

## Conference Reports

### EPA Risk Assessment Principles and Practices

#### BOSC (Board of Scientific Counselors) Workshop, February 2–3, 2005, Washington, DC

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#### 1 Background

In 2003, the Office of Management and Budget, Executive Office of the President, asked stakeholders for comments on the US Federal Government's risk assessment practices. The comments were forwarded to the US Environmental Protection Agency (EPA) and were critical of EPA risk assessment practices. Generally, the nature of these criticisms were as follows:

- EPA must not intermingle policy judgments within the scientific assessment of risk
- Risk assessments should not rely on conservative (worst case) assumptions that distort outcomes and yield estimates that grossly overstate risk
- Risk assessments should acknowledge the presence of considerable uncertainty

In 2004, in response to the comments received, EPA risk assessors prepared a staff paper, *Evaluation of EPA Risk Assessment Principles and Practices*, that presented current risk assessment principles and practices. The examination provided a 'slice of time' discussion of these practices in some detail, including rationale for why EPA uses a particular practice. The paper as it stands does not represent EPA policy and will not be further revised. The purpose was to create a transparent starting point for all risk assessment practitioners to begin a healthy dialogue on how to strengthen, refine, and/or revise the current principles and practices. As part of this dialogue, EPA has met, and continues to meet, with interested and affected stakeholders on how to strengthen and improve these principles and practices. The Board of Scientific Counselors (BOSC) was asked to hold a risk assessment workshop, which was one among a number of interactions with the scientific community on issues raised by the paper, examining particularly the current default assumptions that included high to low dose and interspecies extrapolation approaches. Other professional societies were

asked to provide feedback on the paper in the areas of probabilistic methods in risk assessment, methods of uncertainty analysis, and ecological risk assessment.

In the future, EPA will be pursuing continued efforts to address risk assessment issues and concerns (e.g., working with the Society of Toxicology to convene a workshop on the use of probabilistic analyses for human health risk assessment by learning from other disciplines, e.g., cost/benefit analyses, what probabilistic methods will be practical and useful).

#### 2 BOSC Approach to Request for Stakeholder Discussion of EPA Staff Paper on Risk Assessment Principles and Practices

The BOSC of the EPA's Office of Research and Development (ORD) was established to provide advice, information, and recommendations to ORD concerning the management and scientific approaches used in their research program. In response to the request to address issues in Chapter 4, Considering Information Gaps in Health Assessments: Use of Default and Extrapolation Assumptions, of the staff paper, the BOSC decided that an appropriate format for a workshop on the paper was to first have a speaker describe the current practices of the EPA and then have several speakers provide constructive feedback for refining the EPA's current practices or suggesting alternative approaches for default and extrapolation assumptions that might be used in the future. The BOSC followed this format for three topics: (1) use of default assumptions and uncertainty factors, (2) extrapolation from high to low doses, and (3) extrapolation between species. In each case, a speaker from the EPA described the current practices, which was then followed by three speakers who suggested alternative approaches that might be used in the future. Lively discussions were held at the end of each of the three sections.

### 3 Summary of Major Discussion Points at the Workshop

**Systems biology.** One of the more exciting topics discussed at the workshop concerned the advent of genomics, coupled with bioinformatics, and the opening of new possibilities for understanding the relationship between gene expression and responses at higher levels of biological organization. Although we have long had a qualitative sense of how effects on one level of organization influence a higher level, we are now at the point of understanding those relationships in a quantitative way, which is the province of the new field of systems biology. The implications of systems biology for toxicology are enormous. Fundamental assumptions about interspecies extrapolation, the basis and extent of interindividual variation, and, perhaps most significantly, the relevance of high-dose toxicity results for predicting risk at low exposures may soon be testable. Previous attempts have been made to determine the quantitative relationships between effects at different levels of biology (e.g., Lau et al. 2001). By necessity, these biologically based dose-response models have started at a complex level of biological organization and worked their way down (e.g., what is the rate of cell death at the apparent threshold for malformation; what is the level of DNA synthesis inhibition that leads to cell death, etc.). Not only are there losses in resolving power at each step in the process, but the enterprise depends on having detailed information about mechanism of toxicity before starting. Genomics experiments can provide us with comprehensive information about the effects of a perturbation at a fundamental level, and bioinformatics can help us organize that information into plausible groupings and pathways. Hypotheses about causation can be generated from those groupings and pathways, and with the aid of modern molecular biological techniques, they can also be tested. This approach not only provides enlightenment about mechanism, but also can be used as a starting point for 'bottom up' to complement the 'top down' approach. If successful, approaches such as these will tell us much about biological responses at ambient exposure levels. Changes in gene expression can be measured at lower levels than those causing tissue level effects (e.g., Naciff et al. 2003); therefore, it should be possible to follow the expression levels of genes critical for a given toxic response to lower regions of the dose-response curve. More importantly, this approach should be able to identify instances in which an effect observed at high dose is the result of an overwhelming of homeostasis or a saturation of metabolism.

**Mode of action.** Mode of action as the basis for risk assessment was another important topic for discussion. There was very little information available about the mode of action of most toxicants at the time chemical risk assessment practices were established. The prevailing hypothesis regarding cancer was that a single mutation was sufficient to drive the carcinogenic process. This hypothesis led to the assumption of a linear relationship between dosage and carcinogenic risk, with no threshold, for agents found to cause cancer in animal models. Other manifestations of toxicity were assumed to be at threshold, such that a safety/uncertainty fac-

tor-based approach was sufficient to estimate a safe exposure level. Over time, we have learned that the separation between carcinogenesis and other toxicities is artificial; there are modes of action that can cause multiple manifestations of toxicity, including, in some cases, cancer and non-cancer effects. These examples demonstrate that the separation of cancer and non-cancer risk assessment is artificial, and that more flexible approaches such as has been proposed by the EPA in its draft *Cancer Risk Assessment Guidelines* are warranted. There has been considerable discussion about the merits of and methods for harmonizing cancer and non-cancer risk assessments using mode of action information (Bogdanffy et al. 2001). Mode of action information may also be used to better tailor toxicity testing programs, and as the basis for tiered systems of testing. The prototype for such tiered testing is EPA's proposed *Endocrine Disrupter Screening Program*, in which chemicals are subjected to a mode-of-action-based screening battery, after which positive compounds are further evaluated using traditional testing protocols for reproductive and developmental toxicity (EDSTAC 1998).

**Combining uncertainty factors.** Another point of discussion was how to combine uncertainty factors that are used in risk assessment. The current method is to multiply these factors together, as if each factor were independent of the others. But there is no scientific rationale for assuming independence. No solution to this problem was offered, other than to gain more information on the degree of interdependence of the factors to allow a more rational approach to combining them.

**Using internal dosimetry.** Emphasis was placed on the need to determine the internal dosimetry that leads to an adverse effect. Physiologically based pharmacokinetic modeling was discussed as a tool by which one can go from exposure information (concentration  $\times$  time) to internal dose, to dose to critical organ, to biologically effective dose. Such models can then be coupled with physiologically based pharmacodynamic models, if the mechanism of the induced effect is known. The mathematical models, if validated, should allow one to extrapolate between different exposure scenarios.

**How to handle backgrounds.** Participants provided varied perspectives on the role of background exposures in risk assessment. Risk associated with exposure to a given chemical occurs in a context of exposures to a wide array of naturally occurring chemicals and to anthropogenic chemicals that are so ubiquitous as to be essentially part of the background. Risk assessors can respond in several ways to this problem. One approach is to assume that the basic food supply is 'safe' despite the fact that all foods contain numerous natural chemicals that are toxic, carcinogenic, or both. Current risk assessment methods can be used to estimate the risk associated with these exposures to provide a context for the risk associated with a particular anthropogenic chemical of concern. Thus, if the lifetime cancer risk of exposure to natural chemical 'x' is  $6 \times 10^{-4}$ , we might treat anthropogenic chemical risks much lower than this, or as of limited or no concern.

An alternate approach is to focus on cumulative risk. In this context, the background risk resulting from multiple natural and anthropogenic sources becomes a baseline that cannot be readily avoided. Risk management then focuses on keeping incremental additions to that risk as low as possible. The difference in these two perspectives is, thus, not in the particular risk estimated for an individual chemical, which is the same in both cases. It is rather whether background risks are viewed as a basis for assessing the significance of individual chemical risk or as an unavoidable baseline to which additions are to be minimized.

**BOSC Workshop Presentations.** The BOSC workshop PowerPoint presentations and the EPA staff paper (PDF format) are available through links displayed on the EPA's web site, [http://www.epa.gov/osp/bosc/ra\\_work.htm](http://www.epa.gov/osp/bosc/ra_work.htm).

## References

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### The workshop covered three topics:

- Use of default assumptions and uncertainty factors (Session 1)
- Extrapolation from high to low doses (Session 2)
- Extrapolation between species (Session 3)

#### Session 1 – Extrapolation From High to Low Doses

High-to-Low Dose Extrapolation: Issues and Approaches  
Dr. Weihsueh Chiu, EPA / ORD / NCEA

Biologically-motivated approaches to extrapolation from high to low doses and the advent of systems biology:  
The road to toxicological safety assessment  
Dr. Rory Conolly, CIIT Centers for Health Research

Some Issues Regarding High-to-Low Dose Extrapolation  
Dr. Thomas Starr, TBS Associates

Considerations for Improving High to Low Dose Extrapolation  
Dr. Lauren Zeise, California EPA

#### Session 2 – Use of Default Assumptions and Uncertainty Factors

Default Assumptions, Uncertainty Factors – EPA's Approach  
Dr. Rita Schoeny, EPA / OW

A State's Approach to Risk-Based Analysis: Similarities to and Differences from EPA's Principles and Practices  
Dr. Hillary Carpenter, Minnesota Department of Health

Past and Future Use of Default Assumptions and Uncertainty Factors  
Dr. Michael Dourson, Toxicology Excellence for Risk Assessment

NRDC Comments to BOSC on the Use of Default Assumptions and Uncertainty Factors in EPA Risk Assessments  
Dr. Jennifer Sass, Natural Resources Defense Council

#### Session 3 – Extrapolation Between Species

EPA Risk Assessment Practice: Extrapolation Between Species  
Dr. Kerry Dearfield, EPA / OSA

Mode of Action and Dosimetry Considerations in Interspecies Extrapolation  
Dr. Mel Andersen, CIIT Centers for Health Research

Extrapolation Between Species: Issues and Opportunities for the Future  
Dr. Jim Bus, Dow Chemical

Biomarkers and Species Comparisons (Metabolism & Metabolomics)  
Dr. Susan Sumner, RTI International