

Director of IARC Monograph Programme

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Your ref.:

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28 October, 2005

Dear Sirs,

Comments on public draft of the revised Monograph preamble

CONCAWE is pleased that the IARC Monograph group is seeking public comments on its proposals for revision of the monograph preamble. CONCAWE highly appreciates the thorough scientific evaluations carried out at IARC. Clearly, as science develops and experiences accumulate, there is the occasional need to update the general guidance under which the evaluations are done. Our comments are submitted in a spirit of contributing to the continuous improvement of the monograph process.

We have reviewed the proposed text (posted on the IARC web site on 31 August 2005) and consider the changes as generally for the good which should lead to better, more transparent decisions. The following points are suggested for further reflection or improved clarification:

- Hazard v Risk (p.2): The revised draft has not resolved this issue, which causes much confusion in the scientific and regulatory community. As stated in the preamble, the monograph process is a hazard determination yet the title still contains the word risk. As the monograph team do not consider exposure or dose response relationships we think the monograph title should make it clear that it is an evaluation of carcinogenic hazard not risk and suggest the title should be 'IARC Monographs On The Evaluation Of Carcinogenic Hazards To Humans'.
- Correlation studies (p.8): We agree with the notion about the general weakness of correlation studies for inferring causality in an observed dose-response relationship, but we think that this guidance should be further specified. A serious shortcoming of correlation studies is that dose-response relationships can only be studied for agents which have somehow been measured; unmeasured agents in the same environment, especially if co-varying with the studied agent, can produce serious confounding. Further, multiple correlation studies using an identical design or by a single research group should not be viewed necessarily as independent contributions in a strength-of-evidence approach, as experience has shown that certain choices and assumptions in the analytical process (which are often not described in the publications) can have significant impact on study results.
- Use of Biomarker Data (pp. 11 and 23): the preamble explains how biomarker data could be used in the evaluation. Biomarkers are an important measure of internal exposure and do provide evidence of biological events at a cellular level. They are not however directly linked with a cancer endpoint and hence should be seen as

supporting information rather than being used as the sole rationale for classification. We suggest that all biomarker data be summarised under 'Mechanistic and Other Data' and not in the section on 'Studies of Cancer in Humans'. Also biomarker data should not be used as a sole basis for Cat 2b.

- Potency (p.19): The IARC conclusions are hazard determinations based on 'weight of evidence' for carcinogenic activity. On page 19 it states that does not address potency. This statement needs to be expanded and strengthened to avoid confusion over what an IARC classification really means.
- Two sexes of a single species (p.20): On page 20, there is a new addition in that sufficient evidence for carcinogenicity in animals is based on a) evidence in two or more species b) both sexes of a single species or c) two or more independent studies in one species. This has been introduced without a supporting rationale. Clearly there can be sex specific mechanisms and this could be used to argue that a study with a positive result in one sex is important and may drive a classification. However if the chemical works via the same mechanism in both species it is not justifiable to count this as two positives. If this section remains then IARC will need to provide some scientific rationale for the decision and also consider what happens to any compounds evaluated previously where these criteria have not been used.

Sincerely Yours,

A handwritten signature in black ink, appearing to be 'Jan Urbanus', with a long horizontal stroke extending to the right.

Jan Urbanus
Technical Coordinator, Health Issues