Panel Discussion Questions – Beyond Science and Decisions, Workshop IV, May 22-24

Workshop Goal

The workshop purpose is to advance the recommendations of the NAS (2009) and subsequent framework of ARA (2012) on problem formulation and dose-response analysis, through review of illustrative case studies for further development of methods.

General Workshop Series Objectives:

- Additionally develop the content of the NAS (2009) report on improving the risk assessment process to develop a compendium of practical, problem-driven approaches for "fit for purpose" risk assessments, linking methods with specific problem formulations (e.g., prioritization, screening, and in-depth assessment) for use by risk managers at a variety of levels (e.g., states, regional managers, people in a variety of agencies, and in the private sector).
- Implement a multi-stakeholder approach to share information, ideas and techniques in support of developing practical problem-driven risk assessment methods compendium.

Specific Workshop Objectives:

- Identify useful dose-response techniques for specific issues, including consideration of relevant data, characterization of assumptions, strengths and limitations, and how the techniques address key considerations in the dose-response.
- These techniques should appropriately reflect the relevant biology (including the biology of thresholds), and mode of action information, at a level of detail appropriate for the identified issue.
- Provide methods to explicitly address human variability in cancer assessment, and enhance the consideration of human variability in noncancer assessment, including explicit consideration of underlying disease processes, as appropriate for the relevant risk assessment context.
- Identify methods for calculating the probability of response for noncancer endpoints, as appropriate for the relevant risk assessment context.
- Develop a risk methods compendium that will serve as a resource for regulators and scientists on key considerations for applying selected dose-response techniques for various problem formulations, with suggested techniques and resources.

Panel Role:

The Panel provides input on case study methods being proposed to enhance the risk framework. Panel members provide input on the utility of the case study methods to address specific problem formulations, and identify areas for additional development of the case study and/or method. Inclusion of a method or case study in the framework as an illustration of a technique does not imply panel acceptance of the chemical-specific outcome.

Discussion Questions - Framework Presentation

1. The ultimate goal is for the framework to be self-explanatory, and useful to the risk assessment community as a "one-stop shop" for risk assessment methods and issues, providing links to guidance and examples of how methods are applied.
    a. What changes to the framework (changes in structure, additional information provided, etc.) can help the framework to fulfill this goal?

2. The framework currently includes links to the authors' work for the case studies – case study summary and full case study (revised version, if revised in response to panel comments), and the presentations made at the panel meetings. (Some presentations include useful information not in the case study.) Documentation of the recommendations from the panel is included in the meeting reports, and documentation of changes made after the second workshop were provided with the workshop 3 packet (see Attachment #1 for a sample), but such documentation is not currently directly linked to the framework.
    a. Should the framework more overtly reflect the panel recommendations? If so, how? One idea is to collate the comments for each case study, author response, and any panel re-review comments (see Attachment #2), but this is a rather labor-intensive approach, both in developing the files for each case study and in separate links for each case study. Another approach would be to simply link to the relevant file of panel recommendations from the meeting (or the meeting report) – e.g., as in Attachment #3.

3. See Attachment #4 for recommendations regarding guidances and key publications to be linked to the framework and where the link would go.
    a. Please comment on the appropriateness of linking to these materials and other guidances and key publications to link to.

Generic Case Study Review Discussion Questions

While the panel may not address each of these points explicitly in discussing the case study methods, the following are questions to consider in conducting the review of the case studies:

1. Is this case study a useful addition to the framework?
2. What specific things could be changed to make the method more useful?
3. What are the broader generalizations from this method, and specific lessons?
4. What are key uncertainties and research needs related to the case study that are critical to address in a methodological context?

Case Study-Specific Discussion Questions

See additional discussion questions submitted by the authors of the effect level case study.

Attachment 1 - Changes Made to Case Studies After Workshop #2 (partial list; full list was provided for workshop #3)

Categorical regression – No changes were made. The only recommendation for enhancement by the panel was that the final methods compendium should note that different methods could be used to address similar issues (e.g., there are similarities between categorical regression and the linked dose-response functions approach). This comment refers to the methods compendium, not changes in the individual case study.

Use of human data in cancer risk assessment (1,3-butadiene)[1] – No changes were made. The changes recommended by the panel at the October meeting will be noted in the final report.

Consideration of human kinetic variability (trichloroethylene) - No changes were made. The changes recommended by the panel at the October meeting will be noted in the final report.

Biologically-Informed Empirical Dose Response: Using Linked Cause-Effect Functions (TiO2) – No significant changes were made. The panel asked for a comparison with epidemiology data; this is noted at the beginning of the response to question 2 of the summary. Application of the method to other chemicals would be useful, but funding is needed for such projects.

AEGL methodology - The panel recommended to clarify the difference between an RfC and an AEGL. Because the method is for acute exposures, differences between AEGLs and acute RfC (not chronic) were briefly discussed.

UF Distributions - Text was added to the introduction: "This method is intended for use in risk management rather than as a risk assessment tool. It was developed to address a recommendation provided in Chapter 5 of the Silver Book to develop a way to estimate the probability that an RfD is correct." And a sentence was added to question 4: "Specifically, with the uncertainty factors for subchronic to chronic, and LOAEL to NOAEL, this method is likely to have greater limitations in that those are highly dependent on the study design (i.e., dose spacing)." The new work by Jeff Swartout is still under development, and so was not added.

Multiple Components to Mode of Action and Risk Assessment Modeling (Acrylamide) – The text about assumptions regarding determinants of the dose-response shape was clarified, and the term "multiple modes of action" was modified to multiple components to the mode of action.

[1] Chemical in parentheses is the chemical used in the case study, if applicable

Attachment 2 – Sample Compiled Comments and Response on a Case Study

Assessment of Low-Dose Dose-Response Relationships (Non-linear or Linear) for Genotoxicity, Focused on Induction of Mutations & Clastogenic Effects (Multiple chemicals)	**Presented by: Pottenger, L.; Moore, M.** **Co-authors: Zeiger, E.; Zhou, T.**
Workshop 2 panel comments: The panel supported carrying this method forward. Panel members noted that a key contribution of the case study is in articulating a MOA for gene mutation, and in prompting the risk assessment community to think about mutation in the context of key events. The panel recommended that that MOA framework be used to highlight a critical evaluation of the underlying biology, and that formal statistical tests specifically comparing the tumor dose response slope with that of the mutation dose response slope, would enhance the case study. A panel member noted that information on the background incidence of the various measured endpoints could be used to address the issue of additivity to background.	
Author changes: The changes made to the full case study are highlighted in yellow. When sections are new or substantially revised, the header is highlighted in the table of contents and the text. Smaller changes in the text are highlighted in the text itself. The primary change was the addition of a preliminary analysis of the MOA for mutation conducted for MMS/MNU and EMS/ENU, based on review of selected publications and the MOA for mutation of Pottenger and Gollapudi (2010) (see pp 11-13 in Main case study document and Appendix E).	
Workshop 3 panel comments: In Workshop 2, the panel recommended that the authors enhance the study by conducting a MOA analysis for mutation and by conducting formal statistical tests specifically comparing the tumor dose-response slope with that of the mutation dose-response slope. In the MOA analysis, focusing on recent data, the authors found supporting data for some key events, but there was a lack of data for other events. A panel member suggested that in the future, it would be important to match the low-dose response for mutations with the dose-response assessment for tumors. However, the authors noted that there might not be enough low-dose data, and the panel agreed that this is an important point to stress in the case study write-up. Panel members noted it is important to be clear about where data exist and where they do not; a qualitative VOI analysis could be conducted related to the data gaps. The panel encouraged the study authors to think about identifying the critical data gaps and identifying what is driving the process. A panel member suggested that the authors think mechanistically about whether a hockey stick dose-response shape is due to a fundamental biological nonlinearity or due to background noise.	

Attachment 3 – Sample Summary of Workshop 3 Case Study Discussions

New Case Studies	
Lead-Dose-Response Relationship for Effect on Children's IQ	**Presented by: Carrington C.**
The panel supported carrying this method forward. The panel recommended that the case study be modified to identify the problem formulation, specifically how the analysis helps to support a decision. The panel also recognized that a key limitation to the assessment was that only pooled data were available to the case study author, and that it would be useful if the epidemiology community would make the raw data available for additional analyses. The panel recommended that the author add text regarding what types of additional research could be done with the raw data.	
Quantitative Assessment of Sensitivity and Variability in Humans: Modeling the Effects of Low Dose Exposure to Dietary Residues of Chlorpyrifos	**Presented by Juberg, D.R.; Price, P.**
The panel supported carrying this method forward as an illustration of how data can be used to derive chemical-specific adjustment factors (CSAFs). The panel recommended that the case study emphasize that *in vitro* information on kinetic variability cannot be used directly to calculate CSAFs; one needs to use those data to calculate the impact on tissue *dose*. Potential enhancements noted would be to address cumulative risk, using such resources as market basket surveys or data on biomonitoring. The panel suggested that the authors link more of the discussion to the NAS report and explain how the key case study conclusions address issues raised in the NAS report. For example, the case study addresses the concerns raised in Chapters 4 or 5 of the NAS report about the adequacy of a factor of 10 for the intraspecies uncertainty factor. The case study also challenges the idea that a background response for the apical effect would linearize the dose-response. An important result was the finding that the dietary exposure is expected to have a very small impact on a precursor key event (cholinesterase in the blood), indicating an even smaller effect on an apical response. The panel also noted that it would be useful to include in the case study information on the status and nature of the related EPA review.	

Attachment 4 – Proposed Additions to the Framework

Qualitative Decision- Integration

EPA's sustainable futures program - http://www.epa.gov/oppt/sf/
(new link with the current case study)

Health Canada Categorization of Substances on the Domestic Substances List
http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/categor/index-eng.php
(new box)

Classification systems (new box)

A Guide to The Globally Harmonized System of Classification and Labelling of Chemicals (GHS). United Nations. 2011. Available at http://www.osha.gov/dsg/hazcom/ghs.html

Quantitative Screening

Threshold of Toxic Concern – new bullet with references:

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of Toxic Hazard – A Decision Tree Approach. Food Cosmet. Toxicol. 16, 255-276. Kroes, R., Kleiner, J., Renwick, A., Cheeseman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., Schilter, B., Schlatter, J., van Schothorst, F., Vos, J.G., Wurtzen, G., 2004. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Cosmet. Toxicol. 42, 65–83.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J. 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food and Chemical Toxicol. 45, 2533-2562.

Munro, I.C., Ford, R.A., Kennepohl, E., Sprenger, J.G., 1996. Correlation of structural class with No-Observed-Effect Levels: A proposal for establishing a threshold of concern. Food and Chemical Toxicol. 34: 829-867.

Munro, I.C., Renwick, A.G., Danielewska-Nikiel, B., 2008. The Threshold of Toxicological Concern (TTC) in risk assessment. Toxicol. Lett. 180, 151-156.

Threshold of Regulation - new bullet with references:

FDA (Food and Drug Administration) (2000, revised 2007). Toxicological principles for the safety assessment of food ingredients: Redbook. FDA CFSAN.
http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/Redbook/default.htm

Cheeseman, MA, EJ Machuga, AB Bailey. 1999. A tiered approach to threshold of regulation. Food Chem Toxicol. 1999 Apr;37(4):387-412.

Screening-level safe dose (these methods would be repeated under dose-response methods for the in-depth tab)

U.S. EPA (United States Environmental Protection Agency) (2002). A review of the reference dose and reference concentration processes. EPA/630/P-02/002F,December 2002. At http://www.epa.gov/iris/backgrd.html

IPCS (International Programme on Chemical Safety) (1999) Principles for the assessment of risks to human health from exposure to chemicals. Environmental Health Criteria 210.

Meek, M; Newhook, R; Liteplo, R; et al. (1994). Approach to assessment of risk to human health for priority substances under the Canadian environmental protection act. Environ Carcino & Ecotox Revs C12:105-134.

HC (Health Canada) (1996). Health-based tolerable daily intakes/ concentrations and tumorigenic doses/ concentrations for priority substances; Health Canada, H46-2/96-194E.

Quantitative SAR

Multiple guidances and toolbox from OECD available at http://www.oecd.org/document/2/0,3746,en_2649_34379_42926338_1_1_1_1,00.html

Remove CBEL and PPRTVs (these were initial placeholdes and can be added if we get case studies, but they don't represent novel methods not addressed elsewhere on this tab)

In depth

Endpoint assessment

Test guidelines (new box)

OECD (2007). Test guidelines. http://www.oecdbookshop.org/oecd/index.asp?lang=EN (must search by specific guideline number)

U.S. EPA (United States Environmental Protection Agency) (2007) OCSPP Harmonized test guidelines. U.S.EPA. Washington, D.C. http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series870.htm

FDA (Food and Drug Administration) (2000). Toxicological principles for the safety assessment of food ingredients: Redbook. FDA CFSAN.

http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/Redbook/default.htm

Risk Assessment guidelines by endpoint (new box)

IPCS guidance available at:
http://www.who.int/ipcs/publications/ehc/methodology_alphabetical/en/index.html

IPCS (International Programme on Chemical Safety) (1991). Principles and methods for the assessment of nephrotoxicity associated with exposure to chemicals. Environmental Health Criteria 119.

IPCS (International Programme on Chemical Safety) (2001). Neurotoxicity: Integrated approach to the assessment of neurotoxicity of chemicals. Environmental Health Criteria 223.

IPCS (International Programme on Chemical Safety) (2001). Reproduction: Principles for evaluating health risks to reproduction associated with exposure to chemicals. Environmental Health Criteria 225.

IPCS (International Programme on Chemical Safety) (2008). Skin sensitization in chemical risk assessment. IPCS Harmonization project No. 5.

IPCS (International Programme on Chemical Safety) (2012). Guidance for immunotoxicity risk assessment for chemicals. IPCS Harmonization project No. 10.

U.S. EPA guidance available at: http://www.epa.gov/iris/backgrd.html

U.S. EPA (United States Environmental Protection Agency) (1986). Guidelines for mutagenicity risk assessment. Federal Register 51(185):34006-34012.

U.S. EPA (United States Environmental Protection Agency) (1991). Guidelines for developmental toxicity risk assessment. Federal Register 56(234): 63798-63826.

U.S. EPA (United States Environmental Protection Agency) (1994). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F, October 1994.

U.S. EPA (United States Environmental Protection Agency) (1996). Guidelines for reproductive toxicity risk assessment. Federal Register 61(212): 56274-56322.

U.S. EPA (United States Environmental Protection Agency) (1998). Guidelines for neurotoxicity risk assessment. Federal Register 63(93): 26926-26954.

U.S. EPA (United States Environmental Protection Agency) (2002). A review of the reference dose and reference concentration processes. EPA/630/P-02/002F,December 2002.

U.S. EPA (United States Environmental Protection Agency) (2005). Guidelines for carcinogen risk assessment. EPA/630/P-03/001B, March 2005. http://www.epa.gov/ncea/iris/backgr-d.htm

MOA

– first present the key publications, then the case studies

New box – 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.]*

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

Numerous case studies from IPCS in Critical Reviews in Toxicology (2005). 35(8).

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.

U.S. EPA (United States Environmental Protection Agency) (2007) Framework for determining a mutagenic mode of action for carcinogenicity (external review draft); U.S. EPA, EPA 120/R-07/002-A. Available at http://epa.gov/osa/mmoaframework/index.htm

U.S. EPA (United States Environmental Protection Agency) (2005). Guidelines for carcinogen risk assessment. EPA/630/P-03/001B, March 2005. http://www.epa.gov/ncea/iris/backgr-d.htm

Vulnerable population assessment

New box – key publications:

IPCS (International Programme on Chemical Safety) (1993). Aged population: Principles for evaluating chemical effects on the aged population. Environmental Health Criteria144.

IPCS (International Programme on Chemical Safety) (2006). Children: Principles for evaluating health risks in children associated with exposure to chemicals. Environmental Health Criteria 237.

U.S. EPA (United States Environmental Protection Agency) (2005). Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens.EPA/630/R-03/003F, March 2005.

U.S. EPA. A Framework for Assessing Health Risk of Environmental Exposures to Children (Final). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-05/093F, 2006. Available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=158363

Background

New box – key publications:

IPCS (International Programme on Chemical Safety) (2006) Risk Assessment of Combined Exposures to Multiple Chemicals: A WHO/IPCS Framework.
(http://www.who.int/ipcs/methods/harmonization/areas/combinedexposure.pdf)

Meek ME, Boobis AR, Crofton KM, Heinemeyer G, Raaij MV, Vickers C. (2011). Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. Regul Toxicol Pharmacol. 60(2): S1-S14.

U.S. EPA (United States Environmental Protection Agency) (1986). Guidelines for the health risk assessment of chemical mixtures. Federal Register 51(185):34014-34025.

U.S. EPA (United States Environmental Protection Agency) (2000). Supplementary guidance for conducting health risk assessment of chemical mixtures. EPA/630/R-00/002, August 2000.

U.S. EPA. 2003 Framework for Cumulative Risk Assessment. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington Office, Washington, DC, EPA/630/P-02/001F, 2003.
http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54944
(the placeholders for mixtures guidance and cumulative risk guidance would be removed)

Dose Response Methods

New box – key publications:
Include all references listed in quantitative screening – safe dose

IPCS (International Programme on Chemical Safety) (2005). Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration–response assessment.
(http://whqlibdoc.who.int/publications/2005/9241546786_eng.pdf)

IPCS (International Programme on Chemical Safety) (2010) Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment. (http://www.who.int/ipcs/methods/harmonization/areas/pbpk_models.pdf)

IPCS (International Programme on Chemical Safety) (2009) Principles for modeling dose-response for the risk assessment of chemicals. Environmental Health Criteria 239.

IPCS (International Programme on Chemical Safety) (1999) Principles for the assessment of risks to human health from exposure to chemicals. Environmental Health Criteria 210.

U.S. EPA (United States Environmental Protection Agency) (2000). Benchmark dose technical guidance document.. External Review Draft. EPA/630/R-00/001, October 2000.

U.S. EPA (United States Environmental Protection Agency) (2005). Guidelines for carcinogen risk assessment. EPA/630/P-03/001B, March 2005. http://www.epa.gov/ncea/iris/backgr-d.htm

U.S. EPA 2011. Recommended Use of Body Weight 3/4 as the Default Method in Derivation of the Oral Reference Dose http://www.epa.gov/raf/publications/interspecies-extrapolation.htm

U.S. EPA (United States Environmental Protection Agency) (2006). Approaches for the application of physiologically based pharmacokinetic (PBPK) models and supporting data in risk assessment (Final Report). U.S. Environmental Protection Agency, Washington, D.C., EPA/600/R-05/043F. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=157668

U.S. EPA (2011). External Review Draft of Data-Derived Extrapolation Factors (DDEF http://www.epa.gov/raf/DDEF/index.htm