WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

# *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*

## INTERNAL REPORT 05/001

# Report of the Advisory Group to Recommend Updates to the *Preamble* to the *IARC Monographs*

## 4–6 MAY 2005

LYON, FRANCE
2005

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**Acknowledgement**

IARC thanks the German Federal Ministry of Health and Social Security for financial support for this Advisory Group meeting.

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## Introduction

In February 2003 an Advisory Group to determine priorities for future evaluations within the *IARC Monographs* programme (2003 Advisory Group) made several suggestions for revising the Preamble to the series and recommended that a special group be convened to discuss these (IARC, 2003). As a result, a special Advisory Group to recommend amendments to the Preamble met in Lyon on 4–6 May 2005.

This Report summarizes the discussions of the 2005 Advisory Group in response to issues raised by the staff of the *IARC Monographs* programme or the 2003 Advisory Group. Several other issues were added by the 2005 Advisory Group. The opinions and recommendations of the 2005 Advisory Group follow each issue statement. For convenience, the Report is organized according to the sections of the Preamble.

## 1. Background

This Advisory Group recommends that the description of the historical context for development of the *IARC Monographs* programme be expanded. Reference could be made to emergence of the Programme as a response to a request that IARC provide a 'list of carcinogens'. At that time, no adequate criteria were available to generate such a list, and scientists advising the IARC recommended that documentation of all available evidence in relation to potential carcinogens be regarded as the only adequate basis for identifying the carcinogenicity of particular agents.

## 2. Objective and scope

**Background**. The *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* is an international programme on carcinogenic hazard identification that is achieved by the consensus of experts. The long-term objective is to review critically and evaluate the published scientific evidence on carcinogenic hazards to which humans are exposed. These include chemicals, complex mixtures, occupational exposures, lifestyle factors, and physical and biological agents. Each volume of *IARC Monographs* is the product of an international, interdisciplinary working group of expert scientists, who meet for 8 days at IARC to complete their critical review of the scientific literature and develop a consensus evaluation of the weight of the evidence of the carcinogenic hazard for each agent being considered.

**Issue 2a. The 2003 Advisory Group recommended that the relationship of *IARC Monographs* evaluations to public health principles and implementation of public health measures should be addressed in the Preamble.**

This Advisory Group agrees with the 2003 Advisory Group and suggests that IARC focus on the fact that cancer is preventable: the major use of the *Monographs* series was and still is the implementation of preventive measures to lower the global cancer burden. As a result of the *Monographs* evaluations, measures to reduce exposure to occupational carcinogens, tobacco smoke, ultraviolet light, ionizing radiation and other recognized causes of cancer could be justified on scientific grounds.

Prevention of cancer begins with the recognition of causal factors, which must be followed by the identification of communities or individuals at risk and the implementation of appropriate preventive measures. Such measures may range from the elimination of the causal agent by regulation to the encouragement of change of behaviour or lifestyle that could avoid exposure.

To date, more than 900 agents, exposures or mixtures have been evaluated, which has offered a wide spectrum of opportunities for initiatives in cancer prevention.

Complete knowledge of the mechanisms of carcinogenesis is not always necessary to achieve a reduction in or the elimination of exposure to a carcinogenic agent. However, such knowledge can strengthen the scientific basis of risk reduction, especially for susceptible subpopulations.

Consideration may be given to presenting these statements as the opening section of the Preamble (i.e. before the present Section 1. Background) under the heading 'Monographs in the context of cancer control', or similar phraseology.

**Issue 2b. The 2003 Advisory Group considered that 'risk assessment' should be included as a discussion topic in a broad meeting to assess strategic developments of the *IARC Monographs* programme.**

This Advisory Group recommends that, while quantitative information on carcinogenic risks can be useful, a cautious approach should be adopted in including quantitative risk assessment (QRA) in the *IARC Monographs*. Some applications of QRA may require certain assumptions in order to extrapolate from results of high-dose exposure to low doses, from those in animals to humans or from those of occupationally exposed populations to environmentally exposed populations. When information on carcinogenic risks is available from epidemiological studies on the populations of interest, extrapolation outside the range of the available data may not be required. This Advisory Group recommends that IARC confine its potential involvement in QRA to areas where unverifiable assumptions are not required or very limited.

This Advisory Group considered several ways in which the *IARC Monographs* Programme might implement the cautious approach to QRA recommended above. These include (i) the systematic incorporation of quantitative analysis of carcinogenic risk that do not involve extrapolation outside the range of the available data (this is currently provided for within the Preamble), (ii) the inclusion of a new section in future *Monographs* that would summarize data on carcinogenic risks (which would focus on results that involve minimal or no unverifiable assumptions, and could include standardized measures of risk for comparison with other carcinogenic hazards such as summary relative risks from meta-analyses), (iii) the

development of a handbook on cancer risk assessment that would provide guidance on practical aspects of QRA and (iv) the use of a separate group of experts to develop a supplement to a specific *Monograph* that would deal with quantitative risk assessment. (Such supplements would only be prepared in cases where the data were sufficient to assess carcinogenic risks in quantitative terms, and where there was a potential benefit of conducting a detailed, quantitative assessment of risk.) This Advisory Group suggests that these options might be explored more fully in a future Workshop on quantitative assessment of risks for cancer.

Regardless of which of these approaches is adopted, this Advisory Group emphasizes that any initiatives taken by the *IARC Monographs* Programme in the area of quantitative assessment of risks for cancer should be firmly based on science. This Advisory Group also notes that the development of a programme in QRA will require specialized expertise and a significant commitment of resources.

**Issue 2c. The 2003 Advisory Group recommended that a paragraph be added in the Preamble to outline the limitations of risk assessment statements, which — in contrast to hazard evaluations — pertain to specific populations, regions and exposure conditions.**

This Advisory Group notes that characterization of risk, which combines information on dose–response relationships with levels of human exposure, can vary between populations and with exposure conditions, making an overall characterization that would be applicable globally difficult to achieve.

This Advisory Group notes that the limitations and uncertainties in all aspects of carcinogenic risk assessment, including risk estimation and hazard identification, should be documented as fully as possible. This Advisory Group recommends that variation in risk among subgroups of populations (defined in terms of susceptibility, region and exposure conditions) be described.

**Issue 2d. The 2003 Advisory Group proposed consideration of appropriate changes to the Preamble to address the relationship of evaluations in *IARC Monographs* with those of other organizations. The 2003 Advisory Group also noted that the organization of a meeting on this topic with other evaluating authorities would be useful.**

**Note.** The May 2005 meeting included scientists from several of these organizations (NTP, US EPA, California EPA, German MAK, and EC European Chemicals Bureau), and points to include in these statements were developed at the meeting.

This Advisory Group considers that no changes to the Preamble are needed to clarify the relationship of IARC evaluations with those of other organizations, since it falls outside its scope. This Advisory Group agrees with the 2003 Advisory Group that convening a meeting on this topic could be useful. A meeting of representatives from the different organizations involved to discuss and compare their various systems would provide insights into and may lead to the improvement of carcinogen evaluation, and perhaps move toward harmonization where warranted. The development of a paper for publication in a scientific journal that compares and describes the various classification systems for carcinogens would

also be of interest to users of the *Monographs* and other available programmes that identify cancer hazards.

## 3. Selection of topics for the Monographs

**Background.** Agents are selected for evaluation based on (i) evidence of human exposure and (ii) some evidence or suspicion of carcinogenicity. Agents and exposures can be re-evaluated if significant new data become available. Periodically, IARC convenes Advisory Groups to advise on priorities for future evaluations or re-evaluations. These Advisory Groups consist of scientists from national and international health agencies and research institutions, and include scientists from as many countries as possible. Seeking such advice is designed to ensure that the *IARC Monographs* reflect the current state of scientific knowledge and remain relevant to national health agencies and to the research and public health communities. Between Advisory Group meetings, additional guidance may be received from the IARC Scientific Council and the IARC Governing Council. Suggestions for new topics are welcome at any time.

**Issue 3a. As the list of agents reviewed by the *IARC Monographs* continues to expand, there will occasionally be a need to clarify some particular aspect of the carcinogenic hazard of an exposure (e.g. specific to a given route, such as through water, or a particular population, such as children). How should the IARC determine when to choose to evaluate such studies and how should they be presented? Should this be mentioned in the Preamble in this Section?**

This Advisory Group had considerable discussions on this issue, and tried to clarify when the IARC should undertake such restricted evaluations. The general conclusion of this Advisory Group is that reviews by the IARC should be as complete as possible, using all available data for a given monograph. However, this Advisory Group recognizes that, on occasion, the IARC may need to clarify one aspect of the carcinogenicity of an agent and concluded that this type of monograph, on a limited basis, would be useful and informative. However, when summarizing the results of such a review in the 'List of agents evaluated by the *IARC Monographs*', this Advisory Group cautions having separate entries for each sub-review. The basis for this caution is the concern that, by listing the carcinogenicity for a specific route or for susceptible subgroups of the population, inference would be drawn that other routes or subgroups may be considered to be free of a cancer hazard, which is generally not the intent. This Advisory Group feels that this type of evaluation could be mentioned in the Preamble in Section 3 as an evaluation that will occur 'on a limited basis'.

## 4. Data for the Monographs

**Background.** The monographs include a critical review of each pertinent epidemiological study and long-term carcinogenesis bioassay, plus a summary of selected significant information on human exposure and mechanisms of carcinogenesis. Scientific articles published or accepted for publication are eligible for consideration. Reports and documents from national and international government agencies are considered if they are available publicly. Consensus reports in the published literature are also considered, subject to the same scrutiny as other articles, including consideration of the compo-

sition and balance of the panel that produced the consensus. Research that is not available publicly, including articles in preparation or under review, is not considered.

**Issue 4a. Should working groups continue to consider only publicly available scientific literature, plus articles accepted for publication?**

**Note.** From time to time the Programme receives consultant reports and draft manuscripts that support a particular view. Sometimes the submitter wants to send these directly to Working Group members. The Programme has discouraged these efforts and has asked Working Group members to disregard papers that are not in the public domain.

This Advisory Group supports the general principle that publicly available scientific literature is the predominant source of information considered in the *Monographs*. Raw data that have not been published should not be used.

**Issue 4b. Should there be an explicit, general statement regarding abstracts and PhD theses?**

**Notes.** The Preamble does not mention abstracts, and working groups have used abstracts on a case-by-case basis.

In most cases, abstracts do not provide enough unique information to contribute to an evaluation. Most abstracts are only summaries of posters or talks that appear in the proceedings of a meeting but are not published in peer-reviewed journals. In contrast, some abstracts contain detailed information, and sometimes an abstract provides the first credible indication of a possible cancer hazard.

The criteria for exceptions described in the Preamble should include detailed abstracts and PhD theses that are exceptionally needed for an evaluation.

**Issue 4c. It is difficult to evaluate properly agents for which some pertinent studies have not been published in the scientific literature.**

**Note.** Recent disclosures have revealed cases of pharmaceuticals and pesticides for which pertinent positive studies were not published and not disclosed. An evaluation of carcinogenicity or a summary of other toxic effects may be misleading if important positive studies are not available. Unlike the question of 'publication bias' (which refers to whether non-positive studies are less likely to have been published), there are no statistical methods to analyse whether missing positive studies are likely to be important. The Programme invites discussion on how to conduct credible evaluations of these agents.

With respect to proprietary or confidential data presented in documents published by other institutions, *Monographs* working groups should judge the appropriateness of their use on an ad-hoc basis. The IARC may specify the criteria for inclusion or exclusion of publications in the openly available scientific literature further and find ways in which the use of proprietary or confidential studies may also be considered.

**Issue 4d. The 2003 Advisory Group recommended that the need to refer 'post-evaluation' literature references to the IARC should be emphasized in the Preamble more prominently and specifically than is presently the case.**

**Notes.** A question is whether to make a list of post-evaluation literature available on the IARC website. This could be useful information, but there is also the potential for abuse if one party submitted articles that support only one side of an issue. The Programme does not have the resources to do independent literature searches on agents that have been evaluated in the past.

An intermediate position would be to list only newer studies from sources generally recognized as authoritative, e.g. from the NTP.

Another use of submitted post-evaluation literature would be to keep them for IARC's consideration in future decisions about whether to re-evaluate the agent.

This Advisory Group feels that maintaining an up-to-date, publicly available literature review of all publications on every agent evaluated in the *IARC Monographs* Programme would be burdensome and of little immediate value. This Advisory Group supports the procedure of archiving submitted post-evaluation literature to be available for IARC's consideration on future decisions regarding re-evaluations.

## 5. The Working Group

**Background.** Two principles govern the selection of working groups: (i) to invite the best-qualified experts and (ii) to avoid real or apparent conflicts of interests. Consideration is also given to demographic diversity. Members are chosen on the basis of knowledge and experience, which can come from research into the specific agents to be evaluated or from general experience in conducting or evaluating epidemiological or experimental studies. The working groups are international in nature; a typical working group comprises approximately 20–25 expert scientists from 8–12 countries. To promote consistent evaluations and efficient meetings, some effort is made to include a few scientists who have had prior experience at *Monographs* meetings.

**Issue 5a. The 2003 Advisory Group recommended that the procedure to select and invite *Monographs* meeting participants be described in detail in the Preamble.**

**Note.** The IARC proposes incorporation into the Preamble of some text from Cogliano *et al.* (EHP 2004), which explains that working groups are selected to invite the best-qualified experts and to avoid real or apparent conflicts of interests. It also discusses the roles of Invited Specialists, Observers, Representatives of national and international health agencies, and the IARC secretariat. The Preamble would also mention that participants' names are listed on IARC's website before each meeting and would stress that participants should not be contacted or lobbied.

This Advisory Group recommends inclusion in the Preamble of text from Cogliano *et al.* (EHP 2004), which explains that working groups are selected to invite the best-qualified experts and to avoid real or apparent conflicts of interest. This would include a definition of the roles of Members, Invited Specialists, Observers, Representatives of national and inter-

national health agencies and the IARC Secretariat. A description in the Preamble of the recently adopted procedure of listing participants' names on the IARC website before each meeting (together with the statement that participants should not be contacted or lobbied) is supported. However, as this procedure is relatively recent, the subsequent Preamble meeting (December 2005) may wish to consider any additional experience gained by the IARC in the intervening period. This Advisory Group also feels that the term 'Invited Specialist' is confusing since all Working Group Members are invited and specialists and suggests that IARC consider an alternative name.

**Issue 5b. Should Invited Specialists be permitted to write text on mechanisms and other relevant data (Section 4)?**

**Notes.** An Invited Specialist is an expert with critical knowledge and experience who is recused from certain activities because of a real or apparent conflict of interests. These activities include serving as meeting Chair or Subgroup Chair, drafting text that discusses data on cancer or contributes to the evaluations (Sections 2–4 and 5.2–5.5) and participating in discussions on the evaluations. Invited Specialists are present during Subgroup and Plenary discussions to contribute the benefit of their knowledge and experience.

Allowing Invited Specialists to write Section 4 would be a relaxation of this policy. In the case of agents for which most of the mechanistic research has been supported by an industry that has an interest in the outcome of the meeting, many of the experts who had published these results would be designated as Invited Specialists. Under current policy, this leaves fewer experts to write working papers. If an Invited Specialist were needed to write part of Section 4, this could, perhaps, be accepted on an exceptional basis, with an explanation in the List of Participants discussing the circumstances.

On the other hand, the use of mechanistic data to raise or lower an overall evaluation can be a major source of controversy. Working Group members who are not experts on mechanisms, as well as most readers of the Monographs, rely on Section 4 as a comprehensive and balanced review of the subject. If someone linked to the affected industry wrote this review, there could be a loss of public confidence in the impartiality of the *Monographs*.

This Advisory Group supports the practice of 'Invited Specialists'. An Invited Specialist is a person with critical knowledge and experience who is recused from certain activities because of a real or apparent conflict of interest. To allow invited specialists to write text for Sections 2, 3 or 4 would be a relaxation of current policy. This Advisory Group recommends that IARC continue its current policy not to allow invited specialists to write any section other than Section 1.

**Issue 5c. The 2003 Advisory Group recommended that the issues of 'bias of opinion' and 'conflict of interests' be discussed in the Preamble.**

**Note.** IARC proposes the incorporation into the Preamble of some text from Cogliano *et al.* (EHP 2004) to discuss the WHO *Declaration of Interests* and its use in determining appropriate limitations on an expert's level of participation. It also discusses the importance of identifying the pivotal issues in advance and

convening a Working Group that includes a balanced representation of all scientific views.

This Advisory Group recommends the incorporation into the Preamble of some of text from Cogliano *et al.* (2004) that deals with conflict of interests and apparent conflict of interests, and refers to the WHO Declaration of Interests procedure and its use in determining appropriate limitations on an expert's level of participation. This should not be too detailed, because consistency with WHO procedures (currently under revision) needs to be maintained.

**Issue 5d. Should *Monographs* working groups continue to include scientists who have done research on the topic being evaluated?**

**Notes.** Some people have claimed that the inclusion in a Working Group of authors of papers that are being evaluated is a scientific conflict of interests, and that these authors should not be permitted to judge and vote on the validity of their own hypothesis. In addition, it was claimed that the mere presence of such authors would have a chilling effect on any critical discussion of their findings by other Working Group members.

IARC notes that allowing the experts themselves to write the critical reviews and consensus evaluations is often regarded as one of the strengths of the Programme and distinguishes the *IARC Monographs* from some other programmes on carcinogen identification.

One strength of the *Monographs* process is that reviews are written and evaluated by experts of worldwide standing who have done research on the agent being considered; this practice should continue. The inherent difficulty of a real or perceived bias caused by Working Group members being involved in the evaluation of their own data is recognized. This Advisory Group considers that it would be inappropriate for individual members both to draft initially and then review text discussing their own work, which could detract from the essential peer-review status of *Monographs* evaluations. However, this Advisory Group considers that specification in the Preamble of a particular restriction may not be appropriate and could lead to reduced expert input into the *Monographs* evaluation process. The lack of such a restriction does not preclude action being taken by the IARC to ensure that bias is prevented and scientific peer review is maintained. The Agency may wish to clarify further measures that could be adopted to reduce any perception of bias as discussed above.

**Issue 5e. Should there be public nominations of potential *Monographs* Working Group members? If so, how?**

**Note.** A member of the IARC Governing Council suggested this change. The programme is interested in a discussion of how this could be achieved while avoiding a public debate on Working Group membership.

This Advisory Group considered the desirability of calling for public nominations for potential *Monographs* Working Group members. At present, Working Group members are selected by IARC on the basis of their relevant scientific expertise and lack of conflict of interests. The current selection process has resulted in past *Monographs* Working Groups being comprised of leading scientific authorities in areas of critical importance to the successful evaluation of the carcinogenic potential of the agent in question.

This Advisory Group notes that the receipt of public nominations for *Monographs* Working Group members offers may potentially broaden the selection process, either through a targeted call for nominations from knowledgeable organizations worldwide or through an open call for nominations posted on the IARC website (both options could also be implemented simultaneously). This Advisory Group feels that seeking outside nominations could reduce the possibility of perceptions of bias in the selection process. However, it was not clear to this Advisory Group whether a fully open public nomination process, which could involve a not insignificant addition to the workload in screening the nominations received, would substantially enhance the quality of Working Group membership. If a public nomination process were adopted, this Advisory Group recommends that it not be exclusive and that IARC be allowed to make the final decisions on the choice of *Monographs* Working Group members drawn from internally identified experts as well as public nominations.

In the light of the preceding considerations, this Advisory Group does not recommend that the procedure of a call for public nominations be incorporated into the Preamble at this time. However, this Advisory Group suggests that IARC consider the possibility of incorporating public nominations into the selection process for *Monographs* Working Group members on a non-exclusive, trial basis. This Advisory Group is also concerned that a call for public nominations could result in a large number of biased or less qualified persons applying.

## 6. Working procedures

**Background**. The *IARC Monographs* are published as a series of volumes. Each volume is developed by a separate Working Group at an 8-day *Monographs* meeting. A volume can contain one or more monographs, which can cover a single agent or a group of related agents. Each monograph generally includes the following sections:

1. Exposure data
2. Studies of cancer in humans
3. Studies of cancer in experimental animals
4. Other data relevant to an evaluation of carcinogenicity and its mechanisms
5. Summary of data reported and evaluation
6. References

Before each meeting, Working group members critically review the literature and write first drafts of Sections 1–4. IARC formats these first drafts for review at the meeting.

The objectives of the meeting are review and consensus. The first days of the meeting are devoted to Subgroup work. Four Subgroups, each responsible for one section, peer-review the individual members' drafts, develop a joint revised draft and then write the summaries that become Section 5. During the final days of the meeting, the Subgroups come together in plenary session. The entire Working Group peer-reviews and reaches consensus on the critical reviews in Sections 1–4 and discusses and reaches consensus on the summaries and partial evaluations proposed by the Subgroups. The Working Group then develops and reaches consensus on an overall evaluation of each agent.

After the meeting, IARC scientists review all data cited by the Working Group in their final draft to ensure scientific accuracy and clarity. IARC then publishes and distributes the finished volume.

**Issue 6a. The Preamble suggests that participants are selected approximately one year in advance and that *Monographs* are published 6 months after a meeting.**

**Note.** For many years, these time estimates have not been realistic. The Programme would like to achieve more timely publication of the *Monographs*, but proposes replacing the specific time estimates with less precise but more accurate phrases such as 'before the meeting' and 'after the meeting'.

This Advisory Group agrees with the current time frame (approximately 1 year in advance) used by the IARC as guidance in selecting participants for a *Monographs* Working Group meeting. This Advisory Group also feels that it is appropriate to provide some aspect of this time frame in the Preamble. However, given the historical publication time frame for the *Monographs*, the Group feels that the current Preamble is too prescriptive in describing when a volume will appear following a *Monographs* Working Group meeting; this Advisory Group therefore suggests that this limit be changed to a more reasonable time frame or be dropped completely. This Advisory Group recommends that IARC make an effort to return to a prompt (approx. 6 months) publication time frame.

**Issue 6b. The Preamble states that industry sources may assist in preparing sections on production and use. The IARC has received letters from some parties who claim that the Preamble requires interested industry sources to assist in developing opinions on adverse health effects.**

**Note.** The programme would like to clarify that industry involvement (i) is not required and (ii) is limited only to sections on production and use.

The Preamble clearly states that scientists from industrial associations 'may assist' in the preparation and does not imply this is a requirement. However, there is some room for clarification in this part of the Preamble and IARC is encouraged to do some modest re-writing of this text. This Advisory Group suggests expanding representation to be inclusive of not only industrial sources but also other directly interested parties such as environmental groups and national authorities.

**Issue 6c. Peer review**

**Notes.** The *IARC Monographs* can be described as a peer review of the publicly available scientific literature on a topic. All text in sections 1–4 is peer-reviewed at the *Monographs* meeting. Section 5 is the consensus expert opinion of the peer reviewers who have discussed the scientific literature throughout the 8-day *Monographs* meeting.

It should be noted that WHO regulations specify, "The text of an expert committee report may not be modified without the committee's consent."

This Advisory Group acknowledges and affirms that peer review is the primary criterion and standard for scientific integrity. In its most widely used scientific context, peer review typically involves assessment of manuscripts submitted for publication in scientific journals. This normally necessitates that 2–3 scientists review a manuscript, and there is no requirement for agreement between such referees.

*IARC Monographs* evaluations are the outcome of scientific discussions among 15 or more scientists and each stage of the process may involve consultation and agreement between various members of the Working Group or the Working Group as a whole. Sub-groups of the Working Group produce evaluative documents that are discussed and reviewed at length in plenary by the other members of the Working Group. Subsequently, IARC staff (who have not otherwise drafted the material in question) review the final drafts to ensure the quality of the information in each monograph.

In as much as the content and evaluations reached in the course of *IARC Monographs* Working Group meetings are totally dependent on the outcome of deliberations by many Working Group members, the Monographs attain, and indeed exceed, the standard normally required for peer review. The status of the *Monographs* as a peer review document is hereby asserted by an independent group of experts not convened for the purpose of making a *Monographs* evaluation. This assessment is not that of the IARC staff or of the organization as a whole, but is itself a peer review made by the present Advisory Group, which is a group of international scientists owing no allegiance to IARC except for an implicit commitment to maintain the excellence of the *Monographs* Programme. The convening of such a Group maintains the Agency's tradition of seeking external input for all aspects of the Programme.

Literature search and retrieval processes are sufficiently rigorous that it is highly unlikely that important studies are missed.

Finally, the exceptional nature of the development and deliberative process of the *Monographs* goes far beyond the usual peer review process used by scientific journals. This Advisory Group does not recommend that IARC undertake any further peer review of the draft than already occurs through the *Monographs* process, and does not recommend that the Preamble be modified to discuss peer review.

Evaluations are open to peer-review and other criticism, but it is not practicable to re-convene any *Monographs* Working Group to respond to disputed evaluations. Strictly speaking, peer review of a *Monographs* evaluation would require the deliberation of a comparable group of international experts, as distinct from any individual evaluation. It is arguable, therefore, that 'totally independent' peer review of *Monographs* evaluations is not feasible. This constraint, in the view of this Advisory Group, does not detract from or qualify its conclusion that *Monographs* evaluations are correctly regarded as outcomes of a peer-review process.

## 7. Exposure data

**Background.** Each monograph begins with a section that describes the agent's physical or chemical properties, its production and uses, analytical methods for its detection and measurement, its occurrence in the environment and in the workplace and existing national regulations that are applied to it. This information does not contribute to the evaluation of its potential carcinogenicity. Unlike the sections on cancer in humans and cancer in experimental animals, this section does not need to be a comprehensive review of the literature but should give a good representation of all WHO regions.

**Issue 7a. Information on exposure is sometimes difficult to find, especially from developing countries.**

**Note.** The programme invites suggestions on how to increase the comprehensiveness of this section.

This Advisory Group notes the existence of several national databases that may prove useful in assessing and placing bounds on the range of environmental exposures. Such databases are generally limited to chemicals, and contain little or no information on exposure to biological or physical agents.

A list of databases maintained by the United States Environmental Protection Agency (US EPA) is available. Data related to agents in air, water, food and soil can be useful in the estimation of individual exposures and in some cases those of populations. Other countries have compiled similar databases that could be consulted. The IARC is encouraged to solicit such information from Participating States and pursue the identification of these resources. This Advisory Group especially emphasizes the importance of obtaining data from developing countries, where high exposures that occur may be overlooked. Such exposure data may also prove useful to epidemiologists in the planning of future studies.

The IARC is also encouraged to collaborate with other UN agencies such as WHO/IPCS, UNEP and ILO.

## 8. Studies of cancer in humans

**Background.** Cohort studies, case–control studies and ecological studies of cancer are generally the major contributors to the evaluation of human evidence. Studies of preneoplastic lesions and measurements of biological markers (e.g. DNA or protein adducts) and markers of early stages of carcinogenesis (proto-oncogene mutations) are also reviewed.

**Issue 8a. Given the development of the field of molecular epidemiology since the last update of the Preamble, should there be guidance on consideration of these data? If so, what?**

**Note.** This is a new and evolving field for which no standard approaches to evaluation have been developed. Specific guidance may be useful for promoting consistent approaches by different working groups.

Molecular epidemiology uses molecular biomarkers of exposure, genetic susceptibility and intermediate end-points. Most of these data should be mentioned in Section 8 (c) of the Preamble 'Inferences about mechanism of action', which already includes similar statements, and contribute to Section 4, 'Other data relevant to an evaluation of carcinogenicity and its mechanisms' in a monograph.

Uses of molecular epidemiology for hazard identification and evaluation include:

– the use of biomarkers of internal dose (e.g. DNA adducts) that can reinforce exposure assessment and comparison with animal data;

– the use of end-points markers of intermediate (also known as early-effect biomarkers) such as mutations, chromosomal aberrations or genomic instability that

help to clarify the mechanistic pathways and increase comparability between animals and humans;

- genetic susceptibility (through, e.g. Mendelian randomization and the study of gene–environment interactions) that can increase the biological plausibility of associations by showing that its modulation of risk is consistent with the expected causal pathway; and
- other markers relevant to the study of infectious agents involved in carcinogenesis and markers of inflammatory or immunological responses.

This Advisory Group suggests that a special meeting be organized to explore the potential use of newer markers such as gene expression, promoter methylation and proteomics/metabonomics in the evaluation process. It is stressed that the contribution of such tools should be evaluated with the same degree of stringency as that used for the evaluation of the epidemiological and animal data. The meeting could update recent Workshops held at IARC on biomarkers, with a specific focus on carcinogen identification and evaluation.

Molecular epidemiological data that identify populations that are more susceptible than others to the agent(s) to be evaluated may be important for the identification of carcinogenic hazards to humans. It should be noted, however, that data on genetic susceptibility usually originate from multiple comparisons arising from subgroup analyses. This can generate false-positive results and inconsistencies across studies, and such studies therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent to be evaluated, these data can serve as additional evidence for causality.

**Issue 8b. Where is the best place to report preneoplastic lesions and markers: Section 2 (Cancer in humans) or Section 4 (Mechanistic and other relevant data)?**

**Note.** The Preamble suggests that these data can appear in Section 2, but in practice they generally appear in Section 4.2 (Toxic effects). The rationale is that data on preneoplastic lesions and markers provide indications of mechanisms but do not generally contribute to the evaluation of evidence in humans. If understanding has evolved to the point that preneoplastic lesions and markers can affect the evaluation of evidence in humans, perhaps these data should appear in Section 2. If not, this statement in the Preamble should be changed to be consistent with current practice.

Studies of preneoplastic lesions (such as colorectal adenomas or oral lesions in humans) that have clearly been associated with the development of malignancies may be — and have been — considered in Section 2 (Cancer in humans) and may serve — and have served — in the evaluation of human data. With regard to molecular epidemiological data, markers of internal dose can be included in Section 1 when they are measured in the context of exposure assessment, in Section 2 (‘Studies of Cancer in Humans’) when they are measured in the context of an epidemiological study of cancer or in Section 4 (‘Mechanistic and other relevant data’) when the main focus is on their role in mechanisms of carcinogenesis. Similarly, markers of intermediate end-points and studies on genetic susceptibility could be included both in Section 2 when they are studied in the context of epidemiological studies of cancer and in Section 4 when the main focus is on mechanisms.

### Issue 8c. Meta-analysis of population-based studies

Repeated population-based studies of the same agent may lead to results that are ambiguous. Combined analyses of data from multiple studies have been proposed as a means of resolving this ambiguity.

Two types of combined analysis can be conducted: the first involves combining summary statistics such as odds ratios from individual studies and the second involves a pooled analysis of the raw data from the individual studies. The former approach will be referred to as a meta-analysis and the latter will be referred to as a pooled analysis.

The main advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore interactions and modifying effects that may explain heterogeneity among studies in more detail. The main disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, data collection procedures, measurement methods and effects of unmeasured co-variates that may differ among studies. Despite these limitations, combined analyses, when conducted wisely, can provide a firmer basis for drawing conclusions about potentially carcinogenic agents than individual studies.

It is recommended that the Preamble encourage the use of combined analyses within the Monographs. However, it is important that the same criteria for data quality as would be applied to individual studies be applied to combined analyses, and that such analyses take heterogeneity between studies into account.

Meta-analyses may occasionally be conducted by Working Group members during the course of preparing a monograph, and are identified as original calculations by placing the results within square brackets [...]. These may be de-novo analyses or updates of previously conducted analyses that incorporate the results from new studies. Whenever possible, however, it is preferable that such analyses be conducted prior to the Working Group meeting, either by members of the Working Group or under contract with an expert in this area. Publication of the results of such meta-analyses prior to or concurrently with the *Monographs* Working Group meeting is encouraged for purposes of peer review.

## 9. Studies of cancer in experimental animals

**Background.** Two-year carcinogenesis studies in rats and mice are generally the major contributors to the evaluation of evidence in animals. Studies of administration with co-carcinogens, studies of pre-neoplastic lesions and studies of metabolites and other chemical derivatives are also reviewed.

Depending on the outcome of issue 12d, it may be appropriate to expand this section to include additional study designs.

### Issue 9a. Meta-analysis of animal experiments

Meta-analyses of animal experiments are conducted less frequently than those of population-based studies, largely because of differences in animal species and strains. Because of the use of high doses, experiments on animal carcinogenesis tend to exhibit less ambiguity than population-based studies, and thus the need for meta-analyses to resolve ambiguities is reduced. These observations do not preclude the use of meta-analytical methods to interpret

animal data; however, if such analyses are conducted, they should meet normal standards for data quality.

## 10. Other data relevant to an evaluation of carcinogenicity and its mechanisms

**Background.** The evaluation also considers mechanistic and other relevant data. These include toxicokinetics (absorption, distribution, metabolism and excretion), acute and chronic toxic effects other than cancer, reproductive and developmental effects, genetic and related effects, and information on potential mechanisms for the observed carcinogenic responses.

**Issue 10a. Given the increased understanding of mechanisms of carcinogenesis since the last Preamble update, should there be additional guidance? If so, what?**

**Note.** This is an area requiring considerable judgement, and specific guidance is useful for promoting consistent approaches by different working groups. In contrast, the field is still evolving, and too much detail will soon become outdated. Historically, the Preamble has discussed general principles that are expected to be applicable for many years.

This Advisory Group finds that no definitive guidance can be specified on interpretation of data, because of the wide spectrum of possible mechanisms and the degree to which they may or may not be understood, the relatively rapid developments in the field and the expanding nature of the mechanistic data available. The scientific judgements made by a Working Group during a *Monographs* meeting should reflect the state-of-the-art at the time. Section 4 of the *Monographs* should discuss critically the evidence on mechanisms of carcinogenicity as it pertains to the overall evaluation of carcinogenesis, in the perspective of and in parallel with the discussion of animal and human data in Sections 2 and 3. Section 4 provides the basis for the evaluation of other relevant data in Section 5 in terms of whether there is strong, moderate or weak evidence that any carcinogenic effect observed is due to a particular mechanism; evaluations may also include judgements of whether the mechanisms are similar or different in animals and humans, and within the human population. It is therefore essential that Section 4 provide a critical review of the data on which to base such evaluations. In this regard, this Advisory Group recommends that the guidance given in section 10 of the Preamble for developing the section on 'Other relevant data' in the Monographs (Section 4) be more extended.

This Advisory Group recommends that the procedures for *Monographs* evaluations be modified to provide for a statement regarding evidence of a carcinogenic mechanism (that is, evidence presented in Section 4). The scope of such evidence is unlimited, and the type of studies that may be deemed relevant is continually expanding. Such evidence would at least include toxicokinetics, cellular changes such as DNA binding or induction of DNA damage , alterations in gene expression, such as changes in the expression of tumour suppressor genes and oncogenes, and enhancing effect of the agent on cell proliferation. Where relevant, the literature cited in Section 4 and used to evaluate mechanisms may include studies initially cited in earlier sections, such as molecular epidemiological findings.

For the evaluation of data on mechanisms of carcinogenesis, no elements are available to provide definitions analogous to the categories of sufficient and limited used in Sections 2

and 3. Therefore, it is suggested that these terms should not be used in the process under discussion in Section 4. However, agreement may be reached on the strength of evidence that establishes the mechanism(s) by which a particular agent causes or is likely to cause cancer. It is suggested that the evaluation statement refer to strong, intermediate or weak evidence that a carcinogenic process(es) is induced by the agent under evaluation.

A wide spectrum of possible mechanisms of carcinogenesis has been identified but is still subject to expansion. Some well-recognized pathways to malignant transformation have given rise to widely used terminology such as 'genotoxic' and 'epigenetic'. While the use of such terms may allow unification of many different types of investigation, they should be employed with caution. For example, reference to genotoxicity could include exposures, agents and their metabolites that do not modify DNA *per se* but may result in genomic changes through the production of secondary DNA-reactive intermediates (e.g. reactive oxygen species). Some guidance on how to specify mechanisms clearly would be useful in the Preamble.

The evaluation statement may be made in terms of strength of evidence either for or against a specific mechanism. It may also refer to evidence that the mechanism(s) of carcinogenesis is similar or different in animals and humans, and even within the human population.

This Advisory Group notes that availability of an evaluation of mechanistic data may potentially provide different means to reach the overall evaluation. The overall evaluation may be reached by a comprehensive consideration of all three evaluations (i.e. those related to human carcinogenicity, animal carcinogenicity and mechanism) rather than the present process in which a default evaluation is upgraded or downgraded on the basis of conclusions reached on the mechanism.

**Issue 10b. In order to put more emphasis on relevant mechanistic considerations (Section 4.5), should the sections on toxicokinetics (Section 4.1), toxic effects other than cancer (Section 4.2), reproductive and developmental effects (Section 4.3) and genetic effects (Section 4.4) be shortened to resemble review articles?**

**Note.** Many readers use the *Monographs* as a general reference on toxic effects, and the programme has historically had an interest in covering toxic effects other than cancer, especially reproductive and developmental effects. Nevertheless, Sections 4.1–4.4 have been growing and sometimes constitute more than half of the references and pages of a monograph, although the evaluation is determined by the studies of cancer in humans (Section 2) or experimental animals (Section 3). This leads to two problems. (i) At the meeting, the lengthy review of Sections 4.1–4.4 leaves little time for discussion and joint development of Section 4.5. (ii) In the published monograph, the lengthy presentation of Sections 4.1–4.4 may create a misleading impression of the relative importance of the different lines of evidence and hinder a reader from identifying the key studies among the many reported. What are the benefits of an encyclopaedic study-by-study review of other relevant data? Should some effort be made to reduce the number of studies reviewed or the level of detail reported for each study?

Data on reproductive, developmental and other toxic effects are summarized in a monograph in Section 4 'Other data relevant to an evaluation of carcinogenicity and its mechanisms'. These data are included even when the observations have no apparent relevance to

the cancers observed in epidemiological studies or cancer bioassays. Although the *IARC Monographs* may be a convenient source of such data for some users, the development of these reviews for the *Monographs* can be distracting and may consume more time and resources than are justified by its relevance to the evaluation. The literature for the section must be found and compiled, the section must be written and, at the meeting, the IARC Working Group must review, discuss and agree to its content. The section also has to undergo fact and data quality checking by IARC staff. A related point is that data for certain types of genetic and related effects were found in the consensus report of an IARC symposium to be unsuitable for classifying or predicting carcinogenic hazard, even though they are commonly summarized in the *Monographs* (McGregor *et al.*, 1999). This Advisory Group recommends that IARC need the advice given by this symposium, together with more recent knowledge, and consider limiting the scope of the review to those tests that are considered to be potentially relevant to cancer hazard identification.

This Advisory Group recommends restructuring Section 4 to focus on those data that are critical to the evaluation of carcinogenicity. As an example for monographs on chemical substances (to be discussed by IARC), this Advisory Group considered the following outline for the section on 'Other relevant data', and emphasizes that this is provided as an illustration of an approach, and not an endorsement of any specific outline.

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms
4.1 Pharmacokinetic data
4.2 Mechanistic data
4.3 Data on susceptible individuals, populations and life stages
4.4 Relevant data on toxicity
4.5 Additional relevant data

As in current *Monographs*, Section 4.1 would describe the available basic information on absorption, distribution, metabolism and excretion in animals and humans, and could include more specific information on the saturation of such processes, cross-placental transfer and other issues pertinent to interpretation of the studies and the evaluation of carcinogenicity. However, this section would no longer include a detailed study-by-study description. Instead, it would emphasize features that are critical to the interpretation of human and animal carcinogenicity studies and to the overall evaluation of carcinogenicity for the agent in question, and would take the form of a critical review of the data.

Similarly, Section 4.2 would provide a critical review of the mechanistic data relevant to the evaluation of carcinogenicity. In addition to genetic and other data, Section 4.2 may also include, among others, data on gene expression, alterations in tumour-suppressor genes, oncogenes and growth-controlling pathways, modulation of DNA repair, epigenetic effects, alterations in post-translational modification of proteins, apoptosis, cell immortalization, angiogenesis, metastasis and stroma interaction (see Hanahan & Weinberg, 2000). Certain types of genetic and related effects that are generally felt to be unsuitable for classifying or predicting carcinogenic hazard (see e.g. McGregor *et al.*, 1999) would not be included.

Section 4.3 would be reserved for a critical review of data that have a bearing on the identification of susceptible populations — both animal and human — for example, with respect to genetic effects, age, disease status or other factors. When data are available, these may elucidate further the interpretation of results reported in Sections 2 and 3.

Section 4.4 would provide a critical review of toxicological data that are relevant to the evaluation of carcinogenicity such as information on systemic exposure, possible target organs, immunotoxicity (which may also be relevant to Section 4.2) and endocrinal effects.

To the extent that effects on reproduction, teratogenicity and other developmental effects may be informative for a particular evaluation, they may be noted.

Section 4.5 would review any other additional relevant data that are not included under the earlier sections.

**Issue 10c. Should there be a new sub-section (Section 4.6?) on biologically susceptible populations and life-stages?**

> **Note.** National health agencies have become interested in identifying susceptible populations and life stages. Mechanistic data are increasingly available to suggest which populations and life stages may be particularly susceptible to the carcinogenic activity of an agent.
>
> The recent monograph on human papillomaviruses (Volume 90) included the following evaluation that refers to a susceptible population: "There is *limited evidence* in humans for the carcinogenicity of HPV genus-beta types in skin (squamous-cell carcinoma). In the rare case of epidermodysplasia verruciformis patients, there is compelling evidence for the carcinogenicity of HPV genus-beta types 5 and 8 in skin (squamous-cell carcinoma)."

As outlined above, Section 4.3 would address this issue. This Advisory Group notes that the field is undergoing extensive research and the data presented in Section 4 should emphasize cases where there is evidence of defined populations or individuals at increased risk. See also Issue 8a.

## 11. Summary of data reported

> **Background.** At the meeting, Sections 5.1–5.4 are written to summarize the information reviewed in Sections 1–4.

**Issue 11a. Should the summaries include a limited number of key citations?**

> **Note.** The Preamble does not mention this practice, but summary sections have traditionally not included citations. For example, a typical sentence might read, "Several case–control studies and two cohort studies reported increases in risk for oral cancer." The intention is to make the summaries easy to read. The current practice could be improved by including enough additional information to allow a knowledgeable reader to identify the study specifically without giving the reference (for example, "a cohort study of electronics workers in New York"). In contrast, a citation is unambiguous to the knowledgeable and non-knowledgeable reader alike.

One of the reasons for including key citations in the Summaries is to provide more transparency regarding the basis on which the Working Group reached its conclusions. However, this Advisory Group notes that Section 5, which summarizes the relevant human, animal and other pertinent data and provides the IARC overall and specific summary evaluations, is easily readable. The language is clear and in a form that is easily perused. Section 5 can therefore be used to communicate the findings of an IARC monograph to the public, and provides some general background on the basis for the IARC findings. Addition

of references will make the summary less readable for the general public. Nevertheless, when data sets are large and complicated, it can be difficult to determine from the summaries which studies were pivotal to the conclusions of the Working Group, and which received less weight. Further, nowhere does a Monograph give the full logic of the Working Group's considerations in weighing data and deciding on the different categories of evidence. This Advisory Group recognizes the value in providing greater explanation and transparency on the Working Group's deliberations in the monograph, and recommends that this be done. This should be done without including citations in the final summary.

This Advisory Group discussed different ways of describing and presenting the Working Group's evaluation and weighing of the evidence. One approach would be to include new subsections at the end of Sections 2, 3 and 4, which would provide summaries and integrative evaluations of the data presented. In this subsection, the data would be summarized with references and an explanation given of how the Working Group reached its decision. An alternative possibility would be to provide a detailed overall summary of the evidence, with references, together with the weighing of the evidence, in a section preceding the current Section 5.5. Such a section could be part of the existing Section 5, or included in a section possibly entitled 'Considerations of the Working Group'. This Advisory Group does not endorse either of these but provides them as examples for IARC's consideration. This point is discussed further under issue 12d.

## 12. Evaluation

**Background.** The Working Group reaches a consensus evaluation through a stepwise process that reveals the weight given to each line of evidence. There are separate evaluations of the evidence for cancer in humans and cancer in experimental animals, each choosing one of the descriptors *sufficient evidence*, *limited evidence*, *inadequate evidence* or *evidence suggesting a lack of carcinogenicity*. The evaluation of human evidence is based on whether a causal interpretation is credible and whether chance, bias and confounding can be ruled out with reasonable confidence. The evaluation of evidence in experimental animals is based on whether positive findings were observed in multiple test systems or indicate an unusual result. The partial evaluations are combined into a default evaluation that the agent is *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) or *probably not carcinogenic to humans* (Group 4). The mechanistic and other relevant data are then considered to determine whether the default evaluation should be raised or lowered.

**Issue 12a. Clarify whether National Toxicology Program (NTP) studies in male and female rats and mice should be regarded as independent studies capable of providing *sufficient evidence.***

**Note.** Some Working Group members recently refused to recognize these as 'independent studies' because they were carried out at the same time in the same laboratory using similar protocols.

This Advisory Group recommends that the Preamble be updated so that the finding of carcinogenicity in both sexes of the same species tested in a good laboratory practive (GLP) study that satisfies internationally accepted guidelines or a study of comparable validity could

be treated as providing sufficient evidence. The emphasis should be on whether the body of animal data as a whole supports a finding of causality in animals. Currently, a finding of sufficient evidence of carcinogenicity in animals usually requires unequivocal findings of carcinogenicity in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. This statement is unclear as to whether studies of both genders conducted concurrently in the same laboratory should be treated as independent.

The criteria for sufficient evidence for carcinogenicity in experimental animals were adopted before the current, very extensive GLP studies were devised. GLP studies that adhere to internationally accepted guidelines are well designed and well conducted, and the findings are carefully reviewed. National Toxicology Program (NTP) studies meet these criteria. The NTP Technical Reports and findings are subjected to expert peer review in a public forum and are exposed to formal public comment. Considerable confidence should therefore be placed in findings of clear evidence from NTP studies, as much, for example, as in a single bioassay with a finding of unusual tumours. This Advisory Group therefore recommends that IARC update its criterion on reproducibility for sufficient evidence of cancer in experimental animals and state clearly that GLP studies in both sexes of a single species may be considered as independent.

In addition, given the increased quality of bioassays today, this Advisory Group recommends that IARC expand cases in which a single, well-conducted study provides the basis for an evaluation of sufficient evidence to include strong findings of tumours at multiple sites. Currently, a single study in one species might be considered to provide sufficient evidence when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset. The category ‘multiple sites’ could be added to this list. The use of unusual findings is discussed in the Preamble as an exceptional case. However, the language ‘to an unusual degree’ is sufficiently restrictive to limit the use of findings in single studies and denoting it as an exception does not appear to be necessary.

**Issue 12b. Should there be additional guidance regarding unusual tumours in experimental animals or, more generally, on the use of historical control information to evaluate unusual tumours?**

**Note.** A recent evaluation stalled on the questions of what the Preamble means by ‘unusual’ and whether a particular tumour type should be considered as unusual.

The proper use of historical control data in interpreting the results of animal carcinogenesis bioassays has been a subject of some controversy. When historical control data are highly variable, it has been argued that treatment-related increases in tumour incidence that fall within the historical control range are within the limits of experimental variability, and thus do not necessarily constitute evidence of increased risk for cancer. However, the large variation seen among historical studies may be attributed to factors that affect between-study variation but not within-study variation, which represents the appropriate error term for interpreting a current experiment.

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a current experiment. These methods assign the appropriate weight to historical and concurrent controls, on the basis of the extent of between-study and within-study variation. When historical control data demonstrate a high degree of variability, these methods assign little weight to the historical data in the assessment of dose–response

within a current experiment. When the historical data exhibit little variability and demonstrate tumour-response rates similar to those in the concurrent control, these methods assign much greater weight to the historical data by effectively increasing the size of the concurrent control group.

Because of the potential for misinterpretation of information on historical controls, it is recommended that the Preamble provide guidance on the proper use of historical control data in interpreting the results of laboratory experiments. These methods can be particularly useful in interpreting rare outcomes.

**Issue 12c. The definition of *evidence suggesting lack of carcinogenicity* states that this conclusion is inevitably limited to the "species, tumour sites and levels of exposure studied." Should "age at exposure" be added to this list?**

**Note.** Several studies and analyses have shown that age at exposure is a factor in carcinogenesis, especially during perinatal development.

This Advisory Group agrees that 'evidence suggesting lack of carcinogenicity' should include restrictions regarding the limits set on the interpretation of this finding. While 'age at exposure' could be added, so could a number of other items such as susceptible groups studied (in humans and genetically modified mice) or route (in both humans and animals). The IARC is encouraged to add 'age at exposure' as an element to consider in evaluating both human and animal data and to choose careful rewording to note that other limitations apply to the data set as well.

**Issue 12d. In the time since the Preamble was last updated, an *IARC Scientific Publication* has recommended that mechanistic information be considered in evaluating the evidence of carcinogenicity in experimental animals.**

**Notes.** The consensus report of *IARC Scientific Publication* No. 146 (McGregor *et al.*, 1999) concluded [page 5]:

"Many of the assays described above contribute to the assessment of carcinogenicity in experimental animals. In the absence of data from conventional long-term bioassays of carcinogenesis or from assays with neoplasia as the end-point, consistently positive results in several models addressing several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals."

The Programme invites discussion on updating the definitions of *sufficient evidence* and *limited evidence* in experimental animals to characterize better an agent that displays the hallmarks of a carcinogen in mechanistic studies, but for which lifetime bioassays have not been conducted (and may never be conducted). This could allow pertinent mechanistic information (reviewed in Section 4) to contribute to the evaluation of evidence in experimental animals when long-term bioassays are not available (reviewed in Section 3).

The consensus report of the *IARC Scientific Publication* on the use of data from short- and medium-term bioassays and genetic effects studies in carcinogenicity evaluation (McGregor *et al.*, 1999) noted the following:

> "The numbers of adequately designed, executed and described rodent carcinogenicity tests… have been falling in recent years, and experiments performed and published by academic investigators are now unlikely to be so-called standard two-year bioassays. Thus, the traditional source of experimental evidence for carcinogenicity on which the *Monographs* Programme has historically relied is beginning to disappear, while advances in understanding chemical carcinogenesis have led to the use of short- and medium-term assays with end-points of neoplasia or lesions that are precursors to neoplasia."

This report reviewed various animal models that use neoplasia or preneoplasia as the end-point (transgenic and knock-out mice, non-mammalian systems) and assays for cell proliferation and cell death. Some types of study were found to provide greater evidence of carcinogenicity than others. The symposium concluded that, "in the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models addressing several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals." The group also concluded that for established models of initiation–promotion, the appearance of tumours after exposure to a chemical that was used as an initiator provided evidence of carcinogenicity in rodents. Further, certain other established models in which preneoplastic lesions were produced were considered to be highly predictive of rodent carcinogenicity, and the additional observation of promoting activity was deemed to make the evidence compelling.

The IARC symposium mentioned above was convened in 1997 and further scientific developments that have occurred since that time have increased the body of test systems that provide evidence of possible carcinogenicity in humans. However, data from new bioassays of carcinogenesis in mammalian and non-mammalian species cannot be accommodated within the current IARC classification scheme. This Advisory Group recommends that IARC consider modification of this scheme to accommodate such data.

New whole-animal test systems could be described in Section 3 (Studies of cancer in experimental animals) and given a preliminary evaluation by the subgroup that discusses animal data. Further general guidance on the inclusion of such data and subsequently on how the more varied body of data might lead to an evaluation of sufficient evidence of carcinogenicity in experimental animals would be needed in the Preamble.

In addition to the evidence from whole-animal studies, various *IARC Scientific Publications* and other authoritative reviews support the notion that possible carcinogenicity can be assessed on the basis of other relevant data. For example, the US NTP Report on Carcinogens allows the classification of an agent as 'reasonably anticipated to be a human carcinogen' on the basis of mechanistic and structure–activity data alone. Similarly, an agent for which there is 'less than sufficient evidence' from animal studies (including inadequate evidence) and strong evidence from other relevant data could potentially be classified by IARC in Group 2B if the Preamble were modified. This Advisory Group recommends that IARC consider changing the Preamble to reflect this possibility, also taking into account issues discussed in 10a.

**Issue 12e. The 2003 Advisory Group recommended that information on the target organ for cancer be included when possible in future evaluation statements. They recommended that this issue be addressed in the Preamble, specifically with reference to the evaluation of epidemiological data and the use of a specific format for the statement of such information.**

**Note.** The format endorsed by the 2003 Advisory Group would provide a general sentence on the epidemiological evaluation, followed by a separate sentence to specify the target organ(s) or tissue(s), as in the statement for solar radiation (Volume 55):

"There is *sufficient evidence* in humans for the carcinogenicity of solar radiation. Solar radiation causes cutaneous malignant melanoma and nonmelanocytic skin cancer."

This Advisory Group endorses the recommendation made by the 2003 Advisory Group.

**Issue 12f. The 2003 Advisory Group proposed that the specific criteria for re-evaluation of agents to a category of higher or lower concern — which are outlined in various *IARC Scientific Publications* — be included in the Preamble.**

This Advisory Group disagrees with the 2003 Advisory Group on this issue. It is felt that, in most cases, a re-evaluation of an agent by IARC would be conducted in the context of a new monograph on that agent and the criteria set forth in the Preamble would apply. Adding specific criteria from *IARC Scientific Publications* would unduly burden the Preamble with a number of issues that would possibly be revised by future IARC workshops and scientific publications and would warrant more frequent changes to the Preamble. This Advisory Group considered that a general statement suggesting that, where appropriate, *Monographs* working groups that review agents for which data are available that may include topics that are also covered in an *IARC Scientific Publication* will be provided appropriate guidance from that publication, would be sufficient.

**Issue 12g. Do the evaluations (Section 5.5) provide enough discussion to explain how the Working Group reached its conclusions?**

**Notes.** A typical evaluation section is a series of statements in the form:

There is *limited evidence* in humans for the carcinogenicity of [agent].

There is *limited evidence* in experimental animals for the carcinogenicity of [agent].

[Agent] is *possibly carcinogenic to humans (Group 2B)*.

The Preamble does not specify how much discussion to provide, but standard practice has been rather uniform across *Monographs*. The choice between *sufficient evidence*, *limited evidence*, *inadequate evidence* and *evidence suggesting lack of carcinogenicity* is almost never explicitly discussed. The choice between Groups 1, 2A, 2B, 3 and 4 is generally not discussed if the final evaluation is the default evaluation. If the final evaluation is either raised or lowered after consi-

deration of mechanistic and other relevant data, then an explanation is added. The explanation is generally between two and 15 lines long.

When an agent is re-evaluated, there is generally no comparison of the previous and new evaluations. For example, in Volume 88, formaldehyde, was judged to have *sufficient evidence* in humans for the first time. Without an explicit comparison of the old and new evaluations, there has been some misunderstanding and mischaracterization of the basis for the new evaluation. In another example, in Volume 60, the classification of styrene was raised from Group 3 to Group 2B because styrene is metabolized to styrene-7,8-oxide, which was found in the blood of exposed workers together with DNA adducts, haemoglobin adducts, DNA damage and chromosomal damage, but a re-evaluation in Volume 82 does not mention why these other relevant data did not affect the later classification into Group 2B.

This Advisory Group is of the opinion that the *Monographs* would be improved if information describing the manner in which evaluations were derived with respect to carcinogenicity in humans, carcinogenicity in animals and any evidence of a mechanism were added. Information provided in this context should not necessarily be limited to a specific line of argument favouring the overall evaluation reached, but should, where relevant, indicate differences of scientific view that became evident in the evaluation process. To that extent, the relevant text would have to be drafted and approved by the Working Group after the overall evaluation was reached.

It is proposed that a summation of the Working Group deliberations should not involve detailed argument, but a broad statement of the principal line(s) of argument that emerged. No specific language or terminology is proposed. The section should be brief but should include significant statements and a reasonable indication of the key arguments.

The text proposed for inclusion could follow the evaluation statements in Section 5.5 and might be part of that Section, or might merit a new subheading immediately preceding the evaluations.

The heading ‘Overall evaluation’ should be immediately above, and should include the overall evaluation statement only.

**Issue 12h. When there are strongly held differences of opinion on the overall evaluation, should the evaluation section present only the majority position?**

**Note.** The title page of each volume states, “This publication represents the views and expert opinions of an IARC Working Group...” and the Preamble does not mention this practice. The majority opinion is generally the only one presented, regardless of whether it represents a unanimous consensus or a sharp division decided by one vote. This practice provides for clear-cut classifications with no distinction between, e.g. strong 2As and weaker 2As. In contrast, the state-of-the-science sometimes includes more than one opinion. Some Working Group members have objected to the inclusion of ‘minority reports’, while other Working Group members have complained when alternative scientifically reasoned views are not mentioned.

This Advisory Group feels that the current practice of presenting only the majority opinion in the overall evaluation is the best approach in virtually all cases and that the

Preamble should not be changed substantively. It is anticipated that, when minority views exist, they will be discussed in the integrative section outlined under issues 11a and 12g. This Advisory Group also feels that it is important that IARC provide some guidance on how to describe the extent of disagreement, if any.

**Issue 12i. Is additional characterization needed to clarify what is meant when an agent is classified in Group 3?**

**Notes.** Group 3 is a broad classification, covering agents with positive results that are not adequate for Group 2B, agents with negative results that are not adequate for Group 4, agents that have not been studied adequately for any hint of a conclusion and agents that have been studied adequately to form a conclusion that the mechanisms of carcinogenicity in experimental animals do not operate in humans. Does the Group 3 classification need further discussion in the Preamble? In the individual monographs?

Nevertheless, some clarification is needed to ensure that a Group 3 classification is not mistaken for a determination of non-carcinogenicity or overall safety. For example, several internet pages have appeared with titles such as "IARC scientists confirm safety of mineral wool insulation." A picture of a bare-skinned baby lying on a roll of pink insulation accompanies one such page, suggesting that IARC found no concern even for skin irritation. The Programme proposes the addition of a paragraph to explain that an evaluation of *not classifiable* is not a determination of safety for either cancer or effects other than cancer, and that further testing for carcinogenicity may be needed, especially when exposure is widespread.

This Advisory Group does not feel that additional clarification is needed in the Preamble to explain the broad range of reasons why agents appear in Group 3. However, the Group feels that some clarification could be provided to indicate that categorization into Group 3 is not equivalent to overall safety and the IARC is encouraged to make these changes in both the Preamble and the individual volumes (e.g. in the Note to the Reader).

## Other issues

**Issue 13a. Should the title be changed to "*IARC Monographs on the Evaluation of Carcinogenic Hazards to Humans*"?**

**Notes**. It is a major matter to change the title of a serial publication. The current title is well known, and frequent title changes can be disruptive to library indexing systems. Nevertheless, over the years since the *IARC Monographs* began, the term 'hazard' has evolved to mean a qualitative assessment of whether an agent can cause cancer at some dose, while the term 'risk' has come to mean a more quantitative assessment that considers hazard, dose–response and exposure.

The title has been changed twice in the past. Volumes 1–16 were entitled '*IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*'; Volumes 17–42 were entitled '*IARC Monographs on the Evaluation of the Carci-*

> *nogenic Risk of Chemicals to Humans*'; and Volumes 43–90 were entitled '*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*'.
>
> The *IARC Monographs* have evaluated carcinogenic hazards, not carcinogenic risks, so the current title can be misleading. Conversely, if there is a strong possibility of including some elements of quantitative risk assessment in the near future [taking into account the outcome of the discussion of Section 2 of the Preamble on objective and scope], then the current title would be descriptive of these expanded monographs.

The *Monographs* series is widely referred to and known as a series on hazard evaluation although the title, '*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*', indicates risk. In the vernacular of public health professionals, 'carcinogenic risk' is a quantitative term, and means the chance or probability that an individual will develop cancer under defined conditions. In general usage, 'risk' can be a qualitative term that refers to the possibility of harm, both in English and when translated into different languages.

This Advisory Group does not feel there is sufficient justification to change the title of the *Monographs* at this time. While the use of 'hazard' in the title would be more precise technically, it would also be somewhat disruptive. For example, it would require that libraries change their indexing of the series. There are a few instances in which a quantitative dose–response assessment was published in a monograph, and there is the possibility that IARC may include more such characterizations in the future. This is discussed under Issue 2b above. The *Monographs* also contain a section on exposure, another component of the risk-assessment process.

**Issue 13b. Terminology**

> **Notes.** Some text in the Preamble still refers to 'chemical compounds', which reflects the programme's origins in evaluating chemicals. The Programme proposes substituting the word 'agent' where appropriate.
>
> Over the years since IARC first used the term, 'strength of evidence' has taken on a negative connotation that is often used pejoratively to depict an evaluation that considers only positive studies and not the non-positive or negative studies. This is not what IARC intended, and it is not what IARC does. The Programme proposes to change 'strength of evidence' to 'weight of evidence' as a generally recognized term that more clearly reflects IARC's evaluation process.
>
> The Programme would also be interested in advice about whether the phrases 'evidence of carcinogenicity' and 'evidence for carcinogenicity' are perceived as equivalent, or whether one phrase is more likely to be interpreted as meaning the evidence from positive studies only.

This Advisory Group supports the use of the term 'agent' in place of 'chemical compound', since there are numerous examples of carcinogens (such as viruses and radiation) that are not chemicals.

This Advisory Group discussed the terms 'strength of evidence' and 'weight of evidence' at some length, but was unable to establish a preference for either of the two terms. This Advisory Group recommends that IARC review the scientific and possibly common use

of these two terms, and other similar terms, to determine which is best suited to the *Monographs*.

This Advisory Group does not see any substantive difference in meaning between the phrases 'evidence of carcinogenicity' and 'evidence for carcinogenicity'.

### Issue 13c. Research needs

> **Note.** The Preamble [Section 2] "The *Monographs* may also indicate where additional research efforts are needed." In practice, this generally does not happen. The Programme intends to ask future working groups to identify research needs and would be interested in some discussion about where to present this information and in what form.

This Advisory Group feels that the wording used in the current Preamble is adequate. In discussing where to place research recommendations, this Advisory Group considered that these were implicit in the overall evaluations and did not feel that there was a need for a separate section on this issue. Considering the magnitude of the effort needed to complete a *Monographs* evaluation, this Advisory Group suggests that IARC continue to treat inclusion of research recommendations as an option.

## References

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