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:
  - Meek et al. 2013. A Framework for Fit-for-Purpose Dose Response Assessment. Regul. Toxicol. Pharmacol. Doi: 10.1016/j.yrtph.2013.03.012
- Framework linking case studies to problem formulations
  - http://www.chemicalriskassessment.org
  - And on NLM's Enviro-Health Links http://sis.nlm.nih.gov/enviro/toxweblinks.html (see Associations)

Framework 1.0

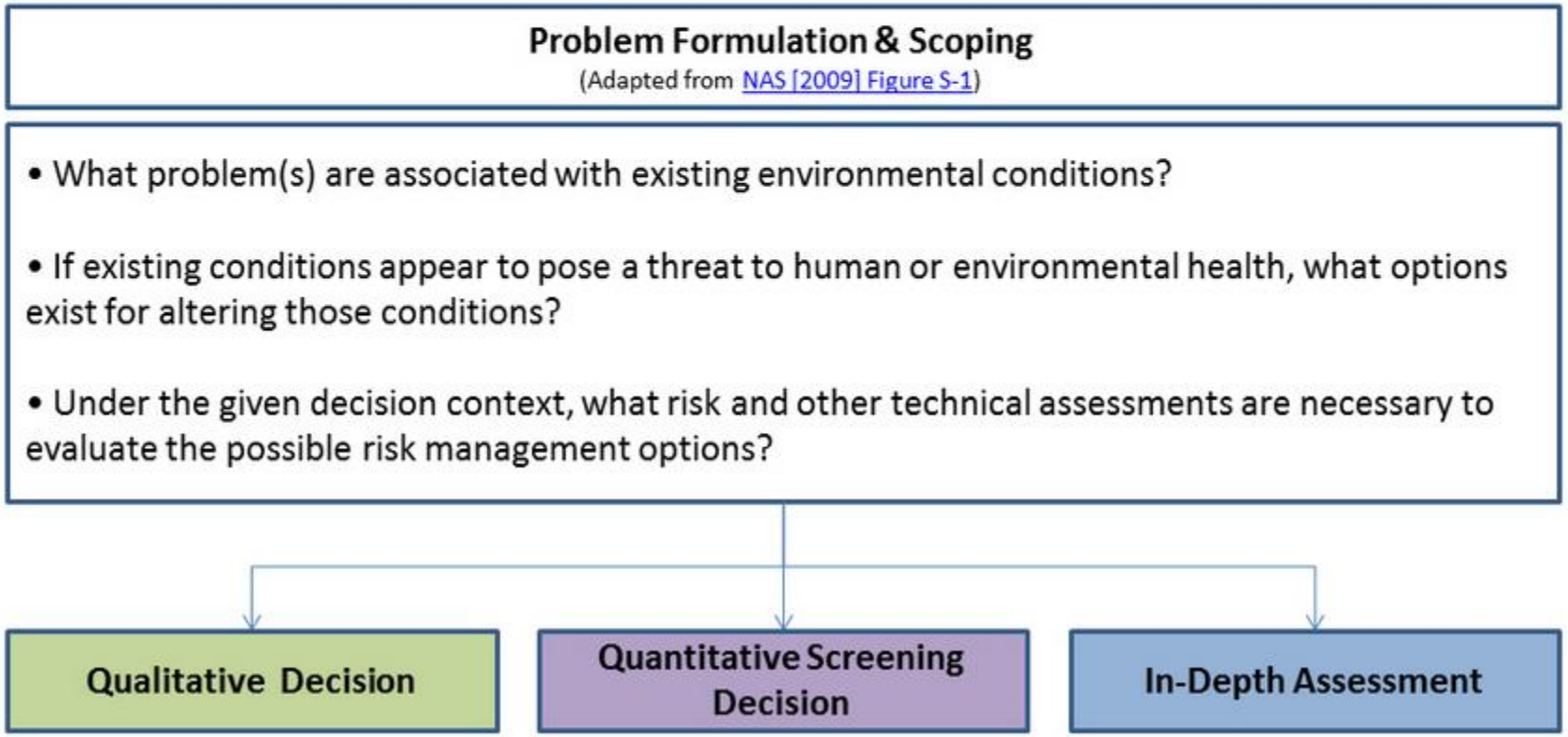
Audience:

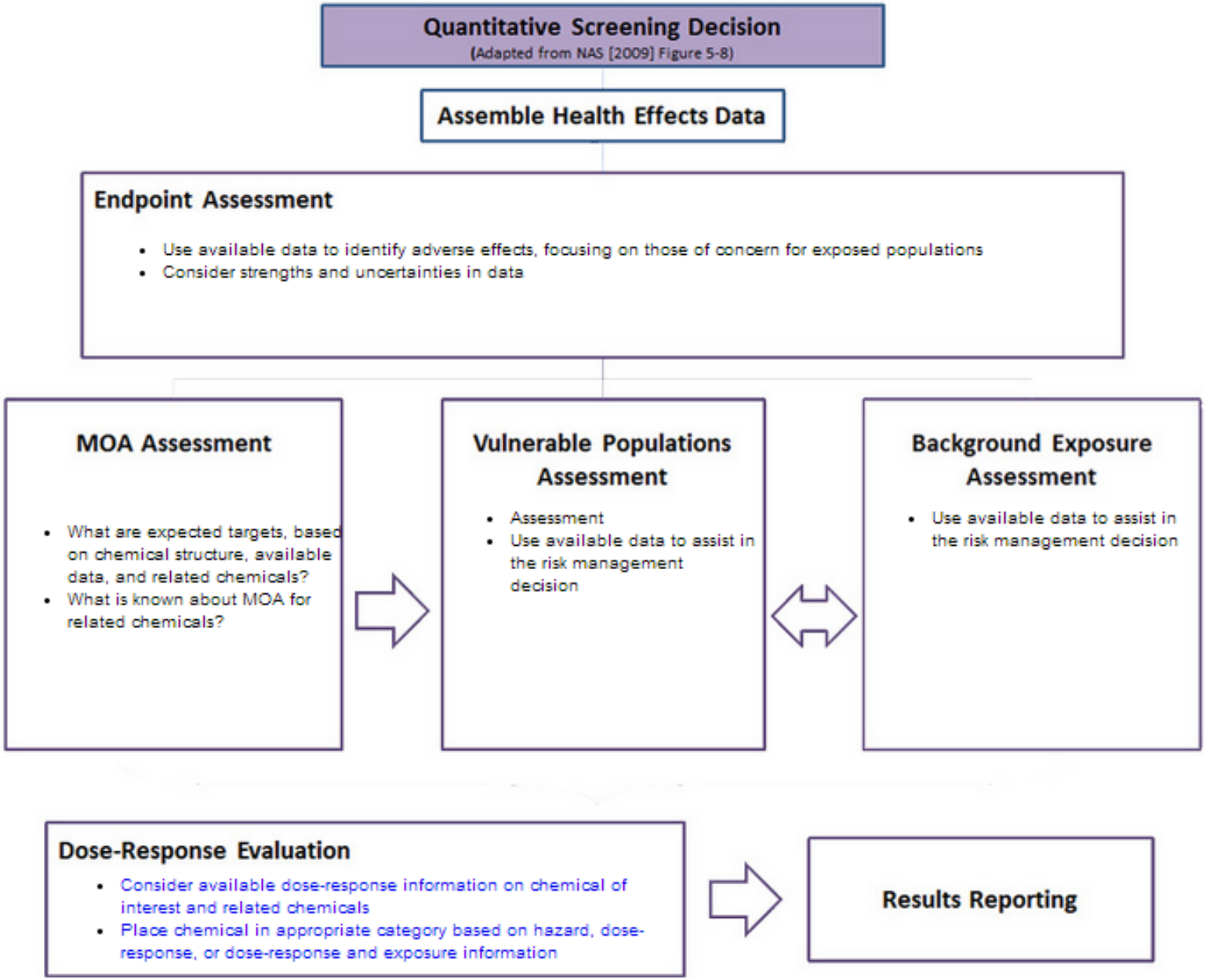
- Science Panel and case study authors

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





ARA Dose Response Framework

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.

Search

Qualitative Decision

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

Continue

Quantitative Screening

An initial evaluation based on health-protective assumptions

Continue

In Depth Assessment

Greater precision in understanding hazard and/or risk is needed

Continue

Search Methods

Find risk assessment methods fast

Enter search term here.

In Depth Assessment

Category	Goals
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

Most Viewed

- Sensitive Disea State/Background
- Risk-Risk Comp comparative carcin neurotoxic potencie tetrachloroethylene bromide)
- Sustainable Fut Method
- Background Ex Publications
- Biomonitoring E

Recent Addit

- Background/Endog Considerations for & Risk Assessment
- Screening-Level Sa Publications
- Dose Response Ke
- Background Expos

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

Last Updated: 1 min ago Boobis, Dellarco, Doe, Heinrich-Hirsch, IPCS, Julien, Meek, Munn, Ruchirawat, Schlater, Seed, US EPA

✚ 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.]

✚ IPCS (International Programme on Chemical Safety) (2007) IPCS framework for analysing the relevance of a cancer mode of action for humans and case studies. (Part I). IPCS framework for analysing the relevance of a noncancer mode of action for humans and case studies. (Part II). (http://www.who.int/ipcs/methods/harmonization/areas/cancer_mode.pdf)

✚ Julien, E; Boobis, AR; Olin, SS; et al. (2009). The Key Events Dose-Response Framework: A Cross-disciplinary mode-of-action based approach to examining dose-response and thresholds. Critical Reviews in Food Science and Nutrition 49(8):682-689.

Most Viewed

- Biologically-Base Factor Distributions approach)
- Modeling Multi-Pr (acrylamide)
- Private: Approach of risk to human hea substances under th environmental protec
- Organisation for Operation and Deve
- Kinetic Variability Polymorphism (Integ Model) for Chlorpyrif

Recent Additi

- Background/Endoge Considerations for D & Risk Assessment
- Screening-Level Saf Publications

Search Methods

Find risk assessment methods fast

Enter search term here.

Biologically-Based Dose Response

- Biologically-Informed Dose-Response Modeling
- Inter-Individual Variability in Cancer Susceptibility
- Biologically-Based Uncertainty Factor Distributions (Hattis approach)

View all 3 articles >

Background Exposure

- Background/Endogenous Damage: Considerations for Dose-Response & Risk Assessment
- Background Exposure Key Publications
- Sensitive Disease State/Background Response

View all 3 articles >

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)

View all 4 articles >

Biomonitoring

- Biomonitoring Equivalents
- Screening Tools for the Interpretation of Chemical Biomonitoring Data

View all 2 articles >

Bench Mark Dose

- Low Dose Extrapolation from the BMD(L)

View all 1 articles >

Classification Systems

- Classification Systems

View all 1 articles >

Cumulative Risk

Data Fusion

Dose Response Evaluation

Most Viewed Methods

- Low-Dose Evaluation for Genotoxicity
- Low Dose Extrapolation from the BMD(L)
- Dose Response Key Publications
- Dioxin case study – Key Events Dose Response Framework
- Human Kinetic Variability (Trichloroethylene)

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

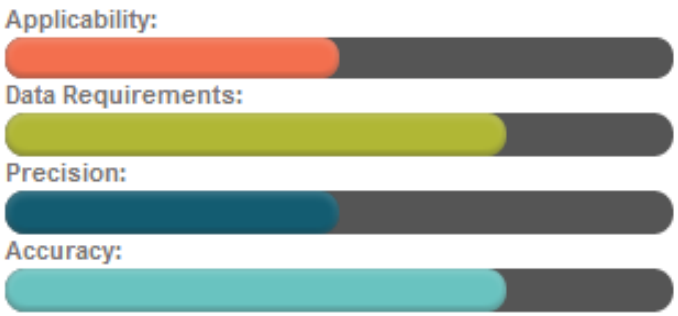
Categories

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

Last Updated: 3 months ago Bus, Potteger, Swenberg

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.

> SUMMARY

> CASE STUDY

Most Viewed Methods

- Low-Dose Evaluation for Genotoxicity
- Low Dose Extrapolation from the BMD(L)
- Dose Response Key Publications
- Dioxin case study – Key Events Dose Response Framework
- Human Kinetic Variability (Trichloroethylene)

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

Categories

Select Category

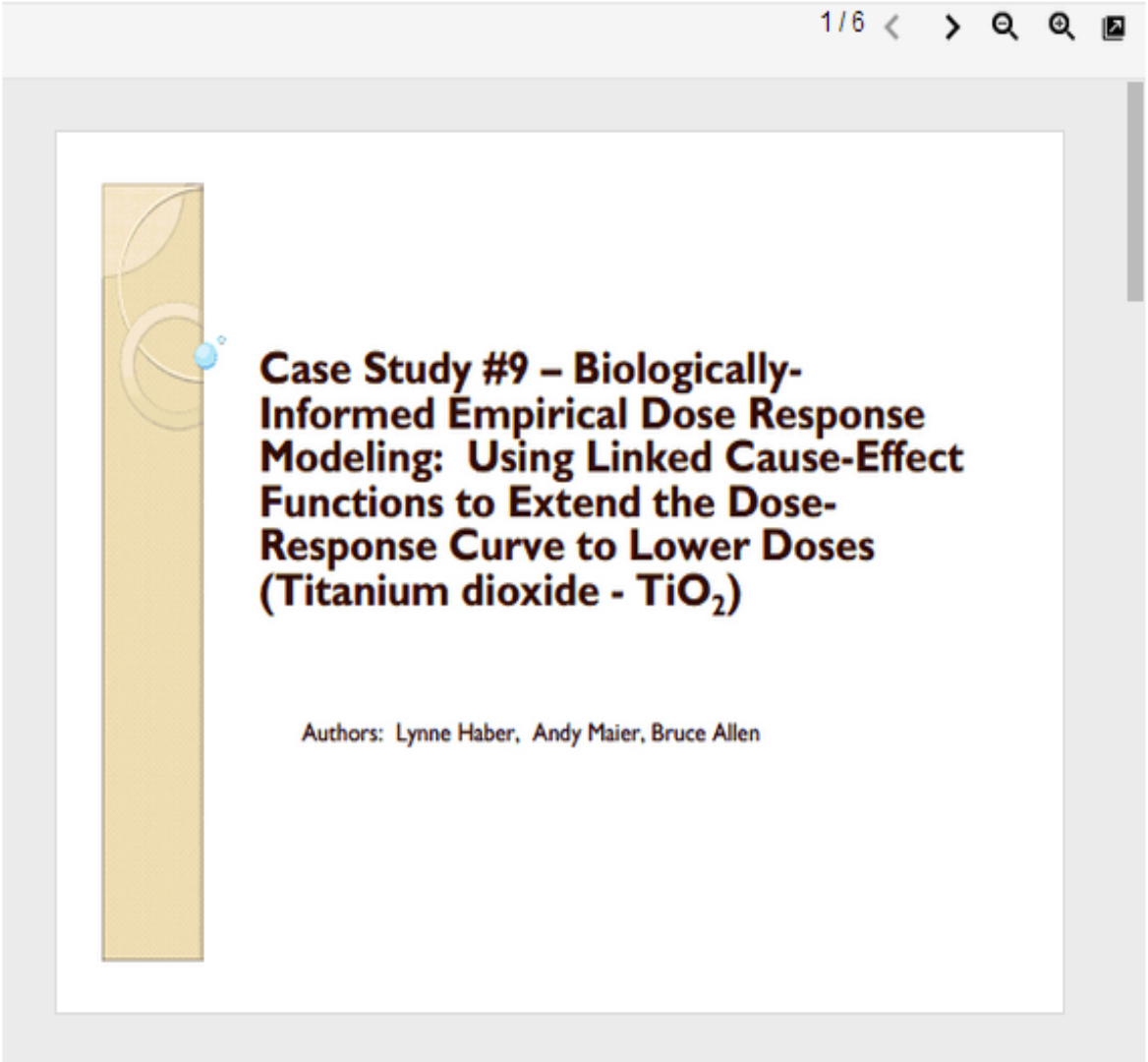
which data were not available.

› SUMMARY

› CASE STUDY

⌄ PRESENTATION SLIDES

1 / 6



Categories

Select Category

Recent Co

Submit Comment

Most Viewed Methods

- Biologically-Based Uncertainty Factor Distributions (Hattis approach)
- Modeling Multi-Pronged MOA (acrylamide)
- Private: Approach to assessment of risk to human health for priority substances under the Canadian environmental protection act
- Organisation for Economic Co-Operation and Development Toolbox
- Kinetic Variability Based on PON1 Polymorphism (Integrated with PBPK Model) for Chlorpyrifos
- PBPK model (part of butadiene, TCE)

Contact Us

framework@tera.org

Resources

Alliance for Risk Assessment

ITER Risk Values

TOXNET

Translate this page

English

English
Français
Español
中文(简体)
Deutsch

Méthodes de recherche

Trouver des méthodes d'évaluation des risques rapide

Enter search term here.

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

Dernière mise à jour: 4 il ya des mois Bus, Potteger, Swenberg

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

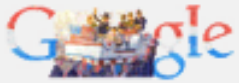
Auteurs: L. H. Pottenger, J.S. Bus, avec le soutien de J.A. Swenberg

Des publications récentes ont mis en évidence la présence significative et continue des dommages causés état stationnaire ADN issu de fond et / ou 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 pro-mutagènes connus, 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 abordés dans l'évaluation des risques, en particulier là où un mode d'action

Méthodes les

- À base biologiq facteurs d'incertitu Hattis)
- Modélisation mu (acrylamide)
- Privé: Approche des risques pour la pour les substance titre de la Loi cana protection de l'envi
- Organisation de de développement boîte à outils de dé
- La variabilité cir PON1 Polymorphis PBPK modèle) pou

Additions réc



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

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About 184,000 results (0.74 seconds)

Did you mean: Contexte / Dommages endogène: Considérations sur la relation dose-réponse ***et*** Évaluation des risques

Endogène | Cadre **dose-réponse** ARA - Alliance for Risk Assessment
chemicalriskassessment.org/methods/.../**endogenous**/?... Translate this page
Jul 29, 2013 - **Contexte / Dommages endogène: Considérations sur la relation dose-réponse & Évaluation des risques**. 0. Contexte / Dommages endogène: ...

exposition de fond | Cadre **dose-réponse** ARA
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Contexte évaluation de l'exposition | Cadre **dose-réponse** ARA
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Réponse de la **dose** biologiquement fondée | Cadre **dose-réponse** ...
chemicalriskassessment.org/methods/category/bbdr/?... Translate this page
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Search Methods

Find risk assessment methods fast

Enter search term here.

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).

EPA (U.S. Environmental Protection Agency). 1998. Guidelines for Ecological Risk Assessment. EPA/630/R- 95/002F. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC. April 1998 [online]. Available: http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=36512

Suter, G.W. 2007. Ecological Risk Assessment, 2nd Ed. Boca Raton, FL: CRC Press.

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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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