



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

OCT 7 2003

THE ADMINISTRATOR

Dr. William Glaze
Dr. Henry Anderson
Science Advisory Board
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Dear Dr. Glaze and Dr. Anderson:

Thank you for providing me with the Science Advisory Board's (SAB) review of U. S. Environmental Protection Agency's (EPA) draft *Trichloroethylene Health Risk Assessment: Synthesis and Characterization*. I applaud the thoroughness of your review. Your review report has been forwarded to the Office of Research and Development's (ORD) National Center for Environmental Assessment (NCEA). In revising the draft assessment, please be assured that NCEA will carefully address the SAB's comments and those from the public.

EPA generally agrees with the review panel's recommendations on a number of important issues. These include developing further analyses to clarify the role of different metabolites in the toxicity of trichloroethylene (TCE), improving the transparency of the modeling methods used, and developing a stand-alone chapter to discuss issues related to children. In the revised document, EPA will also consider and discuss the panel's relevant perspectives on other matters, such as how to improve the quantitative analysis for effects other than cancer and the appropriate method for addressing background exposures. Enclosed is a summary of ORD's response to key SAB review points.

As you know, TCE is a chemical of great importance to the Agency and to many stakeholders. Because of this high visibility and because addressing the issues raised by the SAB review panel will require incorporating new scientific information and analyses, EPA is planning to gather additional scientific input through a number of mechanisms. Activities related to this scientific outreach effort include a public symposium on recently published scientific findings related to TCE, as well as a consultation with the National Academy of Sciences that includes a review of EPA's revised document. In addition, prior to finalization of the TCE assessment, the public will have another opportunity for review and comment.



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I appreciate the SAB's recognition of the assessment's groundbreaking work, as well as your suggestion that EPA separately develop cross-cutting consistent policies on the protection of children, cumulative risk and aggregate exposure. We are committed to progress in these areas, and we welcome the SAB's advice.

Again, my thanks to you both and to the members of the review panel for helping to ensure that the Agency's draft assessment reflects the best scientific analyses.

Sincerely yours,

A handwritten signature in black ink, appearing to read "M. L. Horinko". The signature is fluid and cursive, with a prominent initial "M" and a stylized "L".

Marianne Lamont Horinko
Acting Administrator

Enclosure

EPA Office of Research and Development Staff Response to:
Review of Draft Trichloroethylene Health Risk Assessment: Synthesis and Characterization:
An EPA Science Advisory Board Report
EPA-SAB-EHC-03-002, December 2002

In the fall of 2001, the EPA asked the Science Advisory Board (SAB) to convene a panel to review the Agency's August 2001 Draft *Trichloroethylene Health Risk Assessment: Synthesis and Characterization*. Nine charge questions were developed through a public planning process to address a variety of scientific issues regarding the health risks of trichloroethylene (TCE). We would like to take this opportunity to summarize the Office of Research and Development (ORD) staff's response to the major comments. Below, we quote the conclusions articulated in the Executive Summary of the SAB's peer review report, followed by a description of our intentions regarding further analysis or elucidation regarding those comments.

Charge 1: Does the assessment adequately discuss the likelihood that TCE acts through multiple metabolites and multiple modes of action?

SAB Comments:

"EPA should be commended for its efforts to date to evaluate a wide variety of hypotheses for the carcinogenic and other toxic effects of TCE. The draft assessment could be enhanced by including additional selective quantitative analysis and further evaluation of dose-response relationships, especially relationships that may clarify the role of different metabolites in the toxicity of TCE at human exposure levels. Panel members offered several examples of quantitative analyses that the Agency could use to improve the document."

ORD Staff Response:

We thank the SAB Panel for their suggestions as to further elucidating TCE's mode-of-action, and will use them along with recently published findings from scientific literature in revising the assessment. Of particular interest is a recent paper by Bull (2002) using biomarkers that concludes that both TCA and DCA probably contribute to TCE-induced mouse liver tumors. In addition, as suggested by the SAB Panel, we plan to incorporate information derived from biologically-based-dose-response modeling that clarifies the role of different metabolites.

Charge 2: Is the cancer weight-of-evidence characterization adequately supported?

SAB Comments:

"The Panel commends EPA for compiling an extensive array of scientific literature that included over 80 epidemiological studies and hundreds of toxicological and mechanistic studies and for characterizing the evidence relatively clearly and cohesively. The Panel

feels that the Agency's overall qualitative cancer risk characterization was reasonable based on: a) significant experimental evidence showing tumors at multiple sites in two species (rats and mice); b) epidemiologic evidence in humans showing associations between TCE exposure and several cancers including at several of the same sites seen in animal bioassays; and c) mechanistic data indicating relevance of experimental findings to humans. There was a suggestion that EPA clarify more explicitly for the public what is meant by a 'weight-of-evidence characterization.'

The Panel also advises the Agency to improve the characterization of the cancer weight-of-evidence by evaluating human and animal studies more rigorously, explicitly using Agency criteria for evaluating those studies. On a related issue, several panel members noted that the assessment could be strengthened if the Agency emphasized and integrated information about dose-response and if it presented a coherent analysis of quantitative information available on the mode-of-action of metabolites. The Panel also advises the Agency to provide a more thorough discussion and critical evaluation of the conflicting human epidemiological evidence for kidney tumors.

The Panel suggests that it is important to provide both upper confidence limit estimates and the mean 'expected value' estimate when developing risk ranges to give users confidence intervals. It notes that it will also be important for the Agency to provide risk management guidance that might indicate when it is most appropriate to use mean values, or when to use high end values with confidence intervals."

ORD Staff Response:

We are pleased that the SAB Panel felt that the draft assessment's overall cancer risk characterization was reasonable. We agree with the Panel's recommendation to clarify more explicitly the weight-of-evidence characterization, and plan to base our revision on the Agency's revised Cancer Guidelines. We also intend to provide additional detail in our discussion and evaluation of both the animal and human evidence for each tumor type. Furthermore, as the Panel suggested, we intend to integrate the dose-response information related to mode-of-action, as mentioned in our response to Charge Question 1. Finally, we intend to ensure that the revised assessment addresses the appropriate statistical characterization of the range of cancer risk estimates and provides guidance on the interpretation use of those estimates.

Charge 3: A new feature of the cancer database is molecular information on the von Hippel-Lindau tumor suppressor gene. Is this information adequately discussed and are the conclusions appropriate?

SAB Comments:

"The consensus of the panel is that the discussion in the draft assessment is generally appropriate. The panel generally agrees that EPA is wise not to regard the evidence as entirely conclusive pending independent confirmation. The discussion in the draft

assessment might be improved by including some additional comparative observations from kidney cancers not in the TCE exposed workers.”

ORD Staff Response:

We intend to expand the discussion of the mutations of the von Hippel-Landau gene, concentrating in particular on the specificity of the mutation as a biomarker and incorporating recent scientific literature on the subject.

Charge 4: Does the assessment adequately discuss the use of multiple critical effects in developing an oral reference dose (RfD) and inhalation reference concentration (RfC) for effects other than cancer? Are the uncertainty factors well discussed and well supported?

SAB Comments:

“The Panel commends the Agency for consideration of multiple noncancer endpoints in both the general discussion and in the derivation of the RfD and RfC. TCE clearly has important hepatotoxic, nephrotoxic, neurotoxic, immunologic, developmental and reproductive effects that should be considered in the derivation of the RfD and RfC. The use of multiple critical effects increases one’s confidence that the point of departure dose is at the low end of doses at which adverse effects can be observed.

Some panel members suggested that the characterization of the data at each site of toxicity could be strengthened considerably. The Panel recognizes that a lengthy dissertation of each study cited by EPA would be counterproductive. However, in the opinion of some panelists, the current discussion lacks the type of critical analysis and discussion of the weight-of-evidence that is necessary to understand the Agency’s rationale for selection of endpoints, level of concern, dose-response extrapolation, effect of time-duration on key endpoints, and application of uncertainty factors. Other panel members thought the discussion of non-cancer effects and discussions surrounding the development of the RfD and RfC were quite good and that with relatively limited additional clarification the non-cancer section of the draft assessment would be complete.”

ORD Staff Response:

We thank the SAB Panel for their diverse suggestions regarding the development of the RfD and RfC. We agree with the need to clarify our derivation of the RfD and RfC, and intend to follow the suggestion of several Panel members to synthesize the noncancer toxicity information endpoint-by-endpoint. In addition, we plan to expand the discussion of pharmacokinetic issues and of the bases for determining Uncertainty Factors while ensuring consistency with the Agency’s RfD and RfC guidance.

Charge 5: Does the assessment adequately discuss the derivation of a range of estimates for the cancer risk? Are there any studies that should/should not have been included?

SAB Comments:

“The Panel commends EPA for the derivation of a set of cancer risk estimates or cancer slope factors (CSF) for TCE in the draft assessment. The presentation of a range of estimates is a step forward for EPA towards a more explicit and more quantitative representation of the substantial uncertainties in estimates of cancer risks.

The Panel identifies a key study (Hansen et. al., 2001) that should be included in the revision of the draft assessment. The Panel advises that, where epidemiological studies are the basis of risk estimates, EPA should select the broadest possible array of studies for each endpoint taking into consideration study design, availability of exposure estimates, and the goal of protecting health. The Panel commends the Agency for providing sections on sensitive populations and cumulative risks and added several suggestions for strengthening quantitative aspects of the risk assessment methodology that are important for the refinement of the risk assessment of TCE.”

ORD Staff Response:

We thank the SAB Panel for their useful suggestions for improving the discussion of cancer estimates. We agree with the Panel’s advice to carefully examine and clearly explain the basis for estimating cancer risks, taking into account, for epidemiological studies, the considerations of “study design, availability of exposure estimates, and the goal of protecting health.” As part of this analysis, we plan to incorporate the Hansen et al. 2001 study, as suggested by the Panel.

Charge 6: Please comment on the use of calibrated models and uncertainty analysis to address the question of pharmacokinetic model uncertainty.

SAB Comments:

“The Panel commends the Agency’s inclusion of physiologically-based pharmacokinetic models and its explicit recognition of model uncertainty in the draft assessment. It advises the Agency to explain the modeling methods more clearly, and to make the models, data, and assumptions used available, so that the Agency’s results can be reproduced. The Panel calls on the Agency to compare the two calibrated models used and to show how the models and analyses compare and relate to one another. The Panel advises the Agency to highlight the impact of the uncertainty analysis on the dose estimates of the different models and on the dose response analysis and to explain the differences between the models and the ranges of uncertainty.”

ORD Staff Response:

We agree with the Panel's recommendation that the revised assessment be more transparent as to the pharmacokinetic modeling methods used. In particular, we plan to expand the discussion of these models substantially, providing critical evaluation and comparison of the different models used and ensuring the reproducibility of the results to the extent feasible. We also agree that the impact of the uncertainty analyses needs to be highlighted and explained more fully.

Charge 7: Is it appropriate to consider background exposures and other characteristics of an exposed population as modulating the risk of TCE exposure in that population?

SAB Comments:

“The Panel is pleased that the Agency has taken the first steps of including the issue of cumulative risk in a health risk assessment. Although there was agreement that background exposures to TCE and/or metabolites is a very important issue, there was disagreement about whether the RfD, and the uncertainty factor used to derive it, should be the method by which this background exposure is addressed. The Panel agrees, however, that regardless of EPA's final policy decision on whether or not to include an additional uncertainty factor in the RfD for background exposure, more attention and detail is needed to provide a rationale for the Agency's use of such an uncertainty factor.”

ORD Staff Response:

We thank the Panel for their views on the issue of background exposures, and will take all their perspectives into account in revising the assessment. We intend to provide a clear explanation and rationale as to the final policy decision made, as suggested by the Panel.

Charge 8: Do the data support identifying risk factors that may be associated with increased risks from TCE exposure? Are there any risk factors that should/should not have been included?

SAB Comments:

“The Panel finds that the data support identifying numerous risk factors that may be associated with increased risks to susceptible subpopulations from TCE exposure. The EPA draft assessment has done a good job identifying the general areas of concern related to prenatal, reproductive and developmental risks associated with TCE exposure, especially given the level of information known to date. The Panel agrees with the draft risk assessment's identification of multiple background exposures to ethanol, TCE, and its metabolites, and other chemical solvent mixtures as factors that may be associated with increased risks.”

ORD Staff Response:

We are pleased that the Panel commended our identification of factors that may increase risks associated with TCE exposure. We thank them for their comments on the individual risk factors as well as suggestions regarding additional risk factors, and intend expand the discussion to address the Panel's comments.

Charge 9: Do the data support the possibility that TCE can affect children and adults differently? Should this be reflected in the quantitative assessment?

SAB Comments:

“The Panel reached consensus on the following conclusions related to this charge question: a) the data presented suggest that TCE can affect children differently than adults, although there is a very limited database of TCE in children due to lack of directly applicable studies; b) the draft does not explicitly discuss whether or not the uncertainty factors adequately address risk to children or attempt to develop toxicity values that take children into consideration; c) the Panel advises the Agency to develop a stand-alone comprehensive children's chapter that discusses all the children's issues, including exposure, susceptibility during pregnancy, pharmacokinetics, and pharmacodynamics, in addition to discussing developmental animal and children data in every section; and d) the Panel advises the Agency to support statements about differences between children and adults with a quantitative discussion, whenever possible. Although the Panel differs on the question of whether the Agency should add a quantitative uncertainty factor to protect children above the composite uncertainty factor already in the draft assessment, it did advise the Agency to address this issue explicitly and to clarify how such a factor would relate to other uncertainty factors used.”

ORD Staff Response:

We agree with the Panel's suggestion to develop a stand-alone children's chapter to discuss children's issues, and intend to do so in our revision. We also agree that differences between adults and children should be discussed quantitatively, where possible, and plan to incorporate recent scientific literature on this subject (e.g., Ginsberg et al. 2002, Hattis, et al. 2003). In addition, as part of our revision to the derivation of the RfD and RfC for non-cancer endpoints, we plan to be explicit in taking into account children's susceptibility in developing the Uncertainty Factors while remaining consistent with the Agency's guidance on the subject.

References

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