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INTERNATIONAL AGENCY FOR RESEARCH ON CANCER



*IARC Monographs on the Evaluation of  
Carcinogenic Risks to Humans*

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**Report of the Advisory Group to  
Recommend Priorities for *IARC*  
*Monographs* during 2015–2019**

18–19 April 2014

LYON, FRANCE

2014

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This publication contains the report of the Advisory Group to Recommend Priorities for *IARC Monographs* during 2015–2019, which alone is responsible for the views expressed.

**Report of the Advisory Group to Recommend Priorities for  
*IARC Monographs* during 2015–2019**

Lyon, France: 7–9 April 2014

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IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

**Report of the Advisory Group to Recommend Priorities  
for IARC Monographs during 2015–2019**

Lyon, France: 7–9 April 2014

**1. Introduction**

An IARC Advisory Group to Recommend Priorities for *IARC Monographs* during 2015–2019 met in Lyon, France, on 7–9 April 2014. 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 Scientific Council, WHO Regional Office, and previous participants in the *Monographs*. Nominations were also developed by IARC staff and identified from new evaluations by other national and international authorities.

Detailed assignments were sent to the participants of the Advisory Group and short draft summary recommendations were prepared in advance of the meeting. IARC also asked the Advisory Group for recommendations about other aspects of the *IARC Monographs* Section (IMO).

The membership of the Advisory Group is given in Appendix 1; the Preliminary Agenda is given in Appendix 2. The Advisory Group elected Dr Christopher Portier (USA) as Chair and Dr Bernard Stewart (Australia) as Rapporteur.

The Advisory Group was provided with a range of relevant background information through mailings before the meeting and through presentations during the meeting. During three days of discussions and deliberations, the Advisory Group developed a number of recommendations for IMO to consider regarding activities for the 2015–2019 timeframe.

**2. Issues facing the *IARC Monographs* programme**

**2.1. Experts**

The Advisory Group concurred with the IMO Scientific Review Panel that the current system of selection and use of experts should remain for the cancer evaluations, with strict management of conflict of interest. While some have argued

that substance-specific experts may have preconceived opinions, the Advisory Group considered that IARC had adopted practices to mitigate these concerns.

## ***2.2. Systematic review***

The IMO Secretariat asked for advice on the use of systematic review to increase efficiency and transparency in the development of *Monographs*. The Advisory Group heard a presentation on systematic-review tools being implemented and explored by the United States Environmental Protection Agency (EPA) and the United States National Toxicology Program (NTP), after which there was a thorough discussion. The Advisory Group recognized the progress made by the Secretariat in using computer tools to develop and publish *Monographs* in the most efficient manner. The Advisory Group encouraged the Secretariat to explore the use of systematic-review tools being developed by other national and international health agencies. Standardizing literature searches and creating databases of information on study designs and results could increase transparency and rigour. These can also serve as a starting point for subsequent updates or be shared across health agencies. The Advisory Group recommended that the Secretariat implement systematic-review tools in a manner consistent with the principles for evaluating studies and integrating evidence as outlined in the Preamble to the *IARC Monographs*.

## ***2.3. Evaluation of mechanistic data***

The Advisory Group was asked to consider prospects for the evaluation of mechanistic data in the context of *Monograph* evaluations. The Advisory Group recognized that central to this matter was the outcome and implementation of data analysis in the course of the anticipated *IARC Scientific Publication* based on concordance and mechanisms with respect to Group 1 carcinogens. This analysis has generated 10 characteristics or aspects of carcinogenesis using which relevant data for any carcinogenic agent may be categorized. Using this data review and analysis as a base will provide for a systematic identification of mechanistic data for any carcinogen, including the consideration that certain data may not be available. The same principles will allow mechanistic information in the Monograph to be scrutinized to the extent that such data are consistent with or indicative of possible tumorigenesis in humans and/or experimental animals.

In the context of this discussion, there was recognition of the availability of what may be an overwhelming number of research papers concerning a particular agent. There is a need to avoid comprehensive documentation of such literature. A basis for selection in favour of clear elucidation of mechanistic processes was recognized. Specifically, tabular presentation of mechanistic data may be facilitated.

At a separate level of consideration, the Advisory Group recognized that in the immediate future much biological information, including that which is immediately relevant to carcinogenesis, will involve high-throughput and high-content data streams, including databases involving genomics, transcriptomics, proteomics,



metabolomics and other 'omics'. Nominally, such data are not 'peer reviewed', although it is evident that peer-reviewed publications predicated on high-throughput data are and will be available. If not peer-reviewed, the peer expertise inherent in *Monograph* Working Groups will be able to address this concern, the implication being that Working Group membership will require the necessary expertise to achieve this end. The Advisory Group recognized the need for future *Monograph* Working Groups to analyse and appropriately present high-throughput and high-content data streams.

Moving to the consideration of how mechanistic data are likely to impinge on the evaluation process, the Advisory Group recognized merit in the informative presentation and analysis of mechanistic data irrespective of whether such data played a key role in altering overall evaluations. A different perspective involved recognition of a trend toward decreased or no information regarding either relevant epidemiological studies and/or lifetime testing of agents in experimental animals. In this context, reliance on and recognition of comprehensive databases from government authorities (typically) was acknowledged.

Overall, the Advisory Group acknowledged the need for a broad vision concerning the nature and scope of mechanistic data and the almost certain prospect of increasing reliance on such data in arriving at overall evaluations in the context of particular *Monographs*.

#### **2.4. Quantitative risk characterization**

In November 2013, the Secretariat convened an Advisory Group on Quantitative Risk Characterization (AG-QRC) "to provide advice to the Programme on the advisability of adding aspects of quantitative risk evaluations to the more qualitative evaluations currently undertaken". The AG-QRC recommended that *Monograph* Working Groups should review cancer burden and other risk scenarios from the literature, and summarize exposure–response relationships seen in epidemiological studies, but should not formally review existing national risk assessments. Outside of the Working Group meetings, the AG-QRC identified a need for estimating global cancer burdens and encouraged IARC to pursue cancer-burden evaluations (<http://monographs.iarc.fr/ENG/Publications/internrep/14-001.pdf>).

Recommendations from the AG-QRC were presented to the present Advisory Group. IMO expressed its intention to implement the recommendations concerning quantitative risk characterization progressively over the next 5 years. Activities planned for the near future included: developing improved methods of capturing exposure and risk data, standardizing approaches to exposure–response analysis, and collaborating with other IARC Sections to develop methods for estimating attributable disease burdens. These methods would be pilot-tested in conjunction with selected upcoming *Monographs*. The Advisory Group concurred with the recommendations of the AG-QRC and endorsed the phased approach being used by IMO to begin to incorporate some aspects of QRC into its activities.

## **2.5. Communication**

In presentations to the Advisory Group, the IMO Secretariat asked for advice on improving the dissemination and communication of *IARC Monographs* and evaluations. The Advisory Group encouraged IMO to disseminate the findings of the evaluations as broadly as possible to the scientific and technical community, policymakers and the general public. Such dissemination would enhance the public-health mission of the programme and also increase the recognition of its work. The Advisory Group recommended that resources be made available to develop a lay summary (factsheet) that could be disseminated with the press release to assist national spokespeople to answer media and public inquiries about evaluation results. Such a factsheet could be further disseminated by national and international organizations and media channels and be accessible on the *IARC Monographs* website for the interested public. The Advisory Group did not have the expertise to advise the programme on expanding use of electronic, video and social media; these opportunities should be considered as part of the overall media strategy for the Agency to ensure relevance and broad outreach.

## **2.6. Low- and middle-income countries**

A concern was expressed as to whether the *Monographs* programme was adequately addressing problems related to low- and middle-income countries (LMIC). The Advisory Group discussed this issue, and several suggestions were developed to improve the utility of the *Monographs* for LMIC settings.

If a *Monograph* deals with exposures specific to LMIC, the title of the *Monograph* should make this clear using appropriate words that are readily understood in these countries.

When dealing with exposure data in the *Monograph*, special attempts should be made to include data from LMIC in a reasonably prominent manner.

Special attempts could be made to share *Monographs* findings with LMIC through specific targeted summaries. In these summaries, there should be a focus on cancer prevalence in LMIC. A translation of these summaries into local languages would facilitate ensuring wide dissemination.

A communication system could be established for dissemination of findings in LMIC. For example, IMO could partner with WHO country offices that have direct access to health ministries and other stakeholders in every country.

## **3. Background to priorities**

In 2013, the *IARC Monographs* programme widely distributed a notice requesting nominations for agents or exposures to be evaluated during 2015–2019. The

Advisory Group reviewed the nominated agents and exposures, added several additional ones, and discussed the priority for each. The agents reviewed are described below and priorities are listed for each as 'high', 'medium' or 'low'. The Advisory Group emphasized that placement of an agent in the medium- or low-priority categories did not necessarily reflect the Advisory Group's long-term concerns about the agent. Rather, the rankings reflected a variety of factors, as outlined below.

The Advisory Group also noted that some of these agents (e.g. disinfected water) would best be communicated if aspects of both the risks (beyond cancer) and benefits of the agent were discussed in the *Monograph*. The Advisory Group strongly encouraged IMO to include risks and benefits where appropriate.

### ***3.1. Processing nominations***

Under the public call for nominations to be considered in the context of determining priorities for the *IARC Monographs* for 2015–19, agents and related exposures covering a broad scope were received. To render the task of according priorities manageable, and to facilitate discussion of closely-related agents, nominations were initially categorized primarily with terms commonly employed to identify particular topics: drugs, food contaminants, occupational exposures, etc. The categories used are shown in Appendix 3, which also lists the nominations received. The categories indicate the many scenarios in which exposure to carcinogenic agents may occur. In the first instance, such categorization allowed referral of particular groups of nominations to groupings of individual members recognized as having particular expertise. Accordingly, the global categories of 'biological agents' and 'pesticides' were used to reflect the context of expert advice considered by the Advisory Group as a whole.

While facilitating discussion, it was evident that such categorization as described is arbitrary in a number of respects. For example, certain nominations are readily identified with more than one category. For many single chemicals nominated, an immediate basis for categorization was not readily evident, and these chemicals are listed in Appendix 3 under 'chemicals not accorded particular categorization'. The categorization process did not serve to restrict the scope of data or limit the attention given to particular nominations.

Before the Advisory Group meeting, each nomination was referred to one or more members of the Advisory Group, depending upon the extent of relevant medico-scientific literature to be addressed. In each case, the member(s) was required to review and summarize the published findings in relation to epidemiological and experimental data addressing the carcinogenicity of the agent concerned, independent of information provided in the context of nomination. Such reviews formed the basis for the deliberations concerning each nomination. A summary of such relevant data for each nomination is specified in part 4 of this Report, together with an indication of the reasons for the priority accorded to the nomination as

agreed upon by the Advisory Group. Priority was specified by allocation of the nomination to high or medium or low priority for adoption as the basis of a *Monograph* during 2015–2019. In some cases where the Advisory Group felt that an evaluation was not warranted, the priority given was ‘no evaluation’.

### ***3.2. Specifying agents and exposures***

To be eligible for evaluation by the *IARC Monographs*, an agent is required to meet two criteria: first, there must be some evidence of carcinogenicity of the agent, and second, there must be evidence that humans are exposed to the agent in question. No nominations were excluded for failing to meet these criteria. However, the Advisory Group was often challenged in respect of specific terminology for agents or circumstances of exposure. For example, the term ‘chlorinated drinking water’ clearly includes much relevant epidemiology and experimental data; however, the full scope of such data extends to chemical means of disinfection apart from chlorination and modes of human contact with water apart from drinking. Exposure to the chemical acrylamide occurs both in certain workplaces as well as from consumption of some foods subject to particular circumstances of deep frying and other cooking methods. The bulk of epidemiological research in the last few years has concerned dietary exposure to acrylamide, whereas consideration of all available data is best accomplished by specification of acrylamide as the agent to be evaluated. Red meat and processed meat are clearly distinguishable, but much relevant research is a consequence of studies involving both these foods, and the relevant database may be most usefully addressed by considering all data relevant to red and processed meat together. Finally, some cancer risk factors, such as obesity, lack of physical exercise, and sedentary behaviour are clearly inter-related. In all of the examples above, and in many other circumstances, the Advisory Group adopted terminology that would provide the optimal vehicle for *Monograph* evaluation(s).

### ***3.3. Determining priority***

In according high, medium or low priority to nominated agents or circumstances of exposure, the Advisory Group considered a range of parameters. Availability of a broad scope of data, and/or a comprehensive body of data concerning a particular investigatory approach was recognized to justify and hence facilitate any *IARC Monographs* evaluation. In the case of second or later evaluations in relation to an agent or circumstance of exposure that was previously the subject of a *Monograph*, highest priority was accorded to new data considered likely to warrant a change in the current evaluation. In all such considerations, the Advisory Group was aware of the strict requirement for *Monograph* evaluations to be based on data that are publically accessible, preferably in a peer-reviewed context; this criterion excluded data that may be provided to regulatory authorities on the basis of ‘commercial – in confidence’.

Apart from criteria related directly to eligibility for *Monograph* evaluation, the Advisory Group considered other matters in determining priority from among the nominations made. The primary consideration in this regard involved the public-health ramifications of a *Monograph* evaluation. The Advisory Group recognized that circumstances of exposure to highest known concentrations of industrial chemicals or the most marked impact of infectious agents often occurs in LMIC. Despite a commitment to be aware of such circumstances, the Advisory Group was often obliged to acknowledge scant data concerning, for example, detailed relevant levels of exposure to particular chemicals and related epidemiological data in LMIC.

A further challenge to the Advisory Group involved nominations predicated upon a body of epidemiological and other data that concerned particular circumstances of exposure to an agent already evaluated as *carcinogenic to humans* (Group 1). Examples included exposure to X-radiation through computed tomography scans, usually referred to as CT scans, and exposure to tobacco smoke through use water pipes. The Advisory Group recognized that such an evaluation could have public-health ramifications; however, the Advisory Group was obliged to weigh such considerations against the scope and inherent expense of an evaluation that may, of necessity, involve re-examination of large amounts of data already addressed in the context of, in the case of the examples cited, current evaluations of X-radiation and tobacco smoke.

No simple formula was adopted by the Advisory Group to determine priority for all the nominations. Rather, as indicated in section 3.4 in which criteria for prioritization are described, particular considerations were determinative for individual nominations.

### ***3.4. Criteria for setting priorities***

The Advisory Group considered several factors in making recommendations to IMO on the inclusion of agents in future *Monographs*. The factors considered in building the case for inclusion are listed in general order of importance from highest to lowest:

- Potential for direct impact on public health
- Scientific literature to support suspicion of carcinogenicity from one or more of the following: new evidence of human cancer risk from recent epidemiological studies; availability of new data from animal bioassays, especially when the findings indicate multi-site, multi-species effects (e.g. chloronitrobenzenes, dimethyl-*p*-toluidine); reporting of new mechanistic data relevant to carcinogenicity (e.g. epigenetic effects of DDT), or availability of comprehensive molecular-screening data (e.g. pesticide information from Tox21 and ToxCast).
- Evidence of significant human exposure (e.g. chlorinated drinking water).

- High public interest and/or potential to bring clarity to a controversial area and/or reduce public anxiety or concern.
- Related agents similar to one given high priority by the above considerations (e.g. artificial sweeteners, carbamates, organophosphates).

### **3.5. *Agents recently tested in experimental animals***

There are several chemical agents for which toxicological data would suggest carcinogenicity based on new cancer bioassays. The Advisory Group recommended that IMO review some of the the chemicals listed below and others to develop one or a few volumes focused on chemical agents shown to increase carcinogenicity in experimental studies. Descriptions of these chemicals come from the Report on Carcinogens, Twelfth Edition; United States Department of Health and Human Services, Public Health Service, National Toxicology Program (NTP), Japanese Bioassay Research Center and others. Additional *Monographs* on lower priority agents with positive bioassay results could be added. For many of the agents discussed below, recent animal bioassays prompted the assignment of a higher priority.

## 4. Priorities for *Monographs* during 2015–2019

### 4.1. Acrolein

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 due to 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. IARC evaluated acrolein in 1995 (Volume 63) as *not classifiable as to its carcinogenicity to humans* (Group 3). No epidemiology studies have been reported. No new studies in rodents have been reported since the *IARC Monograph* in 1995. Acrolein is a metabolite of cyclophosphamide and ifosfamide, and is speculated to be the cause of cancer of the bladder in cancer patients treated with these anti-cancer drugs in the long term. A number of 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 to T and G to A mutations at a frequency similar to that found in the *TP53* gene in smoking-associated lung tumours.

**Recommendation:** Medium priority

### 4.2. Acrylamide, furan, 5-hydroxymethyl-2-furfural

Occupational exposure to acrylamide was reviewed in *IARC Monograph* Volume 60 (Group 2A, *probably carcinogenic to humans*), that concluded there was inadequate evidence in humans for the carcinogenicity of acrylamide. Since that evaluation, acrylamide has been identified as a contaminant in baked and fried carbohydrate-rich foods (e.g. French fries, potato chips, bread, and cereals) and other common foods and drinks (e.g. coffee) for which there is considerable human exposure. A number of epidemiological studies have examined the relationship between estimated dietary consumption of acrylamide and specific cancers, most with inconclusive or inconsistent results. These results are not very informative due to the difficulty in estimating dietary intake of acrylamide resulting in potential bias towards the null. The previous *Monograph* concluded that there was sufficient evidence in experimental animals for the carcinogenicity of acrylamide. Four bioassays that have appeared since the previous evaluation demonstrate the carcinogenicity of acrylamide and/or its electrophilic metabolite glycidamide. In addition, a large number of mechanistic studies have been published. Based upon the substantial amount of new data concerning acrylamide, the Advisory Group highly recommended that acrylamide be re-evaluated.

Furan was previously reviewed by IARC in 1995 (Volume 63). The Advisory Group recommended that furan be reviewed with high priority because it is formed at concentrations similar to those of acrylamide during cooking; an NTP bioassay has recently been conducted that encompassed a very wide range of doses, and there have been numerous new mechanistic studies.

5-Hydroxymethyl-2-furfural is a common product of the Maillard reaction and is found in many foods and beverages. Furfural was previously reviewed by IARC in 1995 (Volume 63). There were no studies of cancer in humans exposed to 5-hydroxymethyl-2-furfural. In studies in experimental animals, 5-hydroxymethyl-2-furfural promoted azoxymethane-initiated aberrant crypt foci and microadenoma. 5-hydroxymethyl-2-furfural gave negative results in NTP bioassays in rats and male mice, but caused liver tumours in female mice. Although 5-hydroxymethyl-2-furfural gave negative results in standard assays for genotoxicity, its sulfotransferase-catalysed metabolite, 5-sulfoxymethyl-2-furfural, is mutagenic; this may be important for humans who have higher expression of sulfotransferases than rodents. Based upon these data, the Advisory Group recommended that 5-hydroxymethyl-2-furfural be evaluated together with acrylamide (glycidamide) and furan.

**Recommendation:** High priority

#### ***4.3. Allyl chloride***

Allyl chloride is an intermediate in the manufacture of resins and polymers; 90% of this substance is used to make epichlorohydrin. Allyl chloride was reviewed by IARC Working Groups in 1985 (Volume 36) and 1987 (Supplement 7). A retrospective cohort mortality study has since shown no association between cancer and exposure to allyl chloride among a group of workers. As described in the IARC publications cited above, allyl chloride induced transitional cell carcinoma of the urinary bladder and follicular adenoma of the thyroid in male rats, and also caused an increase in the incidence of Harderian gland adenoma in male and female mice. Allyl chloride is mutagenic in *Salmonella*, and its mutagenicity appears to involve the formation of aldehydes. It also induces chromosome aberration in Chinese hamster lung cells, and binds to DNA in vitro.

**Recommendation:** Medium priority

#### ***4.4. Anthracene***

Anthracene is listed as a chemical with high production volume by the Organisation for Economic Co-operation and Development (OECD). It is used primarily in the synthesis of dyes, but also in smoke screens and in research into organic semiconductors. Anthracene was last evaluated by an IARC Working Group in 2010 (Volume 92), when it was classified as *not classifiable as to its carcinogenicity to humans* in (Group 3). New data on carcinogenicity in rodents, due to be published by the Japanese Ministry of Health, Labour, and Welfare, showed that anthracene induced liver adenoma in male and female rats, liver carcinoma and transitional cell papilloma and carcinoma of the urinary bladder in male rats, and renal cell adenoma and carcinoma in female rats. Anthracene also induced liver adenoma and carcinoma in female mice. Anthracene is generally not mutagenic when tested in standard assays, and there were no epidemiological data.



**Recommendation:** Medium priority

#### ***4.5. Aspartame and sucralose***

Aspartame is a non-nutritive sweetener that has not previously been evaluated by IARC. Many studies of cancer epidemiology and use of dietary non-nutritive sweeteners have been performed and reported essentially negative results. Aspartame has been studied in numerous cancer bioassays in rats and mice, including a recent series from one laboratory that resulted in reports of controversial positive findings for a number of tumour sites. The Advisory Group was aware of plans by an NTP-sponsored Pathology Working Group to further evaluate the more recently reported pathology findings. The Advisory Group accorded aspartame a high priority for review by the *IARC Monographs* because of its widespread use, lingering concern over its carcinogenic potential, and recent reports of positive findings in studies of carcinogenicity in animals.

Sucralose is also a widely used non-nutritive sweetener. There are no studies of cancer in humans on this specific substance, but as noted above, there have been studies of cancer in humans using non-nutritive sweeteners. Sucralose has been evaluated in rats and mice given dietary concentrations of up to 3% in 2-year studies sponsored by the manufacturer. The studies in rats began in utero. No increases in the incidence of tumours in rats or mice were reported.

**Recommendation:** High priority

#### ***4.6. Automotive plastic manufacturing***

Some epidemiological studies have identified increased risks of cancer of the breast in workers in the automotive industry, or in women working in the production of plastics parts for the automotive industry. No specific agents were associated with this risk, although the hypothesis focused on exposure to agents causing endocrine disruption. Some studies evaluated specific exposures through expert assessment, and identified an association with metal-working fluids. Overall, the evidence for an increased risk of cancer of the breast in the plastics departments of the automotive industry was not consistent. This would make an evaluation very complex due to difficulty in specifying the exposure being evaluated.

**Recommendation:** Low priority

#### ***4.7. Biological agents***

##### **4.7.1. Human cytomegalovirus**

Human cytomegalovirus (HCMV) is a herpesvirus that is ubiquitous in most adults worldwide. HCMV has not been previously evaluated by IARC. Infection is generally asymptomatic, but the virus can be reactivated and is believed to be the etiological agent for brain tumours in fetuses and immunocompromised patients. The presence of the HCMV genome and RNA has been reported in various malignant tumours and, more strikingly, in 90–100% of patients with

glioblastoma in several case series. However, cohort and case-control studies are currently lacking. Nonetheless, several recent studies in humans point to a potential role for HCMV in glioblastoma and show: (a) increased 2-year survival in patients with low-grade HCMV infection; (b) positive results in an intervention study of antiviral treatment in patients with glioblastoma; (c) increasing levels of anti-HCMV IgG associated with decreasing risk of glioma; and (d) HCMV-negative non-cancer cells in close proximity to tumours. In addition, strong evidence for the carcinogenic potential of HCMV comes from animal models and mechanistic data.

**Recommendation:** High priority

#### 4.7.2. *Salmonella typhi*

*S. typhi* is transmitted by the faecal-oral route through contaminated food and water, and can cause chronic and persistent infection in humans. Cohort and case-control studies have shown a positive association between chronic infection with *Salmonella typhi* and cancer of the gallbladder, especially in areas of high endemicity of typhoid, such as India. A recent meta-analysis reviewed the data and calculated an overall statistically significant odds ratio for chronic-carrier status. Only a few papers have been published on possible mechanisms of carcinogenesis by *S. typhi*.

**Recommendation:** Medium priority [While making this recommendation, the Advisory Group suggested that other potential etiological agents (e.g. *Helicobacter spp.* other than *H. pylori*) for cancer of the gallbladder should be included in this *Monograph*.]

#### 4.7.3. Dysbiotic gut microbiota

It is increasingly acknowledged that gut microbiota influence the health of the human host and some data suggest that dysbiotic microbiota may be associated with an increased risk of cancers such as colorectal carcinoma.

The Advisory Group recommended that IMO carefully follow the development of this rapidly evolving topic.

The human gastrointestinal microbiota is a complex and abundant microbial community (~10<sup>14</sup> bacteria and many other microorganisms) that forms a symbiotic relationship with the human host. This close partnership plays a key role in health by performing essential tasks (e.g. nutrition/energy, immune-system balance, pathogen exclusion).

Dysregulation of the endogenous gut microbiota may be caused by various events (e.g. infection, diet, stress, inflammation, and medication such as antibiotics or nonsteroidal anti-inflammatory drugs) that may change the microbial composition, leading to the formation of a dysbiotic microbiota. There is a growing body of evidence suggesting that the dysregulation of gut microbiota contributes to gastrointestinal diseases (e.g. inflammatory bowel diseases,

colitis) and extra-intestinal disorders (e.g. obesity and metabolic syndrome), and may be associated with colon tumorigenesis.

Animal models have addressed the role of microbiota composition in the development of colorectal carcinoma, demonstrating that the microbiota composition can have an impact on gut immunity and inflammation. In humans, statistically and biologically significant evidence of such effects from prospective studies is still needed.

A few studies have identified specific bacteria, notably *Fusobacterium*, *pks+* *Escherichia coli*, that may be involved in the etiology of colorectal carcinoma in the context of dysbiotic gut microbiota.

*Fusobacterium*: Recent studies have reported overabundance of fusobacterium in association with colorectal adenoma and cancer. Through a series of experimental studies in vitro and in vivo, mechanisms were investigated by which *F. nucleatum* in the gut could be associated with colorectal carcinoma. It was suggested that *Fusobacterium spp.*, via binding of 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. In humans, a recent case-control study from the USA showed that cases showed a significantly decreased overall microbial diversity and increased carriage of *Fusobacterium* and *Porphyromonas*.

*Pks+ E. coli*: Mucosa-associated *pks+* *E. coli* are virulent strains of *E. coli* that have acquired pathogenicity polyketide synthase (*pks*) islands that encode the genotoxin colibactin. *Pks+ E. coli* are found at a significantly high percentage in the gut microbiota of patients with inflammatory bowel disease or colorectal cancer. In an AOM/Il10<sup>-/-</sup> (azoxymethane/interleukin) 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. From these studies, data suggested that in mice, colitis can promote tumorigenesis by altering microbial composition and inducing the expansion of microorganisms with genotoxic capabilities.

**Recommendation:** Low priority

#### **4.8. Bisphenol A**

Bisphenol A is a synthetic compound widely used in epoxy resins and plastics. The *IARC Monographs* have not previously reviewed bisphenol A. WHO reviewed the carcinogenicity of bisphenol A in 2010 and concluded “...there is currently insufficient evidence on which to judge the carcinogenic potential [of bisphenol A].” Since this review, there have been numerous studies addressing the carcinogenicity of bisphenol A and an ongoing 2-year bioassay by the NTP and Food and Drug Administration (FDA) that includes perinatal exposure (a major data gap identified in the WHO review). The Advisory Group concluded that completion of the NTP/FDA study would provide sufficient data for a review of bisphenol A.

**Recommendation:** High priority

#### ***4.9. Breast cancer, suspected causal agents***

The Advisory Group discussed the possibility of developing a *Monograph* on agents suspected of causing breast cancer. IARC Working Groups have reviewed a number of agents that show limited or sufficient evidence for cancer of the breast in humans; however, there are numerous chemicals that show mammary gland carcinogenesis in experimental animals and that have never been reviewed by IARC or that were reviewed many years ago. Relying on reviews of the literature by others, the Advisory Group was able to identify 223 agents that cause mammary carcinogenesis in experimental animals. Of these, 137 have been reviewed by IARC: 37 were classified in Group 1 (for 21 of these there was limited or sufficient evidence for breast cancer in humans); 20 were classified in Group 2A (with 1 showing limited evidence for breast cancer in humans); and 66 were in Group 2B (with 1 showing limited evidence for breast cancer in humans). Many of the 16 agents in Group 1 without at least limited evidence for breast cancer are industrial compounds for which there are unlikely to be studies in women. Five of the compounds in Group 2A and 29 of the compounds in Group 2B have not been reviewed by IARC since 1987 (Supplement 7). For some of these agents, exposure is widespread. The development of a *Monograph* specifically aimed at only cancer of the breast without review of all of the cancer information from these chemicals would change the focus of the *IARC Monographs* and was not recommended by the Advisory Group. However, a *Monograph* could be developed that would focus on the common underlying mechanisms for many of these compounds, especially those listed in Groups 2A and 2B, and potentially identify additional carcinogens that target the human breast.

**Recommendation:** Medium priority

#### ***4.10. Breast implants***

Breast implants were evaluated by IARC in 1999 (Volume 74) and placed in Group 3 (*not classifiable as to its carcinogenicity to humans*). The Working Group at that time stated that there was evidence suggesting a lack of carcinogenicity in the female breast. Since this evaluation, new information has caused the focus to switch from cancer of the breast to anaplastic large cell lymphoma (ALCL). The FDA is aware of approximately 60 cases of ALCL worldwide in women with breast implants. Implant-associated ALCL appears to be a distinct clinical-pathological entity, which is a less aggressive form of ALCL with better survival. An evaluation of breast implants and cancer may be challenging because of the rarity of ALCL; even large cohort studies would have limited statistical power to detect an effect. With respect to other cancers, findings appear to be conflicting and there is potential confounding (positive or negative) from differences in lifestyle factors between women receiving breast implants and the comparison population. One large cohort study reported an increased risk of cancer of the breast among women receiving a polyurethane-coated subglandular implant in the first 5 years after surgery; however, risks decreased with increasing time since surgery. Polyurethane may degrade into the carcinogen, 2,4-

diaminotoluene. Silicone gel from commercially available breast implants increased the incidence of plasmacytoma in genetically susceptible mice.

**Recommendation:** Medium priority

#### **4.11. 1-Bromopropane**

1-Bromopropane is used in spray adhesives, resulting in high occupational exposures. 1-Bromopropane has not been previously evaluated by IARC. There are no studies of cancer in humans. 1-Bromopropane was recently evaluated by the NTP in a 2-year inhalation study in rats and mice. 1-Bromopropane gave positive results in rats, causing several types of benign and or malignant skin tumour, and rare large intestine tumours. In mice, 1-bromopropane caused lung tumours in females. The concentrations used in these studies were comparable to those measured during occupational exposures.

**Recommendation:** High priority

#### **4.12. Butyl benzyl phthalate**

Butyl benzyl phthalate is commonly used as a plasticizer for vinyl foams that are often used as floor tiles. There is widespread exposure to butyl benzyl phthalate according to biomonitoring data from numerous countries. Butyl benzyl phthalate was evaluated by IARC in 1999 (Volume 73) and is listed in Group 3, with insufficient evidence in for cancer in humans and limited evidence in animals. The Advisory Group was able to identify 28 additional relevant studies in experimental animals and laboratories that were published after the IARC evaluation. There were no new bioassays and only one additional case-control study that gave negative results. The Advisory Group suggested that butyl benzyl phthalate could be grouped with other endocrine-active compounds like bisphenol A and re-evaluated.

**Recommendation:** Low priority

#### **4.13. Calcium-channel blockers**

Calcium-channel blockers disrupt the movement of calcium ions through calcium channels and are used as antihypertensive drugs. IARC has not previously evaluated calcium-channel blockers. The use of calcium-channel blockers has been associated in two recent studies with an increased risk of cancer of the breast. In addition, the use of one specific calcium-channel blocker (nifedipine) has been associated with an increased risk of cancer of the lip. There is little or no evidence to suggest that calcium-channel blockers are carcinogenic in experimental animals, or that they are positive in standard assays for genotoxicity. Given the public-health importance of breast cancer, and the widespread use of these agents, the Advisory Group suggested that IARC should monitor the literature and elevate the recommended priority should additional studies report positive associations.

**Recommendation:** Medium priority

#### 4.14. Cannabis sativa

Cannabis, produced from the *Cannabis sativa* plant, is used in three forms: (a) herbal cannabis, the dried leaves and flowering tops, also known as ‘cannabis’, ‘ganja’, or ‘weed’, among other names; (b) cannabis resin, the pressed secretions of the plant, known as ‘hashish’ or ‘charash’; and (c) cannabis oil, a mixture resulting from distillation or extraction of active ingredients of the plant.

Four case-control studies and two cohort studies have evaluated the use of *C. sativa* and risk of cancer of the lung, upper aerodigestive tract, prostate, and glioma, with conflicting results. Whilst cannabis smoke is reported to be mutagenic in vitro in the Ames test and in skin tests in mice, the evidence pointed to a cytotoxic rather than mutagenic effect. Furthermore, there was no evidence that either tetrahydrocannabinol (the main alkaloid responsible for the psychoactivity of *C. sativa*) or other cannabinoids are mutagenic. Tetrahydrocannabinol is not carcinogenic in the mouse skin assay.

**Recommendation:** Low priority

#### 4.1. Carbon nanotubes, multiwalled

Multi-walled carbon nanotubes are hollow, rolled fullerene sheets, with diameters of 2–100 nm. They have many applications in fields as diverse as electronics, transportation, sports goods, energy, and medicine. Use and manufacture of multi-walled carbon nanotubes are increasing, and so are the number of workers with potential exposures, and environmental pollution. IARC has not previously evaluated multi-walled carbon nanotubes.

No epidemiological studies of cancer in humans have yet been completed.

Like asbestos, several studies in mice and rats given multi-walled carbon nanotubes by intraperitoneal injection have shown that this agent induces peritoneal mesothelioma. Long-term studies in rodents treated by inhalation were due to be completed in 2014 in Japan, and others were planned or have started in the European Union and the USA. The results of these studies were expected to become available within the next 5 years.

Multi-walled carbon nanotubes 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 fibres, the biological effects of nanotubes are dependent on their shape, size and durability.

The Advisory Group recommended that IARC monitor the scientific literature on other carbon-based nanomaterials (i.e. single-walled carbon nanotubes, other fullerenes, carbon fibres).

**Recommendation:** High priority

## **4.2. Beta-Carotene**

The finding that low serum concentrations of retinol were associated with an increased risk of cancer of the lung generated the hypothesis that dietary intervention with beta-carotene might prove protective. Two trials with beta-carotene were launched, with cancer of the lung as the end-point: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study and the *Carotene and Retinol Efficacy Trial* (CARET). The ATBC trial in Finland reported an 18% excess of cancer of the lung among those receiving beta-carotene. The trials found that beta-carotene (+/- retinol) was harmful (increased overall mortality and mortality from lung cancer) in high-risk groups (those exposed to tobacco smoke or asbestos). An excess mortality from all causes, and from cardiovascular disease, was observed. These findings, however, were not seen in other trials with beta-carotene that were not restricted to high-risk individuals.

In the ATBC study, the post-intervention effects (incidence of cancer and for all-cause mortality through national registers) of alpha-tocopherol and beta-carotene were studied after 18 years. Neither supplement had statistically significant effects on post-trial incidence of cancer. Alpha-tocopherol was associated with a decrease in post-trial mortality from cancer of the prostate, while beta-carotene was associated with an increase.

In summary, dietary supplementation with high doses of beta-carotene appeared to increase risk in groups with a high risk of lung cancer. In long-term-follow-up, supplementation with beta-carotene appeared to have no late effects on incidence of cancer.

**Recommendation:** High priority

## **4.3. 3-Chloro-2-methylpropene**

This compound is used as a fumigant with related high potential exposures. The compound was reviewed by IARC (Volume 63) and assigned to Group 3, based on tumours in the forestomach (in mice), kidney, and urinary tract. Since Volume 63, there have been several new studies.

Oral exposure to 3-chloro-2-methylpropene caused tumours in two rodent species and at several different tissue sites. Administration of 3-chloro-2-methylpropene by stomach tube caused benign or malignant tumours of the forestomach (squamous-cell papilloma or carcinoma) in male and female mice and rats; in mice, some of the malignant tumours metastasized to other organs. Tumours of the kidney and urinary bladder in male rats may also be related to exposure to 3-chloro-2-methylpropene. In another study, exposure to 3-chloro-2-methylpropene by inhalation caused benign tumours of the forestomach (squamous cell papilloma) in male and female mice and benign tumours of the Harderian gland (adenoma) in female mice.

**Recommendation:** High priority

#### **4.4. Coal dust**

Exposure to coal dust occurs in coal mining and via multiple other major sources, including outdoor and indoor air pollution, and industrial processes. The previous evaluation by IARC in 1997 (Volume 68) concluded that there was inadequate evidence for carcinogenicity in humans and animals. There were no supporting data on exposure of animals, and the overall evaluation was Group 3. The main cancers discussed were those of the lung and stomach.

The evidence for cancer of the lung has become stronger since the last evaluation. More recent epidemiological studies indicated that the decreases in risk of cancer of the lung seen in the earlier follow-up of cohorts of British and American coal miners were no longer evident in extended follow-ups. Excess risk of cancer of the lung independent of exposure to respirable silica was also observed in a new analysis of the USA cohort.

Recently genotoxicity, in particular primary DNA damage using the comet assay and micronucleus formation, was found to be significantly greater in workers at one of the world's largest open-cast coal mines. There were also other biomarker studies in humans reported in workers exposed to coal dust, some of which are relevant for cancer mechanism. In addition, genotoxicity was shown in studies on wild animals living near the coal-mining areas. No data were available from carcinogenicity bioassays in experimental animals.

**Recommendation:** Medium priority

#### **4.5. Coffee**

In 1991 (Volume 51), the IARC Working Group concluded that coffee was *possibly carcinogenic to humans* (Group 2B) based on a positive association with cancer of the urinary bladder. Since the publication of the IARC evaluation, numerous case-control and cohort studies have been conducted and subsequent systematic reviews and meta-analyses have been published on the subject. The results for the association of coffee drinking with bladder cancer have been inconsistent. Furthermore, whilst reports that maternal consumption of coffee during pregnancy was associated with an increased risk of childhood acute leukaemia, studies have reported an inverse association with cancers of the breast (in postmenopausal women and *BRCA1* mutation carriers), colorectum, oropharynx, and liver, and no association with cancers of the pancreas, larynx, oesophagus, stomach, or ovary. Given the large number of published studies, the Advisory Group supported a review of the evidence.

**Recommendation:** High priority

#### **4.6. Contaminated land and groundwater**

Contamination of land and groundwater is ubiquitous. Humans can be exposed via vapour intrusion into homes (for volatiles), and by migration to the water table, resulting in groundwater contamination and exposure via drinking-water. There were numerous analytical chemistry studies of the contaminants in



groundwater. Dust from contaminated sites can also result in considerable human exposure. Exposure has been characterized by evaluating polycyclic aromatic hydrocarbons in house dust, elemental tracers in soil, and modelling of soil particulates and house dust. A limited number of epidemiology studies have shown some elevated frequencies of cancers of the gastrointestinal tract, bladder, and breast. No studies of cancer in experimental animals have been performed with contaminated soil or groundwater per se; however, there were numerous studies of cancer in animals exposed to the contaminants of soil and groundwater (tested as single agents). There were many studies on the mutagenicity of house dust and soils and, of course, on the individual contaminants of these media. Thus there is limited epidemiology, a lack of studies of cancer in animals and on the contamination site-specific nature of the exposures.

**Recommendation:** Low priority

#### ***4.7. Computed tomography scans***

There is unequivocal evidence of human exposure to X-irradiation through computed tomography (CT) scans, which represent a markedly increasing proportion of the total exposure to ionizing radiation experienced by the average person in the USA. Doses are typically up to approximately 60 mSv per scan for children, and up to approximately 150 mSv for adults. Multiple modelling studies have identified and precisely quantified increases in the number of cases of cancer in various clinical contexts. At least three recent (2012–2014) epidemiological studies of patients exposed as children indicated a consistent increase in the risk of cancer of the brain and of leukaemia, with relative risks ranging from 1.2 to > 3.0. A major study was underway in Europe (Epidemiological study to quantify risks for paediatric computerized tomography and to optimize doses, EPI-CT). There have been public health calls for reduced clinical use of CT scans. The high likelihood, if not certainty, of cancer causation inherently warrants high priority for this evaluation that may contribute to public health. However, acknowledging that CT scans represented exposure to an agent already categorized as Group 1 (*carcinogenic to humans*), the Advisory Group recognized that a full *Monograph* assessment constrained to this mode of exposure to X-irradiation was not justified.

**Recommendation:** No evaluation

#### ***4.8. 2-Amino-4-chlorophenol, 2-chloronitrobenzene; 4-chloronitrobenzene; 1,4-dichloro-2-nitrobenzene; 2,4-dichloro-1-nitrobenzene***

This is a group of related chemicals (intermediates in chemical synthesis in industry) for which there is potential for industrial exposure. The structure and toxicology of these compounds are similar; 2- and 4-chloronitrobenzene were previously evaluated by IARC (Volume 65) and assigned to Group 3 (*not classifiable as to its carcinogenicity to humans*). For all these chemicals, new bioassays in rats and mice treated orally have been published by the Japanese

Bioassay Research Center and pointed to similar tumour patterns and sites for these compounds, mainly in the forestomach, kidney, and urinary tract.

**Recommendation:** High priority

#### ***4.9. Dietary iron and iron used as supplements or for medical purposes***

Iron is essential for life and is maintained in the body within strict physiological limits. Iron deficiency may lead to anaemia, while iron overload may lead to haemochromatosis; too much iron is toxic. Between 50% and 75% of pregnant and lactating women in the National Health and Nutrition Examination Survey III (NHANES III) had daily iron intake exceeding the recommended tolerable limit. Recent meta-analyses found that the risk of cancer of the colon increased approximately 12% for each 1 mg increase in intake of haeme iron. Summary risk estimates per 1 mg increase in intake of haeme iron were also elevated (although not statistically significantly) for cancers of the lung, breast and rectum. The evidence from studies of cancer in humans and total iron intake appeared to be weaker than that for haeme iron. Studies of individuals with hereditary haemochromatosis may also be a supporting body of literature.

Iron dextran, a compound used to treat anaemia, is currently categorized by IARC as *possibly carcinogenic to humans* (Group 2B). Since the last review, several other iron compounds (ferric nitrilotriacetate, ferric ethylenediamine-*N,N'*-diacetate) used for medical reasons have been shown to increase the incidences of lung and renal tumours in experimental animals.

**Recommendation:** High priority

#### ***4.10. N,N-Dimethylacetamide***

*N,N*-dimethylacetamide is a solvent used in manufacture of synthetic fibres, some resins and plastics, and film and coating formulations. *N,N*-dimethylacetamide has not been previously evaluated by IARC. There were no studies of cancer in humans. *N,N*-dimethylacetamide is readily absorbed by inhalation or after dermal exposure. In humans, *N,N*-dimethylacetamide vapour is also well-absorbed by the skin. Biotransformation of *N,N*-dimethylacetamide in humans gives rise to acetamide and *N*-methylacetamide, detected in the urine of workers exposed to this solvent.

**Recommendation:** Medium priority

#### ***4.11. Dimethylformamide***

Dimethylformamide is a chemical produced in high volumes that is commonly used as a solvent in many industrial processes. Dimethylformamide has been previously evaluated by IARC (Volume 71) and classified in Group 3 (*not classifiable as to its carcinogenicity to humans*). Studies of exposure by inhalation and in drinking-water conducted since Volume 71 have shown a high incidence of cancer of the liver. In humans, an epidemiological study showed an association with testicular tumours.

**Recommendation:** High priority

#### **4.12. *N,N-Dimethyl-p-toluidine***

*N,N*-Dimethyl-*p*-toluidine is used as a hardening agent in dental and bone adhesives, resulting in prolonged exposures for patients receiving dental or surgical implants. *N,N*-Dimethyl-*p*-toluidine has not been previously evaluated by IARC. There were no studies of cancer in humans. In 2-year gavage studies conducted by the NTP, *N,N*-dimethyl-*p*-toluidine was found to be a multisite, multispecies carcinogen, causing liver tumours in rats and mice, and nasal cavity tumours in male and female rats. Female mice exposed to *N,N*-dimethyl-*p*-toluidine also had increased incidences of tumours of the lung and forestomach.

**Recommendation:** High priority

#### **4.13. *Disinfected water used for drinking, showering, bathing, or swimming***

Disinfected water (usually chlorinated) was evaluated by IARC in 1991 (Volume 52) when the Working Group concluded that there was inadequate evidence for carcinogenicity in humans or in animals. At the time of the evaluation, most available studies were ecological or death certificate-based. Since that time, many epidemiological studies with improved exposure assessment at the individual level have been published, and have shown a consistently increased risk of cancer of the bladder. The epidemiology of chlorinated drinking-water was reviewed, but not evaluated, by IARC in 2002 in Volume 84, which examined specific water disinfection by-products. There was sufficient evidence that several of these contaminants are animal carcinogens, and there was extensive new mechanistic evidence on specific disinfection by-products, including studies on molecular epidemiology evaluating specific mechanisms. A large body of literature on the mutagenicity of organic extracts of drinking-water shows consistently positive results, as do studies of about 80 disinfection by-products tested individually. Most epidemiological studies have evaluated exposure to chlorinated water as a mixture, using concentrations of trihalomethanes in the water and/or urine as a measure of exposure. Water disinfection (mostly chlorination) is a major public health intervention for prevention of microbial disease, and the Advisory Group advised that IARC should take extreme care in the communication of an evaluation of disinfected (largely chlorinated) water or of other water-disinfection practices, and should also incorporate where possible in this evaluation a quantitative assessment of risk and estimates of global burden. Key to the priority set by the Advisory Group is the ubiquitous exposure to this generally mutagenic and potentially carcinogenic agent by all routes.

**Recommendation:** High priority

#### **4.14. *Electronic cigarettes and nicotine***

IARC has not previously evaluated electronic cigarettes (e-cigarettes) or nicotine. A major concern regarding nicotine is the use of e-cigarettes by individuals who have not been exposed to carcinogens typically associated with tobacco. There

appeared to be no epidemiological data associated with the use of nicotine-containing products in tobacco-naïve individuals. There have been a number of animal bioassays with nicotine. Most of these gave negative results, or the observed increases in tumour incidence did not reach statistical significance. Nicotine has historically been inactive in standard assays for genotoxicity; nonetheless, more recent experiments have indicated the potential for nicotine to cause DNA damage. In addition, exposure to nicotine has been shown to inhibit apoptosis, and stimulate cell proliferation and angiogenesis, responses that appear to be mediated by nicotinic acetylcholine receptors. An IARC evaluation of nicotine would have a significant impact on public health, as the use of e-cigarettes is relatively recent and is increasing dramatically. Accordingly, the Advisory Group encouraged the Secretariat to proceed with this evaluation when an adequate data set should become available.

**Recommendation:** High priority

#### **4.15. Ethyl acrylate**

Ethyl acrylate is an industrial chemical and synthesis intermediate for many consumer products. It was evaluated by IARC in 1986 and again in 1999 (Volumes 39 and 71) and listed in Group 2B (*possibly carcinogenic to humans*). Ethyl acrylate was also listed as a carcinogen in experimental animals for many years by the NTP Report on Carcinogens, based on the occurrence of forestomach tumours in rats and mice in conjunction with significant toxicity in studies where the chemical was administered by gavage. Cancer studies using other routes of exposure gave negative results. There have been many mechanistic studies carried out over the years suggesting that the forestomach-tumour response may be related to irritation and the proliferative cellular response to deposition of the material in the stomach, calling into question the relevance of this finding to human health hazards.

**Recommendation:** High priority

#### **4.16. Food-canning industry**

IARC has not previously reviewed the food-canning industry. There were three case-control studies showing an increased risk of cancer of the breast and/or specific subtypes of breast cancer. Literature searches for food canning, food industry, with cancer yielded no additional studies. The increased risks of breast cancer could be due to exposure to bisphenol A, but there are many other exposures in this industry that could be of concern. These occupational data could be included in a review of bisphenol A and other endocrine-active compounds, but the Advisory Group considered it unlikely that these cancers could be attributed directly to bisphenol A exposure given these studies.

**Recommendation:** Low priority

#### **4.17. Genetically modified organisms**

There were no available relevant data on genetically modified organisms used for foods.

**Recommendation:** Low priority

#### **4.18. Hot mate drinking**

Hot mate drinking was previously classified by IARC as Group 2A (Volume 51, 1991).

Epidemiological data on drinking of hot mate and upper aerodigestive tumours (UADTs) are limited, with case-control studies showing some association, particularly with oesophageal squamous cell carcinoma. However, almost all the studies addressing consumption of hot mate and the risk of cancer did not control for the temperature at which the beverage was consumed. Nevertheless, a recent study that controlled for temperature (indirectly by reference to the time at which the tea was consumed after being poured) clearly showed an association between consumption of very hot tea and risk of oesophageal squamous cell carcinoma.

Recurrent thermal lesions have been shown to occur before the development of the so-called 'thermal' cancers (skin tumours, basal cell carcinoma going through actinic keratosis), such as Kangri cancer and peat fire cancer. These tumours develop at the same skin sites as recurrent thermal lesions caused by direct exposure to heat (in a form of live charcoal used to heat the body).

A recent study in animals (in press) showed that water at different temperatures (from 25 °C to 80 °C) applied three times per week to the oesophagus of Balb/c mice did not induced oesophageal tumours for up to 6 months, but at 70 °C (but not colder) increased the number and shortened the time-to-tumour of *N*-nitrosodiethylamine-induced oesophageal tumours in mice, suggesting that the hot water was acting as a typical tumour promoter.

Mechanistic data were limited, and studies in humans provided suggestions that the carcinogenic action of hot mate happens through chronic inflammation. Additionally, the analysis of *TP53* mutations in oesophageal squamous cell carcinoma of patients who inhabit areas where the consumption of hot mate is frequent presented a high proportion of G:C>A:T at CpG sites. These mutations have been shown to occur at high frequency in tumours that developed after a history of chronic inflammation, such as oesophageal adenocarcinoma that normally develops after a history of chronic reflux.

**Recommendation:** High priority

#### **4.19. Hydrazine**

Exposure to hydrazine occurs primarily in the workplace via its use as a fuel for rockets and spaceships. Hydrazine was classified by IARC as *possibly carcinogenic to humans* (Group 2B) in 1999 (Volume 71) on the basis of sufficient

evidence of carcinogenicity from studies in experimental animals. Since that time, one epidemiological study of rocket-fuel workers found statistically significant exposure–response relationships between cumulative exposure to hydrazine and cancers of the lung and colon. Another smaller epidemiological study found a non-statistically significant increased risk of both of these cancers based on a small number of exposed cases. Hydrazine induces mammary and lung tumours in mice; lung, liver, nasal and colon (few) tumours in rats; liver tumours and thyroid adenoma in hamsters; and also induces gene mutation in bacteria, yeast, and *Drosophila* in vitro, and in mice, rats and hamsters in vivo.

**Recommendation:** Medium priority

#### **4.20. Indium-tin oxide**

Indium-tin oxide is increasingly used in the production of liquid crystal displays, touch-sensitive screens, solar cells and architectural glass. Indium-tin oxide has not been previously evaluated by IARC.

Indium-tin oxide has been reported to cause various kinds of pulmonary lesions in rats and mice. Inhalation of indium-tin oxide has been clearly shown to be carcinogenic in male and female rats. In mice, there is no clear evidence.

Several case reports of pulmonary alveolar proteinosis, fibrosis, and emphysema have been reported from Japan, the USA, and China over the last 10 years. Indium-tin oxide produces inflammatory changes in the lung, associated with oxidative stress, resulting in progression to pre-neoplastic lesions and lung tumours. An increased frequency of micronucleated cells in type II pneumocytes of rats given indium-tin oxide particles by pharyngeal aspiration has been reported.

**Recommendation:** High priority

#### **4.21. Iron oxides**

Iron oxides include ferric oxide ( $\text{Fe}_2\text{O}_3$ ) and ferrous oxide (FeO). Occupational exposure occurs predominantly in the mining industry (primarily to haematite) and in iron and steel founding and manufacturing (e.g. shipbuilding and automobile manufacture). Occupational scenarios that involve exposure to iron (iron and steel founding, Volume 100F; and haematite underground mining, Volume 100D) have previously been classified by IARC as *carcinogenic to humans* (Group 1), and the available epidemiological studies in humans did not appear to be adequate for evaluating specific effects attributable to iron oxides in these studies.

**Recommendation:** Low priority

#### **4.22. Isobutyl nitrite**

Isobutyl nitrite is a pungent colourless liquid that has vasodilatory properties. It is inhaled as a recreational drug ('poppers') to induce a brief euphoria and sexual arousal. Isobutyl nitrite has not been evaluated previously by IARC. Initial

concern regarding isobutyl nitrite and cancer arose due to the association between the incidence of Kaposi sarcoma in HIV-positive homosexual men and the recreational use of isobutyl nitrite. Kaposi sarcoma was later established to be caused by human herpesvirus 8 (HHV-8); nonetheless, it is possible that the use of isobutyl nitrite could further immunocompromise individuals with HIV and thus contribute to susceptibility to Kaposi sarcoma. Exposure to isobutyl nitrite has been associated with increased incidence of cancer in rats and mice. Isobutyl nitrite also gave clearly positive results in standard assays for genotoxicity.

**Recommendation:** High priority

#### **4.23. Job stress**

Work and workplace-related issues are common sources of stress and there is substantial public concern about stress as a causal factor in cancer. Psychosocial stress at work has been shown to be associated with individual unhealthy lifestyle factors such as smoking, heavy consumption of alcohol, physical inactivity, and obesity. A meta-analysis of pooled data for prospective individual participants in 12 European cohort studies found that a harmonized measure of job stress was not associated with an overall increase in risk of cancer, or cancers of the colon, lung, breast or prostate. The recommendation for job stress is based on the availability of human data and the opportunity to address public concern.

**Recommendation:** Medium priority

#### **4.24. Lead**

Lead has been classified by IARC as *possibly carcinogenic to humans* (Group 2B) (Supplement 7, 1987), inorganic lead compounds are *probably carcinogenic to humans* (Group 2A) (Volume 87, 2006) and organic lead compounds are *not classifiable as to their carcinogenicity to humans* (Group 3) (Volume 87, 2006).

Exposure to lead continues to be an important health problem worldwide, including, in addition to other sources, in a substantial number of workplaces, occupations, and jobs where exposure to lead and lead compounds occur.

Epidemiological evidence indicated cancers of the stomach, lung, kidney, and brain in workers exposed to inorganic lead, but not in all studies. A study pooling data from five cohorts with biomarker data available on lead exposure from different countries was being coordinated by IARC.

There were extensive data showing genotoxicity of lead in vitro and in vivo. Numerous studies in humans indicated genotoxicity in occupationally exposed populations, with some variability (Volume 87). Generation of reactive oxygen species by lead has been shown. Modification of global DNA methylation (Alu and LINE-1 repetitive elements) in blood cells of lead-exposed people has been suggested. Similarly, genetic susceptibility to lead exposure related to *ALAD* gene polymorphism has been indicated by some but not all studies. Studies on other

gene polymorphisms proposed to be involved in lead toxicity pathways have largely given negative results.

**Recommendation:** Medium priority (when the epidemiological results from the pooled cohort study become available).

#### **4.25.      2-Mercaptobenzothiazole**

2-Mercaptobenzothiazole has not been previously evaluated by IARC. NTP bioassay data and the results of occupational cohort studies have become available for evaluation. In one of the strongest epidemiological studies, excess occurrence of cancers of the large intestine and bladder as well as multiple myeloma was observed in male production workers exposed to 2-mercaptobenzothiazole while employed in a chemical factory. While there were concerns about confounding exposures in the cohorts studied, the studies were of good quality and merit evaluation.

**Recommendation:** High priority

#### **4.26.      Metal-working fluids**

Exposure to metal-working fluids is of high public-health concern given their widespread use in the automobile and other industries; however, the evaluation of such fluids poses several challenges. Metal-working fluids are complex mixtures that may vary considerably depending on the type of fluid and the additives used. Contamination and other changes in composition can occur during their application by end users when fluids are heated to high temperatures and recycled. There are four major types of metal-working fluids: straight, soluble, semi-synthetic, and synthetic. There are many publications on epidemiological studies on metal-working fluids, but most of the studies that have attempted to evaluate effects due to specific types of metal-working fluid have been from the same population, a large cohort of automobile workers in the USA. These publications have reported excess risks of several types of cancer; however, it was unclear whether there was consistent evidence for a specific type of cancer. One study derived constituent-based metrics of polycyclic aromatic hydrocarbons, water-based metal-working fluids, biocides, and nitrosamines and examined their relationship to cancer incidence in the cohort of automobile workers in the USA. This study identified specific cancers that may be associated with exposure to the different types of metal-working fluid. The NTP has conducted inhalation bioassays on two types of metal-working fluid. Inhalation exposure to Cimstar, a semi-synthetic metal-working fluid, increased the incidences of tumours of the lung and thyroid in female mice, and may have increased the incidence of cancers of the prostate and brain in male rats, and the skin in female rats. The peer review of the technical report was scheduled for May 2014. The technical report for the second metal-working fluid was expected to be completed in 2015.

**Recommendation:** Medium priority



#### **4.27. Methanol**

Methanol is a chemical with a high volume of production and many commercial uses. It is also found in fruit juices and other foods, and in exhaled breath and body fluids. There were no available studies of cancer in humans. Methanol has not been previously evaluated by IARC.

Methanol has been evaluated in three studies of carcinogenicity in animals. In a lifetime study, increases in the incidence of carcinoma of the ear duct, osteosarcoma of the head, and haemolymphoreticular tumours were reported in male and female rats given drinking-water containing methanol. An NTP-sponsored Pathology Working Group did not confirm the reported increases in incidence of haematopoietic tumours, and reported far fewer tumours of the ear, ear canal, cranial bone, and Zymbals gland. A dissertation reported findings from long-term bioassays in male and female Eppley Swiss Webster mice given methanol by dermal application or in drinking-water. Increases in the incidence of malignant lymphoma were reported in male and female mice in the drinking-water study that were reported to be within the normal range of occurrence. In a third study, male and female mice and rats were given drinking-water containing methanol. No carcinogenic effects were seen in mice. In rats, the incidence of pulmonary adenoma/adenocarcinoma combined was increased in males, and the incidence of pheochromocytoma was increased in females. These data were summarized by the EPA from a translation of a report of a study performed in Japan.

**Recommendation:** Medium priority

#### **4.28. Ethyl tertiary butyl ether, methyl tertiary butyl ether, tert-butyl alcohol**

Methyl tertiary butyl ether (MTBE), Ethyl tertiary butyl ether (ETBE), and *tert*-butyl alcohol (TBA) are chemically related and were nominated as a group. MTBE is metabolized to TBA and formaldehyde (which is classified by IARC as Group 1) in humans, and ETBE is metabolized to TBA and acetaldehyde (Group 1, associated with consumption of alcoholic beverages). The structural similarity, similarity of metabolites and toxicology, and potential for coexposure suggest that these three agents should be evaluated together.

MTBE and ETBE are used as fuel additives to reduce emissions. ETBE is mandated in Japan and is used throughout Asia. MTBE is now banned in the USA, but marketed aggressively in less industrialized countries. MTBE is found commonly in human blood in NHANES studies across the USA, despite being banned in the early 2000s. MTBE is found as a contaminant in many groundwater surveys and is highly persistent. Standard water filters used in the home are relatively ineffective at removing MTBE. All three agents are volatile, resulting in exposures by inhalation, and they penetrate the skin.

IARC classified MTBE as Group 3 (*not classifiable as to its carcinogenicity to humans*) in 1998 on the basis of limited evidence in animals and inadequate evidence in humans. Numerous studies have documented the mutagenicity of the

parent compounds or their metabolites. The metabolism of these agents is well-known, as is the tissue distribution in animals.

**Recommendation:** High priority

#### **4.29. Metronidazole**

Metronidazole is used primarily as a drug for the treatment of infection by the parasitic protozoans. Metronidazole was last evaluated by IARC in 1987 (Supplement 7), when it was classified in Group 2B (*possibly carcinogenic in humans*), the Working Group concluding that there was inadequate evidence in humans for the carcinogenicity of metronidazole. Two subsequent epidemiological studies did not indicate a significantly increased risk of cancer. 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. Metronidazole is clearly genotoxic. This has been demonstrated in bacteria and to a lesser extent in mammalian systems.

**Recommendation:** Medium priority

#### **4.30. Carbon nanotubes, multiwalled**

Multi-walled carbon nanotubes are hollow, rolled fullerene sheets, with diameters of 2–100 nm. They have many applications in fields as diverse as electronics, transportation, sports goods, energy, and medicine. Use and manufacture of multi-walled carbon nanotubes are increasing, and so are the number of workers with potential exposures, and environmental pollution. IARC has not previously evaluated multi-walled carbon nanotubes.

No epidemiological studies of cancer in humans have yet been completed.

Like asbestos, several studies in mice and rats given multi-walled carbon nanotubes by intraperitoneal injection have shown that this agent induces peritoneal mesothelioma. Long-term studies in rodents treated by inhalation were due to be completed in 2014 in Japan, and others were planned or have started in the European Union and the USA. The results of these studies were expected to become available within the next 5 years.

Multi-walled carbon nanotubes 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 fibres, the biological effects of nanotubes are dependent on their shape, size and durability.

The Advisory Group recommended that IARC monitor the scientific literature on other carbon-based nanomaterials (i.e. single-walled carbon nanotubes, other fullerenes, carbon fibres).

**Recommendation:** High priority

#### **4.31. Beta-Myrcene**

Beta-Myrcene is an agent used for flavouring and fragrance. Beta-Myrcene has not been previously evaluated by IARC. In 2-year studies conducted by the NTP in rats and mice treated with relatively high doses by gavage, beta-myrcene caused increases in the incidence of renal tubular cell tumours in male rats and liver tumours in male mice.

#### **4.32. Nuclear power-plant worker (occupational exposures)**

There is no IARC evaluation for occupational exposure from work in a nuclear power plant, although ionizing radiation has been classified by IARC as Group 1 (*carcinogenic to humans*). A significant association was seen between radiation dose and all-cause mortality in the 15-Country Collaborative Study of cancer risk among radiation workers in the nuclear industry. This was mainly attributable to a dose-related increase in all-cancer mortality. An update of a study of Canadian nuclear-industry workers showed a reduction in mortality from all solid cancers. Since in most studies, cancers are attributed to exposure to radiation, such an evaluation would be redundant.

**Recommendation:** Low priority

#### **4.33. Obesity and overweight**

More than 1.4 billion adults are overweight, and of these some 300 million women and 200 million men are obese. The IARC Handbooks on Cancer Prevention (2002) concluded that there was sufficient evidence in humans for a cancer-preventive effect of avoidance of weight gain for cancers of the colon, breast (postmenopausal), endometrium, kidney and oesophagus (adenocarcinoma). More recent meta-analyses have found significant associations with body fat (as assessed by increases in body-mass index (BMI) and increased risk of cancers of the colon, breast (post-menopausal), endometrium, oesophagus, gallbladder, kidney and ovary. Approximately 20% of all cancers are associated with excess body weight. Individual foods, such as sugar-sweetened beverages, may be considered in the evaluation. Potential mechanisms of carcinogenicity of obesity are related to hormonal and metabolic abnormalities that are associated with obesity. In addition, oxidative stress induced by high calorie intake was found to be higher in obese than non-obese persons. While there was no doubt that obesity is associated with increased risk of cancer, the reason for suggesting a *Monograph* was twofold: (a) there is a need for a comprehensive review; and (ii) it is incongruent for the *Monographs* not to list as a carcinogen one of the main risk factors in humans.

**Recommendation:** High priority

#### **4.34. Opium**

Opium is a highly addictive narcotic drug acquired in a dried latex form from the opium poppy (*Papaver somniferum*) seed pod and contains approximately 12% morphine. The first report of a potential carcinogenic effect of opium came from

investigations into risk factors for oesophageal cancer in the north of the Islamic Republic of Iran. Since then, opium use has been associated with an increased risk of cancers of the oesophagus, stomach, larynx, lung, and urinary bladder in humans and has never been the subject of a *Monographs* evaluation. Although the present evidence suggested that these associations were possibly causal, further epidemiological studies (particularly prospective studies to collect detailed data about lifetime use of opium and controlling for a broad range of potential confounders) are needed.

While there were very limited data on the possible mechanism of action of opium in carcinogenesis, it has been shown that morphine is able to change the pharmacokinetics of nitrosamines in rats, inhibiting hepatic metabolic activation and increasing oesophageal exposure, with a consequent increase in oesophageal DNA alkylation.

**Recommendation:** High priority

#### **4.35. Pesticides**

The Advisory Group recommended that the *Monographs* programme evaluate pesticides, given that this would be a broad group of related exposures, most of which have not been reviewed for several years, during which time considerable new evidence has emerged. Specific agents can be justified as being of high priority for review, and preparation of a *Monograph* will allow review of a wide range of related exposures and scientific issues.

##### **4.35.1. Atrazine (triazine herbicide)**

There is continuing interest in atrazine due to its high level of use and human exposure, including through water contamination. Atrazine was previously reviewed by IARC in 2001 (Volume 73), when it was assigned to Group 3 (*not classifiable as to its carcinogenicity to humans*). Atrazine is a carcinogen in experimental animals, and an endocrine disruptor; however, the mechanism in rodents does not appear to operate in humans. Recent high-throughput data provided new insights into the extent of biological activity. Recent epidemiological data, including the NCI Agricultural Health Study, showed no association with the cancers being studied.

**Recommendation:** Medium priority

##### **4.35.2. Biphenyl**

Biphenyl is used in many products and processes, including as a fungicide and as a component of agricultural chemicals. There were few epidemiological data available, and as there is no well-documented exposure to humans, it was not clear that ongoing epidemiological studies would be able to assess whether or not there are effects in human populations. Recent experimental evidence from animal models has demonstrated that biphenyl is a carcinogen in mice and rats.

**Recommendation:** Low priority

#### 4.35.3. Carbaryl (carbamate insecticide)

Carbaryl (1-naphthyl methylcarbamate) is a broad-spectrum carbamate insecticide that has been used widely worldwide since the 1950s in agriculture, nurseries, and landscaping, and in residential products (e.g. garden care, flea treatments for pets, and mosquito control). Although residential use is declining due to restrictions on these uses, carbaryl is still used for the treatment of lice on humans. Since carbaryl was last reviewed by IARC in 1987 (Supplement 7), when it was assigned to Group 3 (*not classifiable as to its carcinogenicity to humans*), there have been considerable new epidemiological data, including from the NCI Agricultural Health Study, that reported a significant association with melanoma, and case-control studies and a recent meta-analysis that reported an association with non-Hodgkin lymphoma. Cancer bioassay data suggesting tumorigenic activity were also available. Additionally, recent high-throughput data have provided new insights on the extent of biological activity.

**Recommendation:** High priority

#### 4.35.1. Chlorpyrifos (organophosphate insecticide)

Chlorpyrifos is a broad-spectrum organophosphate insecticide/acaricide that is used in many countries. Chlorpyrifos has not been evaluated previously by IARC. Increased risk of leukaemia in professional applicators has been reported in a cohort study, and of non-Hodgkin lymphoma in several case-control studies. Cancer bioassay data were also available. Mechanistic studies indicated immunotoxic, genotoxic and pro-oxidant properties related to the activation of certain signalling pathways involved in the regulation of cell proliferation and survival. Recent high-throughput screens provided new insights into the extent of biological activity.

**Recommendation:** Medium priority

#### 4.35.2. DDT (organochlorine insecticide)

Dichlorodiphenyltrichloroethane (DDT) is a stable and persistent insecticide, used extensively worldwide for agriculture and pest control until the early 1970s. It remains in use under an exemption to the Stockholm Convention for disease-vector control, when used in accordance with WHO recommendations. DDT was classified by IARC in 1991 (Volume 53) as Group 2B (*possibly carcinogenic to humans*). Since that time, there have been a number of epidemiological studies that demonstrated some associations with multiple myeloma and cancers of the liver, prostate and testis, and breast. Several potential mechanisms have been demonstrated, including those involving global DNA methylation and perturbation of estrogen-receptor transcriptional activity.

**Recommendation:** Medium priority

#### 4.35.3. Diazinon (organophosphate insecticide)

Diazinon is an organophosphate insecticide with widespread uses in plant and animal agriculture. Diazinon has not been previously evaluated by IARC.

Epidemiological data have been reported from the NCI Agricultural Health Study, including a significant exposure–response association with risk of leukaemia and lung cancer (an association with follicular lymphoma subtype was under peer review). Diazinon was previously associated with an increased risk of non-Hodgkin lymphoma in pooled case–control studies from the USA, and in a meta-analysis. Cancer bioassay data were also available. Recent high-throughput data provided new insights into the extent of biological activity.

**Recommendation:** High priority

#### **4.35.4. EPTC (thiocarbamate herbicide)**

EPTC (*S*-ethyl-*N,N*-dipropylthiocarbamate) is a thiocarbamate herbicide used widely to control the growth of weeds and in the agricultural production of a wide variety of food crops. EPTC has not been previously evaluated by IARC. Two recent epidemiological papers from the NCI Agricultural Health Study reported an excess risk of cancers of the colorectum and pancreas. Cancer bioassay data were also available. Given that there was some, limited, current evidence, but recognizing that further data could emerge over the next few years, the Advisory Group recommended that EPTC be reviewed by the *IARC Monographs*.

**Recommendation:** Medium priority

#### **4.35.5. Fonofos and terbufos (organophosphate insecticides)**

Fonofos and terbufos are part of a class of organothiophosphate insecticides that continue to be used widely in agriculture. The 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. IARC has not previously reviewed this class of insecticides. Recent epidemiological evidence from the NCI Agricultural Health Study 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. Cancer bioassay data were also available. Potential mechanisms have been reported, including that terbufos may influence risk of prostate cancer by altering cancer-signalling pathways involved in cellular adhesion, proliferation, and differentiation. Recent high-throughput data provided new insights into the extent of biological activity. Given the emergence of new, albeit limited data, and the lack of a previous evaluation by IARC, the Advisory Group recommended that IARC review this class of insecticides.

**Recommendation:** Medium priority

#### **4.35.6. Glyphosate**

Glyphosate is a widely used broad-spectrum herbicide to which exposures occur occupationally and potentially through residues in foods or in the environment. Glyphosate has not been previously reviewed by IARC. There were some emerging epidemiological data regarding glyphosate, such as from the NCI Agricultural Health Study, that reported that exposure was not associated with

incidence of cancer overall, but it was observed that multiple myeloma warranted further investigation. An association with non-Hodgkin lymphoma has also been reported recently in a meta-analysis. Cancer bioassay data were also available. There was experimental evidence of genotoxicity and pro-oxidant activity both in vitro and in vivo.

**Recommendation:** Medium priority

#### **4.35.7. Hexachlorobenzene**

Hexachlorobenzene (or perchlorobenzene) is a fungicide that was previously used as a seed treatment (e.g. for wheat), which has been restricted in its production and use since the early 1970s. Hexachlorobenzene was classified by IARC in 2001 (Volume 79) as *possibly carcinogenic to humans* (Group 2B) on the basis of increased incidence of cancers of the liver, thyroid, and kidney reported in studies in experimental animals exposed orally. There were relatively few data in humans, although recent epidemiological studies have reported continuing dietary exposures and associations with health outcomes other than cancer.

**Recommendation:** Low priority

#### **4.35.8. Lindane (organochlorine insecticide)**

Lindane (gamma-hexachlorocyclohexane) is an organochlorine insecticide used worldwide until the late 1970s. Limited use for control of lice and scabies continues in selected countries under an exemption to the Stockholm Convention. As a persistent organic pollutant, some population exposure from past use is expected. Since lindane was last reviewed by IARC in 1987 (Supplement 7), when it was assigned to Group 2B (*possibly carcinogenic to humans*), new epidemiological data have been reported, including case-control studies, that were recently summarized further in a meta-analysis that reported a significant association with non-Hodgkin lymphoma. Lindane was also significantly associated with risk of non-Hodgkin lymphoma in an early publication from the NCI Agricultural Health Study, and in a more recent report there was an exposure-response pattern with total non-Hodgkin lymphoma, and with the follicular lymphoma subtype. Animal experiments have shown that oral administration of lindane increases the incidence of liver tumours and thyroid cancers in mice and rats, respectively. Mechanisms that have been reported include production of free radicals and oxidative stress (reactive oxygen species), and lindane has been linked with chromosomal aberration in human peripheral lymphocytes in vitro. Recent high-throughput data also provided new insights into the extent of biological activity.

**Recommendation:** High priority

#### **4.35.9. Malathion (organophosphate insecticide)**

Malathion is an organophosphate insecticide used widely in agriculture and insect control. Since malathion was last reviewed by IARC in 1987 (Supplement 7), when it was assigned to Group 3 (*not classifiable as to its carcinogenicity to*

*humans*), new epidemiological data have been reported, including case-control studies, that were recently summarized further in a meta-analysis that reported a significant association with non-Hodgkin lymphoma. Malathion has also been shown to be significantly associated with cancer of the prostate in the NCI Agricultural Health Study, and in a recent Canadian case-control study. Cancer bioassay data were also available, providing evidence of an increased incidence of liver tumours in rats and mice. Like other organophosphate insecticides, purported mechanisms of action include direct genotoxicity (of either malathion or malaaxon). Recent high-throughput data also provided new insights into the extent of biological activity.

**Recommendation:** High priority

#### **4.35.10. Pendimethalin (dinitroaniline herbicide)**

Pendimethalin is a dinitroaniline herbicide with unrestricted use that is applied to crops, lawns and gardens by farmers, professional applicators, and homeowners. Pendimethalin has not been previously reviewed by IARC. Positive findings in long-term bioassays in experimental animals included thyroid tumours in male and female rats. Recent epidemiological data from the NCI Agricultural Health Study has suggested that pendimethalin is associated with an excess risk of cancers of the lung, pancreas, and rectum. Experiments in animal models concluded that pendimethalin caused thyroid follicular cell adenoma in rats. Recent high-throughput data also provided new insights into the extent of biological activity.

**Recommendation:** High priority

#### **4.35.11. Permethrin (pyrethroid insecticide)**

Permethrin is an insecticide that is used worldwide in agricultural, veterinary, and domestic applications. Permethrin has pharmaceutical uses for the treatment of head lice and scabies. Permethrin was previously reviewed by IARC in 1991 (Volume 53), when it was assigned to Group 3 (*not classifiable as to its carcinogenicity to humans*). An increased risk of multiple myeloma has been reported in the NCI Agricultural Health Study. Increased risks of liver tumours in mice and rats have been observed. 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. Recent high-throughput data also provided new insights into the extent of biological activity.

**Recommendation:** High priority

#### **4.35.1. Pentachlorophenol and 2,4,6-trichlorophenol (organochlorine insecticides)**

2,4,6-Trichlorophenol and pentachlorophenol are chemically related organochlorines used as insecticides and fungicides (polychlorophenols). 2,4,6-Trichlorophenol and pentachlorophenol were classified by IARC in 1999



(Volume 71) in Group 2B (*possibly carcinogenic to humans*). Since that time, there have been several reports from epidemiological studies showing possible associations with non-Hodgkin lymphoma, and inconsistent patterns have been seen for other cancers (e.g. soft tissue sarcoma, multiple myeloma, and cancer of the kidney). Cancer bioassay data were also available.

**Recommendation:** Medium priority

#### 4.35.2. Synergists

Synergists are chemicals that are added to pesticide mixtures to enhance their activity, and include agents such as piperonyl butoxide, which is added to insecticides that contain agents such as pyrethrins and carbamates. Synergists have not been previously reviewed by IARC. Experiments in animals have demonstrated a role for synergists in the development of liver tumours. The role of synergists in mixtures could be considered by IARC as part of the review of other pesticides (e.g. carbamates).

**Recommendation:** Low priority

#### 4.36. Pesticides (*occupational exposure to*)

Occupational exposures to non-arsenical insecticides have been classified as Group 2A (Volume 53, 1991). Since that time, several new epidemiological reports have been published that examined associations between specific pesticides and cancers, such as in the United States National Cancer Institute's Agricultural Health Study. Public concern about pesticides remains high, and there is potential for exposures to occur not only in agriculture, but also in recreational areas and in households.

The Advisory Group recommended that the Working Group on pesticides give careful consideration to the classes of occupational exposures that it will evaluate, framing its occupational evaluations as narrowly as possible. This was because 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 Group 2A evaluation. On the other hand, many pesticide workers are exposed to a wide variety of different pesticides during their employment, making specific occupational evaluations difficult. The Advisory Group also noted that there may now be utility in evaluating occupational exposure to arsenical pesticides, because organic arsenical pesticides are no longer implicitly considered to be in Group 1.

**Recommendation:** High priority

#### 4.37. *Ortho-Phenylenediamine dihydrochloride*

*Ortho*-Phenylenediamine dihydrochloride has not been previously evaluated by IARC. A recent study in rats given drinking-water containing *ortho*-phenylenediamine dihydrochloride showed an increased risk of liver tumours, kidney tumours and gallbladder carcinoma (a very rare cancer in rodents).

**Recommendation:** High priority

#### **4.38.      *Phenyl and octyl tin compounds***

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. Phenyl- and octyl-tin compounds have not been previously evaluated by IARC. Animal bioassays have been performed by industry, but were unpublished. The German MAK-Commission has extracted these studies in its documentation of their review of these compounds. The main carcinogenic action of phenyl- and octyltin compounds appears to be hormonal, leading to pituitary and Leydig cell tumours.

The issue of using unpublished data should be clarified internally by IARC prior to any review of these agents.

**Recommendation:** High priority

#### **4.39.      *Beta-Picoline***

Beta-Picoline is an industrial solvent and chemical intermediate. Beta-Picoline has not been previously evaluated by IARC. In NTP studies in mice and rats given drinking-water containing beta-picoline, there was an increase in the incidence of lung tumours in female rats and female mice, and a marginal increase also occurred in male mice. The incidences of hepatocellular carcinoma and hepatoblastoma were also increased in male mice.

**Recommendation:** Medium priority

#### **4.40.      *Physical inactivity and sedentary work***

Urbanization and industrialization have generally led to a decrease in physical activity that first started in higher-income countries, and that more recently has spread to other countries. Physical inactivity is the fourth leading risk factor for death worldwide and is associated with approximately 3.2 million deaths per year. The available database consisted of studies evaluating physical activity and cancer risk. The *IARC Handbook on Cancer Prevention, Volume 6, Weight Control and Physical Activity* (2002) concluded that there was sufficient evidence in humans for a cancer-prevention effect of physical activity for cancers of the colon and breast and limited evidence for cancers of the prostate and endometrium. More recent meta-analyses have reported that increased physical activity (usually measured in units of metabolic equivalents summarized across different types of physical activity) was associated with a decreased risk of cancers of the endometrium in addition to cancers of the colon and breast (postmenopausal). A recent review also reported that higher physical activity decreased the risk of cancers of the lung, prostate and ovary. The conclusions regarding the benefits of higher physical activity (compared with lower physical activity) on the risks of specific cancers could be interpreted as showing that sedentary ways of life may increase the risk of these cancers. There were some limited studies suggesting that sedentary work (using sitting time as a surrogate) increased the risk of

endometrial cancer. While there was no doubt that physical inactivity is associated with increased risk of cancer, the reason for suggesting a *Monograph* was twofold: (a) there is a need for a comprehensive review; (ii) it is incongruent for the *Monographs* not list as a carcinogen one of the main risk factors in humans. The 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.

**Recommendation:** High priority

#### **4.41. Polycyclic aromatic hydrocarbons as a group**

More than 60 individual polycyclic aromatic hydrocarbons (PAHs) were evaluated by IARC in Volume 103 (2013) and others in Volume 92 (2010). In addition, complex mixtures containing PAHs were evaluated by IARC when evaluating diesel exhaust (Volume 105, 2013), indoor air (Volume 95, 2010), and outdoor air (Volume 109, in preparation). As noted in Volume 103 and to some extent in Volume 92, the mechanisms of action of the various PAHs vary: some are carcinogenic, some are not, and some are mutagenic, and some are not. There are at least three pathways by which these compounds are metabolized, and various PAHs are metabolized preferentially by various pathways. It is not clear how these compounds would be evaluated as a group because: (a) they have already been evaluated individually; and (b) the complex mixtures in which they occur are rarely analysed for the concentrations of more than a few PAHs. In addition, the complex mixtures in which the PAHs are present contain a wide variety of other compounds, such as nitro-PAHs, oxy-PAHs, aromatic amines, metals, etc. Thus, there were almost no studies of exposure to a pure PAH mixture. Consequently, it was not clear what literature would be reviewed to evaluate PAHs as a mixture.

**Recommendation:** Low priority

#### **4.42. Poor oral health, alcohol-containing mouthwashes and acetaldehyde**

Numerous epidemiological studies conducted in various countries have shown that compromised oral health is associated with an increased risk of cancer of the mouth, tongue, oesophagus, and, to a lesser extent, of other sites of the upper aerodigestive tract. There were no bioassays in rodents, and only limited data on the proposed mechanism (through inflammation after bacterial colonization).

Numerous epidemiological studies have been conducted that evaluated the relationship between use of mouthwash and the risk of developing oral cancer, with inconsistent results. A meta-analysis of 12 epidemiological studies on mouthwash and risk of oral cancer found no significant association with risk of oral cancer. In sensitivity analyses, there was no association found when the analysis was restricted to oral cancer only, smokers, non-smokers, and when all possible studies were included.

Acetaldehyde associated with the consumption of alcoholic beverages was previously evaluated by IARC as a Group 1 carcinogen (Volume 100E, 2012). There has been no evaluation of acetaldehyde alone. There were no relevant data in the literature to suggest different results from the conclusion of the last evaluation.

**Recommendation:** Low priority

#### **4.43. Red meat and processed meat**

Red and processed meats are consumed as food worldwide. Several meta-analyses have reported a small but mostly statistically significant elevated risk of colorectal cancer with the consumption of red meat or processed meat. In general, risks remain elevated in subgroup analyses by study design, sex, and studies controlling for specific confounders. Some studies suggested an association between increased risk of cancers of the oesophagus, lung and pancreas with consumption of red meat, and increased risk of cancers of the lung, stomach and prostate with consumption of processed meat. There was also a large database evaluating cooking methods of meats and cancer risk where cooking methods may help to explain the increased risk observed for consumption of red or processed meats. Cooking meat at a high temperature forms carcinogenic heterocyclic amines and PAHs; mechanistic studies provide support for the potential carcinogenicity of meats cooked at high temperatures. Providing information on potential factors such as cooking methods that may affect cancer risk may be more useful to the public than an evaluation of only red meat or processed meats.

**Recommendation:** High priority

#### **4.44. Riddelliine**

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. Riddelliine was evaluated by IARC in 2002 (Volume 82) as *possibly carcinogenic to humans* (Group 2B). There were no data on the carcinogenicity of riddelliine to humans and no epidemiological studies have been reported since the previous evaluation. The previous Working Group concluded that there was sufficient evidence in experimental animals for the carcinogenicity of riddelliine. Since the previous evaluation, there have been no additional bioassays reported on riddelliine; however, there have been a number of studies on the mechanism for the genotoxicity and induction of tumours by riddelliine. The proposed mechanism appears to apply to other carcinogenic pyrrolizidine alkaloids (e.g. retrorsine, monocrotaline, lasiocarpine, heliotrine, clivorine, and senkirkine). If a re-evaluation were undertaken, the Advisory Group recommended that the evaluation be expanded to include other pyrrolizidine alkaloids that appear to act through a similar mechanism.

**Recommendation:** Medium priority

#### **4.45. Salt**

Sodium is a major electrolyte in extracellular fluid and is essential for the body to function normally. The minimum daily requirement for sodium has been estimated at around 500 mg for adults, yet the average adult intake of salt varies by country from less than 6 g to 18 g per day. Salt in the diet usually comes from eating processed foods and/or salt-preserved foods such as salted meats, fish, vegetables, bacon, sausages, and ham. Table salt contributes little to total salt intake. Several meta-analyses, including those conducted by WHO, have found a positive association between salt intake and cancer of the stomach; however, there were concerns about the adequacy of the exposure assessment because most salt in the diet comes from processed food and few studies adjusted for dietary factors. There is potential for confounding or effect modification from *Helicobacter pylori* infection or nitrate intake. In experimental animals, high dietary intake of salt has not been shown to cause cancer alone, although a synergistic relationship between gastric cancer and high dietary salt, gastric carcinogens (*N*-nitroso compounds) and *H. pylori* infection was observed.

**Recommendation:** Medium priority

#### **4.46. Selenium**

In the Nutritional Prevention of Cancer study, there was no reduction in the incidence of second-primary skin cancer was associated with consumption of selenium; however, the authors reported reduced risk of cancer of the prostate. This finding motivated the selenium arm of the Selenium and Vitamin E Cancer Prevention Trial (SELECT), where hazard ratios for prostate cancer were null for selenium. Now, researchers have revisited the effect of baseline selenium status on prostate cancer risk in the SELECT study, using toenail samples prior to randomization, and found that baseline toenail selenium concentration did not correlate with prostate cancer risk. Men with high baseline toenail selenium concentrations who received selenium supplementation (either alone or in combination with vitamin E) were twice as likely to develop high-grade (Gleason score of 7–10) prostate cancer as those who received the placebo. Selenium supplementation did not affect cancer risk in men with low baseline levels.

In the VITamins And Lifestyle (VITAL) cohort, there was no association between selenium supplementation and cancer of the prostate.

**Recommendation:** Low priority

#### **4.47. Shiftwork**

Research on circadian disruption and cancer was stimulated by the IARC evaluation in 2007 (Volume 98) of shiftwork involving circadian disruption as *probably carcinogenic to humans* (Group 2A). That evaluation was based on limited evidence from epidemiological studies and sufficient evidence in numerous animal experiments showing that light at night, simulated chronic jet lag, or circadian timing of carcinogens was associated with increases in tumour incidence. Since 2007, there has been extensive new evidence from studies in

humans and also extensive new studies on mechanisms. Epidemiological studies published since the evaluation have tended to include more extensive information on shiftwork and on potential confounding factors than some of the earlier studies, and also some included analyses on disease subtypes, individual diurnal preference that could modify the effect of circadian disruption, and also information on genetic variation. Overall these studies have provided a more complete set of evidence to evaluate the effect of circadian disruption in humans, focused mostly on circadian disruption due to shiftwork. There are several new ongoing cohort and case-control studies. Circadian disruption due to shiftwork is a major exposure and circadian disruption also affects the general population. There are significant public health and regulatory implications, particularly regarding circadian disruption due to shiftwork.

This is a very active area of research concerning human and mechanistic studies. The Advisory Group suggested that an evaluation should be performed towards the end of the 5-year period, to maximize the quantity of evidence available. The topic of the evaluation should be discussed, specifically to determine whether it should focus on shiftwork or more generally on circadian disruption that also refers to the general population apart from workers.

**Recommendation:** High priority

#### **4.48. Styrene**

Exposure to styrene is widespread and in some workplaces exposures continue to be very high. Styrene was last evaluated by IARC in 2002 (Volume 82) and classified as *possibly carcinogenic to humans* (Group 2B) with limited evidence of carcinogenicity in humans and experimental animals. New epidemiological studies published since 2002 do not modify the overall evidence in humans. There is a plan to update the large multicentric IARC cohort of workers in the reinforced plastics industry in Europe, where the highest exposures to styrene occur. Several new studies evaluating potential mechanisms for the carcinogenicity of styrene have been published since 2002. In addition, styrene metabolite styrene-7,8-oxide was classified by IARC in 1994 (Volume 60) as *probably carcinogenic to humans* (Group 2A) with inadequate evidence in humans, sufficient evidence in experimental animals, and supporting mechanistic evidence.

**Recommendation:** High priority (after the publication of the update of the European cohort)

#### **4.49. Talc**

A previous *IARC Monograph* (Volume 93) concluded that a number of case-control studies of ovarian cancer found a modest, but consistent, excess in risk for perineal use of talc-based body powder, although bias and potential confounding could not be ruled out and the overall evaluation was *possibly carcinogenic to humans* (Group 2B). Additional epidemiological studies examining both ovarian and endometrial cancer have been published since the last evaluation; some have found no association while others found positive

associations. Although the evidence was mixed, the Advisory Group considered that the importance of this exposure for public health and the new evidence warranted an evaluation.

**Recommendation:** Medium priority

#### **4.50. *Tetrabromobisphenol A***

Tetrabromobisphenol A (TBBPA) is a derivative of bisphenol A and is widely used as a fire retardant. TBBPA has not previously been reviewed by IARC. TBBPA is an endocrine disrupter with links to estrogenic, androgenic, and thyroid-hormone activity and has an impact on lysis by natural killer cells. Early-life exposure to TBBPA increased the incidence of thyroid follicular cell adenoma and transitional cell papilloma of the urinary bladder in females in a two-stage model in rats. In a preliminary report, a study by the NTP reported tumours of the testis (rats), uterus (rats), liver, intestines, and also haemangiosarcoma (male mouse).

**Recommendation:** High priority

#### **4.51. *Thalidomide and lenalidomide***

Thalidomide and lenalidomide are used for the treatment of patients with multiple myeloma and other myelodysplastic syndromes. IARC has not previously evaluated thalidomide or lenalidomide. There were no published reports of increased incidence of cancer in patients treated with either drug. Bioassays conducted with thalidomide in mice and rats indicated no thalidomide-related tumorigenic effects; bioassays have not been conducted with lenalidomide. Neither thalidomide nor lenalidomide have given positive results in standard batteries of tests for genotoxicity. On the basis of the lack of epidemiological data coupled with the negative results in bioassays and test for genotoxicity, an evaluation of thalidomide and/or lenalidomide would be unlikely to result in classification in Groups 1 or 2.

**Recommendation:** Low priority

#### **4.52. *Trimethylolpropane triacrylate***

Trimethylolpropane triacrylate (TMPTA) is a multifunctional monomer used in the production of polymers and resins. There were no studies of cancer in humans. In NTP studies, technical-grade TMPTA was administered dermally to male and female rats and mice for 2 years. In male rats, a marginal increase in the incidence of malignant mesothelioma was observed. There was evidence for carcinogenic activity of TMPTA in female mice based on increased incidences of uncommon malignant hepatic neoplasms (hepatoblastoma and hepatobiliary carcinoma) and stromal polyp or stromal sarcoma of the uterus.

Technical-grade TMPTA was also administered dermally to male and female Tg.AC mice. The incidence of papilloma at the site of application was dose related in males and females, and there was a marginal increase in the incidence of forestomach papilloma in female mice.

**Recommendation:** Medium priority

#### **4.53. Tungsten**

Tungsten is a hard, rare metal under standard conditions when uncombined. Tungsten is found naturally on Earth only in chemical compounds. The many alloys of tungsten have numerous industrial, nonmilitary applications. The hardness and high density of tungsten give it military applications in the manufacture of penetrating projectiles.

Cobalt metal with tungsten carbide has been classified by IARC (Volume 86) as *probably carcinogenic to humans* (Group 2A). The evidence came from studies that found an increased risk of cancer of the lung among workers in the hard-metal industry.

There were two studies in rats in which different kinds of tungsten pellet were implanted in the leg muscle to simulate shrapnel wounds. Tungsten/nickel/cobalt pellets produced aggressive rhabdomyosarcoma, while tungsten/nickel/iron or pure tungsten pellets did not. Other experimental studies in vivo and/or in vitro have shown pulmonary inflammation, and the production of reactive oxygen species, as well as increased expression of genes associated with oxidative and metabolic stress and toxicity. Genotoxicity and epigenetic modification have also been indicated.

**Recommendation:** High priority (after completion of on-going bioassay)

#### **4.54. Water pipes, tobacco smoking**

Use of water pipes is highly prevalent in some low- and middle-income countries, as well as among some particular age/socioeconomic/ethnic groups in high-income countries: about 100 million people worldwide use water pipes. Although water pipes were specified in the *Monograph* on Tobacco Smoking (Volume 100E, 2012) as a context in which exposure to tobacco smoke occurs, there was no evaluation statement concerning water pipes in that *Monograph*. Despite clear evidence for exposure, cancer epidemiological data predicated wholly on water pipes are lacking.

The high likelihood of cancer causation consequent upon this particular mode of exposure to tobacco smoke was considered to justify an evaluation. Such an evaluation might contribute to public health; however, the Advisory Group concluded that a full *Monograph* assessment constrained to this mode of exposure to tobacco smoke was not justified.

**Recommendation:** No evaluation

#### **4.55. Welding and welding fumes**

Exposure to welding and welding fumes is common; it has been estimated that up to 1% of the work force globally is exposed occupationally to welding fumes full-time or part-time. Different welding environments represent different and complex profiles of the type and quality of exposure.



Welding fumes have been classified by IARC as *possibly carcinogenic to humans* (Group 2B) with limited evidence in humans for the carcinogenicity of welding fumes and gases, and inadequate evidence in experimental animals for the carcinogenicity of welding fumes (Volume 49, 1990).

Since the latest evaluation, numerous epidemiological studies have been published. In the recent studies and a meta-analysis, increased risks were observed broadly and not just among stainless-steel welders, indicating an association with exposures additional to nickel and chromium compounds. The predominant exposures in mild steel welding are to iron and manganese. In addition, the *IARC Monograph* on ultraviolet light (Volume 100D, 2012) identified a higher risk of ocular melanoma among welders, and concluded that there was sufficient evidence for an increased risk of ocular melanoma among welders.

Studies in experimental animal have suggested lung carcinogenicity attributable to welding fumes. Mechanistic studies in vitro and in vivo have indicated genotoxicity, pulmonary toxicity and inflammation, as well as generation of radical oxygen species and altered gene expression. Studies in welders have shown increased frequency of DNA damage and cytogenetic end-points in those employed in different types of welding activities. Some recent data existed on modification of DNA methylation.

**Recommendation:** High priority

#### **4.56. Zidovudine**

Zidovudine (AZT) is a nucleoside analogue that has been used in the treatment and prevention of HIV infection in adults and children. Zidovudine was last reviewed by IARC in Volume 76 and classified as *possibly carcinogenic to humans* (Group 2B), the Working Group concluding that there was inadequate evidence in humans for the carcinogenicity of zidovudine. Since the last evaluation, there has been one large epidemiology study that evaluated the incidence of cancer in uninfected children born to HIV-infected mothers. The overall cancer incidence did not differ significantly from that expected for the general population. Another study reported that the incidences of cancers of the liver and lung, and Hodgkin lymphoma were increased in individuals receiving 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 zidovudine. The previous evaluation concluded there was sufficient evidence in experimental animals for the carcinogenicity of zidovudine. This has been confirmed in a number of subsequent bioassays. Likewise, studies conducted subsequent to the previous evaluation have confirmed the genotoxicity of zidovudine, including in humans in vivo.

**Recommendation:** Medium priority

**Table 1. Summary of agents to be evaluated with high priority**

Agent to be evaluated with high priority
Acrolein
Acrylamide, Furan, 5-Hydroxymethy-2-furfural
2-Amino-4-chlorophenol, 2-Chloronitrobenzene, 4-Chloronitrobenzene, 1,4-Dichloro-2-nitrobenzene, 2,4-Dichloro-1-nitrobenzene
Aspartame and sucralose
Bisphenol A
1-Bromopropane
<i>tert</i> -Butyl alcohol (TBA), <i>see</i> Ethyl tertiary butyl ether (ETBE)
Carbon nanotubes, multi-walled
Beta-Carotene
3-Chloro-2-methylpropene
2-Chloronitrobenzene, <i>see</i> 2-Amino-4-chlorophenol
4-Chloronitrobenzene, <i>see</i> 2-Amino-4-chlorophenol
Coffee
1,4-Dichloro-2-nitrobenzene, <i>see</i> 2-Amino-4-chlorophenol
2,4-Dichloro-1-nitrobenzene, <i>see</i> 2-Amino-4-chlorophenol
Dietary iron and iron used as supplements or for medical purposes
<i>N,N</i> -Dimethyl- <i>p</i> -toluidine
Dimethylformamide
Disinfected water used for drinking, showering, bathing, or swimming
Electronic cigarettes and nicotine
Ethyl acrylate
Ethyl tertiary butyl ether (ETBE), Methyl tertiary butyl ether (MTBE), <i>tert</i> -Butyl alcohol (TBA)
Furan, <i>see</i> Acrylamide
Hot mate drinking
Human cytomegalovirus (HCMV)
5-Hydroxymethy-2-furfural, <i>see</i> Acrylamide
Indium-tin oxide
Isobutyl nitrite

<b>Agent to be evaluated with high priority</b>
2-Mercaptobenzothiazole
Methyl tertiary butyl ether (MTBE), <i>see</i> Ethyl tertiary butyl ether (ETBE)
Nicotine, <i>see</i> Electronic cigarettes
Obesity and overweight
Opium
Overweight, <i>see</i> Obesity
<i>Pesticides:</i>
Carbaryl (carbamate insecticide)
Diazinon (organophosphate insecticide)
Lindane (organochlorine insecticide)
Malathion (organophosphate insecticide)
Pendimethalin (dinitroaniline herbicide)
Permethrin (pyrethroid insecticide)
Pesticides (occupational exposure)
<i>ortho</i> -Phenylenediamine dihydrochloride
Phenyl and octyl tin compounds
Physical inactivity and sedentary work
Red and processed meats
Sedentary work, <i>see</i> Physical inactivity
Shiftwork
Styrene
Sucralose, <i>see</i> Aspartame
Tetrabromobisphenol A (TBBPA)
Tungsten
Welding and welding fumes

**Table 2. Summary of agents to be evaluated with medium priority**

Agent to be evaluated with medium priority
Anthracene
<i>Salmonella typhi</i> , see Biological agents
Breast cancer, suspected causal agents
Breast implants
Calcium-channel blockers
Coal dust
<i>N,N</i> -Dimethylacetamide
Hydrazine
Job stress
Lead
Metal-working fluids
Methanol
Metronidazole
Beta-Myrcene
<i>Pesticides:</i>
Atrazine (triazine herbicide)
Biphenyl
Chorpyriphos (organophosphate insecticide)
DDT, Dichlorodiphenyltrichloroethane (organochlorine insecticide)
EPTC, <i>S</i> -ethyl- <i>N,N</i> ,-dipropylthiocarbamate (thiocarbamate herbicide)
Fonofos and Terbufos (organophosphate insecticides)
Glyphosate
Pentachlorophenol and 2,4,6-Trichlorophenol (organochlorine insecticides)
... Terbufos, see Fonofos and Terbufos
... 2,4,6-Trichlorophenol, see Pentachlorophenol
Pesticides (occupational exposure to)
Beta-Picoline
Riddelliine

<b>Agent to be evaluated with medium priority</b>
Salt
Talc
Trimethylolpropane triacrylate (TMPTA)
Zidovudine (AZT)

## **Appendix 1: Advisory Group Participants**

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### ***IARC Monographs on the Evaluation of Carcinogenic Risks to Humans***

#### **Advisory Group to Recommend Priorities for IARC Monographs during 2015-2019**

**Lyon, 7-9 April 2014**

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<sup>1</sup> 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. Invited specialists are marked by an asterisk.

Each participant was asked to disclose pertinent research, employment, and financial interests. Current financial interests and research and employment interests during the past 4 years or anticipated in the future are identified here. Minor pertinent interests are not listed and include stock valued at no more than US\$1 000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are listed as significant pertinent interests.

<sup>2</sup> Dr Bolt is a member of the Scientific Advisory Committee of the European Research Group on Environment and Health in The Transport Sector (EuGT), founded by BMW, Daimler, Volkswagen and Bosch. He did not receive any financial support related to this activity.

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## **Appendix 2: Preliminary Agenda**

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**WORLD HEALTH ORGANIZATION  
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER**

**Advisory Group to Recommend Priorities for the  
*IARC Monographs during 2015-2019*  
Lyon, 7-9 April 2014**

**PRELIMINARY AGENDA**

**Monday, 7 April 2014**

- 09:00-09:30 Registration, lobby
- 09:30-10:30 Opening session
- 10:30-11:00 Group photo followed by coffee break, lobby
- 11:00-13:00 Discussions of nominations and recommendations regarding future priorities
- 13:00-14:00 Lunch, IARC cafeteria
- 14:00-15:45 Discussions of nominations and recommendations regarding future priorities (cont.)
- 15:45-16:15 Coffee break and payment of *per diem* & dinner reservation, lobby
- 16:15-18:00 Discussions of nominations and recommendations regarding future priorities (cont.)

**Tuesday, 8 April 2014**

- 09:00-10:30 Discussions on procedural issues for the IARC Monographs
- 10:30-11:00 Coffee break, lobby
- 11:00-13:00 Discussions on procedural issues for the IARC Monographs (cont.)
- 13:00-14:00 Lunch, IARC cafeteria
- 14:00-15:45 Discussions on procedural issues for the IARC Monographs (cont.)
- 15:45-16:15 Coffee break, lobby
- 16:15-18:00 Discussions on procedural issues for the IARC Monographs (cont.)
- 20:00 Group dinner

**Wednesday, 9 April 2014**

- 09:00-10:30 Discussions of nominations and recommendations regarding future priorities
- 10:30-11:00 Coffee break, lobby
- 11:00-13:00 Discussions of nominations and recommendations regarding future priorities (cont.)
- 13:00-14:00 Lunch, IARC cafeteria
- 14:00-15:45 Discussions of nominations and recommendations regarding future priorities (cont.)
- 15:45-16:15 Coffee break, lobby
- 16:15-18:00 Discussions of nominations and recommendations regarding future priorities (cont.)

## **Appendix 3: Nominations received, categorized by topic**

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### ***Drugs and related agents***

Breast implants, Calcium antagonists, Isobutyl nitrite, Lenalidomid and Thalidomide, Metronidazole, Riddelliine, Zidovudine and antiviral drugs

### ***Food, food contaminants or dietary-related matters***

Acrylamide, Aspartame, Beta-Myrcene, Sucralose, Sugar-sweetened beverages

Bisphenol A, Beta-Carotene, Coffee, Food canning industry, GMOs, Hot beverages, HMF [5-(hydroxymethyl)-2-furfural], Iron, iron oxides, Obesity and physical inactivity, Obesity surgery, Red meat and processed red meat, Sedentary work, Selenium, Salt

### ***Generic***

Agents that cause breast cancer

### ***Biological agents***

Dysbiotic gut microbiota, *E. Coli*-pks+, *Fusobacterium*, Human cytomegalovirus, *Salmonella typhi* and *paratyphi*, chronic infection

### ***Personal habits and behaviour***

Acetaldehyde, Alcohol-containing mouthwashes, *Cannabis sativa*, Electronic tobacco, Nicotine, Opium, Poor oral health, Talc (body powder), Water pipes

### ***Occupational exposures***

Automotive plastics manufacturing, Coal dust, Job stress, Lead, Metal-working fluids and cutting fluids, Night shiftwork, Plastics industry with particular reference to breast cancer, Tungsten alloy (military), Welding fumes and welding

### ***Pesticides***

Atrazine, Biphenyl, Carbaryl, Chlorpyrifos, Diazinon, DDT [Dichlorodiphenyltrichloroethane], *S*-Ethyl-*N,N*-dipropylthiocarbamate, Fonofos, Glyphosate (Roundup), Hexachlorobenzene, Lindane, Malathion, Pendimethalin, Pentachlorophenol, Permethrin, Pyrethroid chemical class (synthetic pyrethrin) or Pyrethrins, Synergists (i.e. Piperonyl butoxide, *N*-octyl bicycloheptene dicarboximide), Terbufos, 2,4,6-Trichlorophenol

Pesticide-exposed occupations

### ***Radiation***

CT scans, Occupational exposure from work in a nuclear power plant

### ***Water/water contaminants***

Contaminated land and groundwater, Drinking water, MTBE [methyl tertiary butyl ether], ETBE [ethyl tertiary butyl ether] TBA [tert-butanol, t-butanol] nominated as a group

### ***Chemicals not accorded particular categorization***

1-Bromopropane (*n*-propyl bromide, 1,4-Dichloro-2-nitrobenzene, 2-Chloronitrobenzene, 2,4-Dichloro-1-nitrobenzene, 4-Chloronitrobenzene, 2-Amino-4-chlorophenol, 2-Mercaptobenzo-thiazole, 3-chloro-2-methylpropene, Acrolein, Allyl chloride,  $\beta$ -Picoline, Butyl benzyl phthalate, Dimethylformamide, Ethyl acrylate, Hydrazine, Dimethylhydrazine, Furan, Methanol, *N,N*-dimethylacetamide, ortho-phenylenediamine dihydrochloride, Anthracene, Polycyclic aromatic hydrocarbons, Phenyl- and octyl tin compounds, Indium-tin oxide, *N,N*-Dimethyl-*p*-Toluidine, Tetrabromobisphenol A, Trimethylolpropane Triacrylate, Styrene