Project 7 – Advancing Hazard Characterization and Dose-Response Methods

Allen Davis, Andrew Kraft
National Center for Environmental Assessment
Office of Research and Development

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Risk Assessment Issue Being Addressed

- Project 7 addresses the ongoing need to refine human health risk assessments by defining critical issues during assessment development, and by advancing analytical approaches, applications, and technologies to better incorporate emerging science and effectively implement new models and methods

Project Objectives

- Evaluate, refine, and verify approaches for systematic review and evidence integration to enhance the efficiency, consistency, transparency, and rigor of Agency assessments
- Advance approaches to more accurately define human health hazards, more fully characterize dose-response functions, and better describe the associated uncertainties, thereby improving benefits analyses
- Characterize risk from real-world scenarios (e.g., acute or episodic exposures) to support application of mechanistic data and duration- and life-stage specific assessments

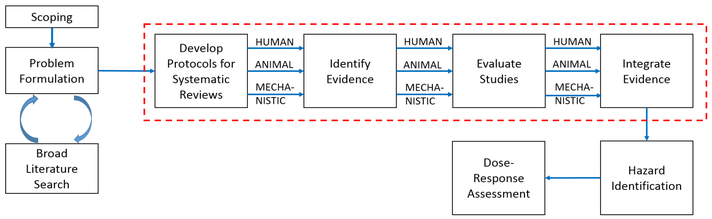

Figure 1. Systematic Review as applied in the IRS process. Adapted from *Review of EPA's Integrated Risk Information System (IRIS) Process.* Washington DC: The National Academies Press, 2014

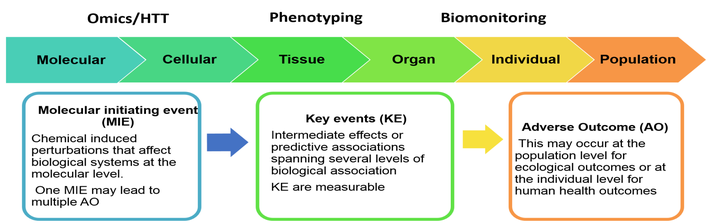

Figure 2. Overview of an AOP framework for integrating mode of action information into chemical risk assessments.

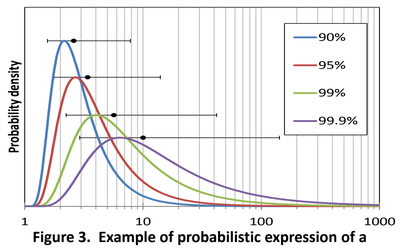

Figure 3. Example of probabilistic expression of a human variability uncertainty factor covering 90, 95, 99, or 99.9% of the population (uncertainty distribution, median and 90% CI)

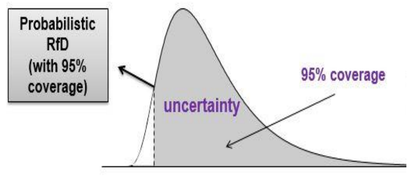

Figure 4. Graphical display of a probabilistically defined RfD

Tasks

❖ Advancing Methods for Systematic Review and Evidence Integration

- Develop and apply consistent processes for hazard identification in HHRA assessments, including systematic review methodology incorporating an increasing amount of mechanistic data (Figs. 1,2) and more transparent and consistent evidence integration frameworks

❖ Advancing Quantitative Methods

- Improve dose-response methods to address model uncertainty, incorporate multivariate or covariate data into modeling schemes, and perform meta-analyses to integrate information across studies and evidence streams

❖ Advancing Methods for Benefits and Uncertainty Analyses

- Evaluate, refine, and apply methods for improving the harmonization of HHRA products with benefits analyses, including probabilistic and other quantitative approaches for characterizing uncertainty (e.g., Figs. 3, 4), and methods defining evidence-based linkages between related health outcomes or precursor events

❖ Characterizing Determinants of Risk: Concentration, Duration, and Timing of Exposure

- Determine the best approach(es) to characterizing risk from real-world exposures, such as acute exposures, episodic exposures, and exposures during susceptible life-stages and windows of vulnerability (Figs. 5, 6)

❖ Science Workshops on Major Risk Assessment Methodology Issues

- Workshops will be convened annually to advance the scientific dialog on major HHRA issues

Major Impacts

- Improved systematic review and evidence integration methods will allow NCEA to develop and document more transparent and defensible scientific decisions
- Consistent approaches to hazard identification for non-cancer effects will facilitate the application of benefits analyses for regulatory decision making
- New dose-response methods will address model uncertainty and quantitative methods to integrate evidence across multiple data streams will increase the scientific rigor of and confidence in Agency assessments
- The application of probabilistic dose-response methods and analytic techniques for the quantification of uncertainty will allow NCEA to characterize the full spectrum of anticipated risks at any specified dose, rather than single point estimates of risk
- Developing approaches to incorporate considerations related to episodic or early-life exposures will ensure the Agency provides sound guidance on timing- or duration-related risk issues for Program Offices, including acute risk estimates

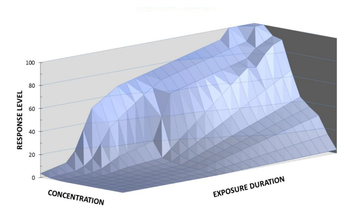

Figure 5. Example of a concentration-duration-response surface.

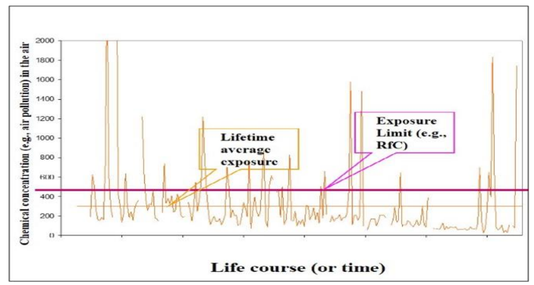

Figure 6. Graph of an episodic exposure to a pollutant where the lifetime average exposure is below the RfC but exposures above the limit do occur.

Allen Davis | davis.allen@epa.gov | 919-541-3789 || Andrew Kraft | kraft.Andrew@epa.gov | 703-347-0221