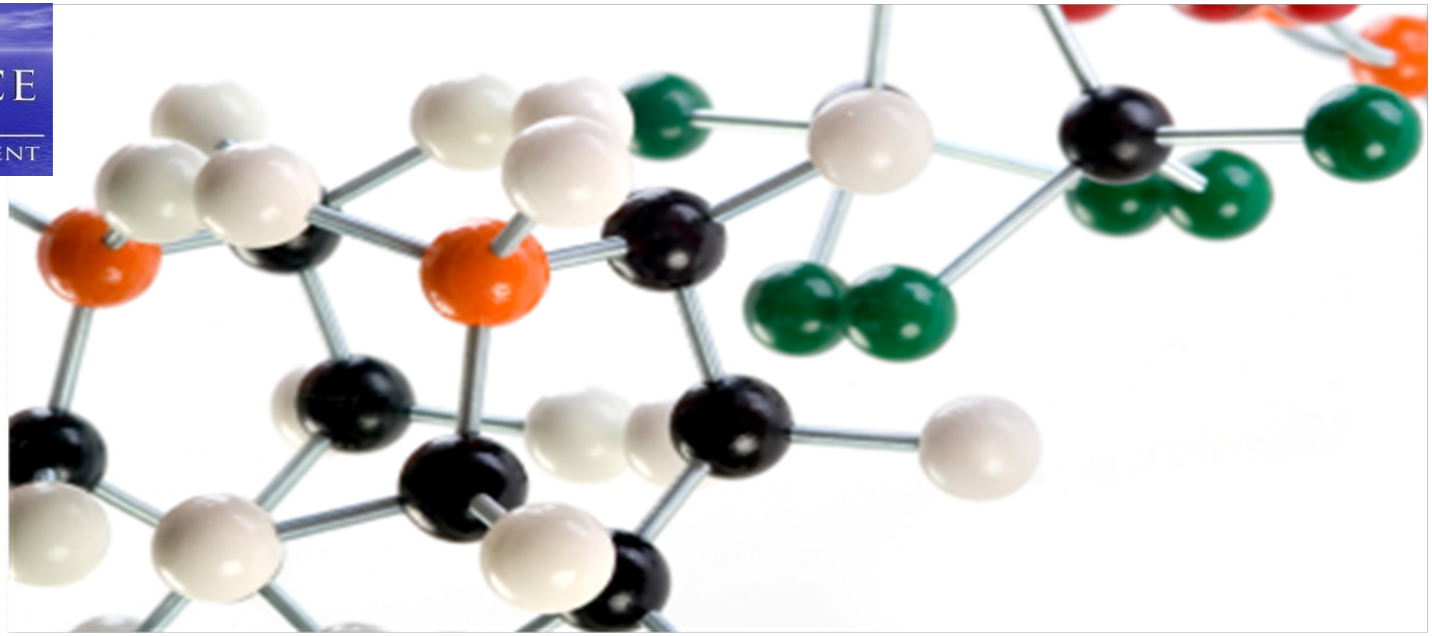


Beyond Science and Decisions: From Problem Formulation to Dose-Response. Workshop II

Date: October 11-13th, 2010

Location: DoubleTree Hotel, Crystal City, VA

WELCOME

- Dose-Response Advisory Committee (DRAC)
- Alliance for Risk Assessment (*ARA*) Steering Committee
- Sponsors

Dose Response Advisory Committee

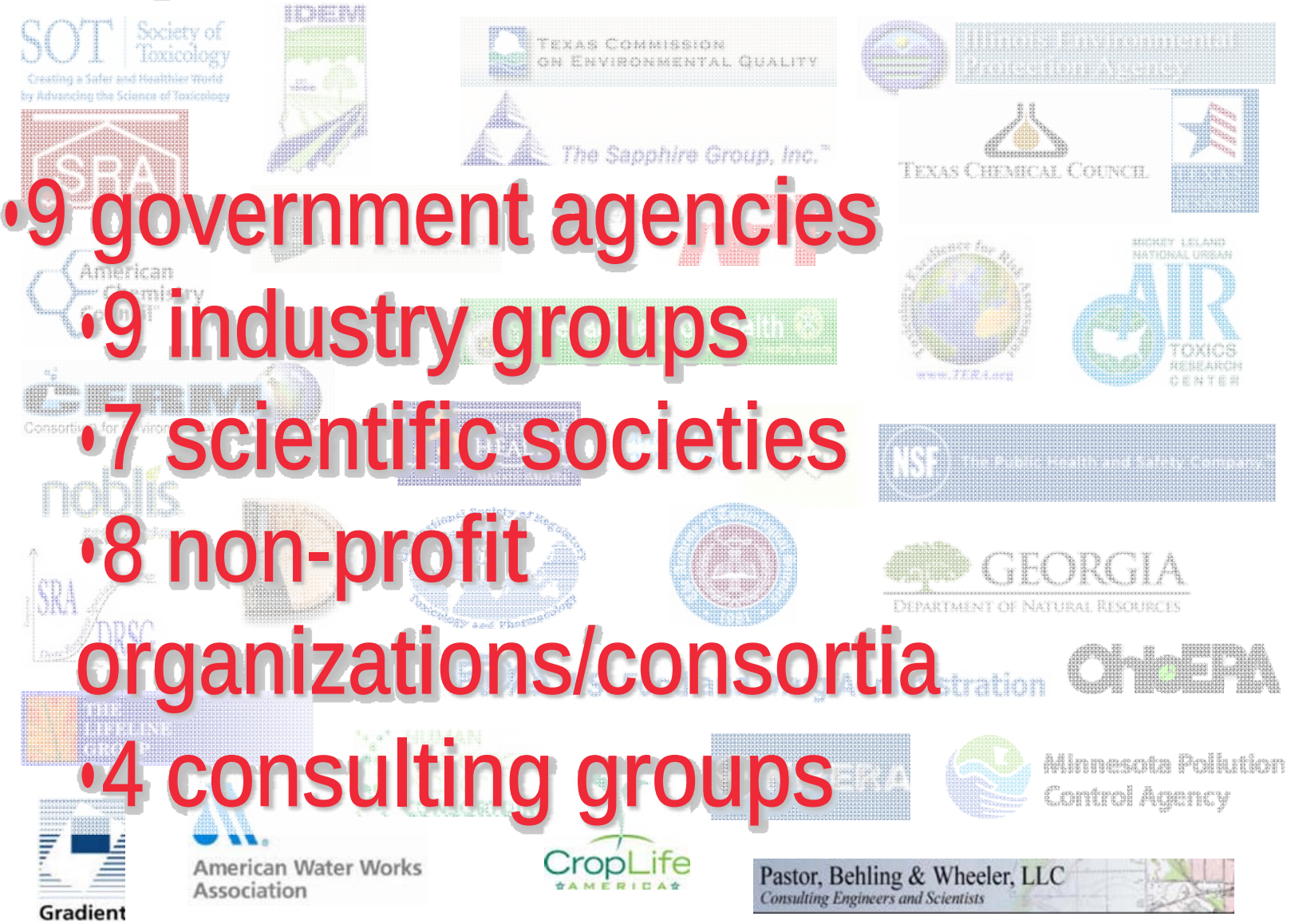
- Rick Becker, American Chemistry Council
- Michael Dourson, Toxicology Excellence for Risk Assessment
- Roberta L. Grant, Texas Commission on Environmental Quality
- Lynne Haber, Toxicology Excellence for Risk Assessment
- Michael Honeycutt, Texas Commission on Environmental Quality
- Lynn H. Pottenger, The Dow Chemical Company

ARA Steering Committee

- Barbara Harper, Confederated Tribes of the Umatilla Indian Reservation
- William Hayes, State of Indiana
- 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
- Ruthann Rudel, Silent Spring
- Phil Wexler, National Library of Medicine
- Michael Dourson, Toxicology Excellence for Risk Assessment (recused)
- Michael Honeycutt, Texas Commission on Environmental Quality (recused)

37 sponsors and collaborators:

- 9 government agencies
- 9 industry groups
- 7 scientific societies
- 8 non-profit organizations/consortia
- 4 consulting groups



Purpose

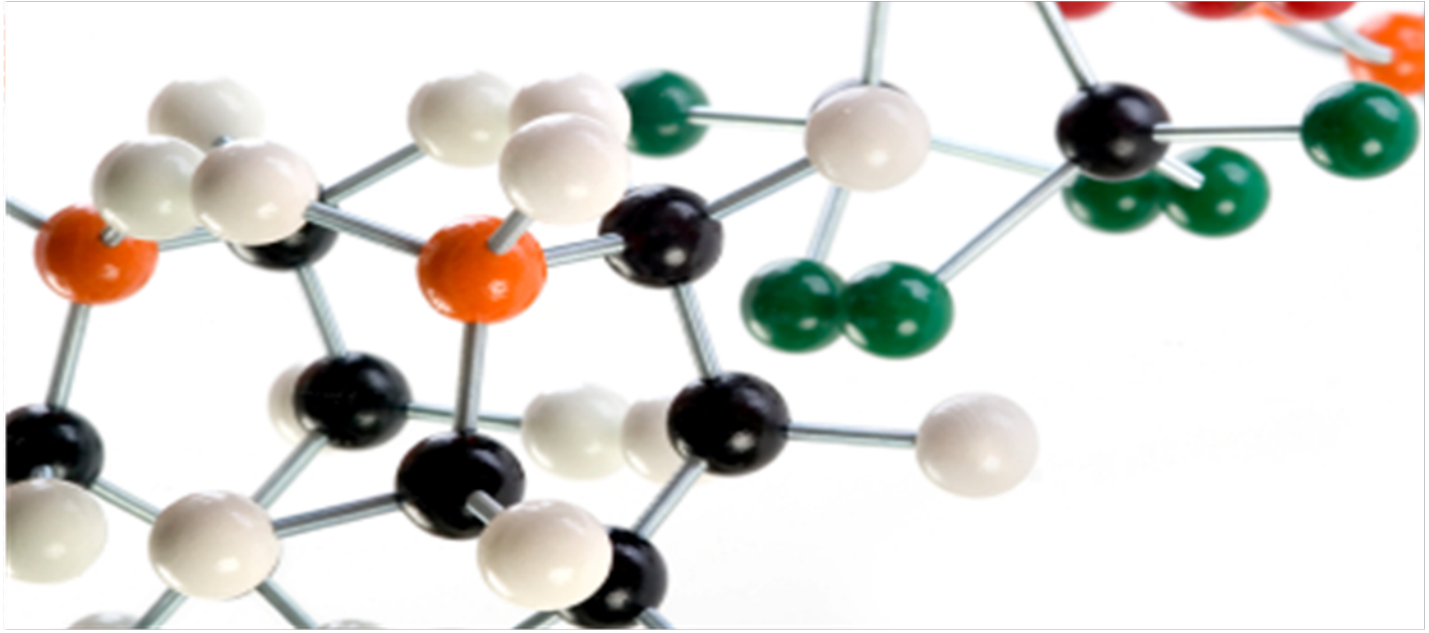
- To advance the recommendations from the NAS (2009) report *Science and Decisions Advancing Risk Assessment* concerning issue identification (problem formulation) and dose-response analysis, through review of illustrative case studies for further development of a methods text

Series of Three Workshops

- **Workshop I**
  - Texas Commission on Environmental Quality, March 16–18, 2010
- **Workshop II**
  - Crystal City, Virginia (in tandem with the Federal & State Risk Assessment & Toxicology Committee), October 11–13, 2010
- **Workshop III**
  - **Tentative Dates**: March 22 – March 24, 2011
  - **Location**: Noblis; Falls Church, Virginia

Overview of Workshop Objectives

- Build off of the NAS (2009) report on improving the risk assessment process to develop practical guidance for use by risk managers at a variety of levels (*e.g.*, states, regional managers, a variety of agencies, and industry) for risk assessment techniques applicable to specific problem formulations.
- Implement a multi-stakeholder approach to share information, ideas, and techniques in support of developing practical, problem-driven risk assessment guidance.



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

Date: March 16-18, 2010

Location: Texas Commission on Environmental Quality

Workshop I Summary

- 60 participants with more than 100 participants *via* webcast
- Brainstorming
  - Ongoing risk assessment activities
  - Perspectives on the NAS (2008) Silver Book
- Selection of case studies
  - Consideration and selection of case studies
  - Focus on the principles of the methodology, not specific chemicals

Meeting 1 Highlights

- Welcome – **Bryan Shaw**, Chairman of Texas Commission on Environmental Quality.
- Keynote Talk –**Bette Meek**, University of Ottawa. Problem formulation and risk assessment needs
- Ongoing activities
  - **Jennifer Seed,** U.S. Environmental Protection Agency. Perspective on the current state-of-knowledge of mode of action as it relates to the dose response assessment of cancer and noncancer toxicity
  - **Martha Moore.** National Center for Toxicological Research. Evaluation of a potential mutagenic MOA based on analysis of the weight of evidence and using the modified Hill criteria
  - **Lorenz Rhomberg**, Gradient. Implications of background and thresholds on dose response assessment

Meeting 1 Highlights (cont.)

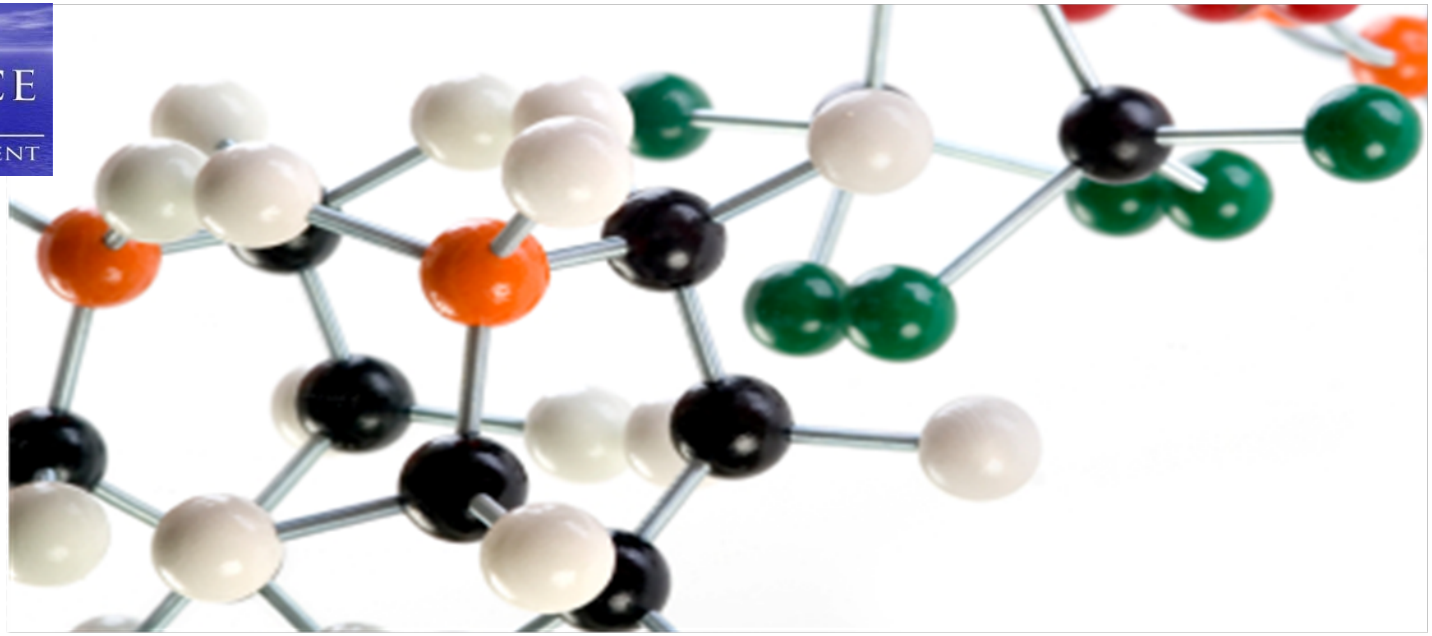
- Ongoing activities (continued)
  - **Steve Olin** and **Beth Julien**, International Life Sciences Institute. Key events dose response assessment framework
  - **Rick Hertzberg**, Biomathematics Consulting. Categorical regression as a predictive tool for determining risks above the Reference Dose (RfD)
  - **Dale Hattis**, Clark University. Probabilistic Reference Dose (RfD): The several ways to determine relevant values
  - **Bos Bokkers**, RIVM (The Netherlands) Integrated probabilistic risk assessment approach for substances in food
  - **Harvey Clewell**, The Hamner Institutes for Health Sciences. Modeling of early key events based on genomics - and potential applications to nuclear-receptor-mediated toxicity
  - **Richard Carrier**, Health Canada. Deriving drinking water guidelines: Health Canada's challenges and progress

Meeting 1 Highlights (cont.)

- **Ongoing activities (continued)**
  - **Paul Price,** The Dow Chemical Company. Using Empirical Data on Toxicity Pathways in the Prediction of Responses at Low Doses
  - **Clif McLellan**, NSF International. Thresholds of toxicological concern (TTC)
- **Perspectives on the NAS (2009) report**
  - **Adam Finkel**, University of Pennsylvania
  - **Jim Bus,** The Dow Chemical Company
  - **Bob Benson,** U.S. Environmental Protection Agency
  - **Michael Honeycutt,** Texas Commission on Environmental Quality
  - **Erik Janus,** CropLife America
  - **Kenny Crump**, Louisiana Tech
  - **John Christopher**, California Environmental Protection Agency (now emeritus) & *TERA* Fellow

Meeting 1 – Case Studies

- 27 Case study proposals received prior to first workshop
- Breakout groups reviewed proposals, recommended the ones to advance to workshop 2, suggested additional case studies
- 24 case studies recommended for workshop 2, including some suggestions for combining studies
- Between workshops 1 and 2, some new case studies or splits in topics, some could not be completed in time
- 18 case studies addressed at workshop 2 – emphasis on method



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

Date: October 11-13th, 2010

Location: DoubleTree Hotel, Crystal City, VA

Workshop II Expert Panel

- Provide guidance during the workshops
  - 12 scientists with extensive expertise in risk assessment methods and toxicology
- Evaluate the case studies during Workshop II
- Build consensus on guidance for dose-response assessment methods during the third workshop

Panel Selection Process

- Announcement of workshops, with a call for Panel nominations
- DRAC also nominated panel member candidates
- ARA steering committee reviewed candidates and developed a prioritized list of nominees – balanced among affiliation and expertise (biology, risk assessment, modeling)
- Invitations were sent to a total of 27 people
- Particular effort was made to include people from the NAS panel and environmental NGOs

Workshop II Expert Panel

- 3 from the US Federal Government, with 2 from EPA
- 2 from industry
- 2 from academia
- 2 from state government, and 1 state government emeritus
- 2 from nonprofit groups
- 1 consultant
- 2 were members of the NAS *Science & Decisions* Panel

Expert Panel

- *Michael Bolger, U.S. Food and Drug Administration (FDA)*
- *James S. Bus, The Dow Chemical Company*
- *John Christopher, CH2M/Hill*
- *Rory Conolly, U.S EPA National Health and Environmental Effects Research Laboratory*
- *Mike Dourson, Toxicology Excellence for Risk Assessment (TERA)*
- *Adam M. Finkel, UMDNJ School of Public Health*
- *William Hayes, Indiana Department of Environmental Management*
- *R. Jeffrey Lewis, ExxonMobil Biomedical Sciences, Inc.*
- *Bette Meek, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa*
- *Paul Moyer, Minnesota Department of Health (MDH)*
- *Greg Paoli, Risk Sciences International*
- *Rita Schoeny, U.S. EPA Office of Water*

Meeting #2 Rapporteurs

- Lynne Haber, Toxicology Excellence for Risk Assessment
- Asish Mohapatra, Health Canada
- Elizabeth Spalt, Indiana Department of Environmental Management
- Allison Jenkins, Texas Commission on Environmental Quality (via webcast)

Presentations at Workshop 2

- Ed Ohanian, U.S. EPA (Keynote address): NRC findings and Current EPA Risk Assessment Forum Efforts
- Adam Finkel, University of Pennsylvania and NAS panelist: Beyond Misleading Underestimation of Carcinogenic Potency: The "Known Unknown" of Human Susceptibility
- Peter Grevatt, U.S. EPA: Issues Related to Children's Health Protection
- Craig Rowlands, The Dow Chemical Company: Risk21. Risk Assessment for the 21st Century: A Vision and a Plan
- Doug Wolf, U.S. EPA: Dose Response Approaches for Nuclear Receptor-Mediated Modes of Action Workshop Preliminary Report

From the Keynote Address: EPA Risk Assessment Forum Efforts to Address NRC Recommendations

- RAF is coordinating EPA response to Science and Decisions; Toxicity Testing in the 21st Century; and Phthalates and Cumulative Risk document
- Workgroups of subject matter experts are reviewing recommendations, identifying related guidance, developing plan for considering recommendations
- Workgroup output will form basis for discussion at internal colloquium at end of October.
- Workgroups are reviewing recommendations on uncertainty and variability, unified dose-response assessment and defaults, and cumulative risk
- A goal of the colloquium is to formulate an action plan for future directions, *considering* NRC recommendation and incorporating the Administrator's priorities

Human Variability in Cancer Response – Adam Finkel (NAS panel)

- For chemicals for which low-dose linear applies at environmentally relevant doses:
- If we assume we have appropriately mapped from rodent data to average human – then we must be underpredicting the sensitive population response.
- NAS recommendation: A factor of 25 would be a reasonable default value to assume as a ratio between the median and upper 95th percentile person's cancer sensitivity for the low-dose linear case

Human Variability in Cancer Response – Discussion

- Raises question of who are we trying to protect, and by how much
- If dose-response is nonlinear, then estimate is wrong for everyone. Biology has lower response than low-dose linear, so linear protects more than the median.
- Question of whether people affected at low doses are unlucky (stochastic), or are more sensitive
- Maybe dose-response is linear in log dose-probit space

Themes of Discussions

- Maximizing use of biological data
- Reality check – biological plausibility of results
- Design experiments to answer key questions
- Themes from NAS addressed in case studies:
  - Additivity to background exposure or response
  - Endogenously formed chemicals
- Generic case studies – methods vs. hypothesis testing of recommendations from the NAS report
- Some well-established methods, some new methods (works in progress) to address existing problems

Linear Extrapolation

NAS panel: Linear as surrogate for no threshold – nonzero slope at low dose regardless of shape at any higher dose.

- Does not mean draw straight line from POD to zero.

- Agrees individual threshold exist, and population thresholds exist for some chemicals
  - Approach suggested by ARA panel member of considering linear in log dose vs. probit space is consistent with NAS –to characterize variability in individual thresholds.

ARA panel:

- Use of biology and understanding biology of thresholds

Considerations for Evaluating Case Studies

- Pragmatism
- Methods tied to problem formulation: NAS focused on full assessments; need different methods for prioritization and screening – several case studies filled in methods for these less detailed assessments
- Scientifically defensible
- Generalizability/Extrapolatability
- Purpose of risk assessment is to inform a decision – risk management
- At each step compare uncertainties for the biologically-based and for the default approach

Evaluating Biological Plausibility of Linear Low-Dose Extrapolation for Risk of Morbidity and Mortality from Hepatic Disease (Ethanol)

- Author: R. Becker & Hays
- **Hypothesis Test**: To test the biological plausibility of predicted risks from low-dose linear extrapolations with a well-studied chemical
- Ethanol (a hepato-toxicant) induces morbidity (liver cirrhosis) and mortality
  - Considered risk at high-dose (alcohol consumption) and low-dose from food (e.g., breads and juices)
- **Results**: Risks overestimated vs. actual incidence in population
- Sensitive populations not explicitly addressed, used large population for point of departure
- Panel recommendations: Consider MOA in choice of extrapolation approach; improve consideration of background; consider genetic variability; consider linear in log dose-probit space

Biologically Informed Empirical Dose Response Modeling: Using Linked Cause and Effect Functions (TiO2)

- **Authors**: Allen, Maier, Willis, Haber
- **Method**: Use quantitative data to describe relationship between successive key events in the MOA using mathematical functions. Addresses need for biologically-informed model between default and complexity of BBDR
- Used information on relationships between successive key events to predict lung tumors based on lung burden, uses data on biomarkers of exposure and effect
- Empirically-based; biological basis, but not modeling biological *processes*
- Panel supported method – pragmatic; addresses desire to use understanding of biology to describe dose-response; recognizes even full BBDR uses some empirical modeling
- Suggestions for extensions discussed

Use of Biomarkers with the BMD Method (Methyl Mercury)

- Authors: Gentry, Van Landingham, Hays and Aylward
- Purpose and method: Extension of BMD approach to allow estimation of risk at doses above RfD when existing human response data are available; hypothesis test
- Four approaches – using different combinations of (1) BMD vs. BMDL as POD and (2) of assumptions regarding risk at the RfD (zero; determined by model; allow model to determine threshold term)
- Illustrates use of human data; % of population exceeding RfD is *not* the same as the percent with an effect – POD is low response
- Panel recommendations: Address MOA as basis for choice of approach; expand using biological indices

Estimate Risk Above the RfD Using UF Distributions (multiple chemicals)

- Authors: Spalt, Kroner; Advisor: Dourson
- Hypothesis test – apply probability density functions (pdfs) to estimate response
- **Method**: Use default pdfs of Swartout et al. (1998) – for all UFs with a value of 10: a lognormal distribution with a median of or 3.16and a 95th percentile value of 10.
- Result is probability that the RfD is correct – not true risk
- **Main Discussion Points**:
  - As used here, is a risk management tool – e.g., for comparing chemicals and prioritizing, not a useful estimate of risk
  - Refine the method using updated work of Jeff Swartout.
  - Need some test of the Silver Book recommendation of using the Hattis method – how does that compare with traditional method?

Apply Linear Low-Dose Extrapolation from Benchmark Dose for Noncancer Risk Assessment (multiple chemicals)

- Authors: Kroner, Haber; Advisor: Dourson
- **Method**: Extend a straight line from the chosen benchmark dose (BMD) (linear extrapolation) for a number of chemicals on IRIS; compare 1E-5 risk with RfD/RfC
  - Used several different methods to estimate conversion from animal POD to equivalent dose/concentration in sensitive human population
- **Main Discussion Points**:
  - Not a true test of the Hattis method – that is needed
  - This method may be useful for screening or priority setting, but should not be presented as an accurate prediction of risk.
  - Consider doing in log dose-probit space (different definition of linear)

Use of Categorical Regression – Risk Above the RfD (Copper; Chemical T)

- Authors: Danzeisen, Krewski, Chambers, Baker, Haber
- Categorical regression applies regression analysis to response data in the form of ordered categories of severity
- Can be used to combine data from multiple different studies, to fill in data gaps not addressed in a single study; to improve exposure-duration-response estimates.
- Case study applied the method for two chemicals – copper and a thyroid-active pesticide (chemical T) to estimate probability of group having response of severity X or greater.
- Was useful for copper to integrate across many studies without dose-response data; described effects from deficiency and excess
- For chemical T, incorporated MOA data in description of severity levels
- General panel support for method

Use of Human Data in Cancer Risk Assessment (1,3-Butadiene – BD)

- Authors: Albertini and Sielken
- Method: Uses mechanistic data and MOA data in the modeling using epidemiological data from occupational exposures.
  - Choice of metric – cumulative vs. high intensity exposure
  - Consider underlying mutagenic mechanisms; different mutational events underlie different types of tumors
  - BD itself is biologically inactive. Tumor induction results from mutagenicity of its metabolites (EB, EBD, DEB)
- Have data in range of exposures of interest; large sample population – could directly estimate risk
- Panel – need to consider what aspects of case study are generalizable; compare with default method to inform strengths of use of data

Quantitative Human Health Non Cancer Assessment based on Ovarian Effects in Rodents (1,3 Butadiene)

- Authors: Kirman and Grant
- **Methodology**: Integrating MOA and background exposures into dose-response assessment
- **Background** : Ovarian atrophy (via follicle depletion) is critical effect – surrogate for premature menopause in human populations. Used information on age-related follicle depletion as measure of human variability for toxicodynamics; incorporated internal dose measure for interspecies extrapolation.
- Method can be used for other chemical assessments where MOA information is available
- Panel: Useful to identify uncertainty in steps using defaults vs. biologically based approaches – provides comfort in use of biology

Apply AEGL Methodology to Develop Acute Exposure Guideline Levels for Ethylbenzene

- Authors: Grant, Erraguntla, Hinz, Camacho, Benson, Bredfeldt and Cagen
- Goal: Development of acute inhalation guidelines for emergency situations
- Method: Development of Acute Exposure Guideline Levels (AEGLs) for detection, disability, or death using available short-term data and judgment
  - Threshold value instead of safe level
  - Once in a lifetime exposure
  - Values for 10-min to 8-hr
  - Uses POD and UFs
- Utility: development of acute levels with stakeholder involvement; pragmatic; widely-used and internationally-accepted method

Framework for Evaluating Alternative Temporal Patterns of Exposure for Risk Characterization

- Authors: Maier, Haber, Haney, Kaden, Carrier, Craft, Hertzberg; Advisor: Dourson
- Goal: Address a real world problem – repeated acute exposures, needs extrapolation from existing criteria
- Method: Tiered Approach
  - Tier I: simplistic time-averaging approach
  - Tier III: quantitative adjustment to exposure or dose-response assessment (e.g., in PBPK)
  - Tier II: qualitative and semi-quantitative method
    - Decision tree for acute and chronic exposures
    - Takes into account chemical's toxicokinetic and toxicodynamic properties
- Work in progress, panel endorsed pragmatic idea; recommended further development, application to more case studies

Sustainable Futures™ Screening

- Authors: E. Becker and Ranslow
- Goal: Evaluate new chemicals in presence of limited data
- Methods:
  - Uses existing databases/QSAR estimation tools as source of information on chemical of interest (e.g., EPISuite)
  - Uses AIM database to determine an appropriate analog
  - Occupational and consumer exposure are estimated with modeling and databases
  - Literature search on chemical and analog
  - Determine a POD using the analog (and any available chemical-specific data)
  - Calculates MOE and considers comfort with MOE
- Tool for priority setting
- Panel endorsed – noted need to explain criteria

Tiered Screening for Acute Inhalation Exposures for Chemicals with Limited Toxicity Data (Pentene)

- Authors: Grant, Phillips, and Ethridge
- Goal: Develop acute air screening levels for chemicals with limited information
- Methods for developing Effects Screening Levels (ESLs):
  - Tier I: default ESL of 1 ug/m^3
  - Tier II: Threshold of Concern / NOAEL to LC50 ratio
    - Database of compounds with known NOAEL and LC50s
    - Categorized by severity of toxicity, or
    - Straight multiplication by NOAEL/LC50 ratio
  - Tier III: Relative Toxicity/Potency
- Screening Tool
- Panel endorsed – pragmatic, reflects data

Review of Data Fusion Methodologies to Integrate Data from Different Organizational Levels

- Authors: Mohapatra, Sadiq, Zargar, Islam, and Dyck
- Work in progress
- Advantages of Method:
  - Integration of heterogeneous sources of data using informatics tools
  - Integration of existing frameworks for use in risk assessment
  - Dynamic toxicological knowledge base
  - Recognize patterns in toxicological datasets
  - Efficient and effective integration of toxicity pathways and biologically based information
- Discussion – addresses a need – integrating across studies

Flexible Dose-Response Model for MOA Including Multiple Pathways (Acrylamide)

- Authors: Hertzberg, Dourson, Allen, Vincent, Haber
- **Goal**: How to model low-dose cancer risk if MOA includes different drivers in different dose ranges
- **Method**: Evaluate MOA using modified Hill criteria; choose model(s) based on MOA
  - Hypothesized MOA – Genotoxicity (dominates in low-dose range), and perturbation of thyroid hormone regulation (dominates at higher doses)
  - Chose dose-response model that captures low-dose linearity consistent with MOA, steeper slope at higher doses

BBDR for Respiratory Tract Carcinogenicity (Formaldehyde)

- Authors: Allen, Clewell, Haney, Kester
- When adequate data on a chemical exist, BBDR modeling can be used to integrate mechanistic information into a quantitative cancer risk assessment in order to provide predictions of dose-response and time-course behaviors.
- Planned enhancements: update regional dosimetry; consider endogenous formaldehyde; consider microarray data; reanalyze dose-time-response surface to address uncertainties
- BBDR modeling getting more generalizable. Of interest to consider what type of chemical useful for next model

Consideration of human kinetic variability (trichloroethylene)

- Authors: Lipscomb, Teuschler, Swartout, Popken, Cox, Kedderis
- Method: Use information on human variability in CYP2E1with PBPK model to estimate in vivo variability in dose of active form
- Results for example: 7x variability in metabolic capacity leads to a 2% change in metabolism *in vivo* – due to blood flow-limited metabolism
- Noted more sophisticated Bayesian MC analysis
- Panel recommendation to show application for chemical-specific adjustment factor (CSAF)

Low-dose dose-response curve shape for genotoxicity

- Authors: Pottenger, Moore, Zeiger, Zhou
- Developed/presented key events framework for mutagenic MOA
- For some direct-acting mutagens, have extensive dose-response data in low-dose region (e.g., EMS/ENU, MMS/MNU)
- For these chemicals:
  - Apparent linearity for biomarkers of exposure (hemoglobin & DNA adducts).
  - Clear, statistically supported evidence for low-dose non-linear/threshold dose-response for induction of mutations and clastogenicity
- Hypothesize biological explanations for nonlinearity
- Idea of key events as failure of compensating systems
- Panel recommended to consider BBDR-type approaches, in addition to stats analyses

Application of Silver Book Methods to Data-Rich Chemical (Dioxin)

- Authors: Simon, Stephens, Yang, Manning, Budinsky, Rowlands
- Goal: Exploration of three conceptual models with a data rich chemical; hypothesis test
  - CM1 – Nonlinear individual response, low-dose linear pop. response with background dependence
  - CM 2 – Low-dose nonlinear individual and nonlinear pop response, low-dose response ind. of background (i.e., a threshold response for which an RfD is most appropriate)
  - CM3 – Low-dose linear individual and linear pop. dose response (i.e., a non-threshold response for which a slope factor is most appropriate).
- Used internal dose measure and PBPK model
- Results: Humans much less sensitive than animals; had data in dose range of interest