



## **Beyond Science and Decisions: From Problem Formulation to Dose-Response Report from Workshop IV - Appendices**

**Workshop Held:**

May 22-24, 2012

Austin, Texas

At the Texas Commission on Environmental Quality

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August 6, 2012

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## **Appendix 1. Biographies for Standing Panel Members and *Ad Hoc* Panel Member**

### ***Science Panel***

#### **Richard Beauchamp, Texas Department of State Health Services**

Richard A. Beauchamp is the Senior Medical Toxicologist for the Texas Department of State Health Services (DSHS) with responsibility for providing advanced toxicological and risk assessment support for the Exposure Assessment, Surveillance, and Toxicology (EAST) Group. As cooperative agreement partners with the Agency for Toxic Substances and Disease Registry (ATSDR), Dr. Beauchamp and other EAST Group members are tasked with conducting Public Health Assessments at abandoned hazardous waste sites that are proposed and added to the Environmental Protection Agency's (EPA's) National Priority List (NPL) of Superfund sites in Texas. Dr. Beauchamp is also involved with conducting other medical and toxicological Public Health Consultations involving exposures to environmental hazardous substances.

After earning his medical degree at the University of Texas Health Science Center at San Antonio (1973-1977), Dr. Beauchamp completed a three year pediatric residency with the Austin Pediatric Education Program at Brackenridge Hospital in Austin, Texas (1977-1980) and began working at the Texas Department of Health as a Public Health Physician Epidemiologist (1980). Early in his career at the health department, he was tasked with developing risk assessment expertise that would be essential for the newly-formed Environmental Epidemiology Program in the evaluation of environmental and chemical exposures. With an undergraduate degree in Electrical Engineering (U.T. Austin) and a strong background in mathematics and computer sciences, Dr. Beauchamp has applied the knowledge gained through participation at numerous risk assessment conferences, symposia, and seminars (sponsored by EPA, NGA, CDC, ASTHO, NIOSH, and others) to the development of his so-called "Risk Assessment Toolkit." Dr. Beauchamp's toolkit consists of a series of Excel® spreadsheets designed for the flexible and rapid evaluation of cancer and non-cancer risks resulting from exposures to a wide variety of environmental contaminants through all of the common exposure pathways. Risks are calculated incrementally using age-specific exposure parameters, including body weights, body surface areas, respiratory daily volumes, and EPA's early-life exposure factors. Risks are integrated over the exposure duration, using up to 46 different age intervals, to insure that childhood exposures are appropriately addressed.

#### **James S. Bus, The Dow Chemical Company**

James S. Bus is the Director of External Technology, Toxicology and Environmental Research and Consulting at The Dow Chemical Company (1989-present). He previously held positions as Associate Director of Toxicology and Director of Drug Metabolism at The Upjohn Company (1986-1989), Senior Scientist at the Chemical Industry Institute of Toxicology (CIIT, 1977-1986), and Assistant Professor of Toxicology, University of Cincinnati (1975-1977). Dr. Bus currently participates in several external institutions including the Board of Directors of The Hamner Institutes (formerly CIIT) and the National Academy of Sciences/National Research Council Board on Environmental Studies and Toxicology (BEST). He has also served as Chair of the American Chemistry Council and International Council of Chemical Associations Long-Range Research Initiatives; the USEPA Chartered Science Advisory Board (2003-2009); and the FDA National Center for Toxicological Research Science Advisory Board (2004-2010). He serves as an Associate Editor of *Toxicology and Applied Pharmacology*, and on the Editorial

Boards of *Environmental Health Perspectives* and *Dose Response*. Dr. Bus is a member of the Society of Toxicology (serving as President in 1996-97), the American Society for Pharmacology and Experimental Therapeutics, the American Conference of Governmental and Industrial Hygienists, and the Teratology Society. He is a Diplomate and Past-President of the American Board of Toxicology and a Fellow of the Academy of Toxicological Sciences (member of Board of Directors, 2008-present; Vice-President and President-Elect, 2010). Dr. Bus received the Society of Toxicology Achievement Award (1987) for outstanding contributions to the science of toxicology; the Society of Toxicology Founders Award (2010) for leadership fostering the role of toxicology in improving safety decisions; Rutgers University Robert A. Scala Award (1999) for exceptional work as a toxicologist in an industry laboratory; and the K.E. Moore Outstanding Alumnus Award (Michigan State University, Dept. Pharmacol. And Toxicol.). He received his B.S. in Medicinal Chemistry from the University of Michigan (1971) and Ph.D in pharmacology from Michigan State University (1975) and currently is an Adjunct Professor in the Dept. Pharmacology and Toxicology at that institution. His research interests include mechanisms of oxidant toxicity, defense mechanisms to chemical toxicity, relationship of pharmacokinetics to expression of chemical toxicity, and general pesticide and industrial chemical toxicology. He has authored/co-authored over 100 publications, books, and scientific reviews.

**Rory Conolly, U.S EPA National Health and Environmental Effects Research Laboratory**

Rory Conolly is a Senior Research Biologist in the Integrated Systems Toxicology Division of the U.S EPA's National Health and Environmental Effects Research Laboratory in Research Triangle Park, North Carolina, USA. His major research interests are (1) biological mechanisms of dose-response and time-course behaviors, (2) the use of computational modeling to study these mechanisms and, (3) the application of computational models to quantitative dose-response assessment. Dr. Conolly received the U.S. Society of Toxicology's (SOT) Lehman Award for lifetime achievement in risk assessment in 2005. He was a member of the National Academy of Sciences Board on Environmental Studies and Toxicology from 2004 until joining the EPA in 2005, President of the SOT Biological Modeling Specialty Section (2000 – 2001), President of the SOT Risk Assessment Specialty Section (1997 - 1998), a member of the SOT Risk Assessment Task Force (1998 - 2000) and is currently a Councilor with the Risk Assessment Specialty Section. He is Adjunct Professor of Biomathematics at North Carolina State University, Faculty Affiliate, Department of Environmental and Radiological Health Sciences, Colorado State University and has four times received awards from the SOT Risk Assessment Specialty Section (1991, 1999, 2003, 2004). Dr. Conolly was born in London, England and raised in Canada and the United States. He received a bachelor's degree in biology from Harvard College in 1972, a doctorate in physiology/toxicology from the Harvard School of Public Health in 1978, and spent a post-doctoral year at the Central Toxicology Laboratory of Imperial Chemical Industries, PLC, in Cheshire, England. He was a member of the Toxicology Faculty at The University of Michigan School of Public Health from 1979 through 1986, and worked with the U.S. Air Force Toxic Hazards Research Division, Wright-Patterson Air Force Base, Ohio from 1986 until 1989. In 1989 Dr. Conolly joined the Chemical Industry Institute of Toxicology (CIIT) and worked there until 2005, when he joined the U.S. EPA.

### **Mike Dourson, Toxicology Excellence for Risk Assessment**

Mike Dourson is the President of Toxicology Excellence for Risk Assessment (TERA), a nonprofit corporation dedicated to the best use of toxicity data in risk assessment. Before founding TERA in 1995, Dr. Dourson held leadership roles in the U.S. Environmental Protection Agency as chair of US EPA's Reference Dose (RfD) Work Group, charter member of the US EPA's Risk Assessment Forum and chief of the group that helped create the Integrated Risk Information System (IRIS). Dr. Dourson received his Ph.D. in Toxicology from the University of Cincinnati. He is a Diplomate of the American Board of Toxicology and a Fellow of the Academy of Toxicological Sciences. Dr. Dourson has served on or chaired numerous expert panels, including peer review panels for US EPA IRIS assessments, US EPA's Risk Assessment Forum, TERA's International Toxicity Estimates for Risk (*ITER*) independent peer reviews and consultations, FDA's Science Board Subcommittee on Toxicology, the NSF International's Health Advisory Board, and SOT's harmonization of cancer and non-cancer risk assessment. He served as Secretary for the Society for Risk Analysis (SRA) and has held leadership roles in specialty sections of SRA and SOT. He is currently on the editorial board of three journals. Dr. Dourson has published more than 100 papers on risk assessment methods, has co-authored over 100 government risk assessment documents, and has made over 100 invited presentations.

### **R. Jeffrey Lewis, ExxonMobil Biomedical Sciences, Inc.**

R. Jeffrey Lewis is a Senior Scientific Associate with ExxonMobil Biomedical Sciences, Inc. In this position, Dr. Lewis is responsible for providing support to ExxonMobil's epidemiology and health risk assessment scientific programs. He currently manages company scientific programs related to children's health, emerging environmental health issues, legislative/regulatory affairs and regulatory impact analysis (e.g., benefit-cost analysis). He has served on a number of industry trade association scientific committees, external science advisory boards (e.g., Peer Consultation panel for EPA's Voluntary Children's Chemical Evaluation Program), and is a member of ExxonMobil's Occupational Exposure Limits committee. Dr. Lewis also has an adjunct faculty appointment at the University of Texas School of Public Health and is currently Treasurer Elect of the Society for Risk Analysis. Dr. Lewis received his Bachelors of Science degree in biology from the University of Kansas in 1985 and a M.S. and Ph.D. in Epidemiology from the University of Texas, School of Public Health in 1987 and 1990, respectively. In addition, he earned a Masters in Business Administration from Rutgers University in 1997.

### **Bette Meek, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa**

Bette Meek has a background in toxicology receiving her M.Sc. in Toxicology (with distinction) from the University of Surrey, U.K. and her Ph.D. in risk assessment from the University of Utrecht, the Netherlands. She is currently the Associate Director of Chemical Risk Assessment at the McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, completing an interchange assignment from Health Canada. She has extensive experience in the management of chemical assessment programs within the Government of Canada, most recently involving development and implementation of process and methodology for the health assessment of Existing Substances under the Canadian Environmental Protection Act (CEPA) and previously, programs for contaminants in drinking water and air.

With colleagues within Canada and internationally, she has contributed to or led initiatives to increase transparency, defensibility and efficiency in health risk assessment, having convened

and participated in initiatives in this area for numerous organizations including the International Programme on Chemical Safety, the World Health Organization, the International Life Sciences Institute, the U.S. Environmental Protection Agency, the U.S. National Academy of Sciences and the U.S. National Institute for Environmental Health Sciences. Relevant areas have included frameworks for weight of evidence analysis including mode of action, chemical specific adjustment factors, physiologically-based pharmacokinetic modeling, combined exposures and predictive modeling. She has also authored over 175 publications in the area of chemical risk assessment and received several awards for contribution in this domain.

### **Greg Paoli, Risk Sciences International**

Greg Paoli serves as Principal Risk Scientist and COO at Risk Sciences International, a consulting firm specializing in risk assessment, management and communication in the field of public health, safety and risk-based decision-support. Mr. Paoli has experience in diverse risk domains including toxicological, microbiological, and nutritional hazards, air and water quality, climate change impacts, medical and engineering devices, as well as emergency planning and response for natural and man-made disasters. He specializes in probabilistic risk assessment methods, the development of risk-based decision-support tools and comparative risk assessment. Mr. Paoli has served on a number of expert committees devoted to the risk sciences. He was a member of the U.S. National Research Council committee that issued the 2009 report, *Science and Decisions: Advancing Risk Assessment*. He serves on the Canadian Standards Association Technical Committee on Risk Management, advisory committees of the National Roundtable on the Environment and the Economy, a US NRC Standing Committee on the Use of Public Health Data at the U.S. Food Safety and Inspection Service, and has served on several expert committees convened by the World Health Organization. Mr. Paoli completed a term as Councilor of the Society for Risk Analysis (SRA) and is a member of the Editorial Board of *Risk Analysis*. Recently, Mr. Paoli was awarded the Sigma Xi – SRA Distinguished Lecturer Award. He has provided training in risk assessment methods around the world, including the continuing education programs of the Harvard School of Public Health and the University of Maryland. Greg holds a Bachelors Degree in Electrical and Computer Engineering and a Master's Degree in Systems Design Engineering from the University of Waterloo.

### **Rita Schoeny, U.S. EPA Office of Water**

Rita Schoeny is Senior Science Advisor for the U.S. Environmental Protection Agency's Office of Water. She received her B.S. in biology at the University of Dayton and a Ph.D. in microbiology from the School of Medicine of the University of Cincinnati. After completing a postdoctoral fellowship at the Kettering Laboratory, Department of Environmental Health, she was appointed Assistant Professor in that department of the U.C. Medical School. Dr. Schoeny has held several adjunct appointments and regularly lectures at colleges and universities on risk assessment. She has given lectures and courses on risk assessment in many areas of the world. Dr. Schoeny joined the U.S. EPA in 1986. Prior to her current position she was Associate Director of the Health and Ecological Criteria Division of the Office of Science and Technology, Office of Water. She has been responsible for major assessments and programs in support of the Safe Drinking Water Act, including scientific support for rules on disinfectant by-products, arsenic, microbial contaminants and the first set of regulatory determinations from the Contaminant Candidate List. She has held various positions in the Office of Research and Development including Chief of the Methods Evaluation and Development Staff, Environmental

Criteria and Assessment Office, Cincinnati; Associate Director NCEA-Cin; and chair of the Agency-wide workgroup to review cancer risk assessments. Dr. Schoeny has published in the areas of metabolism and mutagenicity of PCBs and polycyclic aromatic hydrocarbons; assessment of complex environmental mixtures; health and ecological effects of mercury; drinking water contaminants; and principles and practice of human health risk assessment. She was a lead and coauthor of the *Mercury Study Report to Congress* and was a principal scientist and manager for Ambient Water Quality Criterion for Methylmercury. She has been the chair of an EPA working group on use of genetic toxicity data in determining mode of action for carcinogens. She participates in many EPA scientific councils as well as national and international scientific advisory and review groups. Current involvement includes panels on interpretation of DNA adduct data for risk assessment and evaluation of episodic and less-than-lifetime exposure to carcinogens. Dr. Schoeny is the recipient of several awards including several U.S. EPA Gold, Silver and Bronze Medals; EPA's Science Achievement Award for Health Sciences; the Greater Cincinnati Area Federal Employee of the Year Award; the University of Cincinnati Distinguished Alumnae Award; Staff Choice Award for Management Excellence; and the FDA Teamwork Award for publication of national advice on mercury-contaminated fish.

#### **Alan Stern, New Jersey Department of Environmental Protection**

Dr. Alan H. Stern is the Section Chief for Risk Assessment in the Office of Science of the New Jersey Department of Environmental Protection; Adjunct Associate Professor in the Department of Environmental and Occupational Health of the University of Medicine and Dentistry of New Jersey-School of Public Health. He received a bachelor's degree in biology from the State University of New York at Stony Brook (1975), a master's degree in cellular and molecular biology from Brandeis University (1978), a master of public health degree (1981) and a doctorate in public health from the Columbia University School of Public Health (1987). Dr. Stern is board-certified in toxicology by the American Board of Toxicology (Diplomate of the American Board of Toxicology). Dr. Stern's areas of expertise include risk assessment and exposure assessment including the application of probabilistic techniques to quantitative estimation of exposure and risk. His research interests have focused on heavy metals including lead, mercury, chromium and cadmium. Dr. Stern was a member of the National Research Council/National Academy of Sciences Committee on the Toxicology of Methylmercury (1999-2000) and a member of the recent USEPA Science Advisory Board panel for the National-Scale Mercury Risk Assessment for Coal- and Oil-Fired Electrical Generating Units (June-July 2011) as well as the USEPA Science Advisory Board Panel for Peer Review of the All-Ages Lead Model (Oct. 27-28, 2005). He has also served on numerous USEPA-IRIS review panels including Toxicological Review of Urea (Dec. 13, 2010, Panel Chair), Toxicological Review of Trichloroacetic Acid (Dec. 10, 2009, Panel Chair), Toxicological Review of 2-Hexanone (May 22, 2008, Panel Chair), Toxicological Review of Toluene (Feb. 5, 2004, Panel Chair). Other panels, committees and workshops include, ATSDR Toxicological Profile Review of Revised Minimal Risk Levels (MRLs) for 1,4-Dioxane (March-April, 2010), ATSDR Toxicological Profile Review of Revised Inhalation MRL for 1,4-dioxane (Sept. 2011), USEPA Panel for the Review of Draft Exposure Factors Handbook (March 3-4, 2010), USEPA Workshop on Cardiovascular Toxicity of Methylmercury (Jan. 12-13, 2010), USEPA Panel for Review of —Draft Child-Specific Exposure Factors Handbook (Sept. 19-20, 2007). Dr. Stern has authored numerous articles in peer-reviewed journals, and contributed a book chapter on Exposure

Assessment for Neurotoxic Metals in —Human Developmental Neurotoxicology - D. Bellinger, ed. (Taylor & Francis, New York, 2006.), and the article on *Environmental Health Risk Assessment* in the *Encyclopedia of Quantitative Risk Assessment and Analysis*. John Wiley and Sons Ltd., 2008.

***Ad hoc Panelist***

**Lorenz Rhomberg, Gradient**

Lorenz R. Rhomberg Ph.D. FATS is a Principal at Gradient, a Cambridge, Massachusetts (USA), environmental consulting firm, where he specializes in critical review of toxicological information, human health risk assessment, and science policy issues for environmental and consumer chemical exposures. Before joining Gradient, Dr. Rhomberg was on the faculty of the Harvard School of Public Health. From 1984-1994, he was a risk assessor at the U.S. Environmental Protection Agency in Washington. Dr. Rhomberg earned his Ph.D. in population biology from the State University of New York at Stony Brook and an Honours B.Sc. in biology from Queen's University in Ontario. His interests lie in methodology and science policy for quantitative risk analysis, including dose-response modeling, pharmacokinetic modeling and probabilistic methods, with special emphasis on cross-species extrapolation, chlorinated solvents and endocrine active agents. Dr. Rhomberg has served on several US National Academy of Sciences committees, and numerous review and advisory panels sponsored by government, trade associations, and professional societies. He is the author/editor of several books and more than 60 articles on risk analysis topics. He is a member of several scientific societies, including the Society of Toxicology and the Society for Risk Analysis, for which he is a past Councilor and a Past-President of the New England Chapter. He is a Fellow of the Academy of Toxicological Sciences and was awarded the Outstanding Practitioner of the year award in 2009 by the Society for Risk Analysis.



## Appendix 2. Meeting Agenda

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### Agenda

**Date:** May 22, 23 & 24, 2012

**Location:** Texas Commission on Environmental Quality, Austin, Texas

**Purpose:** To advance the recommendations of NAS (2009) and subsequent framework of ARA (2012) on problem formulation and dose-response analysis, through review of illustrative case studies for further development of methods

\*\*All times are Central Standard Time.

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### Tuesday May 22nd

Welcome (1:00 to 1:15)

- **Roberta Grant, Texas Commission on Environmental Quality**

Introductions and Updates (1:15 to 2:00)

- **Members of the Advisory Committee and Science Panel**

Keynote Talk: Incorporating New Technologies into Toxicity Testing and Risk Assessment: Moving from 21st Century Vision to a Data-Driven Framework (2:00 to 3:00)

- **Rusty Thomas, The Hamner Institutes for Health Sciences**

Afternoon Break (3:00 to 3:30)

Presentation of Beyond Science and Decisions Dose Response Assessment Framework and Discussion (3:30 to 4:15)

- **Lynne Haber, Toxicology Excellence for Risk Assessment**

EPA's Response to NRC Framework Recommendation: Framework for Human Health Risk Assessment to Inform Decision Making (4:15 to 5:00)

- **Rita Schoeny, U.S. Environmental Protection Agency**

Observer Comments (5:00 to 5:30)

Reception (dinner portion hors d'oeuvres, 6:30 to 9:00)

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**Wednesday, May 23<sup>rd</sup>**

Case Study: Criteria Requirements for Data-Driven Carcinogenicity Mode of Action (MOA) Determinations as Exemplified by Chloroform (8:00 to 10:00)

- **Chris Borgert, Applied Pharmacology Toxicology Inc.**

Morning Break (10:00 to 10:30)

Case Study: Methods for Deriving Inhalation Effect Levels for Comparison to Health-Protective Values (10:30 to 11:30)

- **Roberta Grant, Texas Commission on Environmental Quality**

Lunch (11:30 to 12:30)

Updates (12:30 to 2:00)

- **William Gulledge, American Chemistry Council.** Update: EO Mode of Action (MOA)
- **Jimmy Perkins, University of Texas Health Science Center.** Update: The Occupational Alliance for Risk Science (OARS)
- **Lorenz Rhomberg, Gradient.** Update: Naphthalene Mode of Action (MOA)
- **Tiffany Bredfeldt, Texas Commission on Environmental Quality.** Update: Structure Activity Relationships Applied to Short Term Exposures

Afternoon Break (2:00 to 2:30)

Case Study Proposal: Value of Information (2:30-3:30)

- **Eric Ruder, IEC**

Case Study: A Tiered Framework for Interpreting Human Biomonitoring Results (3:30 to 5:00)

- **Rick Becker, American Chemistry Council**

Observer Comments (5:00 to 5:30)

Dinner on your own

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**Thursday, May 24<sup>th</sup>**

Combined Exposures Framework and Discussion (8:30 to 9:30)

- **Bette Meek, University of Ottawa**

Case Study: The Human Relevant Potency Threshold: Reducing Uncertainty by Human Calibration of Cumulative Risk Assessments (9:30 to 11:30)

- **Chris Borgert, Applied Pharmacology Toxicology Inc.**

Morning Break (10:30 to 11:00)

Observer Comments and Closing remarks (11:30)

Adjourn

### Appendix 3. List of Workshop Participants

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## Appendix 4. Panel Discussion Questions

### Workshop Goal

The workshop purpose is to advance the recommendations of the NAS (2009) and subsequent framework of ARA (2012) on problem formulation and dose-response analysis, through review of illustrative case studies for further development of methods.

### General Workshop Series Objectives:

- Additionally develop the content of the NAS (2009) report on improving the risk assessment process to develop a compendium of practical, problem-driven approaches for “fit for purpose” risk assessments, linking methods with specific problem formulations (e.g., prioritization, screening, and in-depth assessment) for use by risk managers at a variety of levels (e.g., states, regional managers, people in a variety of agencies, and in the private sector).
- Implement a multi-stakeholder approach to share information, ideas and techniques in support of developing practical problem-driven risk assessment methods compendium.

### Specific Workshop Objectives:

- Identify useful dose-response techniques for specific issues, including consideration of relevant data, characterization of assumptions, strengths and limitations, and how the techniques address key considerations in the dose-response.
- These techniques should appropriately reflect the relevant biology (including the biology of thresholds), and mode of action information, at a level of detail appropriate for the identified issue.
- Provide methods to explicitly address human variability in cancer assessment, and enhance the consideration of human variability in noncancer assessment, including explicit consideration of underlying disease processes, as appropriate for the relevant risk assessment context.
- Identify methods for calculating the probability of response for noncancer endpoints, as appropriate for the relevant risk assessment context.
- Develop a risk methods compendium that will serve as a resource for regulators and scientists on key considerations for applying selected dose-response techniques for various problem formulations, with suggested techniques and resources.

### Panel Role:

The Panel provides input on case study methods being proposed to enhance the risk framework. Panel members provide input on the utility of the case study methods to address specific problem formulations, and identify areas for additional development of the case study and/or method. Inclusion of a method or case study in the framework as an illustration of a technique does not imply panel acceptance of the chemical-specific outcome.

## **Discussion Questions - Framework Presentation**

1. The ultimate goal is for the framework to be self-explanatory, and useful to the risk assessment community as a “one-stop shop” for risk assessment methods and issues, providing links to guidance and examples of how methods are applied.
  - a. What changes to the framework (changes in structure, additional information provided, etc.) can help the framework to fulfill this goal?
  
2. The framework currently includes links to the authors’ work for the case studies – case study summary and full case study (revised version, if revised in response to panel comments), and the presentations made at the panel meetings. (Some presentations include useful information not in the case study.) Documentation of the recommendations from the panel is included in the meeting reports, and documentation of changes made after the second workshop were provided with the workshop 3 packet (see Attachment #1 for a sample), but such documentation is not currently directly linked to the framework.
  - a. Should the framework more overtly reflect the panel recommendations? If so, how? One idea is to collate the comments for each case study, author response, and any panel re-review comments (see Attachment #2), but this is a rather labor-intensive approach, both in developing the files for each case study and in separate links for each case study. Another approach would be to simply link to the relevant file of panel recommendations from the meeting (or the meeting report) – e.g., as in Attachment #3.
  
3. See Attachment #4 for recommendations regarding guidances and key publications to be linked to the framework and where the link would go.
  - a. Please comment on the appropriateness of linking to these materials and other guidances and key publications to link to.

## **Generic Case Study Review Discussion Questions**

While the panel may not address each of these points explicitly in discussing the case study methods, the following are questions to consider in conducting the review of the case studies:

1. Is this case study a useful addition to the framework?
2. What specific things could be changed to make the method more useful?
3. What are the broader generalizations from this method, and specific lessons?
4. What are key uncertainties and research needs related to the case study that are critical to address in a methodological context?

## **Case Study-Specific Discussion Questions**

See additional discussion questions submitted by the authors of the effect level case study.

## **Attachment 1 - Changes Made to Case Studies After Workshop #2 (partial list; full list was provided for workshop #3)**

**Categorical regression** – No changes were made. The only recommendation for enhancement by the panel 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). This comment refers to the methods compendium, not changes in the individual case study.

**Use of human data in cancer risk assessment (1,3-butadiene)**<sup>1</sup> – No changes were made. The changes recommended by the panel at the October meeting will be noted in the final report.

**Consideration of human kinetic variability (trichloroethylene)** - No changes were made. The changes recommended by the panel at the October meeting will be noted in the final report.

**Biologically-Informed Empirical Dose Response: Using Linked Cause-Effect Functions (TiO<sub>2</sub>)** – No significant changes were made. The panel asked for a comparison with epidemiology data; this is noted at the beginning of the response to question 2 of the summary. Application of the method to other chemicals would be useful, but funding is needed for such projects.

**AEGL methodology** - The panel recommended to clarify the difference between an RfC and an AEGL. Because the method is for acute exposures, differences between AEGLs and acute RfC (not chronic) were briefly discussed.

**UF Distributions** - Text was added to the introduction: "This method is intended for use in risk management rather than as a risk assessment tool. It was developed to address a recommendation provided in Chapter 5 of the Silver Book to develop a way to estimate the probability that an RfD is correct." And a sentence was added to question 4: "Specifically, with the uncertainty factors for subchronic to chronic, and LOAEL to NOAEL, this method is likely to have greater limitations in that those are highly dependent on the study design (i.e., dose spacing)." The new work by Jeff Swartout is still under development, and so was not added.

**Multiple Components to Mode of Action and Risk Assessment Modeling (Acrylamide)** – The text about assumptions regarding determinants of the dose-response shape was clarified, and the term "multiple modes of action" was modified to multiple components to the mode of action.

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<sup>1</sup> Chemical in parentheses is the chemical used in the case study, if applicable

## Attachment 2 – Sample Compiled Comments and Response on a Case Study

<b>Assessment of Low-Dose Dose-Response Relationships (Non-linear or Linear) for Genotoxicity, Focused on Induction of Mutations &amp; Clastogenic Effects (Multiple chemicals)</b>	<b>Presented by: Pottenger, L.; Moore, M. Co-authors: Zeiger, E.; Zhou, T.</b>
<p>Workshop 2 panel comments: 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>Author changes: The changes made to the full case study are highlighted in yellow. When sections are new or substantially revised, the header is highlighted in the table of contents and the text. Smaller changes in the text are highlighted in the text itself. The primary change was the addition of a preliminary analysis of the MOA for mutation conducted for MMS/MNU and EMS/ENU, based on review of selected publications and the MOA for mutation of Pottenger and Gollapudi (2010) (see pp 11-13 in Main case study document and Appendix E).</p>	
<p>Workshop 3 panel comments: In Workshop 2, the panel recommended that the authors enhance the study by conducting a MOA analysis for mutation and by conducting formal statistical tests specifically comparing the tumor dose-response slope with that of the mutation dose-response slope. In the MOA analysis, focusing on recent data, the authors found supporting data for some key events, but there was a lack of data for other events. A panel member suggested that in the future, it would be important to match the low-dose response for mutations with the dose-response assessment for tumors. However, the authors noted that there might not be enough low-dose data, and the panel agreed that this is an important point to stress in the case study write-up. Panel members noted it is important to be clear about where data exist and where they do not; a qualitative VOI analysis could be conducted related to the data gaps. The panel encouraged the study authors to think about identifying the critical data gaps and identifying what is driving the process. A panel member suggested that the authors think mechanistically about whether a hockey stick dose-response shape is due to a fundamental biological nonlinearity or due to background noise.</p>	

### Attachment 3 – Sample Summary of Workshop 3 Case Study Discussions

<i>New Case Studies</i>	
<b>Lead-Dose-Response Relationship for Effect on Children’s IQ</b>	<b>Presented by: Carrington C.</b>
<p>The panel supported carrying this method forward. The panel recommended that the case study be modified to identify the problem formulation, specifically how the analysis helps to support a decision. The panel also recognized that a key limitation to the assessment was that only pooled data were available to the case study author, and that it would be useful if the epidemiology community would make the raw data available for additional analyses. The panel recommended that the author add text regarding what types of additional research could be done with the raw data.</p>	
<b>Quantitative Assessment of Sensitivity and Variability in Humans: Modeling the Effects of Low Dose Exposure to Dietary Residues of Chlorpyrifos</b>	<b>Presented by Juberg, D.R.; Price, P.</b>
<p>The panel supported carrying this method forward as an illustration of how data can be used to derive chemical-specific adjustment factors (CSAFs). The panel recommended that the case study emphasize that <i>in vitro</i> information on kinetic variability cannot be used directly to calculate CSAFs; one needs to use those data to calculate the impact on tissue <i>dose</i>. Potential enhancements noted would be to address cumulative risk, using such resources as market basket surveys or data on biomonitoring. The panel suggested that the authors link more of the discussion to the NAS report and explain how the key case study conclusions address issues raised in the NAS report. For example, the case study addresses the concerns raised in Chapters 4 or 5 of the NAS report about the adequacy of a factor of 10 for the intraspecies uncertainty factor. The case study also challenges the idea that a background response for the apical effect would linearize the dose-response. An important result was the finding that the dietary exposure is expected to have a very small impact on a precursor key event (cholinesterase in the blood), indicating an even smaller effect on an apical response. The panel also noted that it would be useful to include in the case study information on the status and nature of the related EPA review.</p>	

## **Attachment 4 – Proposed Additions to the Framework**

### **Qualitative Decision- Integration**

EPA's sustainable futures program - <http://www.epa.gov/oppt/sf/>  
(new link with the current case study)

Health Canada Categorization of Substances on the Domestic Substances List  
<http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/categor/index-eng.php>  
(new box)

Classification systems (new box)

A Guide to The Globally Harmonized System of Classification and Labelling of Chemicals (GHS). United Nations. 2011. Available at <http://www.osha.gov/dsg/hazcom/ghs.html>

### **Quantitative Screening**

Threshold of Toxic Concern – new bullet with references:

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of Toxic Hazard – A Decision Tree Approach. *Food Cosmet. Toxicol.* 16, 255-276. Kroes, R., Kleiner, J., Renwick, A., Cheeseman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., Schilter, B., Schlatter, J., van Schothorst, F., Vos, J.G., Wurtzen, G., 2004. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. *Food Cosmet. Toxicol.* 42, 65–83.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J. 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. *Food and Chemical Toxicol.* 45, 2533-2562.

Munro, I.C., Ford, R.A., Kennepohl, E., Sprenger, J.G., 1996. Correlation of structural class with No-Observed-Effect Levels: A proposal for establishing a threshold of concern. *Food and Chemical Toxicol.* 34: 829-867.

Munro, I.C., Renwick, A.G., Danielewska-Nikiel, B., 2008. The Threshold of Toxicological Concern (TTC) in risk assessment. *Toxicol. Lett.* 180, 151-156.

Threshold of Regulation - new bullet with references:

FDA (Food and Drug Administration) (2000, revised 2007). Toxicological principles for the safety assessment of food ingredients: Redbook. FDA CFSAN.  
<http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/Redbook/default.htm>

Cheeseman, MA, EJ Machuga, AB Bailey. 1999. [A tiered approach to threshold of regulation.](#) Food Chem Toxicol. 1999 Apr;37(4):387-412.

Screening-level safe dose (these methods would be repeated under dose-response methods for the in-depth tab)

U.S. EPA (United States Environmental Protection Agency) (2002). A review of the reference dose and reference concentration processes. EPA/630/P-02/002F, December 2002. At <http://www.epa.gov/iris/backgrd.html>

IPCS (International Programme on Chemical Safety) (1999) Principles for the assessment of risks to human health from exposure to chemicals. Environmental Health Criteria 210.

Meek, M; Newhook, R; Liteplo, R; et al. (1994). Approach to assessment of risk to human health for priority substances under the Canadian environmental protection act. Environ Carcino & Ecotox Revs C12:105-134.

HC (Health Canada) (1996). Health-based tolerable daily intakes/ concentrations and tumorigenic doses/ concentrations for priority substances; Health Canada, H46-2/96-194E.

#### Quantitative SAR

Multiple guidances and toolbox from OECD available at [http://www.oecd.org/document/2/0,3746,en\\_2649\\_34379\\_42926338\\_1\\_1\\_1\\_1,00.html](http://www.oecd.org/document/2/0,3746,en_2649_34379_42926338_1_1_1_1,00.html)

Remove CBEL and PPRTVs (these were initial placeholders and can be added if we get case studies, but they don't represent novel methods not addressed elsewhere on this tab)

### **In depth**

#### *Endpoint assessment*

##### Test guidelines (new box)

OECD (2007). Test guidelines. <http://www.oecdbookshop.org/oecd/index.asp?lang=EN> (must search by specific guideline number)

U.S. EPA (United States Environmental Protection Agency) (2007) OCSPP Harmonized test guidelines. U.S.EPA. Washington, D.C. [http://www.epa.gov/ocspp/pubs/frs/publications/Test\\_Guidelines/series870.htm](http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series870.htm)

FDA (Food and Drug Administration) (2000). Toxicological principles for the safety assessment of food ingredients: Redbook. FDA CFSAN. <http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/Foo>

[dIngredientsandPackaging/Redbook/default.htm](http://www.who.int/ipcs/publications/ehc/methodology_alphabetical/en/index.html)

Risk Assessment guidelines by endpoint (new box)

IPCS guidance available at:

[http://www.who.int/ipcs/publications/ehc/methodology\\_alphabetical/en/index.html](http://www.who.int/ipcs/publications/ehc/methodology_alphabetical/en/index.html)

IPCS (International Programme on Chemical Safety) (1991). Principles and methods for the assessment of nephrotoxicity associated with exposure to chemicals. Environmental Health Criteria 119.

IPCS (International Programme on Chemical Safety) (2001). Neurotoxicity: Integrated approach to the assessment of neurotoxicity of chemicals. Environmental Health Criteria 223.

IPCS (International Programme on Chemical Safety) (2001). Reproduction: Principles for evaluating health risks to reproduction associated with exposure to chemicals. Environmental Health Criteria 225.

IPCS (International Programme on Chemical Safety) (2008). Skin sensitization in chemical risk assessment. IPCS Harmonization project No. 5.

IPCS (International Programme on Chemical Safety) (2012). Guidance for immunotoxicity risk assessment for chemicals. IPCS Harmonization project No. 10.

U.S. EPA guidance available at: <http://www.epa.gov/iris/backgrd.html>

U.S. EPA (United States Environmental Protection Agency) (1986). Guidelines for mutagenicity risk assessment. Federal Register 51(185):34006-34012.

U.S. EPA (United States Environmental Protection Agency) (1991). Guidelines for developmental toxicity risk assessment. Federal Register 56(234): 63798-63826.

U.S. EPA (United States Environmental Protection Agency) (1994). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F, October 1994.

U.S. EPA (United States Environmental Protection Agency) (1996). Guidelines for reproductive toxicity risk assessment. Federal Register 61(212): 56274-56322.

U.S. EPA (United States Environmental Protection Agency) (1998). Guidelines for neurotoxicity risk assessment. Federal Register 63(93): 26926-26954.

U.S. EPA (United States Environmental Protection Agency) (2002). A review of the reference dose and reference concentration processes. EPA/630/P-02/002F, December 2002.



U.S. EPA (United States Environmental Protection Agency) (2005). Guidelines for carcinogen risk assessment. EPA/630/P-03/001B, March 2005. <http://www.epa.gov/ncea/iris/backgr-d.htm>

### *MOA*

– first present the key publications, then the case studies

New box – key publications:

Boobis, AR; Doe, JE; Heinrich-Hirsch, B; Meek, ME; Munn, S; Ruchirawat, M; Schlater, J; Seed, J (2008). IPCS Framework for Analyzing the Relevance of a Noncancer Mode of Action for Humans, *Critical Reviews in Toxicology* 38:87-96.

Boobis, AR; Cohen, SM; Dellarco, V; McGregor, D; Meek, ME; Vickers, C; Willcocks, D; Farland, W (2006). IPCS framework for analyzing the relevance of a cancer mode of action for humans. *Critical Reviews in Toxicology* 36:781-792 [*This entire issue of Critical Reviews in Toxicology addresses the IPCS framework.*]

IPCS (International Programme on Chemical Safety) (2007) IPCS framework for analysing the relevance of a cancer mode of action for humans and case studies. ([http://www.who.int/ipcs/methods/harmonization/areas/cancer\\_mode.pdf](http://www.who.int/ipcs/methods/harmonization/areas/cancer_mode.pdf))

Numerous case studies from IPCS in *Critical Reviews in Toxicology* (2005). 35(8).

Julien, E; Boobis, AR; Olin, SS; et al. (2009). The Key Events Dose-Response Framework: A Cross-disciplinary mode-of-action based approach to examining dose-response and thresholds. *Critical Reviews in Food Science and Nutrition* 49(8):682-689.

U.S. EPA (United States Environmental Protection Agency) (2007) Framework for determining a mutagenic mode of action for carcinogenicity (external review draft); U.S. EPA, EPA 120/R-07/002-A. Available at <http://epa.gov/osa/mmoaframework/index.htm>

U.S. EPA (United States Environmental Protection Agency) (2005). Guidelines for carcinogen risk assessment. EPA/630/P-03/001B, March 2005. <http://www.epa.gov/ncea/iris/backgr-d.htm>

### *Vulnerable population assessment*

New box – key publications:

IPCS (International Programme on Chemical Safety) (2006). Aged population: Principles for evaluating chemical effects on the aged population. *Environmental Health Criteria* 237.

IPCS (International Programme on Chemical Safety) (1993). Children: Principles for evaluating health risks in children associated with exposure to chemicals. *Environmental Health Criteria* 144.

U.S. EPA (United States Environmental Protection Agency) (2005). Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. EPA/630/R-03/003F, March 2005.

U.S. EPA. A Framework for Assessing Health Risk of Environmental Exposures to Children (Final). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-05/093F, 2006. Available at <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=158363>

### *Background*

New box – key publications:

IPCS (International Programme on Chemical Safety) (2006) Risk Assessment of Combined Exposures to Multiple Chemicals: A WHO/IPCS Framework. (<http://www.who.int/ipcs/methods/harmonization/areas/combinedexposure.pdf>)

Meek ME, Boobis AR, Crofton KM, Heinemeyer G, Raaij MV, Vickers C. (2011). Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. Regul Toxicol Pharmacol. 60(2): S1-S14.

U.S. EPA (United States Environmental Protection Agency) (1986). Guidelines for the health risk assessment of chemical mixtures. Federal Register 51(185):34014-34025.

U.S. EPA (United States Environmental Protection Agency) (2000). Supplementary guidance for conducting health risk assessment of chemical mixtures. EPA/630/R-00/002, August 2000.

U.S. EPA. 2003 Framework for Cumulative Risk Assessment. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington Office, Washington, DC, EPA/630/P-02/001F, 2003. (<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54944> (the placeholders for mixtures guidance and cumulative risk guidance would be removed)

### *Dose Response Methods*

New box – key publications:

Include all references listed in quantitative screening – safe dose

IPCS (International Programme on Chemical Safety) (2005). Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration–response assessment. ([http://whqlibdoc.who.int/publications/2005/9241546786\\_eng.pdf](http://whqlibdoc.who.int/publications/2005/9241546786_eng.pdf))

IPCS (International Programme on Chemical Safety) (2010) Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment. ([http://www.who.int/ipcs/methods/harmonization/areas/pbpb\\_models.pdf](http://www.who.int/ipcs/methods/harmonization/areas/pbpb_models.pdf))

IPCS (International Programme on Chemical Safety) (2009) Principles for modeling dose-response for the risk assessment of chemicals. Environmental Health Criteria 239.

IPCS (International Programme on Chemical Safety) (1999) Principles for the assessment of risks to human health from exposure to chemicals. Environmental Health Criteria 210.

U.S. EPA (United States Environmental Protection Agency) (2000). Benchmark dose technical guidance document.. External Review Draft. EPA/630/R-00/001, October 2000.

U.S. EPA (United States Environmental Protection Agency) (2005). Guidelines for carcinogen risk assessment. EPA/630/P-03/001B, March 2005. <http://www.epa.gov/ncea/iris/backgr-d.htm>

U.S. EPA 2011. Recommended Use of Body Weight  $3/4$  as the Default Method in Derivation of the Oral Reference Dose <http://www.epa.gov/raf/publications/interspecies-extrapolation.htm>

U.S. EPA (United States Environmental Protection Agency) (2006). Approaches for the application of physiologically based pharmacokinetic (PBPK) models and supporting data in risk assessment (Final Report). U.S. Environmental Protection Agency, Washington, D.C., EPA/600/R-05/043F. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=157668>

U.S. EPA (2011). External Review Draft of Data-Derived Extrapolation Factors (DDEF) <http://www.epa.gov/raf/DDEF/index.htm>

### ***Case Study-Specific Charge Questions - Methods for Deriving Inhalation Effect Levels for Comparison to Health-Protective Values***

Please comment on proposed procedures used to develop effect levels, not TCEQ procedures established under agency guidance to calculate health-protective reference values (shown in tables primarily for comparison to effects levels).

1. When both concentration and duration play a role in toxicity, and only a subacute or subchronic animal study is used for developing an effect level, how should the corresponding human exposure duration be determined (e.g., 90-day mouse exposure = x-day human exposure, proportion of lifespan, etc.)?
2. The main purpose of determining effect levels is to provide perspective on the health-protective reference value (e.g., RfC, Rev) and useful information to risk managers and risk assessors conducting health effects reviews of data when an exceedance of a health-protective value is observed. Instead of providing a single effect level value, please comment on the utility of providing “effect level intervals” (e.g., when using animal data and information on interspecies sensitivity is

lacking, providing the air concentration interval corresponding to the lowest exposure at which increased risk was observed as well as a  $10^{-3}$  excess risk level for cancer effect levels).

3. Please comment on the usefulness of providing information on effect levels or effect level intervals to understand potential health effects when health-protective reference values are exceeded.

4. The procedures for developing effect levels that are predictive do not include the application of uncertainty factors (UFs) because when UFs are applied, it often produces an unknown effect on the probability of the response observed at the POD. For example, if a UF of 10 is applied for intrahuman variability and true (but unknown) human variability for the chemical and endpoint is only around 3, the excess UF may result in a value that actually represents a NOAEL instead of an effects level. TCEQ's goal is to estimate human effects levels with as high of a degree of confidence as possible that effects would indeed occur in some individuals, as opposed to speculating about how low an effects level could be in the absence of dose-response data in sensitive subpopulations. Comment on the "meaning" or definition of an effect level if central tendency values of the distribution of  $UF_H$  and  $UF_A$  are applied to effect levels