UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

February 28, 2007

EPA-SAB-07-003

Honorable Stephen L. Johnson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Subject: Consultation on Enhancing Risk Assessment Practices and Updating EPA's Exposure Guidelines

Dear Administrator Johnson:

The EPA Office of Science Advisor requested that the Science Advisory Board (SAB) conduct a consultation to provide input on ways to advance the Agency's human health risk assessment practices. Additionally, the Risk Assessment Forum requested that the SAB provide advice on updating the 1992 Exposure Guidelines. On September 6 and 7, 2006, representatives of the Office of Research and Development (ORD) and several other EPA offices provided informative presentations to the members of the SAB Environmental Health (EHC) and Integrated Human Exposure (IHEC) Committees and several board members of the SAB. The focus of the presentations by EPA representatives for this consultation was on advancements made in human health risk assessment and exposure assessment. On behalf of the committee members, we would like to express our sincerest gratitude to the presenters for their expertise, perspectives and insights. Their contributions greatly increased our understanding of the Agency's current policies, methods, practices and future directions.

The SAB was asked to comment on the relevance and priority of initiatives by the Agency to advance human health risk assessment practices and the Agency's approach for updating the exposure guidelines. They were also asked to suggest other areas and improvements that should be considered and which would be most important. Committee members addressed five major topics that emerged as the focus of both efforts during these consultations; 1) Addressing Aggregate Exposure and Cumulative Risk Assessment, 2) Addressing Populations, Groups, or Life Stages of Potential Concern, 3) Evaluating Uncertainty and Variability, Including Probabilistic Analyses, 4) Involving Communities and Communicating Results, and 5) Use of Data (Mechanistic, Models, Genomics, CompTox, etc.) versus defaults. Feedback on the charge questions was provided by committee members and

summarized according to each of the five topics. A compilation of these comments is appended to the minutes for this meeting. Highlighted in this letter are several key messages that emerged among the Committee members as a result of the Agency presentations and discussions.

The SAB agreed that the Agency has obviously put great effort into advancing human health risk assessment practices in many areas. The Agency has utilized sound principles and science, used external peer review, and is developing guidelines that should result in more transparent assessments. The Agency presented a comprehensive conceptual framework for human health risk assessment. Although this framework identified many scientific and practical needs, it did not provide an assessment of priorities or a plan for meeting those needs. The SAB is providing a number of overarching recommendations to address both advancing human health risk assessment and updating the exposure guidelines because the Agency has focused on many of the same concerns with regard to both efforts. The SAB recommends that the Agency:

- Develop a plan to assess and prioritize the scientific and practical needs for improving human health risk assessment.

Topic 1

- Advance cumulative risk assessment methodologies, in order to reflect real-world human exposure that includes multiple stressors.
- Integrate work completed to better characterize cumulative exposure and risk across age groups, and among children and the elderly.

Topic 2

- Consistently address early life susceptibility in assessments, using weightings for children, prenatal exposure, and lifetime to pregnancy (body burden) exposure.
- Include the elderly subpopulation and existing health, medication, and nutrition status when conducting risk assessments.
- Determine the status of populations in terms of background exposures and disease factors.

Topic 3

- Characterize variability and uncertainty more fully, including extending where scientifically feasible related quantitative analyses to the dose response and hazard identification parts of the Agency's cancer and noncancer risk assessments, and thereby identify ways to minimize uncertainty.
- More systematically, clarify the underlying assumptions used to build probability distributions for the processes and the observations on those processes.
- Incrementally replace the current system of single-point uncertainty factors with a set of distributions using probabilistic methods. (Some of the potential benefits of probabilistic analyses are included in Attachment 1.)
- Continue to develop mechanisms to evaluate both exposure and effects predictions of current and new human health risk assessment models.
- Conduct evaluations to determine whether risk assessment predictions match reality.

Topic 4

- Convene workshops at periodic intervals (2-3 years) to gather new information, including new data, new techniques and new tools.
- Assess, and probably increase, its program of training for both assessors and managers to appropriately interpret, communicate, and effectively utilize probabilistic information in decision-making.

Topic 5

- Whenever possible, use data derived from humans rather than from animals.
- Continue to develop greater understanding of modes and mechanisms of action, including mechanisms of genotoxicity, to improve understanding of the relevance of data from animal models to humans.

Finally, the SAB recognizes that the design and implementation of new methods will require specialized expertise and sustained support. We urge the Agency to provide the necessary resources and support to ensure that continued improvements are made. We look forward to working with the Agency to enhance approaches for exposure and human health risk assessment.

Sincerely,

/Signed/ ***/Signed/***

Rebecca T. Parkin, PhD, MPH
Chair, Integrated Human Exposure Committee and Environmental Health Committee

Granger Morgan, PhD
Chair, Science Advisory Board

Enclosure (Attachment 1)

ATTACHMENT 1

Some Potential Benefits of Probabilistic Analyses include the following:

- In contrast to the current definition of the Reference Dose (RfD)[1], RfDs designed to meet a probabilistic goal would allow the technical vs. policy considerations to be made explicit in quantitative terms—making clear how much confidence the analysts should be able to achieve that risks are below some specified incidence.

- Assessment of uncertainties quantitatively could facilitate "value of information" type analyses to help set research priorities toward the largest and most easily reducible sources of uncertainty.

- A probabilistic RfD system could help reduce the potentially inaccurate implication of zero risk below the RfD. The likelihood of finite risks for some non-cancer effects at low doses is highlighted by the recent example of apparently substantial mortality to vulnerable portions of the population from ambient levels of small airborne particles.

- A probabilistic RfD system would provide a capability to quantify risk below or above the RfD. This would allow EPA to quantify benefits of exposure control measures for OMB-mandated juxtapositions of economic and health consequences of different policy options. Without this capability, reductions in air toxics and non-cancer effects from other exposures are effectively not counted in analyses of benefits in regulatory impact analyses. This may lead to underweighting of efforts to abate such effects in the policy formulation process.

- A probabilistic RfD would remove the apparent contrast in the best current assessments that are highly sophisticated probabilistic exposure assessments joined to simple-appearing single-point representations of information from the field of toxicology.

- A probabilistic RfD system would encourage the generation of better information because it would create a clear regulatory market for such a system. As pointed out in our discussions, this would improve on the World Health Organization International Programme on Chemical Safety's (WHO IPCS) data derived uncertainty factor procedures, that are not rigorously founded in terms of allocation of variances between pharmacokinetic and pharmacodynamic components, or over-constrained by the requirement that default kinetic and dynamic components must multiply to the traditional factor of 10.

- An innovative probabilistic system is more likely to attract the efforts of innovative researchers interested in producing improved technical information and seeing policy responses to that information. Currently researchers in this area have a difficult struggle to achieve acceptance in place of the heritage of prior "case law" choices made from the 1954 Lehman and Fitzhugh "100 fold safety factor" paper to the present.

[1] Reference Dose (RfD): An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments, as defined in the glossary attached to EPA's IRIS database (http://www.epa.gov/iris/gloss8.htm, accessed 1/23/07)

- Examples of the richness of information that could be made available to decision-makers by implementation of probabilistic methods substituting distributions based on empirical data based on observations of other chemicals/drugs instead of the single-point uncertainty factors that are traditionally used) are illustrated in Hattis and Lynch (2007).[2]

[2] Hattis, D. and Lynch, M. K. "Empirically Observed Distributions of Pharmacokinetic and Pharmacodynamic Variability in Humans—Implications for the Derivation of Single Point Component Uncertainty Factors Providing Equivalent Protection as Existing RfDs." In Toxicokinetics in Risk Assessment, J. C. Lipscomb and E. V. Ohanian, eds., Informa Healthcare USA, Inc., 2007, pp. 69-93.