

Consensus statement

This statement was unanimously endorsed by the participants in the Workshop on Tumour Site Concordance and Mechanisms of Carcinogenesis, which was convened by IARC on 16–18 April and 28–30 November 2012 in Lyon.

Introduction

The *IARC Monographs Programme* is an international consensus approach to the identification of chemicals and other agents that may present carcinogenic hazards to humans. The *Monographs* assess the strength of the published scientific evidence for such identifications, which are based primarily on epidemiological studies of cancer in humans and bioassays for carcinogenicity in laboratory animals. Information that may be relevant to the mechanisms by which the putative carcinogen acts is also considered in making an overall evaluation of the strength of the total evidence for carcinogenicity to humans.

The use of mechanistic data to identify human carcinogens is accelerating. Initially, the *IARC Monographs*

required *sufficient evidence* in humans to classify an agent as *carcinogenic to humans* (Group 1). Scientific understanding of the mechanisms of carcinogenesis, accompanied by the development of assays for studying mechanistic events, has led to new ways of identifying human carcinogens. Some examples are the following agents that were classified as *carcinogenic to humans*: ethylene oxide (in 1994), based on strong evidence of genotoxicity and limited epidemiological evidence in exposed humans; 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (in 1997), based on strong evidence of binding to the aryl hydrocarbon receptor and subsequent events; neutron radiation (in 2000), based on the underlying radiation physics; benzidine-based dyes (in 2010), because these substances are metabolized to a carcinogen in humans; and several compounds for which single-agent exposure does not exist because they are components of (complex) mixtures, for example tobacco-specific nitrosamines

(in 2007), benzo[*a*]pyrene (in 2010), aristolochic acid (in 2012), and etoposide (in 2012). Mechanistic evidence was also important in classifying the carcinogenicity of several other agents between 2004 and 2010, and in revising the classification of carcinogenicity for several additional agents in Volume 100.

For Volume 100 of the *IARC Monographs*, a review was undertaken during 2008–2009 of relevant information on all the agents classified in Group 1 (*carcinogenic to humans*) in Volumes 1–99. There was value in a comprehensive review, because about half of the agents classified in Group 1 had last been reviewed more than 20 years earlier. Volume 100 was organized in six parts, each prepared by a separate Working Group, covering: pharmaceuticals (Volume 100A); biological agents (Volume 100B); arsenic, metals, fibres, and dusts (Volume 100C); radiation (Volume 100D); personal habits and indoor combustions (Volume 100E); and chemical agents and related occupations (Volume

100F). Volume 100: *A Review of Human Carcinogens* was published in 2012 as a six-book set.

IARC explored ways to strengthen the scientific value of Volume 100, and embarked on a two-phase project: (i) a review of the Group 1 human carcinogens with respect to 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. Accordingly, this Scientific Publication on Tumour Site Concordance and Mechanisms of Carcinogenesis was proposed.

To prepare for the supplementary analyses in this Scientific Publication, IARC had asked the six Working Groups for Volume 100 to collect additional information, not routinely developed before, on (i) cancer sites in humans for which there was *sufficient evidence* or *limited evidence* in epidemiological studies, (ii) cancer sites for which there was *sufficient evidence* in experimental animals, and (iii) established and likely mechanisms involved in the cancers observed in humans or experimental animals.

To further develop this Scientific Publication, the *IARC Monographs Programme* convened a group of international scientific experts in a two-part Workshop on Tumour Site Concordance and Mechanisms of Carcinogenesis, held in Lyon in April and November 2012. The Workshop participants used the lists of mechanistic events to develop a set of key characteristics to define the mechanistic profile of the agents classified in Group 1.

The main points of consensus, the conclusions, and the recommendations of the Workshop participants are described below.

Tumour site concordance

1. The results developed in Volume 100 of the *IARC Monographs* confirm that the induction of cancer in experimental animals is relevant to the identification of a carcinogenic hazard to humans: all human carcinogens identified to date that have been adequately tested in animals have also been shown to cause cancer in animals.
2. For many human carcinogens, there is tumour site concordance between humans and experimental animals; for many others, there is not. At present, the state of the science does not support tumour site concordance as a general principle. For example, there are four agents for which there is *sufficient evidence* for breast cancer in humans and seven agents for which there is *sufficient evidence* for breast cancer in experimental animals, but only one of these agents causes breast cancer in both humans and animals.
3. The analyses presented in this Scientific Publication are expected to underestimate concordance. One reason is the limited power and other limitations of many observational epidemiological studies that include populations and cancer sites that have not been adequately investigated. Another reason is that – for the purpose of this concordance analysis – an agent was considered to cause cancer at a site in animals only if positive results were replicated at the same specific site in another animal experiment (while recognizing the limitations of a single positive result in a cancer bioassay); however, metabolic or mechanistic considerations might explain tumour induction at different sites in separate animal models.
4. Descriptive statistics of tumour sites identified to date may not be representative of future evaluations or of the incompletely characterized “universe of human carcinogens”. The carcinogens evaluated in Volume 100 include several classes of agents that have been relatively straightforward to investigate; some examples are: alkylating agents that were used in early cancer chemotherapy; viral agents that infect hundreds of millions of people; ionizing radiation, which affects multiple anatomical sites; widespread exposures, such as to tobacco smoke and its related agents and alcoholic beverages; and chemical agents with long histories of occupational exposure at high levels. Agents evaluated in the future may have more subtle effects and different characteristics. Evidence from sources other than human epidemiology will need to be relied upon to identify carcinogenic hazards to humans.
5. Past evaluations have noted cancer in experimental animals at approximately 40 tumour sites in 15 organ and tissue systems. Use of standard terminology for these sites can facilitate the development of databases and their analysis and linkage to other sources of information. The Workshop participants recommend that future *IARC Monographs* Working Groups consider the anatomically based taxonomy of tumour sites

that appears in this Scientific Publication in the analysis of concordance between sites where tumours arise in animals and in humans.

6. The Workshop participants also recommend that in future *IARC Monographs*, the Evaluation section for evidence of carcinogenicity in experimental animals be expanded to include additional information for agents evaluated as exhibiting *sufficient evidence*. For such agents, an additional sentence after the relevant evaluation should refer to the recognized site or sites of tumorigenesis, by using the specification system described in the chapter on concordance analysis (Chapter 21, by Krewski et al.).

Mechanisms involved in human carcinogenesis

7. With increasing scientific understanding and availability of information on mechanisms of carcinogenesis, it is expected that the *IARC Monographs* will make even greater use of mechanistic data in identifying human carcinogens.
8. Until now, there has been no generally accepted method for organizing mechanistic data pertinent to the identification of carcinogenic hazards to humans. The key characteristics presented here offer a promising foundation for the structured evaluation of mechanistic information, and this should increase the utility of mechanistic evidence in future identifications of carcinogenic hazards and the transparency

of systematic reviews of such evidence. The Workshop participants recommend that the *IARC Monographs Programme* use the key characteristics in its evaluations of carcinogenicity.

9. It is notable that in vivo or in vitro mechanistic data are often available in humans. In most cases, when animal data are available for a key characteristic, human data for that characteristic are generally available, too. This supports the notion that carcinogens show their characteristics across species.
10. There should be no expectation that all, or even most, key characteristics operate for any human carcinogen. No key characteristic is necessary for carcinogenesis, and negative results for one or more key characteristics are not an argument against the potential carcinogenicity of an agent. Observation of one or more key characteristics in exposed humans can increase the biological plausibility of *less-than-sufficient evidence* in humans. Observation of one or more key characteristics in experimental animals can increase confidence in the human relevance of *less-than-sufficient evidence* in experimental animals. In interpreting the biological relevance of information pertaining to the key characteristics, it is important to consider aspects of metabolism and kinetics in extrapolating between in vitro and in vivo systems.
11. A human carcinogen may display multiple key characteristics that may interact with each other.

The past practice of according greatest concern to those agents demonstrated to be genotoxic, relative to agents whose carcinogenicity appeared to be mediated by one or more other key characteristics, appears to be overly simplistic.

12. The objective of the *IARC Monographs Programme* is to identify carcinogenic hazards, not to exhaustively list all mechanistic events and pathways that might contribute to carcinogenesis. Future coverage of mechanistic data should increase as the retrieval of such data becomes more systematic and the key characteristics are used as a framework for organization and analysis of mechanistic data.
13. Descriptive statistics of mechanisms identified to date may not be representative of future evaluations. Although genotoxicity is the key characteristic most exhibited by the human carcinogens identified to date, this may reflect the relatively greater attention paid in the past to the investigation of genotoxic agents. Future evaluations of carcinogenic agents may involve a larger set of mechanistic events and pathways that are not yet well developed or understood. Accordingly, future shifts in the distribution of the key characteristics are to be expected. This does not detract from the value of using these characteristics now in evaluations of carcinogenic hazards.

