IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 100: A REVIEW OF HUMAN CARCINOGENS

PROJECT PLAN

The *IARC Monographs* are a series of scientific reviews that identify the causes of human cancer. They have been published continuously since 1971 and represent a worldwide effort that has involved more than 1000 scientists from 51 countries. The 100th volume of *IARC Monographs* is a milestone for the series, and a fitting topic for this volume is a review of the human carcinogens that have been identified to date. The 100th volume is intended to serve as a key reference for scientific information about the agents that are known to cause cancer in humans.

Contents of Volume 100

For each agent that is classified as *carcinogenic to humans* (Group 1),[1] Volume 100 will contain a concise *Monograph* that follows the general structure of other *Monographs*. This volume will contain fewer details on each agent than are typically found in other *Monographs*, but there will be no reduction of scientific accuracy or quality.

Section 1. General information, occurrence, and exposure

This section will identify the agent (CAS Registry Number, important chemical and physical properties, common synonyms) and provide information on occurrence and how people can be exposed. To keep this section short, quantitative information will generally be reported in the aggregate, and details will be provided only when there are substantial time trends or differences among countries or exposure pathways. Other sub-sections (analysis and detection, production, regulations and guidelines) will generally be omitted.

Section 2. Cancer in humans

This section will concisely summarize the study design and important results of the epidemiological studies. This section will also identify the tumour sites with *sufficient evidence of carcinogenicity*[2] in humans, as well as tumour sites that are strongly suspected.[3] Studies will be summarized in less detail than in other *Monographs*, but

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[1] ***Carcinogenic to humans*** **(Group 1):** This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity. [Preamble to the *IARC Monographs*, http://monographs.iarc.fr/]

[2] ***Sufficient evidence of carcinogenicity*** **in humans:** The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. [Preamble to the *IARC Monographs*, http://monographs.iarc.fr/]

[3] Care should be taken to ensure that this list does not become static, because carcinogens may affect multiple tissues at different levels of risk or with different latency. Subsequent studies may identify additional tumour sites that had not been recognized previously. The identification of cancer sites is thus a dynamic process rather than a static conclusion, and attribution of cancer risk at certain sites should not be viewed as precluding the possibility that additional sites may be added in the future.

quantitative information will be reported for important design parameters (eg, cohort size, number of cases and controls) and results (eg, relative risk, confidence intervals). When there are numerous studies, the less-informative studies of poor design quality may be omitted. Presentation of results in tabular form will be encouraged.

Section 3. Cancer in experimental animals

This section will concisely summarize the experimental design and important results of the carcinogenicity bioassays. This section will also identify tumour sites with *sufficient evidence of carcinogenicity*[4] in experimental animals. Again, there will be less detail than in other *Monographs*, but quantitative information will be reported for important design parameters (eg, sample sizes, dose levels) and results (eg, tumour incidences, *p*-values). When there are numerous studies, the less-informative studies of poor design quality may be omitted. Presentation of results in tabular form will be encouraged, and a common format for standard bioassay data will be provided by IARC.

Section 4. Mechanistic and other relevant data

This section will provide a concise description of the agent's toxicokinetics, plausible mechanisms of carcinogenesis, and potentially susceptible populations. To keep this section short, it will be in the form of a review article that selects and cites representative studies. It will also be noted where there are substantial data gaps or plausible mechanisms that have not received adequate investigation. Information on structure-activity relationships and toxic effects other than cancer will generally be included only when they are important to understanding the mechanisms of carcinogenesis.

Section 5. Evaluation and rationale

This section will include the standard evaluation statements ("There is *sufficient evidence* . . .") in humans, experimental animals, and overall. There will also be a description of the rationale that the Working Group used to reach its evaluation (generally one paragraph, but it may be longer where an evaluation of *carcinogenic to humans* is reached with less than *sufficient evidence* in humans). There will not be a separate "Summary" section, because sections 1-4 of these *Monographs* will already be concise.

References

This section will list only those studies cited in the other sections.

As is standard practice for all volumes of *IARC Monographs*, Volume 100 will be developed from working papers drafted by the Working Group Members. There will not be much time at the meeting for extensive revision of sections that are deficient or that do not conform to *Monographs* style. Consequently, it is imperative that the working papers at the meeting be of high quality. To facilitate a better understanding of what is expected in this special volume, IARC scientists will prepare a sample *Monograph* to serve as a model for

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[4] ***Sufficient evidence of carcinogenicity*** **in experimental animals:** The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient* evidence. A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites. [Preamble to the *IARC Monographs*, http://monographs.iarc.fr/]

the working papers that Working Group Members will be asked to write. This will include standard templates for the tables where important study details will be summarized.

Length of Volume 100

Volume 100 will contain approximately 100 separate *Monographs*, as there are somewhat more than 100 agents classified as *carcinogenic to humans*. The largest volume of *Monographs* produced to date contains approximately 1500 pages. Volume 100 is to be similar in size, as a result, the 100 *Monographs* of Volume 100 should average less than 20 pages each.

The Advisory Group recommended that it is wise and appropriate to set page limits for each section, recognizing that exceptions will be necessary. They also felt that more than an average of 20 pages would be required unless the reporting style is changed. Because of the large number of studies available for some agents (e.g. tobacco smoking, benzo[*a*]pyrene), even concise tables may not fit within 20 pages. In view of this, Volume 100 will summarize the available epidemiological studies and carcinogenicity bioassays in tables without page limits. The discussion text, however, will have page limits. The following ranges of page limits will be used as a guideline, with the expectation that the typical *Monograph* in Volume 100 will be in the lower half of each range.

1. General information, occurrence, and exposure	1-5 pages
2. Cancer in humans	1-15
3. Cancer in experimental animals	1-5
4. Mechanistic and other relevant data	1-5
5. Evaluation and rationale	1
Total text	5-30 pages
Tables of epidemiological studies	
Tables of carcinogenicity bioassays	
References	

Although it would be possible to include a few *Monographs* of standard length (more than 100 pages each), this would detract from the balanced treatment of all human carcinogens and would make the volume less useful as a reference.

Scientific Publications Related to Volume 100

After the *Monographs* in Volume 100 are developed, two additional Working Groups will be convened to develop related scientific publications that build on the data that will be summarized in Volume 100. These publications will develop analyses that address important 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 extensive, these analyses should have a high degree of validity and could be regarded as definitive. Each scientific publication will be published in a separate volume that will indicate its relation to Volume 100.

1. Tumour-site concordance between humans and experimental animals

This scientific publication will compare the tumour sites observed in humans with those induced in experimental animals. It will explore the circumstances under which it is reasonable to expect analogous tumour sites to occur in different species. 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 publication may be restricted to

subsets of carcinogenic agents (eg, metals, physical agents, hormonal agents, viruses) or they may be more general in nature.

2. Mechanisms involved in human carcinogenesis

This scientific publication will compile the mechanisms of carcinogenesis that are identified in Volume 100. The publication will be organized by mechanism, not agent-by-agent. Joint consideration of multiple agents that act through a similar mechanism could facilitate development of 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 publication 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.

Special considerations

Publication cut-off date. Approximately 100 different agents will be considered in Volume 100, and each has an extensive database. Volume 100 will review the current scientific literature for each of these agents. Consequently, it will be necessary to impose a publication cut-off date for studies to be considered. The date will be approximately one month before each meeting for Volume 100 (see *Monograph* meetings for Volume 100 below). Notice of these cut-off dates will be posted on the *Monographs* programme website approximately 12 months in advance.

Pre-meeting review. To promote working papers that are comprehensive and of high quality, a round of pre-meeting review will occur before the Working Group convenes. Working Group Members will be expected to send preliminary working papers to IARC at least 5 months before each meeting. IARC will send these papers to other Working Group Members for comment, and the original writer will incorporate these comments and send a revised working paper to IARC at least 1 month before the meeting. This additional review before the meeting is intended to ensure that the text receives more review than can be given during the meeting. The pre-meeting reviewers will also be asked to identify key issues so that the meeting can be planned to allow adequate time for each discussion.

Evaluations of occupational exposures. More than 10 occupations have been classified as *carcinogenic to humans* and will be considered in Volume 100. Two issues involving occupational exposures will need special attention. First, important process changes or worker-protection measures may have been introduced, so that the workplace being evaluated in Volume 100 may be different from what was reviewed in earlier *Monographs*. In these cases the Working Group will decide what to retain from the previous evaluation, which may still be applicable to workplaces that have not adopted the modern processes or worker-protection measures. Second, more detailed occupational exposure data may make it possible to attribute a cancer hazard to specific substances rather than to the workplace in general. In these cases it may be more informative to classify the specific substance as carcinogenic, even if it involves a previously unevaluated agent.

Evaluations for new groups of agents. The Preamble states that “when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for his conclusion is added to the evaluation narrative.” There are a few chemical compounds that IARC has classified as *carcinogenic to humans* (eg, benzidine, 2,3,7,8-TCDD) for which there are mechanistic data that have led national health agencies to extend this classification to a broader group (eg, dyes metabolized to benzidine, poly-CDDs). It would be inappropriate to ignore these mechanistic data, but they may lead to the classification of a broader group of agents than before. Advice was sought at the special planning meeting, and the Advisory Group felt that the Volume 100 Working Group should

be cautious in creating new groupings unless they were certain that they reflect the newly available scientific evidence.

Evaluations for new mixtures of agents. There is one case where the US NTP Report on Carcinogens has classified a mixture of agents as "known to be a human carcinogen," while IARC has evaluated only individual components as *probably carcinogenic to humans*: broad-spectrum ultraviolet radiation. Advice was sought at the special planning meeting about whether IARC should evaluate this mixture as well as its components, and the Advisory Group felt it would be unacceptable to constrain the Volume 100 Working Group from determining its presentation of the scientific evidence.

Nomenclature of previously evaluated agents. It has been standard practice for Working Groups to agree on the best name to describe an agent, and these names can evolve when an agent is re-evaluated. For example, "oestrogen-progestin replacement therapy" from Supplement 7 became "post-menopausal oestrogen-progestogen therapy" in Volume 72 and "combined estrogen-progestogen menopausal therapy" in Volume 91. The Working Group for Volume 100 will have the same ability to modify a name when appropriate.

Monograph **meetings for Volume 100** (see also Schedule for Volume 100 Working Group activities)

The list of agents classified as *carcinogenic to humans* is broad and diverse, and each agent generally has an extensive database. Consequently, it will be a monumental effort to develop and produce Volume 100. A large Working Group will be required, and it would be prudent to split the development of Volume 100 over several meetings.

Six meetings over the course of one year will be dedicated to the development of Volume 100. Each meeting will consider a set of related agents and will last 8 days, from Tuesday to Tuesday.

Subject of meeting	Number of agents	Date
A. Pharmaceuticals	23	14-21 Oct 2008
B. Biological agents[5]	11	24 Feb – 3 Mar 2009
C. Metals, particles and fibres	14	17-24 Mar 2009
D. Radiation	14	2-9 June 2009
E. Lifestyle factors	11	29 Sept – 6 Oct 2009
F. Chemical agents and related occupations	34	20-27 Oct 2009

In determining this sequence of meetings, it was noted that volumes 95-99 may be identifying new Group-1 agents or updating existing Group-1 agents and that these will be lifestyle factors, chemical agents, or related occupations. Accordingly, the meetings on

[5] Includes Human herpes virus 8 and Infection with *Clonorchis sinensis*, currently in Group 2A

lifestyle factors and on chemical agents will occur last so that there will be more time to check the final drafts of volumes 95-99, where new *Monographs* for these agents will appear.

As with most *Monograph* meetings, about half the time will be devoted to subgroup work (cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) and half the time will occur in plenary session.

There will be a triage performed on the agents to be considered. Agents that have received a full *Monograph* review during the past few years will generally need little updating. Accordingly, the text for these can be taken from the recent *Monographs* as much as possible, and their discussion is expected to take only a few minutes at the meeting. This will allow more time to be devoted to updating and discussing the agents that have substantial new information, especially those agents that have not been reviewed in many years.

A special planning meeting in September 2006 (see below) recommended agents to be considered in volumes 97-99 as a means of updating some of the more voluminous *Monographs* for Group-1 agents and to allow more time for the others during the meetings for Volume 100.

Working Group for Volume 100

The effort to produce Volume 100 calls for a larger-than-normal Working Group. Because most agents that are *carcinogenic to humans* have an extensive database of epidemiological studies, the Working Group will include a large number of epidemiologists. Instead of the typical Working Group of 20-25 scientists, there should be about 25-35 scientists for each meeting, with about 15 for the epidemiology sections, 5 for the experimental animal bioassays, and 10 for mechanistic and other relevant data. These scientists will generally be senior-level scientists of worldwide renown, and most will have participated in earlier *Monographs* meetings.

Two additional Working Groups will be convened later to develop the scientific publications related to Volume 100. The membership of these Working Groups will be tailored to their more specialized tasks and may include some scientists who participate in developing Volume 100.

The Advisory Group affirmed its support of the rules and policies outlined in the current Preamble regarding the Working Group, especially those that relate to conflict of interest, the role of Observers, and the designation of Secretariat staff.

Special planning meeting

In September 2006 IARC convened a special planning meeting for Volume 100. Participants included an Advisory Group of approximately 13 senior scientists from 8 countries, plus several senior IARC scientists. Participants were selected to be (a) familiar with the current scientific literature on human carcinogens, (b) able to identify controversial issues and areas that will require special attention during the development of Volume 100, and (c) knowledgeable about the *IARC Monographs* programme and the resources needed to carry out this plan.

The objectives of the meeting were:

(1) To review the plans for developing Volume 100.

(2) To make recommendations on the issues identified in an issue paper and on other issues identified by the Advisory Group.

(3) To identify controversies and issues associated with specific Group 1 agents that will require special attention.

(4) To identify potential new Group 1 agents and recommend a few of these for urgent evaluation in Volumes 97, 98, or 99.

(5) To identify existing Group 1 agents that need extensive updating or in-depth review and recommend a few of these for re-evaluation in Volumes 97, 98, or 99.

The report from the Advisory Group has been posted in the *Monographs* programme website (http://monographs.iarc.fr/).

Schedule for Volume 100 Working Group activities

Oct 2007	Preliminary invitations and request for Declaration of Interests sent to potential participants for all six Working Groups
Nov 2007	Six Working Groups selected and writing assignments sent

Meeting A

Apr 2008	Preliminary working papers and reference lists due from Working Group Members
May 2008	Pre-meeting review comments due from reviewers in the Working Group
June 2008	Meeting of an Advisory Group that will include the provisional co-chairs of all six Working Groups. This Advisory Group will review the first sets of working papers and to make final adjustments to the content of the working papers and the conduct of the six meetings. In view of the diversity of this Advisory Group, they will also make recommendations about high priorities for future IARC evaluations. This meeting is being scheduled for 17-20 June 2008, Tuesday through Friday.
July 2008	Revised working papers and reference lists due from Working Group Members
Oct 2008	First meeting for Volume 100

Meetings B and C

Aug 2008	Preliminary working papers and reference lists due from Working Group Members
Sept 2008	Pre-meeting review comments due from reviewers in the Working Groups
Nov 2008	Revised working papers and reference lists due from Working Group Members
Feb-Mar ‘09	Second and third meetings for Volume 100

Meeting D

Dec 2008	Preliminary working papers and reference lists due from Working Group Members
Jan 2009	Pre-meeting review comments due from reviewers in the Working Groups
Mar 2009	Revised working papers and reference lists due from Working Group Members
June 2009	Fourth meeting for Volume 100

Meetings E and F

Apr 2009	Preliminary working papers and reference lists due from Working Group Members
May 2009	Pre-meeting review comments due from reviewers in the Working Groups
July 2009	Revised working papers and reference lists due from Working Group Members
Sept-Oct '09	Fifth and sixth meetings for Volume 100
2010	Return to normal schedule with Volume 101
2010-2011	Two meetings to develop the two scientific publications related to Volume 100

Posted 12 October 2007

Updated 5 December 2007 to make the number of agents reflect the addition of Infection with *Clonorchis sinensis* to Meeting B and the move of Boot and shoe manufacture and repair from Meeting F to Meeting C

Updated 18 February 2008 to make the number of agents reflect the addition of Dyes metabolized to benzidine, 4-4'-Methylene bis(2-chloroaniline) (MOCA), and *ortho*-Toluidine to meeting F (Volume 99 classified these agents in Group 1)