Beyond Science and Decisions: From Problem Formulation to Dose-Response Workshop II

Appendices

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Appendices (Volume 2)

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Appendix A – List of Participants

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In-Person Attendees

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University of Vermont

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Summit Toxicology, LLP

Marcy Banton
LyondellBasell Industries

Brenda Barry
American Chemistry Council

Richard Becker
American Chemistry Council

Elizabeth Becker
CERM

Virunya Bhat
NSF International

Michael Bolger
FDA

Sarah Brozena
American Chemistry Council

James Bus
The Dow Chemical Company

Stuart Cagen
Shell Health

Iris Camacho
U.S. EPA

Richard Canady
International Life Sciences Institute

Richard Carrier
Health Canada

Patricia Casano
General Electric Company

John Christopher
CH2M Hill, CalEPA (ret)

Rory Conolly
U.S. EPA

Elena Craft
Environmental Defense Fund

Ruth Danzeisen
Intl. Copper Assoc

Kacee Deener
U.S. EPA

Dennis Devlin
Exxon Mobil Corporation

Michael Dourson
Toxicology Excellence for Risk Assessment

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University of Pennsylvania Law School

Julie Fitzpatrick
U.S. EPA

Robinan Gentry
ENVIRON International Corporation

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Texas Commission on Environmental Quality (TCEQ)

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BASF

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Wendelyn Jones
CropLife

Debra Kaden
ENVIRON

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Francis Kruszewski
American Cleaning Institute

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Bette Meek
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Asish Mohapatra
Health Canada

Martha Moore
FDA

Paul Moyer
Minnesota Department of Health

Edward Ohanian
U.S. EPA

Greg Paoli
Risk Sciences International

Lynn Pottenger
The Dow Chemical Company

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ENTRIX

Rita Schoeny
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Ted Simon LLC

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ENVIRON

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Russell White
American Petroleum Institute

Doug Wolf
U.S. EPA

Federal State Toxicology and Risk Assessment Committee (FSTRAC) Attendees

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NJ Department of Health and Senior Services

Julie Fitzpatrick
U.S. Environmental Protection Agency

Helen Goeden
Minnesota Department of Health

Martin Hoagland
U.S. Food & Drug Administration

Robert Howd
California Environmental Protection

Michael Hutcheson
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Brandon Kernen
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Lynda Knobeloch
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Patrick Levallois
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Clifton McLellan
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Pennsylvania Department of Environmental Protection

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U.S. Environmental Protection Agency, Office of Water

Gloria Post
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Kate Sande
Minnesota Department of Health

Melanie Young
U.S. Environmental Protection Agency

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U.S. EPA

Shelly Burman
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Erik Carlson
General Electric Company

Leigh Carson
The Sapphire Group

Sunil Chawla
Seascape Learning

Roberta Dyck
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Mary Dymond
Minnesota Pollution Control Agency

Charles Elkins
Chuck Elkins & Associates

Caroline English
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Neeraja Erraguntla
Texas Commission on Environmental Quality

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Gulan Sun
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Tyra Walsh
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Alison Willis
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American Petroleum Institute

Melanie Young
U.S. EPA, OW/OST/HECD/Human Health Risk Assessment Branch

Amin Zargar

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FDA

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Appendix B – Agenda

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Workshop II Agenda

Date: October 11 and 12, 2010
&
October 13
Joint Meeting with the
U.S. Federal-State Toxicology and Risk Analysis Committee (FSTRAC)

Location: Double Tree Hilton, Crystal City, VA

Purpose: To advance the recommendations in the NAS (2009) report concerning issue identification (problem formulation) and dose-response analysis, through review of illustrative case studies for further development of a methods text

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Day 1: Monday, October 11th

Welcome (8:15 to 8:30)

- **Roberta Grant, Lynn Pottenger and Lynne Haber,** Members of the Dose-Response Assessment Advisory Committee.

Introduction and Opening Remark (8:30 to 8:45)

- **Members of the Science Panel**

Keynote Talk (8:45 to 9:30)

- **Edward Ohanian**, U.S. Environmental Protection Agency (EPA). NAS findings and Current EPA Risk Assessment Forum Efforts.

Morning Break (9:30 to 10:00)

Review of Case Studies[1] (10:00 to noon)

- Methods for calculating risk for noncancer effects (part 1)
  #4 – Evaluating biological plausibility of linear low-dose extrapolation for risk of morbidity and mortality from hepatic disease (ethanol) (R. Becker)
  #9 - Biologically-Informed Empirical Dose Response Modeling: Using Linked Cause-Effect Functions (TiO2) (Haber)
  #21 – Use of biomarkers with the BMD method (Methyl mercury) (Gentry)

Lunch (noon to 1:00)

- **Adam Finkel,** University of Pennsylvania Law School & NAS Panelist, Human variability and extrapolation to low doses.

[1] The **Science Panel** will review case studies developed from the first workshop, suggesting revisions, new directions or curtailment as appropriate to the development of a methods text.

Review of Case Studies Continued (1:00 to 3:00)

- Methods for calculating risk for noncancer effects (part 2)
  #11 – Estimate risk above the RfD using uncertainty factor distributions (multiple) (Spalt)
  #17 – Implication of linear extrapolation to origin (multiple) (Kroner, Haber)
  #18 – Use of categorical regression to calculate risk above the RfD (copper, chemical T) (Danziesen, Haber)

Afternoon Break (3:00 to 3:30)

Observer Comments (3:30 to 4:00)

Review of Case Studies Continued (4:00 to 5:30)

- Methods emphasizing evaluation of mode of action
  #23a - Use of human data in cancer risk assessment (1,3-butadiene) (Albertini, Sielken)
  #23b - Quantitative human health assessment based on ovarian effects in rodents (1,3-butadiene) (Kirman, Grant)

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

Day 2: Tuesday, October 12th

Review of Case Studies (8:00 to 10:00)

- Methods for acute exposure evaluation
  #13 – AEGL methodology (ethylbenzene) (Camacho)
  #D – alternative temporal exposure patterns (benzene) (Haber, Haney)
- Methods for prioritization and screening
  #6 – Sustainable Futures screening (isodectyl acrylate) (E. Becker)
  #25 – Tiered screening approach for acute inhalation exposures (pentene) (Grant)

Morning Break (10:00 to 10:30)

Review of Case Studies (10:30 to noon)

- Methods for integrating complex data sets
  #19 – Data fusion methods (petroleum hydrocarbons) (Mohapatra)
- Methods for safe dose
  #24 – Consideration of human kinetic variability (trichloroethylene) (Lipscomb)

Lunch (noon to 1:00)

- Peter Grevatt, EPA Office of Children's Health Protection (issues related to children's health)

Review of Case Studies Continued (1:00 to 3:00)

- Methods for evaluation of risk for cancer effects
  #5 – BBDR for respiratory tract carcinogenicity (formaldehyde) (Haney)
  #16 – Multiple modes of action and risk assessment modeling (acrylamide) (Hertzberg)
  #26 mod- Low-dose dose-response curve shape for genotoxic chemicals (multiple) (Pottenger)
  #8 –Application of silver book methodology (dioxin) (Simon)

Afternoon Break (3:00 to 3:30)

Observer Comments (3:30 to 4:00)

Science Panel Assignments for Workshop III (4:00 to 5:30)

- Consideration of areas where methods/cases are missing
- Guidance document structure and writing assignments

Dinner on your own

Day 3: Wednesday, October 13th
Joint Meeting with U.S. Federal-State Toxicology and Risk Analysis Committee (FSTRAC)

Summary of *ARA* workshops by rapporteurs (8:30 to 10:00)

Morning Break (10:00 to 10:30)

Open Discussion (10:30 to noon)

- Participants from both meetings will brainstorm issues associated with preliminary outline for methods document that ties together problem formulation, dose-response assessment technique and risk management outcome.

Lunch (noon to 1:00)

- **Doug Wolf ,** U.S. Environmental Protection Agency (EPA). Update on the Nuclear Receptors Workshop
- **Craig Rowlands**, The Dow Chemical Company. ILSI Risk 21 [2]

1:00 PM Adjourn

[2] The objective of this project is to harness the significant scientific advances made in toxicology, molecular biology and exposure sciences to design an improved risk assessment paradigm for the 21st century. Activities will focus on molecular screening and tiered testing for hazard characterization, advanced approaches for dose-response assessment, including mode of action profiling, cutting-edge exposure assessment methods, and scientifically robust methods for determining risks from cumulative exposures. See also. http://www.hesiglobal.org/i4a/pages/index.cfm?pageid=3492

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Appendix C – Panel Member Biographical Sketches

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Expert Panel

Michael Bolger, U.S. Food and Drug Administration (FDA)
Michael Bolger received his bachelor's degree in biology in 1971 from Villanova University and his doctoral degree in physiology and biophysics in 1976 from Georgetown University. After a three year postdoctoral position at the Georgetown University Medical Center, Dr. Bolger became a staff fellow in toxicology with the Bureau of Foods in the U.S. Food and Drug Administration (FDA). Upon completion of his staff fellowship, he accepted a position as a toxicologist with the Contaminants Branch at the FDA. Since 1980 Dr. Bolger has been involved in the hazard/safety/risk assessment of anthropogenic and naturally derived contaminants in food. Dr. Bolger is a board-certified toxicologist by the American Board of Toxicology. Dr. Bolger is the recipient of the 2009 Arnold J. Lehman Award conferred by the Society of Toxicology and the 2010 Outstanding Risk Practitioner Award conferred by the Society of Risk Analysis. Dr. Bolger is currently director of the Chemical Hazards Assessment Staff in the Office of Food Safety which is responsible for the hazard/safety/risk assessment of food borne contaminants, and for reporting FDA monitoring efforts on food-borne environmental contaminants and the conduct of exposure assessments. Dr. Bolger is currently serving as a food safety expert of the World Health Organization and as a member of the Joint Expert Committee on Food Additives and the Foodborne Disease Burden Epidemiology Reference Group of the World Health Organization.

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 has 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 Alumus 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.

John Christopher, CH2M/Hill
John Christopher recently joined CH2M/Hill as a toxicologist. Prior to joining CH2MHill he was a staff toxicologist with the Department of Toxic Substances Control, California Environmental Protection Agency. In this position he reviews, critiques, and approves assessments of risk to human health and ecological risk assessments at military facilities and other hazardous waste sites and permitted facilities in California. He constructs multi-pathway risk assessments to identify numerical criteria for classifying hazardous levels of metals and organic chemicals in waste. He also uses Monte Carlo methods in various exposure settings to identify levels protective of human health. He has received Certificates of Recognition for contributions resulting in the successful transfer of a hazardous waste landfill at a former naval shipyard in Vallejo, CA , for a prescribed burn to uncover unexploded ordnance at a former fort in, Monterey , CA , and also for cleanup of a fleet industrial supply center in Alameda , CA . In addition, he has received a Sustained Superior Accomplishment Award from California Department of Toxic Substances Control for risk assessment of metals in hazardous waste. Prior to his current position with the State of California, Dr. Christopher conducted risk assessments for ICF Kaiser Engineers and IT Corporation. He also worked for research laboratories where he conducted and managed animal studies. Dr. Christopher earned a B.S in Biology from Georgetown University, Washington DC, and a M.A. in Pharmacology from Stanford University, Palo Alto, CA. He received his Ph.D. in Biological Science from Oregon State University, Corvallis OR. Dr. Christopher is a Diplomate of the American Board of Toxicology and a former member of this Board. He has served as President and held several other offices in the Risk Assessment Specialty Section of the Society of Toxicology and also in SOT's Northern California Chapter. He is a peer reviewer for *Toxicological Sciences, Risk Analysis*, *Human and Ecological Risk Assessment,* and *CRC Critical Reviews in Toxicology.*

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 (TERA)
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.

Adam M. Finkel, University of Pennsylvania Law School
Adam M. Finkel is one of the nation's leading experts in the evolving field of quantitative risk assessment and cost-benefit analysis, with 25 years of experience improving methods of analysis and making risk-based decisions to protect workers and the general public from environmental hazards. Dr. Finkel is currently a Fellow at the Penn Law School and Executive Director of the Penn Program on Regulation; he is also a professor of environmental and occupational health at the University of Medicine and Dentistry of New Jersey (UMDNJ) School of Public Health. From 2004-2008, he was a Visiting Professor of Public and International Affairs at the Woodrow Wilson School at Princeton University. From 1995 to 2003, he was Director of Health Standards Programs at the U.S. Occupational Safety and Health Administration (OSHA), and was responsible for promulgating and evaluating regulations to protect the nation's workers from chemical, radiological, and biological hazards, and then served as OSHA's Regional Administrator for the Rocky Mountain states. He recently received the David P. Rall Award from the American Public Health Association for "a career in advancing science in the service of public health protection." Adam has an Sc.D. in environmental health sciences from the Harvard

School of Public Health, a master's degree in public policy from Harvard's John F. Kennedy School of Government, an A.B. in biology from Harvard College, and is a Certified Industrial Hygienist.

William Hayes, Indiana Department of Environmental Management
William Hayes has been a Senior Risk Assessor with the Indiana Department of Environmental Management for 14 years. His career has included work in all of the major environmental programs. Mr. Hayes is the Continuous Improvement Coordinator for the Office of Land Quality, is a Certified Industrial Hygienist, is the Office of Land Quality nanotechnology subject matter expert, and has several publications on environmental topics, including a book on the ISO 14000 standards. His current work focuses on continuous improvement and the development of technical guidance.

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.

Paul Moyer, Minnesota Department of Health (MDH)
Paul Moyer joined the Health Risk Assessment Unit of the Environmental Health Division of the Minnesota Department of Health (MDH) in November 2006. As an environmental research scientist, he is responsible for performing and reviewing toxicological assessments of a variety of chemicals identified as groundwater contaminants as well as developing and applying risk assessment best practices to health protection policy decisions. The unit develops guidance values (upper exposure limits) for air and water contaminants. Paul leads staff in selecting chemicals for review for the purpose of developing state limits for groundwater and promulgating rules for the values that the unit develops. Paul also reviews the values that are developed for other programs in the unit (e.g., water contaminants of emerging concern) and has a leadership role in ensuring consistency between the methods used to develop air and water guidance. Paul has researched and developed health based guidance for a wide variety of agricultural and industrial chemicals that contaminate Minnesota ground water and surface water. Paul reviews the guidance values that others are developing for chemicals in personal care products and pharmaceuticals. Before joining the Environmental Health Division, Mr. Moyer was the Chemical Emergency Response Coordinator for the MDH Public Health Laboratory Division. In this capacity his responsibilities included emergency preparedness and response planning, performing instrumental analyses for chemical agent exposure measurements in clinical matrices, and providing outreach to emergency response partners. Paul continues this work as an emergency response provider for radiological releases and drinking water supply contamination incidents. Mr. Moyer received his B.S. in Microbiology from the University of Pittsburgh, and his M.S. in Environmental and Occupational health from the Graduate School of Public Health, also at the University of Pittsburgh. While living in Pennsylvania, Mr. Moyer worked in the areas of pharmaceutical analysis, bioavailability, and pharmacokinetic assessment, biomedical research, and chemical hazard communication and regulatory consultation.

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.

Appendix D – Summaries of Guest Presentations

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Guest Presentations

There were several guest presentations during the course of the meeting. Where slides were used (i.e., for all talks except that by Peter Grevatt), the slides are available at http://www.allianceforrisk.org/Workshop/CaseStudies/index.htm.

Dr. Edward Ohanian of the EPA gave the keynote address on "NRC findings and Current EPA Risk Assessment Forum (RAF) Efforts." He addressed past and ongoing RAF projects, and noted that the RAF is coordinating EPA efforts to address the recommendations made by the three recent NAS reports (NAS, 2007, 2008, 2009). He noted that EPA will hold an internal colloquium at the end of October to develop an action plan to advance human health risk assessment (HHRA) at EPA, considering the NAS recommendations and incorporating the Administrator's priorities. Workgroups are focusing on uncertainty and variability; unified dose-response assessment and defaults, and cumulative risk assessment. In response to a panelist question about which NAS recommendations would likely be adopted by EPA, Dr. Ohanian stated that determining the answer to that question will be one outcome of the colloquium. The RAF draft action plan will be presented to the EPA Science and Technology Policy Council for comment. A panelist who is involved in the effort stated that the overall HHRA framework would likely be completed within a year, and will take into account other pre-existing guidance documents, both from EPA and other organizations.

Dr. Adam Finkel of the University of Pennsylvania Law School and a member of the NAS (2009) committee, presented a talk entitled "Beyond Misleading Underestimation of Carcinogenic Potency: The 'Known Unknown' of Human Susceptibility." He stated that, for carcinogens that do not have a threshold, no matter how one maps the dose-response information from rodent data to a point estimate of potency to represent humans, then the sensitive population response is under-predicted; all that remains to puzzle out is how many people are under-protected and by how much. He noted the NAS recommendation that a factor of 25 would be a reasonable default value to assume as a ratio between the upper 95th percentile and the median individual's cancer sensitivity for the non-threshold case. (See the additional discussion in the supplementary material posted on the workshop website for more detailed information on his presentation and the resulting discussion.) Dr. Finkel also briefly addressed problem formulation versus solution formulation. He stated that the latter approach focuses more on the decisions that need to be made (rather than focusing on the problem that should be studied), thus highlighting more options to finding the best overall approach, including reconsideration of design standards and alternative approaches. He noted that the Science and Decisions framework refers to "enhanced problem formulation," but that the Committee did not fully endorse his ideas for "solution-focused risk assessment" (Finkel, 2010).

Dr. Peter Grevatt, Director of EPA's Office of Children's Health Protection and Environmental Education, presented a talk about children's risk issues, noting that two of EPA Administrator Jackson's priorities are children's health and environmental justice. He noted that additional stakeholder groups are being engaged around these issues, including bringing in complementary

expertise, since there are few medical doctors in the agency. He mentioned several areas and chemicals of specific concern with respect to children's susceptibility (e.g., lead and neurodevelopmental toxicity in general; asthma), as well as specific initiatives (e.g., the First Lady's "Let's Move" initiative to combat child obesity), and possible endocrine factors related to obesity. He noted that EPA is looking at what additional guidance is needed with regard to susceptibility.

Dr. J. Craig Rowlands, of The Dow Chemical Company, presented a talk entitled: "Risk 21 – Risk Assessment for the 21st Century: A Vision and a Plan," on the ILSI *Risk21* project. The project was stimulated by the NAS (2008, 2009) reports, and seeks to prompt a discussion among experts from industry, academia, the government, and other stakeholders, to identify key advancements in risk assessment. The project then seeks to use that group to guide the development and use of risk assessment approaches that embrace advances in scientific knowledge and methods. The areas of focus are: exposure science, dose-response, tiered testing, and cumulative risk. Key issues for the dose-response group are how mode of action influences low-dose extrapolation, and addressing technical issues for *in vitro* to *in vivo* extrapolation.

Dr. Douglas Wolf, of the EPA, presented a preliminary report on the recent *ARA* workshop on "Dose-Response Approaches for Nuclear Receptor-Mediated Modes of Action." Three nuclear receptors were addressed at the workshop – AHR, CAR/PXR, and PPARα. The workshop participants used the IPCS Mode of Action/Human Relevance Framework and modified Hill Criteria to evaluate each of the receptor-mediated modes of action (MOAs) leading to liver tumors. Potential key events were identified, as well as associated events and modulating factors. Sufficient data were available to describe the MOA in animals for all three receptor types and human relevance was evaluated for each. This is the first time that an expert panel has rigorously applied the MOA framework for the AHR. A meeting report is available at http://www.tera.org/Peer/NuclearReceptor/index.html, and peer-reviewed publications will be prepared for each of the receptor types.

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Appendix E – Summaries of Case Study Discussions

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Overview

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. Broader issues that were discussed in the context of individual case studies are presented in the supplemental material posted on the workshop web page.

Discussion of the case studies was organized into several loose topic categories. For each case study, this Appendix 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. Additional details on each case study are available at http://www.allianceforrisk.org/Workshop/CaseStudies/index.htm .

Summary of 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 R. Becker. Coauthor: S. Hays)

The authors tested the biological plausibility of predicting the risks from low-dose exposure to ethanol in food and drink using linear extrapolation from high-dose data. Two endpoints were evaluated, morbidity (liver cirrhosis) and mortality. Ethanol was chosen for the case study because its mode of action (MOA) is well understood and substantial human data are available. This understanding of the MOA means that the case study can be expanded to include a mode of action or adverse outcome pathway analysis. Quantitative dose response relationships from the published literature for ethanol-induced hepatic cirrhosis morbidity and mortality were identified as empirical "high-dose" exposure-response relationships. Linear extrapolation from a point of departure was used to estimate the risk of mortality and morbidity associated with low, environmentally relevant exposure to ethanol – social consumption of alcoholic beverages and from consumption of trace quantities in fruit juice. In response to a panelist question, the presenter noted that the endpoint was chosen based on the availability of good human data, not because it was the most sensitive endpoint. The authors considered applying the Key Events Dose-Response Framework (KEDRF) (Boobis et al., 2009; Julien et al., 2010), but did not have sufficient time.

The panel discussed whether the case study was an adequate hypothesis test of what many believe was one of the NAS (2009) recommendations - that is, extrapolating from the point of departure (POD) to zero with a straight line. One panel member thought that the case study was a useful common sense example of using linear extrapolation, but the case did not adequately address the question of whether sensitive individuals would experience a low level of risk at exposures much lower than those that would protect the general population. The presenter agreed that sensitive populations were not explicitly addressed, but suggested that this is one of the few chemicals for which good dose-response data are available for the general population; the risk for the general population can be evaluated first, based on an understanding of the biology, and then the analysis can be extended to sensitive populations. The presenter then suggested that the evaluation of risk to sensitive populations could be evaluated further by considering the metabolic profiles of sensitive populations. A panelist asked whether some of the difference between the observed and expected incidences of disease may be related to the exposure scenario, e.g., high-dose being more bolus, vs. dietary exposure. The presenter suggested that this could be addressed using the KEDRF. Another panelist noted that this case allows a more in-depth analysis of the implications of additivity to background of the natural chemicals found in foods considered to represent a baseline of "healthy" (e.g., , fruits and vegetables).

Another panelist asked why the authors chose to use linear extrapolation instead another of the conceptual models provided by NAS (2009). The panelist noted that (1) the NAS report did not intend "linear" to mean linear extrapolation from a high-dose point of departure (see the supplemental material posted on the workshop web page), and (2) the NAS report does recommend that mechanistic thinking be used in determining the extrapolation approach. In light of these points, the panelist questioned why the authors used a linear approach, when the presenter believes that a threshold exists. The presenter replied that the purpose of the analysis was to determine what would happen using linear extrapolation, and suggested that the results support the conclusion that, for chemicals such as ethanol, homeostatic mechanisms are important in the dose-response. One panel member suggested that the data be re-analyzed by plotting the log of dose vs. the response expressed in terms of probits (i.e., using log dose-probit space), since many biological processes are lognormal. Another cautioned about over-generalization from the results of one chemical, and that mechanism should be considered in addressing the issue of linearity vs. non-linearity.

In response to a panel question about how background was addressed, the presenter responded the BMD modeling used "additional" risk, so the calculated risks were on top of the background risk. This led to a broader discussion of issues related to background considerations (see the supplemental material posted on the workshop web page). In the context of this case study, one panelist suggested that the cirrhosis risk due to the average consumption of alcohol be evaluated and compared with the population incidence of cirrhosis. Others recommended that other environmental factors that could place an individual on the pathway to cirrhosis be considered as part of the background, as well as the biology of the lesion, and other stressors. Other panelists asked whether it would be useful to investigate other populations, such as Seventh Day Adventists (abstainers from alcohol) vs. the French population (higher alcohol consumption). One panelist noted the risk-risk tradeoff issue, in light of the benefits to the heart from red wine consumption.

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. However, 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 improving the consideration of background exposure. It was also recommended to consider linearity in log dose-probit space. 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 L. Haber. Coauthors B. Allen, A. Maier, A. Willis)

The purpose of the method is to use quantitative data on early events (biomarkers) to extend the overall dose-response curve to lower doses using biology, rather than default choices of linear extrapolation or uncertainty factors. It addresses a need for a biologically-informed approach that lies between using defaults and the complexity of developing a full BBDR. To conduct the modeling, the authors outlined a hypothesized series of key events describing the MOA for TiO_2. A series of linked "cause-effect" functions were used to mathematically describe the relationship between successive key events in the MOA. The information on relationships between successive key events was then used to predict lung tumors based on lung burden data, based on the relationship between successive biomarkers of exposure and effect. In summary, the method is empirically-based, incorporating an understanding of the chemical's biology, but it does not model specific biological processes. The presenter noted that a weakness of the approach is that it does not explicitly address interspecies differences, but these could be addressed using standard methodologies.

In response to clarifying questions from the panel, the presenter noted that the approach differs from a BBDR because there is not a kinetic component to the model, and that the linkages between key events are empirical, rather than based on specific understanding of the biological processes.

Several panel members noted that the method is pragmatic, incorporates the available biological information to describe the dose-response, and fills a gap by providing a method for a biologically-informed model, between default and a full BBDR. By using biology to describe the dose-response, the result has less uncertainty than the default approach. One panelist noted that even a full BBDR incorporates some empirical modeling, and such methods allow more of the biology to be described as more information is obtained. Another noted that this sort of approach can help to inform experimentalists in the types of data needed to reduce key uncertainties. Another panelist noted that the approach addresses one of the challenges posed by the paradigm of NAS (2007) – how to describe the progression from perturbations to an apical effect. Two panel members expressed a desire to see the method applied to additional chemicals, noting that the approach does appear to be generalizable. One panelist noted that a key component of the proposed MOA is inflammation which may be related to oxidative damage; this suggests that further evaluation of the MOA may suggest a secondary genotoxic response.

One panelist asked whether background exposure and effects can be included in the approach. The presenter replied that background response in each control group used in the analysis was included in the modeling, and suggested that background could be addressed if appropriate studies were available. In response to a panelist question about considering the analysis (once the exposure box is removed) as a generic description of fibrosis, the presenter noted that the original plan was to broaden the approach to include data on other low-toxicity poorly soluble particulates (PSPs) that lead to fibrosis, but insufficient resources were available. Panelists noted that the ability to model the relationship between key events is important and broadly applicable. One panelist suggested that it would be useful to include human data in the case study, and compare the results of the current analysis with the human data on lung tumors from titanium dioxide exposure, recognizing that such a comparison may be difficult. The presenter noted that the available epidemiology studies reported minimal increased tumor incidence, and so incorporation of epidemiology data may be difficult. Another panelist suggested that the predictions of the biologically-based model and those of linear extrapolation could be compared to the human data, to see which is more predictive in the low-dose range.

The panel recommended that this case study move 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 this to a chemical where extrapolation is needed, so that the approach improves the extrapolation method.

Use of Biomarkers with the BMD Method (Methylmercury)

(Presented by R. Gentry. Coauthors: C. Van Landingham, S. Hays, L. Aylward)

This approach evaluated extensions of the BMD approach that allow estimation of risk at doses above the Reference Dose (RfD) when existing human response data are available. Benchmark modeling was conducted based on the human data that form the basis for the current RfD; a factor of 10 was used for the RfD to account for inter-individual variability. Cord-blood and maternal hair concentrations of methylmercury were used as the dose metrics for the BMD modeling. Four approaches were used to estimate risk above the RfD:

(1) A straight line was drawn from both the BMDL and BMD to the RfD, where the RfD is considered to be zero risk;
(2) The appropriate BMD model was extrapolated to the RfD and then the risk at the RfD was truncated to zero;
(3) The appropriate BMD model was extrapolated to the RfD and this risk was allowed to stand as an upper bound;
(4) The appropriate BMD model was extrapolated using a threshold term, where the threshold value was judged to be the RfD, or some higher value.

The presenter noted that one motivation for this case study was that some published studies have reported that exposures above the RfD are associated with risk to a large population of sensitive humans. There are data on methylmercury that can address this and allow for more explicit consideration of the risk. This case study demonstrates that, regardless of which method was

used, the percentage of the population exceeding the RfD was *not* the same as the percentage of the population with an effect.

In response to a panelist question, the presenter noted that the analysis used NHANES data for the general population. She noted that the dataset for methylmercury is very rich, but NHANES data were used because they are available for a large number of chemicals. She noted that most of the NHANES dataset chemicals do have less information about the relationship between internal dose and external exposure than methylmercury

When questioned by the panel, the presenter stated a preference for approach 3, or perhaps approach 2. Approach 1 was not appropriate because there is no evidence of a MOA indicating interaction with DNA. The presenter most preferred model 3, because it did not assume that the risk was zero at the RfD. One of the panel members also expressed a preference for approach 3, since all of the other approaches assume that the risk at the RfD is zero, but another panelist thought all approaches were valid because he believes that the risk at the RfD is zero for many chemicals. This panelist noted that a strength of this case study is that a human BMD is available, which aids in interpreting the data, and shows that not everyone with exposure greater than the RfD is at risk. The panelist recommended including in the case study a discussion of the MOA for methylmercury and how the MOA informs the choice of approach. A third panelist expressed a personal belief that there is some risk at the methylmercury RfD, based on the way that the RfD was developed (as a lower bound on a specified effect level).

Several panelists noted that this case study addresses or demonstrates a number of concepts. One noted that the case study addresses the issue of estimating risk at low exposure for a noncarcinogen, and for some chemicals the exposures of interest are in the range of observation (i.e., not requiring low-dose extrapolation). Another panelist noted that the case study illustrates the use of biomonitoring data, and that this point should be emphasized more, as a generalizable aspect of the case study. A case study coauthor noted that biomonitoring equivalents (BEs) or comparable screening values have been developed for almost 100 chemicals. These values use pharmacokinetic data to convert a value such as an RfD or RfC to an equivalent concentration in a biological medium. One panel member noted that most of the chemicals for which BEs have been developed have short half-lives, while methylmercury has a long half life, This panelist stated that for methylmercury, the effects of interest occur in the range of environmental exposures, while there is a large separation between population exposures and effect levels for short half-life chemicals. Another panelist noted that one implication of this difference is that the defaults may under-protect for long half-life chemicals; this emphasizes the importance of looking carefully at toxicokinetics and toxicodynamics.

In summary, the panel considered this to be a useful case study. 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 BEs.

Estimate Risk Above the Reference Dose (RfD) using Uncertainty Factor Distributions.

(Presented by E. Spalt. Coauthor: O. Kroner, Advisor: M. Dourson)

This method is a straightforward application of that developed by Swartout et al. (1998), and can be adapted as needed with the receipt of additional data on individual uncertainty factors. For the purposes of this case study, however, only the published uncertainty factor distributions of Swartout et al. (1998) were considered. In short, the method calculated various percentile RfDs by dividing the point of departure (POD) on IRIS by the uncertainty factor distributions listed in Swartout et al. (1998), and comparing the result with the existing IRIS RfD. This analysis was used to estimate the percentile at which the IRIS RfD falls for various composite uncertainty factors. The analysis found that, the larger the composite UF, the higher the percentile covered by the IRIS RfD. As described in more detail in the Swartout paper, a single distribution was assumed for all uncertainty factors with a value of 10: a lognormal distribution with a median of $10^{0.5}$ (or 3.16) and a 95^{th} percentile value of 10. This distribution is based on the assumption that 10 is a conservative estimate of each uncertainty factor. This assumption has some experimental support, although the support varies among the uncertainty factors. The various probabilities of Swartout et al. (1998) are combined by multiplication. Other combinations may be possible, but were not pursued in this case study.

The panel discussed the potential benefits of this approach to a risk manager, and potential limitations. One panel member suggested that with this approach, a risk manager could define the desired percentile, and then use that to determine the size of the uncertainty factor. Another panelist noted that the conclusion depends on the assumptions, and the presenter noted that chemical-specific information could be used to enhance the estimate. A third panel member asked whether it would be useful to state regulators to have information on the probability of an effect at a dose or concentration level. One panel member responded that it would depend on the viewpoint of the regulator as to whether it would be helpful, but the method could provide the rationale for hierarchies. Another panelist responded that questions that could be answered by this method do not routinely arise at the state level of risk managers; however, it might be useful for those who develop reference doses (RfDs) or health-based air concentrations. Another panelist suggested incorporating mode of action (MOA) information to develop distributions based on characteristics of the chemical and animal species, and clarified that this method would allow results to be expressed according to the percentage of those affected and those protected. The panelist said that this approach is appropriate for the UFs that address variability. In contrast, the panelist stated that the distributions for UFs based on uncertainty are more reflective of dose spacing than biology, and so would not recommend a probabilistic approach for those UFs. The panelist noted that this method is useful in pushing people to think probabilistically, but that there are often data limitations, and care is needed to avoid over-stating precision. Another panelist stated that there is a utility in being able to tell risk managers what RfD is needed to predict a specified percentage of the population. A third panelist suggested that this approach could be useful for comparing two chemicals. This approach lays out probabilistically the approach that people would go through mentally, that an exceedance of the RfD is of greater concern if the RfD is based on a sensitive population than if there is a large UF. Others countered that this approach recognizes that not all RfDs are created equal (i.e., they differ in the

degree of protectiveness), but the qualitative approach to comparing chemicals and UFs is easier to explain than the quantitative approach. Panel members noted that this approach presents the probability that the RfD is correct, while NAS (2009) recommended calculating a risk specific dose. However, others suggested that this approach is a partial step in the right direction.

It was noted that Jeff Swartout has further extended this work based on knowledge of interspecies differences and Dale Hattis' work, but further details were not available. A panelist clarified that the difference between this case study methodology and that of Dale Hattis is that Hattis (and the recommendations of NAS, 2009) is separating uncertainty and variability to estimate risk at a specific dose. For example, the probability statement at the 99th percentile is that there is a 1% chance that the true sensitive human NOAEL is lower. That allows the RfD to be defined in terms of the sensitive populations being protected and the confidence in that RfD.

In summary, 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.)

Apply Linear Low-Dose Extrapolation from Benchmark Dose for Noncancer Risk Assessment **(Presented by O. Kroner. Coauthor: L. Haber; Advisor: M. Dourson)**

The approach is an extension of the benchmark dose (BMD) method that allows the development of probabilities of adverse effect at any dose at or above a threshold of one molecule. Risks are developed by analogy to the default approach recommended for cancer toxicity (EPA, 2005), by extending a straight line from the chosen BMD, using the recommended procedure for extrapolation from experimental animals to humans when appropriate to develop a human equivalent dose or concentration (HED or HEC). This case illustration is intended as a direct test of the implications on resulting risk values of using linear extrapolation to low doses for all endpoints, regardless of mode of action. This case study is not intended to advocate for, or to oppose linear low-dose extrapolation. Rather, it attempts to characterize the method, describe some of the underlying rationale and assumptions, and then focuses on the quantitative implications of the approach. A critical assumption for this case study is that the threshold for the critical effect for the chemical is one molecule. If the chemical's Mode of Action (MOA) is thought to have a threshold greater than one molecule and exhibit a non-linear dose-response relationship, then this procedure is expected to substantially over-estimate the risk at doses below the biological/population threshold. The case study also noted that the approach would not accurately reflect the risk if there are dose-dependent transitions in the pathway to the development of the critical effect, and the procedure does not accurately reflect potential

processes such as adaptation or hormesis. A key result was that the 1 x 10^{-5} risk for all methods illustrated in the case study is substantially lower than the RfD, and that the method for calculating the HED/HEC had a substantial impact on the estimated risk. In response to a panelist question, the presenter clarified that all of the RfDs examined in this case study were based on BMDs, and so represent a consistent POD.

This case study generated much discussion among the panelists about linearity vs. nonlinearity in the dose-response and the NAS (2009) intent regarding linearity; see the supplemental materials posted on the workshop website. One panelist noted that this approach could be used as a rough tool for a screening assessment, an area not well developed in the NAS (2009) report. Another panelist stated this was an important case study because of its similarity and comparison to the method proposed by Hattis and recommended in the NAS (2009) report. Another panel member countered that this method differs in important ways from the Hattis method. A panelist added that NAS (2009) recommended the use of the slope in the range of the POD to describe the slope in the low-dose range. Based on these clarifications, a panelist highlighted the need for a case study that does apply the Hattis approach and compares it with current approaches, in order to "benchmark" the approach. The panelist noted that one advantage of a probabilistic approach is that it permits sensitivity analyses to identify the most important uncertainties. Another panelist noted that the 1 x 10^{-5} risk comes from the Hattis strawman definition of the RfD; other values could be chosen by risk managers, and so would lead to different results in comparing methods. A panelist advisor on the case study stated the case study was designed to harmonize the cancer and noncancer assessments by adjusting to an HED or HEC and then drawing a straight line. A panelist noted that the case study differs from the approach for cancer assessment in using uncertainty factors in adjusting the POD. The panelist also noted that the NAS (2009) report recommended changes to both the cancer and noncancer assessment approaches, rather than suggesting that noncancer assessment become more like cancer assessment. Another panelist cautioned that this method could give the appearance of more knowledge than exists, and that the focus should be on collecting more information that describes the determinants of risk. Another stated that the method allows one to describe the data in the terms recommended by NAS (2009), but it does not add any new knowledge. One panelist suggested conducting the analysis in log dose-probit space.

In summary, 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. (Presented by L. Haber and R. Danzeisen. Coauthors: D. Krewski, A. Chambers, S. Baker, and R. Hertzberg)

The purpose of this case study is to illustrate some uses of categorical regression. Categorical regression is a well-established method that is useful in analyzing a variety of types of toxicology data in an integrated fashion (e.g., Hertzberg and Dourson, 1993; reviewed by Haber et al., 2001). Similar to benchmark dose modeling, the output from a categorical regression analysis provides a probability estimate that can be used as a point of departure (POD) for

calculating an RfD or other health guidance value (HGV), and, under appropriate conditions, can be used to estimate the risk above a specified HGV. The custom software CatReg, developed by the U.S. Environmental Protection Agency, makes the method accessible to the general toxicologist/risk assessor. Two examples were provided in the case study. In one example, (Chambers et al., 2010), a pool of relevant studies on copper deficiency and excess (both human and animal data) was identified, and severity scores were defined to create a common measure of response. CatReg was used to conduct the exposure-response analysis. Two analyses were conducted to define separate exposure-response curves for copper excess and deficiency, resulting in a U-shaped curve. In another example related to the calculation of risk above the RfD, categorical regression has been conducted on "chemical T," a pesticide, using animal data on successive thyroid endpoints reflecting the order of disease progression and the chemical's MOA to estimate the response between the POD and the RfD. This latter work was done in support of a cost-benefit analysis, where there was a need to determine the number of cases of illness (hypothyroidism and cancer) at different dose levels.

Several panel members expressed support for the method, noting that it is useful for integrating data across the dose-response range and across studies. One panelist noted that the approach is useful for teaching people to use the data more broadly, rather than focusing on a single data point. The ability to connect the approach to the MOA was also noted; one could evaluate the probability of successive key events, rather than the probability of an effect of a specified severity. However, using key events for the categories would be more difficult for chemicals with a complex MOA, such as copper. Thinking across case studies, a panelist noted that one could evaluate the chemical T data using linked dose-response functions.

The panel also discussed several aspects specific to the copper analysis. With regard to severity ratings, one panelist noted that there is less consensus on the differences between severity ratings for the less severe categories. Another panelist noted that the copper dose-response has two curves, reflecting two different MOAs, and these responses should not be assumed to be additive.

In summary, the panel supported carrying this method forward, noting that it is useful for integration of data across a range of studies and dose-responses. The only comment for enhancement is that the final guidance document 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).

Group 2 - Methods Emphasizing Evaluation of Mode of Action

Use of Human Data in Cancer Risk Assessment of Chemicals as Illustrated by the Case of 1,3-Butadiene). (Presented by R. Albertini and R. Sielken)

This case study uses the example of 1,3-butadiene (BD) inhalation exposures in humans to illustrate how available methodology that incorporates mechanistic data rather than defaults may be used for chemical-specific analyses of human cancer risk based on mode of action (MOA) to inform regulatory risk assessments. Aspects of the MOA included in the assessment

include the following: (a) BD requires metabolism in order to exert its biological effects, (b) there are large interspecies differences in this metabolism (with humans being more like the BD-resistant rats than the BD-sensitive mice), (c) the different metabolites of BD have vastly different mutagenic (and carcinogenic) potencies, (d) the mutagenic and carcinogenic responses in one species (rats) imply that there may be a threshold at low exposure concentrations, and (e) there are different mutational events that underlie different malignancies, including different human hematological malignancies, giving different dose-response characteristics. The analysis was based on epidemiology data, using the above five considerations to inform key decision points, such as the choices of modeling method, dose metric(s), and endpoint(s). The modeling incorporated background human hazard rates that reflect human variability and known age-dependent changes in hazard rates. Because the human data were sufficient to determine an EC(1/100,000) in the range of the data, risk could be estimated directly, without extrapolation.

One of the panel members recommended that the authors address the potential for BD genotoxicity. To help address the broader applicability, it was also suggested that the authors identify the approaches for analyzing the data that worked and those that did not. A presenter replied that lumping responses for different types of leukemia did not work, because different types of leukemias reflect different mechanisms. The presenter continued that some of the strengths of the approach were (1) using individual exposure information, (2) use of life table analysis to incorporate information on how age affects risk and survival probabilities, and (3) eliminating the high-intensity exposures and exposure covariates that are not part of the environmental exposures being regulated. The author also noted that although one cannot prove a threshold, there is no positive trend in response in the lower 50% of the dose region. The presenter also noted that regulatory modeling did not require a statistically significant slope.

One of the panelists noted that the assessment was able to incorporate information on human variability in sensitivity; the presenter noted that the analysis included information on the impact of the GSTT1 polymorphism on the in vitro production of a DNA-reactive metabolite. The panelist also asked whether there was a precedent for calculating the EC (1/100,000), as was done in the case study. The presenter responded that it has been done for ethylene oxide; the aim is to identify a POD that is well within the distribution of exposure data. In this case, approximately 1/3 of the person-years are in the range of the dose corresponding to the 1/100000 cancer risk. The presenter also noted that the authors wish to bring their assessment to EPA, recommending that regulation for environmental exposure be based on cumulative exposure after the effects of high intensity exposures (HITs) are removed, since HITs are not part of environmental exposure scenarios. In response to a panelist question, the presenter noted that one of the papers in the case study submission was the MOA paper by Kirman et al. (2010) that applies the IPCS MOA/HRF (human relevance framework). The presenter further explained that in the Kirman et al. paper, the mutagenic mechanism underlying this MOA was used to determine the shape of the dose-response curve, with a quadratic equation corresponding to two hits; low-dose extrapolation was not needed.

The panel discussed generalizable ideas and issues from this case study. Several panelists commented that no extrapolation was needed for this case study, since the risks of interest are in the range of the data. One panelist noted that data from epidemiological studies are often in the exposure range of interest, and that it is important to recognize the difference between

epidemiology and animal studies when discussing methods for low-dose extrapolation. Another panelist suggested that it would be of interest to compare the results of this analysis with that using the animal data and using a linear default extrapolation. The presenter replied that the Fred et al. (2008) paper in the submittal calculated the risk from animal data, taking into account the relative metabolic capacity and cancer incidence in rats and mice. They found that, when the dose is expressed as exposure to mutagenic equivalents, the cancer incidence for rats and mice falls on the same line. Following the same approach in workers, one could calculate human risk in mutagenic equivalents in exposure workers, but the adducts were not quantifiable. A workshop participant noted that EPA conducted the cancer assessment based on using the default approach from the mouse and rat data, and this could be used as a comparison. The presenters noted that their assessment focused on the best estimate, rather than the upper bound risk, and one of the panelists supported the approach of focusing on the best estimate. Another panelist suggested that it would also be interesting to compare the risk predictions from animal and human data in a case where there is high confidence in target concordance, such as angiosarcomas; one of the workshop participants suggested that this comparison was done for EPA's IRIS assessment of vinyl chloride. The panelists suggested that looking at the MOA information across these two comparisons (BD and vinyl chloride) can help in determining the key determinants for interspecies differences.

In summary, 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 the BD case study consider applying the MOA frameworks and key events identified by Pottenger and Gollapudi (2010) and Swenberg et al. (2008).

The Quantitative Human Health Risk Assessment for 1,3-Butadiene Based on Ovarian Effects in Rodents. (Presented by C. Kirman and R. Grant)

This method illustrates how information on MOA can be used to guide key decisions in the dose-response assessment with respect to identifying a dose measure (i.e., diepoxybutane or DEB in blood), low-dose extrapolation method, background exposure, and sensitive subpopulations (i.e., underlying biological processes for menopause). A meta-analysis was conducted in which the available dose-response data from rats and mice were normalized using an internal dose estimate (DEB in blood) that is causally related to ovarian toxicity, as supported by the proposed MOA. The critical effect is ovarian atrophy (as measured by follicle depletion), which is a surrogate for premature menopause in human populations. Information on age-related follicle depletion was used as the measure of human variability for toxicodynamics. Internal dose measures were used for the extrapolation. These methods can be used for other chemical assessments where MOA information is available.

One of the panelists noted that the authors derived several candidate RfCs covering a range of 100. The presenter replied that these values reflect the range of human sensitivities – from sensitive to resistant individuals. The assessment developed a dose-response curve for sensitive

humans, based on the initial follicle count at birth, rather than applying an uncertainty factor for human sensitivity. In response to a panelist question about whether linear extrapolation was considered, the presenter stated that several data points were available with no response in the dose range of interest, and so there was no need for extrapolation to lower doses. The presenter noted that the EPA (2002) RfC derived for BD is substantially lower, because the approach in the case study used an internal dose metric that takes into account interspecies differences in metabolism. A panel member noted that the key difference is the amount of uncertainty in the different approaches. Panelists recommended that the authors present a side-by-side comparison of the relative uncertainties of the EPA assessment and the new assessment. A panelist further noted that people often use defaults because of concerns about confidence in alternative approaches, but people do not often think about the uncertainty associated with the default. Another agreed, noting that describing the biology and linkages between key events and the apical response reduces the uncertainty, even though there are issues about parameter uncertainty.

A panelist suggested that the hypothesized MOA could be tested by administering DEB to rats, to see if there is also an interspecies difference in toxicodynamics, in addition to the toxicokinetic difference. The presenters responded that the studies have been done with the metabolites, and a full MOA evaluation has been conducted for ovarian atrophy by BD. A panelist requested that the table for the MOA evaluation be included in the case study summary.

In summary, 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 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 in the supplemental material posted on the workshop website.

Group 3 - Methods for acute exposure evaluation

Apply AEGL Methodology to Develop Acute Exposure Guideline Levels for Ethylbenzene. (Presented by I. Camacho. Coauthors: R. Grant, N. Erraguntla, J. Hinz)

This case study presents a toxicity assessment method to derive short-term human health guidelines for inhalation exposure for use in chemical emergency response and preparedness programs. This case study applies hazard identification and dose-response assessment (i.e., a toxicity assessment) based on the available toxicity data for the example chemical (ethylbenzene) based on guideline methods in NRC (2001) to develop Acute Exposure Guideline Level (AEGL) values. Appropriate threshold concentration levels for each of the three health effect severity levels (AEGL-1, -2 and -3) are identified or derived for an initial exposure duration in humans or animals. Subsequently, interspecies and intraspecies uncertainty factors are applied (as well as modifying factors, when applicable), followed by time-scaling the resultant values to derive the

AEGL exposure periods of 10-min, 30-min, and 1-, 4-, and 8-hours). Additional information on the Standing Operating Procedures (SOP) for developing AEGLs is found at http://www.epa.gov/oppt/aegl/pubs/sop.htm. The presenter also noted that this method is of particular interest because it was not addressed by NAS (2009). The method was developed with strong stakeholder involvement, and has been applied for more than 270 chemicals.

The panel discussed the differences between AEGLs and RfCs. The presenter noted that AEGLs are thresholds, not safe concentrations, and are designed for a once-in-a-lifetime exposure to high concentrations, not for repeated exposures. One panel member asked if there was a cutoff for sensitive subgroups. The presenter responded that the AEGLs did not have specific cutoffs but did utilize data for sensitive groups (e.g., asthmatics), both for the point of departure and in the choice of the human variability uncertainty factor. A panel member asked if categorical regression is ever used to develop AEGLs. The presenter responded that although it has not been used to develop AEGLs, some analyses have been attempted with categorical regression and would be welcomed if proposed by stakeholders. In response to a panel member question on population variability in odor detection, the presenter responded that odor was not used to derive AEGLs. A panel member asked about the objectives of the program with a focus on the stakeholders. Although the presenter was not able to comment specifically on the objectives at the start of the program, she mentioned that a key goal was to include stakeholders from federal and state agencies to ensure that the AEGLs met the needs of these groups. The presenter further noted that the AEGLs are based on noncancer effects, but a discussion of carcinogenicity is provided in the documentation, including an appendix with the risk specific doses for single exposures. A panel member suggested that this case study might reference the recent workshop on Methodology for Intermittent and Short-Term Exposure to Carcinogens (MISTEC) conducted by the International Life Sciences Institute/ Heath and Environmental Sciences Institute (ILSI/HESI). A panelist asked about whether the AEGLs incorporated cost-benefit analysis, and the presenter responded that they do not. One member of the panel asked about the differentiation among the AEGL levels and whether it would be useful to more formally define the border between serious and not serious. This panel member asked if the severity classification was a judgment call or an operational meaning. The presenter responded that it was a combination of observations and professional judgment and suggested that it would be possible to retrospectively evaluate the database of chemicals that have been evaluated and make a list of endpoints that have been used for each AEGL category. A panel member agreed that this exercise could be useful, given that methods evolve over time.

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 SOPs. It was recommended that the text be revised to clarify the difference between an RfC and an AEGL.

Framework for Evaluating Alternative Temporal Patterns of Exposure for Risk Characterization. (Presented by L. Haber and J. Haney. Coauthors: A. Maier, D. Kaden, R. Carrier, E. Craft, R. Hertzberg. Advisor: M. Dourson).

This case study provides a methodology for addressing alternative exposure patterns (e.g., repeated short-term exposures, exposure durations that do not match available toxicity values).

This case study begins to address the issue by developing and applying a decision tree framework to address this issue. The case study authors noted that the current effort is preliminary and further development is needed. However, in light of the many situations in which this practical problem occurs and the clear need for methods to address the issue, they presented the method to help move the field forward. The method follows a tiered approach to risk characterization. *Tier I* approaches use simplistic time-averaging techniques for the exposure, the dose-response (e.g., point-of-departure), or both. *Tier III* approaches are characterized by the quantitative adjustment to the exposure or dose-response assessment, or both, such as using physiologically-based pharmacokinetic (PBPK) (or similar) models. This case study focused on the *Tier II* approach, which can be used when sufficiently conservative comparisons cannot be made under a Tier I approach to draw health conclusions. Tier II uses a combination of qualitative and semi-quantitative data based on the chemical's toxicokinetic (TK) and toxicodynamic (TD) properties to evaluate the potential for a chemical to cause acute or chronic effects under a given exposure scenario, describing a framework for that evaluation.

A panel member asked about the discussion of this case study that occurred at the first workshop. This case study was proposed to address a specific risk management decision, and it was understood that data from Texas would be used. The presenters noted that while they wanted to use actual data, their goal was broader than to just answer a specific risk management question. One panel member expressed enthusiasm for this case study, particularly its use of decision trees and frameworks. This panel member expressed interest in seeing this case study brought forward and tested with an additional chemical. Another panel member suggested that the testing be done with a chemical with a longer half-life. A panel member recommended including a concentration-duration-severity plot similar to EPA's approach for air toxics. Panel members pointed out that there may be some overlap with the work of the ILSI/HESI subcommittee on Methodology for Intermittent and Short-Term Exposure to Carcinogens (MISTEC), and related follow-on work. In response to a panelist question about using MOA data, the presenters responded that this method uses as much data as possible and that the comparison of the daily exposure with the guidance value should use dose metrics reflecting the appropriate MOA. A panel member pointed out that the industrial hygiene community may provide some useful insight, since exposure in the workplace is frequently episodic.

Overall, 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.

Sustainable Futures™ Screening. (Presenter: E. Becker. Coauthor: P. Ranslow)

This method addresses evaluating risk when there is very little or no toxicity data. This method uses a hybrid approach, based on the available toxicity data for the chemical or class as well as quantitative toxicity data from qualitatively-identified analogues. This case study presents a training tool used by EPA to help industry evaluate data on new chemicals and is intended as a screening tool for priority setting. The method utilizes existing databases (e.g., EPISuite) and estimation tools to gather information on a chemical of interest. Professional judgment is used to identify preferred analogues, focusing on key reactive structural groups that are likely to influence toxicity. Using data available for the analogues, effect levels are identified, and are

combined with estimates of general population, consumer, occupational and aquatic exposure to develop risk assessments for applicable scenarios and targets. The estimated exposure data are then combined with the hazard profile to give an overall risk profile. Risk to human health is established by comparison of any predicted human/mammalian toxicity effect levels (typically LOAELs or NOAELs) with the estimated human exposure dose rates (occupational and general population) to give a margin of exposure (MOE). The magnitude of the MOE determines if the potential for risk to human health exists.

A panel member asked if the method has been tested with a data-rich chemical, to compare results with the method and that using data on the chemical of interest, and noted that this would be a good reality check. The presenter noted that this has not been done, but pointed out that judgment is used in each step of the process and that each time data are assembled, the model is tested, including integrating any available data on the chemical with data on analogues. One panel member noted that similar issues were addressed as part of Health Canada's prioritization process for the Domestic Substances List (DSL), and that process used information from multiple tools and lines of evidence, together with expert knowledge. The panelist noted that transparency of tools and decision rules is important. The presenter responded that documentation of the approach and thinking process is on EPA's website. The same panel member recommended adding information to the case study about how the weight of evidence is applied in conducting the evaluation. A panel member stated that he saw the utility of this method but did not like the use of the terminology "dose-response" when this approach uses margin of exposure (MOE). The presenter agreed that the approach is a screening method that does not evaluate dose-response. Another panelist noted that use of a NOAEL/LOAEL is more appropriate than a BMD for a hazard assessment based on an analogue, since the BMD would imply more precision than is appropriate.

One panel member suggested that it would be useful to have clear documentation of what an appropriate MOE is, based on different points of departure (PODs). However, another panel member noted that the appropriate value of the MOE may depend on the use of the assessment (e.g., screening vs. full assessment). A third panelist added that it would be useful to define situations where an MOE approach is appropriate, and discuss the associated uncertainties. A panel member asked how the case study approach compared to Health Canada's Domestic Substances List (DSL) program. The presenter noted that the Sustainable Futures approach was developed for a specific use, for industry developing chemicals, as a way to determine if additional testing is necessary, and to identify chemicals that are too toxic for further development. The approach is also being used by states for ranking and prioritizations. Another panel member noted that the DSL used some similar approaches but had a different objective. A third panelist noted that the list developed by Health Canada is specific to the Canadian situation, but the tools can be useful elsewhere. A panel member pointed out that the food additive program of the U.S. FDA uses analogues and QSAR for screening. The presenter noted that people around the world are looking for ways to prioritize chemicals.

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.

Deriving Health-Protective Values for Evaluation of Acute Inhalation Exposures for Chemicals with Limited Toxicity Data Using a Tiered Screening Approach. (Presented by R. Grant. Coauthors: T. Phillips, S. Ethridge).

This case study describes how the Texas Commission of Environmental Quality (TCEQ) evaluates chemicals with limited toxicity data (LTD chemicals). A tiered approach is used, with the Tier I Effects Screening Level (ESL) set at a default of 1 $\mu g/m^3$, Tier II using a threshold of concern (TOC approach), along with an extrapolation approach based on ratio of NOAELs to LC_{50} values, and Tier III using a relative toxicity/potency approach. This case study focuses on the procedures used to set health-protective concentrations for LTD chemicals based on a Tier II approach, using pentene as an example chemical. For the Tier II approach, acute inhalation lethality (LC_{50}) data are required. The Tier II approach includes two approaches, one that develops generic ESLs based on a Threshold of Concern approach, and the other based on the ratios of NOAELs and LC_{50}s. To develop the method, the authors categorized 97 compounds with available NOAELs and LC_{50}s into five groups by severity of toxicity (GHS [globally harmonized system] categories). For each GHS category, a generic ESL is developed by dividing the 10^{th} percentile value for NOAELs in that category by an uncertainty factor of 100. To evaluate an LTD chemical, the chemical is first classified into a GHS category based on its LC_{50} value, and then the generic ESL for that category is applied to the chemical of interest. The NOAEL-to-LC_{50} ratio approach takes the 10^{th} percentile of the ratio of the NOAEL to the LC_{50} for 55 compounds. The ESL is then estimated for the LTD chemical by dividing that ratio by 100 (for human variability and interspecies differences), and multiplying the resulting number by the LC_{50} of the LTD chemical. The Tier II approach calculates ESLs by both methods, and uses a weight of evidence approach based on the available information (e.g., chemical structure or the toxicity of the chemical class) to determine which approach is most defensible.

In response to a panelist question, the presenter stated that LC_{50} data are obtained from the published literature, industrial sources, CalEPA, and ATSDR documents. A panel member stated that using the LC_{50} results in different margins of safety, since dose-response curves have different slopes. This panelist asked if the approach takes the LC_{10} into account. The presenter responded that often only the LC_{50} is available, without the underlying data to calculate other response levels. She noted that this approach did undergo a data validation exercise and is conservative compared to values derived from acute data. A panel member noted that Dourson and Stara (1983) reported that 90% of the slopes of log probit curves were greater than 3 on a log-probit scale, so that the majority of chemicals do not have the shallow slopes that would decrease the margin of safety.

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 methods write-up (the case study summary).

Group 4 - Methods for Integrating Complex Data Sets

Review of Data Fusion methodologies to Integrate Data From Different Organizational Levels. (Presented by A. Mohapatra. Coauthors: R. Sadiq, A. Zargar, S. Islam, and R. Dyck)

The method being described is currently a work in progress. This purpose of this case study is to provide approaches to integrate data across environmental and toxicological information related to various organizational levels (biochemical, biomedical, molecular, -omics, cellular, tissue and organs), to aid in developing an overall assessment. Such integration is of increasing importance as data arrays become more complex (e.g., including information on genomics and toxicity pathways) and require a variety of types of expertise. Additional information about the case study method is provided in the case study summary and case study presentation.

The panel members asked a number of clarifying questions regarding the approach. The presenter noted that the fusion approach includes a variety of tools related to assembling data, supplemented by expert judgment to answer key questions. This approach aids in extracting useful information on an integrated relationship across datasets, and can be done qualitatively or semi-quantitatively. In response to a panelist question, the presenter noted that pattern recognition does play an important role in integration across levels of organization. The approach considers methods for grouping data, such as by endpoint, using a dynamic knowledgebase. The presenter explained the "low level data fusion" step as including three categories: (1) toxicology data "cleaning," which selects the data connected to the problem formulation; (2) toxicology data transformation, in which the database /knowledgebase is transformed to answer specific the problem formulation; and (3) toxicological data reduction, which reduces the data sets based on the problem formulation in order to obtain meaningful information. This work would be done by the informatics tool. Higher-level tiers of evaluation would be done by subject matter experts, such as toxicologists or epidemiologists. The approach does address uncertainty and variability at each step, including propagation of uncertainty between the different levels of the analysis.

One panel member suggested that this relates to EPA's work on the next generation of risk assessment, and recommended that the presenter talk to EPA colleagues. The presenter noted that he will be participating in a symposium on the topic with EPA colleagues at the upcoming SRA annual meeting. Other panelists recommended that it would be useful to see demonstration of the application of the method to a specific chemical (e.g., benzene), including a demonstration of how the data fusion approach differs from the traditional approach. The presenter noted that the current phase of the project will be completed by February 15, so that an example should be ready in time for the next workshop.

In summary, 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

Consideration of Human Kinetic Variability. (Presented by J. Lipscomb. Coauthors: L. Teuschler, J. Swartout, D. Popken, T. Cox, G. Kedderis)

The presenter began his presentation with the disclaimer that the focus of the method is on kinetics and human variability, and that the data should not be taken out of context and applied to the near-final IRIS assessment for trichloroethylene (TCE). The case study was designed to test the hypothesis that *in vitro* variability in enzyme activity results in the same variability in tissue dose *in vivo*. The method uses PBPK modeling, together with information on physiological constraints and data on the variability in the enzyme capacity (based on information on enzyme content in the liver, activity of the enzyme, and the overall liver metabolic capacity toward the substrate), to estimate the in vivo variability in the tissue dose of the active form. In the specific example that was investigated, a 7-fold difference in metabolic capacity resulted in only a 2% difference in metabolism *in vivo*, due to– blood-flow limited metabolism in this case at low doses. Because of the high metabolic capacity associated with blood-flow limited metabolism, even low-metabolizing individuals can fully metabolize the limited flow of parent compound. This situation is found for several volatile organic chemical substrates. The presenter noted that the approach can be generalized to other enzymes using same approach. The presenter also noted that when there are competing pathways, more complex approaches are needed. For example, Chiu et al. (2009) used a Monte Carlo analysis to evaluate the entirety of sources of variability, including both uncertainty in population means and variability. That analysis found that the variability depended on the dose metric and the route of exposure. In response to a panelist question, the presenter stated that it is not very hard to get human liver in order to get data on human liver enzymes, but one could conduct similar analyses with other organs.

With regard to the generalizability of the method, one panelist asked whether inclusion of the Bayesian analysis and the 2-dimensional Monte Carlo approach provide useful additions to the overall approach. The presenter replied that EPA is likely to be relying more on these tools over time, and the presenter sees them as useful and validly applied to distributions, noting that hypothetical scenarios can be addressed by using the biology and math to understand the system. In response to a panelist question, the presenter stated that it is hard to "reality test" results from this sort of analysis.

Several panel members expressed support for the case study method, noting that the case study was in the IPCS guidelines for Chemical-Specific Adjustment Factors (CSAFs) (IPCS, 2005). One panelist noted that the case study was useful in illustrating the concept of physiological limits, a key biological concept that needs to be communicated to mathematicians. The panelist noted that a key aspect of the CSAF guidelines is that one uses information on the critical effect(s) and the chemical's MOA to determine the appropriate dose metric for each relevant effect, and then one focuses on the relevant dose metric in calculating the adjustment factor. The presenter agreed, but noted that defense of non-default adjustment factors is complicated when there are multiple effects that are closely spaced on the dose scale, some of which may not be

well-understood. In that case, one needs to weigh uncertainties with different approaches, considering the implications of different endpoints and corresponding points of departure. Another panel member suggested that this example be used to calculate a CSAF for illustrative purposes.

In summary, the panel supported carrying the case study method forward because it integrated *in vitro* 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 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 J. Haney and R. Conolly. Co-authors B. Allen, H. Clewell, and J. Kester)

This case study illustrates the use of a biologically-based dose response (BBDR) model to integrate available data into quantitative cancer risk assessment, providing better dose-response predictions than when default methods and inputs are used. The method relies on mechanistic data known to be relevant biologically and pertinent to the underlying carcinogenic process. Such models can incorporate new knowledge about the exposure-dose-response linkage, as it becomes available, to generate new, high-quality predictions. Thus, use of BBDR modeling reduces risk assessment uncertainties associated with interspecies and high-to-low dose extrapolations by maximizing the use of scientific data. Doing such modeling is generally limited to data-rich chemicals, such as formaldehyde. For the case study of the formaldehyde BBDR, the authors propose to refine the existing BBDR model using new data that has become available in the ten years since this model was developed, including improved dosimetry, consideration of the role of endogenous formaldehyde, consideration of microarray data, reanalysis of dose-time response surface area to address identified uncertainties, and refinement of clonal growth modeling.

Panel discussion first focused on the how the model can aid in addressing uncertainty and variability (inter- and intraspecies). One panel member suggested that it may be possible to consider a suite of different dose-response models. The presenter replied that the initial model development considered multiple models, and the published formaldehyde dose-response paper includes two models, chosen based on plausibility. If data are available, sensitive subgroups can be explicitly considered. Monte Carlo modeling can also address parameter variability, if information on parameter distributions is available; this analysis was not done for the formaldehyde model. One panel member noted the concern expressed by Crump that a more complex model structure has more opportunities for uncertainties. A presenter replied that a better understanding of the linkages in the biology will result in a better mathematical description of the dose-response. Furthermore, BBDR modeling allows one to identify areas of uncertainty and target additional studies to those areas with the greatest uncertainty. While a statistician may see the more complex model as providing more opportunities for uncertainties that predominate over the improved biological understanding, the presenter considered the improved biological understanding as more important. A panelist noted that a key issue for formaldehyde was that

none of the simpler models adequately described what is known about the biology. A presenter noted that the model could also be modified to make predictions for other aldehydes.

Panelists and the presenters also discussed key considerations for choosing the most informative chemical for the next BBDR. Suggestions included (1) a genotoxic carcinogen to look at the shape of the dose-response curve; and (2) carbon monoxide, since there is a lot of human data and data on biomarkers, and human variability could be considered. Regardless of the chemical chosen, it was noted that a key consideration is that it would be useful to choose the chemical based on which chemical would support analyses that shed light on broader issues. It may be possible to develop a generic BBDR to address key issues raised by NAS (2009). Another panelist suggested that a value of information approach could be used to identify the types of chemicals where the BBDR model would provide answers with the largest difference from defaults, and that the economic impact of decisions should also be considered. A presenter noted that the modeling used to be limited by computer power, but is now limited by data availability, and that the process could be substantially enhanced by designing the studies up-front to support model development. A panelist noted that such studies are very expensive, but that using a multi-investigator "big science" approach would ultimately be more cost-effective.

Panel members agreed 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 supplemental material posted on the workshop website, 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.

(Presented by R. Hertzberg. Co-authors M. Dourson, B. Allen, M. Vincent, L. Haber)

The goal of this case study is to determine how to model low-dose cancer risk if the MOA includes different components that drive the dose-response in different dose ranges. If the components of the MOA apply to different dose ranges, the modeling can include multiple independent models, a single model defined differently in each dose range, or a single model whose curve shape mimics the shape of the data. The approach followed in the case was to first evaluate the MOA of acrylamide using the modified Hill criteria, and then choose the appropriate model(s) based on MOA. The hypothesized MOAs for acrylamide are genotoxicity and perturbation of thyroid hormone regulation. Based on an understanding of these MOAs, it is expected that genotoxicity would dominate in the low-dose range, and perturbation of hormone regulation would dominate at higher doses. In the case study, the dose-response model chosen was one that captures low-dose linearity consistent with the MOA, and with a steeper slope at higher doses. This approach requires sufficient dose-response data to adequately characterize that dose-response in each section of the curve dominated by different components of the MOA. Separate dose-response information on individual components of the MOA is ideal.

In response to a panelist question, the presenter clarified that there are no in vivo genotoxicity data in the target tissue of interest in the dose range of interest. A workshop participant also noted that there are limitations to the information that can be gleaned from traditional genotoxicity studies about the shape of dose-response curves. For this case study, the expectation of different primary contributors to the MOA in the low-dose and high-dose region is based on the general understanding of the respective components of the MOA (that is, assuming that a response in the low dose region would be driven by genotoxicity). A panelist noted that a similar assumption was used in the formaldehyde model. Panel members noted that (as reflected in the above text, but not in the original case study), the MOA described the overall sequence of processes. In this case, there is a single MOA, with different components contributing in different dose regions. One panel member questioned why a two-stage clonal growth model was not used. Another panel member responded that the two-stage clonal growth model needs a much richer dataset than is needed for the approach described in the case study.

Panel members 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, but it does not require 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. In summary, the panel concluded that the case study method has utility. Recommendations for enhancements were to be clear about 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 MOA.

Assessment of Low-Dose Dose-Response Relationship (Non-linear or Linear) for Genotoxicity, Focused on Induction of Mutations and Clastogenic Effects.

(Presented by L. Pottenger and M. Moore; Co-authors: E. Zeiger and T. Zhou)

The goal of the case study was to address the shape of the low-dose dose-response curve for genotoxicity, specifically for gene mutation and/or chromosomal effects such as micronucleus induction. The authors postulated a series of key events in the MOA for the induction of gene mutations. They then reviewed published genotoxicity data for six chemicals and considered the shape of the dose response curve for biomarkers of exposure (hemoglobin and DNA adducts) and for biomarkers of effect (mutations and clastogenicity). The authors concluded that, for these chemicals, there is a solid database supporting the conclusion that direct DNA-reactive chemicals can demonstrate non-linear/threshold[3] dose-response relationships for induction of mutation and/or clastogenicity. For EMS/ENU and MMS/MNU the dose-response appeared to be linear for the available biomarkers of exposure (hemoglobin and/or DNA adducts). The authors noted that more work is needed to develop a hypothesis for the biological understanding of the nonlinear/threshold dose-response for genotoxicity. They noted that only a few data sets have sufficient data to adequately test the data, but that further statistical evaluation of the data

[3] The authors noted that they agreed to use this hybrid term to avoid the assumption of a threshold, but to allow for that possibility.

would be needed. They suggested that an eventual goal would be to develop an approach to categorize chemicals with regard to the shape of the genotoxicity dose-response, based on MOA/key events and a hypothesis-driven theoretical understanding of the MOA.

The panel discussed what plausible sequence of key events (i.e., MOA) would result in a threshold. A presenter responded that nonlinearities/thresholds could result from high-fidelity DNA repair (i.e., if an adduct is repaired, then there is no mutation), as well as from cell death, or if there is DNA damage and the cell does not divide to produce mutated daughter cells. One panel member noted that John Tyson and others have modeled the cell cycle and checkpoints; this work could be included in qualitative modeling related to this approach. Another asked if the case study tested the hypothesis of linearity and whether there are other data sets where that test can be done. The presenter responded that some of the data sets that were considered were designed to address the question of whether the dose-response was statistically different from linear. However, not many data sets are available with data at doses sufficiently low to evaluate this issue. One panel member suggested focusing on direct-acting mutagens, since the results are easier to interpret. Another panelist suggested that one could look at the series of key events as the failures of compensating systems, and the nature of the failure (stochastic or not) would determine the shape of the dose-response curve. One panelist described overwhelming DNA repair as a failure of adaptation. Another noted that this approach integrates with a systems biology approach, where cancer can be considered as a cascading series of failures.

In summary, panel members supported carrying this method forward. Panel members noted that a key contribution of the case study is in articulating a MOA for gene mutation, thinking 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 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. A presenter added that an issue for this sort of analysis is the normal range of mutation frequencies; a shallow positive slope could be hidden in the background variability.

Application of National Research Council "Silverbook" Methodology for Dose Response Assessment of 2,3,7,8-tetrachlorodibenzo(p)dioxin. (Presented by T. Simon. Coauthors: M. Stephens, Y. Yang, R.O. Manning, R.A. Budinsky, and J.C. Rowlands)

This case study used the three conceptual models in NAS (2009) to describe the dose response for TCDD. The models are: (CM1) - nonlinear individual response, low-dose linear population response with background dependence; (CM2) - low-dose nonlinear individual and nonlinear population response, low-dose response independent of background (i.e.., a threshold response for which a reference dose is most appropriate); and (CM3) - low-dose linear individual and linear population dose response (i.e., a non-threshold response from which a slope factor is most appropriate). The modeling was conducted using mechanism-based biomarkers of dose and response, such as serum toxicity equivalents (TEQ), fractional activation level of the aryl hydrocarbon receptor (fAHR), and taking into account background processes. The overall approach allowed for a quantitative assessment of variability and uncertainty associated with the

toxicity criterion for TCDD. The case study calculated three different risk specific doses (RSDs) for each of the three conceptual models, as well as confidence limits.

In response to a panelist question, the presenter identified two key messages from the work. The first is that humans are much less sensitive than the laboratory animals used for the studies, and the second is that the number chosen is the most protective of those derived by the three models. A panel member asked for clarification regarding the human-based endpoint for CM2. The author responded that effect is hepatocyte hypertrophy from the NTP study, expressed in terms of fractional AHR activation. Information on background human AHR activation for CM2 was obtained from combining data for three endpoints (endogenous AHR ligands, bilirubin metabolism, and background caffeine metabolism); none of the three effects in humans were adverse, but the author considered the combined data as a good source for the best estimate for a NOAEL. A panel member noted that, for this analysis, there is no need to extrapolate outside the range of the data; another panelist observed that there are an increasing number of situations where extrapolation is not needed, because human observations are available in the range of exposures of interest.

Further discussion addressed the results of the modeling at the three RSDs (corresponding to 10^{-4}, 10^{-5}, and 10^{-6} risk). One panel member noted that the results are clearly not linear, regardless of whether a linear conceptual model was used. The presenter responded that the dose-response was assumed to be linear for CM3 and CM1 (population dose-response), and that the non-linear results are a consequence of the compression that occurs when the model is "run backwards" to calculate the RSD from the internal dose metric. Thus, even when assuming that the individual and population dose-response (based on internal dose) were linear, the dose-response based on applied dose was not linear. The overall approach addressed both uncertainty (regarding the level of endogenous fAHR activation), and human variability (in the point of departure and in background induction).

One panel member suggested that CM2 seems to be a test of the Hattis method; the presenter agreed, and stated that he attempted to do that as well for CM1 and CM3, but was not able to, due to data limitations. The panel member asked about the availability of other data-rich chemicals that could be subjected to a similar analysis. The presenter responded that a chemical would need to have experimental data of the size and quality of an NTP bioassay plus sufficient human data. CM2 could be performed with a small number of chemicals, possibly methyl mercury. Another panelist suggested that the conceptual models could be tested with pharmaceutical chemical data; researchers could join consortia such as ILSI or HESI to forward this approach. A third panelist noted that pharmaceutical companies have begun such collaborations, such as providing data for ToxCast.

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.

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Appendix F – Suggested Additional Case Studies

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Discussion of Additional Needed Case Studies and Missing Methods

A number of ideas for additional case studies were brought forward both during the workshop, and in post-meeting submittals to the workshop organizers. The ideas that had been submitted prior to the designated discussion period were considered by the Science Panel, which made recommendations regarding whether these case studies should be brought to the third workshop. Other case study ideas are listed below, but were not discussed by the panel. 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 guidance document.

Case Study Ideas Discussed by the Science Panel

1. ILSI/HESI project on Key Events-Dose Response Framework (KEDRF) and expanding framework to address how to incorporate dose-response information on key events to choose overall dose-response mode. Case studies exist for KEDRF, but the team is currently looking for case studies for the expanded version. A webinar participant also noted that the ILSI Research Foundation is working on three KEDRF case studies separate from Risk21. A workshop participant recommended that the available/in progress KEDRF case studies be reviewed to determine whether the complexities of NAS (2009) are addressed. Depending on the results of the review, it may be useful to have some new case study to inform the broader discussion. **Panel recommendation:** It would be useful to bring in a KEDRF case study. It would also be useful for the workshop group to interact with Risk21.
2. Enhancement of the formaldehyde BBDR case study (see Appendix p. D-21) using new data that has become available in the ten years since this model was developed, including improved dosimetry, consideration of the role of endogenous formaldehyde, consideration of microarray data, reanalysis of dose-time response surface area to address identified uncertainties, and refinement of clonal growth modeling. **Panel recommendation:** Do bring into workshop #3.
3. Case study(s) from the workshop on Dose-Response Approaches for Nuclear Receptor-Mediated Modes of Action. Three nuclear receptors were addressed in the workshop (AHR, CAR/PXR and PPARα,), as examples for how their biology is linked to key events and dose-response for liver tumors[4]. **Panel recommendation:** Case studies on

[4]The workshop focused on consideration of key events and human relevance of the MOA. Workshop participants may wish to extend the work further to address dose-response.

one or two receptors from the nuclear receptor workshop should be brought forward to the third workshop. One panel member expressed particular interest in CAR/PXR. Others noted that Doug Wolf (U.S. EPA) can be consulted regarding which case studies to bring forward.

4. Estimating risk above the RfD using biologically-based uncertainty factor distributions to calculate probability of response. Jeff Swartout has done recent work on this. **Panel recommendation:** The panel expressed a strong desire to ensure that the Hattis method, as intended by Hattis and described by NAS (2009), is one of the case studies. One panel member expressed a strong desire to include Hattis, at least as a reviewer, to ensure that the method is appropriately applied. Another panelist suggested that although the Hattis method is complex, it is sufficiently well described for others to follow the procedure.
5. Characterization of the shape of the dose-response curve for mutagenic carcinogens (submitted by Bob Tardiff). The approach of this case study would be to collect information on the shape of the dose-response curves for mutagenic carcinogens, and determine whether linear or nonlinear low-dose relationships predominate. Among the compounds of interest to be examined are acrylamide and trichloropropane. **Panel discussion:** There was some discussion of the relationship between this case study, the one on the shape of the dose-response for genotoxic endpoints (See Appendix p. D-23) and the one on consideration of multiple contributors to MOA for tumor modeling (See Appendix p. D-22). **Panel recommendation:** Two of the panel members will review the full e-mail proposal and make a recommendation to the full panel as to whether this case study would provide useful additional information for the overall knowledge base and should go forward. One panelist noted that the evaluation of the dose response should consider the key events, not just the shape of the tumor dose-response curve.
6. The panel noted that the data fusion case study (See Appendix p. D-19) was a work in progress and the full case study will need review at the third workshop.

Case Study Ideas From the First Workshop

A number of case studies that were accepted at the first workshop were not carried through to the second workshop, for a variety of reasons, including insufficient time to develop the case study. Case studies in this category and not in the above list were:

1. IUEBK model prediction incorporating exposure distribution and background exposure (applied to lead)
2. Mode of action for tumors in mice/rats following oral exposure – hexavalent chromium (not ready for second workshop, consider whether it may be ready for the third workshop)
3. DNA damage by intracellularly-generated formaldehyde as a carcinogenic MOA (e.g., methanol, MTBE)
4. Inter-individual variability in cancer susceptibility – 4-aminobiphenyl from the Silver Book (breakout group recommended using formaldehyde as a case study instead – as is being noted in the case study discussion, see Appendix p. D-21)
5. Considering uncertainty in cancer dose-response assessment – develop a method or framework for conducting comparable uncertainty analyses on both default/statistical-

modeling methods and BBDR-based methods. (plenary session recommended that this be addressed in the formaldehyde case study)

6. Consideration of endogenous processes: 1,4-Dioxane from the Silver book (would demonstrate conceptual model 1)
7. Evaluate a series of toxicological values (e.g., pesticide RfDs based on nongenotoxic MOAs) to identify all the health effects endpoints, and group/cluster the chemicals based on toxicity end points, MOA, etc. to develop more generalized approaches.

Case Study Ideas Provided Post-Workshop or After the Panel Discussion

1. A member of an environmental nongovernmental organization (NGO) suggested it might be helpful to include a case study on endocrine disruptors.
2. Biological equivalents method for using and interpreting internal dose metrics. A number of papers have been published on the methods and case studies. Contacts are Sean Hays, Lesa Aylward, Chris Kirman.
8. A case study addressing sensitive life stages, e.g., developmental toxicity, rather than an apical effect based on a chronic study. Mike Bolger of FDA offered to use lead as a case study for this area, with the idea that it would also be a proof of concept for Conceptual Model #3 of NAS (2009) (no individual or population threshold).
9. Other aspects of variability – e.g., disease state, co-exposure, etc. were also noted for potential case studies.
10. A panel member noted the need to include safe dose methods in the methods document, although this panelist did not believe there was a need for a separate case study.
11. One panel member noted the need to include Threshold of Toxicological Concern (TTC) in the methods document, although this panelist did not believe there was a need for a separate case study. TTC is related to the Threshold of Concern (TOC) approach discussed in the context of the case study on tiered screening (Appendix p. D-18). A panelist noted that the ILSI/HESI subcommittee on Methodology for Intermittent and Short-Term Exposure to Carcinogens (MISTEC) used TTC and expanded the approach to other groups of chemicals beyond the initial analysis done by Kroes et al. (2000). A webinar participant (PFC) noted that ILSI North America has done work on TTC as part of its Global Threshold Project[5].
12. Approaches based on QSAR (quantitative-structure active relationship) for developing dose-response relationships. Nina Wong of the U.S. EPA has a paper on the use of QSAR for development of EPA's Provisional Peer-Reviewed Toxicity Values (PPRTVs).
13. A panel member suggested a risk vs. risk comparison (e.g., comparative carcinogenic and neurotoxic potencies of tetrachloroethylene and n-propyl bromide).
14. A panel member suggested a case study to address the impact of human variability in susceptibility on the dose-response for carcinogens acting via a mutagenic MOA (i.e., ones for which linear extrapolation would be done).

[5] Refining the Threshold of Toxicological Concern (TTC) for Risk Prioritization of Trace Chemicals in Food 2009
Authors: S. Felter, R.W. Lane M.E. Latulippe, G.C. Llewellyn, S.S. Olin, J.A. Scimeca, and T.D. Trautman
Journal: *Food and Chemical Toxicology*

15. Several participants noted that additional methods documents exist for acute exposure limits, including ATSDR MRLs, and OECD acute RfC and RfD guidance documents.
16. Demonstration of conceptual models 1 and 3 from NAS (2009).
17. A workshop participant suggested that a group was interested in doing a case study on adducts generated endogenously vs. exogenously

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