of applications}}{525,600 \text{ min per year}} \\ &= \text{total dose in } \frac{f}{cc} \cdot \text{years} \end{aligned}$$

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 m³," and formula to convert the dose from fiber years to total fibers.¹⁰¹ We relied on measurements of infant lung volume from Hall¹⁰² and on median infant respiratory rates calculated by Fleming et al¹⁰³ 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):

$$\begin{aligned} &\left[\text{total does in } \frac{f}{cc} \times \text{years} \right] \times \frac{7,300,000,000 \text{ cc}}{\text{year}} \\ &= \text{Total number of asbestos fibers} \end{aligned}$$

Formula 3:

Formula to convert infant exposures to total fibers based on Hall¹⁰² and Fleming et al¹⁰³:

$$\begin{aligned} &\left[\text{total does in } \frac{f}{cc} \times \text{years} \right] \times \frac{5,512,536,000 \text{ cc}}{\text{year}} \\ &= \text{Total number of asbestos fibers} \end{aligned}$$

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's¹⁰⁴ 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 μ m 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 μ m 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 \times . 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 μ m 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/

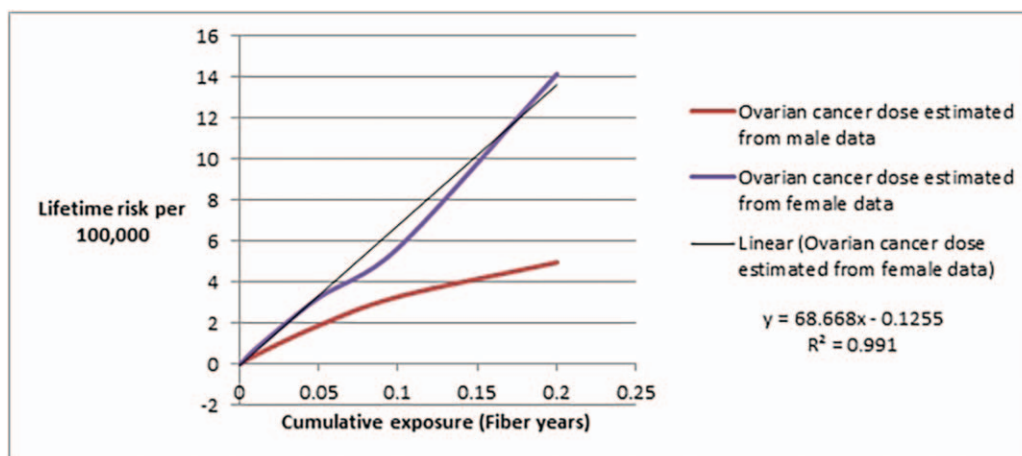
cc) for the talc user personal samples. For area samples, the average total fiber exposure was 0.41 f/cc (0.52, 0.28, 0.42, 0.40 f/cc), the average asbestos exposure was 0.2 f/cc (0.31, 0.20, 0.13, and 0.16 f/cc) and the average fibrous talc exposure was 0.19 f/cc (0.13, 0.08, 0.29, and 0.24 f/cc). The 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 $20.0 \times 16.0 \mu\text{m}$ 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 Warnock¹²⁶ 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’s¹²⁷ 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 Finkelstein¹²⁷ 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 al⁴¹ conducted examination on 50 samples of a single brand of cosmetic talc, sourced from either Montana, North Carolina or Val Chisone. Gordon et al⁴¹ 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 al⁴¹ selected a bottle with 18 million asbestos fibers per gram for the inhalation study. The results for Gordon’s et al.’s⁴¹ 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 al⁹³ 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				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	31.1	Ovary (R)	Platy talc (333 s/g), Fibrous talc (4,000 s/g), Ferro-anthophyllite (3,667 s/g) Fibrous talc (1,200 s/g), ferro-anthophyllite (399 s/g) NSD* — [†] — [‡] NSD* NSD*
2	Poorly differentiated high grade serous ovarian carcinoma	53	1x/d, 36yrs	1x/d, 23yrs	8x/d, 2yrs	7.5x/d, 7.5yrs	4.1	Ovary (L) Fallopian tube (R) Fallopian tube (L) Pelvic Lymph Node (R) Pelvic Lymph Node (L) Ovary A Ovary B Possible fallopian tube A Possible fallopian tube B	NSD* Platy talc (323 s/g) NSD* Platy talc (56,700 s/g), Fibrous talc (4,720 s/g), Tremolite (22,000 s/g) Platy talc (2,001,503 s/g), Fibrous talc (13,343 s/g) Platy talc (12,308 s/g), Fibrous talc (8,202 s/g) Tremolite (15,670 s/g), Winchite (15,670 s/g), Richterite (15,670 s/g) Platy talc (43,829 s/g) Platy talc (2,860 s/g), Anthophyllite (952 s/g) Tremolite (604 s/g) Platy talc (30,000 s/g) Fibrous talc (868 s/g) Platy talc (12,600 s/g) Platy talc (17,600 s/g), Tremolite (2,510 s/g) Platy talc (10,900 s/g), Fibrous talc (1,810 s/g) Platy talc (25,000 s/g), Fibrous talc (5,000 s/g), Tremolite (5,000 s/g) Platy talc (77,200 s/g), Fibrous talc (7,720 s/g), Tremolite (3,860 s/g), Anthophyllite (3,860 s/g) Platy talc (50,600 s/g) (continues)
3	High grade serous carcinoma	49	3x/d, 39yrs	3x/d, 20yrs	8x/d, 2yrs	7x/d, 5yrs	9.6	Ovary, fallopian tube (R) Adnexa, fallopian tube (L) Pelvic lymph node (R) Pelvic lymph node (L) Ovary (R)	Platy talc (323 s/g) NSD* Platy talc (56,700 s/g), Fibrous talc (4,720 s/g), Tremolite (22,000 s/g) Platy talc (2,001,503 s/g), Fibrous talc (13,343 s/g) Platy talc (12,308 s/g), Fibrous talc (8,202 s/g) Tremolite (15,670 s/g), Winchite (15,670 s/g), Richterite (15,670 s/g) Platy talc (43,829 s/g) Platy talc (2,860 s/g), Anthophyllite (952 s/g) Tremolite (604 s/g) Platy talc (30,000 s/g) Fibrous talc (868 s/g) Platy talc (12,600 s/g) Platy talc (17,600 s/g), Tremolite (2,510 s/g) Platy talc (10,900 s/g), Fibrous talc (1,810 s/g) Platy talc (25,000 s/g), Fibrous talc (5,000 s/g), Tremolite (5,000 s/g) Platy talc (77,200 s/g), Fibrous talc (7,720 s/g), Tremolite (3,860 s/g), Anthophyllite (3,860 s/g) Platy talc (50,600 s/g) (continues)
4	Poorly differentiated serous adenocarcinoma	78	1x/day, 43yrs [§]	unknown [§]	unknown [§]	unknown [§]	2.3	Ovary (R)	Platy talc (333 s/g), Fibrous talc (4,000 s/g), Ferro-anthophyllite (3,667 s/g) Fibrous talc (1,200 s/g), ferro-anthophyllite (399 s/g) NSD* — [†] — [‡] NSD* NSD*
5	Low grade serous carcinoma	52	1x/d, 47yrs	1x/d, 47yrs	8x/d, 2yrs	10x/d, 10yrs	6.5	Ovary (R)	Platy talc (333 s/g), Fibrous talc (4,000 s/g), Ferro-anthophyllite (3,667 s/g) Fibrous talc (1,200 s/g), ferro-anthophyllite (399 s/g) NSD* — [†] — [‡] NSD* NSD*

TABLE 2. (Continued)

Case Number	Diagnosis	Age at Diagnosis	Talc Exposure History				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	5.8	Adnexa, tumor/ovary (R)	Platy talc (21,300 s/g)
7	Serous adenocarcinoma	56	1x/d, 37yrs	1x/d, 37yrs	Unknown	7.5x/d, 6yrs	4.3	Adnexa, tumor/ovary (L) Adnexa, fallopian tube (R)	Platy talc (4,720 s/g) Platy talc (12,000 s/g), Tremolite (12,000 s/g), Anthophyllite (12,000 s/g)
								Adnexa, fallopian tube (L) Pelvic lymph node (L) Ovary (R)	Platy talc (13,700 s/g) Platy talc (11,500 s/g) Platy talc (8,740 s/g), fibrous talc (1,090 s/g)
8	High grade ovarian serous carcinoma	44	1x/d, 24yrs	1x/d, 24yrs	Unknown	3.5x/d, 4yrs	2.5	Ovary (L) Fallopian tube (R) Fallopian tube (L) Ovary (R)	Platy talc (10,500 s/g) Platy talc (8,500 s/g) Platy talc (10,900 s/g) Platy talc (3,340 s/g), Ferro-anthophyllite (1,670 s/g), Crocidolite (1,670 s/g)
								Ovary (L) Fallopian tube (R)	Platy talc (799 s/g) Platy talc (9,690 s/g), Fibrous talc (1,380 s/g), Tremolite (1,385 s/g), Anthophyllite (1,385 s/g)
9	Poorly differentiated serous papillary adenocarcinoma ^{II}	41	1x/d, 42yrs [§]	1x/d, 42yrs [§]	8x/d, 2yrs [§]	n/a [§]	4.1	Fallopian tube (L) Ovary (R)	Platy talc (7,400 s/g), Tremolite (1,850 s/g) NSD*
10	High-grade ovarian papillary serous carcinoma	42	2x/d, 32yrs	2x/d, 32yrs	8x/d, 2yrs	8x/d, 4yrs	6.8	Ovary (L) Fallopian tube (R) Fallopian tube (L) Pelvic Lymph Node (L) Ovary, fallopian tube (R)	NSD* NSD* NSD* Fibrous talc (8,770 s/g) Platy talc (10,800 s/g)
								Ovary, fallopian tube (L) Pelvic lymph node (R) Pelvic lymph node (L)	Platy talc (5,520 s/g) Platy talc (79,300 s/g) Platy talc (84,400 s/g)

*No asbestos or talc structures detected.

^ITissue received, but not analyzed.^{II}Richite 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 than 5:1 that were not counted.

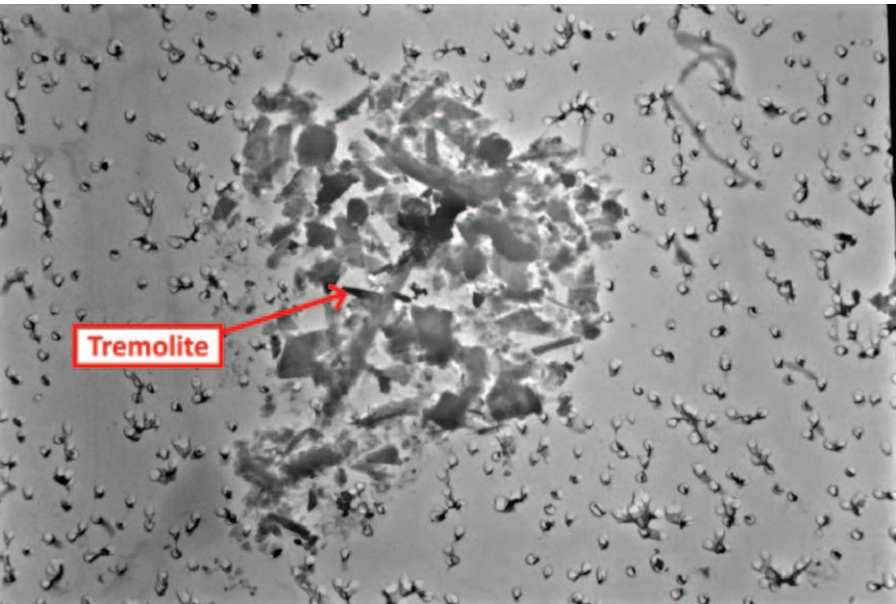


FIGURE 2. TEM image of cluster measuring 20.0 × 16.0 μm composed of 36 counted talc plates, two fibrous talc structures, and one tremolite fiber identified in “possible fallopian tube B” tissue of Case No. 2.

the sampling time.⁹³ Dement et al⁹³ 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 al⁹³ 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 al¹⁰⁰ 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 al⁴¹ 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 al¹⁰⁰ 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 al¹⁰⁰ 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

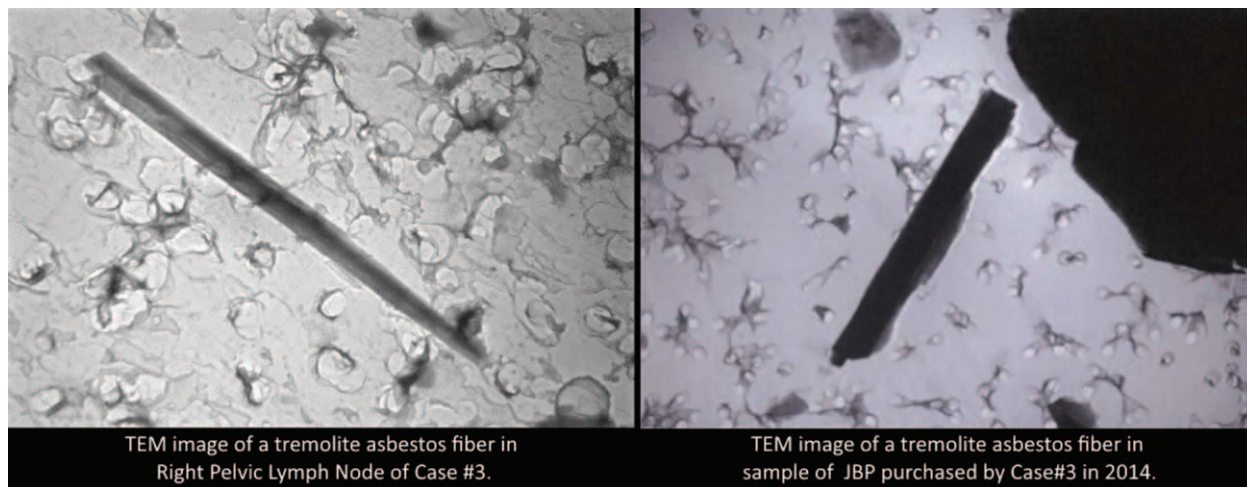


FIGURE 3. TEM images of a tremolite asbestos fibers in Case No. 3 right pelvic lymph node tissue (left) and in sample of JBP purchased by Case No. 3 in 2014 (right).

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 al¹³⁷ created a dose estimation-model for cosmetic talc, relying on previous assessments to predict asbestos exposure, including Moon et al¹³⁸, Gordon et al⁴¹, Russell et al¹³⁶, and Anderson et. al.¹⁰⁰ Burns's et al¹³⁷ 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 al⁴¹ reported, 4.8 f/cc, however, Burns's et al¹³⁷ 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 al⁶⁸ 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
Langer (1971)	n/a	Unknown	Qualitative identification of talc in 12/21 cervical tumors
Heller, Westhoff et al (1996)	Wet weight	PLM	Qualitative identification of talc and chrysotile asbestos in Henderson et al (1971) samples
			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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