# Section of IARC Monographs (IMO)

The first step in cancer prevention is to identify the causes of human cancer. The IARC *Monographs Programme* is an international, interdisciplinary approach to carcinogenic hazard identification. Its principal product is the serial publication, the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, which began in 1971 in accordance with one of the fundamental missions of the Agency: to prepare and disseminate authoritative information on human cancer, 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. Since 1987, each has concluded with an evaluation of the overall evidence of carcinogenicity to humans. In general, three volumes of the Monographs are prepared annually. Since 1971, nearly 950 chemicals, complex mixtures, occupational exposures, physical agents, biological agents, personal habits and household exposures have been reviewed, some of them several times as

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new information became available in the published scientific literature. About 100 of these agents have been identified as carcinogenic, and about 300 as probably carcinogenic to humans (Groups 1, 2A and 2B). The Monographs have evolved into the WHO’s encyclopaedia on the roles of environmental agents in human cancer causation. National and international health agencies use 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. Individuals also use the information and conclusions from the Monographs to make better choices 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.

**Volume 100 of the IARC Monographs**

Volume 100 of the IARC Monographs comprises a reassessment and update of the more than 100 agents classified by the IARC as carcinogenic to humans (Group 1) in Volumes 1–99.

During the period October 2008–November 2009, the IARC Monographs Programme organized six international Working Group meetings of experts in carcinogenesis and public health. It was agreed that no IARC Monographs Working Groups would convene during 2010, so as to consolidate the results of the Volume 100 project and to finalize several earlier volumes (see below). The latter included the checking for scientific accuracy and clarity of over 5000 pages of text and tables, editing of the text, and processing of the books for dispatch to the printers.

**Overview of activities during the biennium 2010–2011**

**Publication of Monographs in print**

The 2010–2011 biennium saw the publication in print of seven volumes of IARC Monographs as listed below (key evaluations and scientific highlights mentioned for each):

- **Volume 92 (853 pp)**
  - Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures
  - **Benzo[a]pyrene** is carcinogenic to humans (Group 1). The Working Group made this evaluation in the absence of agent-specific epidemiological information, taking into account the sufficient evidence of carcinogenicity of benzo[a]pyrene in numerous animal species. Also, the fact that the complete sequence of steps in the metabolic activation pathway of benzo[a]pyrene to mutagenic and carcinogenic metabolites (diol-epoxides) has been demonstrated in experimental animals, in human tissues in vitro and in exposed humans added to this appraisal.

- **Volume 93 (452 pp)**
  - Carbon black, titanium dioxide, and talc
  - The Working Group found evidence of an association between the use of talc for feminine hygiene and ovarian cancer, and decided that there is limited evidence in humans for the carcinogenicity of perineal use of talc-based body powder. It was evaluated as possibly carcinogenic to humans (Group 2B).
Volume 94 (450 pp)
Ingested nitrate and nitrite, and cyanobacterial peptide toxins

Ingested nitrate or nitrite under conditions that result in endogenous nitrosation is probably carcinogenic to humans (Group 2A).

Although the epidemiological evidence was inadequate (for nitrate in food) or limited (for nitrite in food), the Working Group reached this evaluation considering the following:

There is an active endogenous nitrogen cycle in humans that involves nitrate and nitrite, which are inter-convertible in vivo. Nitrosating agents that arise from nitrite under acidic conditions in the stomach react readily with nitrosatable compounds, especially secondary amines and amides, to generate \( \text{N}^- \text{nitroso compounds} \). These nitrosating conditions are enhanced following ingestion of additional nitrate, nitrite or nitrosatable compounds. Some of the \( \text{N}^- \text{nitroso compounds} \) that could be formed in humans under these conditions are known carcinogens in experimental animals.

Volume 95 (430 pp)
Household use of solid fuels and high temperature frying

About half of the world’s population uses solid fuels for cooking or heating, often in poorly ventilated spaces. Many studies show an association between household use of coal and an increased risk for lung cancer. The Working Group made the following evaluations: indoor emissions from combustion of coal are carcinogenic to humans (Group 1), those from combustion of biomass fuel (primarily wood) are probably carcinogenic to humans (Group 2A). Likewise, emissions from high temperature frying are probably carcinogenic to humans (Group 2A).

Volume 96 (1428 pp)
Alcohol consumption and ethyl carbamate

The Working Group confirmed the carcinogenicity to humans of alcoholic beverage consumption. On the basis of sufficient evidence in experimental animals for the carcinogenicity of ethanol, and in view of the epidemiological evidence showing little indication that the carcinogenic effects depend on the type of alcoholic beverage, the Working Group also concluded that “Ethanol in alcoholic beverages is carcinogenic to humans (Group 1).”

Volume 97 was published during the previous biennium.

Volume 98 (804 pp)
Painting, firefighting, and shiftwork

Occupational exposure as a painter is carcinogenic to humans (Group 1). It causes cancers of the lung and the urinary bladder, as well as mesothelioma. There is limited evidence in humans, based primarily on studies of maternal exposure, that painting is associated with childhood leukaemia.

There is limited evidence in humans for the carcinogenicity of occupational exposure as a firefighter and the Working Group reached an overall evaluation that occupational exposure as a firefighter is possibly carcinogenic to humans (Group 2B).

There is limited evidence in humans for the carcinogenicity of shiftwork that involves night work (e.g. nurses engaged in working the night shift). The notion that disturbance of the internal clock plays a role here comes from studies in experimental animals, where sufficient evidence was found for the carcinogenicity of light during the daily dark period (biological night). The Working Group then reached the following overall evaluation: shiftwork that involves circadian disruption is probably carcinogenic to humans (Group 2A).

Volume 99 (692 pp)
Some aromatic amines, organic dyes and related exposures

The Working Group confirmed the carcinogenicity of several agents that had not been reviewed in detail since Monograph Volume 1 (1972). On the basis of the carcinogenicity of benzidine, the Working Group concluded that “dyes metabolized to benzidine” should also be considered carcinogenic to humans (Group 1). “Occupational exposures of hairdressers and barbers” were evaluated as probably carcinogenic to humans (Group 2A), while “personal use of hair colourants” was considered as not classifiable as to its carcinogenicity to humans (Group 3).

With the publication of these volumes, all Monographs up to and including Volume 99 are now available in print.

Publication of Monographs in electronic form

The complete Volumes 48–99 are now freely accessible on the Monographs’ website as pdf files. Earlier volumes are being scanned and added regularly. In addition, the first parts of Volume 100 have been posted; subsequent parts will follow. The complete Volume 100 (A–F) will be printed as a six book series in the first half of 2012.

Improvement of format and layout of IARC Monographs

During this biennium, the Monographs Programme has invested in state-of-the-art publishing software and technologies to accelerate publication of delayed volumes (see above) and to bring the Monographs series into the 21st century. This was achieved by first integrating the use of an XML-based editorial software that – at the click of a button – copy-edits manuscripts to adhere to the WHO Style guidelines, and, more importantly, checks and corrects references automatically against both PubMed and CrossRef databases. This software also creates valid XML to be used for pagination purposes. Here, the Programme invested in another computer programme, built on industry-standard software that automatically lays out XML content. This was first tested with Volume 96 (> 1400 pp) and took 2.5 hours to paginate automatically, as opposed to the six weeks it would have taken doing it manually.

The IARC Monographs Programme also worked on changing the page size and design for Volume 100 (see example below) and subsequent volumes, introducing changes to adhere to the World Health Assembly resolutions on accessibility of WHO publications to all. The development of the e-book format is currently ongoing. When complete it will be readable on e-book readers, tablets, and smart phones.
improvements have been realized by the IARC Monographs Production Team (Ms Russell, Ms Elbers, Mr L Galichet).

**IARC Monographs Volumes 101, 102 and 103**

During the second year of the biennium, the IARC Monographs Programme resumed its regular schedule of preparing three Monographs per year as follows:

**Volume 101**
Some chemicals in industrial and consumer products, food contaminants, and water chlorination byproducts (Working Group meeting, 15–22 February 2011)

In this Monograph, 18 chemical agents were evaluated. A common feature of these chemicals is that they have all been tested recently in two year bioassays in rodents and found to be carcinogenic. On the other hand, although humans are exposed to these substances, there are so far very few or – for some of the agents – no epidemiological studies available. The list comprised chemicals that are found in industrial and consumer products, some food contaminants, and several byproducts of water chlorination.

For all 18 agents, the Working Group concluded that there was "sufficient evidence of carcinogenicity in experimental animals," leading to an overall evaluation – in the absence of adequate epidemiological information – of possibly carcinogenic to humans (Group 2B). The only exception was 2-nitrotoluene, which was placed in Group 2A (probably carcinogenic to humans) on the basis of mechanistic considerations, and in view of the extraordinarily early onset and high tumour incidence in experimental animals treated with this compound.

Some of the other agents evaluated by this Working Group are:
- 4-Methylimidazole - to which the general population is exposed through its presence in class-III and class-IV caramels, which are widely used colourants, particularly in beverages.
- Di(2-ethylhexyl)phthalate (DEHP) - a widely used plasticiser. The general population is exposed to DEHP through leaching from plastic medical devices, such as blood bags and medical tubing, and as a contaminant of food packaged in DEHP-containing materials.
- Bromochloroacetic acid, dibromoacetic acid and dibromoacetonitrile - which are three of the many chlorination byproducts present in drinking water and in swimming pools.

**Volume 102**
Radiofrequency electromagnetic fields, including microwaves, mobile telephones and radar (Working Group meeting, 24–31 May 2011)

The rapid expansion of wireless telecommunication and other emerging technologies has resulted in widespread exposure of the general public and many workers to the electromagnetic radiation emitted by mobile telephones and other devices.

Uncertainties in the science and its interpretation in relation to possible adverse effects on health have led to different conclusions among the scientific community and to public and media concerns, particularly about a possible risk for cancer.

The Working Group considered the radiofrequency segment of the electromagnetic spectrum (30 kHz-300 GHz) with respect to its possible carcinogenic hazard, and reviewed the following exposure categories:
Bitumens are produced by distillation of crude oil during petroleum refining, and also occur naturally. Bitumens can be divided into broad classes according to their physical properties and specifications required for the different uses. The major use of bitumens is in asphalt for road paving; other uses include roofing, waterproofing, and sealing and painting. Application of bitumens may generate hazardous emissions. The Working Group re-evaluated various occupations that entail exposures to bitumens and bitumen emissions, including road paving, roofing, and application of mastic asphalt and concluded that:

- Occupational exposures to oxidized bitumens and their emissions during roofing are ‘probably carcinogenic to humans’ (Group 2A);
- Occupational exposures to hard bitumens and their emissions during mastic asphalt work are ‘possibly carcinogenic to humans’ (Group 2B);
- Occupational exposures to straight-run bitumens and their emissions during road paving are ‘possibly carcinogenic to humans’ (Group 2B).

**Preparation for Volume 100 follow-up meetings in 2012**

In the future, cancer assessments will increasingly rely on molecular epidemiology and information about mechanisms of carcinogenesis. To this end, Volume 100 has summarized the currently available information on the multiple mechanisms of carcinogenesis for the agents known to cause cancer in humans. This will provide insight into how other agents might cause cancer in humans and will be particularly useful in future assessments of new and untested chemicals, for which two year bioassays and epidemiological studies of cancer are unlikely to be available.

The Monographs developed for Volume 100 contain information that will be synthesized in two future IARC Scientific Publications: *Tumour Concordance between Animals and Humans and Mechanisms Involved in Human Carcinogenesis*. Two workshops will be organized in 2012 to compile these publications, which will develop analyses that address important hazard- and risk-assessment questions and will cut across individual agents to discern more general principles. Because the database for each agent that is classified as carcinogenic to humans is generally detailed and highly informative, these analyses should have a high degree of validity. The main topics in these publications are:

**Tumour concordance between experimental animals and humans.**

This part will compare the tumour sites observed in humans with those in experimental animals. It will explore the circumstances under which it is reasonable to expect analogous tumour sites to occur in different species. It should be noted that specific target sites for tumour formation have been identified for experimental animals since the Volume 100 Monographs, and more systematically for humans since Monograph Volume 83.

Other questions include whether there are good animal models for particular human tumour sites, whether particular tumours in experimental animals have predictive value for human cancer – either at an analogous site or at other sites – and whether different tumour sites tend to occur together. The analyses in this part may be restricted to subsets of carcinogenic agents (e.g. metals, physical agents, hormonal agents, biological agents) or they may be more general in nature.

**Mechanisms involved in human carcinogenesis.** This part will compile the mechanisms of carcinogenesis that are identified in Volume 100. It will be organized by mechanism, not by agent. Joint consideration of multiple agents that act through a similar mechanism could facilitate a more detailed description of that mechanism and its common mechanistic steps. 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 part may also identify biomarkers that could be included in future study designs to provide more reliable information about whether a particular mechanism is operating in either humans or experimental animals.
Preparations to organize these two workshops have been initiated in 2011, in consultation with a small group of experts. The development of the database with the Volume 100 information on the two main topics (concordance/mechanisms) is ongoing. The workshops are scheduled to take place in April and November 2012 at IARC.

**Table 1. High priorities for future IARC Monographs**

| Volume 104 | Polyomaviruses (SV40, BK, JC, and Merkel cell viruses) and malaria  
(Working Group meeting, 7–14 Feb 2012) |
| Volume 105 | Diesel and gasoline engine exhausts and some nitroarenes  
(Working Group meeting, 5–12 June 2012) |
| Volume 106, to be decided |

**Topics for future Monographs (2012)**

- **Volume 104**
  - Polyomaviruses (SV40, BK, JC, and Merkel cell viruses) and malaria
  - (Working Group meeting, 7–14 Feb 2012)
- **Volume 105**
  - Diesel and gasoline engine exhausts and some nitroarenes
  - (Working Group meeting, 5–12 June 2012)
- **Volume 106, to be decided**

**Priorities for future IARC Monographs**

In June 2008, IARC convened an Advisory Group to identify high priorities for new *IARC Monographs* during the next five years. Most of the Advisory Group’s recommendations (Table 1) were new topics that had never before been reviewed by IARC or by other public health agencies. This indicates a high level of interest in the continued work of the *IARC Monographs* to provide authoritative evaluations of new or suspected cancer hazards. Topics that meanwhile have been reviewed are indicated in red.

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IARC (2010). Household use of solid fuels and high-temperature frying. IARC Monogr Eval Carcinog Risks Hum, 95:1–430. PMID:20701241

IARC (2010). Alcohol consumption and ethyl carbamate. IARC Monogr Eval Carcinog Risks Hum, 96:3–1383. PMID:21735939


