

Proceedings of the  
U.S. Environmental Protection Agency  
Board of Scientific Counselors Risk Assessment Workshop

Washington, DC  
February 2-3, 2005

## RISK ASSESSMENT AND THE AGENCY

The U.S. Environmental Protection Agency (EPA) conducts risk assessments to provide the best possible scientific characterization of risks based on a rigorous analysis of available information and knowledge. The primary purpose of these risk assessments is to inform the risk manager's decision-making process. Risk assessment is not intended to make or recommend any particular decision; rather, it provides the risk manager information to consider along with other pertinent information (e.g., economic, legal, social, technological, political, and public factors) when making decisions about how to manage risk. Risk assessment informs decision makers about the science implications of the risk in question. EPA uses risk assessment as a key source of scientific information for making good, sound decisions about managing risks to human health and the environment.

EPA completed its first risk assessment document in December 1975, and has issued numerous publications on this topic since then. In 1983, the National Academy of Sciences, published *Risk Assessment in the Federal Government: Managing the Process* (commonly referred to as the "Red Book"). EPA began integrating the principles of risk assessment from this groundbreaking report into its practices and in 1984, the Agency published *Risk Assessment and Management: Framework for Decision Making*. This publication emphasizes making the risk assessment process more transparent, describing the assessment's strengths and

weaknesses more fully, and providing plausible alternatives within the assessment. Shortly after the publication of the Red Book, EPA began issuing a series of guidelines for conducting risk assessments. Although EPA efforts focused initially on human health risk assessment, the basic model was adapted to ecological risk assessment in the 1990s to deal with a broad array of environmental risk assessments in which human health impacts are not directly at issue. EPA continues to update these guidelines and develop new guidelines as needed.

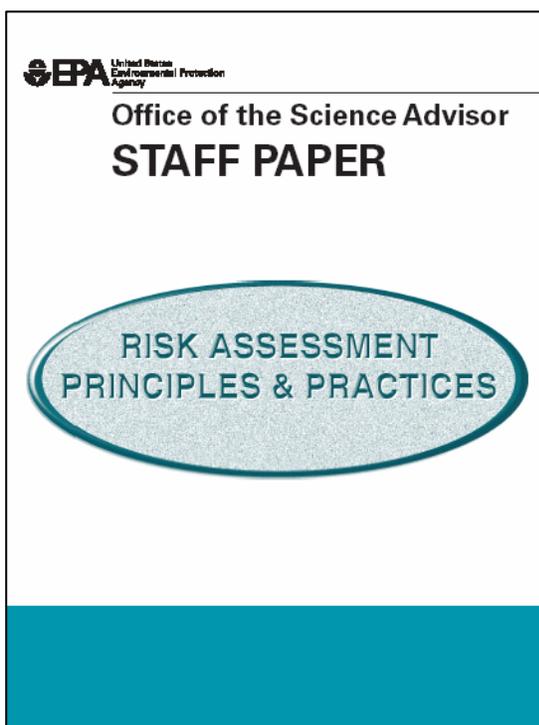
In 1995, EPA updated and issued the current Agency-wide Risk Characterization Policy. This Policy calls for all risk assessments performed at EPA to include a risk characterization to ensure that the risk assessment process is transparent; it also emphasizes that risk assessments must be clear, reasonable, and consistent with other risk assessments of similar scope prepared by programs across the Agency. In 2000, EPA developed the Risk Characterization Handbook to implement the Agency's Risk Characterization Policy.

EPA constantly evaluates its risk assessment principles and practices, mostly via a gradual refinement of particular practices that may not be overtly visible to the public. In early 2002, the position of the EPA Science Advisor was established and given overarching responsibility to coordinate and oversee the scientific activities of the program and regional offices at EPA. Part of this responsibility is to ensure the best use of science at the Agency and in its decisions.

At the Science Advisor's request, EPA staff began looking at the Agency's risk assessment practices and training with the goal of updating them. When the Office of Management and Budget (OMB) solicited comments on risk assessment practices across the federal government, EPA took this as an opportunity to concentrate on a wider review to evaluate current risk assessment practices across programs and regions.

As part of this review, EPA developed a staff paper—*An Examination of EPA Risk Assessment Principles and Practices*—to give the EPA scientific and technical professional staff an opportunity to present what they believe are the current EPA risk assessment principles and practices (see Figure 1). The paper's purpose was first to open a dialogue among EPA risk assessors and risk managers about Agency risk assessment practices, and then to engage those outside the Agency in a continued dialogue about how to move forward together to clarify and strengthen EPA's risk assessment practices.

Figure 1. EPA Staff Paper



Source: EPA, 2004

## RISK ASSESSMENT WORKSHOP

In an effort to open this continued dialogue, the Assistant Administrator for Research and Development asked EPA's Board of Scientific Counselors (BOSC)<sup>1</sup> to organize a workshop to provide a public forum for discussion of Chapter 4 of the staff paper—*Considering Information Gaps in Health Assessments: Use of Default and Extrapolation Assumptions*. The BOSC formed the Risk Assessment Workshop Work Group to plan and coordinate the workshop. The Work Group was chaired by Dr. Rogene Henderson from the Lovelace Respiratory Research Institute. The other Work Group members included Dr. George Daston from Proctor & Gamble, Dr. Clifford Duke from The Ecological Society of America, and Dr. John Giesy from Michigan State University.

The workshop, which was held February 2-3, 2005, in Washington, DC, included three sessions: (1) extrapolation from high to low doses, (2) use of default assumptions and uncertainty factors, and (3) extrapolation between species. For each session, an EPA representative presented the Agency's current practice for risk assessment, followed by three speakers who offered comments and suggestions for alternative ways of conducting the same assessment. Time for discussion and responding to questions from participants was provided at the conclusion of each session.

Copies of the speakers' presentations and these proceedings of the Risk Assessment Workshop are posted on the BOSC Web Site at <http://www.epa.gov/osp/bosc>. In addition, the papers presented by the speakers are expected to be published in a peer-reviewed journal.

<sup>1</sup> The BOSC was established by EPA to provide advice, information, and recommendations about the ORD research program. For more information about the Board see the BOSC Web Site at <http://www.epa.gov/osp/bosc>.

## OVERVIEW OF EPA'S STAFF PAPER

Dr. William Farland, Acting Science Advisor, Office of the Science Advisor, thanked the BOSC for providing a forum for discussion of the staff paper on risk assessment principles and practices. He described the genesis of the staff paper, which began with comments submitted to OMB that were critical of EPA's risk assessment practices. In response to this criticism, EPA developed a Risk Assessment Task Force to collect and analyze the comments on Agency risk assessment practices. The staff paper was published in March 2004, and is available on the Office of the Science Advisor Web Site at <http://www.epa.gov/osa>.

The staff paper describes the perspectives of EPA risk assessors on the way risk assessment is conducted at the Agency and presents staff recommendations for EPA and interested stakeholders to consider regarding the way in which EPA can move forward to strengthen and improve its risk assessment practices. Dr. Farland noted that the staff paper does not represent EPA policy; instead, it describes EPA practice.

Dr. Henderson explained that Chapter 4 of the document, on extrapolation and defaults, is the subject of this workshop. Dr. Farland asserted that the staff paper serves as a vehicle for opening a broad dialogue among EPA staff, Agency managers, and external parties about the practice of risk assessment at EPA. Its publication represents the first step in a multistep process toward refinement and improvement of the Agency's risk assessment practices. A number of additional efforts are underway to achieve this goal.

## SESSION I: EXTRAPOLATION FROM HIGH TO LOW DOSES

Dr. Rogene Henderson, Moderator

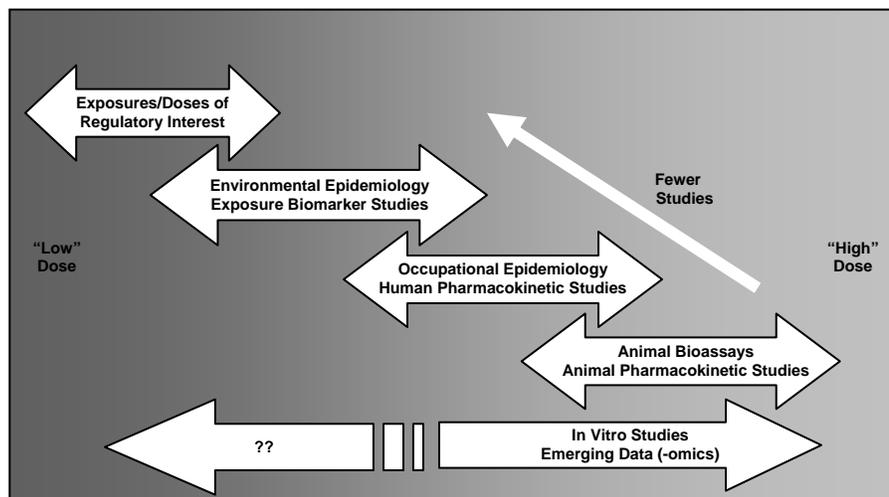
### EPA's Approach

Dr. Weihsueh Chiu, EPA/NCEA

Dr. Weihsueh Chiu of EPA's National Center for Environmental Assessment (NCEA), began his presentation, titled "High-to-Low Dose Extrapolation: Issues and Approaches," by explaining three points: (1) EPA uses a variety of approaches for low-dose extrapolation, (2) a number of important issues must be considered in the choice and implementation of these approaches, and (3) EPA is working to advance the science and methods for low-dose extrapolation and to make use of the best science available for its current risk assessments. He pointed out that EPA often must estimate risks at exposures and doses that are much lower than the range of data, and noted that low-dose extrapolation has both biological and statistical components (see Figure 2).

EPA uses the following approaches for extrapolation below the range of observation: (1) model-independent approaches, (2) model-dependent approaches, and (3) a combination of these approaches. The characteristics of model-independent approaches are separation of observed range and ex-

Figure 2. Range of Data Typically Available for Use in Risk Assessment



Source: Chiu, 2005

trapolation range, choice of linear and non-linear extrapolation depending on knowledge of the mode of action, and consistency in procedures and results. Dr. Chiu articulated a number of characteristics of model-dependent approaches: there is a presumption that the model is valid below the range of observation, they often involve unobserved parameters estimated by fitting models to dose-response data, they are implemented so as to be interpreted as a central estimate assuming the model is “true,” and they are used in combination with model-independent approaches.

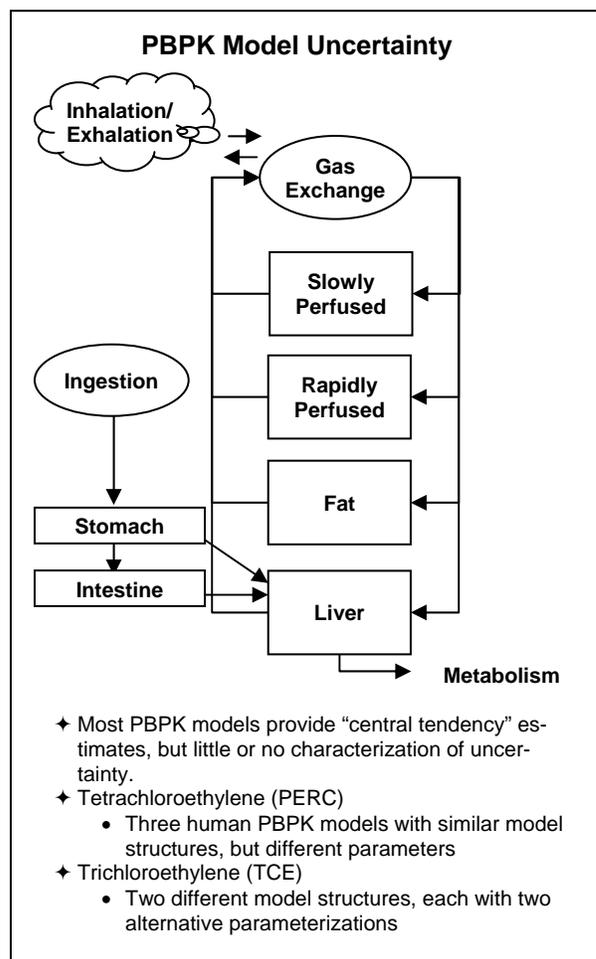
After explaining several examples of model-dependent approaches (one of which is presented in Figure 3), Dr. Chiu summarized the EPA approach to high-to-low dose extrapolation. Both model-independent and model-dependent approaches are used in EPA’s current risk assessments and will be used in future risk assessments. Major issues with choosing and implementing different approaches include knowledge of the mode of action and biological relationships at low dose, the characterization of uncertainty and variability, and the degree of confidence and consistency in the results. EPA is working to advance the science and methods in this area and to use the best science available for its current risk assessments. The Agency welcomes additional ideas and input regarding how to move forward.

### 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

Dr. Rory Conolly, Center for Computational Systems Biology and Human Health Assessment, CIIT Centers for Health Research, began his presentation by suggesting that the focus should be the safety of chemicals rather than their toxicity. He posed the fol-

Figure 3. Typical PBPK Model for a Volatile Organic Compound



Source: Chiu, 2005

lowing question: What do the typical high-dose rodent data tell us about risks and exposures outside the experimental range? The answer is that the data by themselves are not particularly informative. In the absence of data, we make conservative choices to predict risk. After giving a historical perspective about the use of high-dose data to imply human health risk, Dr. Conolly described the current widespread recognition that chemical-specific high-to-low dose extrapolation may differ from default approaches. The concern is that some high-dose mechanisms may not be relevant. The need persists to protect the public health, avoid unnecessary loss of access to useful materials, and promote “good” science in support of human health risk assessment.

The question is, given limited resources, where do we focus our efforts? Should our priority be the study of poisons, their effects, and mechanisms regardless of dose? Or should it be the evaluation of chemical safety, that is, the dose-response in the region of actual or predicted exposure levels? Is safety assessment a practicable alternative? A toxicological safety assessment involves three key elements: (1) exposure, (2) biologically based dosimetry models, and (3) systems biology. Systems biology offers the opportunity to understand, at the molecular level, the transition from normal biology to toxicity.

Systems biology involves the way in which tissue responds to a delivered chemical. The levels of biological organization include molecules, organelles, cells, tissues, organisms, and populations. As we move up the levels of biological organization, we can think of systems at lower levels of organization that create new structures at higher levels. Systems biology is the attempt to understand how, at progressively higher levels of organization systems, agents interact to provide the structures at the higher levels. To draw some inferences about potential dose-response behaviors, Dr. Conolly described several systems of molecules that create signaling pathways in cells. A molecular pathway must be identified, and computational modeling is used to explore the dynamic behavior pathway and iterate that information with the data collection.

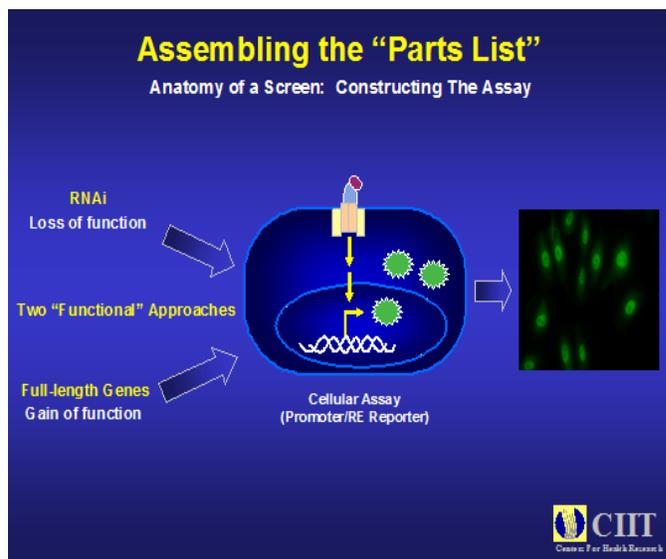
In terms of data in support of this kind of model development, “omics” technology, including genomics, proteomics, and metabolomics (sometimes referred to as “metabolomics”), produces a parts list of the biological machine (see Figure 4). Computational systems biology can organize and integrate data, study dynamic behavior, conduct analysis to determine whether model predictions are consistent with existing data, and make predictions and suggest new experiments. Therefore, modeling integrated

with laboratory research is a powerful tool for processing and analyzing data.

Dr. Conolly offered an example involving skin irritation and the ability to make dose-response predictions relevant to the biological response to exposure to the irritant chemical. The lowest levels of exposure to chemicals produce transient perturbations in the biochemistry of the cells reached by those chemicals. As the doses are increased or the exposure is extended in time, stable perturbations or changes in network topology occur, which can lead to structural changes and eventually functional changes. Systems biology shows how the lowest levels of change can be studied and interpreted to understand the highest levels of change.

Dr. Conolly pointed out that the use of systems biology in human health risk assessment would produce relevant toxicology devoted to a better understanding of what is meant by “toxic.” It also would provide an interesting perspective on the topic of “chemical trespass.” Another payback of systems biology is that resources would be used efficiently to deal with a science-based dose-response assessment.

Figure 4. Assembling the “Parts List” of the Biological Machine



Source: CIIT Centers for Health Research, 2005

## Some Issues Regarding High-to-Low Dose Extrapolation

Dr. Thomas Starr, TBS Associates

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Dr. Thomas Starr, TBS Associates, stated that his comments would complement Dr. Conolly's presentation. EPA's approach involves differentiating between the experimental range, within which things can be reliably measured, and the extrapolation region, within which meaningful measurements are not possible due to technical limitations. The boundary between the experimental range and the extrapolation region is the so-called "point of departure" (POD), the lowest dose in the experimental range at which responses can be reliably measured. It is where science stops and policy begins. Science can be used only to make statements about response at or above the POD. Even at or above the POD, severely limited experimental designs impose artifactual correlations between potency estimates and the reciprocal of the corresponding maximum doses tested (MDTs). Because MDTs are well-correlated across species, it appears, at least superficially, as if we can reliably estimate potency in one species based on estimates in other species, but this is false; the apparent correlation between potency estimates is merely a reflection of the correlation between MDTs across species, and it implies nothing about the true potency values in the extrapolation region.

To reduce to impact on risk assessments of this fundamental difficulty, we need more animals per dose group and unbalanced designs (with many more animals at lower doses than at higher doses). We also need lower doses relative to the MDT, and designs with frequently scheduled sacrifices that can reveal more about the disease process, as well as response biomarkers that are more sensitive indicators of effect than are tumors, and which are causally related to carcinogenesis. In addition, we need extensive mechanistic data and dose-response models that accommodate and make use of

such data. Therefore, it is clear that a major effort is required to improve current risk assessments. There is no easy way to accomplish this.

Recommendations that involve improvement of the POD include: (1) using a central estimate for the POD and then adjusting, if policy dictates, with an explicit uncertainty factor for sampling variability, such as the ratio of a central estimate to its lower 95% confidence bound; (2) using control group variation for continuous endpoints to define PODs in terms of increased probability of an adverse response, facilitating direct comparison of PODs for quantal and continuous endpoints; and (3) explicitly acknowledging sensitivity differences between quantal and continuous endpoints and study designs by identifying the actual "reliable detection limits" of various experimental designs.

Dr. Starr gave an example of how data from a rich experimental design could be used to develop probability distributions for relative potency factors (RPFs) and compared results of this analysis with the current Toxic Equivalency Factor (TEF) for 4-penta-chlorodibenzofuran. Desirable criteria exist for how RPF and TEF values are developed. First, each study should be assessed for parallelism of the dose-responses, including specification of the power to reject the null hypothesis. Second, a common definition is needed for the RPF across different types of endpoints. Third, a central estimate and a confidence interval, standard error, or Monte Carlo sampling distributions for RPFs are needed. Fourth, RPF point estimates or distributions can be combined so as to produce a TEF only after quantitative assessment of heterogeneity, with outlier datasets excluded from the combination process. Fifth, an explicit scientific rationale is needed for the weights used with each RPF, not just a subjective judgment of relative importance that is impossible to explain or reconstruct. Sixth, partial agonists must be included in the TEF scheme.

In summary, Dr. Starr noted that more and better data are needed, as well as better models. There is no easy or quick fix. A consistent, transparent definition of POD also is needed across the various kinds of data that are collected and from which risks are being estimated. Finally, the clear distinction between the roles of policy and science in risk assessments must be maintained.

### Considerations for Improving High-to-Low Dose Extrapolation

Dr. Lauren Zeise, California EPA

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Dr. Lauren Zeise, Office of Environmental Health Hazard Assessment, California EPA, began her presentation by complimenting EPA on its staff paper.

EPA risk assessment practices for high to low dose extrapolation have evolved in response to scientific developments, regulatory need, and stakeholder concerns and to further the Agency's mission to protect the public. The EPA Staff Paper, refreshing in its directness, includes a clear, transparent explanation of practices and underlying rationale for Agency dose response analyses. Dr. Zeise's presentation commented on existing EPA practice first for non-cancer then for cancer assessments, and present issues for consideration in efforts to improve those assessments. This was followed by suggestions regarding efforts to harmonize cancer and non-cancer approaches, and on applications of complex models to robust and varied data sets.

Dose response information for non-cancer endpoints is characterized by a single number, i.e., the reference dose (RfD). Exposures below the RfD are presumed to be without appreciable risks of adverse effect; above it, neither the magnitude nor severity of risk nor quantitative uncertainty characterizations are described. A general statement has been made that the RfD is assumed accurate to within an order of magnitude, al-

though because of the confusion in its interpretation an EPA workgroup is proposing the statement be dropped. Some problems pointed out in the staff paper (page 34) on uncertainty analyses also are pertinent in this regard: without an idea of risk it is difficult to compare outcomes of alternative decisions, and formal quantitative benefits assessments (e.g., as desired under the Clean Air Act) are precluded. The underlying presumption in RfD development is that there is a threshold dose below which effects are absent and above which effects occur. Analyses do not systematically consider the appropriateness of this assumption for the RfD endpoint, even when the background load of the chemical and similarly acting chemicals is high.

The RfD is generally derived from a no-observed-adverse-effect-level (NOAEL) for the most sensitive critical endpoint believed to be relevant to humans in the critical animal toxicity study. Most recently, the NOAEL has been replaced by a benchmark dose (BMD)—the dose estimated through statistical model fits to produce a pre-specified level of risk (e.g., 5% or 10%) for the critical effect in the critical study. Uncertainty and adjustment factors are applied to address interspecies differences in toxicity and human variability in response to similar toxic insults. Additional adjustment factors may be included when the derivation utilizes experiments of limited duration, when only a lowest observed adverse effect level (LOAEL) is available, or when there are other limitations in the data set. Typically in extrapolations from animal studies, in the absence of chemical specific pharmacokinetic data, there is no systematic assessment to ascertain whether the adjustment and uncertainty factors for interspecies uncertainty and interindividual variability are adequate—whether the concern is acute toxicity or subtle neurological change or reproductive system alterations, the effects are difficult or unlikely to detect in standard toxicity protocols. The NOAEL is treated as a

threshold dose in the animal despite the residual risk that may occur at the dose. The BMD also is conceptually treated as equivalent to a threshold even though it is explicitly taken to be a lowest bound estimate on a dose with either 5% or 10% risk, and typically is derived from studies of low statistical power.

To address the limitations in the dose response framework for non-cancer endpoints, probabilistic approaches have been proposed. On page 146 of the staff paper, EPA acknowledges the need to encourage such approaches. There are a variety of methods of utilizing the so-called probabilistic RfD approach discussed in the literature.

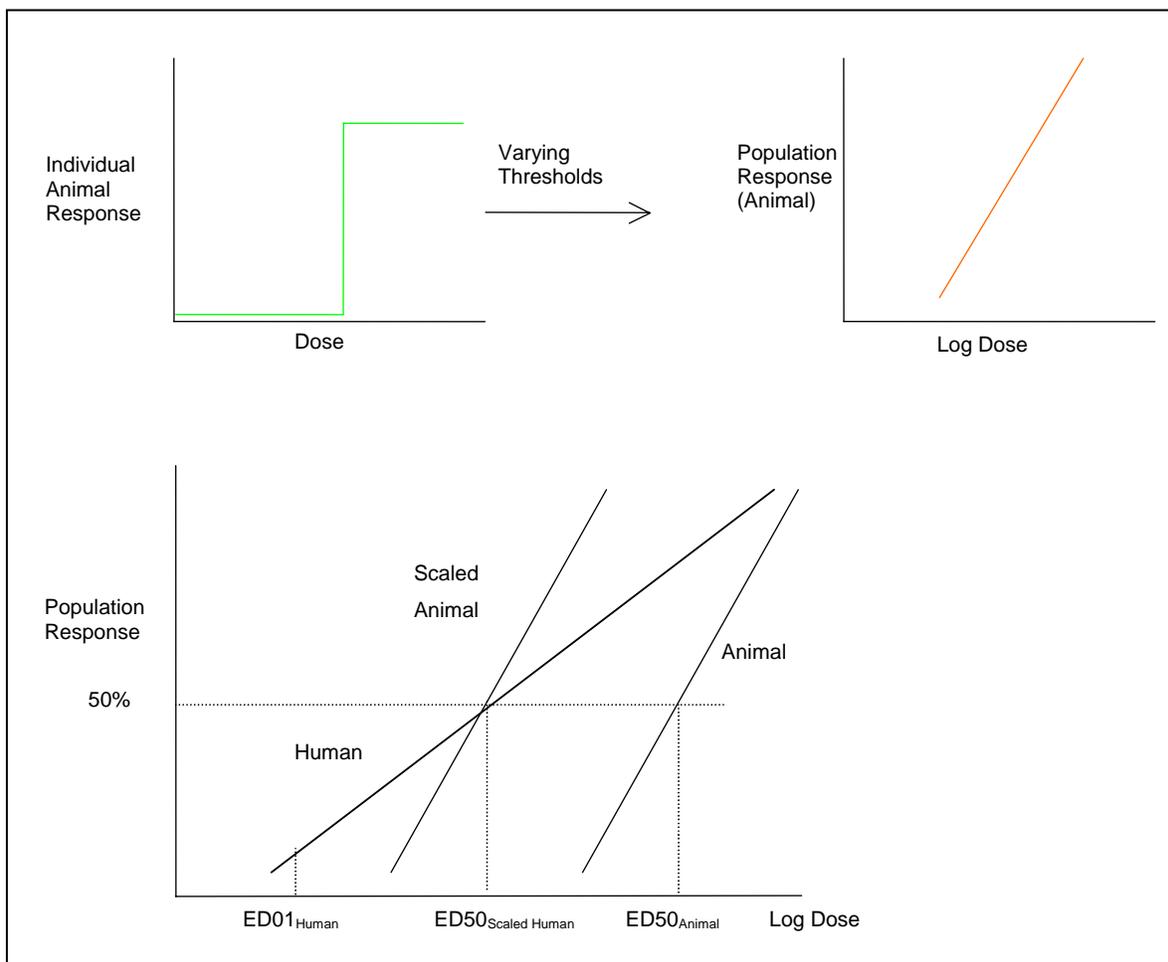
Each adjustment or uncertainty factor is characterized by a probability distribution. The overall goal of the exercise is to use them to characterize human non-cancer dose response as a dose versus risk function. A dose associated with a *de minimis* risk would be derived from this function. The underlying uncertainty in this estimate would be characterized from the uncertainty components of the input distributions. The underlying probability distributions for adjustment/uncertainty factors are derived from data beyond the critical experiment used in traditional RfD development.

Figure 5 illustrates in a little more detail the calculus of a probabilistic approach, borrowing from the framework of Evans and Baird. For each animal a threshold dose is assumed. Thresholds are assumed to vary for the different animals in the critical experiment, as reflected in the form and statistical procedure applied to fit the data. In Figure 5, a probit model is assumed with animal sensitivity assumed to follow a lognormal distribution (on a probit plot the dose response relationship follows a straight line). To construct the human dose response relationship, the animal dose is first scaled to a human equivalent dose, by taking the median value of the interspecies extrapolation

distribution. In Figure 5 this is seen as the translation of the animal log-probit line downward to the human line. This translation uses a single value from the interspecies probability distribution (i.e., the median). The uncertainty described by that distribution is tracked and is input for the construction an overall uncertainty distribution. A distribution assumed to reflect the variability among humans is used to define the spread of the human dose response curve, which in this example is described by lognormal distribution, and also plots as a straight line on log-probit paper. With the ED<sub>50</sub> as a pivot point, this can be visualized in Figure 5 as a tilting of the dose response line. A dose associated with a *de minimis* risk level (e.g., one per hundred thousand) can be established from the resulting human dose response relationship. Quantitative measures of uncertainty in the *de minimis* dose estimate are taken from the probabilistic description of uncertainty. This description is a convolution of distributions representing the uncertainties in interspecies extrapolation, human variability, and any other factors (e.g., data gaps and quality). This distribution is assumed to portray the confidence in the dose estimate associated with *de minimis* risk.

The probabilistic scheme just described replaces the default uncertainty and adjustment factors with probability distributions. Variability due to differences between species and among people is distinguished from the uncertainty associated with such characterizations. Although conceptually appealing, the approach is only as reliable as the data used to construct the distributions are representative. An interspecies distribution has been derived from an acute and subacute toxicity database populated with LD<sub>10</sub> values for different species for cancer chemotherapeutic chemicals (the LD<sub>10</sub> is defined as the dose causing mortality in 10% of individuals in a population). The extent that interspecies differences in lethality would be

Figure 5. Schematic Illustrating the Mechanics in Applying One Probabilistic RfD Approach



Source: Zeise, 2005

quantitatively similar for other endpoints such as neurotoxicity or IQ loss has not been explored. Human heterogeneity has been quantified by considering its components such as uptake, metabolism and pharmacodynamics (Hattis et al. 1999), and represented by unimodal and smooth distributions that do not take into account polymorphisms and distinct highly sensitive populations. Variability in human response is likely to be both chemical and endpoint specific, and dependent on the complexity of the underlying pharmacokinetic and disease processes. The EPA (2004) staff paper in recognizing the promise and limitations of probabilistic analyses aptly points out that “EPA will be able to conduct probabilistic analyses as part of any original analysis, though it is recog-

nized that probabilistic frameworks will be pointless without adequate data to insert (page 49 of the Staff Paper). Genomic and proteomic data coupled with the tools of computational toxicology hold the promise for developing more realistic distributions of human variability.

Implicit in developing a non-cancer RfD is the assumption that there is a threshold dose below which effects are not anticipated. In determining the appropriateness of this assumption, it is important to consider the exposures to the chemical in question and similar chemicals that some of the more highly exposed members of the population may already face. This is not addressed in the EPA Staff Paper. If disease is occurring

in the population by the same process as the chemical in question, the exposure in question may add to existing exposures, which may fall above the population threshold. Incremental increases in exposure then may cause effect. In cases where non-monotonic dose response may be postulated on mechanistic grounds, the same considerations apply. For ubiquitous environmental chemicals, exposure at environmental levels leads to large numbers of molecules per target cell exposure daily (e.g., 120,000 molecules per bone marrow cell for benzene); coincidentally, there can be a wide range of susceptibility in the population. Mechanistic studies and modeling efforts may further facilitate understanding the extent to which the more highly exposed and sensitive members of the population may be affected by environmental exposures.

Often risks are characterized for one chemical for a single circumstance of exposure. The level of risk, however, depends on the exposures to the various chemicals from natural and anthropogenic sources that may operate by the same mechanism. For example, a new source of 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) should be considered in the context of exposures to other sources of dioxin as well as those other chemicals that likely act via the same mechanism, such as the other dioxin-like compounds.

The draft characterization of risks from dioxin and dioxin-like compounds provides an example of an approach where, after considering the level of background exposure, the Agency decided not to develop an RfD, and did not assume thresholds for non-cancer endpoints. Instead, the dose associated with a 1% increase in risk ( $ED_{01}$ ) for the various endpoints was compared to the background doses and body burdens. For some endpoints the human exposures fell above the  $ED_{01}$ s or close below them. Although risk estimates at doses other than the  $ED_{01}$  were not provided, the Agency recognized the

importance of considering background exposures in evaluating the potential exposures to dioxin and like compounds.

For particular endpoints for a growing number of chemicals, epidemiological studies suggest a threshold assumption may not be appropriate for analyzing effects from environmental exposures. Examples include certain effects caused by exposures to ozone, lead, particulate matter, and benzene. With large and sensitive human studies it is possible to detect subtle effects, some of which are difficult if not possible to study in animals *in vivo*. Also, for some chemicals environmental exposures are large and appear to fall above theoretical thresholds.

In contrast to non-cancer endpoints, dose response analyses for cancer endpoints is partly justified on the basis of the background additivity principal, as discussed by Crump et al., 40 years ago. Because the various cancers were found to be common diseases, often involving mutation, a common and widespread biological phenomenon, environmental carcinogens were seen to add to already ongoing processes. Under a variety of mathematical models, the dose response was found to be linear at low dose.

Another assumption unique to cancer dose response analyses based on animal data is that each individual faces exactly the same risk of cancer if given the same dose. The uncertainty bounds reflect the stochastic nature of the experiment, and not the interindividual variability of the animals in the dose group. In epidemiologic studies, differences in cancer susceptibility attributable to genetics and lifestyle are clearly apparent for both mutagenic and non-mutagenic carcinogens. Genetic and other information also indicates that differences in susceptibility to carcinogens are common.

EPA's procedures do not include systematic evaluation of the potential human variability in response to carcinogen exposure, nor de-

fault procedures to address it. Nonetheless, at several points in the EPA (2004) staff paper the Agency implies the cancer risk estimates are protective of sensitive populations. “EPA addresses variability by assessing the risk to sensitive portions of the population. Accordingly, EPA makes explicit choices to characterize the risk at the upper end of the expected distributions (page 33 of the Staff Paper)...EPA attempts to protect those with underlying biological sensitivity” (page 22 of the Staff Paper).

The hope is that knowledge emerging from toxicogenomic and related “omics” studies will provide a basis for characterizing human variability in response to carcinogen exposures. This necessarily will require the development of mathematical and statistical models to capitalize on the science as it develops. Still, progress to explore and characterize variability can be made using existing methodologies and data. Coupling characterizations of physiological and pharmacokinetic parameter variability and covariance with physiologically based pharmacokinetic (PBPK) models and cancer dose response, descriptions of human variability have been derived. PBPK models are limited by the lack of statistical procedures to parameterize and validate the models and characterize the uncertainty in model predictions. A hierarchical Bayesian approach has been developed to provide a statistical framework for model parameterization, and to overcome the difficulty posed by the multilevel error structure of pharmacokinetic data. The approach can be used to quantitatively describe uncertainty in the chemical’s toxicokinetics as well as variability among individuals in toxicokinetic parameters, and is suggested for EPA’s consideration.

In the absence of human cancer, it is assumed when applying the results of pharmacokinetic models to high-to-low dose and other extrapolations that the cancer will occur at the same site in the human as observed in the animal study. The EPA Staff

Paper (page 55) notes where site concordance across sex in the same species is relatively high, across species it is considerably lower. Although EPA notes it does not assume site concordance *a priori*, it typically does so in the application of pharmacokinetic models. This is an area where the development of further guidance would be useful.

It has been the practice when an agent induced cancer at multiple sites to base the dose response characterization on the most sensitive tumor site. This can result in an underestimation of cancer risk. An alternative approach is to account for the multiplicity of sites by combining site-specific cancer potencies based on their individual likelihood functions utilizing a Monte Carlo approach.

In the Staff Paper, EPA acknowledges the importance of life stages and other factors related to vulnerability (pages 42-43). Most recently, EPA has released Supplemental Guidance for Assessing Susceptibility from Early-in-Life Exposure to Carcinogens, which provides default procedures for adjusting cancer potencies in the absence of chemical-specific data on carcinogenicity from exposures early in life. The procedures are based on an analysis of mostly experimental data generated in studies involving exposures in different age windows. EPA intends to apply the adjustments to carcinogens found to operate through a mutagenic mode of action. The Agency held off on adopting age adjustments for non-mutagenic carcinogens noting the lack of consistent findings for them and a limited but growing database. The Agency expressed its expectation to address non-mutagenic modes of action once it finds the data and analyses sufficient to do so. Given the apparent large activity early in life for some hormonally mediated chemicals (e.g., DES, tamoxifen) this remains an additional example of how risks may be under characterized for some chemicals.

In addition to missing early in life exposure in standard bioassays, a significant segment of life also is missed: Bioassays in rats end at 104 weeks although the natural lifespan can be considerably longer, for example 3.5 years. The large bioassays of nitrosoamines by Peto, et al., implies significant under characterization of risk for some cases when the last third or more of the animals life is not studied.

The Staff Paper discusses EPA's presumption of linearity for mutagenic carcinogens but not for chemicals that operate by a non-mutagenic mode of action. When there are exposures to chemicals contributing to disease prevalent in the population by the same mechanism as the environmental contaminant, the linear assumption should be questioned and alternative approaches considered. For example, given the relationship between breast cancer and endogenous estrogen, the non-linear threshold approach may not be appropriate for carcinogens that may bind to the estrogen receptor. In developing quantitative mechanistic models of carcinogenicity to apply to non-mutagens the potential influence of background exposures on dose response is an important consideration.

In recent years, EPA has been moving toward harmonizing cancer and non-cancer approaches to dose response analysis (page 142 of the Staff Paper). Limitations in the treatment of human variability, consideration of background exposures, and incorporation of uncertainty analyses in dose response are some of the differences that have been noted above. For these reasons it may be preferable to selectively take from the two approaches the better characteristics and build an alternative approach, rather than harmonize. Given the lack of knowledge to quantitatively evaluate uncertainty for some of the components of dose response assessment, qualitative approaches might be explored for uncertainty characterizations, and to address other features such as chemical

persistence, severity, and subtlety of effect and the complexity of the toxicological process.

The EPA Staff Paper does little to describe practices in the development of biologically based models (page 32); it does describe common types of model uncertainties and concludes the discussion with a note that EPA relies on specific default assumptions in response to uncertainty. Mechanistic biologically based models of toxicologic processes provide a framework for incorporating into a dose response assessment varied scientific information from studies in animals, tissue culture, and epidemiology. Still, there has yet to be an example where complex models have been used with confidence in low dose risk estimation. Although the extensive data generation and modeling efforts for the EPA dioxin assessment provided qualitative insights into the chemical's mode of action at low doses, the hypotheses and assumptions used in the various models put forward by different parties may have restricted the shapes in the dose response relationship and lead to different low dose behavior. Because the Agency was not sufficiently confident, it relied on default BMD procedures. This experience prompts questions regarding how the Agency peer review and model validation may be best practiced as biological models for cases less intensively studied are proposed, with alternative competing hypotheses not as well explored as they had been for dioxin.

Perhaps in efforts to harmonize processes new terminology should be considered. Variability in response due to genetic and other factors often is confused with uncertainty, and adjustments for variability treated as application of yet another uncertainty factor. NOAELs are taken for threshold no-effect-levels, without regard to study power. Margins of exposure—ratios of human exposure to the BMD—are sometimes understood as margins of safety, despite the likelihood of human response at the BMD. In

mathematical parlance, all dose versus risk curves are non-linear, with risk at high doses typically saturating to 100%. This includes those that are linear at low doses. The terminology may have been chosen with certain political sensitivities in mind—for example, the desire to avoid the “T” word when adopting the extrapolation procedures for carcinogens EPA finds non-mutagenic. To the extent that misconceptions and misunderstandings from terminology may unduly affect decisions, however, the cost of such sensitivity may be too high.

The EPA Staff Paper opens noting the importance of timely decision making with incomplete or imperfect information in an atmosphere of public scrutiny and possible court challenge (pages 2-3). It also states that the Agency conducts risk assessment to provide the best possible scientific characterization of risk based on a rigorous analysis of scientific information. In concluding, the Staff Paper notes the importance of planning and scoping the assessment to meet the needs of the specific decisions and to accordingly use a triage approach to scale risk assessment efforts. A 1996 National Research Council (NRC) publication provides some guidance for scoping and tailoring assessment for decision making in the presence of the usual pressures on regulatory agencies. The Staff Paper also offers a balanced view for addressing the tensions of optimizing scientific rigor in dose response analyses, while responding adequately to public health needs, given resource constraints.

### Panel Discussion

Dr. Rogene Henderson, Moderator

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Dr. Henderson began the discussion period with a comment and question for Dr. Conolly. Referring to the expansion of data resulting from “omics” technology and the high throughput systems, she noted our current ability to examine multiple responses at very low doses. With a continuum of re-

sponses, what approach will lead to a determination of unsafe levels? Dr. Conolly responded that a truly bright line involving toxic effect probably will not appear using systems biology. There will always be a societal value judgment about what is adverse and what is not. The science will inform that judgment. Systems biology will provide a much better fundamental understanding of the changes that environmental chemicals effect in our bodies, but value judgments must still be made. Dr. Zeise added that qualitatively, these models might be very useful, but quantitatively, there will be cascading uncertainty. Dr. Conolly noted that biologically ambitious models with a great deal of structure might introduce uncertainty into an analysis in which there was previously less uncertainty. Using his work with formaldehyde as an example, he posed the question of whether using systems biology has introduced uncertainty into the dose-response analysis relative to the previous analyses using simpler approaches. The answer is that we have not *introduced* uncertainty; we have *uncovered* uncertainty by using an explicit model structure. Illuminating uncertainty is different from introducing uncertainty in an analysis.

Commenting on the RfD distribution discussed by Dr. Zeise, Dr. Mike Dourson, Toxicology Excellence for Risk Assessment, stated that the distribution is not a population distribution; it is a distribution based on the uncertainty factors—a distribution of chemical analyses. Therefore, the interpretation of the probability is chemical specific. Dr. Zeise responded that the approach is one in which a population distribution for the human population is constructed for that one factor. Both uncertainty and variability can be captured and incorporated into the analysis. Dr. Dourson then asked a question involving Dr. Zeise’s statement that there are no thresholds for some chemicals, and the possibility that background exposures already are exceeding the thresholds. Dr. Zeise stated that when we try to consider

what the population is exposed to and how to model it, it is important to determine the status of the population with respect to a universal threshold.

Dr. Melvin Andersen, CIIT Centers for Health Research, asked a question about defaults versus how to deal with information. Defaults are what we do in the absence of information. We can refine mathematical and statistical tools to evaluate data sets and attempt to draw conclusions. We have comfortable approaches in situations in which there are no uncertainty factors or safety factors. How do we move on to responses? How can models describe the threshold and allow us to assess the variability of the human population as it reflects the threshold for toxicity or the activation of gene networks? We must distinguish the conclusions we reach about variability and uncertainty with respect to model structures in which we think we understand an outcome versus defaults. How do we separate using information because it has value versus using information because it is there and we want to add it to defaults? Dr. Conolly commented on thresholds, using an example of the reduction of DNA repair capacity. Depending on how efficiently the xenobiotic induces the DNA repair capacity, situations can exist in which the initial burden of the xenobiotic at the lowest dose actually leads to a decrease in the overall level of DNA damage. The shapes of dose-response curves are properties of the underlying biology. The question is not whether you write a model that contains a threshold; rather, the question is how the biology behaves. Do adaptive processes moderate or modulate the low dose-response and effectively keep the biology in some normal range? If this occurs, there might be some level of tolerance for exposure to a xenobiotic. The dose response is a reflection of the biology.

Dr. Starr commented that the question involves how information is made useful. There are limitations to science; some things

are too small to be measured. There are *casual* associations reported, but these are not *causal* associations until they have been demonstrated clearly in the laboratory. Dr. Zeise added that as we move from the default approaches to approaches that incorporate more science, the issue of “right general description but wrong answer” arises. There is a penalty to pay when we are very wrong. If analyses are conducted in a way that results in a general, qualitative understanding of the science, but we neglect to point out, for example, where or how the population may vary, we might make some major mistakes. Looking at some of the problems we face in a general penalty function framework would be useful.

Dr. Chiu stated that defaults are useful for when there is insufficient information, but they are arbitrary. It is possible that there are new categorical defaults that use decision trees. Can the defaults be science informed and public health protective? What are some minimal data requirements to develop these defaults?

Dr. James Bus, Dow Chemical Corporation, pointed out that we live, not in a single-chemical world, but in a complex world of natural and manmade chemicals. How can a systems biology approach help with understanding how our biology deals with multi-chemical exposure? How can we sort out the real world from the very closely characterized and defined laboratory single-chemical world? Dr. Conolly noted the number of endogenous nutrients that are toxic hazards. We need a better understanding of what toxicity means. Regarding systems biology, correlations between patterns of gene expression and certain modes of action that relate to various kinds of toxic effects are being investigated in the pharmaceutical industry. Looking at patterns of gene expression might result in an understanding of the potential toxicity and therapeutic effect of chemicals. Likewise, high-throughput screens can provide a sophisti-

cated way of looking at biological effect and will result in a better understanding of data in diagnosis. At a more fundamental, mechanistic level, tremendous opportunities will arise for looking at particular biochemical modules within cells, for example, patterns of oxidant stress reaction. The biology is the final common denominator. In time, there is hope of seeing some kind of order or simplifying pattern.

Ms. Patricia Casano, General Electric Corporation, stated that ED<sub>10</sub> is used in risk assessments as a focal point, but other terms were used in the presenters' slides. She asked about the variability in terminology among the three presenters and whether scientific justification exists for selecting one term over the other. Is it a judgment call or a policy call? One panel member responded that it depends on the power of the study; ideally, the extrapolation should be started at the lowest possible point. The other distinction involves the POD at which the extrapolation ends and the target at which to evaluate the risk. Dr. Zeise explained that the ED values in her presentation were the target extrapolation points. The EPA dioxin document describes the ED<sub>01</sub> values for different non-cancer endpoints, in many cases, near the range of the data. Dr. Zeise pointed out that in non-cancer endpoints the ED values are actually effect levels and do not represent thresholds. In the current approach, there is no way of getting below the threshold, which raises another issue about cancer endpoints, to a point where extrapolation is done through some theoretical threshold in which threshold effects are expected.

Dr. George Daston commented on study design and how it might be modified to do better extrapolations. A pyramid approach to study design, with more levels and greater weighting toward the bottom, has benefits and drawbacks in terms of confidence in dose-response and worry about missing hazards. Other issues also are involved. A dis-

cussion should ensue about what can be gained versus what can be lost if we change study designs. Is it time to start thinking in earnest about calling for different, more flexible, more data-rich study designs? Dr. Starr responded that it is time. Most of the studies were never designed for the purposes for which they have been used. It may not be possible to do studies that ideally suit our purposes, but we certainly can design them better. For example, we can give up some of the quantitative precision of response estimates at very high doses and, with an unbalanced design, set the experiment up so that if there were a linear dose-response, we would have equal probability at all the tested doses of seeing a significant response. We could use the lowest such experimental dose as an improved POD with which to begin our policy-driven low-dose extrapolations.

Dr. John Vandenberg, EPA's National Health and Environmental Effects Research Laboratory (NHEERL), commented on the process of expert review. How do we use information most effectively to support risk management? Dr. Zeise explained the two parts of the issue—the review piece and the handoff to the risk manager. EPA's approach to some of the exposure assessment model reviews is different from the approach used to examine toxicological data. Deliberation should be built into the process. Dr. Conolly referred to his involvement in reviews of formaldehyde. Conflict of interest is an issue because manufacturers pay for much of the mechanistic work; therefore, the people with scientific expertise are funded by industry. When it comes time to review the science and consider regulatory issues, some of these people are excluded from the review, or their participation is limited. Perhaps the biases can be balanced on the review panels. Dr. Zeise raised the issue of the extent to which nongovernment organizations participate in peer reviews. Dr. Starr commented that EPA has made efforts to

open the process to outside involvement, and these efforts could be further expanded.

Dr. Robert Brent, Dupont Hospital for Children, referred to Dr. Zeise's list of compounds that might not have a threshold. He called for more responsibility in communicating to the public about thresholds. The mechanism for central nervous system effects with lead is very different at the high level than it is at the low level. Work on the mechanism of action is needed.

Dr. Rita Schoeny, EPA's Office of Water (OW), also referred to Dr. Zeise's list. She mentioned the practical choices that have been made regarding mode of action. She asked for comments about particulate matter and ozone. Dr. Zeise remarked that the examples she listed are those for which close epidemiologic studies find more and more subtle effects at lower and lower doses.

Dr. Andersen posed the following question about defaults: What does a perfect risk assessment look like? He referred to a committee convened 19 years ago by the National Academy of Sciences (NAS) to examine the use of pharmacokinetics as a tool in risk assessment. This approach provided a useful evaluation and should be considered in the future.

Dr. Abby Li with Exponent referenced Dr. Zeise's remarks about the problem of background exposures and the way in which to incorporate that information into a derivation of the RfD. The dilemma is whether background exposures should be part of the RfD calculation. How can that be done? What kind of background exposures should be incorporated routinely into the low-dose extrapolation to an RfD? Dr. Zeise replied that in terms of dose-response function, it is critical to consider the contribution of the background. In the dose-response phase of

the assessment, it is important to study the dose-response curve. We need a systematic way to evaluate highly exposed populations. Dr. Chiu pointed out that the RfD was not designed to address this issue. We need more information about the entire dose-response curve. He noted that there is no quick solution at this point.

Dr. Henderson asked a followup question about background chemicals. Isoprene, a major component of exhaled breath, is a carcinogen in mice. Obviously the body has adapted to isoprene and can tolerate it. Dr. Zeise stated that we must ascertain whether this background level causes disease in the population. Is isoprene adding to some background process that already is causing the disease?

Dr. Dourson asked for a clarification on the RfD. The RfD is based on studies in animals or people that incorporate the total dose of that particular chemical. The question of background arises when the risk is characterized using the RfD. Should low-dose extrapolation incorporate hormesis? Is there a distinction between threshold and non-threshold toxicants? Dr. Conolly stated that the issue is the way in which the organism responds to the dose—its homeostatic capacity, its ability to maintain its internal environment in the face of environmental stress. Oxygen is the biggest toxicant to which we are exposed; therefore, we are capable of adapting to environmental stress. The question of hormesis gets confused with the question of homeostasis and adaptive capabilities—the ability to repair or induce a pathway that processes an environmental stressor. We must examine the fundamental biology of how organisms respond to environmental stressors. Understanding this fundamental biology will lead to understanding hormesis and whether it is really different from homeostasis.

## **SESSION II: USE OF DEFAULT ASSUMPTIONS AND UNCERTAINTY FACTORS**

Dr. George Daston, Moderator

Dr. Daston noted that the purpose of EPA's staff paper was to examine the various risk assessment practices of the Agency, catalog them, and determine best practices. He stated that defaults are used when better information is not available, and, at their best, defaults are based on long practice and are firmly grounded in both empirical science and scientific consensus. Defaults are based on qualitative assumptions about the validity of the hazard or exposure data and their utility for risk assessment. Is the animal model appropriate? Are findings from animal studies relevant for assessing human risk? The introductory material on defaults and extrapolation in Chapter 4 of the staff paper states that the primary goal of the defaults is to be health protective and the secondary goal is to avoid excessive conservatism.

### **EPA's Approach**

Dr. Rita Schoeny, EPA/OW

Dr. Rita Schoeny, Senior Science Advisor in EPA's Office of Water, entitled her presentation "Default Assumptions, Uncertainty Factors—EPA's Approach." She began her presentation with an explanation of defaults and why they are used by the Agency. The National Research Council (NRC) defined defaults in 1983 as "the option chosen on the basis of risk assessment policy that appears to be the best choice in the absence of data to the contrary." Defaults are used to move along the process of risk assessment when data are lacking for an environmental contaminant or a toxicant. Defaults are useful and necessary; they are part of all human conceptual thinking.

*Science and Judgment in Risk Assessment* (NRC, 1994) articulated the following principles for defining and using defaults: protecting public health, ensuring scientific validity, minimizing serious errors in risk

estimation, maximizing incentives for research, facilitating an orderly and predictable process, and fostering openness and trustworthiness.

The biggest change over time in terms of EPA's use of defaults and assumptions is that previously one used defaults unless there were data indicating a departure from the default. Now, EPA uses defaults only if existing data are determined to be inadequate or not usable in the assessment. The current process calls for analyzing the available data and invoking a default option if there is too much uncertainty or if critical information is lacking. Defaults should not be arbitrary. They are based on data as well as scientific consensus and are generalizable. Usually defaults have been peer reviewed and must be identified and described in the risk characterization step of the risk assessment.

She noted that the staff paper makes distinctions between risk management and risk assessment. While EPA's overall goal is to protect public health, Agency science policy holds that assumptions are used to ensure that risk is neither underestimated nor overestimated. Defaults are reexamined as more data are available and methodologies are improved.

Dr. Schoeny gave several examples of assumptions and defaults. The first example involves the assumption that animal data are relevant to human effects. This assumption is the basis for the majority of toxicological testing, but certainly raises the question, "are all data in animals relevant to humans?" Clearly the answer is no, and EPA has issued guidance on specific data types that are not relevant to human health effects. For example, the staff paper discusses whether all benign tumors be counted in a weight-of-evidence discussion or a quantitative risk estimate as well as whether target organ concordance between animal and human tumors is necessary.

Another example involves the assumption that effects at high dose are relevant to low dose. In cancer bioassays, using limited numbers of animals, testing is done at a maximum dose tolerated by the animals—the maximum tolerated dose or MTD. This is to ensure that some effect of the test chemical will be observed in this small population; the assay is not useful if the putative carcinogenic dose has been missed. High doses of toxicants, however, can produce effects that may not be relevant to those seen at environmental doses. EPA guidelines call for considering MTD on a case-by-case basis, inspecting the data and using the results at MTD for extrapolation, and establishing a mode of action.

A third example is the use of a rather gross but common exposure default; the 70 kg spherical human who lives for 70 years and drinks 2 liters of water per day. For some purposes, this is an acceptable approach but the EPA risk assessment philosophy is to examine the data first and use the default only if the data are inadequate.

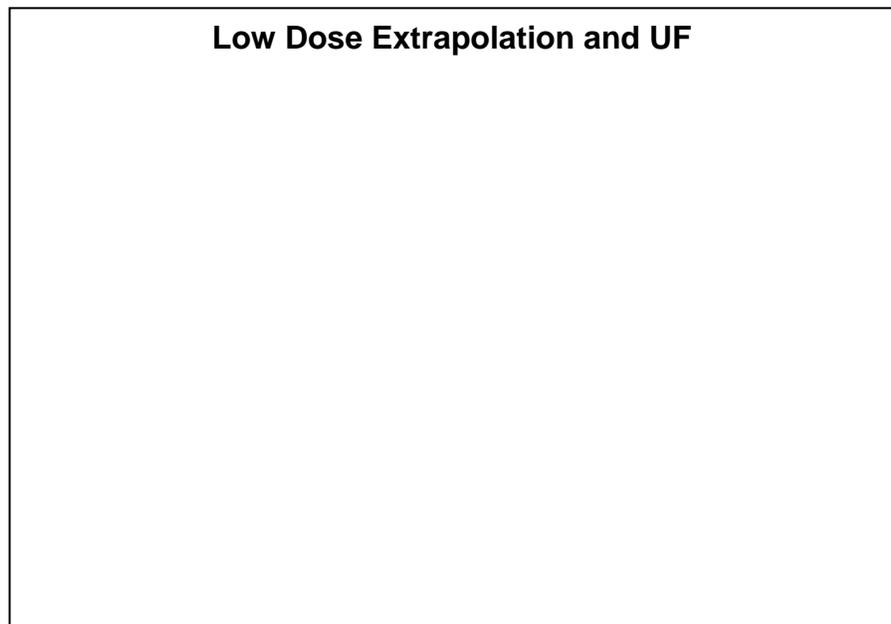
There is a clear pattern to EPA's use of defaults. The usable data trump defaults. As our understanding of mode of action, pharmacokinetics, etc., evolves, more data become usable. We will be using defaults, however, for a long time to come.

A significant default approach in risk assessment is the use of uncertainty factors in non-linear low-dose extrapolation (see Figure 6). In applying uncertainty factors, EPA fol-

lows the RfD/RfC Technical Panel Report (USEPA, 2002). The default uncertainty factors are generally 10-fold. Some typical uncertainty factors are applied for variability and uncertainty in these areas: among human populations, for use of animal data, for use of data from less than lifetime exposure when extrapolating to lifetime risk, and for database insufficiency. EPA follows the same philosophy for the use of uncertainty factors as it does for other defaults; that is, it calls for using the data first to determine the size of the uncertainty factor, or if one is needed in a particular area. The Risk Assessment Forum is working on guidance of data-derived uncertainty factors, and NCEA has compiled a draft analysis of the scientific foundation for estimating uncertainty in reference values.

Dr. Schoeny ended her presentation with comments on approaches to nonlinear low-dose extrapolation. There is likely to arise a hierarchy of risk-predictive or safety assessment approaches that will depend on availability of data to support use of improved models.

Figure 6. Low Dose Extrapolation and Uncertainty Factors



Source: Schoeny, 2005

## A State's Approach to Risk-Based Analyses; Similarities To and Differences From EPA's Principles and Practices

Dr. Hillary Carpenter, Minnesota Department of Health

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Dr. Hillary Carpenter, Minnesota Department of Health, stated that the Minnesota Department of Health (MDH) is responsible for developing health-based values for chemicals that contaminate air and groundwater. EPA has promulgated rules that provide guidelines used by MDH and other state agencies to protect human health. When developing its groundwater and air rules, MDH relied heavily on the risk assessment techniques used by EPA at the time of promulgation. In general, MDH concurred with the default assumptions and uncertainty factors applied by EPA.

Health risk limits (HRLs) are health protective limits for concentrations of chemicals in groundwater. MDH has developed and promulgated HRLs in accordance with Minnesota's Groundwater Protection Act of 1989. HRLs are expressed as micrograms of chemical per liter and are considered to be the concentration of chemicals in drinking water that is likely to pose little or no health risk to humans, including vulnerable subpopulations. HRLs were developed using EPA's algorithm for RfDs.

In August 2002, MDH promulgated its Health Risk Value (HRV) rule, which sets values for concentrations of chemicals or defined mixtures of chemicals emitted to air. The concentrations are unlikely to pose a significant risk of harmful effects when humans are exposed to the chemicals over a specified period of time. The HRV rule is mandated by law and is meant to preserve public health. HRVs are health-based values that are referred to as guidelines and do not apply to the workplace. As with the HRL rule, when MDH developed the HRVs, it re-

lied heavily on the risk assessment techniques used by EPA. MDH currently develops four types of HRVs—acute, subchronic, chronic, and multimedia.

In 2002, the Minnesota legislature passed the Minnesota Health Standards Statute. This legislation called into question the adequacy of current risk assessment practices for protecting the public's health. According to the statute, when developing or modifying air and water quality standards, MDH must include a "reasonable margin of safety" to adequately protect the public health by considering risks involving a number of health outcomes. MDH must determine the adequate or reasonable margin of safety. If safety cannot be adequately demonstrated, the principles and practices currently in place in Minnesota must be changed so that they are more protective. Dr. Carpenter described the proposed changes in the development of HRLs and the impact of the statute on HRVs.

During Minnesota's recent rule revision, a number of questions arose regarding the risk assessment tools and techniques currently used by EPA: (1) What amount of data is necessary before risk assessors are actually willing to consider departing from a default? (2) Has the apparent reluctance of risk assessors to discard defaults hampered research into the validity of defaults? (3) Has risk assessment done an adequate job of addressing the issues of early life exposures? (4) Do the current research strategies and risk assessment practices really protect against less-than-lifetime exposures? and (5) Is there a consensus in EPA about how the database deficiency uncertainty factor should be used? It was suggested by staff of the MDH that the use of defaults has stalled. The assumptions have not been adequately modified to respond to advances in research, especially with regard to early-life exposures.

## Past and Future Use of Default Assumptions and Uncertainty Factors

Dr. Michael Dourson, Toxicology Excellence for Risk Assessment

Dr. Michael Dourson, Toxicology Excellence for Risk Assessment, covered the topics of default assumptions, misunderstandings, and new concepts. He began by providing the definitions of certain terms used in speaking about default assumptions, including adverse effect, adaptive effect, compensatory effect, critical effect, and severity. The estimation of “safe” doses involves several judgments, such as the choice of the most appropriate no observed adverse effect level (NOAEL) or benchmark dose (BMD) of the critical effect and the choice of the appropriate uncertainty factors based on a review of the entire database (see Figure 7).

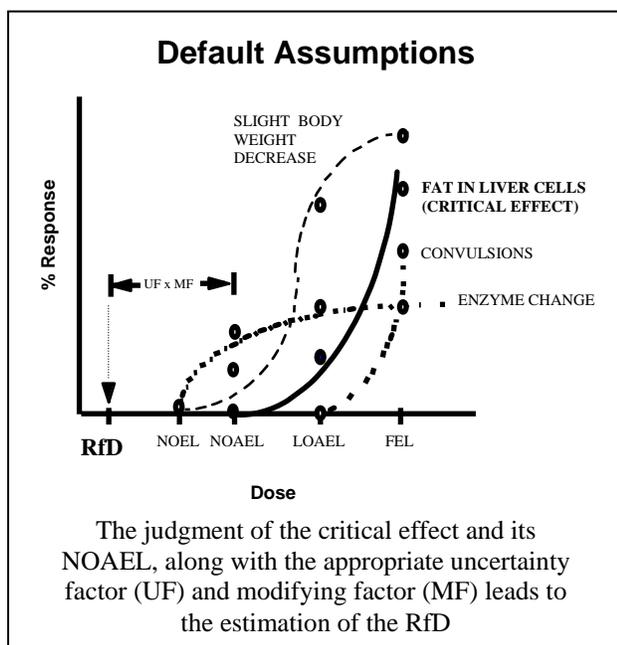
The judgment of the critical effect and its NOAEL, along with the appropriate uncertainty factor and modifying factor, leads to the estimation of the RfD. As defined by EPA, an RfD is an estimate (with uncer-

tainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The resulting range of an RfD has been defined as “perhaps an order of magnitude.” This range is expected because of the imprecision of uncertainty factors. Thus, environmental exposures falling into the range of the sub-threshold estimate generally cannot be scientifically distinguished from the estimate.

The major assumptions are that a population threshold exists, estimates represent sub-threshold doses, and preventing the critical effect protects all. The major strengths are that all data are reviewed for critical effect, and uncertainties are addressed with factors based on judgment. The major limitations are that NOAEL ignores many data, uncertainty factors are imprecise, and risks about the RfD are not estimated.

At least five misunderstandings exist in “safe” dose assessment. The first misunderstanding is that studies with small numbers are not useful. On the contrary, studies with even one subject are important. The second misunderstanding is that uncertainty factors are arbitrary. Actually, uncertainty factors are imprecise. The third misunderstanding is that an uncertainty factor of 10 for within human variability is not enough. In fact, an analysis indicated that it is most often conservative. The fourth misunderstanding is that animal-based RfDs are habitually protective. Human-based RfDs are sometimes lower. The fifth misunderstanding is that RfDs do not protect children. That is the intent, but study design must be improved. Dr. Dourson presented a number of slides to expand on the information about these misunderstandings. One of his conclusions was that misunderstandings should be avoided, and one way to ensure this is to challenge scientists offering opinions as to their understanding of this area of risk assessment.

Figure 7. Default Assumptions and Estimating the RfD



Source: Barnes and Dourson, 1988

Over the past several years, scientists have used more data when choosing uncertainty factors. They also use a number of approaches. Methods range from default (“presumed protective”) to those incorporating more biological data (“biologically based protective”). The categorical default is a new concept that breaks the interspecies and intraspecies uncertainty factors into toxicokinetic and toxicodynamic components. The following conclusions can be drawn from the new concepts: (1) agencies are using other than 10-fold factors on the basis of data, (2) compound-specific adjustment factors (CSAFs) are justified when adequate and specific data exist, and (3) Monte Carlo methods are available and should be used. As a result, in developing subthreshold doses, the first choice should be to use the data to generate a distribution or CSAF; a second choice would be to use the default factor. Dr. Dourson concluded that use of distributions and CSAF will lead to better use of data and fewer uncertainties.

### NRDC Comments to BOSC on the Use of Default Assumptions and Uncertainty Factors in EPA Risk Assessments

Dr. Jennifer Sass, NRDC

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Dr. Jennifer Sass, Natural Resources Defense Council (NRDC), presented ways in which EPA could improve both the transparency and the credibility of its risk assessment process. First, she urged the BOSC to recommend that EPA finalize the 2003 Draft Cancer Guidelines and the Supplemental Guidance for assessing cancer susceptibility from early-life exposures to carcinogens. EPA currently uses the draft 1999 guidelines. (On March 29, 2005, EPA issued final Guidelines for Carcinogen Risk Assessment, along with an associated document entitled Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. Both documents are available at <http://www.epa.gov/cancer-guidelines>.) Second, the NRDC urged the expansion of the default assumption of sus-

ceptibility to early life stages for mutagenic carcinogens to include nonmutagenic carcinogens. Dr. Sass commented that the data support this expansion. Third, NRDC urged EPA to provide clarity on what constitutes “adequate” data to depart from default assumptions of linearity at low dose of mutagenic carcinogens. Fourth, EPA should require rigorous consideration of all plausible modes of action, alternate pharmacokinetic models, and the effects on all the life stages and sensitive populations that might be exposed when departing from default uncertainty factors. EPA’s current practices do require consideration of mode of action, but the Agency provides weak guidance on the way in which the data should be used and considered and what constitutes sufficient data to depart from default assumptions. Fifth, NRDC recommended a requirement for the consistent application of default assumptions, particularly when critical data are lacking. Sixth, the thorough documentation of the underlying assumptions in mathematical models used in risk assessment should be required. Seventh, substantial evidence should be required to categorize agents as “not likely to be carcinogenic” to humans. Finally, NRDC urged consistent consideration of toxic degradates when data are available or the invocation of defaults to adjust for an incomplete database.

### Panel Discussion

Dr. George Daston, Moderator

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Patricia Casano asked Dr. Carpenter if he has worked through any hypothetical or real scenarios with the new adjustment factors to determine levels of a representative chemical or substance to ascertain how the acceptable levels would change using the new adjustment factors. Dr. Carpenter responded that, depending on the endpoint, the decrease is transparent. The number would be sixfold lower for developmental toxins than if we were not using those factors. If it were a chronic non-cancer number, it would be threefold lower. For carcinogenic materials,

with the use of the adjustment factor for intake and the cancer potency factor, the number would be sixfold lower than it would be if those factors were not applied.

Ms. Casano asked Dr. Schoeny about comments from the American Chemistry Council (ACC) that include examples of default assumptions used by EPA that do not appear to be supported by science. Will EPA respond to those examples? Dr. Schoeny stated that the staff paper is the response; EPA will not be responding to specific, individual comments on defaults. She added that the exposure factors handbook is being revised.

A participant commented that legislative action might not be supported by the scientific community. Dr. Carpenter replied that state agencies deal, not with the scientific community, but with scientists who are heavily affected by policy; policy is set in state agencies by the administration in consultation with lawyers. The participant asked what percentage of the Minnesota population exceeds the levels set as a nonrisk dose. Dr. Carpenter responded that the percentage is probably very small for drinking water. The controversy was from two sides—the pesticide industry and the environmental community. The participant addressed another question to Dr. Dourson regarding the percentage of the population that exceeds a set limit. Dr. Dourson explained that in the RfD determination, many databases do not allow us to answer this question in a precise manner. Dr. Schoeny added that in the case of the methyl mercury RfD where the sensitive population is children, we can say with a fair amount of certainty that at 10-fold the RfD for methyl mercury, there are going to be effects in some percentage of the population. When we start backing down from that, however, our predictions are extremely uncertain. Therefore, from the methodology used, it cannot be said that a 1.3-fold increase above the RfD is good, bad, or indifferent. Dr. Dourson added that a common

misperception is that everyone above the RfD is at risk; however, “at risk” here means “percentage of folks above the RfD”; it does not mean “percentage of folks with the effect.”

Dr. Andersen stated that the area of defaults and the way in which they work requires the most explanation to convey what is done in risk assessment to a large audience. He then addressed a question to Dr. Dourson. Dr. Andersen pointed out that with each individual uncertainty factor, we can look at data that give us some understanding of a database version of the uncertainty factor; however, our process of multiplying these terms together as if they are independent variables is inherently flawed. How can we address this concern? Dr. Dourson agreed that considering the variables as independent leads to conservative RfDs, especially if independence is not correct, and then EPA uses an upper limit of 10,000 for uncertainty factors in five areas, instead of a possible 100,000 for this reason. A theoretical paper published in 2001 by Jeff Swartout, EPA, and colleagues built on the basis of the existing data behind each uncertainty factor and it supported EPA’s approach to use 10,000 rather than 100,000 as an upper limit to its five uncertainty factors. In response to another comment by Dr. Andersen, Dr. Dourson stated that he prefers the term “imprecision” to “uncertainty” when describing the quantitative aspect of the factor.

Dr. Chiu stated that some uncertainty factors are adjustments for uncertainty but others are adjustments for body size or rate of metabolism, etc. It is not necessarily true that multiplying factors together is overly conservative. What exactly does protective mean? What do RfDs mean in the risk-based context? Dr. Dourson responded that, in the simplest terms, the RfD is a NOAEL of the critical effect in a sensitive subgroup. If we had the perfect risk assessment, we could step away from the use of default uncertainty factors, but what does the perfect risk

assessment look like? For an RfD, it would be where an uncertainty factor of 1 was used in its derivation. Several examples exist where a NOAEL for a sensitive subgroup was determined and the overall uncertainty factor of 1 was used to estimate the RfD (see EPA's Integrated Risk Information System [IRIS] for nitrate and fluoride).

Dr. Schoeny declared that "a risk assessment never protected anybody." It is the actions that one takes as a consequence of a risk assessment that are protective of human health and the environment. The question to pose is: Who are we trying to protect and to what level and from what? This question has brought us to other approaches to risk assessment.

Dr. Dourson asked Dr. Sass to better define reasons for departure from a linear mode for cancer dose-response assessment. What is enough information to depart from a linear mode? Is there a systematic approach? Dr. Sass responded that the answer will have to be numerically represented. The default should be invoked unless informed otherwise by multiple mutually consistent, adequately powered studies covering a full range of human exposures with reasonable certainty bias, confounding, and chance to provide individual and pooled estimates of risk near unity with narrow confidence intervals. (This is elaborated in Melnick RL, Kamel F, Huff J. Declaring chemicals "not carcinogenic to humans" requires validation, not speculation. *Environ Health Perspect* 2003;111(4):A204.) This statement tries to get at the definition of adequate or sufficient data. In addition, the difference between mechanism of action and mode of action is important. Mode of action should be used to stimulate research. Dr. Schoeny noted that the cancer guideline revision is focused on mode of action in the absence of an understanding of mechanism of action. One of the most useful parts of the revised cancer guidelines is its articulation of a framework for ascertaining a mode of action. It provides

some useful guidance. One of the pieces of the framework is to consider whether your story is the only story or if other plausible modes of action exist. The Agency could not come up with a single story for arsenic. There probably are multiple modes of action for even one health endpoint.

Dr. Daston offered his view of mode versus mechanism. Mode is defined as understanding the critical event beyond which the toxicity is inescapable. We may not know precisely the different pathways that lead to that critical step.

Barbara Henry (Bayer Crop Science) asked Dr. Carpenter about the additivity component to Minnesota's HRL. Dr. Carpenter explained that more endpoints will be provided for additivity. Barbara Henry asked whether the panel thinks it is appropriate to add exposures for a chemical, for example, that causes liver cell size to increase along with one that causes liver cell size to decrease or one that causes an enzyme to be induced and another that causes an enzyme to be depressed. Dr. Dourson responded by referring to EPA's mixture guidelines where additivity, synergism, or antagonism are routinely used in approaching similar questions in site risk assessments. Dr. Carpenter pointed out the process that goes from site-specific to organ-based screening and refinement. Ms. Henry asked another question involving complete databases for evidence of adequate protection. Dr. Carpenter stated that the 2002 legislation outlines what is considered to be a complete data set.

Hans Sanderson (Soap and Detergent Association) stated that when we make decisions based on statistics and discuss NOAELs, we are talking about statistical null hypothesis testing, which has received considerable criticism for ecological risk assessments. We run into inherent problems with the lack of statistical power when looking for small effect sizes. Chemicals are not the same; some have tremendously large human health bene-

fits and others do not. Why do we use the same power values for both? Can we arrive at more accurate assessments?

Dr. Schoeny responded by raising points about how NOAELs and lowest observed adverse effect levels (LOAELs) are not the same; likewise, all BMDs are not the same. How do we treat these in terms of further extending low-dose extrapolation? In addition, Dr. Dourson stated that it is not appropriate to focus only on the “n” of an experiment; the severity of the type of effect must be understood. If you have two hypothetical groups of people with similar “n,” the first where you are studying an effect that is well below the critical effect for a particular chemical, and the second where the only effect monitored is mortality, then you will gain more information from the former group on the chemical’s likely dose response in the area of concern for risk assessment. These two hypothetical studies are looking at different endpoints of severity and the severity of the effect is important in dose response assessment for cancer or non-cancer endpoints. Dr. Daston pointed out that strict protocols and guidelines are followed for various kinds of endpoints. We know the resolving power at those statistical cutoffs for the various kinds of studies. Expert toxicological judgment, not statistical judgment, decides about adequacy. We are not concerned about the chemicals for which we have a great deal of data and reasonable certainty. Are there any principles for screening level exposure assessments? Dr. Schoeny stated that the staff paper discusses the maximally exposed individual. The Clean Air Act gives some requirements for the assessment. Dr. Carpenter commented on the conservatism inherent in the process. Dr. Sass remarked that EPA relies heavily on mathematical models to estimate exposure with very little data. Dr. Dourson stated that the characterization of the risk from a group of chemicals should be done in a comprehensive way so that the individual chemical or mixture can fit within a framework for

decisions in risk management. Dr. Daston mentioned the Voluntary Children’s Chemical Evaluation Program, a pilot program administered by EPA whereby 20 chemicals will be evaluated for the adequacy of the database in terms of understanding whether risk assessments have been protective of children.

Dr. Daston also raised the issue, mentioned by Dr. Sass, of stakeholder involvement in risk assessment. Dr. Schoeny stated that the dioxin reassessment is a good example of obtaining stakeholder input, but ultimately, EPA had to take ownership of the risk characterization. Dr. Sass pointed out that risk assessment evolves. Dr. Carpenter mentioned that Minnesota’s process always has been very open and offers ample opportunity for stakeholder input, and such input has been offered and accepted at a number of meetings.

### **SESSION III: EXTRAPOLATION BETWEEN SPECIES**

Dr. Clifford Duke, Moderator

On Thursday, February 3, Dr. Duke opened the third session of the workshop by stating that extrapolation between species—the topic of this session—cuts across the topics already discussed. High-to-low dose extrapolation is frequently extrapolation from high doses in laboratory animals to low exposures in human populations. He noted that issues of extrapolation across species also exist in default assumptions.

EPA’s Approach

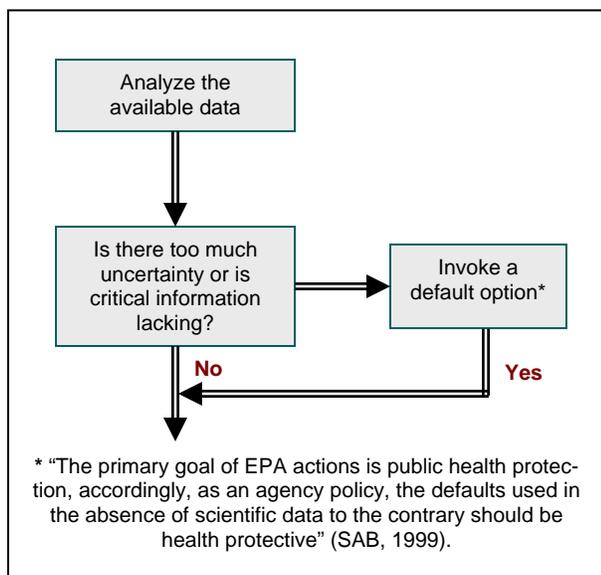
Dr. Kerry Dearfield, EPA/OSA

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Dr. Kerry Dearfield, EPA’s Office of the Science Advisor, entitled his presentation “EPA Risk Assessment Practice: Extrapolation Between Species.” He began with a description of the staff paper, which presents the perspectives of EPA risk assessors on their understanding of how risk assessment is conducted at the Agency. It also presents staff recommendations for EPA and inter-

ested stakeholders to consider regarding how EPA can move forward to strengthen and improve its risk assessment practices. As it stands, the staff paper does not represent Agency policy. As depicted in Figure 8, EPA analyzes the available data before invoking a default option.

Figure 8. EPA Uses Data Before Invoking Defaults



Source: Dearfield, 2005

Dr. Dearfield's presentation covered four topics: (1) relevance of animal data to humans and issues, (2) interspecies extrapolation and issues, (3) target organ concordance, and (4) route-to-route extrapolation.

Dr. Dearfield enumerated the underlying assumptions regarding the relevance of animal data to humans. Positive adverse effects in animal studies indicate that the agent under study can have toxicological potential in humans unless data indicate otherwise. Important similarities exist between the animal models and humans (e.g., most known human carcinogens are positive in animal models). Information from animals that are as similar to people as possible is preferred. The most sensitive responding species (given several data sets to choose from) are selected for the extrapolations so that risk to

humans is not underestimated. Mode of action information is becoming more useful to help determine relevance.

One of the issues regarding relevance of animal data to humans concerns adversity. A contrast must be drawn between adverse and beneficial or adaptive changes that can be observed. Also, a determination must be made regarding if and when adaptive becomes adverse. Other issues that EPA deals with concern the severity of effect, the reversibility of effect, and the paucity of comparative data on metabolism for specific chemicals and other interspecies differences that can affect toxicity.

In terms of interspecies extrapolation, use of physiologically based pharmacokinetic (PBPK) models can enhance the calculation of internal dose for systemic toxicants and help refine the interspecies extrapolation. For example, for RfD derivations, the uncertainty factor of 10 is divided into pharmacokinetic and pharmacodynamic components. For reference concentration (RfC) derivation, pharmacokinetic methods help derive the pharmacokinetic component of the uncertainty factor; the pharmacodynamic component is a default of 3 (unless data are available). Most physiological endpoints scale by body weight to the three-quarters power.

A number of issues are involved in interspecies extrapolation. Do all PBPK parameters scale to the same three-quarters power? There is a considerable amount of uncertainty around the extent of interspecies variability as well as species-specific sensitivity. Another question involves whether the most sensitive animal estimates an average human or the most sensitive human.

Regarding target organ concordance, the staff paper states that there is no evidence that a mechanism in one species is necessarily target organ concordant in another. Site concordance is not assumed *a priori*. If

mode of action is established, however, there is an expectation for site concordance when making the mode of action case. This is a case-by-case circumstance.

Regarding route-to-route extrapolation, the staff paper states that if an agent causes an internal effect by one route of exposure, it will cause the effect by a different route if it is absorbed by the other route to give an internal dose, unless data are available to indicate otherwise. This practice assumes that the internal dose to the tissue of interest is the ultimate determinant of toxicity.

Dr. Dearfield concluded his presentation by referring to three examples from the staff paper. The examples involved (1) the alpha 2u-globulin specific to male rat kidney tumors, (2) thyroid tumors in an animal model, and (3) concordance of endpoint as a weak predictor of developmental effects in people.

### Mode of Action and Dosimetry Considerations in Interspecies Extrapolation

Dr. Melvin Andersen, CIIT Centers for Health Research

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Dr. Melvin Andersen, CIIT Centers for Health Research, stated that he is optimistic about risk assessment, i.e., in the collection of information and its use in making good decisions. He asserted that chemical risk assessment is a process that evolves over time and that the role of mode of action, an understanding of the biological determinants of toxicity, in risk assessment is evolving at a very quick pace. Dr. Andersen's presentation covered: (1) interspecies extrapolation defaults, (2) dosimetry models in risk assessment, (3) mode-of-action modeling and dose-response, and (4) recommendations for improvement.

Defaults involve the process we follow in the absence of information. The default process changes as information becomes available. Dr. Andersen stated that this proc-

ess actually is being done backwards because we fail to ask the following questions: What will we do with the information? What constitutes having perfect information or a good set of information? What kind of information is required for a risk assessment, and what do we do when it is lacking?

Dr. Andersen provided background information about default interspecies scaling. He noted that today there are no quantitative risk models for nonlinear responses that allow prediction of level of risk for particular levels of exposure. Our current approaches can, however, account for dosimetry and tissue response. We can answer questions about how tissue dose varies among species for a given exposure in test animals and humans. A related question is how tissue responses vary between test animals and humans. In this case, we want to know if an equal measure of tissue dose is equally effective (equally toxic) in all animal species. Pharmacokinetic (PK) and pharmacodynamic (PD) tools help us evaluate these relationships. Pharmacokinetics calculates the tissue dose of active forms of the toxic chemical for various doses, dose routes, and in different animal species. Pharmacodynamics calculates the degree of response for any level of tissue dose in different species. There are multiple examples of both PK and PD of these models.

PBPK models have been developed over time and these models make us think that we know what happens with chemicals in the body because we can draw representations of tissues, flows, and sites of metabolism. Although we sometimes have the information to make successful PBPK models, they sometimes fail to predict disposition. In these cases, the structure of these PBPK models, i.e., our hypotheses about the physiological structure of the mammalian organism that controls disposition, needs to be continually updated as we study more and more compounds. In 1985, a PBPK model was used in a risk assessment with

methylene chloride. This work developed an intellectual process for the use of PBPK in risk assessment that is still followed today. We use these models to predict tissue dose. The process goes: (1) identify toxic effects in animals and people; (2) evaluate available data on modes of action, metabolism, chemistry of compound, and metabolites and related chemicals; (3) describe potential modes of action; propose a relationship between response and tissue dose; (4) develop a PBPK model to calculate tissue dose; (5) estimate tissue dose with the PBPK models during toxic exposures; and (6) estimate risk in humans using PBPK models to estimate tissue dose from exposure levels and assuming similar tissue response for equivalent target tissue dose.

The use of PBPK models taught us how to do extrapolations, including high dose to low dose, dose route (inhalation, oral, dermal), between species, across classes of chemicals, from *in vitro* to *in vivo* situations, and for different dosing scenarios. The dosimetry models taught us about: (1) the process of using PBPK models in risk assessment; (2) the broad utility of the technology; (3) how to develop mode of action specific extrapolation defaults; and (4) how to use various analysis tools with the PBPK models. The assumptions in the risk assessment process were made more explicit by using these models, and uncertainty was identified, quantified, and reduced. Today, RfD and RfC calculations distinguish pharmacokinetic and pharmacodynamic components of interspecies uncertainty factor.

The community of people who do risk assessment has not been explicit enough about two types of risk models: the linear model and the threshold, or nonlinear, model. Linear models have some risk probability at all doses, and threshold models use independent uncertainty factors to generate RfC and RfD values. In Dr. Andersen's opinion, the models use individual uncertainty factors for a series of legitimate concerns and then com-

bine them in an irrational way (by multiplying them all together) to give a comfort factor, that is a factor large enough that even if the risk is not being calculated in any direct fashion that the reduction leaves us comfortable that there is no risk below some level. This multiplicative use of uncertainty factors is an area that needs significant discussion if the process by which RfDs and RfCs are calculated is to be improved.

The work on mode of action has been moving toward answering the question of how tissues respond to dose by describing the biological processes that are perturbed by the presence of active forms of chemicals in tissues. Dr. Andersen described his idea of the future direction of the field of toxicology in terms of developing mode-of-action models based on new approaches in systems biology. In general, we have lacked organized information about basic responses of cell signaling pathways to toxic compounds; however, high data content, genomic tools, and signal transduction studies, in a functional genomics context, are changing the situation. Dr. Andersen commented on how ideas related to common signaling themes, MAP-kinase families, MAP-kinase cascades, and nonlinear signal transduction processes will likely provide explanations and quantitative models for biological thresholds in responses to toxic compounds. These models promise to allow development of threshold or nonlinear PD models that calculate risk at any exposure concentration.

Dr. Andersen's recommendations regarding dosimetry modeling in interspecies scaling are as follows: (1) use interspecies dosimetry defaults based on mode of action, (2) develop parameter databases for human PBPK models, (3) encourage dosimetry-based approaches for cumulative and aggregate risk assessments, (4) expand the suite of "validated" human PBPK models, and (5) improve the understanding of parameters important for understanding the pharmacokinetics of lipophilic compounds. Rec-

ommendations that are more fundamental and relate to mode of action (PD models) include the following: (1) develop clear articulation of the underlying models used for risk assessment, including their implicit structures and assumptions; (2) explain how data when available are to be used in these assessments; (3) discuss the rationale for defaults that will be used when data are unavailable; and (4) develop mechanistic, biologically based dose-response models for obligatory precursor cellular responses of cells to toxic stressors or of alterations in signaling pathways affected early in the toxicity pathways for toxic compounds. We believe that development of these models, as happened with the evolution of PBPK models for risk assessment, will help provide clearer questions about use of models if action information in risk assessment, model analysis tools, and guidelines for creating and using appropriate data sets in model building and model validation/calibration are available.

### Extrapolation Between Species: Issues and Opportunities for the Future

Dr. James Bus, Dow Chemical Company

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The presentation by Dr. James Bus, Dow Chemical Company, gave a practical bent to some of the science and discussion of the issues of uncertainty factors and cross-species extrapolation. He touched on three major points: (1) the value of mechanisms, (2) pharmacokinetics, and (3) the context of natural dietary chemicals and implications for current cross-species assumptions.

Regarding the value of mechanisms and mode of action, Dr. Bus stated his belief that the mode-of-action approach, as it progresses in the future and as the science continues to advance, will be very valuable in three ways. First, it will define the relevance of animal species responses. Second, it will affect study design and interpretation. Third, it will result in the applications of new technologies, such as toxicogenomics and trans-

genic animals. The fundamental tenet of dose-response must not be forgotten as the new tools are applied.

In the area of pharmacokinetics, the issue involves how to use pharmacokinetic information to define the relevance of the animal models to humans. Dr. Bus used an example of a Dow Chemical study to pose the question of the model to use for regulation. The relevance of the dog for human risk assessment is considered in a study of 2,4-D. Dogs do not clear 2,4-D adequately. After correction for physiologic factors, the finding is that the dog is a significant outlier. This example demonstrates that pharmacokinetic information can be useful for examining cross-species extrapolation.

Another issue in the area of pharmacokinetics involves how pharmacokinetic information can be used to improve our understanding of dosimetry, that is, how to improve the links of human exposure data to dose in animal toxicology studies. With the emergence of human biomonitoring programs, the real challenge involves how to assess plasma and tissue concentrations under conditions in which toxicology data are generated. We are getting responses in animals that are treated in the diet or the drinking water. What kinds of internal doses are those animals carrying relative to the internal dose that we might be observing in people who are actually environmentally exposed to those same chemicals?

After referring again to Dow's 2,4-D example, Dr. Bus concluded his presentation with remarks about the context of natural dietary chemicals. The baseline assumption is that the basic food supply is "safe" despite containing many chemical substances. The challenge is to work the traditional chemical risk problem "backwards," that is, to start with the standard that the food is safe and test the risk performance of natural food components using the current chemical risk paradigm against that standard. (Our current

paradigm for risk assessment works the opposite way. We start with the problem of an individual chemical, do toxicology studies, understand the hazard, and then try to determine what constitutes a lack of adverse consequences. It is virtually impossible, however, to prove a negative in the field of toxicology.)

The former scenario has been tested with acrylamide, an industrial chemical with a large toxicology database. A conventional risk assessment is available for acrylamide as an industrial chemical. Acrylamide was discovered as a natural constituent in foods and a Food and Drug Administration (FDA) action plan involves further studies for acrylamide. The conundrum is that by initiating the research program to characterize the risk, we are making a *de facto* affirmation of the need to include natural food chemicals in the balance of the risk equation. The key question is what will be done with the data once they are gathered? Acrylamide represents only one of many chemicals present in food. What do we tell the public about chemicals in foods?

### **Biomarkers and Species Comparisons (Metabolism and Metabolomics)**

Dr. Susan Sumner, RTI International

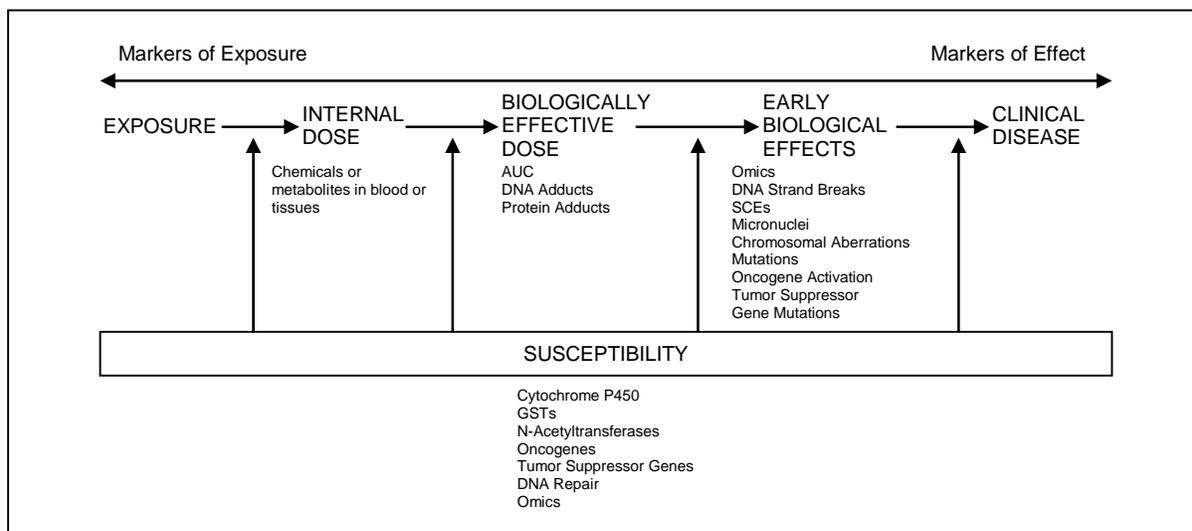
Dr. Susan Sumner, RTI International, commented on species comparison issues, including the relevance of the animal model. Referring to the biomarker continuum (see Figure 9) and biomarkers and species comparisons, Dr. Sumner stated that tissues and biological fluids from rodent dose-response studies might be used to develop markers of exposure, effect, and susceptibility. She noted, however, that understanding the human relevancy of the mode of action in the animal model is crucial for understanding the full utilization of the biomarker. Dr. Sumner discussed the development of biological fluid-to-tissue corollary markers based on dose-response in studies of rodents and the extrapolation to human biological

fluids. She noted that urine and blood-based markers have a good potential for use in human-to-animal model comparisons, and specifically emphasized the importance of urinary markers, because they provide an integrated read-out of events that have occurred over time.

Dr. Sumner pointed out that because metabolizing factors are known to be species and strain specific, the use of global detection methods is necessary to access the human relevancy of markers developed in animal models. Elucidation of xenobiotic metabolism and alterations in endogenous metabolism as a function of chemical exposure, dose level, and response provide a means to develop the causal relationships between metabolites, pathways, and effects. To extrapolate across species, however, global methods rather than targeted methods are needed. Conventional methods are directed to looking for what already is known about the chemical. In cross-species studies, when you “look under the lamp post,” you might not see new or additional responses that are species, gender, strain, or age specific because the methods are selective or not well resolved. Non-directed methods are needed to characterize metabolites and perturbations in metabolism.

Non-directed analytical methods that can be applied to study multiple model systems and then applied to human samples should be chosen. The implications of non-directed approaches are that they enable more informed species comparisons. Referring to a study of <sup>13</sup>C acrylamide metabolism in mice, rat, and man, Dr. Sumner reported qualitative and quantitative species differences in metabolism that were resolved by global detection methods, and would not have been observed using directed approaches. She summarized several studies in which rodents were administered <sup>13</sup>C-labeled xenobiotics for the characterization of metabolism using NMR spectroscopy. In these studies, new

Figure 9. Biomarkers Continuum



Source: Adapted from NRC, 1989

metabolites and new pathways for the xenobiotic metabolism were discovered, and “controversial” metabolites or pathways were either confirmed or denied.

Dr. Sumner also mentioned the importance of adducts as biomarkers for exposure and effect, and reminded the audience that these types of markers should be measured not only as a function of dose and time, but also in target and non-target tissues. She added that adducts of nucleosides typically are examined in studies to elucidate xenobiotic interaction with DNA, but other DNA types of adducts also may be important for generation of some of the observed effects. As an example, Dr. Sumner specifically mentioned the formation of DNA adducts to nucleotides that, depending on structure, can lead to DNA strand breaks. Although these areas have been investigated, there are many opportunities (particularly with molecules that form epoxide intermediates) for further discovery and potential association of markers with effects.

Dr. Sumner recommended that, when using peer-reviewed literature for obtaining data for model construction, each study be assessed to determine the wattage of the light

bulb being used during the study. She noted that many published manuscripts may be of high scientific caliber but never intended for the purpose of cross-species extrapolation; thus, the experimental design and analytical measure may limit their use for that purpose. There must be a requirement for the incorporation of high resolution and non-selective analytical approaches for biomarker analysis with consistency across species when cross-species extrapolation is the key to the study.

“Omics” technologies help us move away from the “lamp post effect”; broadening the opportunity for discovery outside of the known or targeted pathway. As we use these technologies, however, we must consider that they also have limitations. For instance, gene expression profiling is only as good as the selection of genes on the chip. Also, proteomics is only as good as the gel resolution or identification methods. In addition, metabolite profiling (also referred to as metabolomics or metabonomics) picks up only what the specific analytical method measures. With omics technologies, we now can look out of wider windows and with more light, but questions still remain; such as “are we looking out of the right windows?”

Nicholson defines metabonomics as the quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification. Metabonomics (used by some as interchangeable with metabolomics) can be applied to cells, organs, biofluids, and breath. The assessment of changes in endogenous metabolites might help to define patterns to associate with critical events in the exposure to disease continuum. The pathway relationship of these patterns (or markers) might identify mechanisms of injury or susceptibility. In this presentation, endogenous metabolites refer to the entities that map to biochemical pathways. Of course, metabolites from environmental, dietary, and other life-style factors may present as part of the metabolite profile; providing opportunity in health assessments, but also adding an additional layer of complexity in interpretation of metabolite profiles.

A number of analytical methods can capture metabolite signals; NMR spectroscopy and chromatography coupled with mass spectrometry (MS) detection being the most common for metabolomics studies to date. After capture of signals, mathematical methods are used to reduce the data according to study design. For example, groups can be separated by dose, time, or onset of or recovery from disease. Determining the patterns of signals that are responsible for association of the metabolite profile with outcome might yield a marker or suite of markers for association with, for example, toxicity. To fully utilize metabolomics data, smart study designs are needed that result in comprehensive data sets that can be used to tease apart profiles that represent different types of responses, such as efficacy versus toxicity.

A major benefit of metabolomics over other “omics” is the ability to readily analyze human urine and blood samples. For populations in which exposures or diseases are well defined, metabolomic profiles developed for

urine or blood might result in patterns that can be associated clearly with exposure levels or outcomes. Diseases or exposures that result in alterations in endogenous profiles that are well defined from control populations will be more readily associated with specific metabolic perturbations.

Because environmental or potential industrial exposures are typically to low levels of chemicals, the inherent variability in human samples might in fact mask defining the relationship between exposure and outcome. It is likely that controlled studies in humans will help to define the effect of low-level exposures on perturbations in endogenous compounds. Dose-response studies in animal models can be used to understand the mode of action and then to extrapolate the profiles to evaluate the human data. For example, as previously mentioned corollary markers can be developed using tissue and urine from rats for assessment of profiles developed for human urine or blood. Dr. Sumner gave an example of a study to demonstrate how mapping to biochemical pathways is critical in developing markers that can cross species; showing a case example where the most significant endogenous metabolite excreted in rat urine is derived from a synthetic pathway that is not directly relevant to humans.

There are expected effects of chemical exposure on endogenous metabolism; therefore, we must be able to tease apart an occurrence and what is predictive of efficacy or an adverse outcome. We must understand the changes in markers as we move along the exposure to disease continuum. Although metabolomics holds huge promise, we are in the infancy of understanding the utilization of metabolomics in cross-species comparisons. Relevant questions that need to be addressed include: (1) How conserved are mammalian pathways, enzymes, and the regulation of flux? (2) What is the role of diet, diurnal variation, gender, age, seasonal variation, and strain or ethnic origin? and

(3) What is the conservation (compartmentalization) of metabolites across cells, tissue, and biofluids?

Dr. Sumner offered several recommendations. Metabolomic assessments will benefit from samples from relevant controlled human exposures; long-term population monitoring with serial metabolite profile generation and long-term disease association; development of databases to define influence of dietary intake, drugs and chemicals, lifestyle factors, and susceptibility issues on endogenous profiles; associated databases from animal studies (models for onset of and recovery or repair from specific diseases or insults); and development of methods for extrapolation of metabolomics data through pathway analysis.

#### Panel Discussion

Dr. Clifford Duke, Moderator

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Dr. Duke commented that the difficulty in risk assessment involves what is done with the data once they are acquired. A number of the speakers have helped to answer that question.

Dr. Dourson described a hypothetical situation. Suppose one has a database for a chemical and knows its critical effects. The outstanding areas of uncertainty are sub-chronic to chronic, animal to human, and within human variability. There are no specific informative data other than to use the default. The question is: If the three areas of uncertainty were truly independent, would it be appropriate to multiply these uncertainty factors together and get 1,000 and use that as a divisor? What if the areas of uncertainty were dependent? Dr. Andersen responded that if the areas of uncertainty are indeed independent, it would be appropriate to multiply them together. We do not usually know, however, that they are independent. This is a critical issue in risk assessment. We have made a set of assumptions without a solid basis. We have given the public the impres-

sion that we are using a knowledge-based, practical approach to making RfD and RfC calculations. More research on modes of action is needed. We should be cautious about assuming that we should multiply the uncertainty factors every time we have a concern. The issue of what we do in conveying risks has to be put into perspective, and we are failing to do that.

Dr. Bus stated that we must reframe our approach to risk assessment. Dr. Andersen added that the decisions must be informed by mode-of-action information. Dr. Dearfield commented that multiplying is done when there are gaps in knowledge. The key issue is how all the assumptions are combined to form a final decision. The staff paper points out that each of the individual assumptions looks reasonable; risk must be characterized by qualitative analysis.

Ms. Casano commented that her personal understanding is that human data establishing causation preclude the need for animal data. If no such data exist, the animal data are not very informative anyway because of the uncertainty factors. She expressed concern about EPA's statement regarding animal data that tissue concordance is not always necessary. Such an approach causes a loss of the ability to distinguish real risks from hypothetical risks. A new paradigm should be adopted to end the fragmented approach that results in overlooking significant environmental problems while focusing on comparatively minor improvements that contribute little to the overall protection of human health and ecosystems. A reality check is needed in the risk assessment process. Risk assessments affect choices and decisions—sometimes in a negative way. Ms. Casano also called for better communication, noting that information must be put in context in plain English for the public.

Speaking as a representative of General Electric, Ms. Casano reported that a general Web search indicated that EPA's exposure

handbook does not contain a response to the specific criticisms regarding risk assessment practices that were submitted to the Agency. Also, there is no timetable or guarantee that any changes will occur. She suggested that the BOSC recommend that EPA respond to the specific criticisms and make changes based on those criticisms or explain the scientific basis for doing otherwise. EPA cannot claim to have fully evaluated the risk assessment practices if it does not respond to specific criticisms.

Dr. Bus mentioned the issue of resources and toxicology data in terms of the acrylamide issue. What do you do with the data when you have them? What about exploring other toxic chemicals?

Dr. Dearfield commented on the communication issue. EPA is trying to improve the characterization of risk assessment. The Agency has a risk characterization policy and a risk characterization handbook that spells out what can be done to better communicate risk assessment information. Referring to Ms. Casano's comment about EPA not responding to specific criticisms, Dr. Dearfield explained that the staff paper was an attempt to describe what is done in actual practice and was not intended to recommend any changes in that practice. Instead, EPA wants to hear about proposed changes and suggestions and submit them for evaluation and agreement before any changes are implemented to improve the process.

Gary Bangs, EPA's OPPTS, commented on the exposure factors handbook. The handbook is being updated, and workshops are being held on various topics; for example, a soil workshop will be held this spring. Additional references and updates have been posted on the Web site. The handbook will be updated over a period of 7 years.

Judith Graham, American Chemistry Council, asked Dr. Dearfield about animal-to-

human extrapolation. From the very beginning, the RfC methodology included dosimetric calculation to account for pharmacokinetics. A dosimetric calculation and an uncertainty factor of 3 accounted for the pharmacodynamics if a default was needed. That approach was not used for the RfD methodology. What progress is being made on the RfD methodology to move it toward incorporating more pharmacokinetics and an uncertainty factor of 3? Dr. Dearfield responded that the Agency is looking forward to examining all the PBPK models to determine how to use the actual information instead of relying on a default. Dr. Conolly stated that his personal interest is in the generation of data sets to be used in risk assessment. Where will data sets come from to support more advanced kinds of risk assessment? If we agree on the use of pharmacokinetics in support of risk assessment, more detailed mode-of-action data sets, and data sets motivated by systems biology thinking to enhance our understanding of dose-response behaviors, then we must determine the source of the data. Chemical-specific, *ad hoc* efforts are underway to address specific problems, but there does not seem to be any groundswell of movement on the side of government or industry to declare the kinds of data to be collected, especially considering the time and money involved. How do we move forward with generating the data? Dr. Bus responded that the staff paper indicates that EPA is bringing transparency to the process. The scientific community is starting the dialogue about where we should be going and how the process can be improved in the future. The need to improve the true scientific underpinnings of the risk assessment process is clear.

Dr. Sumner expressed her concern about the source of the data. The people who know how to generate the data should understand the risk assessment issues and how to properly design the studies to be used in PBPK modeling or risk assessment. One of the general problems in the past was that scien-

tists did excellent work but the data generated lacked important components. We also should consider the inclusion of omics data (genes, proteins, and metabolites) in longitudinal studies, such as those conducted through the Centers for Disease Control and Prevention (CDC) and EPA. The scientists involved in the risk assessment process also must be involved in understanding the design of the studies. In addition, we should look at the pharmaceutical pipeline for pre-clinical and clinical studies that include human data about adverse responses that did not occur in animal models. From that type of analysis, we can begin to understand more about the relevancy of the animal model to real human data.

Dr. Andersen stated that he is not optimistic that steps will be taken to provide the types of information required to improve risk assessment under the present situation. We have lost the ability over the past 30 years to collect whole-animal data regarding kinetics because of expense and lack of interest. In addition, we do not train toxicologists to think about risk (they are trained to think about hazard). EPA and others who do risk assessments should develop research strategy documents. Dr. Andersen asserted that this is an education issue. A serious discussion is needed about how to train people in risk assessment. How can the whole process of making risk assessments and risk-benefit decisions become part of the education process, especially in toxicology curricula that are geared toward generating hazard identification results rather than developing tools for interpretation of relevance and meaning of the results of these hazard-oriented studies? We must discuss the strategies for risk assessment rather than just the process for a single chemical.

Dr. Daston raised the issue of biomonitoring. Individuals in public health are very concerned that biomonitoring data are being generated without any context. This situation can lead to ill-informed decisions on the

part of patients and clinicians. A system should be developed whereby pharmacokinetic data always are applied at the same time that biomonitoring data are released so that the data can be presented in a risk assessment context. Another point involves the issue of concordance from the animal model to humans. Dr. Daston mentioned the conservation of signal transduction pathways and their reuse in various places in the body and during different life stages. An understanding gained from an animal model about the pathways involved in morbidity would allow us to predict where to look and what we might expect to see in humans. This advance would make monitoring of risk assessment practices more possible in human studies. Dr. Bus stated that the data generated for Dow's 2,4-D studies provided some context for biomonitoring scenarios. Dr. Dearfield mentioned the difficulty in determining where to place information in the risk assessment for biomonitoring. The era of genomics will result in gene expression changes that might indicate some adverse effect. How can that information be placed in context for risk assessment?

Dr. Andersen warned about the danger involved in biomonitoring performed in the absence of tools to interpret the data. In many cases, some tools are moderately well developed to allow pharmacokinetic inferences to be drawn. Resources are needed for improving the process of understanding the dosimetry with those kinetic models. Dr. Andersen also commented on site concordance for responses versus tissue dose. He noted that data are needed to know where to look for a response based on knowledge of disposition of active forms of the chemical within animals and people.

Richard Becker, American Chemistry Council, suggested that the time has come to move away from the dogmatic approach to risk assessment, particularly the practice of basing decisions on hazard characterization, and to begin to approach toxicology the way

we approach pharmacology, which is as a function of dose. We should shift away from the artificial separation of hazard characterization and dose response in a risk assessment paradigm, begin with an understanding of a biological model, and then build in the dosimetry. How far away are we from this approach? Because many concerns involve molecules and are threshold-based, the default should be a threshold model, and departure from it should occur when data indicate otherwise. Dr. Dearfield stated that this suggestion could be adopted with time and resources. We no longer are tied to a rigid model. Dr. Andersen added that a series of efforts is underway to examine toxicity testing. We must redefine the process by which we collect information.

Dr. Bus stated that he is alternately encouraged and discouraged about progress in the risk assessment process and regulation of chemicals. The challenge is to identify the future roadmap regarding the risk assessment paradigm. We need a much more orchestrated strategy than what we have had historically.

Kara Morgan, a risk analyst in the field of decision analysis at FDA, stated that risk analysis is able to calculate the value of new information in terms of reducing uncertainty in the final decision. She suggested creating an incentive for development of information that would reduce uncertainty. Toxicologists could work with decision analysts to characterize the degree to which uncertainty is being reduced and provide the incentive for developing this type of information in the future. Dr. Andersen stated that he worked with decision analysts at the U.S. Air Force and came to appreciate the sensitivity of the decision in terms of risk numbers and data development. Part of the process is understanding the uncertainties. In some decisions, there is no way to quantify uncertainty. The use of tools to quantify risk can result in good decisions about risk, but we are not using those tools routinely. Dr. Dear-

field agreed that EPA should consider the suggestion of working with decision analysts. Dr. Sumner added that people who understand the risk assessment process must provide input to scientists who collect the data. Integration between “omics” scientists and model builders must occur now.

Dr. Farland asked about Dr. Andersen’s perturbation model, which prompts ideas about exposure and outcome. Regarding cross-species extrapolation, he asked the panelists to comment on the benefits or pitfalls of using standard strains of animals for priority-setting and testing as opposed to trying to understand the limited number of pathways for the biology under consideration. Dr. Bus referred to his comments about transgenic animals and mentioned “an unexplored opportunity.” We now can test hypotheses that we could not test before because we did not have the tools. We can create the animal equivalents of what we suspect might be a susceptible individual. Rather than immediately introducing more strains or different types of animals into our standard toxicology testing paradigm, we first should invest in the science and establish some principles. Instead of taking a chemical-specific approach, we should develop key science principles to apply generically across the board. We should develop and explore the hypotheses (i.e., the direction we should go) instead of asking whether we are using the right range of animal strains in our current standard risk assessment paradigm.

Referring to humanized models, Dr. Sumner stated that long-term toxicity testing studies use serial sacrificing to look for the development of adverse response. We may consider adding other measurements (such as omics) to the studies so that we can start to understand the onset of a disease state. For example, looking at the metabolite profile in urine samples very early after exposure to a chemical might help us understand the significance of that profile in relationship to the onset of tumor formation. Because such

studies are designed as a function of dose and time; mathematical algorithms could be developed to identify trends in the data that reveal the patterns of metabolites that can be associated with disease state. Mapping those metabolites to biochemical pathways will help to establish mechanisms. Traditional strains are useful, but we must add newer technologies to the studies, including the use of transgenic models, or comparative studies in sensitive and non-sensitive species.

Dr. Andersen stated that we must really ask ourselves what toxicity testing is meant to do. We want to ensure that humans do not have adverse effects from a chemical through our interpretation of studies done in animals or using cells or tissues. In the past, we have relied on whole animal tests to create ideas that are tested in simpler biological systems. It now is possible to see the effects of chemicals on simpler biological functions by determining the effect of chemicals on cell systems from different species. These studies examine perturbations of cellular processes by chemicals and the target pathways in biological systems, primarily in cells. This kind of signal perturbation is likely to make more widespread use of functional genomic tools.

These studies need to answer some very basic questions: How are target pathways organized in different animals? What are the important components of those pathways? How do these components change from species to species and from strain to strain? In addition, hypotheses could be produced about sensitivity and tested in various cell lines and/or engineered cell constructs to assess interspecies and potential intra-individual differences in chemical perturbations of cellular functions. These perturbations usually are associated with what have been called precursor steps. In some cases, it is clear that preventing those precursors will prevent the disease created by the chemical and could utilize genomic data to create

mechanistic models of various perturbations of cell signaling networks, such as alteration in cell defense mechanisms, and activation of cell survival networks, activation of proliferative signals by endocrine active compounds. During the next 10 years, more work will be done on cell systems, and the interpretations from those systems will affect decisions about the kind of whole-animal work that should be done, and may eventually be important in creating nonlinear risk models.

#### **NEW DIRECTIONS FOR RISK ASSESSMENT AND WORKSHOP WRAPUP**

##### **Risk Assessment at EPA: The Science Behind the Assessments**

Dr. Peter Preuss, Director, EPA/NCEA

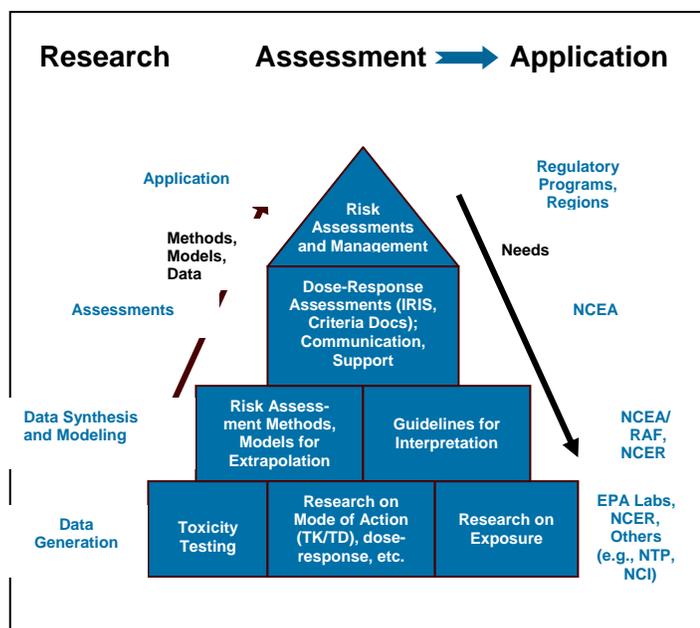
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Dr. Peter Preuss, Director of EPA's National Center for Environmental Assessment (NCEA), thanked the workshop organizers, speakers, and participants and referred to the interesting presentations and discussions of issues regarding uncertainty factors, extrapolation, and risk assessment methods. The staff paper underscores important risk assessment issues. We must understand the staff paper in time and space and recognize that a broader view allows us to see where we have come from and where we are going. The evolution of risk assessment over the past 30 years begins in the 1970s when the first cancer guidelines were issued. As risk assessment evolved, the concept of the RfD developed, as did the Integrated Risk Information System (IRIS) database in the 1980s. Other procedures were developed in the 1990s, including PBPK models and BMD modeling. Dr. Preuss sees the process as an evolution—as new information was discovered, additions and refinements were made to the risk assessment process. A number of issues and problems still plague the Agency and need to be resolved.

To understand what is occurring in risk assessment, one must understand what is oc-

curring in “the other rooms of the house.” A straightforward system has been established over time; an iterative process is in place whereby research is providing methods and generating data that are incorporated into newer models and guidelines for conducting assessments that, when completed, in turn help identify further research to improve future assessments (see Figure 10). Dr. Preuss gave several examples of the kind of research underway in the National Health and Environmental Effects Research Laboratory (human health research), the National Exposure Research Laboratory (exposure assessment research), and the National Center for Environmental Research (funding extramural environmental research).

Figure 10. Iterative Process for Improving Risk Assessment



Source: Tuxen and Vandenberg, 2005

The EPA research program is targeted to improve the scientific basis for health risk assessment. Research is incorporated into assessments when the following questions are answered: When are new methods ready? Do they answer our needs? Is the scientific basis sound? Are the methods too complex?

The risk assessment issues discussed at this workshop include topics that EPA has considered for a long time, including the scientific foundation and use of uncertainty factors. EPA has been conducting a major review of this issue by examining the current RfD and RfC methodologies. The role and application of uncertainty factors is a specific focus. Dr. Preuss reviewed some of the questions for this exercise. Another topic concerns data-derived uncertainty factors. The role of PBPK models is another topic addressed by EPA studies of vinyl chloride, dichloromethane, tetrachloroethylene, and trichloroethylene.

Both model-independent and model-dependent approaches are used in EPA’s current and future risk assessments involving high-to-low dose extrapolation.

Dr. Preuss commented on EPA’s focus on formaldehyde and stated that the Agency is evaluating both the strengths and the limitations of the epidemiologic studies and the parameters, assumptions, and decisions made in the development of the CIIT model to develop a new risk assessment.

In closing his presentation, Dr. Preuss stated that the products of human health research and risk assessment are fundamental to the Agency’s regulatory decision-making process. Innovative and cutting-edge approaches to risk assessment issues are being developed by the Agency. Between research and methods development at EPA and in other places, the Agency is moving forward on all these fronts. Significant progress will be made in the next few years. As illustrated in Figure 11, the future will involve genomics, proteomics, and metabonomics and integrate molecular biology and chemistry to prioritize data requirements and improve risk assessment.

The science challenges in human health risk assessment include issues related to current

approaches that are being refined or reevaluated (e.g., non-cancer human health risk assessment, uncertainty factors approach), issues for which Agency-wide approaches are being developed (e.g., aggregate/cumulative risk, probabilistic risk assessment, and expert elicitation), and emerging science areas that must be factored into human health risk assessment (e.g., systems biology, nanomaterials).

### Meeting Wrapup and Final Remarks

Dr. Rogene Henderson, Workshop Chair

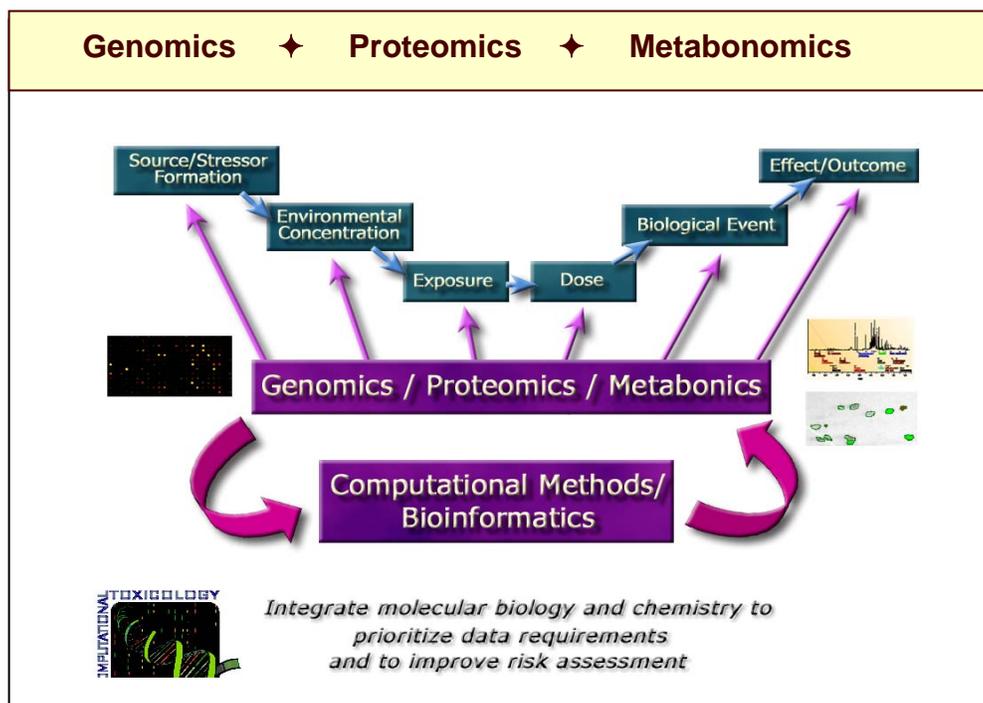
Dr. Henderson closed the workshop by summarizing the focus of the discussions, including the need to look at mixtures, single chemicals, the food we eat, and the chemicals we produce endogenously. The “omics” technologies open windows and allow us to look at the broad response of organisms in terms of their genes, proteins, and metabolites. Background values were discussed and must be considered in terms

of both dose and effects. The value of models also was discussed, as was the use of data-rich risk assessments with systems biology. It was suggested that prototype chemicals be used to develop strong risk assessments to be applied to other chemicals. Concern was expressed for the education of toxicologists and the combining of uncertainty factors, among other topics.

Dr. Henderson thanked EPA for preparing the staff paper and seeking input to improve the Agency’s risk assessment practices. The staff paper facilitated the workshop’s clear discussions of the path forward and recommendations for improvement.

Dr. Henderson thanked the speakers and audience and reminded them that the presentations and a summary will be posted on the BOSC Web Site and abstracts of the workshop presentations will be published in a peer-reviewed journal.

Figure 11. Future Efforts to Improve Risk Assessment



Source: Adapted from *A Framework for a Computational Toxicology Research Program in ORD, EPA, 2003*

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**February 2-3, 2005**

National Academy of Sciences Auditorium  
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**Wednesday, February 2, 2005**

- 8:00a.m. – 8:30a.m. Registration
- 8:30a.m. – 8:45a.m. Welcome and Introductions
- Opening Remarks: Workshop on EPA Chemical Risk Assessment Principles and Practices  
Dr. Rogene Henderson, Lovelace Respiratory Research Institute, BOSC Vice-Chair and Workshop Chair
  - EPA's Staff Paper: Evaluation of EPA Risk Assessment Principles and Practices  
Dr. William Farland, Acting Science Advisor, Office of the Science Advisor, EPA

**Session I: Extrapolation From High to Low Doses**

- 8:45a.m. – 9:00a.m. Introduction to Session I  
Dr. Rogene Henderson, Moderator
- 9:00a.m. – 9:30a.m. EPA's Approach: High to Low Dose Extrapolation: Issues and Approaches  
Dr. Weihsueh Chiu, EPA/ORD National Center for Environmental Assessment
- 9:30a.m. - 10:00a.m. 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
- 10:00a.m. – 10:30a.m. Break
- 10:30a.m. – 11:00a.m. Some Issues Regarding High to Low Dose Extrapolation  
Dr. Thomas Starr, TBS Associates
- 11:00a.m. – 11:30a.m. Considerations for Improving High To Low Dose Extrapolation  
Dr. Lauren Zeise, California EPA
- 11:30a.m. – 12:30p.m. Discussion  
Moderated by Dr. Rogene Henderson
- 12:30p.m. – 1:30p.m. Lunch

## **Session II: Use of Default Assumptions and Uncertainty Factors**

1:30p.m. – 1:45p.m.	Introduction to Session II	Dr. George Daston, BOSC Member and Moderator
1:45p.m. – 2:15p.m.	EPA's Approach	Dr. Rita Schoeny, Senior Science Advisor, EPA Office of Water
2:15p.m. – 2:45p.m.	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
2:45p.m. – 3:15p.m.	Break	
3:15p.m. – 3:45p.m.	Past and Future Use of Default Assumptions and Uncertainty Factors	Dr. Michael Dourson, Toxicology Excellence for Risk Assessment
3:45p.m. – 4:15p.m.	NRDC Comments to BOSC on the Use of Default Assumptions and Uncertainty Factors in EPA Risk Assessments	Dr. Jennifer Sass, Natural Resources Defense Council
4:15p.m. – 5:15p.m.	Discussion	Moderated by Dr. George Daston

## **Thursday, February 3, 2005**

### **Session III: Extrapolation Between Species**

8:30a.m. – 8:45a.m.	Introduction to Session III	Dr. Clifford Duke, BOSC Member and Moderator
8:45a.m. – 9:15a.m.	EPA's Approach	Dr. Kerry Dearfield, EPA Office of the Science Advisor
9:15a.m. – 9:45a.m.	Mode of Action and Dosimetry Considerations in Interspecies Extrapolation	Dr. Mel Andersen, CIIT Centers for Health Research
9:45a.m. – 10:00a.m.	Break	
10:00a.m. – 10:30a.m.	Extrapolation Between Species: Issues and Opportunities for the Future	Dr. Jim Bus, Dow Chemical Corporation
10:30a.m. – 11:00a.m.	Biomarkers and Species Comparisons (Metabolism and Metabolomics)	Dr. Susan Sumner, RTI International
11:00 a.m. – 12:00noon	Discussion	Moderated by Dr. Clifford Duke

## **New Directions for Risk Assessment and Workshop Wrap-Up**

12:00 noon – 1:00 p.m.	A. Risk Assessment at EPA: The Science Behind the Assessments	Dr. Peter Preuss, Director, EPA/ORD National Center for Environmental Assessment
	B. Meeting Wrap-Up	General Discussion, moderated by Dr. Rogene Henderson, Workshop Chair
	C. Final Remarks	Dr. Rogene Henderson, Workshop Chair
1:00 pm.	Adjourn	