IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Summary of Public Comments on the Draft Preamble

Prepared by the Staff of the *IARC Monographs* Programme
28 November 2005

This summary of public comments on the draft Preamble to the *IARC Monographs* will be considered by the Advisory Group that will meet in December 2005 to review the amended Preamble. The summary is organized according to the sections of the Preamble in order to show which areas received comment and whether the views were similar or different. Similar comments are reported together and a single short statement represents the key point. To keep the summary concise, the commenters' detailed rationales are not repeated here, instead, the individual or organization making each comment is identified and the reader is encouraged to view the full original comment. Three commenters (Drs. Huff, Melnick, and Tomatis) also suggested several specific editorial changes. Where not related to a more global issue, these editorial changes are not repeated here, and the Advisory Group will refer to the original comments as it considers the suggested editorial changes.

Introduction

To help ensure that diverse perspectives are considered during the process for amending the Preamble to the *IARC Monographs*, IARC invited comments from the general public, the scientific community, national and international health agencies, and other organizations. The draft Preamble was made available on the *Monographs* website (http://monographs.iarc.fr) on 31 August 2005, and comments were requested by 31 October.

Because the Advisory Group's time is a limited resource and so that they could give full consideration to each comment, IARC requested that public comments be concise, limited to 5000 words (approximately 10 pages), and that organizations not sponsor or coordinate multiple comments. There were no complaints about these limitations.

Comments were received from six individuals and six organizations.

Individuals
Tom Gebel, Federal Institute for Occupational Safety and Health, Germany
Morris Greenberg, Department of Health (retired), UK
Sandro Grilli, University of Bologna, Italy
James Huff, National Institute of Environmental Health Sciences, USA
Ron Melnick, National Institute of Environmental Health Sciences, USA
Lorenzo Tomatis, International Agency for Research on Cancer (retired)

<u>Organizations</u>
American Chemistry Council (ACC), USA
CONCAWE (oil companies' European association), Belgium

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Belgium
International Institute of Synthetic Rubber Producers (IISRP), USA
International Union, United Automobile, Aerospace and Agricultural Implement Workers of America (UAW), USA
Natural Resources Defense Council (NRDC), USA

The comments have been made available to the Advisory Group that will meet in December 2005 to review the draft amended Preamble. The comments have also been posted on the *Monographs* website.

IARC thanks all public commenters for their contributions to the process of amending the Preamble.

1. Background

There were no comments on this section.

2. Objective and scope

2a. Meaning of "consensus." There was a request to clarify whether the introduction of the term "consensus" represents avoidance of the word "vote" or a change from a voting-based process [Huff, ECETOC/IISRP]. There was also a request to describe the process of achieving consensus [ECETOC/IISRP].

2b. Definition of "carcinogen." There was support for including the concepts of latency, severity, and multiplicity in the definition of the term "carcinogen" [NRDC], although there were also requests to clarify the meaning of "severity" [Melnick] or how a reduction in latency or an increase in severity or multiplicity will be determined [ECETOC/IISRP]. There was a suggestion that the definition refer to an "agent," not an "exposure" [Melnick]. There was also a suggestion to consider an increase in total tumours (all sites combined) [Huff].

2c. IARC Scientific Publications. There was a request to specify that conferences that develop IARC Scientific Publications on the use of mechanistic data should follow the same conflict-of-interest procedures as *Monograph* meetings [NRDC].

2d. Quantitative risk assessment. Caution was expressed that developing dose-response assessments in some cases can raise several questions [ECETOC/IISRP]. One commenter thought that carcinogenic potency should be calculated whenever possible, though not for species-specific tumours [Grilli], while another commenter warned that dose-response assessments are difficult and should not be used to declare a "safe" level of exposure on the basis of insufficient data or untested hypotheses [NRDC].

2e. "Hazard" or "risk"? There was support for discussing the distinction between hazard and risk [UAW]. Several commenters thought that the title should refer to carcinogenic "hazards," not carcinogenic "risks" [Grilli, Huff, CONCAWE]. Another commenter noted that the same distinction between "hazard" and "risk" does not exist in languages other than English [Tomatis].

3. Selection of topics for the *Monographs*

3a. Nominations by individuals. There was a request to clarify how individuals can nominate topics and how IARC decides when a re-evaluation is warranted [Melnick].

4. Data for the *Monographs*

4a. Inclusion of studies that are deliberately not published. Concern was expressed that IARC needs to include well designed and well conducted studies that have been deliberately kept confidential [Grilli].

4b. Abstracts. One commenter felt that the use of abstracts is troublesome, because they are often not peer reviewed and provide only sketchy details [ECETOC/IISRP].

4c. Studies not considered by the Working Group. There were requests that intentionally omitted studies should be listed to distinguish them from those that were not found [Huff, Melnick]. If a Working Group judges a study to be inadequate, there is value in stating this so that others cannot claim that there were no criticisms of the study [Huff]. One of the commenters indicated that omission criteria are needed especially for mechanistic data [Melnick].

5. Meeting participants

5a. General comments. There was support for the new text that clarifies the roles of all participants, describes the limitations on Invited Specialists, gives guidance on Observers, and describes the process of obtaining a Declarations of Interests both before the meeting and again at the opening of the meeting [NRDC, UAW]. One commenter requested further clarification about which *Monograph* sections an Invited Specialist may draft [Gebel], and another requested amplification that Invited Specialists may not vote [Huff].

5b. Avoiding conflicts of interests. There was support for the designation of Invited Specialist, including the limitation on writing text [NRDC, UAW]. Some organizations, however, thought that panels should be composed of the most qualified experts irrespective of affiliation, that affiliation alone should not be taken as synonymous with a conflict of interests, and that conflicts of interests should be addressed through disclosure, not through limitations on participation [ACC, ECETOC/IISRP]. These organizations also thought that "commercial interests" should include anyone receiving compensation or support in any manner and, thus, would include individuals from non-governmental organizations that are dependent on agenda-driven foundations [ACC, ECETOC].

5c. Balance of different perspectives. A diverse set of commenters mentioned balance as an important consideration [Greenberg, Melnick, ACC, UAW]. Some thought that even with the limitations on Invited Specialists and the guidance for Observers, there should be balance among Invited Specialists and among Observers. They requested that IARC seek out and fund Invited Specialists and Observers from non-governmental organizations when those with commercial interests are admitted [Greenberg, UAW].

5d. Representatives. There was a suggestion that Representatives should have similar limitations as Observers, both in numbers and in manner of participation [Huff].

5e. IARC Secretariat. One commenter urged that IARC Secretariat involvement in the subgroups be limited to only one staff member [ECETOC].

6. Working procedures

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6a. Production data. One commenter suggested that the Preamble not assert that publishing available production data might disclose confidential information [Huff].

6b. Preparation of first drafts by IARC staff. One commenter suggested returning to the prior text that mentioned that IARC staff could also prepare first drafts [Tomatis].

6c. Public comments on first drafts. There was a request that first drafts should be completed well before the meeting and placed on the IARC website for public comment [ECETOC/IISRP]. Another commenter noted that since first drafts are sent to Observers, they should also be made available to others who request them [Huff].

6d. Connection between exposure assessment and epidemiology. There was a request that the subgroup on cancer in humans should include experts in exposure assessment and that they should summarize the data on exposure levels from the epidemiological studies [UAW].

6e. Consideration of epidemiological studies and cancer bioassays before discussing mechanisms. There was a request that plenary discussions of the sections on cancer in humans and cancer in experimental animals should occur earlier in the meeting to determine whether there is consensus about which responses should be addressed in the section on mechanistic and other relevant data [ECETOC].

6f. Recording of votes. There was a suggestion to record the votes, citing the NTP practice of over 25 years [Huff].

7. Exposure data

7a. General comment. There was support for encouraging Working Groups to obtain exposure data from developing countries, as this should improve relevancy [NRDC].

7b. Modelled exposures. There was a request to state the requirements for validation of exposure estimates that come from models [Melnick].

8. Studies of cancer in humans

8a. Types of studies. One comment noted that the prior definition of relative risk has been replaced by a poorly defined generic term [ECETOC/IISRP]. Another commenter requested that the reliability of mortality and incidence data be discussed [Melnick]. Another commenter requested that the limitations of correlation studies be further discussed, including confounding by unmeasured agents in the same environment and lack of independence of correlation studies of identical design or by a single research group [CONCAWE]. Other commenters requested that case reports and clusters be reviewed in the *Monographs* and described more positively in the Preamble, noting that many carcinogens in the workplace were first identified by case reports [Huff, Tomatis].

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8b. Quality of studies. One commenter requested that "quality" should be more carefully defined when weighing studies, to giver greater weight to studies with higher exposure, latency, observation period, and duration; latency being a stronger indicator than duration because of health-related termination of employment. The same commenter noted that null studies where low-exposed engineers and supervisors are included should be given little weight because of a more pronounced healthy worker effect in these groups [UAW]. There was support for the statement about caution with followup studies that include an index cluster [IISRP].

8c. Meta-analysis. There was a request that the new section on meta-analysis should note that the increased precision does not remove the potential for bias [ECETOC/IISRP].

8d. Inferences about mechanisms. There was support for the new mention of peak exposures as important, and it was suggested that this could be expanded to include intermittency [IISRP]. There was also a request that biomarker data be used only after mechanistic relevance to causality is established by the subgroup on mechanistic and other relevant data [ECETOC/IISRP]. Another commenter suggested that the utility of these data is overblown [Huff].

8e. Criteria for causality. There was a suggestion to cite AB Hill as the original source of the criteria for causality [Huff]. Concern was also expressed about relying too strictly on a cutoff of $p<0.05$ for statistical significance [Huff].

9. Studies of cancer in experimental animals

9a. Benign tumours, mortality adjustments. There was support for the criteria for combining benign and malignant tumours and for using mortality-adjusted tumour rates [UAW].

9b. Cell proliferation and other mechanistic aspects. Some more recent references were suggested to complement the Cohen & Ellwein reference [Huff]. Other commenters suggested that the paragraph be updated to expand the focus beyond DNA damage and cell proliferation to include newer mechanistic aspects, for example, cell death rates and receptor-mediated changes in gene expression [Melnick, Tomatis].

9c. Historical controls. There was support for the text on historical controls [Huff]. There was a request to specify that historical control data should be from the same laboratory, strain, and timeframe [Gebel]. There was also a request for further guidance and a suggestion that IARC need not accept a study investigator's conclusion about historical controls [Melnick].

10. Mechanistic and other relevant data

10a. General comments. There was support that this section should focus on relevant data, not all data [ECETOC]. There was support for following the May 2005 Advisory Group's recommendation to use the term "mechanisms of carcinogenesis" rather than "mode of action" [Huff]. There was a request to be more specific about which mechanistic data are relevant [Melnick]. Diverse commenters thought that the increased focus and new section on susceptibility would result in a more complete discussion [Melnick, IISRP, NRDC]. There was also support for the inclusion of developmental and reproductive toxicity as they pertain

to cancer evaluations [NRDC], and an opinion that these effects are irrelevant to carcinogenesis and that their inclusion needs to be justified in the Preamble [Huff].

10b. Gene inactivation, absence of mutagenicity. There was a request that the paragraphs on genetic toxicity should discuss gene inactivation. The same commenter wanted it noted that the absence of mutational activity provides no evidence for null carcinogenic potential [UAW].

11. Summary and integration

11a. General comment. There was broad support for an integration section that explains the basis of the conclusion, and several commenters thought that this would improve the transparency of the evaluations and increase public confidence and understanding [ECETOC, IISRP, NRDC]. One commenter suggested the word "rationale" instead of "integration" for the title of the new section [Tomatis].

11b. Effects of combined exposures. There was a request to mention the effects of combined exposure of the agent with other agents, for example, co-carcinogens, promoting agents, or modifying agents [Tomatis].

12. Evaluation

12a. Evaluating carcinogenicity in humans. There was general support for identifying the target organ when there is *sufficient evidence* in humans, for expanding the criteria for *evidence suggesting lack of carcinogenicity* in humans, and for expanding the guidance on evaluating mechanisms of carcinogenesis [IISRP]. Another commenter also supported identifying the target organ, but requested that care be taken not to imply that other cancers cannot be attributed to the agent [Tomatis]. There were suggestions to split *inadequate evidence* to identify where there are no data at all [Huff, UAW]. There was also support that *evidence suggesting lack of carcinogenicity* should mention age at exposure and other exposure conditions, but concern was expressed that this descriptor should not be used without overwhelming evidence [NRDC].

12b. "Both sexes of a single species." There was a sharp division over the proposed change that positive results in both sexes of a single species in a GLP study can provide *sufficient evidence of carcinogenicity*. Some supported the change, saying that activity in both sexes is stronger evidence than activity in one sex, and that the issue is the quality of the study [Huff, NRDC, UAW]. Others objected to the change, saying that the certainty afforded by replication in an independent study is not fully replaced by the certainty afforded when a study is conducted under GLPs [ACC, CONCAWE, ECETOC/IISRP].

12c. High spontaneous incidences. There was a suggestion to delete "certain neoplams which may occur spontaneously in high incidences in certain strains," because in such cases statistical significance would be achieved only with an incidence that is considerably increased [Huff].

12d. "Does not operate in humans": a matter of hazard or risk? Some commenters thought that the paragraph that begins, "Current or anticipated levels of human exposure are not used to determine whether a mechanism operates in humans," is somewhat unclear and ambiguous [Huff, Tomatis, ECETOC] or should not apply to exposures that are not

realistically achievable [IISRP]. Another commenter supported the idea expressed in the draft Preamble and advised that determining a dose where a mechanism does not operate in humans is a matter of quantitative dose-response assessment, not of hazard identification [UAW].

12e. Classification system. There was a suggestion to replace Groups 2A and 2B by a classification similar to those used by the European Union or by Italy [Grilli]. There was also a suggestion to introduce another group between Group 2B and Group 3 for "equivocal evidence" [Huff].

12f. Assessing *possible* carcinogenicity based on strong mechanistic data. There were several views about the proposed change allowing a classification of *possibly carcinogenic to humans* (Group 2B) solely on the basis of strong evidence from mechanistic and other relevant data. There was support for this idea as consistent with increasing confidence in mechanistic data from well designed and well conducted studies [NRDC]. Another commenter suggested extending this to permit a classification of *probably carcinogenic* (Group 2A), citing the classification of benzidine-based dyes based on toxicokinetic data as an example [Melnick]. Another commenter noted that the use of mechanistic data as the sole basis for a classification in Group 2B should recognize some clearly inherent limitations [ECETOC/IISRP] and requested that such classification should be based on the full statement from IARC Scientific Publication 146 [IISRP]. On the other hand, it was also felt that biomarker data should be seen as supporting information and should not be used as the sole basis for a classification in Group 2B [CONCAWE]; this commenter also suggested that biomarker data should be summarized under "Mechanistic and other relevant data," not "Studies of cancer in humans."

12g. Downgrading *sufficient evidence* in experimental animals based on strong mechanistic data. One commenter felt that mechanistic data should not be used to downgrade a classification, because this involves extrapolating mechanistic parameters between experimental animals and humans [UAW].

12h. Difference between weight of evidence and potency. There was a request to expand the statement that IARC classifications do not address potency [CONCAWE].

Other comments

13a. General comments. There was support for the recent publication of *Monograph* procedures in *Environmental Health Perspectives*, of *Monograph* meeting results in *Lancet Oncology*, and availability on the website of participant lists and requests for Observer status [NRDC]. There was also support for replacing "chemical compound" by "agent" [NRDC].

13b. Re-evaluations where there had been conflicts of interests. There was a suggestion that IARC should reconsider past evaluations where persons with a conflict of interests had a material role in the classification [UAW].