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Identifying the causes of human cancer is the first step in prevention. The *IARC Monographs Programme* is an international, interdisciplinary approach to carcinogenic hazard identification. Its principal product, the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, is a serial publication that began in 1971 in accordance with one of the fundamental missions of the Agency: to prepare and distribute authoritative information on human cancer and especially on its causes and prevention. Reviews and evaluations of nominated agents and exposures are carried out by Working Groups of scientific experts who are invited to participate on the basis of their contributions to the relevant areas of science. The *IARC Monographs* are a worldwide endeavour that has involved more than 1200 scientists from 53 countries.

Each Monograph consists of a comprehensive, critical summary and review of the published scientific literature, and, since 1987, each Monograph concludes with an evaluation of the overall evidence of carcinogenicity to humans. In general, three volumes of the Monographs are prepared annually. Since 1971, more than 950 chemicals, complex mixtures, occupational exposures, physical agents, biological agents, personal habits, and household exposures have been reviewed, some of them several times as new information

has become available in the published scientific literature. More than 100 of these agents have been identified as carcinogenic (Group 1) and more than 300 as *probably carcinogenic or possibly carcinogenic to humans* (Groups 2A and 2B). The Monographs have evolved into the World Health Organization's encyclopaedia on the roles of environmental agents and lifestyle in human cancer causation. National and international health agencies consult the Monographs as a source of scientific information on known or suspected carcinogens and as scientific support for their actions to prevent exposure to these agents. Likewise, individuals use the information and conclusions from the Monographs to make better lifestyle decisions that reduce their exposure to potential carcinogens and their risk of developing cancer. In this way, the *IARC Monographs* contribute to cancer prevention and the improvement of public health.

Overview of activities during the biennium 2012–2013

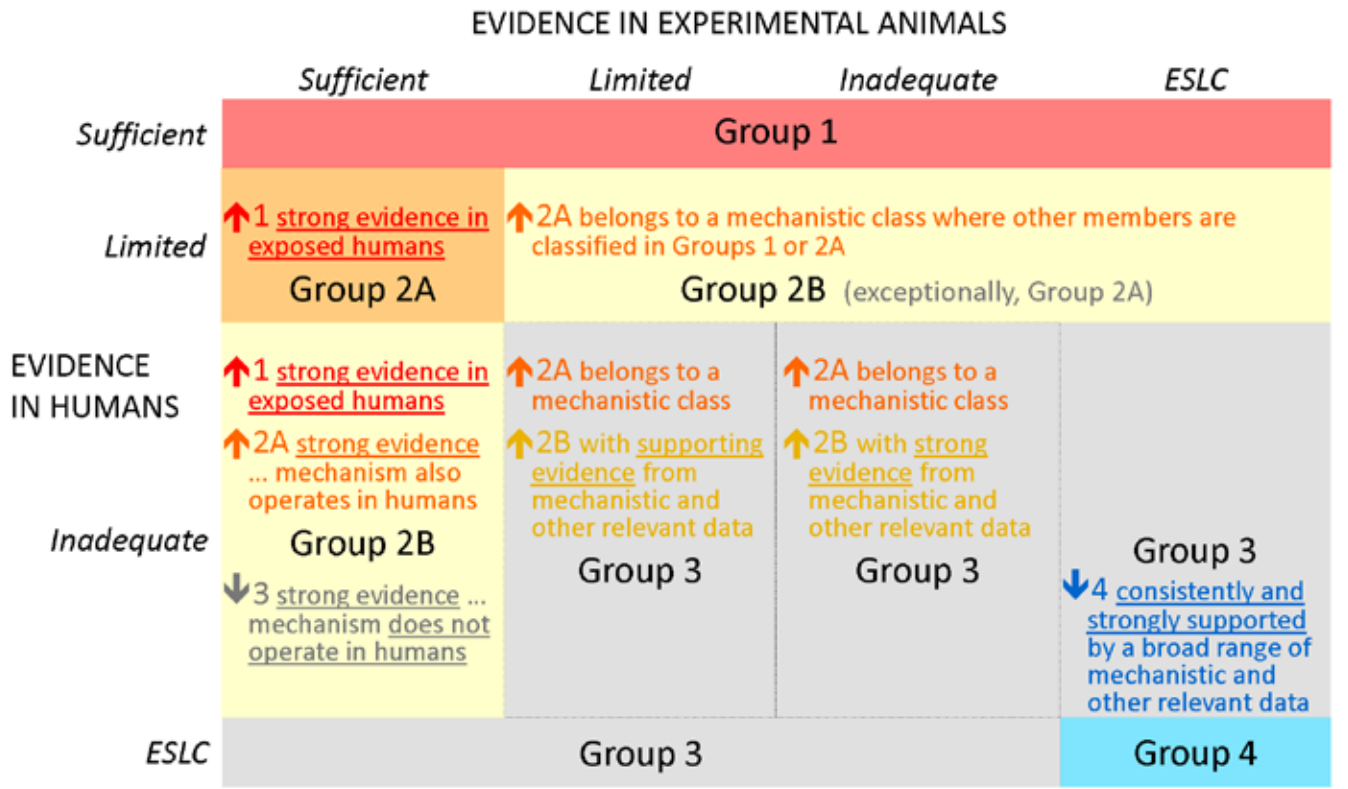
The 2012–2013 biennium saw the publication in print of Volumes 100A–F of *IARC Monographs* updating the more than 100 agents classified by the IARC as Group 1 in Volumes 1–99 (IARC, 2012a–e). Volumes 101–106 (IARC, 2012f; IARC, 2013a–e) were also published online and are freely available on the *IARC Monographs* web site (http://monographs.iarc.fr/). All Volumes since 43 (1989), Supplements 1, 4, and 7, as well as the summary sections of Volumes 1–42 are also available online. Immediately after each meeting, summary reports are published in *The Lancet Oncology*, and these can be freely accessed via the *IARC Monographs* and *The Lancet Oncology* web sites. Six Monographs meetings, two Workshops, and one Advisory Group meeting were held, as listed below.

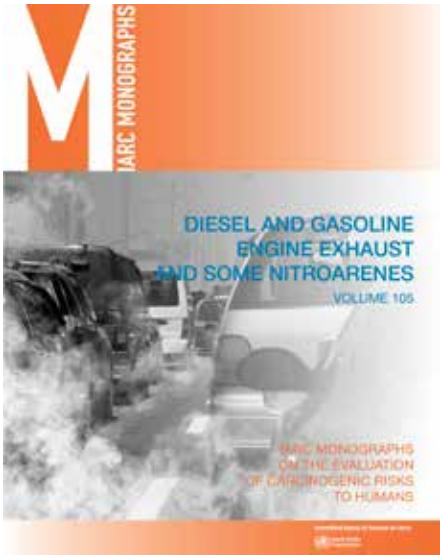
Volume 104: Polyomaviruses (SV40, BK, JC, and Merkel cell viruses) and malaria (7–14 February 2012)

In February 2012, a Working Group (WG) evaluated several polyomaviruses and malaria. The human polyomaviruses BK virus and JC virus are highly prevalent in humans worldwide and are responsible for lethal non-cancerous diseases in immunosuppressed individuals. Based on *sufficient evidence* of carcinogenicity in experimental animals and *inadequate evidence* in humans, both were classified as Group 2B.

An etiological role of Merkel cell polyomavirus in a rare human skin cancer, Merkel cell carcinoma, is supported by a few case–control studies, several case series, and strong mechanistic data, which led to a Group 2A evaluation. In the 1950s and early 1960s, millions of people received Simian virus 40 (SV40)-contaminated poliovirus vaccines. SV40 is highly tumorigenic in rodents, but the extensive data available did not provide compelling evidence that it infects humans and therefore SV40 was classified as Group 3 (*not classifiable as to its carcinogenicity to humans*). "Malaria caused by infection with *Plasmodium falciparum* in holoendemic areas" was classified as Group 2A based on limited epidemiological evidence that malaria is associated with endemic Burkitt lymphoma (eBL), and strong mechanistic evidence that *P. falciparum* can disturb the immature immune system in young children and reactivate the ubiquitous Epstein–Barr virus, a necessary agent for eBL (Bouvard *et al.*, 2012; IARC, 2013c).

Figure 1. The *IARC Monographs'* scheme for overall evaluation of carcinogenicity to humans by combining data on cancer in humans, data on cancer in experimental animals, and other relevant data. ESLC, evidence suggests lack of carcinogenicity.





Volume 105: Diesel and gasoline engine exhausts and some nitroarenes (5–12 June 2012)

In June 2012, a WG reviewed the carcinogenicity of diesel and gasoline engine exhausts. Diesel engine exhaust was classified as Group 1 based on *sufficient evidence* that exposure is associated with an increased risk of lung cancer. The WG also noted a positive association (*limited evidence*) with an increased risk of bladder cancer. The WG concluded that gasoline engine exhaust was *possibly carcinogenic to humans* (Group 2B). The evaluation of 10 nitroarenes (Table 1) led to mechanistic upgrades of 3-nitrobenzanthrone to Group 2B, and of 1-nitropyrene and 6-nitrochrysene to Group 2A; the Group 2B classification of the other seven nitroarenes was reaffirmed (Benbrahim-Tallaa *et al.*, 2012a; IARC, 2013d).

Table 1. Evaluations of the nitroarenes

Agent	Evidence of carcinogenicity in experimental animals	Mechanistic evidence	Overall evaluation
3,7-Dinitrofluoranthene	Sufficient	Weak	Group 2B
3,9-Dinitrofluoranthene	Sufficient	Weak	Group 2B
1,3-Dinitropyrene	Sufficient	Weak	Group 2B
1,6-Dinitropyrene	Sufficient	Moderate	Group 2B
1,8-Dinitropyrene	Sufficient	Moderate	Group 2B
3-Nitrobenzanthrone	Limited	Strong	Group 2B[a]
6-Nitrochrysene	Sufficient	Strong	Group 2A[a]
2-Nitrofluorene	Sufficient	Weak	Group 2B
1-Nitropyrene	Sufficient	Strong	Group 2A[a]
4-Nitropyrene	Sufficient	Moderate	Group 2B

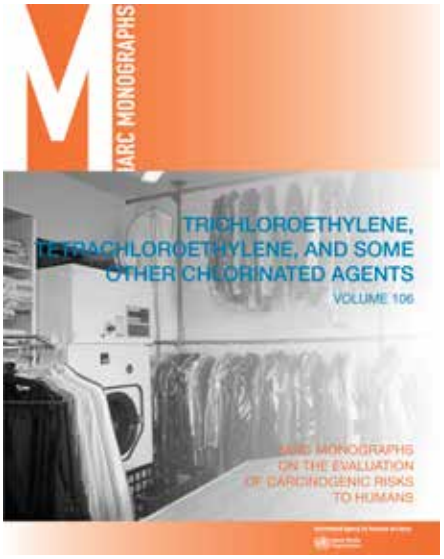
Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans.

[a] Strong mechanistic evidence contributed to the overall evaluation (see text).

Source: Benbrahim-Tallaa *et al.* (2012a); reproduced with permission from Elsevier.

Volume 106: Trichloroethylene, some other chlorinated solvents, and their metabolites (2–9 October 2012)

In October 2012, a WG reviewed the carcinogenicity of several chlorinated solvents (trichloroethylene, tetrachloroethylene, 1,1,1,2-tetrachloroethane, and 1,1,2,2-tetrachloroethane) and some of their metabolites (dichloroacetic acid, trichloroacetic acid, chloral hydrate). Trichloroethylene was classified as Group 1 based on sufficient evidence for an increased risk of kidney cancer; there was also *limited evidence* for an association with liver cancer and non-Hodgkin lymphoma. Tetrachloroethylene was classified as Group 2A based on limited epidemiological evidence for an increased risk of bladder cancer. Evidence for the carcinogenicity of chloral hydrate was inadequate in epidemiological studies but sufficient in experimental animals. Chloral hydrate was upgraded to Group 2A on the basis of strong evidence of its genotoxicity in most experimental systems and exposed humans. Multiple chronic bioassays in mice demonstrated that dichloroacetic acid, trichloroacetic acid, 1,1,1,2-tetrachloroethane, and 1,1,2,2-tetrachloroethane increased the incidence of hepatocellular tumours as well as tumours in other organs. These agents were classified as Group 2B based on *sufficient evidence* of carcinogenicity in experimental animals (Guha *et al*., 2012).



Volume 107: Polychlorinated and polybrominated biphenyls (12–19 February 2013)

A total of 209 possible polychlorinated and polybrominated biphenyl (PCB and PBB) congeners have been defined, which differ in the number and position of the chlorines and bromines, respectively. PCBs have been widely used in electrical equipment, while PBBs have been primarily used as flame retardants; numerous studies have reported exposure of workers to these industrial chemical mixtures in many different settings. Due to their widespread use and their chemical stability, PCBs have become ubiquitous as environmental contaminants. On the basis of sufficient evidence in humans that PCBs cause skin cancer and *sufficient evidence* of carcinogenicity in experimental animals, the WG classified PCBs as Group 1. PCBs with a toxic equivalency factor (TEF) as defined by the World Health Organization and commonly referred to as "dioxin-like PCBs," were also classified as Group 1 on the basis of *sufficient evidence* of carcinogenicity in experimental animals and of extensive evidence of an aryl hydrocarbon receptor (AhR)-mediated mechanism of carcinogenesis that is identical to that of

2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD). The carcinogenicity of PCBs overall cannot be solely attributed to the carcinogenicity of the dioxin-like PCBs. On the basis of similarities with PCBs in terms of structure and biological activity, and together with inadequate evidence of carcinogenicity in humans and *sufficient evidence* in experimental animals, PBBs were upgraded to Group 2A (Lauby-Secretan *et al.*, 2013).

Volume 108: Some drugs and herbal medicines (4–11 June 2013)

In June 2013, a WG reviewed the carcinogenicity of 14 drugs and herbal medicines. The drug pioglitazone was classified as Group 2A based on *limited evidence* in humans that its use is associated with urinary bladder cancer and *sufficient evidence* of carcinogenicity in experimental animals. The drugs digoxin and hydrochlorothiazide were classified as Group 2B based on *limited evidence* in humans that digoxin use is associated with breast cancer and that hydrochlorothiazide use is associated with squamous cell carcinoma of the skin and lip. The drugs primidone, sulfasalazine, pentosan polysulfate sodium, and triamterene, and the herbal medicines (or their components) whole leaf extract of *Aloe vera*, goldenseal root powder, *Ginkgo biloba* leaf extract, kava extract, and pulegone were classified as Group 2B based on sufficient evidence of carcinogenicity in experimental animals. The drugs rosiglitazone and methylene blue were evaluated as Group 3 (Grosse *et al.*, 2013).

Volume 109: Outdoor air pollution (8–15 October 2013)

In October 2013, a Working Group reviewed the carcinogenicity of outdoor air pollution. A complex mixture of pollutants, outdoor air pollution originates from many natural and anthropogenic sources, including transportation, power generation, industrial activity, biomass burning, and domestic heating and cooking. Air pollution levels also range widely over space and time. The levels of most air pollutants have declined in Europe and North America, while they have risen sharply in some rapidly industrializing countries in Asia and South America. The Working Group unanimously classified outdoor air pollution and particulate matter from outdoor air pollution as Group 1, based on *sufficient evidence* of carcinogenicity in humans and experimental animals and strong mechanistic evidence. Exposure to outdoor air pollution, as measured by several indicators including the concentrations of pollutants in the air and measures of exposure to traffic, is associated with increased risk of lung cancer. There is also limited evidence of an association with bladder cancer. Exposure to particulate matter in outdoor air pollution, as measured by the mass concentration of particles, is also associated with increased risk of lung cancer. In addition, the Working Group concluded that there is strong evidence that exposure to outdoor air pollution is associated, in humans and several other species, with increases in genetic damage, including cytogenetic abnormalities, mutations in both somatic and germ cells, and altered gene expression, which have been linked to increased cancer risk in humans (Loomis *et al.*, 2013).

Air Pollution and Cancer (IARC Scientific Publication No. 161)

Air Pollution and Cancer, published in October 2013 as an e-book, presents the scientific background and rationale for Monograph Volume 109, Outdoor air pollution. The initial drafts of most of the 13 chapters were developed as background documents for the meeting of a Special Advisory Group convened in 2004 to plan a series of Monographs on air pollution, including Volumes 92, 93, 95, 103, and 105, as well as 109. The original chapters were updated and two new chapters and a Working Group report were added to provide a broad overview of the current state of the science related to air pollution and cancer. The topics covered by the report include the characteristics and sources of air pollution, issues in assessing exposure, biomarkers, household sources and exposures, and experimental and mechanistic considerations.

Workshops on Volume 100: Tumour concordance and mechanisms of carcinogenesis: lessons learned from Volume 100 of the IARC Monographs (16–18 April 2012 & 28–30 November 2012)

As a follow-up to Volume 100, two Workshops were organized on "Tumour concordance between humans and experimental animals" and "Mechanisms involved in human carcinogenesis." The database capturing cancer data in animals and their concordance (or discordance) with human cancers has been finalized and is now subject to biostatistical analysis. The second Workshop redefined and fine-tuned the outline for the database on mechanisms. The proposed content of the forthcoming IARC Scientific Publication, with assigned chapters on concordance and mechanisms, was also discussed. The biostatistical analyses of both databases will be part of this publication.

Advisory Group meeting on Quantitative Risk Characterization (18–19 November 2013)

This Advisory Group (AG) was requested by IMO and asked *"to provide advice to the Programme on the advisability of adding aspects of quantitative risk evaluations to the more qualitative evaluations currently undertaken".* Through two days of discussions and deliberations, the AG developed a number of recommendations for IMO to consider regarding quantitative risk characterization activities. During these discussions, members of the AG

stressed the importance and public health impact of the qualitative hazard identifications that have been the focus of IMO to date and expressed the opinion that expansion of the *Monographs Programme's* focus into more quantitative evaluations should not be done at the expense of hazard identification. The AG recommended a cautious evolution towards more quantification with a more systematic review of quantitative data, particularly from epidemiological studies on cancer in humans but also on exposure distributions in populations, and description of exposure levels at which cancers in bioassays and other pertinent effects in mechanistic studies were observed. Further, the Monograph Working Groups could review cancer burden and other risk scenarios from the literature. Given limited time and resources, the AG felt that Working Groups should not formally review published risk assessments from other national or international agencies. Outside of the Working Group meetings, the AG identified a need for estimating global cancer burdens and encourages IARC to pursue cancer burden evaluations. The AG also outlined modifications to consider in the Preamble, suggested strengthening the science behind epidemiological exposure–response analyses using workshops and scientific publications, and suggested using databases to capture information from Monograph reviews of the literature. The AG also felt that IARC could play a key role in developing estimates for the global cancer burden from agents reviewed in the Monographs and encouraged IARC to explore ways to implement this. Recommendations from this Advisory Group will be presented at the meeting of the next Advisory Group on Future Priorities for the *IARC Monographs,* which is planned for April 2014.

Financial support from the following bodies is gratefully acknowledged:

European Commission, Brussels, Belgium
National Cancer Institute, National Institutes of Health, USA
National Institute of Environmental Health Sciences,
National Institutes of Health, USA