

## FINAL MINUTES

### **MINUTES FROM THE EPA SCIENCE ADVISORY BOARD Environmental Health Committee and the Integrated Human Exposure Committee Public Meeting September 6 and 7, 2006**

**PURPOSE:** The Environmental Health Committee and the Integrated Human Exposure Committee of the EPA Science Advisory Board (SAB) met on September 6 and 7, 2006 at the SAB Conference Center in Washington DC. The purposes of the September 6, 2006 consultation were: 1. to briefly review the Agency's key communication activities since publication of the staff paper, and the input the Agency has received; 2. to bring the SAB up to date on some current EPA research efforts related to human health risk assessment; 3. to describe specific projects in three Offices to illustrate progress in EPA practices; 4. to outline a few ideas and thoughts about EPA's future directions; and 5. to provide the public with another opportunity for comment in a Federal Advisory Committee Act (FACA) setting. The objective of the September 7, 2006 consultation was to review and comment on the approach and proposed content of the update for the Agency's Exposure Assessment Guidelines. The Agency sought this consultation as one of several outreach efforts to identify the needs of the user community and the major relevant technical issues that should be incorporated into the update. Attachment A is the Federal Register notice announcing the meetings (71 FR 155, August 11, 2006). A meeting agenda is included as Attachment B.

**LOCATION:** SAB Conference Center, Woodies Building, 3<sup>rd</sup> floor, 1025 F St., NW, Washington, DC

**DATE AND TIME:** September 6, 2006 from 9:00 AM - 5:00 PM and September 7, 2006 from 8:30 AM – 3:00 PM Eastern Time.

**PARTICIPANTS:** The following individuals participated in this meeting: SAB Committee and Board Members - Drs. Rebecca Parkin (Chair), Timothy Buckley, James Bus, George Corcoran, Deborah Cory-Slechta, Noel Cressie, Norman Drinkwater, Benjamin Gitterman, Sidney Green, Dale Hattis, Montserrat Fuentes, James Kehrer, Ulrike Luderer, Mark Miller, David Ozonoff, Robert Schnatter, Anne Sweeney, Jed Waldman, and Lauren Zeise. The Consultative Panel roster is included as Attachment C and a set of biographical sketches is included in Attachment D. SAB Staff - Dr. Vanessa Vu, SAB Staff Office Director, and Dr. Sue Shallal, Designated Federal Officers (DFO); EPA Presenters - Drs. George Gray, William Farland, Peter Preuss, Lynn Flowers, Lee Hoffman, Ana Lowitt ; Other Participants – Approximately 40 other EPA Staff and members of the public were present in the audience. Sign-in sheets are attached (Attachment E).

**MEETING SUMMARY:** The meeting followed the agenda (Attachment B). A summary of the meeting follows.

Convene the Meeting and Introductory Remarks – Dr. Suhair Shallal, Designated Federal Officer (DFO), opened the meeting at 9:00 AM. She presented background information on the SAB panel formation process and informed the audience that the SAB

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operates under the rules and regulations of FACA where all meeting that have deliberations are held in public. She also reminded the members of the panel and the audience that the background materials for the September 6, 2006 meeting and the September 7, 2006, including the charge questions (Attachments F and G), are located on the SAB website.

Welcome - Dr. Parkin then reviewed the agenda and explained the purpose of the consultation. She stated that we will begin with presentations from the Agency and the panel members will be able to ask clarifying questions only. Any discussion was to be reserved until the "Discussion Period" scheduled for the afternoon.

Presentations - Dr. William Farland presented some of the background regarding the Principles and Practices Staff Paper (Attachment H). He stated that it had been written in response to comments received from the public on EPA risk assessment practices. A taskforce comprised of EPA representatives from all the offices and regions who deal with risk assessment. The Staff Paper represented a "snapshot" in time of how EPA conducts risk assessment. The taskforce members developed some recommendations that are outlined in the staff paper. He stated that the EPA was interested in getting feedback from the SAB regarding their efforts to enhance risk assessment principles and practices and to give an opportunity for the public to provide their input.

Dr. Ana Lowit of the Office of Pesticide Programs (OPP) followed with a presentation entitled the "Cumulative Risk Assessment and Incorporation of Probabilistic Approaches in Exposure Assessment" (Attachment I). She explained the provisions in the Food Quality Protection Act of 1996 that require the EPA to consider cumulative risks. She described how cumulative risk assessments have been conducted in the EPA Office of Pesticide Programs. She listed the steps in a cumulative risk assessment and highlighted the approaches used. She also provided examples to illustrate the utility of these assessments. She noted that there are several modeling software packages that are used mainly to estimate exposure levels and most are available to the public for a small fee. She continued to explain the input for these models and how the results are incorporated in the risk assessment. She then concluded her presentation by summarizing the next steps that OPP intends to take to improve their cumulative risk assessment approach.

The representative from the Office of Solid Waste and Emergency Response (OSWER), Dr. Lee Hofmann was the next presenter. Her presentation was entitled "Use of Probabilistic Risk Assessment (PRA) in the Office of Solid Waste and Emergency Response" (Attachment J). She stated that 2 program offices within OSWER use PRA in their risk assessments, Office of Solid Waste (OSW) and Office of Superfund Remediation and Technology Innovation (OSRTI). She explained that different program offices in EPA vary in their use of PRA depending upon their specific regulatory requirements and decision-making procedures. OSWER uses a tiered approach that considers the level of effort required, the potential benefits and the value added of a probabilistic approach to risk assessment. The main focus of PRA in OSWER is on modeling of leaching, fate and transport processes.

The next speaker was Dr. Lynn Flowers, of the National Center for Environmental Exposure. Her presentation was entitled "Recent Innovations in IRIS Health Assessments" (Attachment K). She provided an overview of the EPA's Integrated Risk Information System (IRIS). She

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explained how the IRIS program conducts toxicological assessments and the recent advances in the program. She presented case studies to illustrate different types of assessments; e.g., less-than-lifetime toxicity values, use of human data, data-derived adjustment factors, data arrays and organ-specific toxicity values and use of mode of action data.

Dr. Preuss, Director of the National Center for Environmental Exposure, talked about EPA's advances in risk assessment ([Attachment L](#)). He presented the risk assessment process that EPA uses. He also explained the organization of EPA research centers and laboratories and their core missions. He described the topics that are currently being addressed in order to improve human health risk assessment at EPA; these included, Mode of Action, Uncertainty Analyses, High to Low Dose Extrapolation, and PBPK Modeling. He concluded that risk assessment approaches are evolving as the understanding of biological mechanisms improves, but significant uncertainties remain and are being addressed. There are many challenges for risk assessors, such as the need to evaluate when additional data are important for decision-making and when to collect, integrate, and make use of information on a variety of scales.

The final speaker was Dr. George Gray, the Assistant Administrator of the Office of Research and Development at EPA. He presented the future directions for EPA Risk Assessment practices ([Attachment M](#)). He spoke of the challenges that EPA faces in doing risk assessments and he stated that enhancing risk assessment practices will better support the many different risk management decisions EPA must make. He explained that many efforts are underway to develop, demonstrate and use state-of-the-art risk assessment practices. He asked the SAB for advice on areas of focus, specific tools and approaches that may enhance risk assessment practices at EPA.

Dr. Parkin then asked the public commenters to proceed with their presentations.

### **Public comments**

Public Comments were presented by Pat Casano and Rick Becker.

Pat Casano of GE expressed concern about the public involvement process. She indicated the SAB should comment on the "over-conservatism" of EPA risk assessments. There should be more reliance on scientifically sound data. She also indicated that there was too much emphasis on cumulative risk. She then suggested that individual assessments should be done correctly before attempting to do cumulative risk assessments. She stressed the importance of allowing for greater involvement by the public in the assessment process.

Rick Becker of the American Chemistry Council (ACC) then commented that he felt the consultation was helpful and offered an opportunity for the public to provide input. He stated that ACC and the Chemical Industry Institute of Technology (CIIT) have been at the forefront in working to improve risk assessment. He commended EPA and Dr. Farland on their work. He also noted that while today's presentations have presented probabilistic approaches to risk assessment, EPA's risk assessments are still dominated by the use of default values. He urged EPA to implement the approaches that were presented by EPA representatives. He also suggested that EPA convene workshops or symposia on these subjects and include stakeholders.

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The EPA representatives were then asked to join the SAB committee members at the table and a dialogue ensued. A variety of issues were discussed including, pharmacokinetic data and its impact on improving risk assessment, toxicogenomics, uncertainty factors, the use of probabilistic approaches for hazard assessment, the reliance on human data, transparency of models, etc. The dialogue continued and committee members were encouraged to submit their ideas in written format. Some panel members provided individual recommendations; those comments have been appended to this document (Appendix A).

Committee members had been assigned to one of five focus groups: 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. The lead discussant from each group then presented their group's collective view point. Each of the group summaries have also been appended to this document (Appendix B).

The first day's meeting adjourned at 4:50 PM.

### **September 7, 2006**

The meeting then reconvened at 8:30 AM on September 7, 2006 by the DFO, Dr. Sue Shallal. After a short introduction and a review of the agenda by the Chair, Dr. Rebecca Parkin, committee members had an opportunity to further discuss their group summaries. After this brief diversion, the meeting followed the agenda (Attachment N).

Gary Bangs of the Risk Assessment Forum (RAF) presented (powerpoint attached, Attachment Q) an overview of the Exposure Assessment Guidelines. He began by describing the work of the RAF. He explained the process that they intended to use in order to update the Guidelines. He presented the information that is currently found in the guidelines and what information was to be added in order to update the guidelines. He also discussed the various efforts and outreach activities that the RAF has undertaken to receive input from stakeholders.

He was then joined by Dr. Jerry Blancato of the National Center for Computational Toxicology. Dr. Blancato focused on the new and emerging science and data and how the RAF intended to incorporate this information into the update of the guidelines (powerpoint attached, Attachment P). He described the role of toxicogenomics and PBPK modeling in enhancing exposure assessments. Dr. Blancato responded to questions posed by committee members regarding the feasibility and utility of some of this new data. He received some suggestions from SAB members on including more cautionary guidance on the use of some of this new information and on ways of improving the guidelines. There were also suggestions on how to structure the document so that it could be updated in sections, and not necessarily as a whole. This is needed in order to have more frequent updates to incorporate the most up-to-date science. There should be different levels of complexity to make it useful to a variety of users, including, laypersons, exposure assessors, scientists, etc.

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Responses to the charge questions posed to the SAB have been incorporated into the comments for the September 6, 2006 discussion. The members were informed that they should revise their summaries and/or individual comments and submit them to the DFO in 2 weeks (All committee member comments have been appended to this document).

The meeting was adjourned at 2:40 PM.

Respectfully Submitted:

*/Signed/*

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Dr. Suhair Shallal  
Designated Federal Officer,  
EPA SAB PFOA Review Panel

I certify that these minutes are accurate to the best of my knowledge:

*/Signed/*

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Dr. Rebecca Parkin  
Chair,  
EPA SAB IHEC-EHC Consultative Panel

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<u>Attachment A</u>	Federal Register notice (71 FR 155, August 11, 2006)
<u>Attachment B</u>	Meeting agenda- September 6, 2006
<u>Attachment C</u>	Consultative Panel roster
<u>Attachment D</u>	Biographical sketches
<u>Attachment E</u>	Sign-in sheets
<u>Attachment F</u>	Charge questions for September 6, 2006 meeting
<u>Attachment G</u>	Charge questions for September 7, 2006 meeting
<u>Attachment H</u>	Powerpoint presentation by Dr. William Farland
<u>Attachment I</u>	Powerpoint presentation by Dr. Ana Lowit
<u>Attachment J</u>	Powerpoint presentation by Dr. Lee Hofmann
<u>Attachment K</u>	Powerpoint presentation by Dr. Lynn Flowers
<u>Attachment L</u>	Powerpoint presentation by Dr. Peter Preuss
<u>Attachment M</u>	Powerpoint presentation by Dr. George Gray
<u>Attachment N</u>	Meeting agenda- September 7, 2006
<u>Attachment O</u>	Powerpoint presentation by Capt. Gary Bangs
<u>Attachment P</u>	Powerpoint presentation by Dr. Jerry Blancato
Appendix A	Individual Comments
Appendix B	Focus Group Comments

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## APPENDIX A

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### Comments from Dr. James Bus

#### Charge Questions

1. Agency's efforts on track
  - A. in advances in areas presented?
  - B. in the Agency research?

Animal toxicology data constitute a significant input element into risk assessment. EPA needs to expand efforts to better define the currently simplistic descriptions of chemical exposures in toxicology tests, e.g., mg/kg or ppm, and move to approaches that encourage evaluation of "internal dose" such as blood and/or tissue/cell concentrations of parent compound or relevant metabolite(s). These data should be used to explore mechanisms to more effectively link chemical doses applied in toxicology studies to the emerging body of human biomonitoring data. EPA should also promote improved dose selection approaches for toxicology test protocols, with a particular emphasis on selection of high-end doses (maximum tolerated dose, MTD) including means of identifying test conditions exhibiting dose-dependent transitions likely not relevant to human risk extrapolation. Methods should also be developed to refine options for selection of doses at the low end of the dose-response curve, and in particular, doses that are more relevant to actual real-world human/environmental exposures. To accomplish these objectives, EPA will need to offer further refinements to its toxicology testing pharmacokinetic and testing guidelines.

EPA needs to continue its efforts to identify improved mechanisms for applying weight of evidence approaches for incorporation of mode of action (MOA) data into risk assessments. A key element must include strategies for defining "how much is enough" and identification of what types of data are most valuable to these evaluations. Failure to accomplish this objective ultimately will serve as major disincentive for collection of MOA information.

2. Other areas that should be considered?

Opportunities to identify mechanisms to "reality check" both exposure and human health predictions of risk assessment models must be developed. In order to improve the credibility of and confidence in science-based risk assessment, human health predictive models must be able to better differentiate potential anthropogenic environmental exposures of concern from those resulting from the large and complex chemical exposures of the natural environment, i.e., healthy food. Current models perform extremely poorly in this differentiation.

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Current cancer risk assessment practice continues to be heavily influenced by yes/no evaluations of genotoxicity, i.e., compounds classified as genotoxicity are defaulted to conservative linear no-threshold based risk models. Further research should focus on defining dose-response issues in genotoxicity tests and how such data could be used to defining further risk assessment model options.

### **Comments from Dr. Sidney Green**

For September 6 discussion:

Comments on attachment C, recent chemical reviews by the National Center for Environmental Assessment (NCEA) in the Office of Research and Development;

Efforts by the NCEA in ORD seem to be on track to advance EPA risk assessment practices. Increasing use of MOA data makes for better decision regarding low-dose extrapolation which addresses “overarching issue #1”.

The issues raised by the NCEA regarding MOA on page 27 are all very important, but I think the issue of “what data are needed to determine whether a certain MOA supports a particular approach to low dose extrapolation” is critical.

For September 7 discussion:

Regarding topic 5, “Updating Exposure Assessment with New and Emerging Science: computational, genomics, and other Biometrics and Social Sciences”, I believe this area is highly relevant and of priority, for there is no doubt about toxicology becoming more quantitative and more molecularly-oriented. This should provide a wealth of information to assist in making decisions about risk assessment particularly with respect to exposure. Much research still needs to be accomplished, however. Computational toxicology is an excellent example of use of modeling to assist in providing information about potential exposure to an agent. The use of the social sciences in assisting in providing information about exposure is an approach that could become a morass for the agency given, as admitted, the complexities of human behavior.

As far as a strategy to keep the document as relevant and up-to-date as possible, I think it should be possible for the EPA to convene workshops e.g. biomonitoring, at periodic intervals (2-3 years), to gather information on use of biomonitoring for exposure assessment. This would depend on the progress of the science and that could be determined by a Federal Register announcement asking for information from interested parties conducting research in this area or by the ORD conducting literature searches.

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### **SAB Meeting Notes, Dr. Ulrike Luderer**

#### **Enhancing EPA's Risk Assessment Practices**

##### **Charge Questions**

(Note: I list the charge questions here for my own information. My comments, which follow the charge questions, are not yet organized by question.)

1. Do the Agency's efforts seem on track to advance the EPA risk assessment practices and are they in line with comments and recommendations received with respect to advances in the areas presented and the agency's research?
2. What other areas and improvements should be considered and which are most important?

#### **EPA's Exposure Assessment Guidelines**

##### **Charge Questions**

- 1, Please comment on the relevance and priority of the topics listed to the current practice and future directions of exposure assessment (both measurement and modeling).
2. Please describe any other relevant topics which should be included in the revisions and their relationship to the topics presented and the overall guidelines.
3. What case examples or other references should be draw upon to illustrate the science and practice of exposure assessment?
4. How and to what extent can the current and emerging databases of human biomonitoring be used to inform exposure assessments? Please include the potential use of genomics and other biometrics to the degree they are relevant.
5. Given that the guidelines are intended to provide general principles of the practice, and updated infrequently, what strategy could we explore to make (and keep) the document as relevant and up-to-date as possible?

##### **Topic: Use of data versus defaults**

Generally using high quality data should be preferred over using defaults, but, as the staff paper on Risk Assessment Principles and Practices pointed out, this is not always compatible with time and budgetary constraints. The dichotomy between data and defaults may not be as

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stark if the defaults themselves are based on data. As described in the staff paper, the defaults currently used by EPA have been based on available data, have undergone peer review, and have evolved over time as additional data became available. For example, pharmacokinetic and pharmacodynamic models are being used by the agency in risk assessments to model the tissue levels of active metabolites of toxicants, the tissue levels at which effects are observed, and differences in these among species. As a result of the development and application of PBPK models, the interspecies uncertainty factor now considers pharmacokinetic and pharmacodynamic components (BOSC Feb 2005 Workshop Proceedings). One continuing challenge with using such models is to make the assumptions that went into the models explicit to readers of the risk assessment, as well as to make explicit how using different assumptions would affect the conclusions of the risk assessment.

Recently, consideration of the mode of action of a chemical has been incorporated into EPA risk assessment guidance in the Cancer Risk Assessment Guidelines. Clearly better understanding of modes and mechanisms of action is critical for understanding the relevance of data from particular animal models to humans. It is also critically important for cumulative risk assessment. Genomics, proteomics, and metabonomics coupled with systems biology have the potential to greatly accelerate our understanding of mechanisms of action of toxicants. However, it seems overly optimistic to think that omic in vitro and in silico studies will soon replace in vivo animal studies. At present much omic data is still derived from in vivo studies.

Another potential benefit of omics technologies is to identify susceptible subpopulations, as mentioned on page 59 of the Staff Paper, and in Dr. Blancato's presentation. For example, with microarray technology, thousands of different single nucleotide polymorphisms can be measured in a single assay. Such data can help to quantify the variability in susceptibility within a population.

Omics methods may also be used to better characterize exposures to human populations. For example, using metabonomics, genomics and proteomics to identify signature patterns of metabolite changes, and gene and protein expression changes associated with exposures to particular toxicants or classes of toxicants.

Charge question 4: Human exposure databases should have great utility in exposure assessments for characterizing background exposures in the population, particularly as the agency moves away from assessing the risk to human health from exposure to a single chemical by a single route at a time and towards cumulative risk assessment.

### **Other topics**

#### **Cumulative toxicity**

Dr Lowit's examples of organophosphates and N-methyl carbamates as two groups of pesticides for which OPP has performed cumulative risk assessments raise the obvious question as to whether it would be useful to evaluate the cumulative risk from these two classes of pesticides combined in that they both act by inhibiting acetylcholinesterase, albeit by different molecular mechanisms. A related, but broader question is whether similar methods can be used to assess the cumulative risks from chemicals that act within a common pathway

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but by different mechanisms. Examples (relevant to Charge Question 3) are agents that alter male reproductive system development by disrupting androgen receptor signaling by various different mechanisms, including receptor antagonism and inhibition of androgen synthesis. Dr. Earl Gray's group from EPA presented a poster at the 2006 Society for the Study of Reproduction meeting comparing how well dose addition, response addition, and integrated models predicted the effects of exposure to mixtures of such chemicals on male reproductive system development (Rider et al, 2006, *Biology of Reproduction Special Issue*, Abstract 293).

The Figures in Appendix A show MOEs, and the paper gives a detailed discussion of how the exposure distributions were arrived at, but not how the "numerators" (effect levels) were arrived at. From the paragraph on page 8, it appears that the points of departure were BMDs calculated from multiple studies for a particular chemical.

### **Evaluating Uncertainty/ Probabilistic models.**

These models have mostly been used to characterize variability and uncertainty in exposure. Less has been done to use these methods to characterize variability and uncertainty in toxicity values like RfDs and RfCs. This would be very useful. An example of this is given on page 23 of the paper by Hofman on "Use of Probabilistic Risk Assessment by OSWER." The example cited is of ecological risk assessments where variability in sensitivity to toxicity between species and uncertainty in ecological toxicity reference values (TRVs) are being addressed. It would seem possible to apply a similar approach to human data on variability in susceptibility to carcinogens for example among individuals with polymorphisms in xenobiotic metabolizing enzymes or to animal data derived from genetically modified mouse models that lack key genes involved in the xenobiotic response.

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### **Comments from Dr. Robert Schnatter**

Without the benefit of what I'm sure are rich discussions taking place, I would like to offer the following feedback. This feedback is based on the background materials and five presentations that you forwarded recently. Most comments cover risk assessment practices, only a couple pertain to new exposure assessment guidelines.

First, I want to reiterate that the staff paper on risk assessment practices was very well done and refreshingly candid regarding current agency practices.

Risk Assessment Practices:

Charge questions

*1. Do the Agency's efforts seem on track to advance EPA risk assessment practices and are they in line with recommendations in the areas presented and in the agency's research.*

Regarding aggregate exposure and cumulative risk:

The plan laid out for addressing aggregate exposure (id target populations, id sources, routes, etc. determining exposure frequency and duration, and estimating source/route's contribution) is a logical framework. The relevant exposure metric is also important (e.g. peaks, chronic/cumulative). In addition, relevant windows of exposure are also important and should be given more consideration.

I found the passage (p.6) that said "EPA program office activities may employ varying combinations of central tendency and high-end values on a case-by-case basis, depending on the situation and target populations exposed" very troubling. From a scientific perspective, central tendency estimates should always be preferred. The passage implies that non-scientific issues can weigh prominently in aggregate exposure estimates.

Regarding other areas:

The progress for employing distributional estimates for dose response assessments is slow. The anticipated 2007 asbestos assessment seems to be the only active example in the human health area. For the asbestos assessment, I am a bit confused and concerned about the passage (p.24 Hofman) that says 'random variation in number of cases' will be accounted for. Random variation in number of cases should not affect plausible dose response estimates. The number of cases due to asbestos may affect the dose response estimates, but this is not due to random variation. I think that too much emphasis on disease misclassification may also produce something Gray's presentation alluded to: "Propagation of uncertainty". Research into guarding against propagation of uncertainty may be warranted. Also, in estimating uncertainty due to errors in disease classification, it is hoped that both plausible under and over diagnosis is factored in. Also, I would hope this assessment would examine alternative dose response

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models, not only a linear risk model for lung cancer and a relative risk model for mesothelioma. The general literature supports the notion that prolonged lower exposures can cause mesothelioma, but higher exposures are necessary for lung cancer. A linear risk model for lung cancer that passes through the origin would probably conflict with this consistent observation.

There is a paper by Fayerwether et al. (2000), that illustrates how epidemiologic data can be used for distributional risk estimation, using formaldehyde data. It includes alternative model choices. If you want the exact reference, please let me know.

*2. What other areas and improvements should be considered and which would be most important?*

The 7th most frequent comment: "separating risk assessment from risk management" is perhaps under-represented. This is because it is likely also captured in the most frequent comment ("level of conservatism"). More effort should be given to keeping the scientific assessments true to the science (e.g. risk assessment), and invoking the Agency's mandate to be health protective in the risk management step. To often, decisions such as the use of the UCL, low dose linearity, etc. , are thought to be the best science by risk managers. One simple action that could be employed to better convey the most accurate science, is that when UCL's are presented as plausible upper estimates of risk, LCL's should be presented as equally plausible lower estimates of risk.

My main point is that the Agency should place more effort on having risk assessments rely on the science, and health protection be a risk management step.

The Agency should consider developing more precise criteria on when human epidemiologic study should be used instead of animal data. In addition, criteria for when human data should be used as a consistency check for animal predictions should be developed. Hertz-Piccioto (1995) has a good paper in this regard.

Sincerely,  
Rob Schnatter

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## APPENDIX B

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### **Comments compiled by Dr. Tim Buckley**

Below are the written comments from the Topic 1 group (Buckley, Drinkwater, and Corcoran). These comments do not necessarily represent a consensus or even a deliberation of our group, but rather a compilation of our individual lists.

**Charge Question:** Do the Agency's efforts seem on track to advance EPA risk assessment practices and are they in line with the comments and recommendations received with respect to:

- A. the advances in the areas presented and
- B. in the Agency's research

What other areas and improvements should be considered and which would be most important?

### **Topic 1 Response (Buckley, Drinkwater, and Corcoran)**

1. EPA conceptually recognizes the value of cumulative risk assessment, however, little progress has been made in the actual incorporation of cumulative risk in EPA's risk assessments. This is viewed as a critical need to reflect real-world human exposure that includes multiple stressors including not only chemical, but physical, biological and psychosocial as well.
2. Risk assessment is critical to the Agency in providing the scientific underpinnings for EPA regulation designed to protect public health, however, currently the Agency lacks the means for evaluating how well risk predicts actual human health threat.
4. EPA presented a comprehensive conceptual framework for risk assessment within the Agency. Although this framework identified many scientific and practical needs, it did not provide an assessment of priorities or a plan for meeting those needs. What are the research NCEA priorities going forward? Do we need more data / better / different methodologies and data? What are the criteria upon which EPA will establish priorities? This information was not provided and is critical for evaluating whether EPA is "on track".
5. It appears as though EPA is backing away from the need for human data in risk assessment. If this is true, it needs to be corrected.
6. A phenomenon known as auto-protection exists in which an exposure to a single agent resulting in no or minimal toxicity lessens the toxicity of a future exposure to this agent known to be in the toxic range. Does the agency give credence to these literature findings, and if yes, how will this phenomenon be addressed?

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7. Some models I have familiarity with may not address all relevant life stages. Specifically, in 2005, LifeLine did not have adequate representation of children less than 3 years of age, or the human elderly population. Have these been addressed?
8. When cumulative evaluations consider a common mechanism groups (CMG), how are their target effects of non-stressors addressed if at all? If they are addressed, how are they integrated into the cumulative risk assessment? The example given by Dr. Gray of AChE inhibitors in potato skin is one example of this issue.
9. Under cumulative risk assessments, Relative Potency Factors are developed and the default is to add RPFs to obtain an index of total presence of stressors acting by the common mechanism. Dr. Lowit presented one slide showing good concordance between AChE inhibition and the sum of RPFs for mixed NMCs. However, this is not rigorous support for the default of additivity. It seems to reason that there will be significant deviations from additivity. Rather than conducting studies to explore additivity, has the Agency conducted studies under conditions of increased likelihood of non-additivity? To increase confidence in the current approach and default, the Agency should rigorously examine conditions for potential mixed agonist, agonist, and synergist interactions.
10. Some cumulative risk assessment models have used anthropomorphic characteristics such as compartment size and blood flow (liver, fat) to predict agent disposition. This is not effective or appropriate. What steps are being taken to replace this approach, if this has not already been done?
11. Agency guidance of the use of Uncertainty Factors states that they are to use results of models of the most sensitive populations. This often focuses on life stages, in some cases based on statutory reasons. In the absence of data, it is reasonable to speculate that disease sub-populations will be the most sensitive populations for many non-cancer endpoints. Thus, risk assessment should take into account major human diseases as key factors in establishing uncertainty factors for non-cancer effects. This is also true for cancer endpoints for a small sub-set of humans harboring known defects in DNA repair pathways, who have significant pre-existing benign tumor burdens. Can the use of probabilistic risk analyses advance risk analysis centered on human disease sub-groups?
12. In 2004 or 2005, this advisory board forwarded recommendations to the Agency which emphasized several key requests. One was that the agency continue its stated intent to replace use of defaults with data derived from humans. The second was to increase the use of probabilistic risk assessment. Based on presentations on September 6, it is not clear that the Agency remains committed to increasing the acquisition and use of data derived from humans, but rather appears to be receptive to using more data from in vitro models. It is understood that evaluating non-drug chemicals in humans is a controversial possibly even charged topic. Nonetheless, the Agency should make clear where it stands on its previously stated goal of replacing defaults with data obtained from humans.

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### **Comments compiled by Dr. Mark Miller**

Below are the written comments from the Topic 2 group (Miller, Sweeney, Cory-Slechta).

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### **Addressing Populations, Groups, or Life Stages of Potential Concern**

The agency has obviously put great effort into advancing risk assessment practices in many areas. It has utilized sound principles and science, external peer review, and is developing guidelines which should result in more transparent assessments.

Since EPA is still required much of the time to use data on industrial chemicals that have been inadequately tested, there is still a role to play for uncertainty factors. While occasionally assessments may be too conservative, lack of adequate toxicity testing makes it very hard to move way from uncertainty factors and towards a totally data-driven risk assessment. In particular, probabilistic analysis will be limited by limitations in available data to adequately describe distributions. Also, since data reflecting the risks from early life exposure are rare, uncertainty factors representing this and other sensitive time periods will continue to be required in the foreseeable future.

The concept of these time periods as important windows of susceptibility were especially noted in early studies focusing on endocrine active compounds, or “endocrine disruptors” and developmental and neuropsychological outcomes. And similarly, although the specific timing of exposure to environmental contaminants is less clear, there is evidence that impacts on age at onset of puberty is associated with environmental exposure (Selevan et al., 2003). Several recent papers have emphasized the need to incorporate the periconceptual and perinatal intervals into the risk assessment process, including the reports emanating from the 1999 workshop entitled “Critical Windows of Exposure for Children’s Health”, hosted by the Environmental Protection Agency in order to determine the influence of age at exposure to environmental contaminants on various aspects of child health (Selevan et al., 2000), and a peer review of the literature regarding reproductive and developmental effects of exposures at low doses to endocrine disrupting chemicals, conducted by the National Toxicology Program. The EPA workshop examined the impact of early periconceptual and perinatal exposures on several adverse health outcomes, including effects on the immune, respiratory, cardiac, and reproductive systems as well as potential neurobehavioral and carcinogenic events (Dietert et al., 2000; Pryor et al., 2000; Lemasters et al., 2000; Adams et al., 2000; Bart Jr., et al., 2000; Olshan et al., 2000). The NTP likewise recommended research to evaluate current testing protocols in terms of relevant dosing, animal-model selections, and outcome measures as well the age of the animals being tested (Melnick et al., 2002).

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EPA needs to consistently address early life susceptibility in assessments and put into action the potency weighting for children delineated in the 2005 children's cancer guidelines. Vinyl chloride is an example of early life potency weighting. The agency should develop weightings for prenatal exposure and lifetime to pregnancy (body burden) exposure. As well, EPA needs to develop cancer risk assessment guidance on early life exposure to non-mutagenic carcinogens. For example, clearly there is increased sensitivity early in life to some hormonally active carcinogens, e.g. DES. Inclusion of the prenatal time period in cancer risk assessments including development of prenatal potency values would be an important step. Currently, the prenatal potency assumption is zero.

The agency has made beginning efforts to address the elderly as a potentially uniquely vulnerable life stage. Additional delineation of these vulnerabilities and the approach to incorporating this information into risk assessments should continue. In particular, the roles of polypharmacy, nutritional status, and concurrent illness need to be addressed. Coupled with this is the need to look at intercurrent disease state as a risk factor in defining uncertainty; this will be coupled, in many cases with aging, but may also impact at other points in the life cycle (e.g., children with asthma).

Agency should work on exposure modeling of the fetus considering maternal intake and placental transfer, biotransformation by the placenta (both activation and detoxification pathways) and so on. Complex kinetic models have been developed to do this.

Integrating the substantial work that the agency has done on developing guidance on age groupings, framework to children's risk assessment, children's cancer risk assessment, cumulative exposure assessment, and aging initiatives should be a priority. The research agenda should include developing data that fits the needed binning of assessors. In particular, integrated exposures for early age groupings as needed for carcinogen early life age-weighting (0-2, 2-15).

EPA should investigate more of the chemical "family" approach to risk assessment to help in some ways account for lack of data and try to cover more chemicals. This approach has been used to look at both the parent compound and metabolites where enough data exists to apply a kinetic model and model the peak or steady-state concentrations in both parent and metabolites. One can apply the NOAEL to both parent and metabolites, thereby covering more than one chemical in the same Reference Dose. Also, more use of structure-activity analogies may help to cover additional chemicals. Further development of structure-activity models and wider use throughout the agencies programs would be valuable. Wider public access to these structure-activity programs would assist efforts at greater transparency. These approaches are not substitutes for adequate toxicity testing but may help bridge the current gap.

Finally, the inclusion of U.S. veterans into the assessment of the impact of environmental exposures and human health also needs to be considered. There have been numerous examinations of these issues among veterans of the Vietnam and Gulf Wars, encompassing a wide range of adverse health effects to various and diverse classes of chemical exposures (Institute of Medicine 2000(a); 2003(b), 2004(c); 2006(d)).

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Cumulative Risk Assessment - The EPA has a very restrictive approach to cumulative risk assessment in that they only include chemicals that have the exact same mechanism of action in a cumulative assessment. This excludes chemicals that may act on the same target tissue in a different way and have cumulative adverse effects. Also, it may miss the boat even with the same mechanism chemicals. The basis of the assessment was acetylcholinesterase inhibition, but the developmental neurotoxicity of chlorpyrifos (and possibly others) at least in part is independent of this mechanism. The long range agenda for the agency should include developing methods which reflect the population health risk from actual chemical exposures (aggregate and cumulative) beyond the current narrow definition towards a model that describes the true cumulative risk from all pathways and mechanisms. It should include factors such as stress that might identify most sensitive populations as well as background exposures to exogenous and endogenous chemicals that affect the toxicity network.

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### **Comments compiled by Dr. Dale Hattis**

Below are the written comments from the Topic 3 group (Hattis, Cressie, Fuentes, Zeise).

#### **Topic 3- Comments from probabilistic subpanel**

The panel wishes to encourage EPA in its efforts to further develop and apply probabilistic techniques in exposure analyses. In this area EPA needs to reconsider its conception of probabilistic analyses as solely a “value-added” feature of the most resource-intensive and data-rich assessments. If anything, probabilistic modeling should be more, rather than less helpful in “data poor” circumstances. Additionally, EPA should undertake a series of sophisticated probabilistic exposure assessments intended to reevaluate the calibration of its baseline deterministic assumptions in a representative set of “Tier 1” assessments.

EPA should also 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 under different enabling statutes administered by EPA.

In addition, the panel believes it is important to extend quantitative analyses of uncertainty and variability to the dose response and hazard identification parts of EPA’s cancer and noncancer risk assessments. Understanding the quantitative consequences of various causes of variability in susceptibility in the population with the aid of new epidemiologic and clinical studies may be particularly important for public health protection for both cancer and non-cancer effects. Work to date in the carcinogenesis area appears limited and despite some epidemiological explorations of the consequences of some metabolic polymorphisms, these have rarely been reflected in EPA assessments.

Dr. Flowers outlined several useful initiatives to improve risk assessments undertaken within the IRIS system. One new approach was, for a given general endpoint (e.g., neurotoxicity), to fit mathematical models to results from multiple experiments to obtain a measure of central tendency of point of departure for the set of experiments, along with uncertainty bounds around that central point. Where experiments are in different genders or strains or report on different specific endpoints, this approach can obscure the inherent heterogeneity in the toxicity data, that may in turn reflect potential heterogeneity in humans as well as differing dose response characteristics for different specific endpoints. This is also a departure from selecting the most sensitive species, gender and adverse endpoint for setting an RfD. The new approach needs to be applied with care so that more sensitive human population groups are adequately protected. The approach has obvious validity for describing uncertainty where there are multiple experiments conducted using the same protocol - measuring the same effect, in similarly treated animals, of the similar ages, in the same gender and strain. Where experimental designs differ, biological explanations for differing results and the implications in terms of sensitive subpopulations of humans should be considered and guide the way in which results of

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different studies are aggregated to derive estimates of central tendency and uncertainty for points of departure for specific responses.

Also, not included in Dr. Flowers' outline is a response to some of the types of innovation mentioned by Dr. Preuss—a long term effort to define health protection goals for RfDs in probabilistic terms reflecting both variability and uncertainty. This could take the form, for example, of a specification that at the RfD there should be an expectation that there is no more than X risk for the Yth percentile of the population (addressing variability) with Z% confidence. Such a redefinition would also respond to the concern mentioned by Dr. Gray—that the existing RfD process may well have lead to inconsistencies in the amount of “conservatism” (or lack thereof) incorporated in the values recommended for different chemicals. This could have lead to suboptimal allocations of priorities in prevention efforts by decision makers in the public and private sectors that use the IRIS values for a variety of decision making purposes not fully envisioned by the creators of the system.

Such a long term effort will eventually involve replacement of the current system of single-point uncertainty factors with a set of distributions—ideally adapted to as many specifics of the different kinds of chemicals, biological effects and co-occurring population disease processes as possible. Moreover, specification of such probabilistic goals for the RfD will require extensive consultation with risk managers who can reflect the needs for risk information under EPA's diverse regulatory authorities, relevant decision-makers elsewhere in the U.S. executive and legislative branches, the private sector, and internationally. The current EPA program is best understood as an incremental approach to incorporating probabilistic approaches in risk analyses, but in the long run there is no way to avoid the fact that this will be a significant departure from prior practice. Because this kind of change will be difficult it is important to articulate the potential benefits from such a change from the current system of single-point “uncertainty factors”.

In contrast to the current definition of the RfD, 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 noncancer 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

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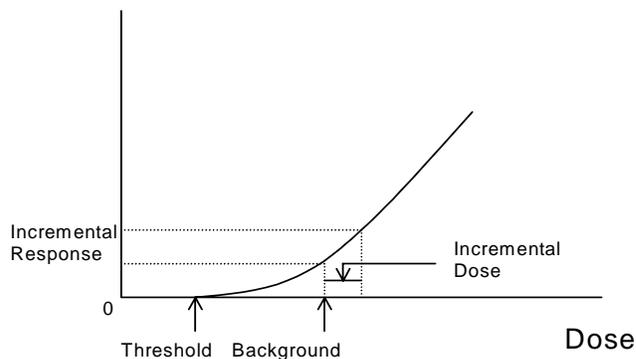
analyses. This may lead to underweighting of efforts to abate such effects in the policy formulation process.

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 it. As pointed out in our discussions, this would improve on the WHO IPCS data derived uncertainty factor procedures, which are not rigorously founded in terms of allocation of variances between pharmacokinetic and pharmacodynamic components, or overconstrained 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.

The premise for the development of non-cancer RfDs and guidance levels for carcinogens believed to act by non-linear mechanisms is that there is a threshold dose below which adverse effects should not occur. Typically not considered are the myriad of other exposures from endogenous and exogenous sources that may affect the toxicity pathways or networks by which the chemical operates. The chemical under assessment adds to these exposures, and in some cases these exposures may in toto fall above the population threshold, as illustrated in the figure below. Examples where this appears to be the case include neurodevelopmental effects of lead and methylmercury, particulate matter and certain respiratory endpoints, the impact of ozone on respiratory function, and perhaps the impact of dioxin-like compounds on a variety of endpoints. This issue of the status of the population in terms of background exposures and disease factors is critical for advancing methods in risk assessment – in moving toward probabilistic descriptions in lieu of the RfD, in describing the uncertainty in the RfD, and in trying to ascertain the variability in response among people exposed. The general issue of background variability in sensitivity resulting from ongoing pathological processes and other



exposures in a diverse human population deserves considerably more attention than it is currently receiving.

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The problem of properly accounting for known sources of uncertainty is not straightforward and has led to localized studies of various pieces of the uncertainty puzzle. Hierarchical (Bayesian) statistical modeling offers a coherent framework that prescribes data uncertainty (measurement error, censoring, spatial and/or temporal misalignment of datasets, confounding of effects in observational studies), and model uncertainty of the chemical's action through the various steps in a causal pathway. Multiple pathways require further care in specifying the links, whose presence or absence is another source of model uncertainty. One way of handling of all these sources of uncertainty is achieved by constructing what mathematicians call an "Acyclic Directed Graph" (ADG) (i.e. "causal pathway") implied by the exposure and toxicological action mechanisms together with their uncertainties. Statistical inference is based on the posterior distribution of all unknowns in the model, given the available data. Computation of the posterior distribution is achieved by Markov Chain Monte Carlo (MCMC). One great advantage of the methodology is that in principle it is extendable to cumulative studies where more than one chemical or other disease-causing conditions are of interest. This requires models of covariabilities as well as the usual one-at-a time variabilities. Hierarchical Bayesian approaches have been implemented in physiologically based pharmacokinetic modeling, resulting in improvements in the statistical treatment of uncertainty and interindividual variability, and enabling the integration of various types of data within a coherent framework. The agency is encouraged to explore such approaches in the area of PBPK modeling and elsewhere, with the expectation that improved characterizations of uncertainty and variability will result.

Peer review of models, particularly those of this degree of complexity, is important and may often require considerable resources. Generally an interdisciplinary set of independent researchers should review the fundamental assumptions of the model, and be able to exercise the model to assess whether it performs appropriately under conditions where outputs are predictable.

**Comments compiled by Dr. Ulrike Luderer**

**Enhancing EPA's Risk Assessment Practices**

**Topic 5, Use of data versus defaults (Luderer, Green, Kehrer, Bus)**

*Charge Question 1. Do the Agency's efforts seem on track to advance the EPA risk assessment practices and are they in line with comments and recommendations received with respect to advances in the areas presented and the agency's research?*

Many of the public comments received were related to the perceived "conservatism" and reliance on defaults of the risk assessment process. The public concern was conservatism, but the goal of improved assessment is to use better data and to better characterize variability and uncertainty, while retaining conservatism in the sense of being health protective. This seems essential given a practical inability to address risks in the many possible subpopulations and life stages. However, by using better data when available, fewer default assumptions will need to be made. Thus, while conservative assumptions will need to be maintained at some level, these can be done from more accurate starting points.

Generally using high quality data is preferred over using defaults,. But, as the staff paper on Risk Assessment Principles and Practices pointed out, this is not always compatible with time and budgetary constraints. For those cases when it is necessary to use defaults, the risk assessment process would benefit from the use of defaults that are themselves based on data. As described in the staff paper, the defaults currently used by EPA have been based to some extent on available data, have undergone peer review, and have evolved over time as additional data became available. Further improving the database on which defaults are based would seem to be an efficient use of resources that would move risk assessment forward. For example, the extent of variability in human susceptibility has not been well characterized. This is an area which could benefit from the application of omics technologies to identify susceptible subpopulations, as mentioned on page 59 of the Staff Paper. With microarray technology, thousands of different single nucleotide polymorphisms can be measured in a single assay. Such data can help to quantify the variability in susceptibility within a population.

Increasing use of MOA data should improve low-dose extrapolation, and thereby address the overarching theme of conservatism. Incorporation of consideration of the MOA into the Cancer Risk Assessment Guidelines demonstrates progress by EPA in this area. Clearly better understanding of modes and mechanisms of action is critical for understanding the relevance of data from particular animal models to humans. It is also critically important for cumulative risk assessment. Genomics, proteomics, and metabonomics coupled with systems biology have the potential to greatly accelerate our understanding of MOA of toxicants. However, it seems overly optimistic to think that omic in vitro and in silico studies will soon replace in vivo animal studies. At present, much of the omic data are appropriately still derived from in vivo studies.

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*Charge Question 2. What other areas and improvements should be considered and which are most important?*

Further improving the database on which defaults are based, as described above.

Animal toxicology data constitute a significant input element into risk assessment. The issues raised by the NCEA regarding MOA on page 27 are all very important. The issue of “what data are needed to determine whether a certain MOA supports a particular approach to low dose extrapolation” is critical. In addition, risk assessments based on MOA may be problematic if they assume a single MOA per chemical. Many, if not most, chemicals likely have more than one MOA, which may vary depending on the endpoint and/or the dose. EPA needs to continue its efforts to improve mechanisms for applying weight of evidence approaches for incorporation of MOA data into risk assessments. A key element must include strategies for defining “how much is enough” and identification of what types of data are most valuable to these evaluations. Failure to accomplish this objective ultimately will serve as major disincentive for collection of MOA information.

EPA needs to expand efforts to better define the current descriptions of chemical exposures in toxicology tests, e.g., mg/kg or ppm, and move to approaches that encourage evaluation of “internal dose” such as blood and/or tissue/cell concentrations of parent compound or relevant metabolite(s). These data should be used to explore mechanisms to more effectively link chemical doses applied in toxicology studies to the emerging body of human biomonitoring data.

There were divergent opinions about whether EPA should promote modifying dose selection approaches for toxicology test protocols. One opinion held that EPA should place a particular emphasis on modifying the selection of high-end doses (maximum tolerated dose, MTD), including means of identifying test conditions exhibiting dose-dependent transitions likely not relevant to human risk extrapolation. This opinion further held that methods should also be developed to refine options for selection of doses at the low end of the dose-response curve, and in particular, doses that are more relevant to actual real-world human/environmental exposures. An alternative point of view held that the rationale for using doses higher than those to which humans might be environmentally exposed in toxicology testing so as to have adequate statistical power to detect effects while testing a reasonable number of animals was still relevant. Additionally, it was noted that the assumption that the MTD is not relevant to human exposures is not necessarily true for occupational exposures. While EPA is more concerned with environmental exposures to the general population, the results of toxicology testing at higher doses may be relevant for risk assessment in occupational settings. The group members all agreed that omic technologies could prove to be very useful for clarifying these issues, particularly for defining the low end of the dose-response curve and for understanding mechanisms of action and their implications for human risks.

Opportunities to identify mechanisms to “reality check” both exposure and human health predictions of risk assessment models must be developed. In order to improve the credibility of and confidence in science-based risk assessment, human health predictive models must be able to better differentiate potential anthropogenic environmental exposures of concern from

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those resulting from the large and complex chemical exposures of the natural environment, i.e., healthy food. Current models perform extremely poorly in this differentiation.

Current cancer risk assessment practice continues to be heavily influenced by yes/no evaluations of genotoxicity, i.e., compounds classified as genotoxic are defaulted to conservative linear no-threshold based risk models. Further research should focus on defining dose-response issues in genotoxicity tests and how such data could be used to define further risk assessment model options. Equally important is defining the mechanism of the genotoxicity for the mechanism really determines whether a linear or threshold dose response is operating. Chemicals directly acting on DNA are thought to act linearly whereas those acting indirectly more than likely operate through a threshold type response.

As EPA uses probabilistic and distributional approaches to a greater extent, it is important that the underlying assumptions and the data distributions that were used to build the models be made clear to both the scientific and the lay public. In particular sensitivity analyses and other methods should be used to make explicit how the conclusions of the risk assessment might change if different model parameters or data sets or indeed different models were used.

### **EPA's Exposure Assessment Guidelines**

#### **Topic 5: Use of data versus defaults/ new and emerging science and technology (Luderer, Green, Kehrer, Bus)**

#### **Charge Questions**

*1. Please comment on the relevance and priority of the topics listed to the current practice and future directions of exposure assessment (both measurement and modeling).*

There seem to be two overarching issues – a need to make better decisions, and a need to make more decisions given the number of chemicals involved. The goal is to make evidence-based decisions, and to that end there is a need to improve exposure assessment. The topics listed in the document – aggregate exposure and cumulative risk, populations/groups/life stages of special concern, probabilistic analysis of uncertainty and variability, community involvement and risk communication, and incorporating new and emerging science in exposure assessment – are all very relevant to improving the capacity to make these kinds of evidenced-based decisions.

Use of probabilistic analysis of uncertainty and variability and community involvement and risk communication are nearer term goals in that much is already being done in these areas by EPA. Aggregate and cumulative risk assessment, taking account of differentially exposed or differentially sensitive groups and life stages, and incorporating new and emerging science in risk assessment appear to be longer term goals. Regarding the latter, there has been extensive discussion of the promise of omics, computational biology, and systems biology to change the practice of toxicology, but clearly much work needs to be done before these become standard tools for exposure assessment. The focus on using these tools to develop high-throughput screening assays that may be used to identify chemicals that warrant further toxicological investigation seems very worthy of effort. The statement was made in one of the presentations

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that one promise of omics is to replace in vivo studies with in vitro and in silico studies, However, many of the potential uses of omics for exposure assessment proposed in the presentation, such as to estimate dose resulting from different routes of entry into the body or to estimate equivalence between different exposure routes, will require omic technologies to be coupled with in vivo studies for the foreseeable future. A nearer term use of omics would seem to be to increase the information obtained from in vivo studies in that many potential biomarkers of exposure and effect can potentially be measured from a single sample using these methods. However, it is not clear how much data are enough to make the regulatory decisions to protect human health. There seems to be an assumption that more data and new models will improve assessments, but this needs to be verified, particularly given the finite nature of resources and the need to move forward more rapidly. Uncertainty must be diminished, but in the end, whether decisions are going to be *materially* improved via these new procedures and having more data needs to be addressed.

One group member commented that the use of the social sciences in assisting in providing information about exposure is an approach that could become a morass for the agency given, as admitted, the complexities of human behavior.

*2. Please describe any other relevant topics which should be included in the revisions and their relationship to the topics presented and the overall guidelines.*

During the public comment period, the issue was raised that in some specific risk assessments, the use of multiple exposure-related defaults resulted in exposure scenarios that were characterized as unrealistic by the commenter. EPA should evaluate exposure condition defaults and assumptions to determine if they can be brought closer to the real world.

*3. What case examples or other references should be drawn upon to illustrate the science and practice of exposure assessment?*

One case example that bridges exposure assessment and cumulative risk assessment involves agents that alter male reproductive system development by disrupting androgen receptor signaling by various different mechanisms, including receptor antagonism and inhibition of androgen synthesis. Dr. Earl Gray's group from EPA ORD presented a poster at the 2006 Society for the Study of Reproduction meeting comparing how well dose addition, response addition, and integrated models predicted the effects of exposure to mixtures of such chemicals on male reproductive system development (Rider et al, 2006). The conclusion for these endpoints was that the different models performed well and that there were not major differences among the models in terms of fitting the data.

Dr Anna Lowit's examples of organophosphates and N-methyl carbamates as two groups of pesticides for which OPP has performed cumulative risk assessments could be used as case examples (presentation given on September 6). They also raise the obvious question as to whether it would be useful to evaluate the cumulative risk from these two classes of pesticides combined in that they both act by inhibiting acetylcholinesterase, albeit by different molecular mechanisms. A related, but broader question is whether similar methods can be used to assess the cumulative risks from chemicals that act within a common pathway but by different mechanisms.

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*4. How and to what extent can the current and emerging databases of human biomonitoring be used to inform exposure assessments? Please include the potential use of genomics and other biometrics to the degree they are relevant.*

Human exposure databases such as NHANES should have utility in exposure assessment for characterizing background exposures in the population, particularly as the agency moves away from assessing the risk to human health from exposure to a single chemical by a single route at a time and towards cumulative risk assessment. However, as was discussed at the meeting, a problem with using NHANES data in risk assessment is that it is not possible to reconstruct exposures from these biomonitoring data.

*5. Given that the guidelines are intended to provide general principles of the practice, and updated infrequently, what strategy could we explore to make (and keep) the document as relevant and up-to-date as possible?*

It should be possible for the EPA to convene workshops e.g. biomonitoring, at periodic intervals (2-3 years), to gather information on use of biomonitoring for exposure assessment. This would depend on the progress of the science and that could be determined by a Federal Register announcement asking for information from interested parties conducting research in this area or by the ORD conducting literature searches.

## REFERENCES

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