GENERAL REMARKS

Part F of Volume 100 of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* contains updated assessments of several chemical agents, complex mixtures, and related occupations that were classified as *carcinogenic to humans (Group 1)* in Volumes 1–99.

Volume 100 – General information

About half of the agents classified in Group 1 were last reviewed more than 20 years ago, before mechanistic studies became prominent in evaluations of carcinogenicity. In addition, more recent epidemiological studies and animal cancer bioassays have demonstrated that many cancer hazards reported in earlier studies were later observed in other organs or through different exposure scenarios. Much can be learned from updating the assessments of agents that are known to cause cancer in humans. Accordingly, IARC has selected A Review of Human Carcinogens to be the topic for Volume 100 of the *IARC Monographs*. It is hoped that this volume, by compiling the knowledge accumulated through several decades of cancer research, will stimulate cancer prevention activities worldwide, and will be a valued resource for future research to identify other agents suspected of causing cancer in humans.

Volume 100 was developed by six separate Working Groups:

Pharmaceuticals
Biological agents
Arsenic, metals, fibres, and dusts
Radiation
Personal habits and indoor combustions
Chemical agents and related occupations

Because the scope of Volume 100 is so broad, its *Monographs* are focused on key information. Each *Monograph* presents a description of a carcinogenic agent and how people are exposed, critical overviews of the epidemiological studies and animal cancer bioassays, and a concise review of the toxicokinetic properties of the agent, plausible mechanisms of carcinogenesis, and potentially susceptible populations and life-stages. Details of the design and results of individual epidemiological studies and animal cancer bioassays are summarized in tables. Short tables that highlight key results appear in the printed version of Volume 100, and more extensive tables that include all studies appear on the website of the *IARC Monographs* programme (http://monographs.iarc.fr). For a few well-established associations (for example, tobacco smoke and human lung cancer), it was impractical to

include all studies, even in the website tables. In those instances, the rationale for inclusion or exclusion of sets of studies is given.

Each section of Volume 100 was reviewed by a subgroup of the Working Group with appropriate subject expertise; then all sections of each *Monograph* were discussed together in a plenary session of the full Working Group. As a result, the evaluation statements and other conclusions reflect the views of the Working Group as a whole.

Volume 100 compiles information on tumour sites and mechanisms of carcinogenesis. This information will be used in two scientific publications that may be considered as annexes to this volume. One publication, Tumour-Site Concordance between Humans and Experimental Animals, will analyse the correspondence of tumour sites among humans and different animal species. It will discuss the predictive value of different animal tumours for cancer in humans, and perhaps identify human tumour sites for which there are no good animal models. Another publication, Mechanisms Involved in Human Carcinogenesis, will describe mechanisms known to or likely to cause cancer in humans. Joint consideration of multiple agents that act through similar mechanisms should facilitate the development of a more comprehensive discussion of these mechanisms. Because susceptibility often has its basis in a mechanism, this could also facilitate a more confident and precise description of populations that may be susceptible to agents acting through each mechanism. This publication will also suggest biomarkers that could render future research more informative. In this way, IARC hopes that Volume 100 will serve to improve the design of future cancer studies.

Introduction to Volume 100F

This sixth and final part of Volume 100 of the *IARC Monographs* contains updated assessments of several chemical agents, complex mixtures, and related occupations that were classified as *carcinogenic to humans (Group 1)* in Volumes 1–99. In the early 1970s, the *IARC Monographs* began as a programme to evaluate chemical substances; among the agents considered in the present volume, 4-aminobiphenyl, auramine production, and benzidine were first reviewed in Volume 1 (IARC, 1972), benzo[*a*]pyrene in Volume 3 (IARC, 1973), and 2-naphthylamine, bis(chloromethyl)ether, and chloromethyl methyl ether in Volume 4 (IARC, 1974). For most of these chemicals, the cancer hazard was recognized already when they were first reviewed, although the classification in Group 1 was formalized later, in Working-Group meetings for Supplements 1, 4, and 7 (IARC, 1979, 1982, 1987).

Some workplace conditions entail complex exposures to varying chemical mixtures. This makes it difficult to attribute an excess cancer risk to specific causal agents, particularly in the absence of long-term follow-up studies showing a reduction of risk following the removal of specific agents from the workplace. Accordingly, this Volume 100F also contains updated assessments of chemical-related occupations and industries that were classified in Volumes 1–99 as *carcinogenic to humans (Group 1)*.

The agents that are assessed in the present volume were last reviewed during *IARC Monograph* meetings dating from 1987 till 2008 (see Table).

It should be noted that, in the present volume, some of these agents are named slightly differently, compared with previous evaluations.

Agents reviewed in this volume

Agent	Volume Number	Year of meeting
4-Aminobiphenyl	Volume 99	2008
Benzidine and dyes metabolized to benzidine	Volume 99	2008
Methylenebis(chloroaniline) (MOCA)	Volume 99	2008
2-Naphthylamine	Volume 99	2008
ortho-Toluidine	Volume 99	2008
Auramine production	Volume 99	2008
Magenta production	Volume 99	2008
Benzo[*a*]pyrene	Volume 92	2005
Coal gasification, occupational exposures during	Volume 92	2005
Coal-tar distillation, occupational exposures during	Volume 92	2005
Coal-tar pitch (paving and roofing with), occupational exposures during	Volume 92	2005
Coke production, occupational exposures during	Volume 92	2005
Mineral oils (untreated and mildly treated)	Supplement 7	1987
Shale oils	Supplement 7	1987
Chimney sweep, occupational exposure as a	Volume 92	2005
Aluminium production	Volume 92	2005
Aflatoxins (naturally occurring mixtures of)	Volume 82	2002
Benzene	Supplement 7	1987
Bis(chloromethyl)ether and chloromethyl methyl ether (technical grade)	Supplement 7	1987
1,3-Butadiene	Volume 97	2007
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin	Volume 69	1997
Ethylene oxide	Volume 97	2007
Formaldehyde	Volume 88	2006
Sulfur mustard	Supplement 7	1987
Vinyl chloride	Volume 97	2007
Isopropyl alcohol manufacture (strong-acid process)	Supplement 7	1987
Strong-inorganic-acid mists containing sulfuric acid (occupational exposure)	Volume 54	1991
Iron and steel founding	Supplement 7	1987
Painter (occupational exposure as a)	Volume 98	2007
Rubber-manufacturing industry	Supplement 7	1987

Specific remarks about some of the agents reviewed in this volume

Four aromatic amines (4-aminobiphenyl, benzidine, 2-naphthylamine, *ortho*-toluidine) and two related industrial processes (auramine production, magenta production) were re-affirmed as Group-1 carcinogens based on *sufficient evidence* that they cause cancer of the urinary bladder in humans. The Group-1 classification of dyes metabolised to benzidine was based on *sufficient evidence* of carcinogenicity for some of these dyes in experimental animals and strong mechanistic evidence indicating that the metabolism of these dyes leads to the release of free benzidine – a re-affirmed Group-1 carcinogen – and to the subsequent induction of chromosomal aberrations in all experimental animal species studied, and in humans exposed to these dyes. Likewise, the Group-1 classification of 4,4′-methylenebis(2-chloroaniline) was based on *sufficient evidence* of carcinogenicity in experimental animals and strong mechanistic evidence, indicating that the toxicological profile of this genotoxic amine is similar to that of *ortho*-toluidine (a re-affirmed Group-1 carcinogen), that it forms DNA adducts in human urothelial cells *in vitro* and haemoglobin adducts in the blood of exposed workers, and that it causes cytogenetic alterations in urothelial cells and lymphocytes of exposed workers.

Exposure to polycyclic aromatic hydrocarbons (PAHs) causes cancers of the skin and lung in humans. Although there are no epidemiological studies of benzo[*a*]pyrene as a single exposure, it is carcinogenic in numerous animal species. There is mechanistic evidence indicating that benzo[*a*]pyrene is metabolized to highly reactive diolepoxides that form covalent DNA adducts, which have been shown to induce mutations in the K-*RAS* oncogene and the *TP53* tumour-suppressor gene in human lung tumours, and in corresponding genes in lung tumours in mice. Exposures to benzo[*a*]pyrene and benzo[*a*]pyrene-containing complex mixtures also induce cytogenetic alterations, DNA breakage, oxidative DNA lesions, and specific mutations in oncogenes and tumour-suppressor genes, all of which can contribute to the carcinogenic effects of benzo[*a*]pyrene and benzo[*a*]pyrene-containing complex mixtures in exposed humans. This consistent and coherent mechanistic evidence from experimental and human studies provides biological plausibility to support the overall classification of benzo[*a*]pyrene as a Group-1 carcinogen.

Two PAH-containing mixtures (chimney soot, coal-tar pitch), and occupational exposures in four PAH-related industries (coal-tar distillation, coal gasification, coke production, aluminium production) were confirmed as Group-1 carcinogens.

Workers in the rubber-manufacturing industry have an increased risk for leukaemia, lymphoma, and cancers of the urinary bladder, lung, and stomach. Due to the diversity and complexity of the exposures during rubber-manufacturing, the Working Group – like the previous one three decades ago (*IARC Monograph* Volume 28, 1982) – could not identify specific causative agents. However, there continues to be strong evidence of genotoxic and cytogenetic effects in workers in this industry.

There is consistent evidence that untreated or mildly treated mineral oils cause cancer of the skin, specifically of the scrotum, in humans. The association is highly unlikely to be due to chance, bias, or confounding, given the large case series, supportive epidemiological evidence, the rarity of scrotal cancer, and the intensity of exposure during the period of interest. Despite the fact that a significant proportion of workers exposed occupationally to mineral oils and shale oils are women, epidemiological studies established a statistically significant risk only for skin cancer in the scrotum, because of the extreme rarity of this type of cancer at this site. This observation does not imply that the skin-cancer hazard is restricted to males.

Evidence from three cohort studies indicated that exposure of humans during the manufacture of isopropyl alcohol by the strong-acid process causes cancer of the paranasal sinuses, an extremely rare cancer. The risk for laryngeal cancer may also have been elevated in these workers. This evaluation re-affirms the conclusion of a previous Working Group (IARC, 1987). It was noted that since that time none of these cohorts nor any other isopropanol-manufacturing unit has been evaluated for cancer mortality or incidence without the inclusion in the study population of workers in other production units. An increased incidence of other cancers in the upper respiratory tract was observed in these studies, but it was not possible to attribute these cancers to exposures during isopropanol production. Therefore, the possible association of these tumours with this specific exposure could not be evaluated.

The Working Group reviewed more than 100 epidemiological studies of benzene and confirmed its carcinogenicity, with *sufficient evidence* for acute non-lymphocytic leukaemia and *limited evidence* for acute and chronic lymphocytic leukaemia, multiple myeloma, and non-Hodgkin lymphoma. The Working Group noted the extraordinary expansion in the epidemiological literature on benzene-related cancers since the previous evaluation, the diversity of industrial and environmental exposure scenarios where benzene has been studied, and the evolution in the histological classification of leukaemias and lymphoid neoplasms over the past decades, and suggested that a re-evaluation of the cancer hazards from exposure to benzene be conducted in due time.

Dioxin (2,3,7,8-tetrachlorodibenzo-*para*-dioxin, TCDD) was previously classified in Group 1, based on *limited evidence* of carcinogenicity in humans, *sufficient evidence* in rodents, and strong evidence in humans and animals for a mechanism via initial binding to the aryl-hydrocarbon receptor (AhR), which leads to changes in gene expression, cell replication, and apoptosis. There is now *sufficient evidence* from epidemiological studies for all cancers combined, making TCDD the first agent classified initially in Group 1 based on *sufficient evidence* of carcinogenicity in experimental animals and strong mechanistic data, to be later confirmed by increased cancer incidence in humans. This highlights the ability of mechanistic information to provide robust evidence of carcinogenicity. Like TCDD, 2,3,4,7,8-pentachlorodibenzofuran and 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126) are complete carcinogens in experimental animals, and there is ample evidence that they act through the same AhR-mediated mechanism. The Working Group classified these two chemicals in Group 1. The Working Group discussed the possibility of evaluating an additional 26 polychlorinated dibenzodioxins, dibenzofurans and biphenyls for carcinogenicity, based upon data showing similarity to the mechanism outlined for TCDD. According to the *IARC Monographs* Preamble (Part B, Section 6d), an evaluation may be made for a broad group of agents, even including substances for which there is no direct information on cancer in humans or experimental animals, if it is warranted by the overall evidence. Recognizing the complexity of the mechanistic evaluation, the Working Group decided this time to make evaluations for two indicator chemicals, 2,3,4,7,8-pentachlorodibenzofuran and 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126), for which there are recent positive NTP bioassays, supported by data on a wide range of mechanistic events. The Working Group suggested that a future generic evaluation be focused on the entire class of dioxin-like compounds, taking into account the available mechanistic data.

The Working Group unanimously reaffirmed the classification of formaldehyde in Group 1, based on *sufficient evidence* in humans of nasopharyngeal cancer. A possible association with leukaemia was considered strong "but not sufficient" by a previous Working Group, mainly because of the lack of a plausible mechanism. Since that time, the epidemiological evidence has become stronger: a recent

study found that embalming was significantly associated with an increased risk for myeloid leukaemia, with cumulative years of embalming and with increasing peak-exposure to formaldehyde. In addition, a recent study of a small group of workers exposed to formaldehyde showed numerical chromosomal aberrations in myeloid progenitor cells (chromosome-7 monosomy, chromosome-8 trisomy) as also observed in myeloid leukaemia, and haematological changes in peripheral blood that are indicative of effects on the bone marrow. A small majority of the Working Group concluded that, overall, there is *sufficient evidence* of a causal association between exposure to formaldehyde and an increased risk for leukaemia, particularly myeloid leukaemia.

Identification of tumour sites

One of the goals of the review of Group-1 carcinogens in Volume 100 of the *IARC Monographs* is the identification of tumour sites with *sufficient evidence* in humans. The tumour-site identification in this volume was – naturally – limited by the research that has been published to date, and it should be noted that many plausible tumour sites identified in rodents have not been considered in humans. For example, several aromatic amines induce mammary gland tumours in rats, and there is mechanistic evidence that supports a potential for aromatic amines to cause this cancer, but the epidemiological studies on cancer associated with exposure to these substances have not considered breast cancer, mainly because the industrial cohorts were generally small and did not include women. In addition, no case–control studies are available on breast cancer associated with exposure to aromatic amines. Similarly, mammary gland tumours are the only tumour induced by 1,3-butadiene in both rats and mice, but epidemiological studies – while demonstrating an increased risk for leukaemia – have just started to explore the possibility of this chemical being associated with breast cancer.

Changes in occupational exposures over time

Changes in occupational hygiene or industrial processes can alter the profile of workplace exposures over time. Moreover, regulations and working conditions may differ greatly from one country to another. For these reasons, it is useful to identify the specific agents responsible for excess cancer risks whenever possible (see *IARC Monographs* Preamble Part B, Section 6a). It is important to recognize that new studies of modern and improved workplaces would not reflect risks that might still exist in areas where adequate regulations or process improvements are not fully implemented. Consequently, previous evaluations of occupations that were classified as *carcinogenic to humans* stand as a historical record of hazards that are known to cause cancer. In future monographs, as historical exposures described as occupations are reduced and risk is abated, previous findings should be noted as indicative of potential carcinogenic risk in this occupation should historical exposure levels return or continue to exist elsewhere. Also, as industrial processes change, carcinogenicity profiles in the workplace will change and evaluations need to take these changing processes into account.

Incorporation of new mechanistic data in future evaluations

The ever-increasing understanding of the molecular mechanisms underpinning the classical concepts of initiation, promotion and progression in cancer provides a challenge for its integration into cancer-hazard identification. In most instances, genotoxic pathways have been considered central to the carcinogenic process and mechanistic studies characterizing these outcomes have provided important supporting information for the evaluation. The panel of genotoxic endpoints has been extended over the years, from classical mutagenicity in bacteria to the current demonstration of mutation induction in oncogenes and tumour-suppressor genes.

Mechanisms of non-genotoxic carcinogenesis are being identified for an increasing number of chemicals evaluated by the IARC *Monographs*. In the future, this area will undoubtedly expand into processes mediated by epigenetic events. Collectively, new types of information are being used to assess these mechanisms, such as epigenomics, proteomics, metabolomics and systems-biology approaches. These strategies have identified changes in specific genes, proteins, signalling pathways, networks of pathways, cell-cycle genes and transcription factors. Other studies have focused on changes in methylation, and on patterns of microRNA expression and effects of small interfering RNA (si-RNA). Proteomics studies have identified post-translational modifications, and metabolomic studies have revealed how endogenous metabolite patterns change after exposure. These studies are conducted in human and non-human cells, tissues from experimental animals, and in human tissues following occupational and/or environmental exposures. It is recommended that IARC convene an Advisory Group to develop guidelines for the evaluation and incorporation of this type of information to support a specific mechanism and/or to derive an evaluation of carcinogenicity for a specific exposure.

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