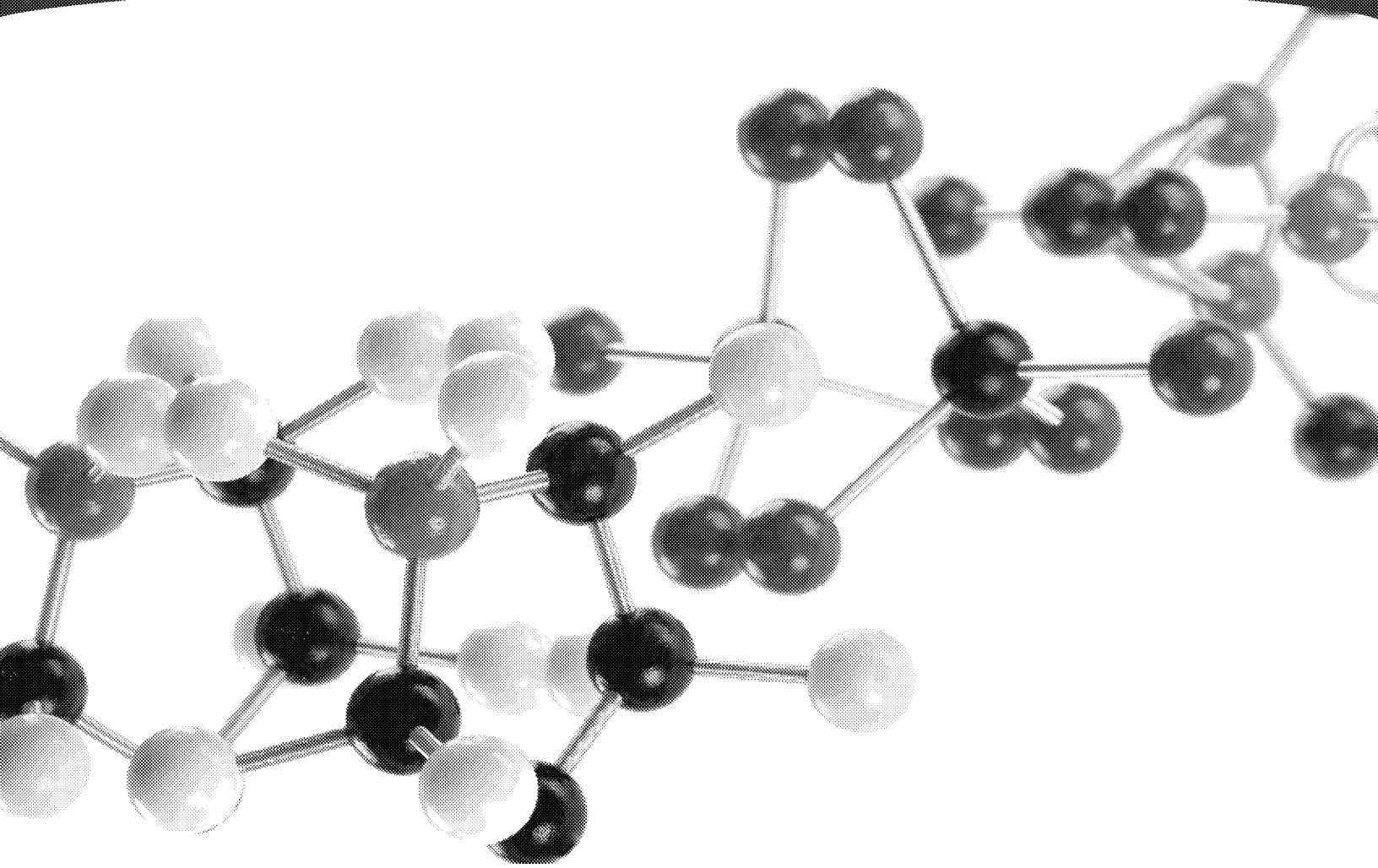

Beyond Science & Decisions: From Problem Formulation to Dose-Response Workshop VI

May 28, 29, & 30, 2013
U.S. Environmental Protection Agency
Arlington, VA

A Project of the
Alliance for Risk Assessment

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Workshop Information

Workshop Title: Beyond Science and Decisions:
From Problem Formulation to Dose-Response Assessment
Workshop VI

Workshop Site: United States Environmental Protection Agency
Potomac Yard, Arlington, Virginia

Workshop Dates: May 28, 29, & 30th, 2013

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Workshop Series Sponsors

The Alliance for Risk Assessment would like to sincerely thank our sponsors who brought this workshop to life. This would not have been possible without the collaborative efforts of federal and state government agencies, scientific societies, industry groups, consulting firms, and environmental non-profits. The *ARA* would like to recognize:

- Academy of Toxicological Sciences
- Agency for Toxic Substances and Disease Registry
- American Chemistry Council Center for Advancing Risk Assessment Science and Policy
- American Cleaning Institute
- American Petroleum Institute
- American Water Works Association
- Center for Food Safety and Applied Nutrition of the US Food and Drug Administration
- Council of Producers & Distributors of Agrotechnology
- Chemical Producers and Distributors Association
- Chemical Specialty Products Association
- Consortium for Environmental Risk Management LLC
- CropLife America
- Dose Response Specialty Group of Society for Risk Analysis
- Electric Power Research Institute
- ENVIRON
- Ethylene Oxide Panel of the American Chemistry Council
- The Hamner Institute for Health Sciences
- Georgia Department of Natural Resources
- Georgia Pacific
- Gradient
- Grocery Manufacturers Assocation
- Hawai'i State Department of Health; Hazard Evaluation and Emergency Response
- Human Toxicology Project Consortium
- Illinois Environmental Protection Agency
- Indiana Department of Environmental Management
- Industrial Economics, Incorporated
- International Copper Association
- International Society of Regulatory Toxicology and Pharmacology
- The LifeLine Group
- The Mickey Leland National Urban Air Toxics Research Center
- Minnesota Pollution Control Agency
- The Naphthalene Council
- National Center for Toxicological Research
- New Zealand Ministry of Health
- Nickel Producers Environmental Research Association
- Noblis
- NSF International
- Ohio Environmental Protection Agency
- Ontario Ministry of the Environment
- Personal Care Products Council
- Pastor, Behling & Wheeler, LLC
- Regulatory and Safety Evaluation Specialty Section of Society of Toxicology
- Risk Assessment Specialty Section of Society of Toxicology
- The Sapphire Group
- SC Johnson & Son
- Society of Chemical Manufacturers Association
- Society for Risk Analysis
- Society of Toxicology
- Styrene Information and Research Council
- Summit Toxicology
- Ted Simon Toxicology
- Texas Association of Business
- Texas Chemical Council
- Texas Commission on Environmental Quality
- Texas Industry Project
- Toxicology Excellence for Risk Assessment
- U.S. Environmental Protection Agency

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Workshop Background & Purpose

The workshop series is continuing and expanding upon the discussion set forth by Science and Decisions: Advancement of Risk Assessment (NAS, 2009); these meetings are conducted under the aegis of the Alliance for Risk Assessment (*ARA*), a broad-based non-profit, government and NGO coalition. The first phase of the workshop series was three workshops over the course of about a year. The first workshop was held at the Texas Commission on Environmental Quality (TCEQ), Austin, Texas, and focused on brainstorming and selection of case studies illustrating various dose-response methods for different problem formulations. A broad range of case studies proposed at the first workshop was then developed by workshop participants and discussed by the Science Panel at the second workshop, held in Crystal City, Virginia. In considering the case studies, the Science Panel members provided input on the utility of the case study methods to address specific problem formulations, and identified areas for additional development. The Science Panel and interested workshop participants developed an interactive framework (http://www.allianceforrisk.org/Workshop/Framework/ProblemFormulation.html) for organizing case study methods, and the Panel used the framework to identify additional case studies that address important gaps in methodology; the third workshop (held at the Noblis facilities in Falls Church, Virginia) focused on these case studies and associated issues. The framework references specific risk assessment methods, illustrated by case studies, and is intended for use by risk assessors and managers in a variety of settings (e.g., federal, state, and local agencies, industry). It is based on the fundamental premise that the appropriate methodology for dose-response assessment is necessarily based on objectives specific to that application, including varying levels of analysis. A manuscript describing the framework and workshop process is in preparation.

The workshop series has transitioned to an "evergreen" approach, including a standing panel that reviews methods and issues on a semi-annual basis, leading to updating of the framework. The standing panel was constituted in February 2012. Core panel members will serve for 2-3 years; members may be added to the standing panel to ensure expertise on specific topics. Panel members were selected by the ARA Steering Committee to reflect a diversity of affiliations and areas of expertise, particularly biology/toxicology, risk assessment, and statistical/modeling. Under this evergreen approach, the workshop series is funded by organizations that desire technical feedback on the methods underyling case studies that might fit within the developing framework, from small grants to continue the development of the framework, and by donated time and in-kind resources. In addition, the funding is anticipated to cover a limited number of case studies and/or methods papers on broader topics chosen by the science panel.

Under this model, the fourth workshop was held at the TCEQ in Austin, Texas, and included four case studies submitted by sponsoring organizations, as well as several updates on topics of broader interest to the risk assessment community. The fifth workshop was held entirely via webinar, and focused primarily on presentations of interest to the risk assessment community, with one preliminary case study review. All presentations and case studies from the entire workshop series are available at the workshop website, http://www.allianceforrisk.org/workshop/casestudies/index.html.

Workshop Goal

The workshop purpose is to advance the recommendations of the NAS (2009) and subsequent framework of *ARA* (Meek et al., 2013) on problem formulation and dose-response analysis, through review of illustrative case studies for further development of methods.

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General Workshop Series Objectives:

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

- Implement a multi-stakeholder approach to share information, ideas and techniques in support of developing practical problem-driven risk assessment methods compendium.

Specific Workshop Objectives:

- Identify useful dose-response techniques for specific issues, including consideration of relevant data, characterization of assumptions, strengths and limitations, and how the techniques address key considerations in the dose-response.

- These techniques should appropriately reflect the relevant biology (including the biology of thresholds), and mode of action information, at a level of detail appropriate for the identified issue.

- Provide methods to explicitly address human variability in cancer assessment, and enhance the consideration of human variability in noncancer assessment, including explicit consideration of underlying disease processes, as appropriate for the relevant risk assessment context.

- Identify methods for calculating the probability of response for noncancer endpoints, as appropriate for the relevant risk assessment context.

- Develop a risk methods compendium that will serve as a resource for regulators and scientists on key considerations for applying selected dose-response techniques for various problem formulations, with suggested techniques and resources.

Stakeholders

Alliance for Risk Assessment (ARA)

The Beyond Science & Decisions Workshop Series is a project of the Alliance for Risk Assessment, a collaboration of organizations teaming to take on projects that are too big or too complex for an individual company or organization to address. The work of the *ARA* focuses resources to help meet the needs of State, Local, and Tribal risk assessors. Learn more at www.allianceforrisk.org.

ARA Steering Committee

The Alliance for Risk Assessment Steering Committee (*ARA* SC) provides oversight of the workshop series. The Steering Committee advises the Dose Response Advisory Committee (DRAC) on charge questions and has the final decision on members of the Science Panel after a review of all nominations. The ARA SC membership has included of a broad range of state, tribal, federal government, academic, and environmental NGO representatives. The SC consists of 9 representatives of state, tribal, and federal government, academia, and NGOs, two of whom recused themselves on aspects of this project due to membership on the DRAC. See www.allianceforrisk.org/ARA_Steering_Committee.htm.

Annette Dietz, Oregon Department of Environmental Quality
Michael Habeck, Indiana Department of Environmental Management
Bette Meek, University of Ottawa/Health Canada (liaison with the DRAC)
Anita Meyer, United States Army Corps of Engineers
Edward Ohanian, United States Environmental Protection Agency
Ralph Perona, Neptune & Company, Inc.
Phil Wexler, National Library of Medicine

Michael Dourson, Toxicology Excellence for Risk Assessment (recused)
Michael Honeycutt, Texas Commission on Environmental Quality (recused for meetings I to III)

Dose-Response Advisory Committee (DRAC)

The workshop sponsors are composed of federal, state, industry, and NGO organizations. The Dose-Response Advisory Committee interacts with these various sponsors in the development of workshop structure and charge questions, and recruitment of presenters. The DRAC has the final decision on workshop structure, presenters, and content, after consultation with the *ARA* Steering Committee and Science Panel. Current members include:

Rick Becker, American Chemistry Council
Tiffany Bredfeldt, Texas Commission on Environmental Quality
Michael Dourson, Toxicology Excellence for Risk Assessment
Julie Fitzpatrick, U.S. Environmental Protection Agency
Roberta L. Grant, Texas Commission on Environmental Quality
Lynne Haber, Toxicology Excellence for Risk Assessment
Lynn H. Pottenger, The Dow Chemical Company
Jennifer Seed, U.S. Environmental Protection Agency

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Workshop VI Agenda

Agenda
Date: May 28, 29 & 30, 2013

Location: U.S. Environmental Protection Agency, Washington, D.C.

Purpose: To advance the recommendations of NAS (2009) and subsequent framework of *ARA* (Meek et al., 2013) on problem formulation and dose-response analysis, through review of illustrative case studies for further development of methods

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Tuesday May 28th

Welcome (1:00 to 1:15)
- Julie Fitzpatrick, U.S. Environmental Protection Agency

Introductions and Updates (1:15 to 1:30)
- Lynne Haber, TERA, on behalf of the Dose-Response Advisory Committee
- Introductions - Members of the Science Panel

Case Study: Endogenous Formation Implications for Formaldehyde Carcinogenicity (1:30 to 3:00)
- Robinan Gentry, Environ International Corporation
- Tom Starr, TBS Associates
- Jim Swenberg, University of North Carolina Chapel Hill
- Jeffry Schroeter, Applied Research Associates

Afternoon Break (3:00 to 3:30)

Case Study: Endogenous Formation Implications for Formaldehyde …continued (3:30 to 5:30)

Reception (dinner portion hors d'oeuvres, 6:30 to 8:30)

Wednesday, May 29th

Keynote Talk (8:30 to 9:30)
- Ken Olden, U.S. EPA, National Center for Environmental Assessment

Pathway-Based Regulatory Toxicology and Alternatives to Animal Testing (9:30 to 10:00)
- Thomas Hartung, Johns Hopkins Bloomberg School of Public Health (via webinar)

Morning Break (10:00 to 10:30)

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International Developments on Mode of Action (10:30 to 11:00)

- Bette Meek, University of Ottawa

The HESI RISK21 Roadmap: Practical Application to Pyrethroid Human Safety Assessment (11:00 to 11:30)

- Tim Pastoor, Syngenta Crop Protection, Inc.

The HESI RISK21 Quantitative Key Events Dose Response Framework (Q-KEDRF) (11:30 to noon)

- Ted Simon, Ted Simon, LLC

Lunch (12:00 to 1:00)

Case Study: Hypothesis-Driven Weight of Evidence Review for Naphthalene Carcinogenicity (1:00 to 2:30)

- Lorenz Rhomberg, Gradient
- Lisa Bailey, Gradient

Afternoon Break (2:30 to 3:00)

Case Study: Hypothesis-Driven continued… (3:00 to 5:00)

Observer Comments (5:00 to 5:30)

Thursday, May 30th

Case Study: Interpretation of 24-hour Sampling Data (8:30 to 10:00)

- Roberta Grant, Texas Commission on Environmental Quality
- Joseph "Kip" Haney, Texas Commission on Environmental Quality
- Allison Jenkins, Texas Commission on Environmental Quality
- Denis Jugloff, Ontario Ministry of Environment
- Julie Schroeder, Ontario Ministry of Environment (in absentia)

Morning Break (10:00 to 10:30)

Case Study: Interpretation of 24-hour Sampling Data (cont) (10:30 to 12:30)

Observer Comments (12:30 to 1:00)

Adjourn (1:00)

Closed Panel Discussion (1:00 to 5:00)

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Biographical Sketches

Welcome

Julie Fitzpatrick, U.S. Environmental Protection Agency

Julie Fitzpatrick is the Coordinator of the U.S. Environmental Protection Agency's Risk Assessment Forum. Ms. Fitzpatrick has 25 years professional experience focused on human health risk assessment. Julie leads the Risk Assessment Forum's effort to respond to the National Research Council's recommendations focusing on advancing human health risk assessment. Previously, she managed expert working groups, for the International Life Sciences Institute (ILSI) Research Foundation in advancing risk assessment science. Her experience also includes providing risk assessment technical support to CERCLA and RCRA staff in EPA's Region 4 office, independent risk assessment consulting services, and technical and project management staff at several environmental consulting firms. She is currently the chair of the Society for Risk Analysis' Dose Response Specialty Group. Ms. Fitzpatrick received a Master of Science degree from Georgia Institute of Technology.

Science Panel

Richard Beauchamp, Texas Department of State Health Services

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

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

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duration, using up to 46 different age intervals, to insure that childhood exposures are appropriately addressed.

James S. Bus, Exponent

James S. Bus is a Senior Managing Scientist in the Center for Toxicology and Mechanistic Biology in the Health Sciences Group of Exponent, a leading global consulting firm (May 2013-present). His primary responsibilities at Exponent are to provide toxicology expertise for addressing client product stewardship and regulatory needs associated with industrial and pesticide chemicals. Prior to joining Exponent, Dr. Bus retired from The Dow Chemical Company as Director of External Technology, Toxicology and Environmental Research and Consulting (1989-2013). He also 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 serves on the Boards of Directors of The Hamner Institutes (formerly CIIT) and the ILSI Research Foundation. He has also has served as Chair of the American Chemistry Council and International Council of Chemical Associations Long-Range Research Initiatives; the Board of Directors of ILSI-HESI; the USEPA Office of Research and Development Board of Scientific Counselors (1997-2003) and Chartered Science Advisory Board (2003-2009); the National Toxicology Program Board of Scientific Counselors (1997-2000); the FDA National Center for Toxicological Research Science Advisory Board (2004-2010); and the National Academy of Sciences/National Research Council Board on Environmental Studies and Toxicology (BEST; 2005-2011). He has served 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; President, 2010-2011). Dr. Bus received the Society of Toxicology Achievement Award (1987) for outstanding contributions to the science of toxicology; the Society of Toxicology Founders Award (2010) for leadership fostering the role of toxicology in improving safety decisions; Rutgers University Robert A. Scala Award (1999) for exceptional work as a toxicologist in an industry laboratory; and the K.E. Moore Outstanding Alumnus Award (Michigan State University, Dept. Pharmacol. And Toxicol.). He received his B.S. in Medicinal Chemistry from the University of Michigan (1971) and Ph.D in pharmacology from Michigan State University (1975) and currently is an Adjunct Professor in the Dept. Pharmacology and Toxicology at that institution. His research interests include mechanisms of oxidant toxicity, chemical and pesticide modes of action, defense mechanisms to chemical toxicity, relationships of pharmacokinetic and exposures information to expression of chemical toxicity, and general pesticide and industrial chemical toxicology. He has authored/co-authored over 100 publications, books, and scientific reviews.

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

Rory Conolly is a Senior Research Biologist in the Integrated Systems Toxicology Division of the U.S EPA's National Health and Environmental Effects Research Laboratory in Research Triangle Park, North Carolina, USA. His major research interests are (1) biological mechanisms of dose-response and time-course behaviors, (2) the use of computational modeling to study these mechanisms and, (3) the application of computational models to quantitative dose-response assessment. Dr. Conolly received the U.S. Society of Toxicology's (SOT) Lehman Award for lifetime achievement in risk assessment in 2005.

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He was a member of the National Academy of Sciences Board on Environmental Studies and Toxicology from 2004 until joining the EPA in 2005, President of the SOT Biological Modeling Specialty Section (2000 – 2001), President of the SOT Risk Assessment Specialty Section (1997 - 1998), a member of the SOT Risk Assessment Task Force (1998 - 2000) and is currently a Councilor with the Risk Assessment Specialty Section. He is Adjunct Professor of Biomathematics at North Carolina State University, Faculty Affiliate, Department of Environmental and Radiological Health Sciences, Colorado State University and has four times received awards from the SOT Risk Assessment Specialty Section (1991, 1999, 2003, 2004). Dr. Conolly was born in London, England and raised in Canada and the United States. He received a bachelor's degree in biology from Harvard College in 1972, a doctorate in physiology/toxicology from the Harvard School of Public Health in 1978, and spent a post-doctoral year at the Central Toxicology Laboratory of Imperial Chemical Industries, PLC, in Cheshire, England. He was a member of the Toxicology Faculty at The University of Michigan School of Public Health from 1979 through 1986, and worked with the U.S. Air Force Toxic Hazards Research Division, Wright-Patterson Air Force Base, Ohio from 1986 until 1989. In 1989 Dr. Conolly joined the Chemical Industry Institute of Toxicology (CIIT) and worked there until 2005, when he joined the U.S. EPA.

Mike Dourson, Toxicology Excellence for Risk Assessment

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

Annie M. Jarabek, U.S. EPA, Office of Research and Development (Tentative)

Annie M. Jarabek is a senior toxicologist in the immediate office of the National Center for Risk Assessment (NCEA) within the US EPA's Office of Research and Development (ORD). Annie is the principal author of the US EPA's Methods for Derivation of Inhalation Reference Concentrations (RfC) and Application of Inhalation Dosimetry, which introduced dosimetry and physiologically-based pharmacokinetic (PBPK) model structures and reduced forms into the RfC methods for interspecies adjustment. She has worked on several high-priority and interdisciplinary Agency assessments including the risk characterization of perchlorate ingestion and the inhalation of particulate matter (PM); and has served in an advisory capacity on other methods and assessments, including the guidance on body-weight scaling for harmonizing noncancer and cancer approaches for the interspecies adjustment of ingested chemicals. Her current research efforts focus on multi-scale modeling of dose-response and decision analysis. Annie has twice received awards for best manuscript in risk assessment application from the Risk Assessment Specialty Section (RASS) of the Society of Toxicology (SOT), along with several best

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abstract awards. She has also received the Lifetime Achievement Award from the University of Massachusetts, the Risk Practitioner of the Year award from the Society of Risk Analysis (SRA), the Superfund National Notable Achievement Award, and several award medals (1 gold, 1 silver and 5 bronze) and "S awards" for scientific leadership from the Agency for her various contributions. Annie has served as an elected Councilor to the Society for Risk Analysis and as the vice-president/president of the SOT RASS. Annie has also served the SOT on its awards, communications, nominations, and scientific program committees. She is currently on the editorial board of the international journal "Dose-Response."

R. Jeffrey Lewis, ExxonMobil Biomedical Sciences, Inc.

Dr. R. Jeffrey Lewis is currently Section Head of the Epidemiology, Health Surveillance and Quality Assurance group at ExxonMobil Biomedical Sciences, Inc (EMBSI). In this position, Dr Lewis is responsible for managing EMBSI's Epidemiology and Health Surveillance group, the company's laboratory quality assurance program, and for providing support to ExxonMobil scientific programs related to 1,3-butadiene, naphthalene, asphalt, legislative/regulatory affairs and regulatory impact analysis (e.g., benefit-cost analysis). He has served on a number of industry trade association scientific committees (e.g., the American Chemistry Council's 1,3-butadiene Work Group), external science advisory boards (e.g., the Alliance for Risk Assessment Expert Science Panel) and is a member of the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) Committee. Dr. Lewis also has an adjunct faculty appointment at the University of Texas School of Public Health and is Past Treasurer for the Society for Risk Analysis. Dr. Lewis received his Bachelor 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 Master of Business Administration degree 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.

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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.

Alan Stern, New Jersey Department of Environmental Protection

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

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New York, 2006.), and the article on *Environmental Health Risk Assessment// in the Encyclopedia of Quantitative Risk Assessment and Analysis*. John Wiley and Sons Ltd., 2008.

Speaker Biographies & Abstracts

Ken Olden, U.S. Environmental Protection Agency

Dr. Ken Olden joined the National Center for Environmental Assessment as Director in July 2012 with a strong legacy of promoting scientific excellence in environmental health. From 1991-2005, Ken served as the Director of the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP) in the U.S. Department of Health and Human Services. Ken made history in this role as the first African American to direct one of the National Institutes of Health. In 2005, he returned to his research position as chief of The Metastasis Group in the Laboratory of Molecular Carcinogenesis at the NIEHS, and for academic year 2006-2007, held the position of Yerby Visiting Professor at the Harvard School of Public Health. Most recently, Ken served as the Founding Dean of the School of Public Health at the Hunter College, City University of New York.

He has published extensively in peer-reviewed literature, chaired or co-chaired numerous national and international meetings, and has been an invited speaker, often a keynote, at more than 200 symposia. Ken has won a long list of honors and awards including the Presidential Distinguished Executive Rank Award, the Presidential Meritorious Executive Rank Award for sustained extraordinary accomplishments, the Toxicology Forum's Distinguished Fellow Award, the HHS Secretary's Distinguished Service Award, the American College of Toxicology's First Distinguished Service Award, and the National Minority Health Leadership Award.

Alone among institute directors, he was awarded three of the most prestigious awards in public health--the Calver Award (2002), the Sedgwick Medal (2004), and the Julius B. Richmond Award (2005). Most recently, he received the Cato T. Laurencin MD, PhD Lifetime Research Award from the National Medical Association Institute, the largest and oldest national organization representing African American physicians and their patients in the United States. He was elected to membership in the Institute of Medicine at the National Academy of Sciences in 1994 and appointed member of the Visiting Committee for the Harvard University Board of Overseers from 2007-2010.

Thomas Hartung, Johns Hopkins Bloomberg School of Public Health, Centers for Alternatives to Animal Testing

Thomas Hartung, MD PhD, is Professor of Toxicology (Chair for Evidence-based Toxicology), Pharmacology, Molecular Microbiology and Immunology at Johns Hopkins Bloomberg School of Public Health, Baltimore, and University of Konstanz, Germany; he also is Director of their Centers for Alternatives to Animal Testing (CAAT, http://caat.jhsph.edu/) with the portal AltWeb (http://altweb.jhsph.edu). CAAT hosts the secretariat of the Evidence-based Toxicology Collaboration (http://www.ebtox.com/) and the industry refinement working group. As PI, he heads the Human Toxome project funded as an NIH Transformative Research Grant. He is the former Head of the European Center for the Validation of Alternative Methods (ECVAM), Ispra, Italy. He has authored more than 370 scientific publications.

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Abstract: Pathway-Based Regulatory Toxicology and Alternatives to Animal Testing

A mechanistic toxicology has evolved over the last decades, which is effectively relying to a large extent on methodologies which substitute or complement traditional animal tests. The biotechnology and informatics revolution of the last decades has made such technologies broadly available and useful. Regulatory toxicology has only slowly begun to embrace these new approaches. Major validation efforts, however, have delivered the evidence that new approaches do not necessarily lower safety standards and can be integrated into regulatory safety assessments, especially in integrated testing strategies. Political pressures especially in the EU, such as the REACH legislation and the 7th amendment to the cosmetic legislation, further prompt the need of new approaches. In the US, especially the NAS vision report for a toxicology in the 21st century and its most recent adaptation by EPA for their toxicity testing strategy have initiated a debate how to create a novel approach based on human cell cultures, lower species, high-throughput testing and modeling. The report suggests moving away from traditional (animal) testing to modern technologies based on pathways of toxicity. These pathways of toxicity could be modeled in relatively simple cell tests, which can be run by robots. The goal is to develop a public database for such pathways, the Human Toxome, to enable scientific collaboration and exchange.

The problem is that the respective science is only emerging. What will be needed is the Human Toxome as the comprehensive pathway list, an annotation of cell types, species, toxicant classes and hazards to these pathways, an integration of information in systems toxicology approaches, the in-vitro-in-vivo-extrapolation by reversed dosimetry and finally making sense of the data, most probably in a probabilistic way. The NIH is funding since September 2011 by a transformative research grant our Human Toxome project (http://humantoxome.com). The project involves US EPA ToxCast, the Hamner Institute, Agilent and several members of the Tox-21c panel. The new approach is shaped around pro-estrogenic endocrine disruption as a test case.

Early on, the need for quality assurance for the new approaches as a sparring partner for their development and implementation has been noted. The Evidence-based Toxicology Collaboration (EBTC, http://www.ebtox.com) was created in the US and Europe in 2011 and 2012, respectively. This collaboration of representatives from all stakeholder groups aims to develop tools of Evidence-based Medicine for toxicology, with the secretariat run by CAAT. All together, Tox-21c and its implementation activities including the Human Toxome and the EBTC promise a credible approach to revamp regulatory toxicology.

Bette Meek, University of Ottawa

See Panel biography.

Abstract: International Developments on Mode of Action

The WHO/IPCS mode of action/human relevance (MOA/HR) framework has recently been updated to reflect evolving experience in its application and to incorporate recent developments in toxicity testing and non-testing methods. The modified framework is incorporated within an iterative roadmap, encouraging continuous refinement of problem formulation, mode of action based testing strategies and risk assessment. It can be used as originally intended, where the outcome of chemical exposure is known,

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or in hypothesizing potential effects resulting from exposure, based on information on putative key events in established modes of action from appropriate in vitro or in silico systems and other evidence.

The implications of the experience acquired in application of the framework in addressing documented (adverse) effects to inform the more limited knowledge base in these more predictive applications are addressed. This is illustrated in various case examples including the use of mode of action analysis in prioritizing substances for further testing, in guiding development of more efficient testing strategies and in identifying critical data gaps and testing strategies in read-across.

In addition to clarifying terminology related to the essentially conceptually synonymous terms of mode of action and adverse outcome pathways, the Bradford Hill (BH) considerations have also been articulated as a basis to simplify their application in considering weight of evidence for hypothesized modes of action. Templates for extension of the species concordance table in the original framework to dose–response analysis and comparative assessment of weight of evidence and associated uncertainty for various modes of action based on the simplified BH considerations have also been developed.

Contribution of these developments to international initiatives on advancement of integrated test strategies based on evolving methods will also be addressed.

Ted Simon, Ted Simon, LLC

Dr. Simon is the principal and owner of Ted Simon, LLC, providing scientific consulting services to clients that include large and small private sector companies, attorneys, industry trade groups, environmental assessment and remediation firms, state, federal and international regulatory agencies, universities and others. He provides scientific support in the areas of toxicology, environmental risk assessment, product liability, statistics, drug and alcohol abuse, and other issues. He has taught graduate level university courses He has provided litigation support as expert testimony and consultation for both private sector clients and EPA. As a consulting scientist, Dr. Simon has worked on environmental and toxicological issues related to dioxin, PAHs, PCBs, arsenic, chromium, mercury, and other chemicals. He has performed pro bono work for the Georgia Department of Natural Resources and the International Life Sciences Institute and others. Previously, Dr. Simon was employed by the Environmental Protection Agency, Region 4, in Atlanta. While at EPA, Dr. Simon served as the senior toxicologist in the Waste Management Division.

Abstract: Quantitative Key Events Dose Response Framework from ILSI and RISK21

Advancing the existing MOA / Human Relevance Framework (HRF) and Key Events / Dose-Response Framework (KEDRF) to make best use of quantitative dose-response and timing information for Key Events produced the Quantitative Key Events / Dose-Response Framework (Q-KEDRF). The Q-KEDRF provides a structured quantitative approach for systematic examination of the dose-response and timing of Key Events from the initial dose of a bioactive agent to the potential adverse outcome. Two concepts are introduced as aids to increasing the understanding of MOA—Associative Events and Modulating Factors. These concepts are illustrated using two case studies; 1) cholinesterase inhibition by the pesticide chlorpyrifos, which illustrates the necessity of considering quantitative dose-response information when assessing the effect of a Modulating Factor—here, enzyme polymorphisms in humans, and 2) estrogen-induced uterotrophic response in rodents, which demonstrates how quantitative dose-response modeling for Key Events, the understanding of temporal relationships between Key Events, and a counterfactual examination of hypothesized Key Events can determine whether they are Associative Events or true Key Events.

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Tim Pastoor, Syngenta Crop Protection, Inc.

Dr.Tim Pastoor obtained his Ph.D. in toxicology from the University of Michigan, is certified by the American Board of Toxicology (DABT), and is a member of the Society of Toxicology. Dr. Pastoor has over 30 years of international experience in fundamental toxicity testing, mode of action research, and human health risk assessment.

At Syngenta Crop Protection, Dr. Pastoor led the toxicology and risk assessment group in developing human safety data for regulatory and research purposes. In his current role as Principal Scientist for Syngenta Crop Protection, Dr. Pastoor oversees toxicological research projects and product development and is a frequent lecturer on toxicology and risk assessment subjects.

Abstract: The HESI RISK21 Roadmap: Practical Application to Pyrethroid Human Safety Assessment

The RISK21 Roadmap is a straightforward, efficient, and systematic way to achieving a transparent assessment of human health risk to chemicals. The Roadmap is a problem-formulation based, exposure-driven, and tiered methodology that seeks to derive only as much data as is necessary to make a safety decision. This presentation will use a RISK21 "pseudomethrin" case study to focus on how existing information and tiered data development can be used in human safety decision making. Pseudomethrin is envisioned as the next pyrethroid in a group of 11 well-tested pyrethroids. Problem formulation asks how much data is needed to decide that pseudomethrin could be used on bed netting with reasonable certainty of no harm. The RISK21 exposure-driven process that utilizes prior information on existing pyrethroids shows what toxicological data would be necessary to achieve this decision.

Rapporteur

Lynne Haber, Toxicology Excellence for Risk Assessment

Dr. Haber is the Associate Director of *TERA*, responsible for strategic direction, training and overall quality initiatives at *TERA*. She has 18 years of experience in development of assessment documents and in risk assessment methods development, including consideration of mechanism/mode of action. She was the lead author of more than 30 major documents for multiple EPA offices, other government agencies, and private sponsors, and has been a coauthor or reviewer of 100's more. She has served as a panel chairperson or panel member for scientific peer reviews organized by *TERA*, EPA, and other U.S. and foreign government agencies. She has also served on two panels for the NAS/NRC. Dr. Haber is active in communicating her findings to the broader scientific community through participation in professional societies, routine publication of her work, authoring book chapters, service as an editorial reviewer for scientific journals, and through presentation of invited lectures. She has experience in benchmark concentration/ benchmark dose (BMC/BMD) modeling and categorical regression modeling, and served as a peer reviewer for EPA's BMD modeling guidelines. Other methods development work includes the combination of PBPK and BMD/BMC modeling in the development of RfDs and RfCs; research into methods for improving the scientific basis for uncertainty factors by addressing genetic polymorphisms; consideration of mode of action in cancer risk assessment; toxicology issues related to children's risk; and use of biomarker data in risk assessment. She served as chair-elect, vice president and councilor of the SRA Dose-Response specialty group and as an officer of the SOT Risk Assessment Specialty Section (RASS), and is a Diplomate of the American Board of Toxicology. She is one of the lead teachers for *TERA*'s Dose-Response Assessment Boot Camp, developed a course on issues related to children's risk assessment, and presents specialized risk assessment courses to diverse groups of risk assessors and at professional society meetings.

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Case Studies

Case Study: Endogenous Chemical Risk Assessment: Formaldehyde as a Case Example

Robinan Gentry, Environ International Corporation; Tom Starr, TBS Associates; Jim Swenberg, University of North Carolina Chapel Hill

Abstract

Conducting a dose-response assessment for endogenous compounds presents several challenges. The Science and Decisions (2009) report has indicated that it is possible that the dose-response curves for these types of compounds may be threshold-like, depending upon the magnitude of the background concentrations and toxic response. In addition, the dose-response curves may also appear to be linear if a detectable background level of toxicity occurs even without exogenous exposure and the exogenous exposure adds to or augments the background toxicity process, assuming the exogenous exposure does not induce an adaptive response. Formaldehyde provides an example of research and modeling activities being conducted to understand the endogenous concentrations of formaldehyde and the potential contribution of exogenous formaldehyde to the potential for health effects following inhalation exposure. The approaches demonstrate both the challenges in collecting the information needed to characterize internal doses in the low-concentration range, which is of significance to ambient exposure, as well as interpreting the results and the impact on understanding the dose-response for an endogenously present compound. These approaches can be extended to other compounds with endogenous DNA adducts that are identical to those produced by such chemicals as acetaldehyde, ethylene oxide and vinyl chloride. They may also be indicative of general phenomena related to endogenous DNA damage, as our DNA contains large amounts of endogenous DNA damage that are the reason for the well-known non-zero background of mutations, the biomarkers of effect that may be considered causal key events in carcinogenesis.

1. Summary of Method Illustrated by Case Study.

An understanding of the effects of background processes or endogenous concentrations is important in characterizing the shape of the dose-response curve in the low-dose region (e.g., linear versus nonlinear) for endogenously present compounds. Measuring concentrations of formaldehyde resulting from endogenous production versus exogenous exposure is a challenge, especially since formaldehyde is a reactive compound. However, recent studies in both rats and nonhuman primates employing stable isotope-labeled formaldehyde have differentiated between formaldehyde DNA adducts of endogenous and exogenous origin (Lu et al. 2011, 2012, Moeller et al. 2011). DNA adducts have been used as molecular dosimeters to reflect the internal dose of a genotoxic chemical in target tissues following exposure. These studies employed [13CD2]-formaldehyde for exogenous exposure, coupled with highly sensitive mass spectrometry detection methods. The results from these studies provide an alternate characterization of exposure that can be incorporated into dose-response assessments for the potential carcinogenicity of formaldehyde. The purpose of this case study is to discuss endogenous and exogenous formaldehyde DNA adducts and their application in two risk assessment approaches that accommodate endogenous production of formaldehyde: 1) a "bottom up" approach; and 2) a biologically-based dose-response (BBDR) model.[1]

[1] BBDR models for formaldehyde include computational fluid dynamic (CFD)-generated predictions of the regional flux of formaldehyde into tissues and parameters that are linked to two modes of action proposed for tumor development. These modes of action are described by parameters of a two-stage clonal growth model, which

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Empirical dose-response modeling, such as with empirical Weibull or multistage models, are based on statistical fits to the tumor dose-response in the observable range. These models are then used to extrapolate downward to environmentally relevant external exposure concentrations. The "bottom up" approach uses a simple linear model (Starr and Swenberg 2013) that can be extrapolated upward from background (endogenous) exposure and response levels, rather than downward from the observable response range. The approach is consistent with the ''additivity to background'' concept and yields both central and upper-bound risk estimates that are linear at all doses. In addition, it requires only information regarding background risk, background (endogenous) exposure, and the additional exogenous exposure of interest in order to be implemented. In the case of formaldehyde, the bottom-up approach uses DNA adduct levels arising from endogenous formaldehyde as the relevant dose metric to account for background risk.

In addition, the case study team is currently working on refining the target tissue dosimetry component of the formaldehyde biologically-based dose-response (BBDR) model to include a description of endogenous formaldehyde and characterize its impact on tissue uptake of exogenous formaldehyde (Schroeter et al. 2013). This revised characterization of target tissue dosimetry can be incorporated into the full BBDR models (Conolly et al. 2003, 2004) to characterize a range of plausible risk estimates.

2. **Describe the problem formulation(s) the case study is designed to address. How is the method described in the case useful for addressing the problem formulation?**

Conducting a risk assessment for a compound that is present endogenously poses several challenges. First, methods are needed to quantify endogenous production and differentiate DNA damage arising due to endogenous production from biochemically identical damage arising from exogenous exposure. Once such methods are developed and results are obtained, the additional challenge to the risk assessor is determining how to best interpret the results and incorporate those results into an appropriate dose-response assessment. The risk assessor must also attempt to determine whether exogenous exposures can increase the tissue levels sufficiently to create biological perturbations that culminate in detectable adverse effects.

Formaldehyde is present endogenously in all living cells; it is an essential metabolic intermediate. It also has numerous exogenous sources including vehicle emissions, off-gassing from building materials, and tobacco smoke; it arises as well as from the metabolism of foods, chemicals and drugs. In the case of formaldehyde, there are several questions that need to be addressed in conducting a dose-response assessment:

- How can we accurately assess the risk of exogenous formaldehyde in the presence of a substantial background of endogenous formaldehyde?
- What is needed to conduct a dose-response assessment considering the "background" concentrations that are always present in biological systems?
- If a specific marker is used to differentiate endogenous from exogenous exposure, can this be a biomarker of exposure or a biomarker of effect (related to the mode of action)?

The current case study has multiple purposes, the first of which focuses on the use of recent research on specific formaldehyde DNA adducts to characterize biomarkers of exposure for both endogenous and

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describes cancer as a succession of genetic changes and altered growth behaviors that lead to progressive conversion of normal cells into cancer cells. While the clonal growth model may not be an accurate representation of the actual cellular mechanism of formaldehyde carcinogenesis, it does provide insight into the relative importance of direct mutagenicity and cellular proliferation related to cytotoxicity in tumor development at high exogenous doses.

exogenous formaldehyde. The application of this information into two methods for estimating the dose-response curve (bottom up and BBDR) and the potential impact on the shape of the dose-response curve in the low concentration region are also discussed.

3. **Comment on whether the method is general enough to be used directly, or if it can be extrapolated, for application to other chemicals and/or problem formulations. Please explain why or why not.**

The approaches in this case study are not specific to formaldehyde. They can be extended to other compounds that may or may not be endogenously present. Initial work is underway to extend these methods to other endogenous compounds that produce DNA adducts such as acetaldehyde, ethylene oxide and vinyl chloride. The two approaches in this case study in which endogenous production has been accommodated (bottom-up approach and a component of the BBDR model) demonstrate the challenges that exist in collecting the appropriate information needed to characterize the dose-response curve in the low-concentration range, which is of great practical significance in estimating and bounding risks from ambient exposures. The DNA adducts relied upon in the case study may also be indicative of general phenomena related to endogenous DNA damage.

4. **Discuss the overall strengths and limitations of the methodology.**

Strengths:

- Use of biomarkers, such as specific DNA adducts, which are closer to the critical "target tissue" concentrations than is the corresponding external exposure concentration.
- Reliance on a highly sensitive and accurate method that differentiates between exogenous and endogenous concentrations.
- Approaches for the measurement of exposure biomarkers and application of the "bottom up" approach can be extended to other compounds.
- CFD modeling has been conducted to investigate the impact of the presence of endogenous formaldehyde on the site-specific absorption of exogenous formaldehyde in the nasal cavities of rats, monkeys, and humans.

Limitations:

- Reliance of the "bottom-up" approach on the assumption of a linear dose-response relationship restricts it to bounding low-dose cancer risks; it may not be appropriate for bounding risks in the observable response range, where nonlinear processes can dominate the dose-response relationship, or for developing "best" or central estimates of risks.
- Pharmacokinetic assumptions are required to convert the quantified biomarkers of exposure (DNA adducts) that are obtained in short-term animal studies to corresponding estimates arising from continuous lifetime exposures in humans.
- Potential variability in the endogenous concentrations present in humans has not yet been quantified, although interanimal variation in endogenous concentrations has been quantified and this variation has been employed explicitly in developing lower bound estimates of background endogenous concentrations in different tissues and species.

5. **Outline the minimum data requirements and describe the types of data needed.**

- Biomarkers of exposure that are plausibly linked to either the noncarcinogenic or carcinogenic process to characterize the endogenously present concentrations, as well as the contributions arising from exogenous exposure.

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- PK and, possibly, BBDR models to characterize the target tissue dosimetry associated with endogenous and exogenous exposure.
- Incorporation of data into the 'bottom up" approach and interpretation of results.

How this assessment addresses issues raised in Science & Decisions:

B. **Address background exposures and responses?** This case study demonstrates for an endogenously present compound the impact of endogenous and exogenous exposure on target tissue dosimetry and upper bounds on the dose-response curve in the low concentration region.

G. **Work practically?** The bottom up approach is a relatively easy method to apply, as long as the critical data are available.

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Case Study: Hypothesis-Based Weight of Evidence (Naphthalene as an Example)

Lorenz Rhomberg, Gradient

Abstract

Human health risk assessment consists of bringing to bear a large body of *in vitro*, animal, and epidemiologic studies on the question of whether environmental exposures to a substance are a potential risk to humans. The body of scientific information is typically less than definitive and often contains apparent contradictions. Often various possible conclusions about potential human risks may be drawn from the data and these may vary from very strong to tenuous. The task, therefore, is to communicate the uncertainties in the inferences from the data effectively, giving proper consideration to contrary data and alternative scientifically plausible interpretations. We describe an approach, Hypothesis-Based Weight of Evidence (HBWoE), to organize, evaluate, and communicate the large body of available relevant data on a given chemical, using naphthalene as an example. The goal for our use of the term "weight of evidence" (WoE) is broad in that we express the relative degrees of credence that should be placed in alternative possible interpretations of the naphthalene data and hypothesized carcinogenic modes of action, expressed in a way that shows how such credence is tied to specific scientific interpretations, considering consistencies, inconsistencies, and contradictions within the data set. Guided by the outcome of our WoE evaluation, we are conducting a dose-response evaluation of naphthalene exposure and neoplastic and non-neoplastic lesions, with the ultimate goal of deriving naphthalene toxicity values applicable to human health risk assessment that are consistent with an integrated evaluation of all realms of evidence for naphthalene (epidemiology, animal toxicology, mechanistic, and toxicokinetic). Our approach is to consider the applicability and limits on the animal responses – specifically the rat nasal tumors – to serve as a basis for estimation of potential human respiratory-tract cancer risk. We are doing this by considering the mode of action underlying the animal tumors seen in bioassays, including evaluation of the metabolic activation and detoxification of inhaled naphthalene as they depend on air concentration, as well as the nature, tissue locations, and dependence on tissue-dose of key precursor responses. Species differences in tissue dosimetry are used to evaluate whether parallel tissues in humans, or other tissues in the respiratory tract, will be subject to tissue doses that could prompt the key events of the apparent mode of action. The points of departure derived from rodent dose-response evaluations will be extrapolated to human equivalent concentrations through application of a rat/human PBPK model that describes cross-species dosimetry of the upper respiratory tract, lung, and liver.

1. Summary of Method Illustrated by Case Study

The Hypothesis-Based Weight of Evidence (HBWoE) framework is described in, and has evolved with, several of our recent publications (Rhomberg *et al.*, 2010; 2011; Prueitt *et al.*, 2011; Bailey *et al.*, 2012). It is hypothesis-based in the sense that it emphasizes articulation of the proposed bases for the relevance of the data to the causal question at hand, specifying the logic and reasoning. The approach integrates all of the relevant data (epidemiology, animal toxicology, mechanistic, toxicokinetic, *etc.*), both positive and negative, in terms of quality and relevance to humans in a way that allows each data set to inform interpretation of the other. The approach further synthesizes all of the data to determine overall plausibility for causality in humans, considering uncertainties and inconsistencies in the data sets and ad hoc assumptions that may be required for some of the hypotheses put forth.

The hypothesized basis for inference about human risk from particular data should be seen not just as an extrapolation, but as a generalization. It is a proposal about something in common regarding the causal processes in the study situation and the human population of interest. As a generalization, it ought to apply to other situations as well, or at least have reasons why it does not, and one can evaluate the success

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of the hypothesis at being in accord with the whole suite of relevant observations at hand. If there are limits to the generalization (*e.g.*, it applies to one species but not another, to males but not females, at this dose but not that dose), then the plausibility of such exceptions in view of available evidence and broader knowledge becomes part of the evaluation of the hypothesis against available data.

Often the mode of action (MoA) is what provides the underlying commonality, or explains the lack of commonality, across species, and its consideration is key to weighing and integrating evidence from a large dataset in the HBWoE framework. This is particularly true if there are contrasting modes of action that have been put forth within the scientific community. If an MoA is yet to be established, however, the HBWoE approach can ask appropriate questions of the available data to inform future studies and a potential MoA hypothesis.

Although intended to be flexible in its application, the HBWoE approach generally consists of the following seven aspects:

1. Systematically review individual studies relevant to the causal question at hand, focusing on evaluation of study quality.
2. Within a given realm of evidence (e.g., epidemiology, animal toxicology, mechanistic, or toxicokinetic), systematically examine, organize, and present the data for particular endpoints.
3. Identify and articulate overarching hypotheses that bear on the available data and on establishing potential human risk.
4. Evaluate the logic of the proposed hypotheses with respect to each realm and line of evidence, considering plausibility, specificity, and consistency across studies.
5. Evaluate the logic of the proposed hypotheses with respect to all realms and lines of evidence so that all of the data are integrated and allowed to inform interpretation of one another.
6. Describe and compare the various accounts of the observations at hand, with a discussion of how well each overarching hypothesis is supported by all of the available data, the uncertainties and inconsistencies in the data set, and any *ad hoc* assumptions required to support each hypothesis.
7. Formulate conclusions and any proposed next steps (e.g., sharpening or reworking of proposed hypotheses already put forth; propose additional testing to clarify data gaps).

As discussed, our approach has evolved over several publications. Although the seven aspects described here formed the basic guide to our HBWoE evaluation for naphthalene (Rhomberg *et al.*, 2010), they are more explicitly presented in our later publications (Rhomberg *et al.*, 2011; Prueitt *et al.*, 2011), and more generally in Bailey *et al.* (2012). Although these steps should be generally adhered to, they are not intended to be a checklist, and may involve an approach that is not necessarily in the order presented.

Steps 4 and 5 describe the data integration portion of the evaluation. We find it useful, as part of these steps, to articulate specific questions regarding consistency and plausibility across studies that have become apparent while working through steps 1-3, and in answering these questions, to discuss how the data, as a whole, fit together, noting similarities across studies, strengths and limitations, and discordance. The answers to these questions provide a basis for judging the weight of evidence in support of a causal association.

A key aspect of the HBWoE framework is the importance of analysis of these lines of argument, or consideration of alternate "accounts" (or interpretations) of the available data and how each is supported by the available data. Hill (1965) makes explicit the importance of considering alternative "accounts" of the observations at hand in stating:

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> None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do with greater or less strength, is to help us to make up our minds on **the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?** (Hill, 1965) [emphasis added]

Therefore, a key outcome of the HBWoE framework is the evaluation and comparison of these alternative and contrasting accounts (Step 6). In the end, each account (that is, each tentative "story" as to why the facts are as they are) can be compared to other accounts. In this way, various competing overarching hypotheses can be weighed by comparing their relative success at explaining phenomena seen in the data, the relative reasonableness of ad hoc assumptions needed for each, and the relative naturalness and plausibility of the means whereby potentially refuting observations are reconciled with the account's central hypothesis. Although it is hard to reduce this evaluative process into checklists, scores, or enumerations, the hope is that, by not simply conducting such evaluations of alternative accounts but also by writing them down to be scrutinized and debated, the relative explanatory success of each account, and the relative "epistemological baggage" associated with defending each alternative interpretation, will be evident. This can then serve as the basis for assigning the relative degree of credence that should be given to each account. For example, it provides the basis for comparing an account that asserts the existence of a causal role of the exposures of interest in the disease versus accounts that ascribe apparent patterns of association of exposure and disease to other noncausal factors. In addition, from this assessment, one can more clearly define hypotheses and propose areas of research needed to fill data gaps for each account or to put their hypotheses to the test.

As part of the comparison of accounts, the HBWoE approach considers all data relevant to the causal question at hand, even negative data and (particularly when they are the bases for a particular line of argument) data of questionable quality or from studies with significant design shortcomings. In this last case, it is important to demonstrate the analysis and logic of how poor quality data have been interpreted within an account, how critical they are to the account's assertions, and the ad hoc assumptions required to fit these data to the proposed hypothesis. In the HBWoE framework, such questionable data are automatically down weighted by their poor ability to discriminate between accounts. This is because the face-value of interpretation of these data is not markedly more compelling than alternative explanations that ascribe the outcomes to those extraneous factors or alternative possible causes that better-designed studies would have eliminated. That is, the results are relatively easily and credibly explained away as artifacts.

As discussed in our recent HBWoE evaluations (Rhomberg *et al.*, 2010, 2011; Prueitt *et al.*, 2011; and Bailey *et al.*, 2012), the explanations in each account need not be proven—what is important is that one set out the following questions to be considered throughout the evaluation:

- What is being proposed as causal and generalizable phenomena (i.e., what constitutes the basis for applying observations of biological perturbations or realized risks in other contexts to project potential risks to exposed humans)?
- In the case of observations that do not fit the hypothesized causal model, what is being proposed as the basis for these deviations (i.e., that would otherwise be counterexamples or refutations)?
- What assumptions are made that are ad hoc (i.e., to explain particulars, but for which the evidence consists of their plausibility and the observations they are adduced to explain)?
- What further auxiliary assumptions have to be made, and how reasonable are they in view of our wider knowledge and understanding?
- What is relegated to error, happenstance, or other causes not relevant to the question at hand?

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- For those events or processes proposed as critical for a given account, what other observable manifestations should they have? Are these other manifestations indeed found?
- If either the operation or necessity of the proposed critical events for a given account were disproven, how else would one explain the array of outcomes?

Clearly, there may be many accounts, but the major contending accounts will be those that require the fewest ad hoc explanations for why certain observations do not fit with the data at hand. As an explicit process to the HBWoE framework, the scientific judgment (or logical rationale) required for each account needs to be illustrated and discussed in narrative text to describe how the data are being weighed, and what ad hoc assumptions are required to account for some of the problematic facts within the observations at hand. Different methods can be applied (e.g., organizational tables or figures), depending on the nature of the data, to organize and illustrate the consistencies and inconsistencies of the data as applied to various lines of evidence and various accounts. The point is to illustrate how one is tracing the logic through various competing accounts, and this will vary depending on the data set, likely requiring illustration as well as narrative text. As such, each HBWoE analysis can be constructed in a way that optimizes transparency and logic for the particular set of relevant data.

Table 1 provides an example table that can be used to illustrate the comparison of accounts. The table should present the overall "big picture" assumptions, and should tell the story for how the data are used to support both hypotheses, focusing on how each addresses uncertainties and inconsistencies in the data. The content of the table should deal predominantly with the more uncertain and controversial issues within the data set; *e.g.* inconsistencies across species and tissues, human relevance, and threshold vs. non-threshold MoA. Ad hoc assumptions should be pointed out, and assumptions for which there is unlikely to be further support from additional data, based on what is already known from the current data set, should also be pointed out. There should also be text accompanying the table that clearly summarizes the basis for the reasoning and walks through the table. By this point in the text (should be presented in the conclusion of the HBWoE), however, these assumptions and categorizations should be very clear. There should be nothing new at this point. The table should be a point-by-point comparison of the reasoning for one account against the other. The point of the table is to be explicit about each time an assumption is considered ad hoc or that additional data will not support it, based on what is already known, and to clearly spell out the counter arguments so that the relative weights of the accounts can be assessed. The weaker account is the one with more ad hoc assumptions and/or where additional studies are unlikely to support assumption.

The HBWoE approach has some similarities to other frameworks, but also some important differences. Like the Mode-of-Action/Human-Relevance (MoA/HR) Framework, HBWoE uses an assessment of the understanding of mode of action and its component key events to probe the relevance of animal studies to human risk potential. The MoA/HR approach, however, is focused on assessing the human relevance of *particular* studies based on an assessment of whether the agent's ability to cause all of the key events in the MoA (to which the study's results are attributed) are known to, or can be expected to, operate in parallel in humans. The MoA/HR starts by asking whether the animal MoA is known, and if not, it does not proceed, whereas the HBWoE can play through the evaluation of a hypothetical mode of action, assessing both the plausibility of the MoA in animals (based on weighing available evidence for and against) and the implications for that MoA in humans, if it were true. Indeed, several alternative MoA hypotheses, and their differing human risk consequences, can be evaluated to show how conclusions are contingent on accepting certain assumptions about MoA. A second difference is that, where MoA/HR focuses on the applicability of particular animal studies and endpoints to humans (a question of extrapolating how particular studies and outcomes relate to human risk potential), HBWoE has a broader focus on evaluating the whole base of available studies. HBWoE asks not only how each study relates to human risk potential, but also how those studies relate to one another in terms of consistency in outcomes, further evidence for or against the proposed MoA events and their roles, or insights into how well the

proposed causal effects generalize across situations. Importantly, it tracks what further assumptions might be needed to reconcile apparent contradictory or inconsistent results among the set of studies, and the plausibility of these assumptions (and evidence for and against them) becomes part of the overall weight-of-evidence evaluation. In short, HBWoE is not just about assessing applicability of pieces of evidence, but about integrating interpretation of bodies of evidence. As such, it is naturally focused on important questions such as how to incorporate both animal and human data into evaluations, how to bring to bear *in vitro* information about metabolism, kinetics, gene expression, and so on. This integration is not just adding up bits of evidence, but rather using the whole array of information to aid in the interpretation of each part. It uses, for instance, animal study results to help in the interpretation of whether an epidemiology study's observed patterns of association are consistent with understanding of biology of the agent and its interaction with living systems.

Finally, it is noteworthy that, although the HBWoE approach is not explicitly about dose-response uncertainty, it has important contributions to make to this question. Dose-response analysis has "statistical" uncertainties about curve fits and measurement errors, but the larger uncertainties are more qualitative – which endpoints are reliably concluded to be caused by an agent, which data sets best represent those endpoints, which models (with which low-dose extrapolations) should be used, what interactions with other agents or background processes might contribute to risk levels, what basis for variation in human sensitivity might exist, *etc.* These are not readily treated as quantitative measures of uncertain extrapolations, but the uncertainty in dose-response evaluation can be better characterized by doing a dose-response analysis for each viable choice, and the relative defensibility among the various alternatives assessed by noting the judgments about their relative appropriateness and plausibility as drawn from the HBWoE analysis. That is, HBWoE provides a route for using the insights into the basis for (and uncertainties about) human risk inference that are developed during the Hazard Characterization process and bringing them to bear on the understanding of uncertainty in quantitative risk of the dose-response relationships for those hazards

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Example Table 1. Comparative Reasoning for Accounts

Account for Hypothesis #1	*Ad hoc* explanation?	Plausibility that additional data will support explanation	Account for Hypothesis #2	*Ad hoc* explanation?	Plausibility that additional data will support explanation
Animal Data					
explanation and reasoning for key observation	yes	plausible	explanation and reasoning for key observation - may be counter to hypothesis #1		plausible
explanation and reasoning for key observation		plausible	explanation and reasoning for key observation - may be counter to hypothesis #1		plausible
explanation and reasoning for key observation		plausible	explanation and reasoning for key observation - may be counter to hypothesis #1		plausibility can reasonably be excluded
Epidemiology Data					
explanation and reasoning for key observation		plausible	explanation and reasoning for key observation - may be counter to hypothesis #1		plausibility can reasonably be excluded
Mechanistic Data					
explanation and reasoning for key observation		plausible	explanation and reasoning for key observation - may be counter to hypothesis #1		plausibility can reasonably be excluded
Human Relevance					
explanation and reasoning for key observation	yes	plausible	explanation and reasoning for key observation - may be counter to hypothesis #1		plausibility can reasonably be excluded
explanation and reasoning for key observation		plausible	explanation and reasoning for key observation - may be counter to hypothesis #1	yes	plausibility can reasonably be excluded
Relative weight of evidence for accounts	stronger			weaker	

Shaded cells are *ad hoc* assumptions and/or where additional data are unlikely to support explanation.
Accounts with the fewest *ad hoc* assumptions and/or assumptions where additional data are unlikely to support explanation are considered

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Example Table 1. Comparative Reasoning for Accounts

Account for Hypothesis #1	*Ad hoc* explanation?	Plausibility that additional data will support explanation	Account for Hypothesis #2	*Ad hoc* explanation?	Plausibility that additional data will support explanation

stronger.

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2. Problem Addressed by the Method

The National Academy of Sciences (NAS) Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde (NRC, 2011) proposed a "roadmap" for reform and improvement of the Agency's risk assessment process. Specifically, it called on the Agency to undertake a program to develop a transparent and defensible methodology for weight-of-evidence (WoE) assessments. In a broad sense, all chemical risk assessment is a form of WoE evaluation, in that it involves the interpretation of a body of scientific studies to discern what they can tell us about estimation of potential exposure impacts on populations and/or systems of interest. This means that risk assessment needs a way to clearly illustrate the methodology and logic applied to the WoE processes; *i.e.*, sorting out the potential interpretations with respect to the methods of science, acknowledging data limitations, combining and integrating evidence, providing a basis for applying sound judgment, and identifying the most supportable conclusions.

The HBWoE approach provides a framework for weighing evidence for large and complex datasets in a way that can be clearly and logically applied to the risk assessment process, and therefore addresses the ultimate goal expressed in the NAS review. HBWoE provides a practical and transparent approach that takes the reader through the logic of the WoE analysis – how and why available data are considered to inform the judgments about the existence and nature of causal processes. On a case-specific basis, problem formulation within the HBWoE approach occurs as one of the first steps in the evaluation, and is aimed at articulating the various, and often competing, overarching hypotheses, and articulating the goal of creating a thorough characterization of current scientific knowledge to judge the potential toxicological hazards or risks of a particular agent, in a manner that illustrates sufficiently the tracing of the logic through the various competing accounts of the data so that the various interpretations can be compared.

The approach does not eliminate the need for scientific judgment, and often may not lead to a definitive choice of one interpretation over the other, but it will clearly lay out the logic for how one weighs the evidence for and against each interpretation. Only in this way is it possible to have constructive scientific debate about potential causality that is focused on an organized, logical "weighing" of the evidence.

3. General Applicability of the Method

The HBWoE method is generally applicable to all chemical risk assessment. The approach is particularly useful when the data sets are large and complex and contain conflicting results that are difficult to interpret. Although weighing evidence in a clear and transparent manner is also necessary for small data sets, a full HBWoE evaluation is not required for data sets that are more clearly consistent across studies, or when the data sets are such that the accounting of the data and how they bear on the conclusions of the assessment are not so varied within the scientific community. That is, although it is necessary to integrate the data from various realms of evidence and to take the reader through the logic of how the available data support the conclusions of the assessment (even for small, less complicated data sets), a full comparison of accounts for these types of data sets is not likely to be necessary.

Another aspect to consider is whether potential modes of action for a given agent have been clearly articulated. Depending on how rich the data base is for a given chemical, there may or may not be enough data to bear on a potential mode of action. Since the proposed modes of action often form the basis for overarching and competing hypotheses, a thin data set may not lend itself to a full weighing of the evidence and comparison of accounts based on proposed modes of action. In this case, the approach can be applied to lay out the key pieces of information that are available and ask appropriate questions of the data to guide future studies aimed at obtaining a full data set (*i.e.*, epidemiology, animal toxicology, mechanistic, and toxicokinetic) that can be integrated in a way that will allow the different realms of evidence to inform interpretation of each other, with the ultimate goal of proposing a robust, biologically plausible mode of action that can be used to guide risk assessment processes.

4. Overall Strengths and Weaknesses of the Method

The strengths of the HBWoE method are that it:

- emphasizes tracing the logic of how the available data support (or refute) the conclusions of the assessment;
- compares the tracing of logic for alternate accounts of the available data and how each is supported (or refuted) by the available data;
- emphasizes integration of all realms of evidence (*i.e.*, epidemiology, animal toxicology, mechanistic, and toxicokinetic) so that different realms of evidence are allowed to inform interpretation of each other;
- emphasizes the need to clearly convey (through use of illustrations, tables, *etc.*) the comparison of accounts and overall WoE analysis results so that the analysis can guide constructive discourse with the scientific community and future risk management decisions; and
- is flexible in specific application, yet systematic in the overall goal as guided by the seven aspects of the framework.

One may consider a weakness of the method to be that, by necessity, it is flexible and therefore may not always be applied adequately; *i.e.*, one cannot assume that use of the method will simply provide the best analysis. The approach requires judgment that needs to be checked by those interpreting the results, and may lead to disagreements and stimulate further scientific debate and discussion, and possible refinement of proposed modes of action or other overarching hypotheses. This is, in fact, part of the method. As such, the HBWoE method should be viewed as being iterative, interactive, and flexible. And, therefore, the approach will often feel unstructured and complex. The challenge is keeping the ultimate goal in mind – integration of all relevant data logically and transparently so that biological plausibility and human relevance will guide future risk assessment processes.

5. Minimum Data Requirements and Types of Data Sets Needed for Method

There are no minimum data requirements for the HBWoE method. As discussed in #3 above, however, depending on how rich the data base is for a given chemical, there may or may not be enough data to bear on potential modes of action. Or the data may not contain significant uncertainties and inconsistencies from which various interpretations have been made that require a full comparison of the different accounts. Although rich, complex data sets are not a requirement for application of the method, these types of data sets benefit most effectively from the HBWoE framework. The framework can be useful for smaller, less complicated data sets as a guide for proposing new biologically plausible modes of action, or for developing a more complete data set that can further inform the risk assessment processes.

Importantly, no matter where one is in the processes of weighing evidence, the ultimate goal should be to ask the appropriate, logical questions of the available data (no matter how much) to either guide further studies or the natural tracing of the logic within the evidence at hand to reach conclusions that are scientifically sound, supported, and biologically plausible.

6. Does the Case Study:

A. Describe the dose-response relationship in the dose range relevant to human exposure?

As described in the case study, and guided by the results of our HBWoE evaluation, our approach is to consider the applicability and limits on the animal responses to serve as a basis for estimation of potential human risk. We do this by considering the potential mode of action underlying the effects seen in animal bioassays, including evaluation of the metabolic activation and detoxification, as well as the nature, tissue locations, and dependence on tissue-dose of key precursor responses. Species differences in tissue dosimetry (*via* application of PBPK models, if available) are used to evaluate whether parallel tissues in

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humans will be subject to tissue doses that could prompt the key events of the apparent mode of action. Our approach further considers whether the tissue doses required to prompt a particular mode of action are achievable with typical human exposures; therefore, describing the dose-response relationship in the dose range relevant to humans.

Further, HBWoE does not treat different quantitative modeling approaches for given endpoints as quantitative measures of uncertain extrapolations. Rather, the uncertainty in dose-response evaluation can be better characterized by conducting dose-response analyses for each viable choice. The various analyses can then be compared and the relative defensibility among the alternatives assessed by noting the judgments about their relative appropriateness and plausibility as drawn from the HBWoE analysis.

B. Address human variability and sensitive populations?

The HBWoE approach accommodates an evaluation of human variability and sensitivity, if necessary, for a given chemical agent, and can be a key part of the evaluation if the data support it. Questions about variability and sensitivity in the human population should be asked upfront as part of the initial organizing of the relevant studies, and these studies should be integrated into and given appropriate weight in the evaluation similarly to how all other data are considered. Studies of human variability and sensitivity constitute lines of evidence within the epidemiology or mechanistic (*e.g.*, polymorphisms of genes known to be involved in the mechanism of action) data that need to be considered within and across all realms of evidence so that the data can be fully considered and integrated as part of the WoE evaluation. The practical outcome of working these data through the WoE evaluation may be realized through application of, or proposals to gain more insight into, appropriate uncertainty factors that are based on a more scientifically sound understanding of the actual variability within a human population and that can be used in place of default values.

C. Address background exposures or responses?

The results of the HBWoE approach, particularly if applied to quantitative risk assessment for a given chemical, should be presented in a clear and transparent manner allowing for practical application of toxicity values to risk management decisions. As such, the ultimate goal of the HBWoE evaluation is to present a biologically plausible MoA that is most strongly supported by the WoE (comparing and contrasting to other proposed modes of action), the associated exposure concentration that would be necessary to lead to that MoA and associated adverse effect in humans, and how that exposure concentration compares to background and typical human exposure concentrations.

Consideration of background levels of cancer incidence in the human population may also be important in the HBWoE evaluation. For example, nasal cancer in the human population is very low. Therefore, occurrence of nasal cancer in naphthalene-exposed individuals should have been notable had it occurred (Rhomberg *et al.* 2010). This observation is an important part of the data integration phase of HBWoE evaluation.

Further, consideration of background levels of biomarkers of exposure or effect are important in the HBWoE evaluation. For example, interpretation of studies that evaluate formaldehyde DNA adduct or blood levels requires an understanding of how these levels compare to endogenous levels (Rhomberg *et al.* 2011), and is a key part of the data integration phase of HBWoE evaluation.

D. Address incorporation of existing biological understanding of the likely mode of action?

Yes. As discussed above, the mode of action is what provides the underlying commonality across species and its understanding is key to weighing and integrating evidence from a large dataset in the HBWoE framework, particularly if there are contrasting modes of action that have been put forth within the scientific community. HBWoE can be used to evaluate data within the current data set or to guide future studies aimed at obtaining a full data set (*i.e.*, epidemiology, animal toxicology, mechanistic, and toxicokinetic) that can be integrated in a way that will allow the different realms of evidence to inform

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interpretation of each other, with the ultimate goal of proposing a robust, biologically plausible mode of action that can be used to guide risk assessment processes.

E. Address other extrapolations, if relevant – insufficient data, including duration extrapolations, interspecies extrapolation?

The HBWoE method focuses on integration of all relevant data (*i.e.*, epidemiology, animal toxicology, mechanistic, and toxicokinetic), including consideration of data quality and sufficiency, null and negative as well as positive studies, data from all species, tissues, and exposure durations. Therefore, this integration allows for a form of extrapolation that is more of a "generalization" across realms of evidence, guided by the need to identify something in common regarding the causal processes in the study situation and the human population of interest. This generalization is a form of extrapolation that involves initial qualitative evaluation and integration of the data that can then be used to guide a more quantitative extrapolation of the data for derivation of human toxicity values.

F. Address uncertainty?

The HBWoE approach is especially suited to deal with complex and conflicting data sets with large numbers of uncertainties. Thus, the HBWoE approach aids in addressing uncertainty in a qualitative manner, although it does not provide a quantitative uncertainty analysis.

G. Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?

As discussed above in A and C, the ultimate goal of the HBWoE evaluation is to present a biologically plausible MoA that is most strongly supported by the WoE (comparing and contrasting to other proposed modes of action), the associated exposure concentration that would be necessary to lead to that MoA and associated adverse effect in humans (derivation of toxicity values), and how that exposure concentration compares to typical human exposure concentrations. Thus, it aids in the evaluation of risk, although no novel methods are presented for calculating probability of response.

H. Work practically? If the method still requires development, how close is it to practical implementation?

Yes, the method is considered to work practically and has been applied to several chemicals (Rhomberg *et al.*, 2010, 2011; Prueitt *et al.*, 2011; Bailey *et al.*, 2012), evolving with each application. Refinement of the method is likely through further application. It should be noted, however, that improvement of the method is likely to take the form of demonstration of its flexibility across different chemicals and data sets (thereby providing examples of different approaches) rather than becoming more structured. That is, the goal of the HBWoE is to integrate data across realms of evidence in a way that is transparent and logical. Therefore, the WoE practitioner will need to apply different approaches for different chemicals depending on the specific nature and quality of the data, overarching hypotheses, and uncertainties/inconsistencies within the dataset.

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Case Study: Interpretation of 24-hour sampling data

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Abstract

Both the Ontario Ministry of the Environment (MOE) and the Texas Commission on Environmental Quality (TCEQ) set science-based ambient air quality values to protect human and environmental health, prevent damage to the physical environment and minimize offensive odours. The MOE sets ambient air quality criteria (AAQC) and the TCEQ sets air monitoring comparison values (AMCVs). This case study will discuss different approaches the agencies use to set health-based values to interpret 24-hour (hr) ambient air monitoring data.

Both agencies review the toxicology of the substance. From this, the dose-response relationships for an array of adverse health effects considered critical are assembled. For chemicals with a threshold, a point of departure is determined and uncertainty factors are applied to set the limit that represents the AAQC or AMCV. For chemicals without a threshold, a risk-based approach is followed and a unit risk factor is developed. The MOE has a risk goal of 10^{-6} excess cancer risk for AAQCs whereas the TCEQ has a risk goal of 10^{-5} excess cancer risk for AMCVs. The panel is not asked to comment on the different risk goals of the agencies. The major differences between the two agencies are the approaches used to evaluate different averaging times. Different air permitting procedures/regulations contribute to the need for different approaches.

TCEQ

For chemicals detected in the TCEQ ambient air monitoring network, acute 1-hr AMCVs based on acute studies and chronic AMCVs based on chronic studies have generally been derived to evaluate 1-hr measured concentrations of chemicals of interest or calculated annual average concentrations, respectively. These averaging times correspond to averaging times evaluated in air permitting. However, 24-hr ambient air samples (i.e., canister samples collected every 3rd or 6th day) may be collected and used to calculate annual averages for comparison to chronic AMCVs. A 24-hr sample is an acute-exposure duration significantly longer than 1-hr. It is not appropriate to use a short-term, 1-hr AMCV or long-term AMCV to evaluate a 24-hr ambient air sample. Thus, the development of a 24-hr health-based AMCV to evaluate a single 24-hr exposure would allow the TCEQ to evaluate 24-hr data for possible health concerns. Ideally, an acute study of 24-hr exposure duration would be used to develop a 24-hr AMCV, but such toxicity studies are rare. Therefore, the purpose of this case study is to obtain comments from the panel on guidelines presented in the case study to develop health-based 24-hr AMCVs and the strengths and limitations of using effects-based 24-hr AMCVs. Since the 24-hr AMCV is specific to the exposure period and health effect being considered, it may be used to conduct a risk assessment in combination with 1-hr and annual AMCVs, although it cannot replace the 1-hr or annual AMCVs.

Ontario MOE

The vast majority of the MOE AAQCs are based on chronic effects and are used as targets for general air quality. A challenge of the annual AAQC, however, is that air quality can only be assessed after sufficient air quality data are collected to reflect an annual average. That is, annual AAQCs are not useful for evaluating individual 24-hr exposures. The MOE has addressed this issue by converting AAQCs with annual averaging times to 24-hr AAQCs via a meteorological-based conversion factor. Therefore, two AAQCs are set for a single substance: an effects-based annual average AAQC, and a converted 24-hr AAQC. In this case, the converted 24-hour AAQC is used to provide an indication of whether the annual

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AAQC would be exceeded rather than to evaluate possible health concerns within the 24-hour timeframe. The MOE may also set 24-hour AAQCs directly from chronic data, for cases in which a critical and/or short-term window of exposure is associated with an adverse effect (e.g., developmental effects). The purpose of this case study is to demonstrate how both toxicological and implementation considerations may influence the setting of an AAQC and, in turn, the interpretation of 24-hr air quality data. Comments are invited from the panel on the strengths and limitations of the approaches employed by the MOE to set and interpret 24-hr AAQCs, as outlined in their case study.

Texas Commission on Environmental Quality Approach

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1. **Describe the problem formulation(s) the case study is designed to address. How is the method described in the case useful for addressing the problem formulation?**

The Texas Commission on Environmental Quality (TCEQ), a state regulatory agency, employs several interactive programs to ensure concentrations of air toxics do not exceed levels of potential health concern (Capobianco et al. 2013): comprehensive air permitting, extensive air monitoring, and the establishment of Air Pollutant Watch List Areas if monitoring data indicate concentrations above levels of concern. This case study will focus on the air monitoring program and the need to evaluate 24-hr ambient air concentrations for potential health effects.

For chemicals evaluated in the TCEQ ambient air monitoring network, acute 1-hr Reference Values (ReVs) and chronic ReVs have generally been derived to evaluate 1-hr measured concentrations of chemicals of interest or calculated annual average concentrations, respectively. These averaging times correspond to averaging times evaluated in air permitting. However, 24-hr ambient air samples (e.g., 24-hr canister samples collected every 3rd or 6th day) may be collected for special projects and also at permanent monitoring sites to calculate annual averages for comparison to chronic ReVs. A 24-hr sample is an acute exposure duration significantly longer than 1-hr. Toxic effects induced by 24-hr exposure may be governed by modes of action somewhat different than those influencing toxicity due to 1-hr or chronic exposure. It is not appropriate to use a short-term, 1-hr ReV or long-term ReV to evaluate a 24-hr ambient air sample. Thus, the development of a 24-h ReV would allow the TCEQ to fully evaluate 24-h data for possible health concerns and could be used for risk communication purposes.

Sometimes, members of the public will compare 24-hr measured air concentrations to chronic ReVs. It is often thought that if a chemical concentration measured in a 24-hr sample exceeds a chronic ReV, then adverse health effects will occur. A 24-hr ReV predictive of health effects that may occur due to a 24-hr exposure may provide useful information and important context for risk managers and the general population. This information can be an important part of the risk communication process. In addition, this information is helpful to risk assessors for performing health effects reviews when 24-hr air monitoring data exceed chronic ReVs.

The following case study concerns guidelines to develop 24-hr health-based ReVs for comparison to 24-hr ambient air data. A 24-hr ReV is derived for human health hazards associated with threshold dose-

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response relationships (typically effects other than cancer) and is defined as an estimate of an inhalation exposure concentration that is likely to be without an appreciable risk of adverse effects to the human population (including susceptible subgroups) for a single 24-hr exposure. However, exposure to chemicals may occur on an intermittent basis. The 24-hr ReV would be protective of intermittent 24-hr exposures at the ReV if the time period between intermittent exposures is sufficient for adequate toxicokinetic and toxicodynamic clearance such that a toxicologically significant accumulation of neither the particular causative agent nor effect is expected. The 24-hour ReV is derived to evaluate a single 24-hour exposure. In order to determine if intermittent exposures that occur frequently at or below the 24-hour ReV would cause adverse health effects, chemical-specific information such as additional dose-response data (e.g., subchronic) and toxicokinetic/toxicodynamic information would have to be evaluated in the context of the specific exposure scenario, based on actual air monitoring data.
The methods described in the case study are useful for addressing the problem formulation because they present guidelines to calculate 24-hr ReVs based on MOA, toxicokinetics/ toxicodynamics, and the dose-response relationship. Procedures used to develop 24-hr ReVs are similar to procedures used to develop 1-hr and chronic ReVs (TCEQ 2012).

2. **Provide a few sentences summarizing the method illustrated by the case study.**

This method involves development of guidelines to develop ReVs to evaluate measured 24-hr ambient air concentrations. It is an extension of the hazard identification and dose-response methods used to derive ReVs to evaluate air concentrations for a short-term 1-hr averaging time or long-term annual averaging time. An inhalation ReV is defined as an estimate of an inhalation exposure concentration for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse effects. A 24-hr ReV is based on the most sensitive noncarcinogenic adverse health effect relevant to humans reported in the scientific literature. ReVs are derived by adjusting an appropriate point of departure (POD) with uncertainty factors (UFs) to reflect data limitations and to derive a value that is below levels where health effects would be expected to occur. Examples of PODs include the benchmark concentration lower confidence limit (BMCL) and the no-observed-adverse-effect-level (NOAEL).

Ideally, an acute study of 24-hr exposure duration would be used to develop a 24-hr ReV, but such toxicity studies are rare. Thus, this method is to provide guidelines on incorporation of information on mode of action (MOA), toxicokinetics/toxicodynamics, and the dose-response relationship to develop ReVs applicable for conducting a health effects evaluation for 24-hr ambient air monitoring data. Appendix A of the case study provides the draft guidelines developed by the TCEQ (TCEQ 2011a) for developing 24-hr ReVs. The TCEQ did not finalize the draft guidelines because the TCEQ wanted to test their utility through chemical-specific examples using available data as well as to submit chemical-specific 24-hr ReVs for 1,3-butadiene, acrolein, and benzene to the panel for additional review (Appendix B of the case study).

The purpose of this case study is to obtain comments from the panel on procedures to develop 24-hr ReVs, not on procedures to calculate the1-hr or chronic health-protective ReVs.

3. **Comment on whether the method is general enough to be used directly, or if it can be extrapolated, for application to other chemicals and/or problem formulations. Please explain why or why not.**

The methods to develop 24-hr ReV are general enough to be used by others. They are based on guidance developed by OECD (2010) to develop an acute reference concentration (ARfC) and are derived using basic procedures for developing 1-hr and chronic ReVs (TCEQ 2012). The examples in the case study are for specific chemicals and are written specifically for evaluation of 24-hr ambient air data. This method can be used by others who need to communicate health risks with managers and the general

public when 24-hr ambient air monitoring data exceeds chronic values. When conducting a health effects review, the monitoring data is reviewed to evaluate the possibility of accumulation of toxic moiety or effects due to high peak or repeated exposure in temporal proximity.

To the extent possible, determinations of 24-hr ReVs should have a reasonable degree of certainty associated with them. This method is not useful for chemicals with limited toxicity information.

4. Discuss the overall strengths and limitations of the methodology.

There are several overall strengths to this methodology. The procedures in Appendix A of the case study were a part of proposed guidelines (TCEQ 2011a) that have been peer-reviewed (TERA 2011). They are based on guidance developed by OECD (2010). Since the 24-hr ReV is specific to the exposure period and health effect being considered, they may be used toconduct a health effects review in combination with 1-hr and annual ReVs, although they cannot replace the 1-hr or annual ReVs.

The methods and approaches used to develop 24-hr values are similar to approaches used to derive 1-hr or chronic ReVs (TCEQ 2012). Ideally, an acute study of 24-hr would be used to develop a 24-hr ReV, but such toxicity studies are rare. Available literature should be researched to determine if data are available to guide the derivation of a 24-hr ReV. Many chemicals have a poor database, making the derivation of a 24-hr ReV at best difficult. In these instances, professional, scientific judgment must be used to decide whether sufficient data exist to support a scientifically-defensible 24-hr ReV.

For a data-rich chemical, it may be possible to perform PBPK modeling or categorical regression from studies that are conducted at other durations than 24 hr. For chemicals with limited data, a POD may need to be developed based on an acute study, subacute study or subchronic study and appropriate duration adjustments used to develop a 24-hr value. The best approach for developing a 24-hr ReV is to examine all available acute and subacute studies (and possibly subchronic studies) and develop an exposure response array if it can provide needed insight. Then a consideration of physical/chemical parameters, MOA, toxicokinetics/toxicodynamics, dose-response assessment etc. should be used to determine the most appropriate adverse effect relevant to humans for a 24-hr exposure duration. Development of several potential 24-hr ReV values based on different studies of different durations may be needed to aid in the decision-making process. When 24-hr ReVs are developed, a narrative that discusses the uncertainties associated with the values should be included.

As with most methodologies there are also limitations. The following are considerations for the use of 24-hr ReVs:

- the methods to develop 24-hr ReVs are data- and resource-intensive.
- evaluation of only a 24-hr ambient air concentration would allow for some fairly high peak exposures for certain hours at a time, which could result from periodic high emissions or meteorological variation. Therefore, a 24-hr ReV may be used mainly for informational purposes and may have significant caveats depending upon the available information.
- exposure to chemicals may occur on an intermittent basis. The 24-hr ReV would be protective of intermittent 24-hr exposures if the time period between intermittent exposures is sufficient for adequate toxicokinetic and toxicodynamic clearance such that a toxicologically significant accumulation of neither the particular causative agent nor effect is expected. TCEQ toxicologists would conduct a health effects review of air monitoring data to evaluate whether repeated 24-hr peak exposure occur which would result in adverse health effects.

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- intermittent exposure near to or at the 24-hr ReV may cause an increase in the calculated annual average concentration, which could cause the chronic ReV to be exceeded and suggest the potential for chronic health effects to occur. (Note: Throughout the year, TCEQ toxicologists calculate yearly rolling averages for chemicals of concern to evaluate whether the rolling average concentration may be near the chronic ReV. The yearly rolling average is compared to the yearly rolling averages from previous years to discover whether unusual patterns of high peak exposures occurred that would affect the annual average.)

- Twenty-four hour canister data is collected every 3rd or 6th day. Therefore, there is uncertainty about chemical concentrations on days where an air sample is not collected. The annual average based on 24-hr canister data compares well with annual averages calculated from data from 1-hr auto gas chromatographs. Therefore, 24-hr canister data are representative samples of typical 24-hr concentrations.

5. **Outline the minimum data requirements and describe the types of data needed.**

Development of 24-hr ReVs should be conducted for those chemicals with adequate toxicity information, not for chemicals with limited toxicity data. As mentioned previously, the best approach for developing a 24-hr ReV is to examine all available acute and subacute studies (and possibly subchronic studies) and develop an exposure response array if it can provide needed insight. Then a consideration of physical/chemical parameters, MOA, toxicokinetics/ toxicodynamics, etc. should be used to determine the most appropriate adverse effect relevant to humans for 24-hr exposure duration. The minimum data requirements for developing 1-hr or chronic ReVs would apply to developing 24-hr ReVs (e.g. appropriate PODs for the critical effects should be available (i.e., the NOAEL, LOAEL or other appropriate points of departure ($BMCL_{10}$ and BMCL)); if an animal study is used, then data should be available to evaluate whether the effect in animals is relevant to humans, etc.)

HOW THIS ASSESSMENT ADDRESSES ISSUES RAISED IN SCIENCE & DECISIONS:

A. **Describe the dose-response relationship in the dose range relevant to human exposure**?

Yes, to the extent possible. Procedures for calculation of 24-hr ReVs are for acute health effects that have a threshold dose-response relationship, not for chronic health effects that have a nonthreshold dose-response (typically carcinogens). Standard uncertainty factors (UFs) are used to extrapolate down to human exposure levels.

When human data are available for determination of 24-hr ReVs, the levels are more relevant to human exposure. When animal data are used as the basis of 24-hr ReVs, there is frequently uncertainty that the levels are relevant and predictive of effects in humans. Guidance discussed as part of an IPCS framework (e.g., MOA information, species sensitivity) should be considered to determine the extent to which 24-hr ReVs from animal studies are relevant and predictive for humans (Boobis et al. 2006, 2008). If MOA information is not available, then it is assumed as a default that responses in animals are relevant to humans.

B. **Address human variability and sensitive populations?**

Yes, to the extent possible. If human data are available in known or potentially sensitive subpopulations, those data should be used for determining 24-hr ReVs. Otherwise, an intraspecies uncertainty factor (UF_H) is used to address human variability and sensitive populations.

C. Address background exposures and responses?

These methods do not directly address background exposures or responses in people, but indirectly reflect background exposures and responses to the extent that they contributed to the effects observed in the key studies. The 24-hr ReVs are acute values, and are typically well above background exposures.

D. Address incorporation of existing biological understanding of the likely mode of action (MOA)?

MOA information is very useful for development of 24-hr ReVs. Since toxicity studies conducted at 24-hr are usually not available, MOA data can be used to more fully understand the relevance and/or predictiveness of toxicity studies conducted at shorter or longer durations as the basis of a 24-hr ReV. MOA information can inform the type of duration adjustment used to derive 24-hr ReVs. When animal data are used as the basis of 24-hr ReVs, MOA information should be considered to determine the extent to which levels from animal studies are relevant to humans (Boobis et al. 2006, 2008). MOA information is useful to understand the relevance and/or predictiveness of the 24-hr ReV when animal data from different species are available.

E. Address other extrapolations, if relevant – insufficient data, including duration extrapolations, interspecies?

Yes, the applicability of such extrapolations is considered and discussed. A 24-hr ReV should not be developed for chemicals with insufficient toxicity data. The best approach for developing a 24-hr ReV is to examine all available acute and subacute studies (and possibly subchronic studies) and develop an exposure response array if it can provide needed insight. Then a consideration of physical/chemical parameters, MOA, toxicokinetics/toxicodynamics, etc. should be used to determine the most appropriate adverse effect relevant to humans for a 24-hr exposure duration.

A crucial decision for developing a 24-hr ReV is whether to adjust for duration, since toxicity studies are not typically conducted for 24 hrs. For duration extrapolations, a variety of modeling approaches are available to identify the POD upon which a 24-hr ReV may be derived. The model that may be chosen to identify the POD from a key study is dictated by the quantity and quality of the data available for a chemical of interest:

- a PBPK model may be used to identify a POD_{ADJ} for a chemical based on an exposure duration of interest when such a model is available;
- exposure response arrays may be generated as a means of estimating what a logical POD for a 24-hr ReV might be (OECD 2010);
- categorical regression is a valuable tool to assess toxicity across studies and exposure durations to identify an appropriate POD_{ADJ}, which may be used to derive a 24-hr ReV where duration adjustment is unnecessary (OECD 2010).
- default approaches for duration adjustments as discussed in Chapter 3 of the TCEQ Guidelines (2012) and in OECD (2010) may be used.
- Appendix A, Section 4.4 of the case study provides a discussion of the use of subacute, subchronic, and chronic studies to derive a 24-hr value.

- Interpolation between 1-hr acute and chronic values is considered (Appendix A, Section 4.44 of the case study)
- It is important to evaluate the reasonableness of the duration adjustment, as discussed in Appendix A, Section 4.44 of the case study.

The approach used to identify the POD for a 24-hr ReV is highly dependent on the data available for a given chemical. While several approaches may be developed, the final approach used to derive a 24-hr ReV will be selected using best scientific judgment.

F. Address uncertainty.

UFs are used to address uncertainty. The same UFs used to develop a 1-hr ReV (TCEQ 2012) are used to develop the 24-hr ReV.

G. Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?

A 24-hr ReV is derived for human health hazards associated with threshold dose-response relationships (typically effects other than cancer) and is defined as an estimate of an inhalation exposure concentration that is likely to be without an appreciable risk of adverse effects to the human population (including susceptible subgroups) for a 24-hr exposure. Risk estimates could not be calculated at environmentally-relevant concentrations.

H. Work practically? If the method still requires development, how close is it to practical implementation?

The procedures for calculation of 24-hr ReVs were included in proposed *TCEQ Guidelines to Develop Inhalation and Oral Cancer and Non-Cancer Toxicity Factors* (TCEQ 2011a) and have undergone a peer review (TERA 2011). They are based on guidance from OECD (2010) for ARfCs. They are practical and readily implemented by trained risk assessors. However, no 24-hr ReVs have been included in TCEQ Development Support Documents as of this time. As mentioned previously, the TCEQ did not finalize the draft guidelines because the TCEQ wanted to test their utility through chemical-specific examples using available data as well as to submit chemical-specific 24-hr ReVs to the panel for additional review. This case study is designed to provide 24-hr ReVs for acrolein, benzene, and 1,3-butadiene as example chemicals to demonstrate the practical implementation of the method. After the scientific panels' review, the TCEQ plans to refine the guidelines on developing 24-hr values and submit the guidelines and the proposed 24-hr values for several chemicals for an additional public comment period.

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Ontario Ministry of the Environment Approach

Describe the problem formulation(s) the case study is designed to address. How is the method described in the case useful for addressing the problem formulation?

The Ontario Ministry of the Environment (MOE) sets science-based ambient air quality criteria or AAQCs to evaluate regional air quality data. An AAQC is a desirable concentration of a contaminant in air that is unlikely to adversely affect human health or the environment. The term "ambient" is used to reflect general air quality independent of location or source of a contaminant.

Ontario's 24-hour AAQCs are based on health effects and are set at concentrations that are protective against effects that may occur during continuous lifetime exposure. In comparison, the Texas Commission on Environmental Quality develops reference values to be used as 24-hour Air Monitoring Comparison Values (AMCVs), to compare to measured 24-hour ambient air concentrations, although the TCEQ also develops acute 1-hr and chronic AMCVs to evaluate 1-hr measured concentrations of chemicals or calculated annual average concentrations, respectively. This case study describes the Ontario approach and discusses how the Ontario AAQCs and Texas AMCVs may be applicable, depending on the science and implementation considerations.

The MOE currently employs two approaches to assign an averaging time of 24 hours to AAQCs meant to be protective in continuous lifetime exposures: 1) based on concerns about effects that may develop after short-term exposures (e.g., developmental); or 2) through conversion of an AAQC with an annual averaging time. These two approaches for setting 24-hour AAQCs are described below.

In this case study we aim to demonstrate how both toxicological and implementation considerations may influence the setting the averaging time of an AAQC and, in turn, the interpretation of 24-hour air quality data.

Provide a few sentences summarizing the method illustrated by the case study.

Generally, AAQCs are used in monitoring programs to assess air quality resulting from the contributions of a contaminant to air from all sources. AAQCs may also be adopted or adapted as regulatory air standards in Ontario, which are used mostly to evaluate the modelled contributions of a contaminant to air by a single regulated source. Air standards are used to assess regulatory compliance, identify needs for abatement and also to inform permitting decisions. While the focus of this problem formulation is on the AAQC component of our air quality program, it will also be relevant to air standards.

The MOE develops 24-hour AAQCs based on an assumed continuous lifetime exposure. Therefore, if the 24-hour AAQC is met, then no adverse effects are expected to a person continuously exposed over a lifetime.

Establishing 24-hour AAQCs for Continuous Lifetime Exposures

Approach 1– Effects Caused After Short-term Exposure

The MOE may set 24-hour AAQCs directly based on adverse effects when short-term exposures may be sufficient to cause the effect. For example, this approach may be relevant for developmental effects resulting from prenatal exposure (e.g. dioxins), or with critical windows of exposure (e.g., manganese) .

Approach 2 - Conversion from Annual AAQCs

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Similar to what is done by the Texas Commission on Environmental Quality (TCEQ), the MOE assigns annual averaging times to AAQCs to protect against adverse health effects elicited after long-term air exposures. If the annual AAQC is met then no effects are expected over continuous lifetime exposures. However, the annual AAQC does not allow assessment of short-term periods of elevated exposure that may cause a different effect from that used to set the annual AAQC or increase the risk of the same effect used to set the annual AAQC. Another limitation of the annual AAQC is that air quality can only be assessed after sufficient air quality data are collected to reflect an annual average. That is, longer averaging times require more sampling and longer delays in order to get enough data to compare to an air quality criterion.

To address the limitations of the annual AAQC, the MOE converts the annual AAQC to a 24-hour value using a conversion factor and the *converted* 24-hour AAQC is used to assess 24-hour air quality data. Conversion factors were originally derived from empirical data of monitored ambient air levels of sulphur dioxide (SO_2) in urban areas, and also near point sources, and atmospheric dispersion modelling of specific sources. The urban ambient air data, acquired in eight of the largest U.S. cities, together with Ontario data available at that time, showed a relationship between a 1 hour average and an annual average exposure at the respective monitoring locations. **The MOE used this information to select a conversion factor of 5 to convert from an annual to a 24-hr average and a conversion factor of 3 to convert from a 24-hr to a ½ hr average.** These generic conversion factors are derivable from an exponential equation (i.e. the commonly used power law) that has also been used for other averaging times (i.e. 1 hr value, ½ hour and 10 minutes), which the MOE references in its local air quality regulation:

$C_{long} = C_{short} (t_{short}/t_{long})^p$

Where C_{long}= the concentration for the longer averaging time
C_{short}= the concentration for the shorter averaging time
T_{short} = the shorter averaging time (in minutes)
T_{long} = the longer averaging time (in minutes)
and, p = the power law exponent, 0.28

A review of the various literature sources for, and assumptions made by, different regulatory bodies in selecting the basis for the exponent, and the value for *n* to use in the commonly used power law is discussed in greater detail in the case study. Briefly, this conversion is based on a general relationship between emissions and meteorological influences, based on empirical monitoring data; it reflects variability in emissions and resulting exposures, rather than how a chemical's toxicity varies with duration.

The conversion factor is relied on to ensure that if the shorter-term AAQC for a compound (i.e.., the converted 24 hour AAQC) is met, as observed in monitored 24-hour data, then a AAQC with longer-term exposures (e.g., an annual average effects-based AAQC) will not be exceeded, and no effects are expected over long-term continuous exposures. This way, an 'equivalency' or 'link' between the converted 24-hour AAQC and the effects-based annual AAQC is established. That is, the converted 24-hour AAQC is a health protective value for long term exposure, rather than a value that can be used to estimate health risk directly associated with a single 24-hour exposure. That said, the converted 24-hour AAQC is also likely protective against potential adverse effects associated with short-term exposures, as long as the conversion does not result in a converted 24-hour AAQC that is above a concentration of concern for the short-term exposure associated effect.

An additional assessment would be required to evaluate the potential for short-term effects if the converted 24-hour AAQC were exceeded on repeated occasions.

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The methodology of creating a converted 24-hr AAQC would be applicable for all chemicals with assigned annual AAQCs, which are designed to protect against adverse health effects elicited after long-term air exposures (i.e., carcinogens, and most non-carcinogens). As mentioned above, those chemicals with a critical window of exposure (i.e., divalent and trivalent chromium, manganese, dioxins), would not normally be assigned an annual averaging time, and thus would not be applicable to the development of a converted 24-hr AAQC.

Comment on whether the method is general enough to be used directly, or if it can be extrapolated, for application to other chemicals and/or problem formulations. Please explain why or why not.

Both approaches are general enough to be used directly as benchmarks for the evaluation of air quality data based on an assumption of continuous lifetime exposure.

Approach 1 may be directly applied by other agencies through consideration of specific effects and critical windows of exposure.

Approach 2 may be applied after selection/validation of appropriate conversion factors in other jurisdictions / air sheds and contaminants. With regard to the MOE, the province-wide application of the 5-fold annual-to-24 hour conversion for AAQCs is supported by urban data sets. Urban ambient air monitoring data includes the contribution of diverse emitting sources to general air quality and hence supports the conversion of an annual AAQC to a 24-hr AAQC, which can be used to interpret air quality data in the absence of annual data. This methodology has thus been utilized for a wide range of ambient air contaminants in diverse settings within Ontario.

In addition to utilizing these conversion factors for environmental assessments, the MOE uses it as a tool when comparing ambient air quality concentration levels from other jurisdictions. Specifically, when converting a guideline developed by another jurisdiction for use in MOE, if there are no details available about the specific averaging time conversion factors used by other jurisdictions in order to derive the guideline, or if no conversions were performed by a jurisdiction, then MOE conversion factors may be used. It should be noted, however, that if the agency used a specific averaging time conversion factor to derive their guideline, for the sake of consistency the MOE first applies the inverse of the other agency's conversion factor, and then applies MOE conversion factors, if necessary.

Discuss the overall strengths and limitations of the methodology.

Approach 1:
The MOE's 24-hour AAQC can be used to set targets for air quality and can be used to readily assess air quality relative to these targets, when compared to single 24-hr monitored data points. If the 24-hour AAQC is met then no adverse effects are expected over a continuous lifetime exposure. Another strength of this approach is that it is based on chemical-specific data. As well, while this approach also protects for the potential adverse effects from single or rare short-term peaks in exposure, the 24-hour AAQC is not appropriate for assessing the health risk associated with single or rare exposures above the AAQC. This gap is filled by the direct development by the TCEQ of a short-term effects-based value. The ministry currently evaluates single or rare exposures above the 24-hour AAQC on a case-by-case basis.

Approach 2:
Strengths
A strength of this approach is that it is science-based, using empirically derived conversion factors from measurements of several contaminants in air. The use of a conversion factor of 5 to convert an annual to a 24-hour number has generally been found to be protective, with varying levels of conservatism depending on the emissions and air dispersion scenario. However, meteorological anomalies may not be captured under this conversion method, or in physical situations where regional ambient air variability may not

apply due to local topography (i.e., specific local areas exposed to air tunnel-like effects, as with mountain valleys).

Another strength of the approach is that the converted 24-hour AAQC is protective against effects in both long-term and short-term exposure (provided that short-term effects do not occur at concentrations less than five times the annual AAQC (i.e., the converted 24-hr AAQC)). Theoretically, if short-term adverse effects which may occur within 24-hours at levels less than a value equal to 5x the annual AAQC were of concern, then an additional short-term AAQC specific to that other effect would be warranted. Assuming the minimal data requirements to set an annual AAQC for long-term exposure are available, no other data are necessary to create the converted 24-hour AAQC.

Limitations

The converted 24-hour AAQC is not directly linked to an effect and instead provides an indication whether the effects-based annual AAQC may be exceeded. This limitation does not impact this AAQC's use as an air quality target but has been criticized when used to set regulatory air standards for evaluating the contributions to air of regulated emitters. MOE's stakeholders have argued that compliance with an air standard should not be evaluated based on a converted value. In response, the MOE introduced annual air standards, for the first time, for six contaminants in 2011. However, the MOE will continue to use converted AAQCs to evaluate ambient air quality.

The converted 24-hour AAQC is not appropriate for interpreting single or rare exposures above the AAQC. In such cases, the MOE evaluates exposure on a case-by-case basis. This limitation is further explored below by comparison of converted 24-hour AAQCs to the proposed 24-hour AMCVs developed by the TCEQ.

The conversion factors applied are based on analysis of monitoring information for a selected group of chemicals, with the assumption that the conversion factor derived from this analysis is applicable to all chemicals in air. This limitation is balanced by the selection of a value from the dataset that could be considered conservative in most scenarios.

Outline the minimum data requirements and describe the types of data needed.

To derive 24-hour AAQCs, the MOE undertakes an approach similar to other comparable jurisdictions; specifics may change, but the underlying goal is to base the AAQC on the most sensitive relevant adverse health effect reported in the medical and toxicological literature, and have it set at a level designed to protect sensitive individuals in the population by the inclusion of margins of safety and conservatism, via usage of uncertainty factors or extrapolation to a target risk value. Thus, the minimum data requirements are similar to those for developing other chronic exposure limits – adequate data from subchronic or chronic exposure to identify a point of departure for an effect relevant to humans; shorter duration studies may provide the point of departure if they identify a lower effect level. Uncertainty factors are used to address data gaps, as for other chronic exposure limits.

HOW THIS ASSESSMENT ADDRESSES ISSUES RAISED IN SCIENCE & DECISIONS:

A. Describe the dose-response relationship in the dose range relevant to human exposure.

The MOE takes into consideration a number of dose-response factors in determining whether to assign a 24-hour or annual average to an effect-based AAQC designed to protect for long-term exposure. These include the following:

1. Patterns and duration of exposure. Is exposure episodic with short term peaks or does it involve long-term repeated exposure to relatively low concentrations?

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2. Nature of the relevant critical effect(s), including critical windows of exposure. Developmental effects are of particular interest in this context, given the relatively short critical window of exposure during pregnancy.
3. Mode of action for critical effects including relevant dose metrics (i.e., whether, for example, the effect is likely to be associated with area under the blood concentration time curve or Cmax – i.e., the maximum concentration in blood).

As such, this approach uses standard UFs in the development of an AAQC, be it 24-hour or annual, and so does not generally attempt to describe the human dose-response in the range of human exposures.

B. Address human variability and sensitive populations?
C. Address background exposures and responses?
D. Address incorporation of existing biological understanding of the likely mode of action (MOA)?
E. Address other extrapolations, if relevant – insufficient data, including duration extrapolations, interspecies?
F. Address uncertainty.

For B-F: While such issues are addressed in the establishment of the effects-based AAQCs, they are not revisited in the assignment of averaging time or in the derivation of a conversion-driven 24-hour averaged AAQC. The purpose of this case study is to obtain comments from the panel the strengths and limitations of the approaches employed by the MOE in interpreting 24-hour monitoring data, and not in the development of an effects-based AAQC.

G. Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?

While both approaches are intended to identify a safe dose level, the 24 hours AAQC developed through the two approaches above are treated differently, with regard to risk assessment.

The 24-hour AAQCs developed through Approach 1 are specific to the assessment of risks from long-term continuous exposures and are directly linked to an adverse health effect being considered; so they may be used in assessments of long-term risk.

In comparison, as the converted 24-hour AAQCs developed though Approach 2 are not *directly* linked to an adverse health effect, they are not appropriate for risk calculations. In these cases, the monitored value would be *converted back to an annual equivalent* (i.e, divided by 5), to get an equivalent annual average value from which long-term risk calculations (e.g. cancer probability) could be calculated.

H. **Work practically? If the method still requires development, how close is it to practical implementation?**

Both methods are already implemented in Ontario. As discussed above, the practicality of the converted 24-hour AAQCs is one of the strengths of this approach.

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Logistics

On-Site Logistics

Location

The workshop is being held at:

U.S. Environmental Protection Agency
Potomac Yard, Room South 1204/06
2777 Crystal Drive
Arlington, VA 22202

The closest METRO stop is Crystal City which is about a mile away from the building.

Parking

Onsite parking is available for a fee:

Colonial Parking

1 Hour	$6
2 Hours	$9
3 Hours	$13
Max	$16
Early Bird	$10(In by 9am)
Weekends	$5

Meals

Coffee, tea, refreshments, and light snacks will be provided to workshop attendees every day. Complimentary lunch will be offered Wednesday, including vegetarian and vegan options. Lunch will not be provided Tuesday or Thursday, please plan accordingly.

Reception

On Tuesday evening all participants are invited to join us for a reception at the Hyatt Regency Crystal City from 6:30 to 8:30. Dinner portion hors d'oeuvres will be available to attendees. The reception will be held at 2799 Jefferson Davis Highway, Arlington VA 22202. The venue is approximately a 3 minute walk from the meeting facility.

1. Head south on Crystal Dr toward S Potomac Ave
2. Turn right onto 27th St S
3. Turn right onto S Clark St
4. Sharp left. Destination will be on the left - 2799 Jefferson Davis Hwy, Arlington, VA 22202

We will meet in the Tidewater Room.

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For other food options please see the map of nearby restaurants at the end of this meeting packet.

Webinar Logistics

We are pleased to be broadcasting this workshop to those offsite using Adobe Connect. We hope in this way to make the talks and discussions available to a broader audience who was not able to attend in person. Feel free to ask colleagues to join you and view the webinar via your computer

Webinar participants are invited to submit questions and comments for the Q&A periods by sending them to Oliver Kroner at kroner@tera.org. We will do our best to have these questions addressed during the Q&A session. However, due to the large number of participants, we anticipate receiving more questions than we will have time for, and apologize in advance if your question is not read during the workshop.

All Case Studies and Presentations will be posted online at www.allianceforrisk.org.

If you have trouble connecting, please visit Adobe's Support Center.

Workshop Evaluation

We would love you feedback on what went well and what could be improved. A workshop survey will be available at http://www.allianceforrisk.org/ARA_Dose-Response.htm.

Contact

If you have any trouble please contact Oliver Kroner at kroner@tera.org.

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Antitrust Statement and Procedures - Toxicology Excellence for Risk Assessment (TERA)

(approved by TERA BOD on November 27, 2012)

The mission of Toxicology Excellence for Risk Assessment (TERA) is to support the protection of public health by developing, reviewing and communicating risk assessment values and analyses; improving risk methods through research; and, educating risk assessors, managers, and the public on risk assessment issues. Much of TERA's work is conducted through meetings and committees of diverse external parties wherein discussions are held to promote understanding and resolution of scientific issues. Participants in TERA-organized meetings:

- Discuss scientific data and interpretations of data for purposes of assessing human and ecological risks.
- Identify data gaps and needs and develop research plans and protocols to address these needs.
- Support and promote research and educational programs to enhance risk assessment.

Participants in TERA-organized meetings shall fully comply with all anti-trust laws. Participants in TERA meetings shall **not**:

- Discuss prices or pricing policies, or any discussions which have a direct or indirect effect on pricing or any other terms of sale, such as costs, discounts, terms of sale, profit margins, or credit terms.
- Discuss allocation or divisions of markets or customers.
- Discuss refusing to deal with or boycott suppliers, purchasers, or competitors.
- Disclose any competitively sensitive information.

All TERA sponsored meetings shall comply with anti-trust laws. To ensure compliance the following guidance shall be followed by TERA staff organizing and conducting meetings at which competing members of industry are present.

1. A TERA staff person shall be designated as the "TERA meeting manager" and be responsible for monitoring compliance with this policy. The TERA meeting manager shall be present at all meetings and no unscheduled or informal meetings shall be held.
2. A detailed agenda shall be provided prior to the meeting and followed during the meeting.
3. TERA staff shall provide accurate minutes of the meeting and distribute to all attendees post meeting.
4. Discussions of prices, costs, sales, markets, production quotas, "fair" profit levels, warranty terms, other terms of sale, or any other discussions as outlined above will be avoided. If any such discussion is initiated, it is the responsibility of all attendees to immediately stop such conversations and notify the TERA meeting manager. If the

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participants refuse to stop these discussions, the TERA meeting manager shall immediately adjourn the meeting and leave the room.

5. At the beginning of all meetings, the TERA meeting manager shall read the following statement:

> "Participants in this meeting may include those who represent competing businesses. To avoid violation of anti-trust laws or any appearance of violations it is important that all participants agree to avoid any comments or actions that encourage joint action by participating firms to restrict competition, discussion of pricing or pricing policies, allocations of customers or markets, or boycotts. Competitively sensitive information should not be discussed. If at any time during the course of this meeting you think that discussions have strayed into these areas, you are required to notify the chair immediately. Please see the provided TERA anti-trust policy for further information."

6. If there is any doubt about the propriety of any action, the TERA meeting manager shall consult with TERA management or legal counsel before proceeding.

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Thank you to our Sponsors

The Alliance for Risk Assessment would like to sincerely thank our sponsors who brought this workshop to life. This would not have been possible without the collaborative efforts of federal and state government agencies, scientific societies, industry groups, consulting firms, and environmental non-profits. The *ARA* would like to recognize:

- Academy of Toxicological Sciences
- Agency for Toxic Substances and Disease Registry
- American Chemistry Council Center for Advancing Risk Assessment Science and Policy
- American Cleaning Institute
- American Petroleum Institute
- American Water Works Association
- Center for Food Safety and Applied Nutrition of the US Food and Drug Administration
- Council of Producers & Distributors of Agrotechnology
- Chemical Producers and Distributors Association
- Chemical Specialty Products Association
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- Hawai'i State Department of Health; Hazard Evaluation and Emergency Response
- Human Toxicology Project Consortium
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- International Copper Association
- International Society of Regulatory Toxicology and Pharmacology
- The LifeLine Group
- The Mickey Leland National Urban Air Toxics Research Center
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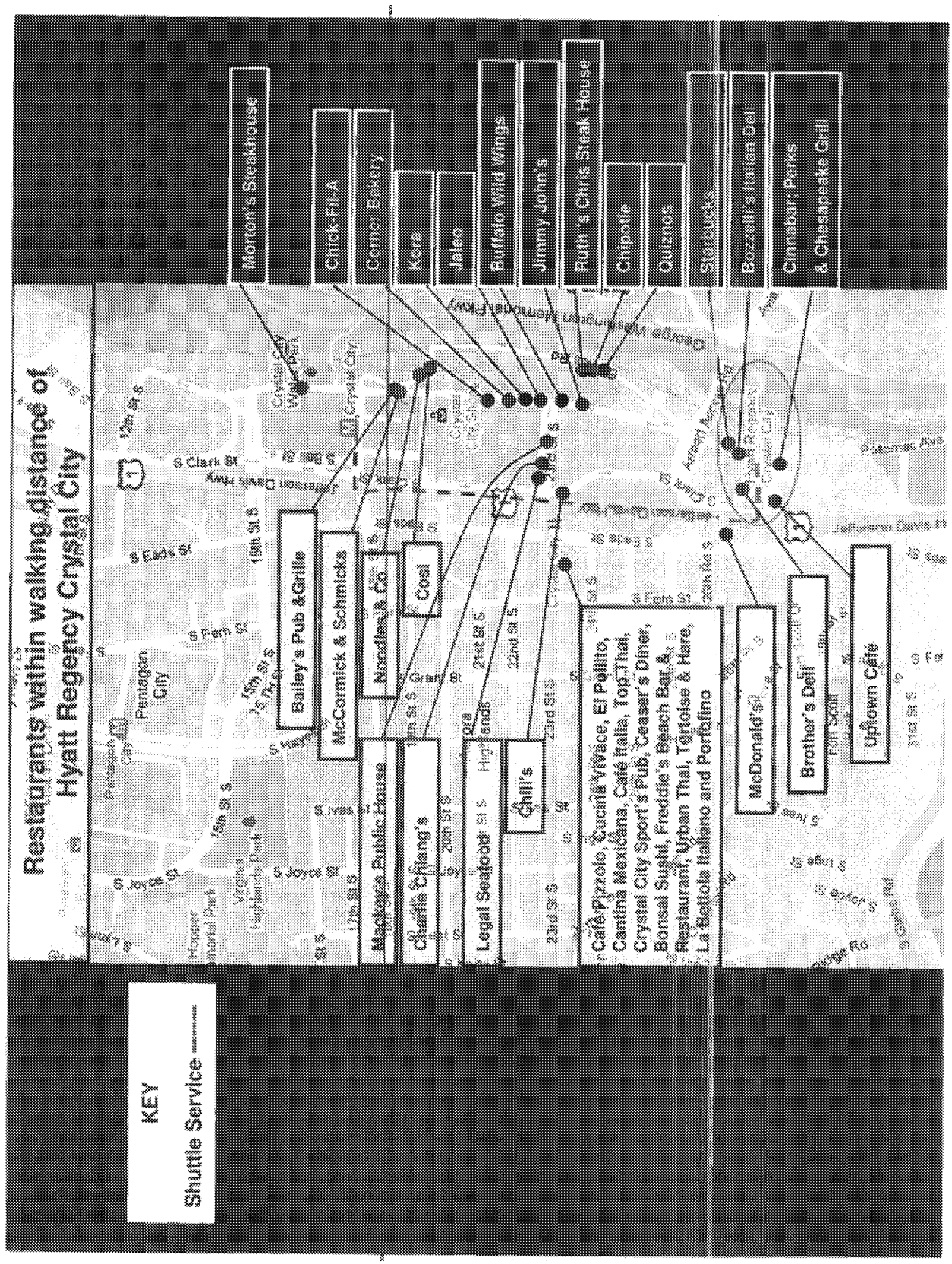
- Texas Industry Project
- Toxicology Excellence for Risk Assessment
- U.S. Environmental Protection Agency

Map of Nearby Restaurants



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