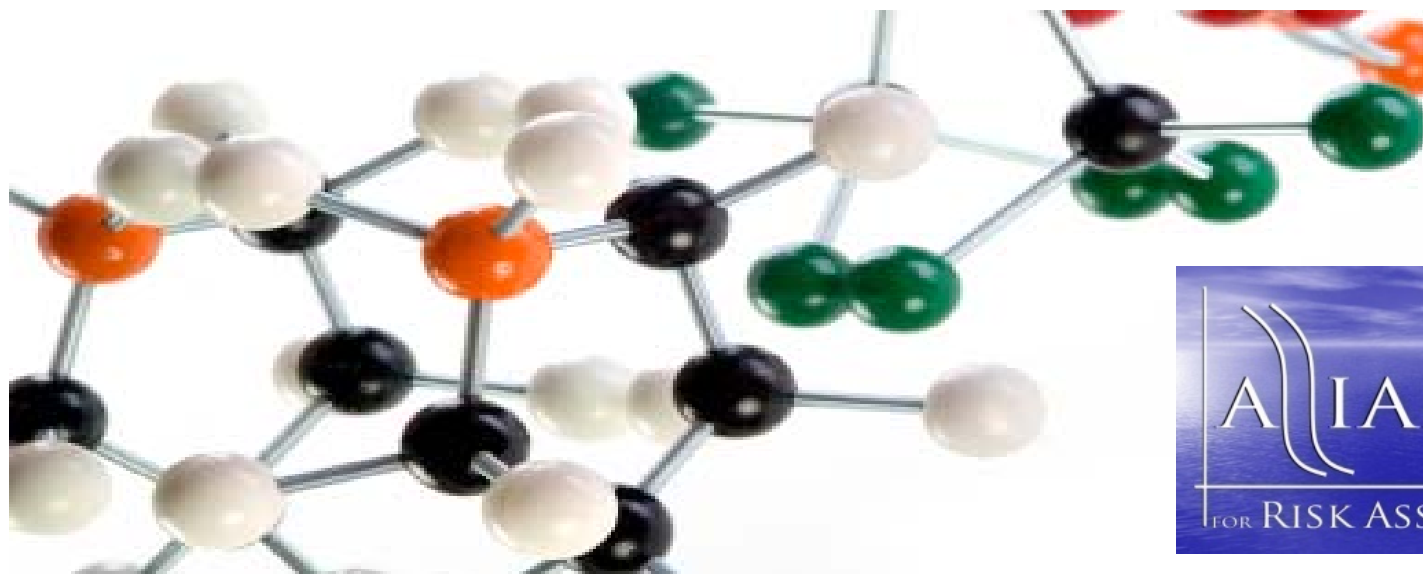


The Collaborative ARA Adventure: Extending & Expanding Discussions of Problem Formulation & Dose-Response

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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
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- ▶ **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

PHASE 1: Problem Formulation & Scoping

(Adapted from [NAS \[2009\] Figure S-1](#))

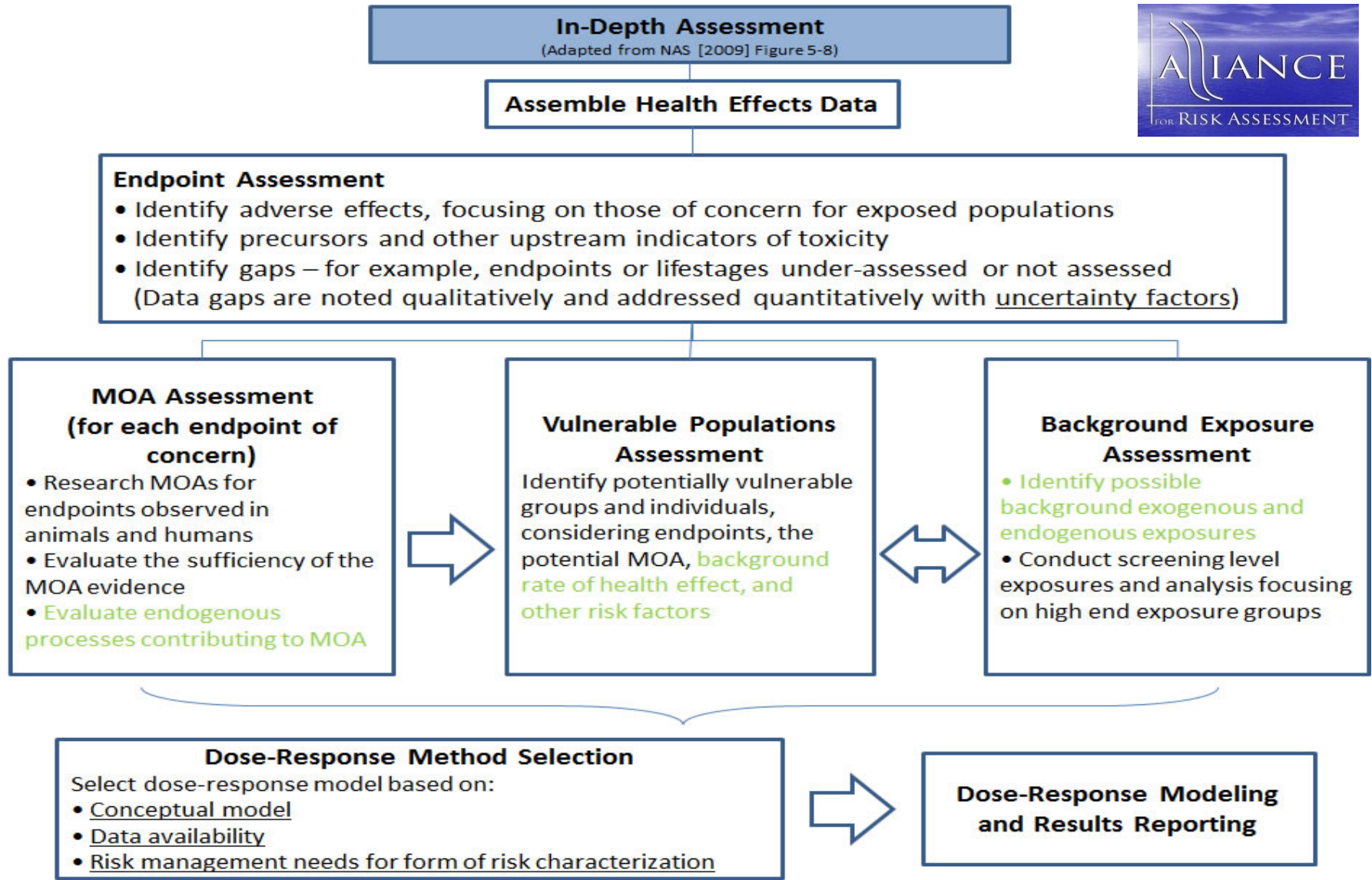
- What problem(s) are associated with existing environmental conditions?
- If existing conditions appear to pose a threat to human or environmental health, what options exist for altering those conditions?
- Under the given decision context, what risk and other technical assessments are necessary to evaluate the possible risk management options?

Qualitative Decision

Quantitative Screening
Decision

In-Depth Assessment

In-Depth Dose-Response Assessment



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.

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Thank-you!