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

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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](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

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In-Depth Dose-Response Assessment

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

Assemble Health Effects Data

Endpoint Assessment
- Identify adverse effects, focusing on those of concern for exposed populations
- 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 addressed quantitatively with uncertainty factors)

MOA Assessment (for each endpoint of concern)
- Research MOAs for endpoints observed in animals and humans
- Evaluate the sufficiency of the MOA evidence
- Evaluate endogenous processes contributing to MOA

Vulnerable Populations Assessment
Identify potentially vulnerable groups and individuals, considering endpoints, the potential MOA, background rate of health effect, and other risk factors

Background Exposure Assessment
- Identify possible background exogenous and endogenous exposures
- Conduct screening level exposures and analysis focusing on high end exposure groups

Dose-Response Method Selection
Select dose-response model based on:
- Conceptual model
- Data availability
- Risk management needs for form of risk characterization

Dose-Response Modeling and Results Reporting

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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

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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!