Introduction

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The *IARC Monographs*

The *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, published by the International Agency for Research on Cancer (IARC) of the World Health Organization, are a series of scientific reviews that identify the causes of cancer in humans. Since its inception in the early 1970s, the *IARC Monographs Programme* has evaluated more than 1000 chemical, physical, and biological agents and classified almost 500 of these as *carcinogenic*, *probably carcinogenic*, or *possibly carcinogenic* to humans.

Agents are identified as subjects for *IARC Monographs* evaluations based on evidence of human exposure and some evidence or suspicion of carcinogenicity. Agents may be re-evaluated when substantial new information becomes available. Periodically, IARC convenes Advisory Groups of experts from national and international health agencies and from research institutions to recommend agents for evaluation or re-evaluation. Otherwise, agents may be reviewed in response to an urgent public health need.

International, interdisciplinary Working Groups of expert scientists develop each volume of the *IARC Monographs*. IARC selects participants in the Working Groups based on their knowledge and experience, and absence of conflicting interests. Working Group members generally have published research on the carcinogenicity of the agents under review. IARC also gives consideration to demographic diversity among Working Group members and to a fair balance of scientific findings and views. The *IARC Monographs* are a worldwide endeavour that, since 1971, has involved more than 1200 scientists from more than 50 countries.

For each agent, the Working Group writes a critical review of the pertinent studies of cancer in exposed humans, cancer after administration of the agent to experimental animals, and representative mechanistic and other relevant data, as well as general information on the agent and human exposure to it. The Working Group meets at IARC, in Lyon, France, for eight days to discuss the critical reviews and to develop consensus evaluations that classify each agent into one of the following categories:

- *carcinogenic to humans* (Group 1);
- *probably carcinogenic to humans* (Group 2A);
- *possibly carcinogenic to humans* (Group 2B);
- *not classifiable as to its carcinogenicity to humans* (Group 3);
- *probably not carcinogenic to humans* (Group 4).

Each volume of the *IARC Monographs* opens with the Preamble, which describes the objective and scope of the *IARC Monographs Programme*, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered, and the scientific criteria that guide the evaluations (IARC, 2006).

Volume 100: a review of human carcinogens

For Volume 100 of the *IARC Monographs*, a review was undertaken of relevant information on all the agents classified in Group 1 (*carcinogenic to humans*). There was value in such a comprehensive review, because about half of the agents classified in Group 1 had last been evaluated more than 20 years earlier. For advice on the development of Volume 100, IARC convened an Advisory Group (IARC, 2007) chaired by Dr Lorenzo Tomatis, who had founded the *IARC Monographs Programme* and later become the second IARC Director.

Volume 100 follows the practice within the *IARC Monographs Programme* of occasionally updating the evidence for a large number of agents from earlier Volumes. Supplement 1 updated the available data for 54 agents from Volumes 1–20 for which studies of cancer in humans were available, Supplement 4 updated the information for 155 agents from Volumes 1–29, and Supplement 7 reviewed 189 agents from Volumes 1–42 (IARC, 1979, 1982, 1987b). Supplement 7 was preceded by Supplement 6, which updated and summarized the findings from tests for genetic and related effects of the same agents (IARC, 1987a). More recently, Volume 71 updated the evidence for 121 agents, most of them classified in Groups 2A and 2B, by using a mini-*Monograph* format to present the findings for most of these agents (IARC, 1999).

Group 1 agents are diverse and include chemicals and chemical mixtures; occupations; metals, dusts, and fibres; ionizing and non-ionizing radiation; viruses and other biological agents; personal habits; and pharmaceuticals. The precise number of agents classified in Group 1 cannot be given, because generic categories such as "nickel compounds" and "human papillomaviruses" include multiple agents that were evaluated together.

IARC explored ways to strengthen the scientific outcome of Volume 100 (IARC, 2012a, b, c, d, e, f). For several prominent human carcinogens, of which asbestos and benzene are examples, active scientific debate was focused on the implications of mechanistic studies that had not been conceived when these agents had last been reviewed, more than 20 years earlier. For other agents, including alcoholic beverages and vinyl chloride, there were questions about whether additional cancer sites in humans had been established by more recent research. There were also cross-cutting questions about the relevance to humans of certain cancer sites or mechanistic pathways in animals. It was recognized that there would be scientific value in a systematic identification of the cancer sites observed in humans and those observed in experimental animals, and in a compilation of mechanistic events for agents known to cause cancer in humans. The outcome of Volume 100 would thus encompass a bridge from the past focus on cancer studies in humans and experimental animals to a future that promises increasing availability of mechanistic data. Therefore, IARC initially planned the project in two phases: (i) a review of human carcinogens that would accrue information on cancer sites and mechanistic events, followed by (ii) supplementary analyses of tumour site concordance between humans and experimental animals, and of mechanistic events deemed relevant to the carcinogenicity of these agents. The reviews and analyses were discussed during a two-part Workshop on Tumour Site Concordance and Mechanisms of Carcinogenesis, which was convened by IARC on 16–18 April 2012 and 28–30 November 2012 in Lyon. This Scientific Publication is the report of that Workshop.

Scientific Publication on tumour site concordance and mechanisms of carcinogenesis

This Scientific Publication analyses the information on cancer sites and mechanistic events that was documented for the more than 100 agents classified by IARC in Group 1 (*carcinogenic to humans*). The corresponding *Monographs* are organized by agent, with a separate *Monograph* for each agent or group of closely related agents. The chapters of this Scientific Publication are organized in other ways, in order to develop insights about larger groupings of agents, cancer sites, and mechanistic events.

Two data sets bring together information across all Group 1 agents evaluated up to and including Volume 109. The first data set contains the information about cancer sites in humans and in experimental animals (see Annex 1, by Grosse et al.). It is organized to facilitate the investigation of tumour site concordance across species (see the concordance analysis in Chapter 21,

by Krewski et al.). It has long been recognized that concordance between human and animal tumour sites is not evident for carcinogens of all types considered as a single category. Concordance can be analysed for a grouping of agents (e.g. aromatic amines) or for a cancer site (e.g. haematological cancers). Such analyses could explore the predictive value for human cancer of tumours in experimental animals, based on the information collected to date. These types of analyses may also identify human cancers for which there currently are no good animal models; for these cancers, it might be advantageous to focus on understanding mechanistic pathways to design new experimental models that could identify agents linked to these cancers.

The second data set contains the information about established and likely mechanistic events (see Al-Zoughool et al., 2019 and Birkett et al., 2019). It is organized to facilitate the investigation of patterns across mechanistic events and agents (see the mechanistic analysis in Chapter 22, by Krewski et al.). Data can be aggregated for groupings of agents that involve common mechanistic events or common cancer sites. Such analyses could identify biomarkers that could be incorporated into future epidemiological studies. They also could identify populations and developmental stages that may be especially susceptible to the occurrence of certain mechanistic events. Ultimately, they could lead to the confident identification of human carcinogens based on mechanistic information in the absence of adequate cancer studies in humans or experimental animals.

To accommodate the different degrees of precision with which cancer sites have been identified (e.g. "liver cancer" for one agent and "hepatocellular carcinoma" for another), the database uses designations that are more general in nature ("liver cancer" in this example). Likewise, a detailed list of 24 mechanistic events that was initially proposed was subsequently condensed to a set of 10 "key characteristics" (see below). This level of aggregation is necessary to avoid fragmenting the data into large numbers of categories with few data points; this makes it possible to conduct analyses across reasonable numbers of agents. Further research will change our understanding of mechanistic events and will establish additional associations of agents with mechanistic events in the future.

Five additional human carcinogens, identified after the completion of Volume 100, are included in the data set: (i) diesel engine exhaust (reviewed in Volume 105; IARC, 2013), (ii) trichloroethylene (evaluated in Volume 106; IARC, 2014), (iii) polychlorinated biphenyls (PCBs) and dioxin-like PCBs (reviewed in Volume 107; IARC, 2016b), and (iv) outdoor air pollution and (v) particulate matter in outdoor air pollution (both evaluated in Volume 109; IARC, 2016a).

The two data sets are linked. Concordance in the first data set may find support from the mechanistic information in the second. Lack of concordance in the first data set may or may not be explained by the mechanistic information in the second. Accordingly, the analyses in this Scientific Publication do not stop at a superficial analysis of concordance or discordance. They seek to determine whether there is *coherence*, which can be understood as concordance confirmed or discordance explained.

The chapters in this Scientific Publication address what we have learned about some major mechanisms for agents known to cause cancer in humans. The Consensus Statement was unanimously endorsed by the Workshop participants. The chapters in Part 1 discuss various groupings of carcinogenic agents, such as electrophilic agents, metals, constituents of tobacco smoke, and human tumour viruses. These chapters illustrate the types of analysis that can be undertaken for groups of carcinogenic agents, including those that act at a common site or through a common mechanism.

Chapter 10 (by Smith) discusses our observation that all human carcinogens evaluated in Volume 100 (and subsequent *Monographs* as mentioned above) display one or more of what are called key characteristics of carcinogens: is electrophilic or can be metabolically activated to electrophiles; is genotoxic; alters DNA repair or causes genomic instability; induces epigenetic alterations; induces oxidative stress; induces chronic inflammation; is immunosuppressive; modulates receptor-mediated effects; causes immortalization; and/or alters cell proliferation, cell death, or nutrient supply. Chapter 11 (by Stewart) places the key characteristics in the context of other viewpoints, such as the hallmarks of carcinogenesis. Subsequent chapters in Part 2 discuss the role of several of the key characteristics individually, followed by chapters that discuss susceptibility.

The analyses of concordance and mechanisms are presented in the chapters in Part 3. To facilitate similar analyses by cancer researchers worldwide, Annex 1 (by Grosse et al.), Al-Zoughool et al. (2019), and Birkett et al. (2019) provide a description of the databases of concordance and mechanisms that were developed from the information compiled for Volume 100 and for several subsequent Volumes.

We regard this Scientific Publication as the beginning, not the end of the lessons to be learned from the information in Volume 100 of the *IARC Monographs*. We encourage all scientists to continue to analyse these data and to develop further insights into the causes of cancer in humans.

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