



Workshop Report

A framework for fit-for-purpose dose response assessment

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Special note: This paper is dedicated to the memory of Dr. Randall Manning of the Georgia Department of Natural Resources. Dr. Manning was an early and avid supporter of this collaborative effort, making constructive comments during its 3rd meeting, and listening well and supporting others in their efforts to find common scientific ground on seemingly intractable risk assessment issues. His humor, kindness and intellect are sorely missed.

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ABSTRACT

The NRC report *Science and Decisions: Advancing Risk Assessment* made several recommendations to improve chemical risk assessment, with a focus on in-depth chronic dose–response assessments conducted by the U.S. Environmental Protection Agency. The recommendations addressed two broad elements: improving technical analysis and utility for decision making. To advance the discussions in the NRC report, in three multi-stakeholder workshops organized by the Alliance for Risk Assessment, available and evolving risk assessment methodologies were considered through the development and application of case studies. A key product was a framework (<http://www.allianceforrisk.org/Workshop/Framework/ProblemFormulation.html>) to guide risk assessors and managers to various dose–response assessment methods relevant to a range of decision contexts ranging from priority setting to full assessment, as illustrated by case studies. It is designed to facilitate selection of appropriate methodology for a variety of problem formulations and includes a variety of methods with supporting case studies, for areas flagged specifically by the NRC committee for consideration – e.g., susceptible sub-populations, population variability and background. The framework contributes to organization and communication about methodologies for incorporating increasingly biologically informed and chemical specific knowledge into dose–response analysis, which is considered critical in evolving fit-for-purpose assessment to address relevant problem formulations.

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Abbreviations: ARA, alliance for risk assessment; CPF, chlorpyrifos; MOA, mode of action; NAS, National Academy of Sciences; NGO, non-governmental organization; NRC, National Research Council; PBPK/PD, physiologically-based pharmacokinetic/pharmacodynamic; RfD, reference dose; VOI, value of information.

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1. Introduction

In 2009, the National Research Council of the National Academy of Sciences (NAS) released a report entitled *Science and Decisions: Advancing Risk Assessment* (NRC, 2009 also known as the Silver Book). Recommendations encompassed two broad elements: (1) improving technical analysis, namely developing and using scientific knowledge and information to promote more accurate characterization of risk; and (2) ensuring that risk assessments provide meaningful support to allow discrimination among risk management options. Specifically, recommendations addressed the following areas: design of risk assessments, uncertainty and variability, selection and use of defaults, a unified approach to dose–response assessment, cumulative risk assessment, improving

the utility of risk assessment and stakeholder involvement and capacity-building within the U.S. Environmental Protection Agency (U.S. EPA).

As illustrated in Figure S-1 of NRC (2009), the authors of the report expanded the risk assessment paradigm of NRC (1983), principally through inclusion of a problem formulation step including framing of the assessment to address specific risk management options, explicit consideration of stakeholder input, and confirmation that the assessment addressed the issues identified in the problem formulation. The report (see Figure 5–8) provided additional guidance on considerations for dose–response assessment, including endpoint assessment, assessment of mode of action (MOA), vulnerable populations and background exposure, conceptual model selection, and dose–response method selection.

In response to recommendations of this report and other NRC and international initiatives (e.g., NRC, 2007; IPCS, 2006, 2007; Meek and Armstrong, 2007; Meek et al., 2011), improvement of risk assessment practice continues to be explored in a series of initiatives, including the workshops described here, organized by the Alliance for Risk Assessment (ARA, a coalition of non-profit organizations).

The purpose of the workshop series, entitled “Beyond Science and Decisions: From Problem Formulation to Dose–Response Assessment” (henceforth, the ARA workshop series) was to extend these discussions, with the goal of developing a practical compendium of dose response assessment methods for fit-for-purpose dose–response analysis and potentially in future, other components of risk assessment. While not referenced in the NRC report, the concept of fit-for-purpose assessment has been widely adopted recently in legislative mandates requiring greater efficiency in consideration of much larger numbers of substances (see for example, Meek and Armstrong, 2007) and in research initiatives, for example in Lee et al. (2006), who described a fit-for-purpose approach for biomarker method development and validation. Fit-for-purpose dose–response analysis encourages application of a level of rigor commensurate with the intended purpose and use of an assessment. As recommended by the NRC (2009) report, the nature and extent of the assessment needs to be considered in the problem formulation stage, with level and complexity to be no greater than that needed to identify the best choice among risk management options (i.e., “fit for purpose”). In practice, this is accomplished by having a variety of available tools (e.g., tools for acute vs. chronic exposures) and using tiered approaches, proceeding down the tiering only as far as necessary to set an issue, exposure or chemical aside (as not of concern) or to target it for further assessment and/or management.

Three multi-stakeholder workshops were held in 2010 and 2011. The workshops explored available and evolving methodologies through the development and application of case studies. While these case studies covered a number of important aspects of the NAS text, particular attention was focused on problem formulation, use of information on MOA and endogenous and background exposure during solicited speaker presentations and panel discussions. This paper summarizes the outcome of the ARA workshops and the resulting ARA fit-for-purpose dose response assessment methods framework. This framework, which is illustrated by case studies, is designed for use by risk managers and scientists in a variety of settings (e.g., government agencies, industry), for a range of applications and/or levels of analysis including distributional, non-threshold methods for estimating risk-specific doses for toxic effects other than cancer. Case studies were selected to be illustrative of various approaches rather than as assessments for any specific environmental contaminant. However, the scope and variety of included case studies are anticipated to assist in the determination of appropriate assessment strategies and relevant risk management options. Additional case studies are

also being sought for consideration in the context of the framework.

2. Description of the workshop series

2.1. Workshop objectives and structure

The Dose–Response Advisory Committee (DRAC), which includes state, federal, industry, and NGO representatives, organized the workshop series on behalf of the now more than 50 workshop sponsors. The DRAC determined the agendas in consultation with the Science Panel. The Steering Committee of the ARA, which includes representatives from state, tribal, the federal government, academia, and environmental NGOs (www.allianceforrisk.org/ARA_Steering_Committee.htm) provided oversight of the workshop series.

The workshops were designed to address technical aspects (methods development) based on robust process (stakeholder engagement), as described in Table 1. Important aspects included (1) broadly advertising the workshops; (2) providing for web-based participation; (3) posting all workshop-related materials on the web; (4) providing an open process for interested parties to develop and submit case studies; and, (5) sponsorship by a group of more than 50 diverse organizations.

The first workshop included two primary elements. About half of this workshop was devoted to presentations by thought leaders from various sectors on activities related to issues raised in the NRC (2009) report, as well as perspectives on the NRC report. The other half of the workshop was devoted to brainstorming and evaluation of the impact for the NRC recommendations of 27 submitted proposals for case studies developed by volunteer teams of scientists from numerous organizations. Some of the case studies reflected previously published work, while others were designed to evolve specific methodological issues identified in the NRC (2009) *Science and Decisions* report, such as approaches for low-dose extrapolation. Based on the recommendations from Workshop 1, case studies were developed and presented to the Science Panel at Workshop 2 for their review, recommendations, and consideration for incorporation into the Framework (see Section 3.1).

Workshop 3 was organized primarily around three cross-cutting topics identified by the Science panel: (1) problem formulation, (2) use of mode of action information, and (3) endogenous/background exposure. Discussion of each of these themes was initiated by a presentation by an expert on the topic, followed by Science Panel discussion in the context of the case studies presented.

Presentations, meeting material and reports from all three of the workshops are available at, http://www.allianceforrisk.org/ARA_Dose-Response.htm.

2.2. The science panel

Following an open nomination process, the ARA Steering Committee selected a Science Panel designed to reflect a range of affiliations, perspectives, and expertise (e.g., biology, risk assessment, modeling). Particular effort was made to include representatives from the NRC *Science and Decisions* committee and environmental NGOs. Invitations were sent to 27 nominees, with 13 individuals accepting the invitation. The Science Panel members for Workshops 2 and 3 are listed at <http://www.allianceforrisk.org/Workshop/Panel.htm>. Science Panel members provided input on the utility of the case study methods to address specific problem formulations, and identified areas for additional development of the case study and/or method. After the first three workshops, a

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