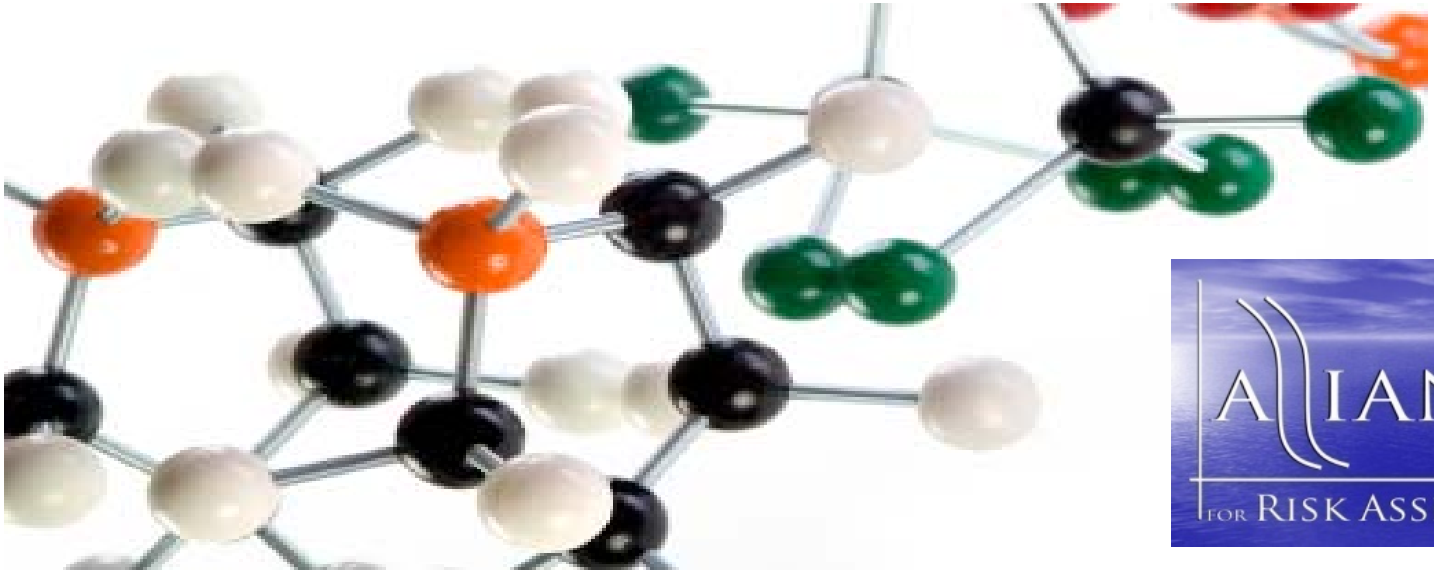
The Collaborative ARA Adventure: Extending & Expanding Discussions of Problem Formulation & Dose-Response

Lynn H. Pottenger, PhD, DABT
The Dow Chemical Company



ALLIANCE for RISK ASSESSMENT

2011 SRA Symposium

Pressing Forward:
Improving problem formulation & dose-response “Beyond Science and Decisions”

Double Symposium: Pressing Forward: Improving problem formulation & dose-response

- Introduction: The ARA Collaborative ARA Adventure (Pottenger)
- Improving Problem Formulation: Overarching Recommendations of the *ARA* Expert Panel (Paoli)
- The Centrality of MOA: Overarching Recommendations of the *ARA* Expert Panel (Meek)
- Where the Rubber Meets the Road: A Practical Guidance Compendium for Risk Assessors (Haber)
- Case Study: Application of Dose-Response Method Selection for Risks at Specified Doses for Systemic Toxicity (Hattis)
- Case Study: Application of Source-to-Outcome model to Quantitatively Assess Sensitivity and Variability in Humans (Price)
- Case Study: Biomonitoring Equivalents - the Hazard Quotient / Hazard Index Approach Based on Internal Dose-Response (Aylward)
- Panel Discussion: Recommendations for Improving Collaborative Activities for Evolving Risk Assessment Methods (Panelists are the Speakers of the Session)

Changing world of toxicology…

- So many new ideas and technologies available
  - ‘Omics, epigenetics, high-throughput or high-content data…
  - Cheminformatics (formerly known as *in silico*)
  - *in vitro* vs *in vivo* and 3 R’s
- What is the best way forward?

- An abundance of guidance…
  - 2001 IPCS MOA/HRF
  - 2005 EPA Cancer RA guidance
  - 2007 NAS TT21C
  - 2009 NAS Science & Decisions (Silver Book)
  - 2011 NAS Formaldehyde report

- How to integrate all of this to best inform risk assessment?

Changing world of risk assessment…

- ACC ARASP Framing Workshop (12/2009):
  - Review 2009 NAS *Science & Decisions* recommendations for general awareness and discussion
    - Problem formulation is key
    - Unified approach to cancer & non-cancer risk assessment
    - Identified 3 dose-response approaches; linear low-dose preferred based on human variability & uncertainty
    - Default preferred ahead of data in many cases
  - Identify topics for further, more in-depth discussion as multi-stakeholder effort to broaden & deepen effort

- ARA-sponsored series of workshops focused on
  - Problem formulation
  - Dose-response assessment methodologies

ARA-sponsored workshop series

Purpose:

- Through the development and application of case studies, to additionally evolve the methodologies in specific areas and address cross-cutting issues raised by *Science and Decisions Advancing Risk Assessment*

- Series of 3 workshops held over ~1 & ½ years
  - March 2010; October 2010; May 2011
- Multi-stakeholder, case study selection & presentations; deliberations led by Expert Panel

Overview of Workshop Objectives

- Build off the NAS (2009) report
  - To implement a multi-stakeholder approach to share information and resources on resolution of risk issues
  - To develop practical, problem-driven guidance in “fit for purpose” risk assessments that links methods with specific problem formulations for use by risk managers at a variety of levels
- Specific objectives include:
  - To identify useful dose-response techniques that reflect relevant biology and MOA information
  - To provide methods that address human variability and probability of response
  - To develop publications and guidance documents.

Dose-Response Advisory Committee

- **Rick Becker**, American Chemistry Council
- **Michael Dourson**, Toxicology Excellence for Risk Assessment
- **Julie Fitzpatrick,** Environmental Protection Agency
- **Roberta 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
- **Jennifer Seed**, Environmental Protection Agency

ARA Steering Committee

- **Barbara Harper**, Confederated Tribes of the Umatilla Indian Reservation
- **William Hayes**, State of Indiana
- **Bette Meek**, University of Ottawa
- **Anita Meyer**, United States Army Corps of Engineers
- **Edward Ohanian**, U. S. Federal Government
- **Ruthann Rudel**, Silent Spring
- **Phil Wexler**, National Library of Medicine

-----recused-----

- **Michael Dourson**, Toxicology Excellence for Risk Assessment
- **Michael Honeycutt**, Texas Commission on Environmental Quality

Supporting Participants

Workshop I
Date: March 16-18, 2010
Site: Texas Commission on Environmental Quality

- Over 160 participants from a variety of organizations
- Presentations of a variety of on-going risk-related activities & perspectives on NAS Silver Book
- Brainstorming by all participants on proposed dose-response assessment techniques and their utility for different applications
- Selection of case studies by focus groups
  - Consideration and recommendations on case studies
  - Focus on the principles of the methodology, not specific chemicals
- Case study leaders & team members proposed or agreed

Workshop II/III Expert Panel

- Provide guidance during the workshops
- Review the case studies during Workshop II/III
- Use case studies to evolve methodologies and address cross-cutting issues raised in NAS *Science & Decisions* report
- Balanced across affiliation & expertise in risk assessment and toxicology specialties

Expert Panel

- **Michael Bolger**, U.S. Food and Drug Administration
- **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 (W-II only)
- **R. Jeffrey Lewis**, ExxonMobil Biomedical Sciences, Inc.
- **Randy Manning**, Georgia Department of Natural Resources (W-III)
- **Bette Meek**, University of Ottawa (Chairperson)
- **Paul Moyer,** Minnesota Department of Health (MDH) (W-II only)
- **Greg Paoli**, Risk Sciences International
- **Rita Schoeny**, U.S. Environmental Protection Agency

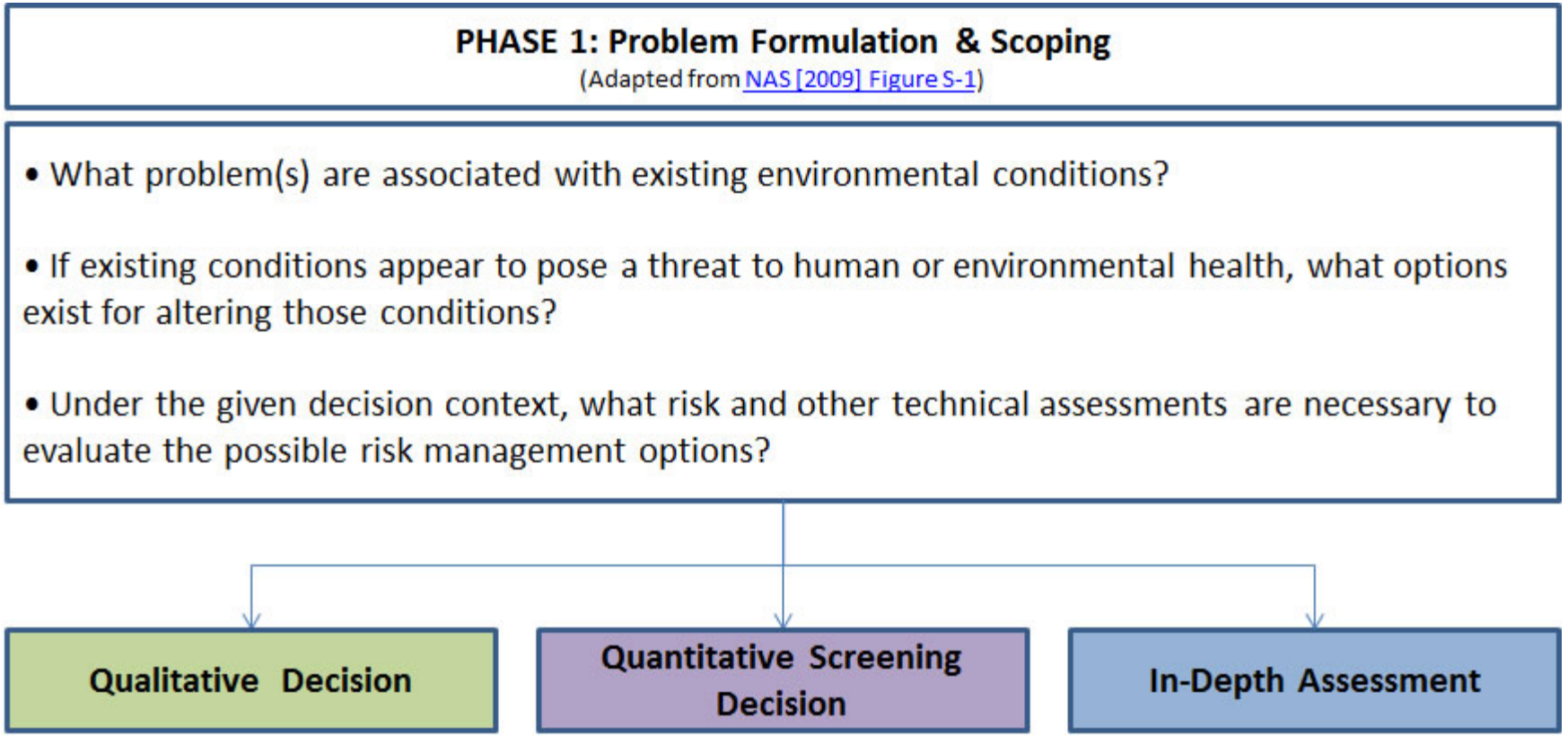
Workshop II
Date: October 11-13, 2010
Site: Crystal City, *in conjunction with* FSTRAC (U.S. Federal-State Toxicology Risk Analysis Committee)

- Over 135 participants from a variety of organizations
- Presentation of 18 cases for Panel discussion
- Several additional case studies suggested by panelists and/or workshop participants
- Panel suggested the development of a framework showing where the existing case study methods fit within NAS *Science & Decisions* (2009).
- Initiated discussion of several cross-cutting issues.

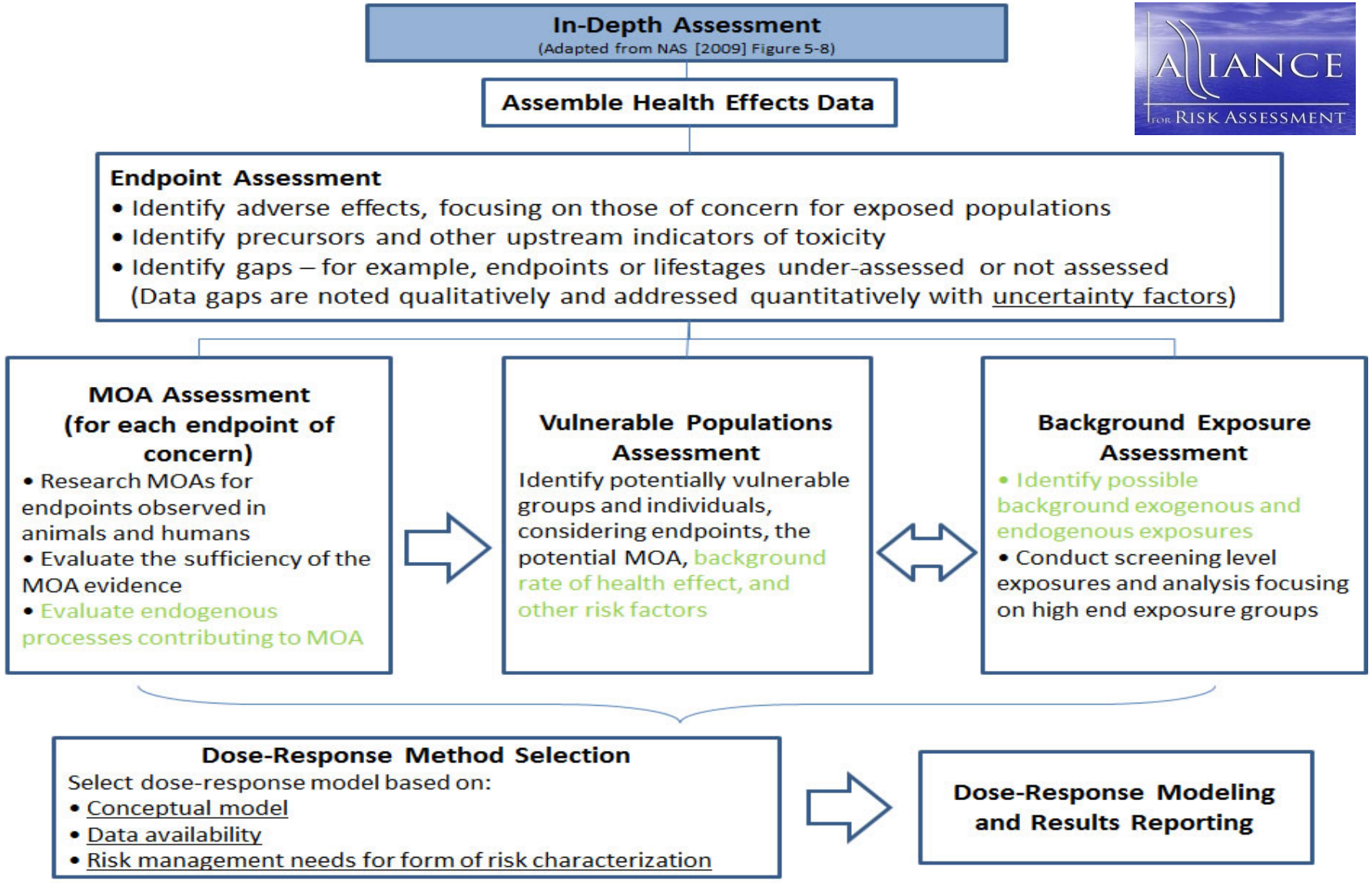
Activities Between Workshops II & III

- Panel reviewed additional case studies
- A draft risk framework was developed and posted on the *ARA* website (http://www.allianceforrisk.org/Workshop/Framework.htm)
- New case studies were proposed and submitted to the Panel for consideration.
- Panel used framework to identify areas & methodological issues where additional illustrative case studies were needed.
- Those case studies were invited to Workshop III.

Organizational Framework: Dose-Response Methods Presented



In-Depth Dose-Response Assessment



2011 SRA: Pressing Forward: Improving problem formulation and dose-response

Workshop III
Date: May 4-6, 2011
Location: Noblis, Falls Church

- Over 80 participants from a variety of organizations
- Panel reviewed 7 new case studies, chosen to address gaps in methods, and revisited 5 revised case studies
- Panel & participants discussed areas that needed additional methods, assisted by the Framework tool
- Panel discussion then focused on cross-cutting issues raised by NAS (2009),
  - Problem formulation, MOA, use of defaults, background & endogenous exposures,
  - Informed by presentations by invited speakers, and related case studies

Results

- **Case studies: 24** were developed by outside parties and reviewed by the Expert Panel.
  - Additionally evolved methodologies in specific areas,
  - Explored cross-cutting issues raised by NAS (2009), including---but not limited to---problem formulation, MOA, background & endogenous exposures, & linear dose-response for noncancer toxicity.
- The Expert Panel determined that:
  - Problem formulation and value of information are areas deserving increased attention;
  - MOA analysis is useful for a variety of problem formulations and should serve as the organizing principle;
  - Background and endogenous exposures should be considered relative to effect levels; and
  - Linear extrapolation for noncancer endpoints is problematic.

Next Steps

- Website that organizes case study methods with Framework tool will be made evergreen,
  - showing linkages among problem formulations–methods–solutions as demonstrated by case studies and resolutions of cross-cutting issues.
- A standing Panel will meet twice a year to review additional case studies and issue resolution papers.
- Additional sponsors/participants invited to join in the overall effort.

Double Symposium: Pressing Forward: Improving problem formulation & dose-response

- Introduction: The ARA Collaborative ARA Adventure (Pottenger)
- Improving Problem Formulation: Overarching Recommendations of the *ARA* Expert Panel (Paoli)
- The Centrality of MOA: Overarching Recommendations of the *ARA* Expert Panel (Meek)
- Where the Rubber Meets the Road: A Practical Guidance Compendium for Risk Assessors (Haber)
- Case Study: Application of Dose-Response Method Selection for Risks at Specified Doses for Systemic Toxicity (Hattis)
- Case Study: Application of Source-to-Outcome model to Quantitatively Assess Sensitivity and Variability in Humans (Price)
- Case Study: Biomonitoring Equivalents - the Hazard Quotient / Hazard Index Approach Based on Internal Dose-Response (Aylward)
- Panel Discussion: Recommendations for Improving Collaborative Activities for Evolving Risk Assessment Methods (Panelists are the Speakers of the Session)

Thank-you!