IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
ADVISORY GROUP TO RECOMMEND UPDATES TO THE *PREAMBLE*
Lyon, France: 4-6 May 2005

Comments from recent meeting chairs and subgroup chairs on the 1991 version of the *Preamble*

Introduction

Scientists who have chaired an *IARC Monographs* meeting have an important perspective on how the principles and procedures described in the *Preamble* work, and whether they reflect best scientific practice.

In March 2005, IARC asked meeting chairs from the past 10 years and subgroup chairs from the past 5 years for suggestions about what to revise, based on their experience. If someone's expertise covered carcinogenic agents other than chemicals, IARC also asked where the *Preamble* could be broadened to better cover these other agents.

After allowing 5 weeks for response, IARC compiled the comments received and organized them according to the sections of the *Preamble*. This report contains those comments. A table at the end identifies the scientists who were surveyed and who responded.

These comments were considered by the Advisory Group to recommend updates to the *Preamble*, which met during 4-6 May 2005.

General comments

Detmar Beyersmann:
In general, I feel that the preamble is excellent and still is valid in most aspects.

Dudley Goodhead:
Having now re-read the existing Preamble, I must admit that no particular needs for change have come to mind. It is several years since I chaired a Monograph evaluation working group and no burning issues regarding the Preamble have remained in my mind from that time; we had no difficulties with it.

Nigel Gray:
I really would only have reservations about sections 8 and 12. The rest still looks pretty good.

Manolis Kogevinas:
The IARC Monographs are an extraordinary important activity that has given wide credibility and recognition to IARC and, more importantly, has served at the international level for the identification and prevention of cancer and as one of the most authoritative sources of information on carcinogenic agents. However, some of the procedures followed by the Monographs are clearly obsolete and correspond to evaluation procedures used in earlier

times. I refer particularly to the closed nature of the procedures that may correspond to an obsolete view about IARC's role in the international society as a whole. The evaluation procedure should have been much more open to the international community. It is surprising that IARC has not done this re-evaluation of the Preamble earlier and to this extent I consider this review of the Preamble as timely and extremely important.

Douglas McGregor:

I've mentioned "transparency" twice in this message. If you think this important (I'm sure you do), then a third suggestion would to see where this element might be improved throughout the Monographs.

Tony Miller:

I have been through the preamble and was reminded how complete it was! Having chaired the first working group on biological agents (HBVs) I was reminded again that it served us well, even then. So, I do not have any suggestions for change!

Benedetto Terracini:

In my mind the preamble is OK and the Monographs program also.

1. Background

Jerry Rice:

Add references to Monographs Programme book-length review documents related to updates of criteria for mechanism-based evaluations, including "Peroxisome Proliferation" (a technical report); Capen et al., IARC Scientific Publications No 147 (1999); "Forestomach and Gastric Neuroendocrine Tumours" IARC Technical Publication No 39 (2003).

2. Objective and scope

Detmar Beyersmann:

For some agents, quantitative risk estimates are feasible. Even if IARC would not make such estimates of their own, it would assist the users of the Monographs if such estimates would be reported in the Monographs. Furthermore, in some cases data are accumulating that point to thresholds for non-genotoxic agents. Again, if IARC would not draw conclusions themselves, such information could be reported.

Erik Dybing:

Since the Monographs Programme (so far) only has dealt with hazard identification, I suggest that the name of the programme should be changed to 'IARC Monographs Programme on the Evaluation of Carcinogenic Hazards to Humans'.

An important part of hazard assessment is hazard characterisation which involves potency consideration. So far, the Programme has not dealt with potency *per se*, which I think is a limitation. I suggest that for the future, the Monographs should also address the potencies of the agents under evaluation, for individual chemicals this could include presenting TD50, T25 and/or LED10 values. I here refer to the IPCS draft report on dose-response modelling which you know all about. A simpler descriptor would simply be the LED values for the various agents in the different test systems, as is already done for mutagens.

Len Levy:

I would also pay more attention to the value and use of mechanistic data as I do believe it can supply better answers to true human risk and allow reduction of exposure measures to be applied where they really will make a difference to the human cancer burden. To emphasize the point, I have just read today that in the UK, male lung cancer rates for the last decade have been drastically reduced reflecting the reduction in smoking, whereas for women the results are not so encouraging, but also reflecting the smoking patterns. One very important aspect of the IARC evaluations for me is to get more into true cancer risk rather than cancer hazard so that we can direct attention to where exposure reduction can make a real difference.

Damien McElvenny:

Are there circumstances in the absence of dose-response data in humans, where dose-response data from animal experiments might be used to estimate possible dose-response relationships in humans?

Given the information on exposures and production and use, should attempts be made to estimate a geographical and possibly temporal distribution of cases attributable to the carcinogenic exposure of interest?

Would it be worth making a statement on an exposure level below which there is no prima facie evidence for carcinogenicity?

Hartwig Muhle:

The terms “risk” and “hazard” are used in different definitions in various agencies and in various countries. The question is whether there should be an attempt to harmonize these definitions when the preamble of the IARC Monographs is revised.

In toxicology, the use the definition of “risk” is preferred in a quantitative sense. It characterizes the incidence of a defined adverse effect in dependence of an exposure. Ideally, the dose-response relationships should be known.

“Hazard” indicates the potential of inducing adverse health effects.

The title “IARC Monographs on the evaluation of carcinogenic risks to humans” could suggest that the monographs aimed to evaluate risk in a quantitative meaning. However, the second paragraph under 2. “Objectives and scope” currently says explicitly “quantitative extrapolation from experimental data to the human situation is not undertaken”. A harmonization of the title of the monographs to the mentioned statement may be considered.

Jagadeesan Nair:

Page 1- 2nd para. Detailed quantitative evaluations may be made in the monograph, within the range of available carcinogen exposure data, wherever is possible.

Page 2 line 1. Relevant information on mechanisms should be identified and added, wherever is possible, as a brief description to support the evaluation.

Günter Oberdörster:

The definition of the term "carcinogen" could include an emphasis of relevant exposures and relevant doses. There should also be a greater emphasis on mechanisms, most of all at the molecular level, and consideration of the impact of doses on mechanisms: To paraphrase *Paracelsus*: the dose can make the mechanism; for example, extremely high dose carcinogenicity of rather benign inhaled particles in rats raise the question: How great of a concern is that for humans? Very often you see very high dose studies in animals which result in a tumor response, but may really have no relationship to realistic human exposures. I think

this ought to be considered and discussed, and some guidance provided, even in the Preamble, for the review process.

On another issue, my concern lies also in over-emphasizing toxicological studies with completely irrelevant routes of exposure, in addition to extreme dose levels. Mechanistic data should be most valuable for the evaluation process and could provide useful information with respect to extrapolation to humans. Obviously, well-executed epidemiological studies showing positive (tumorigenic) results in humans - the ultimate species of interest - will always be a gold standard. But, so should also be results from well-performed peer-reviewed epidemiological studies reporting negative results. If there are positive relevant animal data: what are the mechanisms, are these likely to be operative in humans?

Steve Olin:

The definition of "carcinogen" (as used in the monographs) is interesting, in that it includes the concept of exposure: "… an exposure that is capable of increasing the incidence of malignant neoplasms; the induction of benign neoplasms may in some circumstances (see Section 9) contribute to the judgement that the exposure is carcinogenic." While the intent in using the term 'exposure' is, at least in part, to include not only chemicals but also biological agents, lifestyles and habits, and complex mixtures, I think it is also quite appropriate to acknowledge (as is implied in this definition) that carcinogenicity is a complex property that includes the agent(s), the host (human, animal) and the exposure. Going forward, IARC may want to consider whether, and how, to more fully acknowledge and capture the exposure component of the carcinogenicity in its evaluations.

Has there been an update to the 1988 "users' survey"? Are there more current data that can be cited regarding the utility (utilization) of the IARC Monographs?

Jerry Rice:

Expand the reference to 'the first step in carcinogenic risk assessment' to state explicitly that, despite their name, the Monographs are an exercise in carcinogenic hazard identification.

Availability: needs updating. Will IARC Press definitely be disbanded? What is being done now to assure availability of all Monographs volumes on-line and by CD-ROM, now that the contract with GMA Industries has been terminated?

Mark Schiffman:

The main point I thought needed to be addressed was quantitation. The fundamental problem of strength of evidence vs strength of carcinogenicity must be clarified, given how the data are distilled first to a concentrate, then to a bouillon cube of information. The Lancet Oncology summary [of volume 90], which was widely seen, already lost some critical nuance despite our best efforts. So the preface and directions need to permit a summarized sense of carcinogenic strength somehow (for my kind of topic). I have no idea how to achieve that.

3. Selection of topics for the Monographs

Manolis Kogevinas:

Evaluations done by major other bodies/institutes such as the EPA and the committees of the EU could also be mentioned as a source that IARC uses to identify topics.

"Exposures to mixtures of agents may occur in occupational exposures …" should also include environmental exposures since this is another obvious field where mixtures are likely to be evaluated, e.g. air-pollution.

Finally, in the past some monographs where far too heterogeneous e.g. aflatoxin. This leads to a working group with just one expert per topic and this is something to be avoided.

Len Levy:

Meanwhile, there is one thing that perhaps needs spelling out quite clearly to avoid the political pressures on the work of you and your colleagues, and of the Monograph experts, and that is in relation to when you re-evaluate substances. I think it should be made absolutely clear that the re-evaluation of a substance, or process, is exactly what it means - it is a completely new look at the data set with no preconceptions coming from previous evaluations, but simply using the guidelines as if it were a new evaluation. I would thus counsel against using the terms "Upgrading" or "Downgrading" of previous evaluations as these do have political overtones that are inappropriate to an independent scientific evaluation.

Steve Olin:

Are the directories of agents being tested and of cancer epidemiology studies really still used in selecting topics for the Monographs?

In general, this is a subject of considerable interest to those outside the IARC Secretariat who are potential users of the Monographs or are potentially affected by their evaluations, so I wonder if it is timely and possible to expand a bit on the description of the process of selection of topics.

Jerry Rice:

Delete references to discontinued IARC serial publications and projects, specifically on agents being tested for carcinogenicity and the now-defunct Directory of Ongoing Research in Cancer Epidemiology.

Add (update) reference to the ad-hoc advisory group which met in 2003, and also the special advisory groups on infectious agents (two internal technical reports) and on radiation (one internal technical report).

Doug Wolf:

Change the first sentence to: "Topics are selected on the basis of two main criteria: (a) there is evidence of <u>significant</u> human exposure, and (b) there is evidence of carcinogenicity <u>(c) or there is likelihood of a carcinogenic risk based on mechanistic information from similar agents</u>."

4. Data for the Monographs

Erik Dybing:

I believe the preamble updating discussion should take on board about clearer criteria for inclusion and exclusion of scientific documentation, as currently is being done when performing systematic reviews. Also, the discussion should revisit the issue of non-inclusion of industry data that have not been published in the scientific literature. It is obvious that important data under the present guidelines are omitted for review for important groups of chemicals, such as pesticides.

Manolis Kogevinas:

References on the ongoing directories should be deleted.

Jerry Rice:

State the actual Monographs practice: for adequate studies of carcinogenicity in animals and epidemiology in humans, literature coverage seeks to be comprehensive, and is not restricted to studies published in English.

Michael Waalkes:

I do not believe that work appearing only in abstract from should be included as it has in the past. This should be clearly stated in the preamble.

Doug Wolf:

What about primary data reported in a secondary source such as confidential business information reported through a publicly available data evaluation record. Or technical reports that may have been reviewed by a government agency but were not themselves peer reviewed, personally I think more information and completeness is better than ascribing to an old notion that only data published in a journal is of value, the goal is to be accurate, complete, and make a scientifically defensible assessment of cancer risk, not just review the published literature.

5. The working group

Paul Demers:

There is nothing regarding conflict of interest or the role of observers and the working group process is not really discussed. I think those are important additions to make in these times when transparency is so important. There should be additions to sections 5 and 6 on this area. I remember that your presentations to the working group were very clear on these topics and summarizing those would be helpful.

Manolis Kogevinas:

This section is obsolete and needs to be rewritten to include issues such as the role of observers and the secretariat, conflicts of interest, openness of the procedures.

It is absolutely unacceptable to have participants come to Lyon without having signed and submitted the conflict of interest document as happened in the monograph that I chaired.

Observers. The role of the observers has to be well re-evaluated. For one thing observers should reflect a wider spectrum of the "society" (though admittedly the "society" and its constituents parts in the case of an international organisation such as IARC is more difficult to define than in national settings). I do not share the criticisms that IARC has shown an industry bias. However, I do believe that IARC is obsolete regarding the openness of the evaluation procedures. It would be impossible to establish procedures similar to those used by the USEPA, but measures should be taken to identify interested parties and to allow the expression of their views. This later could be done through the presence of a few partners at the meeting in Lyon (say corresponding to a max of 10-20% of the number of voting members in the working group), and also procedures that allow the submission of written comments to the working group even if not present.

A minor issue concerning the secretariat refers to the fact that it is not clear how does IARC decides who among IARC personnel should participate or not in each monograph. I don't recall to have identified any major problem with the participation of members of IARC, on the contrary the secretariat has been extremely helpful. I am not sure whether there are any stated criteria for the participation. I presume that the criteria used are those of expertise for

senior IARC members and also educational for younger members. Perhaps this could be stated.

Two issues related to this is the openness of the procedures. First that the members of the working group should be made public before the meeting. The arguments that this would lead to pressures towards the members of the group that has been brought forward by the previous leadership of IARC is false since the bodies that could apply such pressures have in any case the means to find out who are the members of the group. A second issue to be considered is to make public the draft monograph prior to the meeting so as to allow persons or bodies outside the working to review and comment prior to the meeting.

Finally, for reasons of completeness in this or the next part, some additional less important issues could also be mentioned such as the description of subgroups of the working group.

Hartwig Muhle:

Under chapter 5 "The working group" the rules may be more precisely described how to control a conflict of interest for the members of the working group.

Günter Oberdörster:

The issue of the independence of the members of the review panel should also be addressed, some form of disclosure of activities could be requested to confirm that there is no conflict of interest; for example, use the procedure that EPA or other Federal U.S. committees are routinely using.

Steve Olin:

The section needs to be updated to identify the roles of participants, invited specialists, representatives, observers, and secretariat. This description need not be lengthy but, I think, would be helpful in the interest of transparency.

Does IARC want to add a short paragraph here describing the enhanced procedures to identify and, where possible, avoid real or perceived conflicts of interest among participants, and to document real or perceived conflicts of interest among invited specialists?

Jerry Rice:

Redefine who may apply to observe Working Groups meetings and under what limitations of interaction with voting members, and define the status of your recently-established category of non-voting members.

Benedetto Terracini:

Rules of practice are also needed with regard to declarations on conflicts of interest of working group members.

Paolo Vineis:

Perhaps the issue of conflicts of interest could be included in the Preamble (e.g. page 3: who is qualified to participate in the WG or as an observer?).

6. Working procedures

Manolis Kogevinas:

"…The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are

given in square brackets." This is a major issue that should be carefully evaluated. It seems obsolete not to use systematically summary quantitative measures of association such as meta-analyses. I am fully aware that such analyses require considerable effort but, in many occasions, these analyses are absolutely necessary to derive valid conclusions not only of the magnitude of the risk but also on the presence or absence of risk. If metanalyses were to be used systematically this would mean a change in the working procedures since such metanalyses should have been completed before the working group meeting starts.

Jagadeesan Nair:

Page 3 last para. In the recent monographs that I participated, the full first draft was not sent early enough. I recognize the time pressure on both IARC and the working group member responsible for writing, nevertheless, the procedure should be implemented strictly as stated in this section. This will help in identifying any left out important studies and false statements crept in the draft, by all members of the working group.

The procedure for selecting the relevant publication is not defined. At times IARC sent a long list of publications searched for key words, yet another times the member responsible for writing had made the search and selected the publications. It will be more efficient to ask the member responsible for writing, to compile the relevant publications and send IARC to check the completeness.

When dealing with complex mixtures, such as tobacco and areca nut, the guidelines for writing about pathological, pharmacological or toxic effects of the main component (not necessarily the carcinogenic one e.g. nicotine) is lacking. This, in the past created large documents that had to be cut short considerably by the working group during the sub-group meeting that resulted in time constrain.

Similar comment is true for description of epidemiological data that deal with diseases unrelated to cancer.

Steve Olin:

Timeframes need to be updated, or reality needs to better conform to the stated procedures.

IARC may want to add to the end of the first paragraph a statement similar to the following: "Meeting participants who are asked to prepare first drafts of specific sections are invited to supplement the IARC literature searches with their own searches."

Following the first sentence in the second paragraph, the remainder of the paragraph should read: "Representatives from industry or industrial associations may be invited to provide input to the sections on production and use. Information on production and trade is obtained from governmental, trade, and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g., not collected or made public in all producing countries, production is small, publication could disclose confidential information). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Jerry Rice:

Modify your stated goal of time required to produce a book: 12 months is a realistic gestation period.

Mention your website, monographs.iarc.fr, and that conclusions from recent working group meetings are available on it before the books appear.

Michael Waalkes:

The subgroup leaders should read the relevant portions of the preamble to their sub group prior to assessment.

7. Exposure data

Jagadeesan Nair:

Page 4-last para. Recommendation of methods may not be implied, however, evaluation of the quality of the method will help in identifying ambiguous data.

Steve Olin:

Several minor revisions [underlined] are suggested below:

> Sections that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are included at the beginning of each monograph.
>
> Most monographs on individual chemicals, groups of chemicals or complex mixtures include sections on chemical and physical data, on analysis, on production and use, and on occurrence and human exposures. In monographs on, for example, physical agents, occupational exposures and cultural habits, other sections may be included, such as: historical perspectives, description of an industry or habit, chemistry of the complex mixture or taxonomy. Monographs on biological agents have sections on structure and biology, methods of detection, epidemiology of infection and clinical disease other than cancer.
>
> For chemical exposures, the Chemical Abstracts Services Registry Number, the latest Chemical Abstracts Primary Name and the IUPAC Systematic Name are recorded; other synonyms are given, but the list is not necessarily comprehensive. For biological agents, taxonomy and structure are described, and the degree of variability is given, when applicable.
>
> Information on chemical and physical properties and, in particular, data relevant to identification, occurrence and biological activity are included. For biological agents, mode of replication, life cycle, target cells, persistence and latency and host response are given. [Move the preceding sentence to the end of the paragraph.] A description of technical products of chemicals includes typical trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.
>
> The purpose of the section on analysis or detection is to give the reader an overview of current methods, with emphasis on those widely used for regulatory purposes. Methods for monitoring human exposure are also given, when available. No critical evaluation or recommendation of any of the methods is meant or implied. The IARC publishes a series of volumes, Environmental Carcinogens: Methods of Analysis and Exposure Measurement (IARC, 1978-93), that describe validated methods for analysing a wide variety

of chemicals and mixtures. [Suggest the preceding sentence be deleted – the series apparently was discontinued in 1991.] For biological agents, methods of detection and exposure assessment are described, including their sensitivity, specificity and reproducibility.

The dates of first synthesis and of first commercial production of a chemical or mixture are provided, when available; for agents which do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided. [Suggest the preceding sentence be deleted – this is not routinely reported in the Monographs.] In addition, methods of synthesis used in past and present commercial production and different methods of production which may give rise to different impurities are described.

The countries where companies that report that they produce the chemical are located (and the number of companies in each country) are identified. Available data on production (including trends over time), international trade and uses are obtained for representative regions, which usually include at least Europe, Japan and the United States of America. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

Information on the occurrence of an agent or mixture in the environment and on human exposures is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. In the case of mixtures, industries, occupations or processes, information is given about all agents present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with time and place. For biological agents, the epidemiology of infection is described.

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included for some countries as indications of potential exposures, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccines and therapy, are described.

[This Exposure Data section, as modified, reflects current Monograph practice. Going forward, as noted above under Objective and scope, IARC may want to consider how the exposure component of carcinogenicity should be more fully captured in the overall evaluation.]

Jerry Rice:

Expand the current description to include explicit mention of individuals and populations exposed to infectious agents.

8. Studies of cancer in humans

Detmar Beyersmann:

I propose that clear associations obtained from a single big cohort in an excellent study with may be overwhelming and should not be regarded inferior to data from several populations which may not be necessarily of better quality. Having recently participated in the hard metal evaluation, in hindsight, I feel that the epidemiology was underrated with the argument that it covered the French hard metal workers only and that the research groups carrying out several studies on this cohort and parts thereof, were interlinked by persons.

Nigel Gray:

Under 8c there is a good discussion on the inferences about mechanism of action.

Manolis Kogevinas:

Section 8a. Types of studies considered: The Preamble should specify that the criteria for the selection of studies should be explicitly mentioned. This part was at a time when criteria for valid reviews had not been extensively discussed in the scientific community. Texts such as those suggested by the Cochrane collaboration should be incorporated.

Section 8c. Inferences about mechanism of action: This should be completed to incorporate recent types of evidence particularly studies evaluating genetic susceptibility and gene-environment interactions.

Damien McElvenny:

Section 8a. Worth saying a little more about the relative merits of cohort and case-control studies with respect to evidence for carcinogenicity?

Mention molecular epidemiology studies also at this point?

Section 8b. Local comparisons may not always be better than national ones (e.g. denominators for local rates may not have negligible error associated with them; e.g. in the case of a rare tumour, the comparison population may contain a non-trivial number of cases also contained in the numerator).

Section 8c. Where data permit, use also might be made of data on peak exposures (if biologically plausible)?

Be more explicit about the possible role of meta-analysis as part of the review?

Jerry Rice:

In the section that alludes to inferences regarding mechanisms of carcinogenic action, references should be made to the use of biomarkers of susceptibility, exposure and biological effect (sci pub 142 [1997], 148 [1999], and 157 [2004].

Leslie Stayner:

Change in section 8a:

> Cohort and case-control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of relative risk

(mortality or incidence rate ratios, rates in cohort studies and odds ratios in case-control studies).

Change in section 8b:

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. By 'bias' is meant the operation of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between disease and an agent, mixture or exposure circumstance. 'Confounding' is a form of bias which occurs when the relationship with disease is made to appear stronger or to appear weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. In evaluating the extent to which these factors have been minimized in an individual study, working groups consider a number of aspects of design and analysis as described in the report of the study. Most of these considerations apply equally to case-control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

Change in section 8b:

Secondly, the authors should have taken account in the study design and analysis of other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than those with national rates. Internal comparisons of disease frequency among individuals at different levels of exposure is also a highly desirable feature in cohort studies, since it minimizes the potential for confounding related to differences in risk factors between an external referent and the study population.

Change in section 8b:

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. [DELETE: The methods used should preferably have been the generally accepted techniques that have been refined since the mid-1970s.] These methods have been reviewed for case-control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

Paolo Vineis:

The possibility of performing meta-analyses (e.g. in the Cochrane collaboration style) could be explored.

The classification of epidemiologic studies, page 5 [section 8a], is a bit scholastic. Insert sentences on different study designs (PMR, prevalence studies, case-only) that can be reconducted to the canonical designs.

Page 6 [section 8b], omission of studies: should be specified better, to avoid arbitrary omissions by some WG.

In the mechanism paragraphs mention of gene-environment interactions and mendelian randomization should be made, i.e. the identification of genetic susceptibility that

is consistent with known metabolic/repair pathways for an agent reinforces the causal assessment.

Page 7, 7 lines from bottom [section 8d]: if the diseases and/or exposure is common.

Doug Wolf:

[section 8d] The presence or identification of putative precursor lesions or events in the carcinogenic pathways in human populations or samples should be considered supporting evidence of relevance. Likewise, the absence of these precursor events when looked for in well conducted studies should be used as part of the evaluation for sufficiency of causality.

[section 8d] Some consideration should be given to lack of data to support a mode of action which would be supportive of lack of causality.

9. Studies of cancer in experimental animals

Saveria Campo:

I suggest that "experimental" be removed from the section heading, and the section be divided into a. natural occurring cancers in animals (as for instance PV-induced cancers), and b. experimentally induced cancers in animals (including transgenic animals). This will cover possible future instances in which a biological agent is too species-specific to be tested in experimental animals. The rest of the section would follow this short introduction.

> These can be divided into two categories: a. studies of naturally occurring cancers in animals exposed to an agent and b. studies of cancers experimentally induced with that agent in animals.
>
> It is not always possible to perform both types of study for a given agent. This is the case particularly for biological agents such as viruses. Many viruses are species-specific and do not cross species barriers even in experimental circumstances. In this case, human viruses cannot be evaluated in animals. Instead, results obtained with animal viruses, analogous to the human virus being evaluated, may be considered as being relevant to the understanding of the process of carcinogenesis in humans. Studies of cancers experimentally induced by a biological agent, including studies in transgenic animals, can provide mechanistic evidence of carcinogenicity.
>
> Both naturally occurring and experimentally induced cancers in animals can strengthen and support a conclusion that the agent in question is carcinogenic in humans.

Jagadeesan Nair:

No specific guidelines for experiments conducted with gene/s modified animals for carcinogenicity.

Some better guidelines are needed that deal with carcinogenicity of an agent with nutritional imbalances, as this may be the case for humans.

Steve Olin:

In the third paragraph under (a) Qualitative aspects, the first item might be modified to read: "(i) <u>how clearly the agent was defined and how adequately the sample characterization, including the stability of the chemical under conditions of administration to the experimental animals,</u> was reported;…"

Jerry Rice:

After reference to possible carcinogenic mechanisms that do not operate in humans, repeat references to the IARC publications (e.g., Capen et al, Sci Pub No 147, 1999) mentioned in my comments on section 1 above.

Next-to-last paragraph: strike reference to "non-linear dose response relationships," since ALL d/r relationships are non-linear over a complete range of exposures.

Doug Wolf:

[section 9] It is important to include information that supports the biological plausibility that the tumors that arise in the animal studies suggest that tumors could arise in humans, following the framework in Cohen SM, Klaunig J, Meek ME, Hill RN, Pastoor T, Lehman-McKeeman L, Bucher J, Longfellow DG, Seed J, Dellarco V, Fenner-Crisp P, Patton D. Evaluating the human relevance of chemically induced animal tumors. Toxicol Sci. 2004 Apr;78(2):181-6. Epub 2004 Jan 21.

[section 9a] The dose-response assessment is critical, particularly in evaluating the quality of the study. Assessment of how the MTD was determined, was the MTD exceeded in the study, and did the tumors only arise at the MTD should call into question the human relevance of such a study.

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

Detmar Beyersmann:

A more recent publication than that of Montesano et al. 1986 should be cited, since considerable progress has been made since that time and several up-to-date reviews are available in Mutation Research (Dr. Baan might have the best knowledge in this area). Structure-activity relationships should receive more attention. This is self-evident in the case of homologous series of organic chemicals, but should also be regarded as a stronger point in the case of metals and their compounds. As a participant in the nickel monograph, in hindsight, I feel that nickel metal has been unnecessarily devaluated because of lack of data about this very compound; however, human data clearly show that elementary nickel after its inhalation is oxidized and solubilized in the lung and available systemically. Hence, the epidemiological results with soluble nickel salts combined with the data on solubilization of nickel metal should allow a conclusion about the metal.

James Bond:

One aspect of the *Preamble* that I would recommend revising deals specifically with Section 4 (Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms). I offer my comments based on my personal experience over the years both as an IARC Working Group member and chairman assigned to Subgroup 4 during deliberations and review of data appropriate for this section (Monograph volumes 65, 71, 82, and 87). My comments deal with reviewing what oftentimes can be a large body of data that, in my opinion, is almost never considered when Section 4.5 (Mechanistic considerations) is developed for review by the Subgroup and ultimately Plenary. These large (and perhaps irrelevant) data sets ultimately are included in the Monograph and can oftentimes detract from the actual relevant data that are also included in this section.

To be more specific, I have found over the years serving as a Working Group member that frequently there is a large body of toxicological data that is initially summarized in the draft Section 4.0. Examples of such type of data may include reproductive toxicology,

developmental toxicology, immunotoxicology, and neurotoxicology to name just a few examples of toxicology sub disciplines that are typically reviewed and discussed. More often than not I have seen that while the data are certainly of interest from a toxicological perspective most of the time these robust data sets have little relevance when it comes to ascertaining mechanisms for carcinogenicity, either in laboratory animals or humans. There have, of course, been instances where these types of toxicological data can shed light on mechanisms, but these important data sets can be buried amidst the other set of data that have no bearing on mechanisms.

Perhaps an example will best illustrate my point. When I was chairing the Subgroup for Monograph 87 (Lead) the Subgroup spent days discussing and reviewing the very large data sets such as that for lead neurotoxicity, reproductive toxicity, and hematotoxicity in both laboratory animals and humans. Most all of the literature reviewed and cited did not shed light to any significant extent on mechanisms for lead carcinogenicity and very little was ultimately carried forward to Section 4.5. As Chairman I felt obligated to have the group review written materials since it is clear that some committee members had expended a great deal of effort to summarize the numerous publications as part of their initial writing assignments. I clearly could not dismiss these contributions outright but found myself being frustrated that I could not adhere to the initial planned schedule for review as outlined by the Working Group Chairman. I would have much preferred to have our group concentrate on the relevant data that would be appropriate for Section 4.5. Section 4.5 is clearly a critical subsection of Section 4 and ultimately for the entire Monograph and I think frequently insufficient time is spent discussing this Section and ensuring that it carefully reflects the current state-of-knowledge on mechanisms.

First, I want to be clear that I am not advocating a wholesale dismissal of inclusion of irrelevant data, but I think it would be prudent that the IARC emphasize (and I underscore that word) to Working Group members charged with reviewing data that they need to have a fine filter when it comes to selecting literature for Section 4. I would suggest that the language in the *Preamble* be modified to underscore that only data relevant to mechanisms should be included in Section 4. It should be clear that if the data is not relevant in terms of mechanisms the data will not be considered as part of the overall evaluation. I think it would be appropriate to include strong language acknowledging that there may certainly be a large body of literature for a specific agent, but that not all of it is necessarily relevant for mechanisms and hence is not reviewed for inclusion in the Monograph. However, there are certainly merits for including appropriate review articles that can capture a large body of data that may not necessarily be relevant for Section 4.5.

From a practical standpoint, there is always the temptation for Working Group members to be all inclusive when reviewing the literature for a particular agent. But one way to discourage this is to perhaps draw on my most recent experience with Monograph 87. For that Monograph in which I chaired Subgroup 4, Robert Baan and I agreed that it would be appropriate to call on specific Subgroup members to develop in advance of the meeting draft sections on mechanisms as it related to the specific area they were reviewing. My task was to compile all the different mechanistic contributions into a single draft Section 4.5 for consideration by the group when we were at IARC. This turned out to be a very efficient way of developing a first draft of Section 4.5. I think here is where the charge to committee members would be to consider only data in their review of the literature that would have any bearing for Section 4.5. This would help them to focus their review of the literature in ways that will make a difference for the final product. In this way, Working Group members would not feel compelled to review all the literature. Unfortunately, for this particular Monograph meeting we were unable to dissuade Subgroup members to exclude irrelevant literature in their draft contributions to Section 4.

Paul Demers:

In addition, although mechanisms are discussed, the preamble doesn't really give the impression that they are very important. Perhaps I have only attended unusual meetings recently, but mechanisms seemed to play a much bigger role than when I first attended meetings in the early 1990's. I will have to read sections 10 and 12 more carefully before I could make specific recommendations.

Erik Dybing:

The preamble should, of course, be revised in accordance with the IPCS Conceptual Framework for Cancer Risk Assessment.

Manolis Kogevinas:

The evaluation of data on reproductive outcome takes considerable effort and is rarely, if ever, used for the evaluations. The preamble could specify that these data be only briefly summarised when relevant.

Douglas McGregor:

Another suggestion would be to use, in the Mechanisms of Carcinogenic Action section, whatever Framework we arrive at following the April meeting in Bradford. This would include the extension to any proposed MOA in humans. It would also be a worthy subject for discussion at your Preamble meeting to question whether the Monographs should always accept that genotoxicity is the MOA of any substance that is clearly genotoxic. Obviously, carcinogenesis is more than genotoxicity and so I would suggest that it should not be uncritically accepted that because it is assumed that genotoxicity is the MOA in animal experiments, this is a mechanism that could equally occur in humans, with the facile up-grading consequence in which this results. This happened many times in the Vol. 71 (1999) meeting, for which I was the responsible officer.

With a requirement, in the Monographs, to pass through a rigorous MOA framework, as we are now discussing in the IPCS project, there should be a more confident acceptance of any up-grading that results from the process. Although the data will already have been summarised and references in the preceding sections of the monograph, I think it would help transparency if the statements in the mechanistic section were referenced again.

Jagadeesan Nair:

Bulk of the work is done in this section, however, may not be required for a final evaluation. This is rather disappointing. From this section, pertinent studies that contribute to `information on mechanism ` should be used for a brief description as mentioned above. This will become more important as studies on genetic polymorphisms, and the data on genomics and proteomics will available for more and more cancer causing agents.

Information on mechanism could be misused for downgrading the evaluation of an agent, especially when it is considered for a re-evaluation. Adequate safeguards should be provided in the Preamble to resist such attempts.

Michael Waalkes:

One thing I think should be better spelled out is that "mechanisms and other data" should be clearly relevant only to carcinogenesis. Our lead "mechanisms" group had to go through an enormous amount of neurotoxicity, etc., and this detracted from the ability to focus on the mechanisms of lead carcinogenesis. This, in the end, may well have impacted the final Evaluation as we just then started important discussions about the mechanistic

impact of the forms of lead and a clearer mechanistic concept that included prior focus on the nature of the ultimate carcinogenic species would have greatly aided this discussion. I think that this would be a key issue with many of the compounds that are reviewed - not just metals.

Jerry Rice:

In paragraph 4, delete mention of GAP and its website, which has been discontinued by the U.S. EPA. Delete accompanying literature citation (Waters et al., 1987).

Paolo Vineis:

The sections on mechanisms of carcinogenesis are almost entirely based on mutations/structural changes in DNA. A paragraph on gene expression and epigenetics (e.g. DNA methylation) should be added.

Page 11, lines 3-10 from bottom: this does not seem the right place for such technicalities.

John Whysner:

Cancer mechanism data needs to be summarized in some detail at the end of this section, and in a separate subsection, if the Working Group is to make an argument for either upgrading or downgrading based on mechanistic data. For examples see #73 section 4.5 for *d*-limonene, atrazine, saccharin or # 79 section 4.6 for sulfamethazine.

If there is an IARC scientific publication that described the criteria by which a chemical should be judged for cancer mechanism not relevant to humans (see the Capen et al. reference for limonene [Scientific Publication #147] and others), then the data should be discussed in terms of those criteria.

Doug Wolf:

[para 2] You will have to address genomic, proteomic, and metabonomic data separately and how it will be evaluated in context of potential human cancer risk, development of cancer pathways, relevance of particular animal models, particularly with differential metabolic pathways.

[para 7] Add at the end of the first sentence: " . . . described and should be evaluated with respect to their biological plausibility in humans." Many cancers are driven by epigenetic events so it is important to describe these and use the data to support the epidemiology or question it when the epidemiology in less than sufficient or equivocal.

11. Summary of data reported

Detmar Beyersmann:

(d)(ii): In accordance with the prior text, the examples of genes mentioned here should not only comprise proto-oncogenes and tumor-suppressor genes but also and more generally genes that regulate cell-proliferation and cell death (apoptosis).

Manolis Kogevinas:

Section 11b. Carcinogenicity in humans: This text seems much less complete than the one immediately following on animal experiments. The text on animal carcinogenicity could be nearly entirely applied also to the studies in humans.

Also the text could specify that summary statistics including recalculations done by the working group should be presented.

References: Adding key references could be considered. This would make easier and clearer the writing of some sections. The absence of references in this section obliges the working group to have to describe basic characteristics of some studies, so that the reader can identify them by going to the main text.

Douglas McGregor:

I think that the Formaldehyde example is an excellent reason why some key references should be included in the Section 5 summaries. Today, transparency is particularly important and since Section 5 is the part that is most accessible to the public, this is also the part that should be most readable, understandable and transparent. The Monographs have never been easy reading! I should hope that this would not be too difficult get agreed by your advisory group.

Steve Olin:

Does IARC want to note in the introductory paragraph that data summarized in these sections must also appear (usually with more details and literature citations) in the relevant text section?

Under (a) Exposures, a few small changes are suggested: "Human exposure to chemicals and complex mixtures is summarized on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and determinations in human tissues and body fluids. Quantitative data may be given, when available, in comparing exposures in different occupations and environmental settings or noting time trends. Exposure to biological agents is described in terms of transmission, and prevalence of infection.

Under (c) Carcinogenicity in experimental animals, quantitative data are rarely presented in this Summary, which I think is appropriate.

Jerry Rice:

Add a statement that narrative summaries of all evaluations are freely available at monographs.iarc.fr.

John Whysner:

Summary of genotoxicity in ORD: Because genotoxicity data is so important in making an overall determine of whether a mechanism is epigenetic (non-DNA reactive), an overall determination of whether or not one can say that the agent is or is not genotoxic should be made, if possible. There is a tendency to just repeat the information from the previous section here for genotoxicity without providing some overall judgment.

Doug Wolf:

[section 11b] The biological plausibility of a proposed mode of action should be discussed and data gaps identified.

[section 11c] Change the last sentence to "Dose-response and other quantitative data should be described." A statement of relevance when tumors are only see at the MTD should be made.

[section 11d(ii)] Add to the end of the sentence: " . . . including identification or description of major toxicity or cancer pathways that are altered (see Hanahan D, Weinberg RA. The hallmarks of cancer.Cell. 2000 Jan 7;100(1):57-70)."

[section 11d(iii)] Should have a statement of the evidence for biological plausibility in humans.

[section 11d(iv)] Should have information on identification and description of precursor effects in the cancer pathway.

12. Evaluation

Detmar Beyersmann:

According to my opinion, the rules stated are of sufficient clarity. A further fixing in the sense of freezing more strict rules would limit the remaining flexibility.

Nigel Gray:

In section 12 I find the classifications offered still OK in general but perhaps in need of a way of adding qualifications to our final classification.

However, having sat through the monograph on smokeless tobacco I found two episodes that gave me some difficulty. The first was the decision not to classify NNK as class 1 carcinogen - I thought Steve Hecht's paper was pretty conclusive but it didn't seem to get NNK into class1 - I missed some of the discussion but came away feeling that the evidence for class 1 was strong.

This becomes an important issue because it seems that we really need an industrial catastrophe to put things into class 1, whereas I would be inclined to accept softer evidence in a situation where the compound is not a necessary environmental component. If we'd classified NNK as Class 1 there would have been implications both for regulators to insist on it's removal from tobacco products, and also possibly in litigation over cases of adenocarcinoma of the lung - which makes the decision as to it's class even more crucial and threatening!

Secondly, comments received since suggest some of my colleagues thought the black and white classification of smokeless tobacco as carcinogenic lumped Snus in with other more toxic forms of tobacco, and there may come a time when such products as snus are regulated and permitted as harm reduction products (it will be a VERY tough debate). BUT, there is a difference between low nitrosamine snus and Indian smokeless tobacco. I was involved in drafting the section on snus and was happy with that particular section but I'm not sure how much of that got into the material that was released to the public (I don't have that in front of me). In essence, as with tobacco smoke, I think there is pretty good evidence of a dose response spectrum, but in the case of snus it seems to be of relatively low carcinogenicity and we don't seem to have found a way to say this in the final classification.

Manolis Kogevinas:

I am aware that after particularly problematic monographs, working groups members tend to suggest modifications of the groups of evidence used by IARC (Group 1, 2A etc.). I firmly believe that in IARC should not change these groups or the names of the groups. These groups are widely known and used, have functioned well in most occasions and there is a value for keeping them.

(i) Carcinogenicity in humans: The beginning of this section that discusses mixtures seems out of place and probably should be moved further down since it is a detail that should follow the main definitions.

Phrasing for the Definition of Group 1: "…Exceptionally, an agent (mixture) 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 (mixture) acts through a relevant mechanism of carcinogenicity.

The phrase "less than sufficient" could be substituted by "limited" since it is not conceivable that an agent for which there is inadequate evidence in humans should be classified in Group 1.

"...strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity." I think that this sentence is far too much influenced by the type of tests in fashion in the early 1990s, such as adducts, cytogenetics and could be substituted by the sentence used for the upgrading from 2B to 2A: "strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans". This latter phrasing describes better what actually what should be verified, it is more general and open to the wide spectrum of evidences available and gives more options to the working group to critically evaluate this evidence.

Definition of Group 2A: "…Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of limited evidence of carcinogenicity in humans." It could make sense to make such an exception when evaluating mixtures or exposure circumstances for which animal data are rarely available. It is not clear to me why should this exception be extended to the evaluation of specific agents. I would suggest not to allow an upgrading of specific agents to group 2A only on the basis of limited epidemiological evidence.

Damien McElvenny:

Statements on carcinogenicity could be more clearly linked to individual tumour types.

Hartwig Muhle:

Under chapter 12 "Evaluation" (a) it is said in regard to the evidence for carcinogenicity: "These categories refer only to the strength of the evidence that an exposure is carcinogenic and *not to the extent of its carcinogenic activity (potency) nor to the mechanism involved*". Under the light of the information presented above under (2) IARC may reflect whether these statements should be kept.

Also under chapter 12 (ii) "Carcinogenicity in experimental animals" it is said under "Limited evidence of carcinogenicity" , criterion b: "there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study". If the Working Group follows this statement then "sufficient evidence" in experimental animals becomes "limited evidence".

This paragraph was of essential importance in the Working group meeting of man-made vitreous fibres (IARC Monograph 81). In the case of vitreous fibres not a single study but dozens of studies which were done after intraperitoneal injection were declared as "unresolved questions regarding the design". Previous Working Groups of IARC were of a different opinion on this issue (IARC Monographs 43 and 68). In the latter Monograph on Sepiolite and Palygorskite the route of intraperitoneal injection was regarded as relevant. As a consequence, in the case of man-made vitreous fibres overall evaluation had to be changed from Group 2B into Group 3.

The reason for mentioning this disagreement is that formal declaration of "there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study" is essential. Before calling in a Working Group, special attention should be focussed on this issue. This would give all members who prepare chapters on animal experiments a

better chance to be prepared in arguing and for the entire group to vote on best information on this on this subject.

In 1998 the German "Commission for the investigation of health hazards of chemical compounds in the work area" (MAK commission) has decided to introduce categories of carcinogens which differentiate between carcinogens (Categories 4 and 5). Among other reasons the observation was taken into account that some compounds may act as carcinogens only after very high exposure concentrations which may unrealistic for working conditions. As many studies which investigate a potential carcinogenicity in experimental animals do follow the principle of the "Maximum Tolerated Dose" (MTD) this is surly not a question of only academic interest.

Vice versa it may be that threshold concentrations can be defined where "no significant contribution to human cancer risk is to be expected". In the publication of the Deutsche Forschungsgemeinschaft, List of MAK and BAT Values 2004, Wiley-VCH Verlag, Weinheim, Germany, these groups are defined as:

> " 4. Substances with carcinogenic potential for which a non-genotoxic mode of action is of prime importance and genotoxic effects play no or at most a minor part provided the MAK and BAT values are observed. Under these conditions no significant contribution to human cancer risk is expected. The classification is supported especially by evidence that, for example, increases in cellular proliferation, inhibition of apoptosis or disturbances in cellular differentiation are important in the mode of action. To characterize the cancer risk, the manifold mechanisms contributing to carcinogenesis and their characteristic dose-time-response relationships are taken into consideration.
>
> 5. Substances with carcinogenic and genotoxic effects, the potency of which is considered to be so low that, provided the MAK and BAT values are observed, no significant contribution to human cancer risk is to be expected. The classification is supported by information on the mode of action, dose-dependence and toxicokinetic data pertinent to species comparison."

The reason for mentioning this problem is that for some materials it may be problematic to define a carcinogenic hazard as an intrinsic material property but carcinogenic effects may be observed only under doses and routes which are potentially non-realistic for human exposure.

If IARC would follow this line it implies that more quantitative aspects have to be introduced in the risk evaluation of carcinogens. However, it is acknowledged that defining the value where "no significant contribution to human cancer risk is expected" may be problematic.

Günter Oberdörster:

With respect to evaluation, I suggest to also consider including a category of animal carcinogen when data show that the mechanism is not operative in humans; when exposure routes or doses are irrelevant for humans; and when human epidemiological data do not indicate carcinogenicity.

Steve Olin:

Does IARC want to add a statement under (c) Overall evaluation, acknowledging the now-standard practice of providing a summary of the rationale for the evaluation, particularly when it uses "other relevant data"?

Jerry Rice:

Do not change the criteria for evidence of carcinogenicity in humans from epidemiologic studies; these are o.k. as they are.

Carcinogenicity in animals: THIS NEEDS SIGNIFICANT UPDATING, SINCE THE ORIGINAL TEXT PRECEDED THE ERA OF GLP LAB PROCEDURES AND REFLECTED THE PUBLICATION OF SMALL EXPERIMENTS OF LIMITED SCOPE THAT PREVAILED BEFORE ABOUT 1980. THE INSISTENCE ON REPRODUCIBILITY MAY NO LONGER BE AS APPROPRIATE AS IT ONCE WAS.

Specifically, consider modifying the criteria for sufficient evidence. GLP studies today (cf NTP) are unlikely to be replicated and published, so the key IARC criterion of reproducibility often can't be met. Consider accepting "clear evidence (NTP)" by GLP in 1 sex of 1 species. Otherwise, it will not be possible to achieve "sufficient evidence" that in the IARC procedure is necessary before issues of mechanism can be considered, especially mechanisms possibly limited to non-human species.

OVERALL EVALUATIONS: During 1996-2002, people were constantly agitating either to increase or decrease the number of Groups. I would do this very carefully, if at all.

Definitions of Groups 1, 2A and 2B should not, in my view, be changed. However, the adjectives "possibly" and "probably" are often (wilfully?) misinterpreted as quantitative indicators of potency. It needs to be explicitly stated that these are used by the Monographs simply as descriptors of different levels and kinds of evidence for carcinogenicity, and have no numerical significance.

Group 3 as currently defined might usefully be divided into 3A (sufficient evidence for carcinogenicity in experimental animals, but good evidence that the carcinogenic mechanism is non-predictive of human hazard) and 3B (inadequate evidence for evaluation, as was the case before 1991). This is now the practice in several countries that have sophisticated national carcinogen evaluation systems (e.g., the MAK commission in Germany).

Leslie Stayner:

The main issue that I would like to see addressed is the criteria for judging lack of carcinogenicity for human studies. During the MMFibers meeting, one of the participants was arguing for applying this category to glass and rock wool. The way this was written, it seemed like a reasonable argument could be made and I think this needs to be tightened up a bit. I have proposed the following additional criteria which are outlined in the paragraph below:

> Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that human beings are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent, mixture or exposure circumstance and any studied cancer at any observed level of exposure. <u>The results from these studies alone or combined should have tight confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1). Bias and confounding should be ruled out with reasonable confidence, and the studies should have a an adequate length of followup (e.g., minimum 20 years for solid cancers.</u> A conclusion of 'evidence suggesting lack of carcinogenicity' is

> inevitably limited to the cancer sites, conditions and levels of exposure and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

These changes are consistent with the text of the human studies section (page 8, last paragraph of the human studies section [section 8d]).

Benedetto Terracini:

I think that more consideration should be given to the extent of unanimity among members of the working groups. Readers of the monographs ought to be informed on this point. When a substantial number of members of the working groups dissent from the majority's opinion, this should be reported in the monograph.

Paolo Vineis:

The idea of species-specific mechanisms is unclear to me and should be more substantiated. Carcinogenesis is likely to be multistage, so that it is unlikely that an agent causes cancer through a single sufficient mechanism that operates only in one species.

"Evidence suggesting lack of carcinogenicity": add "with sufficient latency between start of exposure and disease onset, and with sufficient statistical power".

Page 18 [Groups 3 and 4]: the sentences starting with "exceptionally" and "in some instances" do not persuade me. First one is allowed to downgrade an agent with sufficient evidence in animals when a mechanism is found that does not operate in humans. Then one is allowed to downgrade an agent with inadequate evidence in humans but lack of evidence in animals on the basis of other (not specified) relevant data. Mechanistic evidence seems to work only in one direction, i.e. downgrading. What about a mechanism that is present only in humans, so that there is apparent lack of carcinogenicity in animals? This seems to be mainly speculation, given the multistage nature of carcinogenesis. However, one should be consistent.

John Whysner:

The following, which is from the electronic version of the Monographs (GMA Industries, Inc., IARC Press, Release 2.0) under "Read This First" should be incorporated into the beginning of this section:

> In the ranking of carcinogenic hazards and their classification into groups, the terms "probably carcinogenic to humans (Group 2A)" and "possibly carcinogenic to humans (Group 2B)" are used. In this context, the adverbs "probably" and "possibly" have no mathematical significance. They are used simply as descriptive terms for different levels of evidence for carcinogenicity to humans, "probably carcinogenic" connoting stronger evidence than "possibly carcinogenic."

I think that this statement clears up a lot of misunderstandings about the terminology that we use.

Doug Wolf:

[section 12a(i)] A statement should be included with the final conclusion as to the biological plausibility for example sufficient evidence and the data suggest a biologically

plausible mode of action or Sufficient evidence but no data on biological plausibility; it is important to put the conclusions in context and use all the data.

[section 12a(ii)] One should use the same approach as above in that you also state whether there is a clear mode of action, equivocal mode of action, or insufficient data to support a mode of action.

[section 12b, para 1] Need to add omics here.

[section 12b, para 2] Data that suggests a mode of mechanism that is not operative in humans should cast doubt on the biological plausibility of cancer risk.

[section 12c, Group 1] Change in the last sentence "relevant mechanism of carcinogenicity" to "biologically plausible mechanism."

[section 12c, Group 2A] Delete the last sentence: "Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of limited evidence of carcinogenicity in humans."

[section 12c, Group 2B] Add "substantial" to the last sentence: " . . . limited evidence of carcinogenicity in experimental animals together with substantial supporting evidence from other relevant data may be placed in this group."

[section 12c, Group 3] Split Group 3 as follows:

> 3A Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.
>
> 3B Agents, mixtures and exposure circumstances that do not fall into any other group are also placed in this category. [This is actually very different than 3A above and results in an incorrect interpretation combining these two together into the same category]

[section 12c, Group 4] Change the descriptor to "The agent (mixture) is not likely carcinogenic to humans."

[section 12c, Group 4] Add to the end of the last sentence: " . . . or if the tumors that arise in experimental animals are through a mechanism that is not operative in humans."

Other comments

Manolis Kogevinas:

References: References should be updated, e.g. Montesano 1986 and other.

IARC website: IARC should improve the website so as to make easier the access to the Monographs that should probably have a direct link on the main page of IARC's web.

Publicly available Monographs: I am not sure what are the future plans for the publication in paper and the web of the Monographs. IARC should make all the Monographs publicly available through the web in pdf format. This is extremely important and it is not understandable how can IARC have delayed this for s long. IARC has been out of line in this from ALL other major agencies doing evaluations.

Delay in publication: The delay in the publication of some monographs recently has been far too long (two years for the tobacco and the arsenic monographs!). Although I understand that there are circumstantial reasons for this, the Chief of the CIE Unit and IARC's Director should be aware of special difficulties in specific monographs and commit more resources for their timely completion.

Saman Warnakulasuriya:

I was planning to suggest to you that the current layout of the monograph with reference to the section 5.5 Evaluation, does not stand out well in the monograph particularly to a reader who is not familiar with the system.

For example, in Volume 85 Monograph 1 this section appears in pages 238-239.

Could the editors look in to how this section could be portrayed in a more prominent position to the casual reader?

Recent meeting chairs and subgroup chairs

Volume, date	Meeting chair	Subgroup chair, Exposure data	Subgroup chair, Cancer in humans	Subgroup chair, Cancer in animals	Subgroup chair, Other relevant data
v90, Feb '05	Harald zur Hausen	Denise Galloway	Mark Schiffman**	Saveria Campo**	Paul Lambert
v89, Oct '04	Jerry Rice**	Scott Tomar	Prakash Gupta	Rajani Bhisey	Stephen Hecht Saman Warnakulasuriya**
v88, Jun '04	Michel Gérin	Paul Demers**	Leslie Stayner**	Morando Soffritti	Doug Wolf**
v87, Feb '04	Len Levy**	Elaine Jaffe	Jørgen Olsen	Michael Waalkes**	James Bond**
v86, Oct '03	Detmar Beyersmann**	Yukinori Kusaka[x]	Damien McElvenny**	Joe Roycroft	Bruce Fowler
v85, Jun '03	Stephen Hecht	Saman Warnakulasuriya**	Prakash Gupta	Pieter Slootweg	Jagadeesan Nair**
v84, Oct '02	Manolis Kogevinas**	Steve Olin**	Kenneth Cantor	Anthony DeAngelo	David DeMarini
v83, Jun '02	Jonathan Samet	Nigel Gray**	Paolo Vineis**	Gary Stoner	Stephen Hecht
v82, Feb '02	Len Levy**	Steve Olin**	Jack Siemiatycki	Ronald Herbert	James Bond** Douglas McGregor**
v81, Oct '01	Agnes Kane	Steve Olin**	Aage Andersen	Hartwig Muhle**	Gunter Oberdörster**
v80, Jun '01	Nick Day	Maria Stuchly[x]	Jørgen Olsen	David McCormick	Carl Blackman
v79, Oct '00	CC Capen	Steve Olin**	Jørgen Olsen	Gordon Hard	John Whysner**
v78, Jun '00	Dudley Goodhead**	Per Hall[x]	Sarah Darby	BB Boecker[x]	John Harrison[x]
v77, Feb '00	Erik Dybing** Michel Gérin				
v76, Oct '99	Miriam Poirier				
v75, Jun '99	Carl Shy[x]				
v74, Feb '99	WJ Gillespie[x]				
v73, Oct '98	CC Capen Benedetto Terracini**				
v72, Jun '98	Carlo La Vecchia				
v71, Feb '98	Benedetto Terracini**				
v70, Jun '97	N Müller[x] SH Chan[x]				
v69, Feb '97	George Lucier C Rappe[x]				
v68, Oct '96	Carl Shy[x] Agnes Kane				
v67, Jun '96	RJ Biggar Robin Weiss				
v66, Feb '96	George Lucier Tony Miller**				
v65, Oct '95	A Brøgger[x] Leslie Stayner**				
v64, Jun '95	Jack Cuzick KV Shah[x]				

** Comments included in this report

Recent meeting chairs and subgroup chairs

Volume, date	Meeting chair	Subgroup chair, Exposure data	Subgroup chair, Cancer in humans	Subgroup chair, Cancer in animals	Subgroup chair, Other relevant data

[x] Unable to contact