



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON D.C. 20460

September 1, 2004

THE ADMINISTRATOR

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

Dear Dr. Glaze:

Thank you for the Science Advisory Board Supplemental Guidance for Assessing Cancer Susceptibility Review Panel's review of the Agency's *Draft Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens* (EPA-SAB-04-003).

The SAB SGACS Review Panel provided thoughtful, constructive comments that will make a positive contribution to EPA's analyses of early-life exposures to carcinogens. Based on the Panel's recommendations, EPA is revising the *Guidance* and is implementing a number of suggestions that were highlighted in your cover letter. Enclosed is the Agency's response to the Panel's *Summary of Recommendations*.

Again, my thanks to you and the Panel for your efforts.

Sincerely,

*/ Signed /*

Michael O. Leavitt

Enclosure

cc: Dr. Henry Anderson, Chair  
SGACS Review Panel

## **EPA Response to the SAB Review Panel's Recommendations on the Draft Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens**

A Review Panel of the EPA Science Advisory Board (SAB) met on May 12-14, 2003 to review the Agency's Draft *Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens* (Supplemental Guidance). The SAB Review Panel, known as the Supplemental Guidance for Assessing Cancer Susceptibility (SGACS) Review Panel (hereinafter, Review Panel), was composed of members of the SAB Environmental Health Committee (EHC) and Radiation Advisory Committee (RAC) along with members of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) and the Children's Health Protection Advisory Committee (CHPAC).

The Panel's report provides support for the actions that the Agency is taking to develop guidance for adjustments to the cancer slope factor for early-life exposure to carcinogens acting through a mutagenic mode of action. The Review Panel concurred with the Agency's conclusions and with the overall approach adopted by the Agency of using adjustment factors to account for increased susceptibility due to early-life exposure. The Panel also agreed that the values chosen for the cancer slope adjustment factors in the Supplemental Guidance appear to be reasonable from consideration of the literature. The Agency agrees with the Panel's suggestion that the Agency improve the statistical analysis of the data and provide a more extensive discussion of how the Agency arrived at the choice of the adjustment factors.

The Agency also appreciates the Review Panel's insightful responses to the charge questions. As indicated in the responses below, implementing the suggestions has improved our analyses and the support for our conclusions. A response to each of the major comments, as summarized in the SAB's cover letter, is presented below.

### **SUMMARY OF COMMENTS AND RESPONSE BY AGENCY**

- **The Review Panel agrees with the Agency that the science supports the conclusion that early-life exposures result in increased susceptibility to carcinogens that act through a mutagenic mode of action as compared to adult exposures. The Review Panel notes that a broader look at the scientific literature beyond the studies included in the Supplemental Guidance analysis would strengthen that conclusion.**

RESPONSE: A more comprehensive search of the scientific literature has been undertaken to identify additional studies that would provide information regarding early-life exposure to carcinogens. As a result of this search, additional studies have been included both in the quantitative and qualitative analyses.

While studies for more than 50 chemicals were initially identified based on titles and abstracts that indicated early life exposure, most could not be included in the quantitative

analysis because relatively few studies met the criteria for inclusion in the quantitative analysis. Often, these studies demonstrated carcinogenesis following perinatal exposure, but did not directly compare exposures at different ages, e.g., adults. A large number of studies addressed *in utero* exposures only. Others lacked controls for strains or species of animals for which historical control values were not available.

To expand the data base for quantitative analysis, consideration was also given to the Review Panel's recommendation to include tumor incidence data following exposures at different life stages from different studies or laboratories but in the same animal strain. A literature search was conducted to identify studies with suitable juvenile data only (with no adult data) in order to inform the size and nature of the data set. The studies identified correspond to chemicals that were already included in the analysis. As such, they were considered as supporting evidence only, because they would not increase the number of chemicals included in the quantitative analysis but would increase the potential uncertainty in this analysis.

The description of the criteria for inclusion/exclusion of data in the analysis is being augmented in the revised Supplemental Guidance. The decision to limit the quantitative analysis to studies that compared tumor incidence between early-life and adult exposures yields is being retained. Additional studies are being used to provide a more comprehensive discussion of supporting evidence for analyses of early-life stage susceptibility.

- **The Review Panel notes that for certain groups of non-mutagenic chemicals with known modes of action (e.g., estrogen receptor agonist/antagonist) there is sufficient evidence supporting increased susceptibility to cancer with early-life exposure. The Review Panel suggests the Agency include a discussion of these agents in the Supplemental Guidance. Non-mutagenic carcinogens with known modes of action should be assessed on a case-by-case basis as suggested by the Agency.**

RESPONSE: A larger discussion concerning the data found on the effects of early life exposures to carcinogens with a non-mutagenic mode of action is being added, with a particular emphasis on estrogenic agonists and antagonists. Until we have sufficient data and resources to analyze other modes of action, we agree with the Review Panel that chemicals should be assessed on a case-by-case basis.

**The Review Panel supports the use of slope factor adjustments in developing default approaches. Application of an adjustment to the adult cancer slope factor seems to be the most transparent and practical approach for risk assessment.**

RESPONSE: The Agency appreciates the Review Panel's critical review and support of the default approach of adjusting adult slope factors to account for early-life stage sensitivity.

- **The Review Panel reviewed age-specific human vulnerabilities and concludes that it would be useful to include an additional age grouping (age 9 –15) to recognize the potentially important vulnerabilities during puberty. Thus, four**

**age groupings would be appropriate (0-2, 3-8, 9-15, 15+) to represent critical periods of human growth and development.**

RESPONSE: The Agency agrees with the Review Panel that puberty, and the associated biological changes that occur during ages 9 - 15, clearly include many biological processes that could lead to changes in the sensitivity to the effects of some carcinogens depending on the mode of action and, therefore, a separate age grouping for ages 9 -15 warrants consideration. The current guidance focuses on carcinogens with a mutagenic mode of action. For any mode of action, the Agency is interested in identifying lifestages that may be particularly sensitive or refractory for carcinogenesis, and believes that the mode of action framework as described by EPA's 2003 "Draft Final Guidelines for Carcinogen Risk Assessment"(and final version of these Guidelines, when they become available), is an appropriate mechanism for elucidating these lifestages. In general, our analyses of lifestages that may be sensitive will depend on three factors: (1) establishing the mode of action for carcinogenesis; (2) using knowledge about the biological and toxicological key events in that mode of action that are likely to be affected by lifestages; and (3) the availability, or development, of data that allows analysis of the effects of chemicals acting by that mode of action during the relevant ages. For each mode of action evaluated, therefore, the various age groupings determined to be at a differential risk, which may differ significantly from those proposed for the mutagenic mode of action, is expected to be evaluated independently of other modes of action.

With regard to the current guidance, the limitations of the available database would not allow us to breakdown the 2 -15 age grouping into finer increments. The potency adjustments for chemicals that are carcinogenic through a mutagenic mode of action were initially selected based on the available data, i.e., for the laboratory animal equivalent of birth to < 2 years. (The Review Panel noted, and the Agency recognizes, the complexity of estimating the human equivalent age(s) to laboratory animal age(s). We are aware that some analyses that attempt to use various biological points of comparison are on-going, and we expect to evaluate those analyses as they become available, to better define this complex relationship.) More limited data and information on biological effects are being used to determine a science-informed policy regarding 2 to < 16 years. The Agency concludes that at this time the data are not available to refine the latter age group. If more data become available regarding carcinogens with a mutagenic mode of action, the age groups may be modified.

- **The Review Panel suggests that the Agency consider alternative analyses that might allow them to use more of the available data and directly test hypotheses concerning the appropriateness of the adjustment values for predicting the dose-response from early-life exposure.**

RESPONSE: The data to be analyzed have been recompiled to include all tumor endpoints for chemicals previously included in the analysis, additional studies that were identified, and lifetime study designs (i.e., combined perinatal and adult exposure) to create a more complete representation of the published literature on differential age sensitivity to chemical

carcinogenesis. This recompilation corrected errors noted by the Review Panel and/or public comments.

Following the suggestion of the Review Panel, the data were reanalyzed using equations that describe the probability of tumors as an exponential function of dose, with variations appropriate for the different study designs (i.e., acute exposure, repeated exposures during perinatal or adult periods, and lifetime repeated exposures). The ratio of juvenile to adult cancer potencies were calculated by fitting this model to the data for each age group. Parameters in these models were estimated using Bayesian methods, and all inference about the ratios were based on the marginal posterior distribution of the logarithm of the ratio. Summary ratios were constructed from the individual ratios within a group, by inverse variance-weighting the means of each ratio to obtain geometric means of the ratios. This permitted summarization and comparisons by study design, modes of action for carcinogenesis, and target tissue. This completely revised analysis is being incorporated into the revised Supplemental Guidance.

- **The Review Panel recommends that a priority for the near term would be the development of mode of action approaches for endocrine disruptors, beginning with estrogenic agents.**

RESPONSE: Extending the analysis to estrogenic agents and chemicals acting through other processes resulting in endocrine disruption is a reasonable priority in light of the human experience with diethylstilbesterol and the existing early life animal studies. In addition, the ongoing multigeneration studies at the National Toxicology Program with genistein, nonylphenol, and ethinyl estradiol are anticipated to provide valuable insights on this issue. It is worth noting, that in contrast to the finding of difference tumor sites with perinatal exposures to potent estrogenic compounds, the thyroid hormone disrupting chemical ethyl thiourea analyzed in the current effort showed little impact on thyroid tumors with perinatal exposure and no tumors unique to the perinatal exposures. This suggests that each mode of action for endocrine disruption will require separate analysis.

- **The Review Panel cannot recommend at this time a feasible method for incorporating transplacental or in utero exposure data. However, the Review Panel believes this to be an important issue that requires further research.**

RESPONSE: The Agency agrees with this conclusion. The Review Panel has made worthwhile suggestions about approaches that may prove useful for resolving this issue in the future. These suggestions will be useful as we continue to explore methods for using such data.

- **The Review Panel recommends that the Agency work more closely with the research community to encourage the evaluation of early-life stage susceptibilities. For chemical agents that are known to increase cancer risk, carcinogenic potency and the extent of exposure should be used in deciding which chemicals to study first.**

RESPONSE: The Agency is engaging in activities to raise the awareness of the need for research on early-life susceptibilities with the scientific community. Agency scientists have presented their analyses at scientific meetings and will be doing so at future meetings. Agency scientists will be publishing the results of the reanalysis to promote awareness in the scientific community. In addition, the database has been and will be available to others for analysis and publication of their findings. Discussions have occurred with other organizations within the Federal Government concerning the need for research. Recommendations also have been made to the National Toxicology Program for selected studies in this area as part of EPA's nomination of some chemicals.

- **Certain groups of non-mutagenic carcinogens with known modes of action serve as important examples in support of applying a default factor to non-mutagenic carcinogens when the mode of action is unknown. The Review Panel suggests that the Agency reconsider limiting the application of adjustment factors only to mutagenic agents and instead apply a default approach to both mutagenic and to non-mutagenic chemicals for which mode of action remains unknown or insufficiently characterized.**

RESPONSE: The Agency appreciates this recommendation and has reconsidered both the advantages and disadvantages to extending the default potency adjustment factors to carcinogenic chemicals for which the mode of action remains unknown. At the present time, EPA is recommending these factors only for carcinogens acting through a mutagenic mode of action based on a combination of analysis of available data and long-standing science policy positions which set out the Agency's overall approach to carcinogen risk assessment. In general, the Agency prefers to rely on analyses of data, rather than general defaults. When data are available for a sensitive lifestage, they should be used directly to evaluate risks for that chemical and that lifestage on a case-by-case basis. In this analysis, the data for non-mutagenic carcinogens, when the mode of action is unknown, were judged to be too limited and the modes of action too diverse to use this as a category for which a general default adjustment factor approach can be applied. In this situation, per the Agency's *Guidelines for Carcinogen Risk Assessment*, a linear low-dose extrapolation methodology is being recommended. It is the Agency's long-standing science policy position that use of the linear low-dose extrapolation approach (without further adjustment) provides adequate public health conservatism in the absence of chemical-specific data indicating differential early-life sensitivity.

As discussed above, the Agency expects to produce additional supplemental guidance for other modes of action, as data from new research and toxicity testing indicate it is warranted. EPA intends to focus its research, and work collaboratively with its federal partners, to improve understanding of the implications of early life exposure to carcinogens.