Beyond Science and Decisions:
From Problem Formulation to Dose-Response
Report from Workshop V

Webinar Held:
November 2, 2012

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Final report: February 13, 2013

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Introduction

Workshop Scope and Objectives

The workshop series, Beyond Science and Decisions: From Problem Formulation to Dose-Response continues and expands upon the discussion initiated by the National Academy of Science report: *Science and Decisions: Advancement of Risk Assessment* (NRC, 2009). The workshops utilize a multi-stakeholder format to support the development of a practical and solution-oriented compendium of risk assessment methods. Conducted under the aegis of the Alliance for Risk Assessment (*ARA*), the workshop series explores both currently available and evolving methodologies, through the development and application of case studies. The workshop series is based on the fundamental premise that the appropriate methodologies for dose-response assessment need to be based on objectives specific to the intended application; this will include varying levels of analysis.

The workshop series continues to advance the framework of *ARA* (2012) on problem formulation and dose-response analysis (beta version available at http://www.allianceforrisk.org/Workshop/Framework/ProblemFormulation.html).

The purpose of this workshop report is to document and communicate the workshop results to the workshop participants and interested others. The report contains summaries of the Science Panel discussions with the authors of invited presentations, as well as the Science Panel review of case studies presented at the workshop. The draft Workshop report was reviewed by the panel and presenters, and their comments have been incorporated into the final report.

Science Panel

The standing Science Panel chosen by the *ARA* Steering Committee prior to Workshop IV continued its service for Workshop V. Additional information about the panel selection process is included in Appendix 1, and panel biographies are provided in Appendix 2, as well as at http://www.allianceforrisk.org/Workshop/Panel.htm .

Workshop V Organization

The workshop was organized by the Dose-Response Advisory Committee (DRAC) on behalf of the more than 50 workshop sponsors. The DRAC determined the agenda (see Appendix 3) in consultation with the Science Panel. The sponsors of the workshop series are listed at http://www.allianceforrisk.org/ARA_Dose-Response_Sponsors.htm. The morning presentations were on topics of interest to the Science Panel and the general risk assessment community. The afternoon began with a Science Panel discussion of the *ARA* Dose-Response Assessment Framework, followed by a preliminary discussion of a case study. The webinar was open to the

public; participant comments were invited at selected times during the workshop. The list of participants is included in Appendix 4 of this report.

The following were invited presentations at the meeting. Summaries of the panel discussions following the presentations are provided in this report.

- Becki Clark, U.S. Environmental Protection Agency. The WHO Risk Assessment Network: A New Global Collaborative Initiative
- Annie Jarabek, U.S. Environmental Protection Agency. *Advancing Multi-scale Integration of Human Health and Environmental Data: Computational and Conceptual Interoperability*
- J. Craig Rowlands, The Dow Chemical Company. *FutureTox: Building the Road for 21st Century Toxicology and Risk Assessment Practices*
- Dan Krewski, University of Ottawa. *EPA's NexGen Program*

The preliminary discussion of the case study began with a brief presentation by the case study author(s) on key elements, followed by a panel discussion. The purpose of the panel discussion was to identify areas for additional development of case studies and/or methods. The following preliminary case study was presented:

- Robinan Gentry, ENVIRON. *Endogenous Chemical Risk Assessments using Formaldehyde as a Case Example*

All presentations are available at http://www.allianceforrisk.org/Workshop/WS4/CaseStudiesWS4.html.

Panel Discussions of Presentations

The WHO Risk Assessment Network

On behalf of the World Health Organization (WHO), Becki Clark of the U.S. Environmental Protection Agency and Kathy Hughes of Health Canada made a presentation entitled "The WHO Risk Assessment Network: A New Global Collaborative Initiative." The network is still in early stages of implementation, and no materials have been posted on the web as of yet. The goal of the network is "to improve chemical risk assessment globally through fostering and facilitating sustainable interaction between institutions on chemical risk assessment issues and activities." The project emphasizes collaboration, and recognizes differences between the needs of low- and middle-income countries and those of developed countries.

In response to questions from the audience, the presenters clarified that the intent of the initiative is to complement existing initiatives, rather than to replace them. The organizers are in the process of developing the business plan, including defining who would be included in the network. With regard to a question about whether trade associations would be included, the presenters noted that no group is currently excluded, but criteria for inclusion would include

consideration of conflict of interest and whether the goal of a group is commercial or to share information.

Multi-scale Integration of Human Health and Environmental Data

Annie Jarabek of the U.S. Environmental Protection Agency made a presentation entitled "Advancing Multi-scale Integration of Human Health and Environmental Data: Computational and Conceptual Interoperability." Her presentation addressed EPA's Global to Genome (G2G) project and the Society of Toxicology's (SOT) Contemporary Concepts in Toxicology (CCT) workshop on "Building for Better Decisions (B4BD): Multi-scale Integration of Human Health and Environmental Data," held in May, 2012 with many sponsors from a range of sectors. The goal of the G2G project is "specification of a computational platform for agency-wide, seamless data flow and computational modeling in support of health, ecological, and climate risk characterizations." EPA is developing a central online tool that provides access models, spreadsheets, and other tools, as well as information and metadata to aid research and decision making. The CCT workshop was highly interdisciplinary, noting the need to communicate across disciplinary silos and to understand the respective assumptions in each discipline. A key motivation for the workshop was the need to be able to integrate data across different levels of organization and along the source to outcome pathway. Products of the workshop will include a synthesis summary of the meeting, accompanied by manuscripts from each discipline that identify the state of the science and information technology needs for that discipline. Benefits of increased operability include increased transparency, improved communication, increased efficiency, and the ability to repurpose data.

In the discussion after the presentation, it was noted that EPA is thinking about health risk assessment and how risks are managed in the context of sustainability, including broader consideration of economic effects of risk management. Thus, cost-benefit analysis can be part of a multicriteria assessment of alternatives. The breakout group at the workshop that addressed cost-benefit and related topics included primarily people with expertise in life-cycle assessment, rather than economists, and so did not address how to use different health endpoints in cost-benefit analysis.

FutureTox: Building the Road for 21st Century Toxicology and Risk Assessment Practices

Dr. J. Craig Rowlands of The Dow Chemical Company made a presentation entitled "FutureTox: Building the Road for 21st Century Toxicology and Risk Assessment Practices," reporting on an SOT CCT workshop by the same name held in October 2012. He noted that, despite many advances in toxicological sciences, most risk assessments use methods from the 1990s. The goal of the workshop was to lay out a roadmap for reaching the goals laid out in the NRC (2007) report on Toxicity Testing in the 21st Century (TT21C). Key topics were: (1) Risk assessment roadmaps and methods for using 21st century methods; (2) TT21C approaches for safety assessment (including testing methods); (3) TT21C approaches for exposure assessment; and (4) reframing risk assessment practices. A key conclusion was that achieving the desired goal, of having where high throughput testing largely supplanting whole animal toxicity testing, will

likely require significant changes in the current operational assumptions and practices of toxicology and risk assessment. The focus of testing needs to be redirected towards improving the understanding of the context of biological/toxicological responses in high throughput systems to real-world, dosimetrically anchored, human exposures.

Due to time limitations, there were no questions or discussion.

EPA's NexGen Program

Dr. Daniel Krewski of the University of Ottawa made a presentation entitled "NexGen: The Next Generation of Risk Science." The three cornerstones of EPA's NexGen program are (1) the new paradigm for toxicity testing (TT21C – toxicity testing in the 21st Century), based on perturbation of toxicity pathways; (2) advanced risk assessment methodologies, including those addressed in *Science and Decisions*; and (3) a population health approach, looking at multiple health determinants and multiple interventions. Dr. Krewski contrasted the classical approaches and NexGen approaches for addressing the key methodological issues related to adversity definition, variability, susceptible populations, dose and species extrapolation, mixtures and multiple stressors, and uncertainty analysis. Case study prototypes have been developed under the NexGen program. These included a tier 1 (screening and ranking) analysis of dispersants in the context of the Deepwater Horizon spill, a tier 2 (limited scope) assessment that compared transcriptomic and classical benchmark doses from *in vivo* exposure (Thomas et al., 2012), and a tier 3 (major) assessment developing a biologically based dose response (BBDR) model incorporating 'omics data, for lung injury from ozone exposure.

Panel members noted the need to include clinicians in the process, to provide advice on what is an adverse effect and in connecting adverse outcome pathways (AOPs) with apical effects. Dr. Krewski agreed that this is important, and that Kim Boekelheide is a clinician working with the team on that issue. A panel member also noted the need to differentiate between doses that cause (non-adverse) biochemical changes and those that cause adverse effects; concern was expressed that regulating based on biochemical changes could have unintended adverse consequences (e.g., economic effects). Dr. Krewski agreed that a good understanding of the AOP is needed, as well as dosimetry for in vitro to in vivo extrapolation, to ensure that a perturbation is relevant prior to setting guidelines based on the perturbation. He also noted that further refinement may not be needed if an adequate margin of exposure (MOE) is determined based on an initial assessment. A panel member expressed concern that if the mode of action (MOA) is not known, it may not be possible to determine that the in vitro tests are informative regarding the MOE. Dr. Krewski replied that if the AOP is not known, the wide range of *in vitro* tests is diverse enough to identify a wide spectrum of biology changes, although currently integrative effects can be captured only *in vivo.* The ultimate goal is to understand and map all of the toxicity pathways, and then indentify how individual perturbations interact, with the idea that if individual pathway perturbations are avoided, effects on integrative endpoints would also be avoided.

Framework Discussion

Dr. Rory Conolly reviewed a concept for a portal to the framework that he had provided to the panel members previously (Appendix 5). The portal shows the source to outcome continuum on the x axis, with data availability on the y axis. Clicking on individual boxes could lead to elements of the framework. Additional information on problem formulation/scoping could also be an up-front element of the portal. This portal could be organized in a manner to reflect increasingly data-informed approaches (i.e., a tiered approach). Another panel member suggested an entry page prior to the portal that could be targeted to different users. In a manner analogous to the SOT home page http://www.toxicology.org/ , buttons could be available for (for example) the public, press, risk analysts, and other groups. The risk analyst button could lead to Rory's portal, a button for "my problem is" could lead to the current framework, and other buttons might lead to more descriptive information about the framework and process. A third panelist suggested that the portal could pose a series of questions that could lead to drop down boxes identifying potentially relevant case studies.

The panel considered ways to make the framework more self-explanatory and more useful as a central resource for risk assessors that aids in selecting "fit for purpose" risk methods. Key points were:

- An index is needed. The index could be organized by types of data, or could be a decision tree – e.g., type of dose- response, is the MOA known?
- A process for key word assignment and documentation of that process is needed
- Assistance from someone with a background in library science may be useful
- For each case study, the following information needs to be extracted: problem formulation, application, what the methodology contributes (either in the context of the NRC 2009 report or as a general method), how the method can be used.
- The case studies would also need to be characterized by the two dimensions of Rory's portal – where they fall on the source to outcome pathway and data availability. The latter dimension could also be organized by depth of approach (e.g., qualitative screening, quantitative screening, in depth assessment).
- Panel review of the extracted information and case study characterizations is needed.
- Different approaches may be needed to address the aim of a compendium of risk methods and of addressing issues related to the NRC (2009) report.
- There is a need to identify gaps in case study methods.
- The framework needs to be more visible. Currently, the framework is buried on the *ARA* and NLM websites.
- It is important to think about the target audience(s).

The panel also discussed the goals and purpose of the framework, and the implications for structure of the framework. Panel members agreed on the need to clearly identify what the framework offers to the risk assessment community, an issue that would be addressed at least partially by the enhancements noted above for organizing and presenting case studies. Several panel members noted that the framework is based on the frameworks in the NRC (2009) report, and considered whether it is useful to maintain that approach. One advantage of maintaining the

link to the NRC report is to illustrate that the workshop participants have taken the advice from the report on some approaches and looked at how to apply and extend the methods described in the report. Another advantage recognizes that NRC (2009) highlighted the importance of problem formulation, but did not provide a good example of how that relates to the dose-response figure (Figure 5-8 of the NRC report); the case studies in the framework can aid in making that connection. A panelist also noted that the NRC (2009) report challenged the risk assessment community to identify additional methods for moving away from the cancer/noncancer dichotomy, such as methods for low-dose extrapolation. A panelist suggested defining the questions raised by NRC (2009) and determining the degree to which the questions have been addressed, and what case studies are needed in order to address the remaining questions. Another panelist noted that lists of the questions raised by NRC (2009) have been developed, although not in the context of this workshop series.

Panelist shared several ideas regarding the ultimate goals of the case studies and framework. One panelist suggested that the framework should lay out risk assessment methods, starting with an exposure pathway, through development of a risk value (e.g., RfD) and the risk characterization. Others noted that the initial plan was to not have a textbook on how to do risk assessment, but instead to focus on the dose-response portion, while discussing some aspects of hazard characterization and exposure assessment. The possibility for expanding from the initial focus on dose-response assessment to exposure assessment was also noted, recognizing that exposure is much more important for problem formulation. Another panel member considered the framework to be aimed at the experienced risk assessor, illustrating opportunities for the next generation of risk assessment. Thus, a key goal of the case studies is to refine risk assessment methods and to move the science of risk assessment forward. Another panelist suggested that the framework could help provide guidance for challenging risk assessment issues, such as how to address dose-response assessment (for a carcinogen) when the full mode of action is not known, but a threshold is presumed based on the available data.

The panel agreed on the need for further discussion on how to move the framework forward from the NRC (2009) report as an evergreen tool, as well as the need for clarity on what the framework offers (e.g., connection to problem formulation, methods enhancements).

Summary of Framework and Case Studies for the NAS IRIS Panel

A panel member noted that a new National Academy of Sciences panel has been constituted on Review of the IRIS Process, and suggested that the *Beyond Science and Decisions* Science Panel could submit a request to make a presentation to the NAS panel. Several panel members supported the general idea of such a presentation. In response to a panelist question about whether the Science Panel has reached consensus decisions that could be presented to the NAS panel, it was noted that the presentation could present some case studies related to recommendations of the NRC (2009) report, and consensus decisions reached by the Science Panel that reviewed those case studies. A panelist expressed reservations about consensus decisions reached by a previous panel. The need for some government employees to consider consensus decisions relative to their governments' policies was also noted. Some presentations are available that include some case studies relevant to the NRC (2009) report (e.g. presentation

to the New England Chapter of the Society for Risk Analysis (SRA), available at http://www.allianceforrisk.org/ARA_Dose-Response.htm). Panel members suggested that clarity on the purpose of the presentation is needed prior to developing the presentation. Improved framing and identification of what the framework contributes will also aid in identifying the key points of the presentation, but a panelist noted that two of the key points relate to assessments being based on MOA, and the application of increasingly data-informed approaches. A workshop participant noted the need to relate the presentation to the scope of NAS IRIS Review project (EPA's methods for evidence-based data review and weight of evidence analysis). The panel agreed that Science Panel member Mike Dourson may lay out a presentation for review by the panel if he wishes, and individuals may sound out panel members at the annual meeting of the SRA in December, but that the *ARA* Science Panel would not move forward yet with any official request to present to the NAS panel.

Case Study Discussion

One preliminary case study review was presented. Panel input was sought on the utility of the method to address the specific problem formulations, and on areas for additional development.

Table 1. Workshop V-Summary of Case Study Discussion

New Case Study	
Endogenous Chemical Risk Assessments using Formaldehyde as a Case Example	**Authored by: Gentry, R. C.**

The purpose of the case study is to address methods for accurately evaluating the dose-response for the risk of exogenous formaldehyde in the presence of a substantial background of endogenous formaldehyde. The method builds on the work described by Swenberg et al. (2011) for a "bottom up" approach for risk assessment that extrapolates upward from background (endogenous) exposure and response. The "bottom up" approach assumed linearity at low doses attributed all background risk to endogenous exposure, and provided an independent "reality check" on extrapolations from high-dose data. Large discrepancies between the bottom-up and top-down approaches suggest that the top-down approach may be overly conservative. The project team is working on refining the formaldehyde biologically-based dose-response (BBDR) model to (1) include a description of endogenous formaldehyde, (2) recalibrate the model against the original data as well as the new data from Swenberg and colleagues, and (3) use the results to characterize the range of plausible risk estimates.

The panel discussed the relationship between the formaldehyde-DNA adducts (crosslinks) and tumors. The adducts were considered a biomarker of effect, as a surrogate rather than necessarily being causally related to tumors; tumors could result via a different mechanism. Although it is recognized that not every adduct leads to a mutation that leads to tumors, the initial BBDR made the conservative assumption that the adducts were quantitatively related to tumor development. Similar thinking would need to be applied to endogenous adducts, since the body cannot distinguish between adducts related to endogenous and exogenous exposure. The body may treat exogenous and endogenously formed formaldehyde differently, but once the adduct is formed, there is no difference.

The approach being followed in the case study assumes that formaldehyde plays a causal role in leukemia risk, and that all relevant leukemias result from adduct formation. In response to panelist questions, the presenter noted that the bottom up approach uses the adduct levels from endogenous exposure to account for background risk.

A panel member pointed the case study authors to the International Programme on Chemical Safety (IPCS 2010) guidance on use of physiologically-based pharmacokinetic (PBPK) models in risk assessment, recommending that they use the IPCS template to facilitate understanding by risk assessors; a key consideration is comparing the uncertainties of the PBPK/BBDR model with those of the default approach. Another panel member suggested that the team consider using the signal-to-noise crossover dose approach described by Dr. Krewski in his talk, as the basis for a point of departure. The case study author noted that the approach could be used to characterize when adducts rise above baseline levels. Another panelist suggested that data from an early bioassay of methyl chloride and data on drugs that are N-demethylated could help refine the BBDR model.

A panel member noted that endogenous formation of nasal adducts is sufficiently high that exogenous formaldehyde exposure does not contribute significantly at low doses, and suggested that the curve for adducts from endogenous formaldehyde should be constant with increasing levels of exogenous formaldehyde (slide 16 of the presentation). In response to a question about thresholds, a panelist with expertise in formaldehyde noted that the lowest concentration where nasal tumors were seen in the animal bioassay (6 ppm) is also cytotoxic. This panelist emphasized that a threshold for formaldehyde is not being postulated; instead, there is unlikely to be a quantitatively meaningful increase in tumors in the absence of cytotoxicity. The current BBDR includes both cytotoxicity and a low-dose linear component based on the DNA-protein adducts; the goal of the current work is to refine the latter piece. A panel member noted that there are probably more than two components to the dose-response curve, since each of the steps of adduct formation, mutation, cytotoxicity, etc., would have its own dose-response. The BBDR is consistent with the results of a HESI (Health and Environmental Sciences Institute) project addressing the relationship between adducts and cancer, which recommended breaking down each part of the process (Jarabek et al., 2009; Himmelstein et al., 2009).

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