

# Where the rubber meets the road: A practical methods compendium for risk assessors

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# ABSTRACT

new interactive tool for selecting a dose-response technique based on the risk assessment's problem formulation, data availability, and regulatory context. With an abundance of dose response techniques available, and the rapid rate of new method development, it can be challenging for a risk practitioner to be aware of all relevant methods to address a specific problem formulation, and even more challenging to select the appropriate method(s). The Framework builds on the risk-assessment framework proposed by the National Academy of Sciences' Science & Decisions: Advancing Risk Assessment (2009), to provide a "roadmap" of current dose-response evaluation techniques. Methods are systematically organized into three categories; qualitative decision, quantitative screening decision, and in-depth assessment. Within each category, the risk assessor is guided to methods that address key issues, such as Mode of Action assessment, vulnerable population assessment,

endogenous/background exposure, and data integration. Methods interlink with case studies to illustrate real-world application, and summaries that outline the minimum data requirements, and evaluate the method's ability to address human variability, sensitive populations, and background exposures or responses. Given the ever-evolving progress of risk science, the ARA Dose-Response Framework is envisioned as an evergreen database, providing the necessary flexibility to grow and adapt over time. A standing panel is envisaged to guide future content development. The Framework is currently available in draft form at:

http://allianceforrisk.org/Workshop/Framework/ProblemFormulation.html.

# WORKSHOP GOALS

General Workshop 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

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 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.

# SCIENCE PANEL

James S. Bus, The Dow Chemical Company John Christopher, CH2M/Hill Rory Conolly, U.S. Environmental Protection Agency Michael Dourson, Toxicology Excellence for Risk Assessment \*Adam M. Finkel, UMDNJ School of Public Health William Hayes, Indiana Department of Environmental Management

R. Jeffrey Lewis, ExxonMobil Biomedical Sciences, Inc. Randy Manning, Georgia Department of Natural Resources

Bette Meek, University of Ottawa (Chairperson) Paul Moyer, Minnesota Department of Health (MDH)

\*Greg Paoli, Risk Sciences International Rita Schoeny, U.S. Environmental Protection Agency

\*On NAS Science and Decisions panel

# CASE STUDY PROCESS

- Process encouraged engagement from wide variety of stakeholders
- Proposed in brainstorming prior to first workshop
- Initial vetting and review in breakout groups at first workshop
- Presentations at second workshop

Additional case studies and issues identified at second workshop

- 30+ case studies proposed

- 24 case studies presented and reviewed by panel

#### METHODS REVIEW

- Panel members provided input on the utility of the case study methods to address specific problem formulations, and identify areas for additional development of the case study and/or method. Inclusion of a method or case study in the framework as an illustration of a useful dose-response technique does not imply panel acceptance of the chemical-specific out-

- Methods linked to case studies to illustrate real-world application
- Summaries that briefly describe method, provide key references, outline the minimum data requirements, describe strengths and weaknesses

- Summary addresses the method's potential to address human variability, sensitive populations, and background exposures or responses.

In depth full case study

# WORKSHOP RESULTS

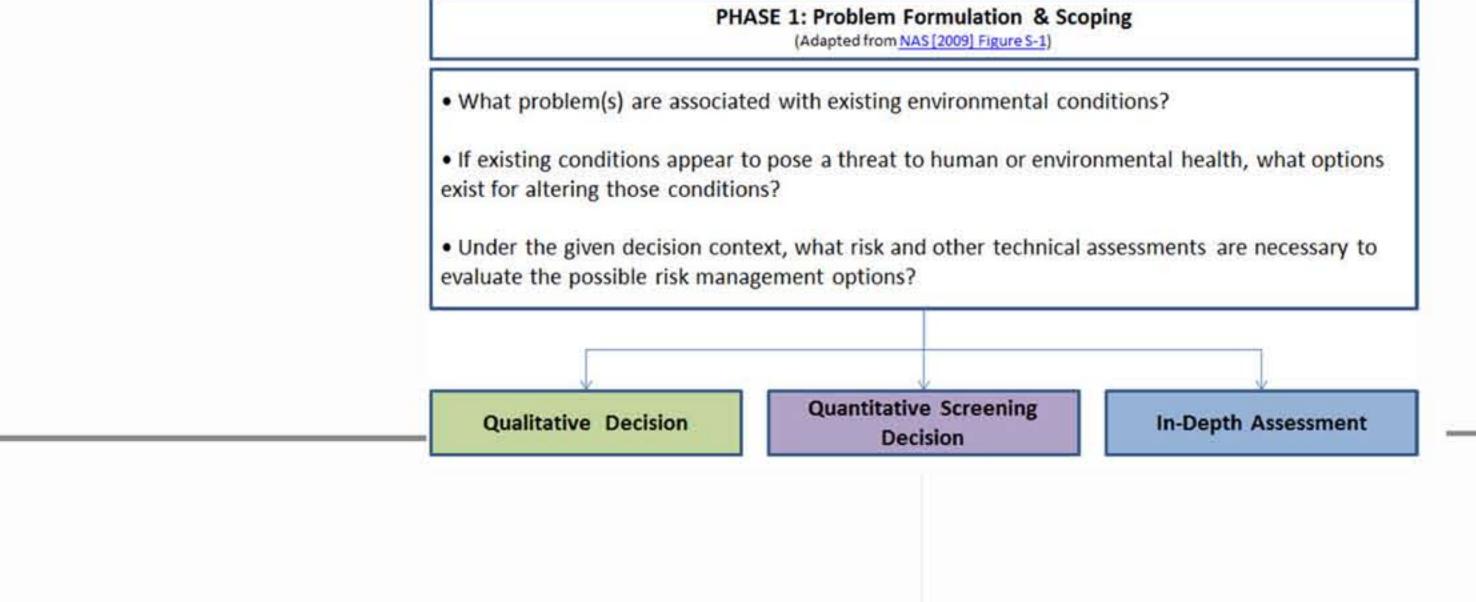
- 24 case studies were developed by outside parties and reviewed by the expert panel.

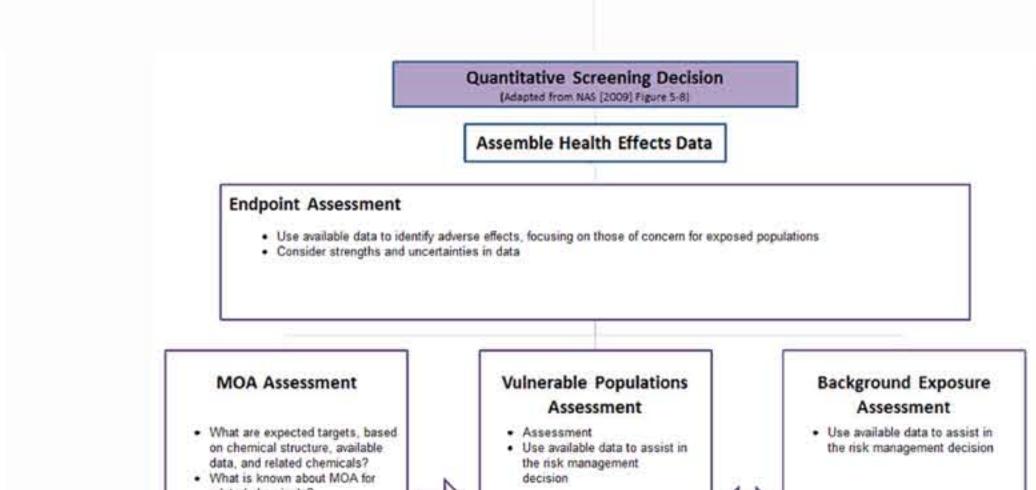
Additionally evolved methodologies in specific areas

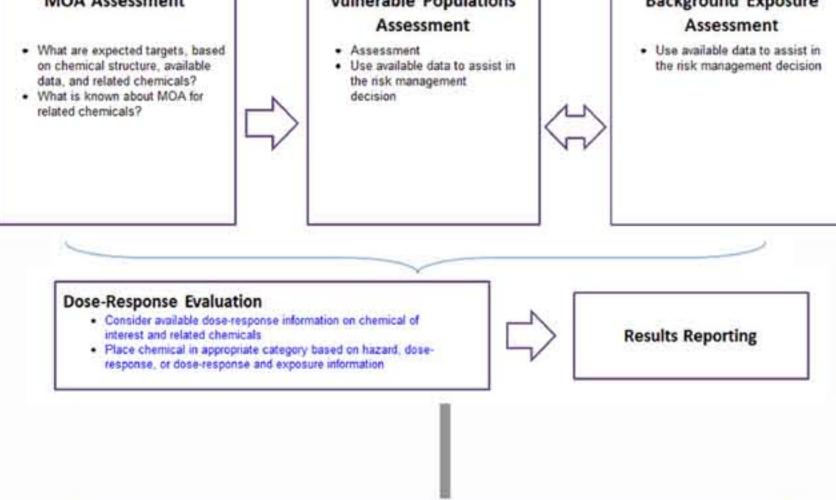
- Explored crosscutting issues raised by NAS (2009), including---but not limited to---problem formulation, Mode of Action (MOA), background & endogenous exposures, & dose response methods

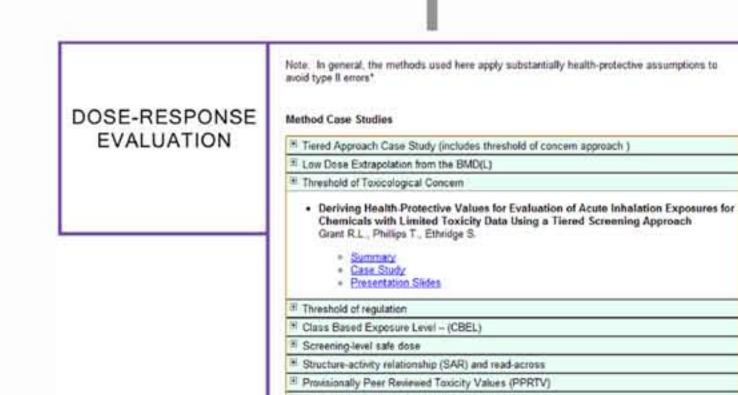
- Paper on workshop series and framework in preparation

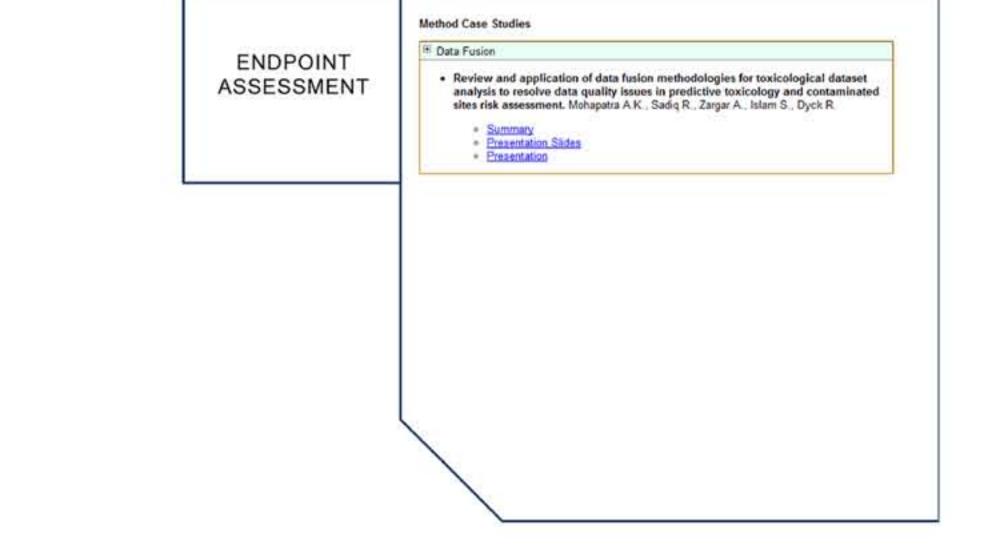
# ARA DOSE RESPONSE FRAMEWORK











In-Depth Assessment (Adapted from NAS [2009] Figure 5-8)

Assemble Health Effects Data

Identify precursors and other upstream indicators of toxicity
Identify gaps – for example, endpoints or lifestages under-assessed or not assessed (Data gaps are noted qualitatively and

Vulnerable Populations

· Identify potentially vulnerable

MOA evidence

• Evaluate endogenous processes contributing to MOA

potential MOA, background rate of health effect, and other risk factors

Dose-Response Method Selection

Conceptual model
 Data availability
 Risk management needs for form of risk characterization

Problem Formulation > In-Depth Assessment > Endpoint Assessment

Assessment

**Background Exposure** 

Assessment

Identify possible background exogenous and endogenous

Dose-Response Modeling

and Results Reporting

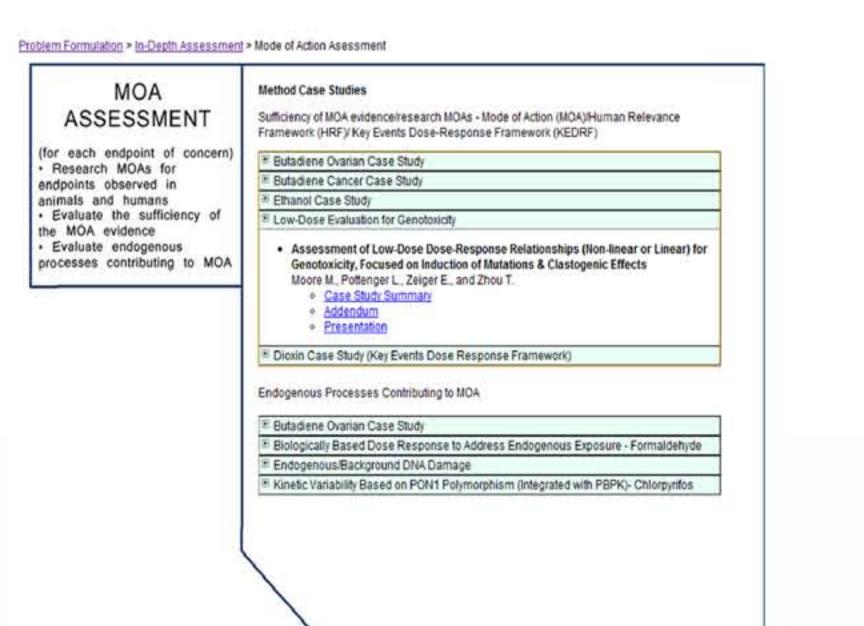
focusing on high end exposure

addressed quantitatively with uncertainty factors)

**MOA Assessment** 

concern)

(for each endpoint of



# DOSE RESPONSE FRAMEWORK

- Mode of action assessment
- Vulnerable population assessment Endogenous/background exposure
- Dose-response methods reflecting different
- Conceptual models
- Data availability
- Risk management needs Links to case studiies that illustrate real world application

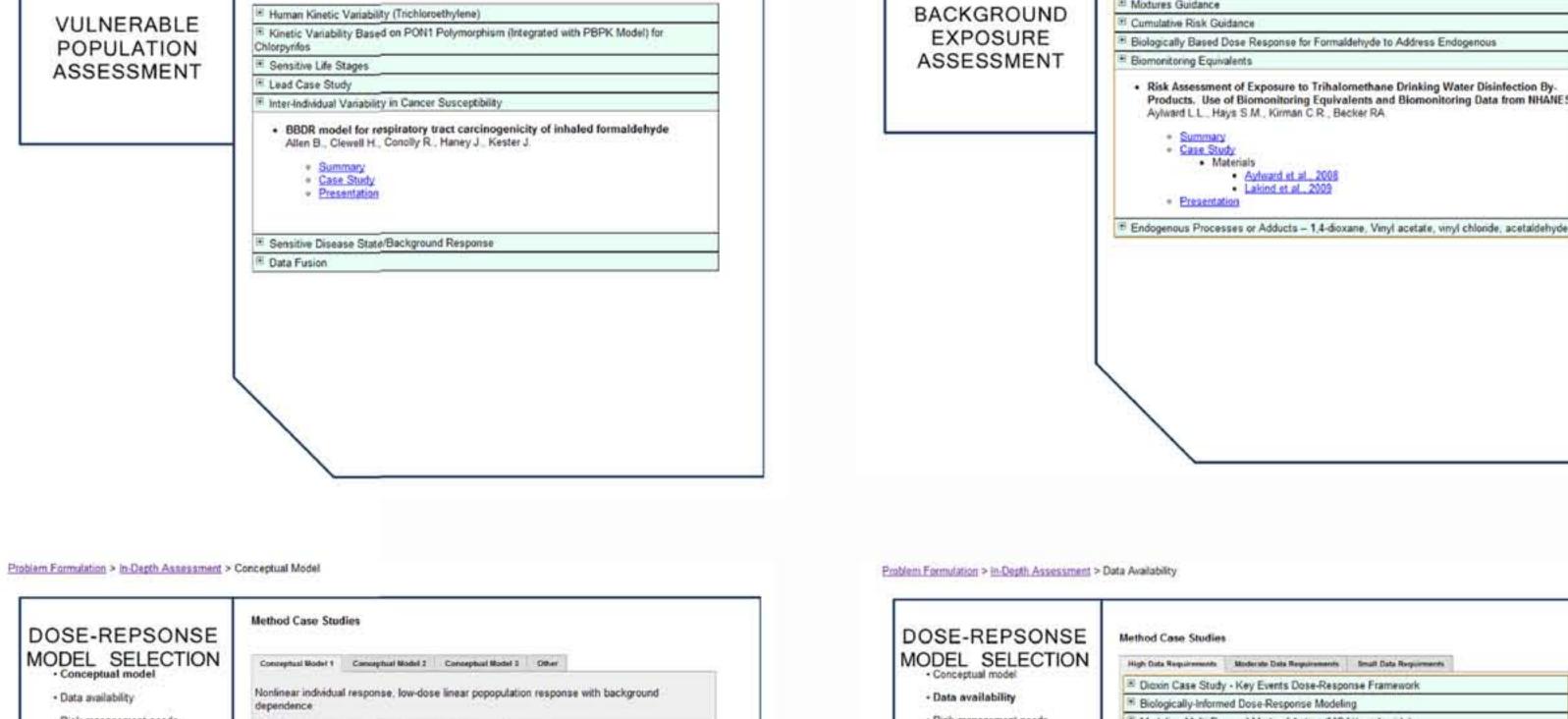
#### NEXT STEPS

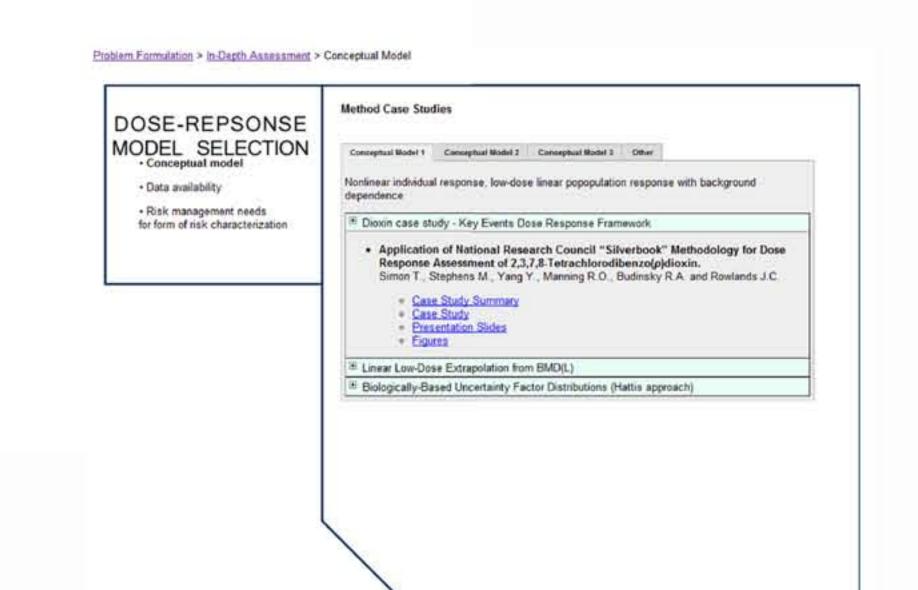
- Framework will be "evergreen," growing and evolving over time. It will be updated with additional methods and guidance documents, illustrated by case studies and with papers addressing and resolving cross-cutting issues.

- The National Library of Medicine has expressed interest in hosting the Framework. Some structural changes needed

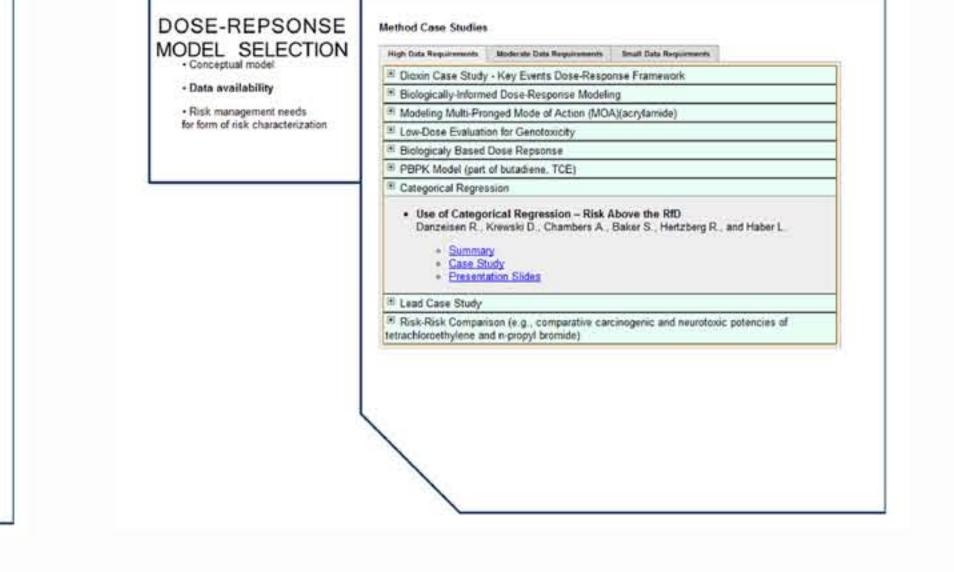
- A standing panel has been formed to meet twice a year to review additional case studies and issue/resolution papers.

Workshop 4 will be held May 22-24 in Austin, TX at the Texas Commission on Environmental Quality. Registration is available at www.allianceforrisk.org





Problem Formulation > In-Depth Assessment > Vulnerable Population



































Qualitative Decision (Adapted from NAS [2009] Figure 5-8)

Assemble Health Effects Data

Background Exposure Assessment

. Use available data to assist in

the risk management decision

. Use available data to identify adverse effects, focusing on those of concern for exposed populations

Vulnerable Populations

Assessment
 Use available data to assist if

Estimate Risk Above the RfD Using Uncertainty Factor Distribution

Summary
 Case Study
 Presentation Stides

Sustainable Futures Screening Method
 Low Dose Extrapolation from the BMD

Consider strengths and uncertainties in data

lace chemical in appropriate category based on hazard, dose

COLLABORATORS

American Chemistry Council Center for Advancing Risk Assessment Science and Policy

Center for Food Safety and Applied Nutrition of the US Food and Drug Administration

Hawai'i State Department of Health; Hazard Evaluation and Emergency Response

Academy of Toxicological Sciences

American Water Works Association

Environmental Protection Agency

Electric Power Research Institute (EPRI)

Human Toxicology Project Consortium

International Copper Association

Industrial Economics, Incorporated

Illinois Environmental Protection Agency

The Hamner Institute for Health Sciences

Georgia Department of Natural Resources (EPD)

Indiana Department of Environmental Management

International Society of Regulatory Toxicology and Pharmacology

American Petroleum Institute

Agency for Toxic Substances & Disease Registry

Consortium for Environmental Risk Management LLC (CERM)

Dose Response Specialty Group (Society for Risk Analysis)

Ethylene Oxide Panel of the American Chemistry Council

response, or dose-response and exposure information

What are expected targets, based on chemical structure, available data, and related chemicals?
What is known about MOA for



his work was supported by more than 46 sponsors and collaborators, including government agencies, industry groups, sci-

The LifeLine Group

NSF International

SC Johnson & Son

Summit Toxicology

Society for Risk Analysis

Texas Chemical Council

Texas Association of Business

Texas Commission on Environmental Quality

Society of Toxicology

Ted Simon Toxicology

Texas Industry Project

Minnesota Pollution Control Agency

Ohio Environmental Protection Agency

Pastor, Behling & Wheeler, LLC

entific societies, non-profit organizations/consortia, and consulting groups. We wish to thank all of the workshop participants

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The Mickey Leland National Urban Air Toxics Research Center

Nickel Producers Environmental Research Association

Risk Assessment Specialty Section (Society of Toxicology)

National Center for Toxicological Research of the US Food and Drug Administration

Regulatory and Safety Evaluation Specialty Section (Society of Toxicology)































