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

Webinar will convene at 12 PM EST.
ARA DOSE RESPONSE FRAMEWORK
Oliver Kroner
Overview of Workshop
Objectives

• Build off the NAS (2009) report
  – Develop practical guidance for use by risk managers at a variety of levels
  – Risk assessment techniques applicable to specific problem formulations.

• Implement a multi-stakeholder approach to share information, ideas, and techniques

• Develop a risk methods compendium as a resource for regulators and scientists on key considerations for applying selected dose-response techniques for various problem formulations
Collaborators

55+ sponsors and collaborators:

- 12 government agencies
- 19 industry groups
- 7 scientific societies
- 9 non-profit orgs/consortia
- 8 consulting groups
Accomplishments to Date

• >30 presentations, including award-winning case studies
• Open access manuscript in press:
• Framework linking case studies to problem formulations
  – [http://www.chemicalriskassessment.org](http://www.chemicalriskassessment.org)
Framework 1.0

Audience:
• Science Panel and case study authors

Purpose:
• Tool for organizing case studies presented to Workshop Science Panel
• Help categorize methods according to NAS Framework
  – Sort methods by problem formulation
  – Identify what needs were being addressed, where we have gaps
ARA Dose-Response Framework >
Problem Formulation

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

Assemble Health Effects Data

Endpoint Assessment
- Use available data to identify adverse effects, focusing on those of concern for exposed populations
- Consider strengths and uncertainties in data

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

Vulnerable Populations Assessment
- Assessment
- Use available data to assist in the risk management decision

Background Exposure Assessment
- Use available data to assist in the risk management decision

Dose-Response Evaluation
- Consider available dose-response information on chemical of interest and related chemicals
- Place chemical in appropriate category based on hazard, dose-response, or dose-response and exposure information

Results Reporting
Framework 1.0 Limitations

- Not easy to search
- Not indexed by search engines
- Difficult to expand
- Easy to get “lost within site”
- Visually uninspired
Panel Recommendations

• Identify target audience and purpose of the case studies, and design the template accordingly.

• The framework no longer needs to be tied to the figures in the NAS Science and Decisions report.

• Identify “descriptors” for tagging case studies.
Panel Recommendations

• Key information on the case study should be readily apparent on the case study page
  – Bring critical elements forward
  – Suggestion for a rubric
• The framework should exist as a stand alone website, with its own URL
• Goal to bring methods to light, make others aware
Framework 2.0 (beta)

• **Audience:**
  - Risk assessors seeking information on risk methods

• **Purpose:**
  - One-stop-shop for risk methods
  - To catalogue, organize, and highlight key aspects of risk methods
  - To demonstrate real world application of the methods
Search Methods

Find help! Enter search term here.

Qualitative Decision

Only a qualitative categorization of hazard and/or risk is needed

Quantitative Screening

An initial evaluation based on health-protective assumptions

In Depth Assessment

Greater precision in understanding hazard and/or risk is needed
## In Depth Assessment

<table>
<thead>
<tr>
<th>Category</th>
<th>Goals</th>
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| 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) |
| Mode of Action         | - Research Mode of Actions (MOA) for endpoints observed in animals and humans  
                          - Evaluate the sufficiency of the MOA evidence  
                          - Evaluate endogenous processes contributing to MOA |
| Vulnerable Populations | - Identify potentially vulnerable groups and individuals, considering endpoints, the potential MOA, background rate of health effect, and other risk factors |
| Background Exposure    | - Identify possible background exogenous and endogenous exposures  
                          - Conduct screening level exposures and analysis focusing on high end exposure groups |
Mode of Action (MOA) Assessment

- Mode of Action (MOA) Key Publications
- Low-Dose Evaluation for Genotoxicity
- Modeling Multi-Pronged MOA (acrylamide)
- Ethanol Case Study
- Dioxin case study – Key Events Dose Response Framework

Vulnerable Populations

- Vulnerable Population Assessment Key Publications
- Human Kinetic Variability (Trichloroethylene)
- Sensitive Disease State/Background Response
- Inter-Individual Variability in Cancer Susceptibility
- Lead Case Study
- Kinetic Variability Based on PON1 Polymorphism (Integrated with PBPK Model) for Chlorpyrifos
- Data Fusion

Background Exposure Assessment

- Background/Endogenous Damage: Considerations for Dose-Response & Risk Assessment
- Background Exposure Key Publications
- Biomonitoring Equivalents
- Biologically-Based Uncertainty Factor Distributions (Hattis approach)
Mode of Action (MOA) Key Publications

Boobis, AR; Doe, JE; Heinrich-Hirsch, B; Meek, ME; Munn, S; Ruchirawat, M; Schlater, J; Seed, J (2008). IPCS Framework for Analyzing the Relevance of a Noncancer Mode of Action for Humans, Critical Reviews in Toxicology 38:87-96.

Boobis, AR; Cohen, SM; Dellarco, V; McGregor, D; Meek, ME; Vickers, C; Willcocks, D; Farland, W (2006). IPCS framework for analyzing the relevance of a cancer mode of action for humans. Critical Reviews in Toxicology 36:781-792 [This entire issue of Critical Reviews in Toxicology addresses the IPCS framework.]


Background/Endogenous Damage: Considerations for Dose-Response & Risk Assessment

Authors: L. H. Pottenger, J.S. Bus, with support from J.A. Swenberg

Recent publications have emphasized the significant and continuous presence of steady-state DNA damage stemming from background and/or endogenous exposures. The relatively recent and growing recognition of the fact that DNA is not pristine, but rather that every cell is continuously handling a significant burden of a variety of DNA lesions including known pro-mutagenic lesions, has yet to play a role in improving how human health risk assessments are conducted. The existence of this ubiquitous background/endogenous DNA damage provides key information that needs to be addressed in risk assessment, especially where a mutagenic mode-of-action (MOA) causes or contributes to a carcinogenic response observed in laboratory animals. Drawing mainly from published data from Swenberg’s lab, this case study will lay out some of the issues that should be considered in order to adequately inform the assessment of risks of DNA-reactive chemicals to human health.
Case Study #9 – Biologically-Informed Empirical Dose Response Modeling: Using Linked Cause-Effect Functions to Extend the Dose-Response Curve to Lower Doses (Titanium dioxide - TiO₂)

Authors: Lynne Haber, Andy Maier, Bruce Allen
Contexte / Dommages endogène: Considérations sur la relation dose-réponse & Évaluation des risques

Last updated: 4 days ago 🗓️ Bus, Potteger, Swenberg

Contexte / Dommages endogène: Considérations sur la relation dose-réponse & Évaluation des risques

Auteurs: L. H. Potteger, J.S. Bus, avec le soutien de J.A. Swenberg

Des publications récentes ont mis en évidence la présence significative et continue des dommages causés par l'état stationnaire ADN issu de fond et / ou des expositions endogènes. La reconnaissance relativement récente et croissante du fait que l'ADN n'est pas vierge, mais plutôt que chaque cellule gère en permanence une charge importante d'une variété de lésions de l'ADN, y compris des lésions promutagènes connues, doit encore jouer un rôle dans l'amélioration de la façon dont la santé humaine risque. Les évaluations sont menées. L'existence de cette omniprésence fond / dommages de l'ADN endogène fournit des informations clés qui doivent être abordées dans l'évaluation des risques, en particulier là où un mode d'action
Contexte / Dommages endogène: Considérations sur la relation dose-réponse et Évaluation des risques
FAQ

What is Problem Formulation?
What is the Alliance for Risk Assessment?
How can a dose-response method be added to the framework?
How often is the Framework updated?
How was the ARA Dose-Response Framework created?

What is Problem Formulation?

In risk assessment, problem formulation is the phase in which the risk managers’ charge to the assessors is converted into an actionable plan for performing the assessment (EPA 1998; Suter 2007).


What is the Alliance for Risk Assessment?

The Alliance for Risk Assessment (ARA) is a collaboration of organizations that fosters the development of technical chemical risk assessment products and services, through a team effort of specialists and organizations dedicated to protecting public health by improving the process and efficiency of risk assessment, and to increasing the capacity for developing risk values to meet growing demand. The ARA will coordinate with Federal and State Agencies whenever possible, to ensure the best use of available resources, and to avoid duplication of effort. To learn more about the Alliance and its projects, please visit www.allianceforrisk.org.

Most Viewed Methods

- Sensitive Disease State/Background Response
- Risk-Risk Comparison (e.g., comparative carcinogenic and neurotoxic potencies of tetrachloroethylene and n-propyl bromide)
- Sustainable Futures Screening Method
- Background Exposure Key Publications
- Biomonitoring Equivalents

Recent Additions

- Background/Endogenous Damage: Considerations for Dose-Response & Risk Assessment
- Screening-Level Safe Dose Key Publications
- Dose Response Key Publications
- Background Exposure Key Publications
- Vulnerable Population Assessment Key Publications
Framework 2.0 (beta)

www.chemicalriskassessment.org/methods/

• Simplified site structure, focused on search for key terms
• Methods are organized by keyword, making it easier to browse the content by topic
• Each method provides an overview synopsis for quick scanning, highlighting key information
• Translation equipped
Panel Questions:

Content

1. Is the organization of the site sensible? Is the layout intuitive? How can it be improved?
2. What information is missing or could be enhanced?
3. The initial summary paragraph for each case study is currently copied from the case study prepared. Is this appropriate? Or some other approach?
Panel Questions:

Features

1. What features (e.g., advanced search methods) are missing or could be enhanced?

2. Are additional changes needed to make it easier to search for methods to address specific issues/problems? If so, what?

3. The site was designed without emphasis on the chemicals featured in the various case studies. Would it be useful to allow users to sort and filter methods by chemical for identifying chemical specific information?
Panel Questions:

Rubrics

1. The Framework currently includes measurements of applicability, data requirements, accuracy, and precision for each case study, on a four point scale. (Slide 18)

   a) Are these useful metrics? What other metrics would be useful?

   b) What is the best method for establishing a “score” for these metrics?

   c) What other critical elements can be brought forward?
Other Considerations (Time Permitting)

1. Is Dose Response Framework an appropriate name?
2. Should methods related to exposure assessment or other aspects of risk assessment (e.g., value of information, risk communication, etc.) be included?
3. How can we proceed to make this a sustainable project?
Clarifying Questions?

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ARA Dose Response Framework