COMMENTS ON PROPOSED IARC PREAMBLE CHANGES

Section 2. Objectives and Scope

- Further clarification needed regarding classification decision process (voting vs "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.

- Further clarification and justification needed for expanded definition of '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. Also, it is unclear how IARC will assess whether an exposure reduces latency (will latency be examined in an unexposed group and compared with an exposed group's latency, will there be a 'standard' assumed 'causal latency' duration used to assess studies?). 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 explicitly referred to in the preamble although they have greatly improved monograph discussions and interpretation of cancer hazard.

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

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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

- Reduced scientific rigor of data inclusion criteria

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

- Inappropriate focus on potential financial/other conflicts of interest rather than on scientific expertise

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 (but not grounds for exclusion).

Section 6. Working procedures.

- Opportunity to capture relevant data and improve transparency through posting of working drafts for public comment

  IARC should consider making working drafts available for public comment prior to Monograph meetings. This would have the benefit of identifying significant information that may have been overlooked and enhance transparency of the process.

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Section 8. Studies of cancer in humans in humans.

- Reduced scientific rigor of definition for '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. IARC should retain the original definition of 'relative risk'.

- Appropriate inclusion of meta-analysis, but need for enhanced description of limitations

A new subsection is added indicating that 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. Several limitations of meta-analysis are noted, but IARC fails to indicate that 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 (this additional limitation should be explicitly stated).

- Potential 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 Mechanistic/ORD group and before consideration of any evaluation of causality. The Mechanistic/ORD group would also give significant scientific weight to absence of responses seen in well conducted molecular epidemiology studies.

- Appropriate recognition of the potential role of peak exposures and impact of 'clusters' on follow up investigations

An important addition that strengthens the proposed preamble is the recognition of the potential importance of peak exposures (page 10, line 24). However, this could be further strengthened by inclusion of consideration of exposure profile (i.e., both peak and intermittency). Finally, the proposed preamble appropriately cautions in the interpretation of studies where follow up investigations include the original index cluster (page 9, lines 5-7).

Section 10. Mechanistic and other relevant data.

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- Appropriate increased focus on use of mechanistic data but more explicit definition needed in certain areas

  The proposed preamble appropriately places greater emphasis on mechanistic data and its integration. Paragraphs have been added on mechanisms for structural changes, functional changes and morphological, physiological or behavioral changes. Also, a paragraph has been added regarding increased susceptibility. The purpose of these additions will be to present a more complete and up-to-date discussion of current state of knowledge, including existing data gaps.

  However, there are two areas that could be strengthened with regard to the use of mechanistic data. Note: these are applicable to and first appear in Section 12 of the proposed preamble.

  1) IARC states that a conclusion that a mechanism does not operate in humans is not based on exposure or risk, but purely on hazard potential. This is unfortunate since there are cases where it is possible for an agent to be carcinogenic at exposures not realistically achievable and yet would not have any carcinogenic potential through alternate mechanisms at lower exposures.

  2) The classification of cancer based solely on mechanistic data is potentially problematic. The conclusions of the Expert Working Group contained in Volume 146 were as follows:

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

  The proposed preamble paraphrases the above text as "strong mechanistic data", which can by itself lead to a cancer classification. IARC should use the explicit definition provided by the Working Group rather than the simple phrase "strong mechanistic data".

Section 11. Summary and Conclusions

- Improved transparency of Monograph evaluations

  Section 11 of the proposed preamble is a new subsection, which makes it 'mandatory' for the Monograph to include important factors that have heretofore been absent. These include: a) reasoning and rationale for the Working Groups evaluation, b) integration of the human, animal and mechanistic data, c) principle line(s) of argument including strength of evidence, identification of pivotal studies and Working Group's reasoning in weighing data and making evaluations, and d) when consensus could not be reached the differences in scientific opinion and their relative degree of support should be discussed.

Section 12. Evaluation

- Improved description of target organ for Sufficient human evidence category

  The proposed preamble has added the requirement to describe the target organ where cancer increases are observed in humans.

- Improved specificity of criteria for human evidence suggesting a lack of carcinogenicity in humans.

  The proposed preamble includes further definition of criteria for reaching a conclusion of no effect. The text indicates that studies should have tight confidence intervals with upper confidence limits near 1.0. Follow-up should be of adequate length and there should be reasonable confidence that bias and confounding can be ruled out.

- Improved criteria for evaluating mechanism of action data but more explicit definition needed in certain areas

  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.

  The proposed preamble 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 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). As noted earlier for **Section 10. Mechanistic and other relevant data,** there is a need for a more explicit definition of 'strong mechanistic' data and its use to elevate a cancer classification in the absence of evidence of neoplasia. Finally, there are inherent limitations in the sole use of surrogates to assess cancer hazard which also should be recognized and stated in any evaluation.

- Reduced scientific rigor 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) (new) "both sexes of a single species in a study conducted under Good Laboratory Practices [e.g., a U.S. National Toxicology Program study], and 3) (modified) 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.

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Revision #2 above suggests that IARC believes that findings in the second sex endorses the validity of a finding. However, findings in the second sex in fact offers no information about the repeatability of the finding in another strain, species, or in another laboratory, or under a different experimental protocol. In other words, findings in the second sex contribute to evidence of consistency of findings, but do not provide any information regarding the repeatability of findings. 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).

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