



**Beyond Science and Decisions:
From Problem Formulation to Dose-Response.
Report from Workshop II**

Workshop Held:
October 11-13th, 2010
Crystal City, Virginia

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1.0 Introduction

The second in a series of three workshops aimed at implementing a multi-stakeholder approach to share information, ideas and techniques in support of developing a practical, solution-oriented, human health risk assessment methods compendium was held October 11-13, 2010 in Arlington, Virginia. Over 135 scientists from a broad range of organizations participated in the workshop (see Appendix A), either in person or via webinar; the workshop was held in tandem with the Federal-State Toxicology and Risk Analysis Committee (FSTRAC) annual meeting, with one overlapping session.

1.1 Background & Purpose

This workshop series was designed to expand upon concepts included in the National Academy of Science report: *Science and Decisions: Advancement of Risk Assessment* (NAS, 2009) in a multi-stakeholder format, in support of developing a practical, solution-oriented, risk assessment methods compendium. The methods compendium is intended for use by risk managers and scientists at a variety of levels (*e.g.*, federal and state agencies, and industry). Conducted under the aegis of the Alliance for Risk Assessment (ARA), the series of three workshops is designed to explore available and evolving methodology to maximize the use of biological knowledge of how chemicals act at the molecular, cellular, and systemic levels in risk assessment and decision-making.

The risk assessment field is rapidly evolving, with important contributions from the ongoing efforts of governmental and international agencies, advisory committees, universities, collaborative efforts such as *Tox21*, and key recent NAS publications (NAS, 2007, 2008, 2009). This workshop series aims to build on these various initiatives and broaden and deepen the discussions on appropriate approaches to dose-response analysis for various problem formulations.

This series of workshops has been organized by the ARA, a collaboration of organizations working to support the protection of public health by encouraging cooperation among interested stakeholders on issues and projects related to human health and environmental risk assessment, through the use of shared resources, expertise, and planning. The workshop series has been developed and supported by a large number of people and broad range of organizations, including federal, state, industry, and nongovernmental organizations (NGOs). The ARA Steering Committee is providing guidance and oversight of the workshop series and panel selection. The Dose-Response Advisory Committee (DRAC) is the organizing committee for the workshop. The DRAC consists of representatives from major workshop sponsors, and developed the workshop structure and agenda (see Appendix B). A panel of expert scientists (Science Panel) was selected by the Steering Committee of the ARA to provide specific guidance and oversight during each of the second and third workshops. The panel led the evaluation of the case studies during the second workshop, and will build consensus on the methods compendium for dose-response assessment during the third workshop. Toxicology Excellence for Risk Assessment (TERA) is providing organizational and technical support to the workshop effort. As of the second workshop, over 38 diverse organizations had provided in-kind or monetary support for the workshops (see http://www.allianceforrisk.org/ARA_Dose-

[Response_Sponsors.htm](#) for a complete list). This widespread support brings a broad range of diverse scientific viewpoints to the discussions, which will strengthen the ultimate conclusions and recommendations.

The workshops are focusing on human health risk assessment methods to address specific problem formulations. Case studies illustrating the relevant methods, based on application to one or more chemicals, are being used to support a consideration of whether the methods are appropriate for including in the methods compendium. The first workshop was devoted to presentations of ongoing related activities, and brainstorming and selection of case studies to evaluate proposed dose-response assessment techniques and their utility for different applications, as delineated in problem formulations. In the second workshop, several additional presentations were made of ongoing activities, and the Science Panel led a discussion of the potential utility of approaches illustrated by presented individual case studies, and recommended revisions. A third workshop scheduled for May of 2011 will review additional case studies, and seek consensus on a methods compendium highlighting key considerations for applying dose-response techniques for common risk assessment applications.

1.2 Workshop I

The first workshop was held at the Texas Commission on Environmental Quality (TCEQ) in Austin, Texas on March 16-18, 2010. Over 60 people participated in person, and more than 100 additional people participated via webcast and teleconference. A series of speakers shared ongoing risk assessment activities from various organizations and others provided a range of perspectives on the NAS (2009) recommendations. Twenty-seven individual case study proposals were received prior to the workshop. These were developed by volunteer teams of scientists from multiple organizations. Some reflected previously published work, while others were new ideas. Full copies of the proposals and supporting information are available at <http://www.allianceforrisk.org/Workshop/Materials.htm>. The workshop participants worked in six breakout groups; each one reviewed a subset of the proposals. The groups recommended case studies that showed promise for inclusion in the ultimate guidance document and that should be further developed and carried forward to Workshop II for review and evaluation. They also suggested additional case studies covering other techniques that would be useful to include at Workshop II. A report summarizing the case study proposals and break out groups' comments from Workshop I is available at http://www.allianceforrisk.org/ARA_Dose-Response.htm.

In preparation for Workshop II, case study summaries addressing key aspects of the case studies were developed, and new case studies or refinements were developed for those case studies endorsed at Workshop I and not already completed (see <http://www.allianceforrisk.org/Workshop/CaseStudies/index.htm>). A total of 18 case studies were carried forward for discussion at Workshop II. A broad range of methods was addressed, including additional methods that developed problem formulations not addressed in the NAS (2009) report (e.g., acute exposures and screening assessments), dose-response methods not considered in the NAS (2009) report (e.g., categorical regression, biologically-informed dose-response modeling), and case studies designed to test the implications of specific recommendations in the NAS (2009) report.

1.3 Selection of Science Panel

Prior to Workshop II, a science panel was selected to lead discussions of the proposed methods and case studies during Workshop II and build consensus for dose-response assessment methods during the third workshop. The panel was designed to be balanced and reflective of a range of affiliations and perspectives, as well as types of expertise (biology, risk assessment, modeling), and particular effort was made to include people from the NAS panel and environmental NGOs. An open nomination process was used and the ARA steering committee reviewed candidates and developed a prioritized list of 27 nominees, considering the desire to balance among affiliation and expertise. Invitations were sent in order of priority, resulting in the following 12 Science Panel members:

- ▶ *Michael Bolger, U.S. Food and Drug Administration*
- ▶ *James S. Bus, The Dow Chemical Company*
- ▶ *John Christopher, CH2M/Hill*
- ▶ *Rory Conolly, U.S EPA National Health and Environmental Effects Research Laboratory*
- ▶ *Michael L. Dourson, Toxicology Excellence for Risk Assessment*
- ▶ *Adam M. Finkel, University of Pennsylvania Law School¹*
- ▶ *William Hayes, Indiana Department of Environmental Management*
- ▶ *R. Jeffrey Lewis, ExxonMobil Biomedical Sciences, Inc.*
- ▶ *Bette Meek, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa*
- ▶ *Paul Moyer, Minnesota Department of Health*
- ▶ *Gregory Paoli, Risk Sciences International¹*
- ▶ *Rita Schoeny, U.S. EPA Office of Water*

Biographical sketches for Science Panel Members are found in Appendix C.

1.4 Workshop II

Workshop II was held on October 11-13, 2010, at the Double Tree Hotel in Arlington, Virginia. The emphasis of the second workshop was on the Science Panel's discussions of the methods as illustrated through the case studies. The purpose of the case studies was to provide illustrative information on dose-response methods that can be carried forward into the methods compendium that will be developed in Workshop III. While some case studies have focused on specific chemicals for illustrative purposes, the charge of the Panel related only to utility of the methodology.

Roberta Grant and Lynn Pottenger of the DRAC opened the workshop and introduced the Science Panel, who began the workshop with the selection of a Chair for the panel. Two panel members were nominated - Michael Dourson, who declined the nomination, and Bette Meek, who accepted. The group selected Dr. Meek by acclamation and she in turn asked Dr. Dourson to assist her as co-chair; he accepted. Dr. Edward Ohanian of the U.S. EPA provided a keynote address on *NRC Findings and Current EPA Risk Assessment Forum Efforts*. The remainder of

¹ Member of the NAS *Science & Decisions* panel

the workshop focused on discussion of the methods and case studies and four lunch-time talks. The case studies were divided into thematic groups for presentation and discussion. Authors of the case studies made brief presentations, and were available to answer Science Panel questions. The case studies were organized into the following categories

- ▶ Methods calculating risk for non-cancer effects
- ▶ Methods emphasizing evaluation of mode of action
- ▶ Methods for acute expose evaluation
- ▶ Methods for prioritization and screening
- ▶ Methods for integrating complex datasets
- ▶ Methods for safe dose calculation
- ▶ Methods for evaluation of risks for cancer effects

Workshop participants (including those participating via the webcast) were provided opportunities to ask questions and make comments at specific points during the workshop.

Several speakers presented on topics of interest during the lunches:

- ▶ Adam Finkel, University of Pennsylvania Law School and NAS panelist: *Beyond Misleading Underestimation of Carcinogenic Potency: The “Known Unknown” of Human Susceptibility*
- ▶ Peter Grevatt, U.S. EPA: *Issues Related to Children’s Health Protection*
- ▶ Craig Rowlands, The Dow Chemical Company: *Risk21. Risk Assessment for the 21st Century: A Vision and a Plan*
- ▶ Douglas Wolf, U.S. EPA: *Dose-Response Approaches for Nuclear Receptor-Mediated Modes of Action Workshop Preliminary Report*

Summaries of the guest presentations are provided in Appendix D.

On Day 3 of the workshop, the attendees included participants from an overlapping session of the Federal-State Toxicology and Risk Analysis Committee (FSTRAC), which includes representatives from state and tribal health and environmental agencies and the U.S. EPA. After a presentation on results of the previous two day’s discussions by the workshop rapporteurs, the combined group shared ideas on issues related to the workshop and future steps.

1.5 Organization of This Report

Several scientists served as Rapporteurs: Lynne Haber, Toxicology Excellence for Risk Assessment (lead rapporteur); Elizabeth Spalt, Indiana Department of Environmental Management; Allison Jenkins, Texas Commission on Environmental Quality; Asish Mohapatra, Health Canada; and Amy Rosenstein, Independent Consultant. They provided summary reports during the workshop and prepared this report. This report is organized into six areas. First is a series of opening remarks, followed by clarification of the intent of the NAS report with regard to two issues, a summary of the case study discussions, comments from the workshop participants, a summary of next steps, and overall workshop conclusions.

2.0 Science Panel Opening Comments

Science Panel members were invited to make opening comments before the case study discussions. Many noted the need to use all the available science to help improve the tools for risk assessment and strengthen decisions made with risk assessment information. Several suggested the panel consider information from additional key documents to evaluate improvements to risk assessment (*e.g.*, the EPA's Guidelines for carcinogen risk assessment [U.S. EPA, 2005]; Toxicity testing in the 21st century: A vision and a strategy [NAS, 2007]; Phthalates and cumulative risk assessment: The task ahead [NAS, 2008].) These reports provide different perspectives on ways to improve risk assessment, and their recommendations need to be synthesized for a best overall approach; the workshop series was noted as a useful venue for sharing methods across organizations and among disciplines, as a step toward this goal. Several panelists emphasized the need for pragmatism and practical outcomes from this series of workshops, with one noting that public health is protected by the *application* of the risk assessment, not the assessment itself. Several noted that risk managers need confidence in risk assessments and that the assessments must be defensible in the court of scientific understanding, the court of public opinion, and in legal courts.

3.0 Clarification of Issues in the NAS Report

3.1 Linearity in the Context of NAS (2009)

A major area of discussion related to the recommendations in the NAS (2009) report regarding conceptual models for dose-response evaluation, particularly to the discussion of low-dose linear extrapolation. A panelist who was on the NAS (2009) Committee clarified that the NAS committee intended something other than the current use of linear in human health risk assessment (that is, linear extrapolation from the point of departure [POD] to the origin). He quoted from the report's definition of "low-dose linear" in order to clarify the intent:

"low-dose linear means that at low doses 'added risk' (above background) increases linearly with increasing dose; it does not mean that the dose-response relationship is linear throughout the dose range between zero dose and high doses" (NAS, 2009, p. 142).

The panelist explained that this means that the NAS panel used the term "low-dose linear" as a surrogate for "no threshold at the population level," and did not intend that a straight line be drawn from the POD to zero except where the mode of action would suggest that this extrapolation is preferable. In other words, the complete dose-response function could be "piecewise linear," with different slopes in different regions. The dose referred to by the NAS panel should also be understood to be an additional dose of interest (*e.g.*, population exposure from a specific source or media) rather than the absolute dose. So low-dose linear, as discussed by the NAS panel, refers to incremental dose above background, with the response being at the population level. With this additional clarification, "low-dose linear" is not incompatible with the notion of individual response thresholds.

Further discussion of this topic is presented in the supplemental material on the workshop website.

3.2 Consideration of Background

A member of the Science Panel asked the expert panelists who had been on the NAS (2009) Committee to explain the NAS Committee's thinking regarding the recommendation to take into account background exposures and disease processes. In posing the question, the panelist noted that control groups reflect the background *response* rate, since the background is the response in the unexposed groups. The panelist continued, that if there is concern about background *exposures*, these are most appropriately addressed using the approach outlined in EPA's mixtures guidelines (EPA, 1986, 2000, 2003). These guidelines state that if data are not available on the mixture of interest, then one first assesses the components individually, and then adds the doses or responses (depending on whether the components are toxicologically independent), to estimate risk. The panelist continued that application of the mixtures guidelines means that it is inappropriate to modify the approach for individual chemical dose-response to reflect background exposures, and then to apply the mixtures approach. Doing so would be double-counting, since the impact of exposure to other chemicals would be taken into account in both the individual chemical dose-response and then in the overall mixture evaluation. The panelist also noted that NAS (2009) raises the issue of background disease, and noted that this issue needs to be considered separately, and could result in chemical exposures being over the threshold for response for the population, but that this does not obviate the concept of threshold.

One of the NAS (2009) Committee members replied that this was not his focus on the Committee, but that his recollection is that the issue was applying the threshold concept to evaluations of one chemical at a time. He believes thresholds exist, but the question is whether other exposures have pushed some people above the threshold, based on the pathway for the effect. He stated that this is not double-counting, because a mixtures assessment cannot assess every single exposure that occurs. He agreed that if the entire pathway of toxicity and all exposures were well-characterized, this would be double-counting, but one rarely has all of that information. Another of the NAS panelists suggested that this could be addressed in terms of the incremental risk associated with a specific exposure, in the context of the ethanol case study (See Appendix p. E-3).

Another panel member suggested that another possible interpretation of the consideration of background by NAS (2009) relates to the background of some key event (e.g., cell death). The panelist suggested that one might think that adding to the background of cell death would result in a linear dose-response, but that this would not make biological sense. Cells die all the time, but do not die in vast numbers in a particular location unless there is an endogenous or exogenous stimulus. Another panelist noted that the issue of additivity to background response assumes that the organism is already stressed maximally, so that any increment of dose results in an increased incidence of the apical effect. But, this panelist noted that the organism's ability to adapt needs to be considered; additivity to background needs to be considered in terms of homeostasis and the ability to up- and down-regulate responses.

4.0 Case Study Discussions

The majority of the workshop time was devoted to the Science Panel review of 18 individual case studies. The panel members considered whether the case studies were scientifically defensible, useful relative to the problem formulation, practical, and made biological sense. The panelists were also asked to identify areas where case studies may need additional work. The panel focused on the case study *methods*, and did not review key decision points or final risk assessment results for the case studies that involved specific chemical assessments.

A number of broad, cross-cutting issues arose during the discussions of the individual case studies. Because of the broader relevance of these issues to the risk assessment process, they are noted separately in supplemental material on the workshop website, with cross-references as needed to the case study discussions. However, it should be recognized that this section merely documents the preliminary panel discussion on these issues, and the panel did not attempt to reach consensus on the issues.

Discussion of the case studies was organized into several topic categories. For each case study, this report (Appendix E) provides a brief summary of the case study method, a summary of the most significant panel discussion points, and the final conclusions and recommendations of the Science Panel. Table 1 provides a list of case studies and key conclusions. Additional details on each case study are available at <http://www.allianceforrisk.org/Workshop/CaseStudies/index.htm>.

Table 1. Summary of Case Study Discussions

Group 1: Methods for calculating risk for noncancer effects	
Evaluating Human Dose-Response of Morbidity and Mortality from Hepatic Disease: Are the Predicted Risks from Low-Dose Linear Extrapolation to Environmentally Relevant Concentrations Biologically Plausible? (Ethanol)	Presented by: Becker, R. Coauthor: Hays, S.
The panel supported carrying this method forward. However, the panel considered the case study useful for hypothesis testing of issues raised from NAS (2009), as opposed to being a method recommended for specific problem formulations. Panel members recommended a number of enhancements to the case study. In particular, they recommended that the case study consider MOA in the choice for the extrapolation approach, and address sensitive populations (including genetic variability), as well as improve the consideration of background exposure. It was also recommended to consider linearity in log dose-probit space (i.e., plotting log of dose versus response in probit). It may also be useful to include comparisons of populations with different levels of wine consumption.	
Biologically-Informed Empirical Dose Response Modeling: Using Linked Cause-Effect Functions to Extend the Dose-Response Curve to Lower Doses (Titanium Dioxide - TiO₂)	Presented by: Haber, L. Coauthors: Allen, B.; Maier, A.; Willis, A.
The panel supported carrying this method forward and suggested that it would be useful to also evaluate other chemicals with this method. The panel recommended that the focus should be on	

the MOA, and it would be useful to apply the method to a chemical where extrapolation is needed, so that the approach improves the extrapolation method.	
Use of Biomarkers in the Benchmark Dose Method (Methyl mercury)	Presented by: Gentry, R. Coauthors: Van Landingham, C.; Hays, S.; Aylward, L.
The panel supported carrying this method forward. The panel recommended that the case study address how MOA is used to inform the choice of approach, and expand the approach using biological indices, such as biomonitoring equivalents.	
Estimate Risk Above the RfD Using Uncertainty Factor Distributions (Multiple Chemicals)	Presented by: Spalt, E. Coauthor: Kroner, O. Advisor: Dourson, M.
The panel stated that this case study and methodology would be useful in risk management, but not in risk assessment. That is, the approach is useful to inform comparisons, rather than predicting response percentiles. The method should be clarified to note the difference in utility of application of the distributions for uncertainty factors (UFs) that address uncertainty and those that address variability. The method described in this case study is the least informed of the options for describing UF distributions, and additional data should be incorporated to characterize the distributions. The case study should be explicit regarding how it relates to the recommendations of Chapter 5 of NAS (2009) (i.e., that it addresses the probability that the RfD is correct, rather than calculating a risk specific dose). Panel members also suggested it would be useful to enhance the case study with Jeff Swartout's follow-up work (for which publication is soon planned.)	
Application of Linear Low-Dose Extrapolation from Benchmark Dose for Noncancer Risk Assessment (Multiple chemicals)	Presented by: Kroner, O. Coauthor: Haber L. Advisor: Dourson M.
The panel concluded that this case study and methodology may be useful for screening or priority setting, but should not imply that it accurately predicts risk. This case study highlighted the need for a case study applying the Hattis approach for multiple chemicals. It would be of interest to conduct the analysis in log dose-probit space.	
Use of Categorical Regression – Risk Above the RfD (Copper and “Chemical T”)	Presented by: Haber, L.; Danzeisen, R. Coauthors: Krewski, D.; Chambers, A.; Baker, S.; Hertzberg, R.
The panel supported carrying this method forward. The panel noted that the method is useful for integration of data across a range of studies and dose-responses. The only comment for enhancement was that the final methods compendium should note that different methods could be used to address similar issues (e.g., there are similarities between categorical regression and the linked dose-response functions approach).	
<i>Group 2: Methods Emphasizing Evaluation of Mode of Action</i>	
Use of Human Data in Cancer Risk Assessment of Chemicals as Illustrated by the Case of 1,3-Butadiene	Presented by: Albertini, R.; Sielken Jr., R.L.

<p>The panel supported carrying this method forward. However, the panel recommended comparison of the results with those obtained using default approaches. The panel also recommended that the authors consider what aspects of the case study are generalizable, recognizing that the panel members may need to help in that determination. In the context of a later case study discussion, one panel member also recommended that the authors of this case study consider applying the MOA frameworks and key events identified by Pottenger and Gollapudi (2010) and Swenberg et al. (2008).</p>	
<p>The Quantitative Human Health Risk Assessment for 1,3-Butadiene Based Upon Ovarian Effects in Rodents</p>	<p>Presented by: Kirman, C.R.; Grant, R.L.</p>
<p>The panel supported carrying this method forward. Furthermore, the panel concluded that in this case, the chemical-specific approach was “clearly superior” to the default. The panel recommended that the case study summary include the MOA evaluation table. The panel also recommended that the case study compare the EPA (default) and chemical-specific approaches, including a comparison of the uncertainties at each step of the assessment. It would also be useful to consider making the approach more generalizable, addressing broader considerations of how target cell size could be used to quantify toxicodynamic variability, as discussed under in the supplemental material on the workshop website.</p>	
<p>Group 3: Methods for Acute Exposure Evaluation</p>	
<p>Apply AEGL Methodology to Develop Acute Exposure Guideline Levels for Ethylbenzene</p>	<p>Presented by: Camacho, I.A. Coauthors: Grant, R.; Erraguntla, N.; Hinz, J.</p>
<p>The panel supported carrying this method forward. One panelist particularly appreciated the stakeholder involvement aspect of this method, and noted that the method has been clearly documented in the Standard Operating Procedures. It was recommended that the text be revised to clarify the difference between an RfC and an AEGL.</p>	
<p>Framework for Evaluating Alternative Temporal Patterns of Exposure for Risk Characterization (Benzene and generic)</p>	<p>Presented by: Haber, L.; Haney, J. Coauthors: Maier, A.; Kaden, D.K.; Carrier, R.; Craft, E.; Hertzberg, R. Advisor: Dourson, M.</p>
<p>The panel supported carrying this method forward and recommended that the presenters evaluate additional chemicals. The panel also recommended revising the case study for clarity, and that the case study authors consider overlap with occupational risk assessment approaches.</p>	
<p>Sustainable Futures™ Screening (Isodecyl acrylate)</p>	<p>Presenter: Becker, E. Coauthor: Ranslow, P.</p>
<p>The panel supported carrying this method forward since it has utility for priority-setting but noted that this case study should be defined as a priority-setting method, rather than as a method for estimation of risk. Recommendations for enhancements included (1) adding text about the method with a focus on the basis for the judgment calls related to toxicology; (2) addressing how the weight of evidence determinations are done; (3) explaining sources and resources for data and analog identification; and (4) explaining the source for decisions related to adequacy of margins of exposure.</p>	

Deriving Health-Protective Values for Evaluation of Acute Inhalation Exposures for Chemicals with Limited Toxicity Data Using a Tiered Screening Approach (Pentene)	Presented by: Grant, R.L. Coauthors: Phillips, T.; Ethridge, S.
The panel supported carrying this method forward because it considered this case study to provide a useful method for the stated purpose that is practical, and has the advantages of a tiered approach. A panel member recommended that additional information on the criteria for selection of LC ₅₀ data used in the categorization and screening be included in the case study summary.	
Group 4: Methods for Integrating Complex Data Sets	
Review and Application of Data Fusion Methodologies for Toxicological Dataset Analysis to Resolve Data Quality Issues in Predictive Toxicology and Contaminated Sites Risk Assessment	Presented by: Mohapatra, A.K. Coauthors: Sadiq, R.; Zargar, A.; Islam, S.; Dyck R.
This case study method was described as belonging to the category of exploratory methods. The panel acknowledged that methods to mine data are needed, but requested that the case study better explain the pragmatic application of this approach.	
Group 5: Methods for Safe Dose	
The Impact of Cytochrome P450 2E1-dependent Metabolic Variance on a Risk-relevant Pharmacokinetic Outcome in Humans (Trichloroethylene)	Presented by: Lipscomb, J.C. Coauthors: Teuschler, L.K.; Swartout, J.; Popken, D.; Cox, T.; Kedderis, G.L.
The panel supported carrying this method forward because the case study method integrated <i>in vitro</i> data on enzymatic variability with a physiologically based pharmacokinetic (PBPK) model to estimate variability in tissue dose, and both types of data are becoming more prevalent. The only recommended enhancement was to calculate a chemical specific adjustment factor (CSAF) for illustrative purposes.	
Group 6: Methods for Evaluation of Risk for Cancer Effects	
BBDR Model for Respiratory Tract Carcinogenicity of Inhaled Formaldehyde	Presented by: Haney, J.; Conolly R. Co-authors: Allen, B.; Clewel, H.; Kester J.
The panel supported carrying this method forward because the method was thought to be useful. The panel agreed with the authors that it would be very useful to modify the model to include the role of endogenous formaldehyde. A panel member recommended that a key aspect of the case study is identifying what has been learned in the process of model development. As noted in the Crosscutting Issues section (above), the panel discussion with the presenter identified efficient experimental study design to support model development as one key lesson, and suggested that a generic model may be useful to address several of the issues raised by NAS (2009).	
Multiple Modes of Action and Risk Assessment Modeling (Acrylamide)	Presented by: Hertzberg, R. Co-authors: Dourson, M.; Allen, B.; Vincent, M.; Haber, L.

<p>The panel supported carrying this method forward because it concluded that the case study provides a useful additional tool by illustrating the use of statistically robust modeling approaches that maximize the information utilized for the chemical, while not requiring a data set that is rich enough to develop a BBDR. In particular, one panel member noted that if the shape of the model is determined by high dose points, and overestimates the response at low doses, then the extrapolated risk would be overestimated. This approach is useful in illustrating a way to use the available MOA data for the chemical to inform the description of the response at the lower doses. The panel recommended enhancements to make clear the assumptions underlying the statements of the determinants of the dose-response shape, and to be careful about terminology and distinction of key events and mode of action.</p>	
<p>Assessment of Low-Dose Dose-Response Relationships (Non-linear or Linear) for Genotoxicity, Focused on Induction of Mutations & Clastogenic Effects (Multiple chemicals)</p>	<p>Presented by: Pottenger, L.; Moore, M. Co-authors: Zeiger, E.; Zhou, T.</p>
<p>The panel supported carrying this method forward. Panel members noted that a key contribution of the case study is in articulating a MOA for gene mutation, and in prompting the risk assessment community to think about mutation in the context of key events. The panel recommended that that MOA framework be used to highlight a critical evaluation of the underlying biology, and that formal statistical tests specifically comparing the tumor dose response slope with that of the mutation dose response slope, would enhance the case study. A panel member noted that information on the background incidence of the various measured endpoints could be used to address the issue of additivity to background.</p>	
<p>Application of National Research Council “Silverbook” Methodology for Dose Response Assessment of 2,3,7,8-Tetrachlorodibenzo(p)dioxin</p>	<p>Presented by: Simon, T. Coauthors: Stephens, M.; Yang, Y.; Manning, R.O.; Budinsky, R.A.; Rowlands J.C.</p>
<p>The panel agreed that the case study should move forward, as a useful way to test the conceptual models described in the NAS (2009) report. The authors should clarify the purpose early in the case study.</p>	

5.0 Workshop Participant Comments

At two points in the workshop, workshop participants were invited to comment and discuss issues with panel members. Key themes in these comments were experience from Health Canada’s work in prioritization, issues related to risk communication, and human variability.

Noting the connection between screening/prioritization methods and ongoing efforts to modernize TSCA, a participant suggested that the United States look for a process to learn from Health Canada’s work prioritizing (categorization and screening) its domestic substances list (CSDSL). The participant and panelists agreed that it would be useful to organize a 1-1½ day session where US scientists can learn from what the Canadians did with the CSDSL approach; they suggested it would be useful to include people in EPA and the private sector involved in the EPA’s Sustainable Futures™ program in the discussion.

Several participants noted issues related to communication with the public. One participant noted that it is important to think about approaches for communication to the public as the field moves from default methods to science-based decisions. The participant noted that it can be hard to communicate the reasons for allowing higher exposures based on the improved science. The participant also raised concerns about whether current methods adequately address human variability and about exposures to mixtures, particularly in light of exceedances of guidance or screening levels that occur. The participant noted that it is hard to communicate the health-protectiveness of the general approaches in the context of multiple exceedances. A panelist agreed that risk communication is important, and noted that factors other than science (e.g., economics and technology) may play a role in regulatory value development. In response to a panelist question regarding whether the general public is aware of EPA's mixtures risk assessment guidelines, the participant stated that it is hard to explain such methods to the general public. Part of the public's concern relates to an environmental justice perspective. A panelist noted that technology may drive the approach for addressing multiple chemicals, since treatments will remove multiple chemicals at the same time. Another panelist noted the additional complexity of evaluating risk from exposures to mixtures.

State regulators among the workshop participants also highlighted risk communication issues. One noted that an improved communication approach would be to identify exposures where effects start to occur, rather than the current approach of identifying exposures that are safe. She noted that the State of Texas risk managers look at the basis of the Effects Screening Level (ESL) (e.g., the size of the uncertainty factor, the nature of the critical effect), to determine how concerned one should be about an exceedance of the ESL. Another participant suggested risk assessors could present percentile information to communicate the level of risk, but a state regulator explained that such approaches are difficult to explain in public meetings. It was also noted that communication to risk managers is different from communication with the public.

The discussion also addressed issues related to variability. A panel member noted the need to address uncertainty and variability in acute exposure assessments. A workshop participant cautioned against over-generalizing from one analysis of human variability, noting the need to consider multiple dose metrics; the size of the adjustment depends on the choice of dose metric and dose level. Others referred to the guidance from the International Programme on Chemical Safety (IPCS) that one calculates chemical-specific adjustment factors based on the dose metric that is predictive of the critical effect, considering the key determinants of human variability, and that other potential critical effects need to be considered if the calculated adjustment factor is less than the default.

6.0 Joint Meeting with FSTRAC Scientists

On the third day of the workshop, the rapporteurs provided a summary of workshops 1 and 2 to a joint session of ARA and FSTRAC participants. Afterwards, an opportunity was provided to each attendee to voice his or her opinion on what they considered the important issues related to the workshop, including those associated with the development of the case studies, with the final methods compendium, or other broad issues. Many of the key issues that were brought up over the first two days of the workshop during the case study reviews were repeated, although there were also new perspectives from the attendees of the FSTRAC meeting (who were largely from

State and Federal agencies). There were suggestions on how to improve, test, and evaluate the case studies and the proposed dose-response models. Many individuals stressed the importance of clearly defining technical terms and outlining the variability and uncertainties associated with each case study or model.

In terms of communication, several individuals focused on the need for *ARA* to develop clear communication regarding the case studies and dose-response methods, and emphasized the importance of including multiple stakeholders in the workshop process. They mentioned the connection between science and policy-making, pointing out that states have unique issues, in that they have to balance the development of standards that protect public health with incorporating information from new scientific methods. Several commenters noted that the methods outlined in this workshop will have utility in terms of supporting risk management decisions. Therefore, they consider it important to consider the risk management decisions up front and in the problem formulation step. As summarized below, a variety of suggestions for future directions for risk assessment, as well as general, risk-related subjects, were communicated, some of which were not addressed in the existing case studies, suggesting the need for additional case studies. Suggestions related to the format of the Workshop Report were also received.

Participants also noted that the workshop drew attention to the common ground among the stakeholders in this process, as well as the areas where improvement in the dose-response applications will benefit all stakeholders. It will be important to ensure that the Workshop Methods compendium ties together problem formulation, dose-response assessment technique(s), and risk management outcome.

6.1 List of “Brainstorm” Comments and Issues

The following is a bulleted list of key issues that were identified in the large group brainstorm session: (Note that the issues are presented as described by the participant, without additional comment.)

- How to **improve the case studies**
 - Make sure to note that chemicals may have multiple MOAs/key events; consider not only the primary tumor site, for example, but other, perhaps more minor, effects
 - Test all distributions and choose the best - cannot exclude linear
 - Need an understanding of the biology to see how it informs the decision of how to do the dose-response
 - Endogenous mutagens should be considered, where the chemical or major metabolite is present endogenously
 - Consider the physiological response mechanisms
 - Consider the homeostatic response (perturbation of homeostasis idea from Toxicity Testing in the 21st Century document)
 - Address sensitive populations
 - Apply information on polymorphisms to risk assessment

- How to **test/evaluate the models** proposed in the case studies
 - Get pharmaceutical data (e.g., failed drugs, etc.)
 - Test the case studies with human data
 - Include human biomonitoring data in the evaluation
 - Susceptibility: are there situations where protection of susceptible groups can be tested
 - Compare results of default and biologically-based methods

- **Definitions** are important and should be clear and useful to risk managers. In particular:
 - Linear/non-linear
 - Threshold/non-threshold

- Explicitly address **uncertainty and variability**:
 - What data are needed to consider variability?
 - Be sure to address for acute exposure case studies
 - Address the differences in variability that may exist between high and low doses of the same agent
 - Is the net variability the sum of its parts? Could use trichloroethylene case study as a way to test this idea
 - Address life stage variability, along with exposure duration and timing of exposure during a life stage; would like to see a case study where variability is addressed for life stage, disease state, co-exposure, etc.

- **Risk communication/stakeholder involvement**
 - A communications strategy should be developed to communicate the results of the Workshop to risk managers and the public
 - Importance of multiple stakeholders to address/solve issues; include the public in the process of standard-setting from the beginning
 - Importance of public communication; hard to explain these ideas to the public
 - Bring risk management up front
 - Consider what information a risk manager needs
 - Successful problem formulation helps by focusing on potential risk management options and on key questions
 - Consider problem formulation in terms of supporting a risk management decision
 - Connection between scientists and rule-making; states have to balance the need to have standards that protect public health with incorporating information from new methods; states need practical products and methods

- Suggestions for **future directions**
 - A meeting to reconcile the two NRC documents - *Toxicity Testing in the 21st Century* and *Science and Decisions*
 - Guidelines for multiple exposure durations
 - Guidelines for ecological/aquatic environments

- Guidelines for essential elements, as one can't apply uncertainty factors in the traditional approach, because one ends up in the range of doses associated with deficiency
 - Exposure assessment:
 - Need appropriate exposure estimation tools
 - Better exposure modeling and exposure science - need to work into framework
 - Interest in intermittent exposures
 - How do the new technologies improve our understanding of low-dose issues, mixtures, etc.
 - Guidance on how to include data on exposure markers
 - Guidance on how to use *in vitro* data
 - Need to prioritize these efforts
 - Lack of consensus on the use of these data
 - Need to encourage use of probabilistic risk assessment in daily risk practice; would be useful to have training in probabilistic risk assessment
 - Identification of risk determinants and population health status (baseline)
- **General**
 - Integration of data across subjects and disciplines, including clinical toxicology, biology, and epidemiology
 - Need to decide on acceptable risk and appropriate level of confidence; noted that in some cases, these levels are set by law
 - Need to consider personal lifestyle choices
 - Need for validation of acute/emergency exposure standards
 - Need to direct resources to biggest risk reductions
 - Ideas for the **Workshop Report**
 - Present at a technical level with references to other tools that are available
 - Try to tie case studies to decision points in the framework
 - Be aware of different perspectives and needs; continue dialogue so the guidance is user-friendly
 - Consider having a short public communication summary up-front for each case study (elucidate how this case study improves risk assessment)
 - Clarify how/why specific chemicals were selected for each case study

7.0 Next steps

Several additional potential case studies were suggested by panel members and/or workshop participants, either prior to the workshop, or during the workshop. In considering what additional case study methods are needed, the panel suggested that it would be useful to have a framework showing where the existing case study methods fit within the risk assessment paradigm, so that gaps can be identified. Workshop participants were invited to participate in developing that framework. The draft framework will be provided to the Science Panel for comment and revision, and the Science Panel will then use the framework to prioritize additional case studies for the next workshop and for inclusion in the methods compendium. The potential

new case studies and significant case study modifications are listed in Appendix F. The panel also discussed approaches to work towards the methods compendium.

8.0 Conclusions

Over the course of the 3-day workshop, the panel reviewed 18 case studies. One case study was identified as not being very helpful, several needed minor revision, and the panel recommended more significant revisions to a larger number of case studies. Workshop participants provided a number of suggestions for improving case studies and for enhancing the final methods compendium.

9.0 References

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