



EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS AISBL

COMMENTS ON PROPOSED IARC PREAMBLE CHANGES

Section 2. Objectives and Scope

- Uncertainty whether classification decision process is being revised from a voting to a "consensus" evaluation

The proposed preamble has added wording in several places indicating that classification decisions will be consensus-based (see page 2, line 4 and page 6, line 23). If this is a real change from the current voting-based procedure, how will consensus be achieved? Can one dissenter prevent a change in the classification? In summary, the preamble should clarify and specify the meaning and process of deciding classifications based on consensus.

- Expansion of the definition of a 'carcinogen'

In the current preamble a *carcinogen* denotes "an exposure that is capable of increasing the incidence of malignant neoplasms." The proposed preamble expands this definition to also include exposures capable of "reducing their latency, or increasing their severity or multiplicity" (page 2, lines 10-11). It is not clear how or whether this expanded definition can be determined. For example, current epidemiological analyses often ignore latency and use lag instead. Additionally, it is unclear what the term "severity" means, e.g., does this refer to aggressiveness of the tumor, case fatality ratios, etc. Finally, presumably multiplicity refers to the number of malignant sites, but this and the other terms need better definition.

- Appropriate incorporation of IARC Scientific Publications on use of specific mechanistic data in human cancer evaluation

IARC has a strong track record in publishing state-of-the-art evaluations of mechanistic data (e.g. Species Differences In Thyroid, Kidney And Urinary Bladder Carcinogenesis, Report 147, 1999 and Peroxisome Proliferation and its Role in carcinogenesis, Report 24, 1995). Previous to now, these publications have not been referred to in the preamble but have greatly improved monograph discussions and interpretation of cancer hazard.

- Apparent expansion of 'charter' to include dose-response/extrapolation in addition to hazard identification

The current preamble specifically states that quantitative extrapolation from experimental data to human situations is NOT undertaken. This text has been removed and replaced with text indicating that IARC may estimate dose-response "within the range of the available epidemiological data, or it may compare the dose-response from experimental and epidemiology studies." (page 2, line 49 to page 3, line 3). Further, in some cases a separate publication may be prepared on dose-response analysis (page 3, line 3). The concept of a separate publication on dose-response raises several questions, such as will the objective be to identify a benchmark dose, will the new publication be a hazard identification or a risk assessment, etc?

Section 4. Data for the Monograph

- Loosening of criteria for data that can be included

The proposed preamble now allows for abstracts and doctoral theses to be used by the Working Group on an ad hoc basis if considered pertinent (these data sources are not allowed under the current preamble). The use of abstracts in particular is troublesome in that abstracts are often not peer reviewed, provide only sketchy details on methods, etc.

Section 5. Meeting participants

- Exclusion of experts from Working Groups who have perceived or real conflicts of interest

The proposed preamble indicates that experts with real/perceived conflicts of interest will be excluded from Working Groups but can be "Invited Specialists" (page 4, lines 37-38 and line 42). Invited Specialists cannot serve as meeting chair or subgroup chair, cannot draft text that pertains to cancer data, or participate in the evaluations. Based on the above criteria, it would seem that industry scientists could never be a Working Group member, even though they may have generated critical data and have an excellent scientific track record. We would suggest that scientific knowledge and expertise [e.g., actual conduct of key studies] take precedence, and that any potential or real conflicts of interest be addressed through declaration.



The challenge for IARC is to assure that the best expertise has a seat, and voice, at the table. This can be realized by seeking a balance in expertise with an insistence that all potential conflicts be fully and transparently declared. It is unclear how IARC's new policy of including "specialists" in the review process achieves this goal given that Cogliano et al. (2004) appears to exclude individuals with "commercial interests." It is important to recognize that "commercial interests" would include individuals having, seeking, or who in the future could seek grants on the basis of IARC decisions. "Commercial interests" would also include individuals from NGOs who are dependent on gifts and grants from agenda-based foundations, individuals, etc. (i.e. the NGO could lose funding if said agenda is not fulfilled to the satisfaction of donors). If IARC is effective at achieving a balance of expertise, they should be confident that no specific individual could drive inappropriate science conclusions that would not otherwise be counterbalanced by other experts in the Working Group.

IARC staff members are very important to the process of each subgroup at a Monograph meeting, to help with format, to provide needed literature, etc. However, in the interest of transparency, we urge that IARC staff involvement in the subgroups should be limited to the one staff member assigned to the subgroup. This would avoid any perception that the deliberations, and subsequent conclusions of the subgroup and even the overall Working Group, could be overly influenced by IARC staff opinions. We express this concern particularly due to the fact that when styrene was last reviewed (Vol. 82), more than half of the epidemiology subgroup was IARC staff members.

Section 6. Working procedures.

Selection of participants a year in advance is commendable, but we would urge that there needs to be more emphasis on completing draft sections 1-4 sufficiently before the Monograph meeting in order to allow adequate review by participants. In some past instances, drafts were not made available to Monograph Workgroup participants in advance of meetings. We further recommend that the drafts should be made available on the IARC Website, and that the public be allowed to comment, in order to enhance the transparency of the Monograph process. Again, as noted above, many industry, scientific, and academic organizations that conduct research on a particular chemical or substance may have significant sound scientific comments to offer, which could contribute to and enhance the Monograph process. We therefore believe that comments from the public should be fully considered by Workgroup participants.

Section 8. Studies of cancer in humans.

- Removal of definition of 'relative risk'

The strong definition of 'relative risk' in the previous preamble is removed and replaced with the very generic, poorly defined term 'effect' (page 8, line 22). Lack of a clear definition and replacement with a generic term reduces the scientific rigor of the document.

- Addition of new section on meta-analysis

A new subsection is added indicating meta-analyses and combined analyses can be considered. While meta-analysis is clearly a useful and important tool, the text tends to imply that meta-analysis is a solution to small study limitations. It should be noted that the possible increased precision from meta-analysis does not remove the potential for bias, i.e., the underlying limitations of the original data remain, as do inherent questions of interpretation.

- Possible mis-use of molecular epidemiology data

The proposed preamble introduces the use of mechanistic biomarkers in the assessment of causality by the Epidemiology Working Group (page 11, line 3). This text states that the marker data will be used either only in the Other Relevant Data (ORD) subgroup or the Epidemiology subgroup. However, the use of marker data by the Epidemiology subgroup should proceed only after the mechanistic relevance to causality is first established by the ORD and before consideration in any evaluation of causality.

Issue 10a. The issue is whether there should be additional guidance on the understanding of mechanisms in the Preamble.

The Advisory Group says that the Monograph should reflect the state-of-the-art at the time of the Monograph and therefore, additional discussion in the Preamble would be outdated. The comment says “Section 4 of the Monographs should discuss critically the evidence on mechanisms of carcinogenicity as it pertains to the overall evaluation of carcinogenesis, in the perspective of and in parallel with the discussion of animal and human data in Sections 2 and 3.”

Comment:

Since Section 2 and 3 are not finalized until voted on the last day, it is not clear how it is possible to develop a Section 4 reflecting the conclusions of Sections 2 and 3. Plenary discussions on Section 2 and 3 should be taken earlier in the process, even if not voted on

until the last day. An earlier discussion would determine if there were consensus, and what potential carcinogenic responses should be addressed.

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

The Advisory Group commented on the vast amount of time spent on wording of many toxicological studies, which have no impact on a cancer classification. And recommended changing Section 4 to:

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Pharmacokinetic data

4.2 Mechanistic data

4.3 Data on susceptible individuals, populations and life stages

4.4 Relevant data on toxicity

4.5 Additional relevant data

Comment:

The previous Monographs have provided a good literature source for a chemical and are often relied on as a thorough description of exposure and toxicity of a chemical. In contrast, the U.S. Environmental Protection Agency states that their Toxicological Review of a chemical is of studies relevant to the endpoints and not necessarily comprehensive. It seems that the chemicals that have the most mode of action data also have the most general toxicity data. Thus, a comprehensive toxicity summary seriously reduces the amount of time for discussion and evaluation of mode of action. We agree that Section 4 should focus on relevant data, not all data.

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

This Advisory Group recommends that the Preamble be updated so that the finding of carcinogenicity in both sexes of the same species tested in a good laboratory practice (GLP) be treated as providing sufficient evidence. The emphasis should be on whether the body of animal data as a whole supports a finding of causality in animals. Currently, a finding of sufficient evidence of carcinogenicity in animals usually requires unequivocal findings of carcinogenicity in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different

laboratories or under different protocols. This statement is unclear as to whether studies of both genders conducted concurrently in the same laboratory should be treated as independent.

Comment:

This proposal raises a more fundamental issue for evaluating chemicals. The guidelines appear to be geared to identifying as many chemicals as possible as carcinogens, without regard to human risk from these chemicals. This proposal appears to make it possible to list more chemicals as carcinogens.

In the last statement above, the Advisory Group seems confused about plain language that currently says unequivocal findings “(b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols” are required for sufficient evidence. There is nothing in the current statement that suggests that males and females tested concurrently should be treated as independent studies. There is only one protocol; the laboratory schedule calls it one study. Even NTP, who provides evaluations of the degree of evidence separately for males and females, in the report describe “2 Year Study in Rats” and 2 Year Study in Mice.”

Furthermore, the evaluation should be made on a weight of the evidence of all studies on a chemical, not on the number of positives. For many chemicals evaluated there will be only one study in a given species and the description of two positive studies for sufficient evidence makes sense. But for many chemicals there are multiple studies in a given species. At present, if there were a case where there were 10 valid rat studies of a chemical, with 9 having no increase in tumors, and 10 valid mouse studies, with 9 having no increase in tumors, the IARC evaluation would be Sufficient Evidence in animals. Scientifically that cannot be justified. With the proposed change, if 1 of those 20 studies had increased tumors in both males and females and no others had increased tumors, it would be classified as Sufficient Evidence.

The proposal underlines the basic problem with trying to set rules to decide causality rather than using judgment based on weight of evidence. Consider two chemicals; one that causes testicular cancer in rats in an unequivocal, dose related manner; and a second that causes a marginal increase in liver cancer in both males and female rats in a non-dose related manner. After due consideration, it might be concluded that the liver cancers in case 2 were probably related to treatment. Would that provide more “suggestive evidence” of a carcinogen than case 1, where there was no doubt that the testicular cancer was caused by dosing with the chemical?

It should also be remembered that deciding on causality of cancer in laboratory animals is only the first step in considering whether a compound can cause cancer in humans. The concept is based on trying to answer the question “Does the compound cause cancer in humans?” It is becoming much more important to also ask the question “What are the

circumstances in which the compound can cause cancer?” This question has been discussed by Greim and Reuter (Toxicology, 2001, Vol. 166, pp11-23) in relation to the management of potential carcinogens by the MAK Commission in Germany.

Section 12. Evaluation

- Improved criteria for evaluating mechanism of action data

The proposed preamble has added two paragraphs related to mechanism of action. The key points made are: a) conclusion that a mechanism exists is strengthened by consistency, plausibility and coherence, b) consideration should be given to the possibility of multiple mechanisms, and c) demonstration of a mechanism at much higher levels than occur in humans seems to be considered irrelevant. However, the wording is somewhat unclear and ambiguous: “Current...levels of human exposure are not used to determine whether a mechanism operates in humans. In terms of the risk assessment paradigm...a conclusion that a mechanism does not operate in humans is a matter of hazard, not exposure or risk. Such a conclusion should be valid in the case of accidental and unanticipated human exposures that are difficult to foresee at present.” (page 22, line 7-17)

- Loosening of criteria for Sufficient Evidence of Carcinogenicity in Animals

The proposed preamble has revised the criteria for what constitutes sufficient evidence of carcinogenicity in experimental animals. Under the proposed preamble, there would now be three scenarios under which data would be considered Sufficient:

1. Neoplasms in two or more species,
2. Both sexes of a single species in a study conducted under Good Laboratory Practices [e.g., a U.S. National Toxicology Program study] (new) and
3. Two or more independent studies in one species or a single study in one species and sex when there is unusual occurrence of malignant neoplasms (incidence, site, type, age at onset) or a strong finding of tumors at multiple sites (modified).

Revision #2 above suggests that IARC believes that findings in the second sex endorse the validity of a finding. However, findings in the second sex in fact offer no information about the repeatability of the finding in another strain, species, or in another laboratory. As such, it is of less scientific rigor compared with scenarios 1 and 3 above. Therefore, revision #2 should remain under Limited evidence of carcinogenicity (note: this does not preclude the application of mechanistic data to elevate the cancer classification).

- Greater influence for mechanistic data in elevating cancer classifications

The proposed preamble now states that "possible carcinogenicity can be assessed solely on the basis of strong evidence from mechanistic and other relevant data" [i.e., it would now be possible to elevate from a Group 3 - Not Classifiable, to a Group 2B – Possibly Carcinogenic, based solely on strong mechanistic or other relevant data] (Page 23, line 35). This new addition indicates the influence of mechanism and genetic toxicology data. However, there are clearly inherent limitations in the sole use of surrogates to assess cancer hazard, which must be recognized.

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

The Advisory Group Notes. A typical evaluation section is a series of statements in the form:

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

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

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

This Advisory Group is of the opinion that the Monographs would be improved if information describing the manner in which evaluations were derived with respect to carcinogenicity in humans, carcinogenicity in animals and any evidence of a mechanism were added.

The Advisory Group further noted that this lack of stated reasoning led to confusion when chemicals were re-evaluated and it was not clear what led to a change. The Advisory Group cited styrene as an example. "In another example, in Volume 60, the classification of styrene was raised from Group 3 to Group 2B because styrene is metabolized to styrene-7,8-oxide, which was found in the blood of exposed workers together with DNA adducts, haemoglobin adducts, DNA damage and chromosomal damage, but a re-evaluation in Volume 82 does not mention why these other relevant data did not affect the later classification into Group 2B."

Comment:

For all evaluations a short sentence on the basis of the conclusion would be very helpful.