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

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OFFICE OF
RESEARCH AND DEVELOPMENT

Dr. Joan Daisey
Chair
Office of the Science Advisory Board
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

SUBJECT: Response to SAB Review of the Proposed Revised Guidelines for Carcinogenicity Risk Assessment (EPA-SAB-EHC-97-010)

Dear Dr. Daisey:

The Office of Research and Development values the recommendations of the Science Advisory Board (SAB) for revisions to the Agency's cancer risk assessment guidelines.

In February, 1997 the Environmental Health Committee (EHC) of the Science Advisory Board met to review the Agency's "Proposed Guidelines for Carcinogen Risk Assessment" which were published in the Federal Register on April 23, 1996. The Agency's Risk Assessment Forum (Forum) had provided a charge to the EHC which included specific questions and issues that Agency scientists and members of the public regarded as particularly important matters of science and science policy to be addressed in making the guidelines final. The EHC provided its review report "Guidelines for Cancer Risk Assessment" in September, 1997.

The report provides support for the new directions in the Agency's proposal regarding characterization of cancer risks, but points out certain science policy considerations that need to be addressed further. In addition, the report recommends additions to aspects of the guidance itself and to the case examples that illustrate it. The Forum technical panel responsible for writing the final guidelines and for responding to comments of the public and of the EHC has considered the report and agrees with the EHC's major conclusions and recommendations. The report is particularly informative in its presentation of the diversity of opinions among committee members on some of the issues. In large part, these issues are in areas of risk assessment practice that are most affected by new scientific understanding of the biology of cancer. As recognized and supported by the EHC, one of the major directions of the proposal is to make risk assessment practices responsive to new science. At the same time, both the Agency and the EHC recognize that this requires attention in the guidelines themselves as well as continual use of scientific peer

review to assure decision makers and the public that change is disciplined and represents good science.

The technical panel of the Risk Assessment Forum is in the process of revising the draft guidelines and will be preparing specific responses to the SAB and public comments. Since the drafting of the detailed changes and additions is currently underway, this letter offers the Forum's interim response to the SAB's report. Ongoing revisions to the proposed guidelines will be presented to Agency scientists for review through the Forum and then by the Forum to EPA program managers. As we proceed with these revisions, the Forum technical panel would like to consult with the EHC to further refine our positions.

The technical panel is currently addressing all of the issue areas discussed in the EHC's report. Major additions to the guidelines as suggested by the SAB will include-

- **Hazard Characterization: Descriptors/Narratives.** In regard to hazard assessment, the EHC had a number of recommendations. Prominent among these were recommendations with respect to the question of how to state conclusions about the weight of evidence for carcinogenicity. The Forum agrees with EHC views on the problems with the proposal and will make changes that will address these problems. As supported by the EHC, the revised guidelines will include the weight of evidence narrative and standard descriptors will be used. The final revisions will clarify and simplify the descriptor system as recommended. The descriptors are not meant to replace an explanation of the nuances of the biological evidence, but rather to summarize it. Applying a descriptor will be a matter of judgment and cannot be reduced to a formula. Each standard descriptor may be applicable to a wide variety of potential data sets and weights of evidence.

- **Mode of Action/Dose Response Assessment.** Specific guidance for judging the validity and adequacy of data on mode of action will be added. The framework for evaluation of mode of action evidence is being developed in conjunction with an international cancer risk assessment harmonization effort being convened under the auspices of the World Health Organization. The dose response section of the guidelines will be revised to explain when it is appropriate to use precursor response data in dose response assessment. Case study examples, as suggested by the EHC, will be added to illustrate the different dose response approaches. In conjunction with revisions to the guidelines, a statistical modeling approach for dose response assessment in the observed range is under development. The approach will be peer reviewed and presented in a Risk Assessment Forum "purple book" and the quantitative methodology will be made available to users via the Internet. The additional recommendations contained in the SAB's report on the dose response section will be incorporated also.

- **Margin of Exposure (MoE) Analysis.** Guidance on the margin of exposure approach will be extensively revised to include explanation of the margin of exposure in the context of dose response analysis. Significant advances in

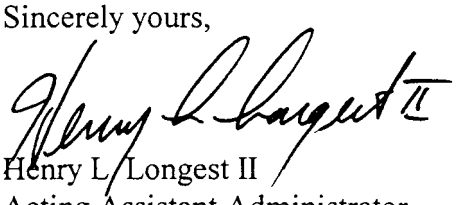
Agency (Forum) thinking have occurred since this issue was discussed with the EHC.

- **Human Variability in Susceptibility.** Guidance will be added on consideration of differential susceptibility, particularly of the young, but also of other subgroups. There has been increasing attention and research investment in the issue of variability in human susceptibility and the current state of the science will be discussed in the revised guidelines. In particular, mode of action and metabolism data will be discussed for their implications in this regard. The revised guidelines will also reflect the Administrator's policy on evaluating health risks to children which was issued subsequent to publication of the proposal. This policy is in keeping with the EHC recommendation that the guidelines recognize developing infants and children as a subgroup and that risk assessments account for the differential susceptibility of the young when data permit.

Finally, the Agency is applying the principles of the guidelines in ongoing EPA assessments and cosponsoring cases studies with organizations such as the International Life Sciences Institute. The final guidelines will reflect these experiences.

The EHC has provided review comments that will make a fundamental and positive contribution to the future cancer risk assessment practices of the Agency. The Agency appreciates the thoughtful and extensive investment of time and effort by committee members which is clearly reflected in the report and looks forward to a continuing dialogue with the EHC on these challenging issues as we move forward to finalize the guidelines.

Sincerely yours,



Henry L. Longest II
Acting Assistant Administrator

cc: Administrator
Deputy Administrator
AO-Mr. Deloatch
Science Advisory Board