UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

December 15, 1999

EPA-SAB-EC-LTR-00-001

Honorable Carol M. Browner
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Subject: Science Advisory Board's review of the Draft Chloroform Risk Assessment and Related Issues in The Proposed Cancer Risk Assessment Guidelines

Dear Ms. Browner:

The Chloroform Risk Assessment Review Subcommittee of the Science Advisory Board was convened to review the Office of Water's draft risk assessment for chloroform, with particular attention to the mode of action analysis for chloroform-induced cancer, and the application of the relevant sections of the Proposed Cancer Risk Assessment Guidelines. The Subcommittee met on Wednesday and Thursday, October 27th and 28th in Washington, DC, to address these (and related) issues (A copy of the full Charge is provided in Appendix A).

A full report documenting the findings of the Subcommittee is currently in preparation. This brief letter report, which addresses one element of the Charge, was developed at the request of the Office of Water (OW) in order to provide rapid feedback on their application of a key element of the Proposed Cancer Risk Assessment Guidelines (GLs) (section 2.5, Mode of Action Framework for Analysis) to the chloroform risk assessment. The specific question posed by the OW asked:

> "Based on its application to the chloroform risk assessment, please identify any specific text in the draft Cancer Risk Assessment Guideline's framework for mode of action analysis (section 2.5) which you would advise being changed prior to their publication."

After deliberating on this issue, the Subcommittee wishes to express its overall support for the GLs' (July 1999 draft) framework for determining the importance of different modes of action. Nothing was identified that should hold up their publication. There were, however, a few suggestions that arose

during the Subcommittee's discussion of the Guidelines that would aid in their implementation that we would like to convey to the Agency for consideration:

a) The Subcommittee believes that the mode of action determination should include a step that identifies gaps in knowledge when presenting conclusions in the draft GLs' human relevance section on page 2-35. Gaps that relate to the potential for effects in sensitive populations and/or subpopulations are particularly important in this regard. In this vein, the Subcommittee also suggests that the Agency consider establishing a checklist addressing populations of concern (such as pregnant women and children), similar to that developed by the Food and Drug Administration (FDA), to be considered in each mode of action analysis. This would serve to identify uncertainties in the determination that could be buttressed by further research.

b) The following statement from the draft GLs provides little guidance: "Generally, 'sufficient' support is a matter of scientific judgment in the context of the requirements of the decision maker or in context of science policy guidance regarding a certain mode of action." In the implementation of the GLs, it is suggested that some greater specificity as to what the term "sufficient" means would be useful, as would a statement to the effect that a determination of a mode of action should be based upon experimental evidence. The fact that the hypothesis remains consistent with a number of distinct experimental challenges builds confidence that a certain mode of action is essential to the induction of cancer by a given chemical. Consistency between endpoints related to mode of action and carcinogenic responses should be sought in experiments that give both positive and negative results. The Subcommittee suggests that the statement "Findings that show that other chemicals having parallel toxicological properties also result in a carcinogenic response strengthen the conclusion that a particular mode of action is causal" be included as an additional bulleted item following line 24 of page 2-34 of the GLs.

c) Some attention needs to be paid to terms that are used in describing a mode of action. For example, what is meant by "sustained" when referring to cytotoxicity, cell replication, or regenerative hyperplasia? This usage seems to imply that the effect must recur for some minimum period of time. Some guidance is needed, since most studies of such effects are of very limited duration. The use of the terms "linear" and "non-linear" dose-response curves in the GLs also create some confusion and should be more clearly defined. It may be that all dose-response curves for cancer have some non-linear character and linear relationships can have non-zero intercepts.

d) There is an implicit recognition that mutations are an inherent part of carcinogenesis in the GLs. It would be useful to point out that the carcinogenic activity of some chemicals appears to involve modifications of cell division and cell death processes.

Such chemicals act to 1) permit the expression of previously experienced genetic damage and 2) promote clonal expansion of cells containing mutations that result in autonomous growth. In this case the mutations can be produced by a variety of endogenous and exogenous processes, which collectively are said to arise "spontaneously." This is a generic idea that provides some perspective with respect to a number of modes of action that can contribute to a carcinogenic response without direct interaction with DNA, including cytotoxicity, cell replication, and reparative hyperplasia. Such a discussion might be usefully placed in section 2.5.3 of the GLs where a number of potential modes of action are identified.

We appreciate this opportunity to review an application of the Agency's proposed Cancer Risk Assessment Guidelines and look forward to receiving the responses of the Assistant Administrators of the Offices of Water and Research and Development. The Subcommittee will work to bring our deliberations on the other elements of the Charge for this review to an early conclusion.

Sincerely,

/ s /

Dr. Joan M. Daisey, Chair
Science Advisory Board

/ s /

Dr. Richard J. Bull, Co-chair,
Chloroform Risk Assessment
Review Subcommittee
Science Advisory Board

/ s /

Dr. Mark J. Utell, Co-chair,
Chloroform Risk Assessment
Review Subcommittee
Science Advisory Board

APPENDIX A - CHARGE

General Purpose: Review the Mode of Action Determination and Selection of Nonlinear Dose-Response Approach for Chloroform under EPA's Proposed Cancer Risk Assessment Guidelines Revisions, and identify specific statements or text in section 2.5 of the draft Cancer Risk Assessment Guidelines which, based on its application to the chloroform risk assessment, you would advise be changed prior to final publication.

Charge 1: Based on its application to the chloroform risk assessment, please identify any specific text in the draft Cancer Risk Assessment Guideline's framework for mode of action analysis (section 2.5) which you would advise be changed prior to their publication.

Charge 2: Specific questions:

a) In the draft chloroform risk assessment document, are the conclusions as to the following issues adequately supported by the analyses presented in the health risk assessment/characterization (as supported by the ILSI report) and the framework analysis?

(1) chloroform's mode of action

(2) consideration of a nonlinear approach to dose-response, and the possibility that mutagenesis might play a role in the carcinogenic response.

(3) the relationship of low-dose pathology to the doses that induce tumors.

(4) epidemiologic evidence on chlorinated drinking water as to the carcinogenicity of chloroform, including comment on any conclusion to be drawn from the epidemiologic data about mode of action.

b) Does the assessment of children's risk for chloroform appropriately address the risk concerns, including ontogeny of drug metabolizing enzymes), given the data available?

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