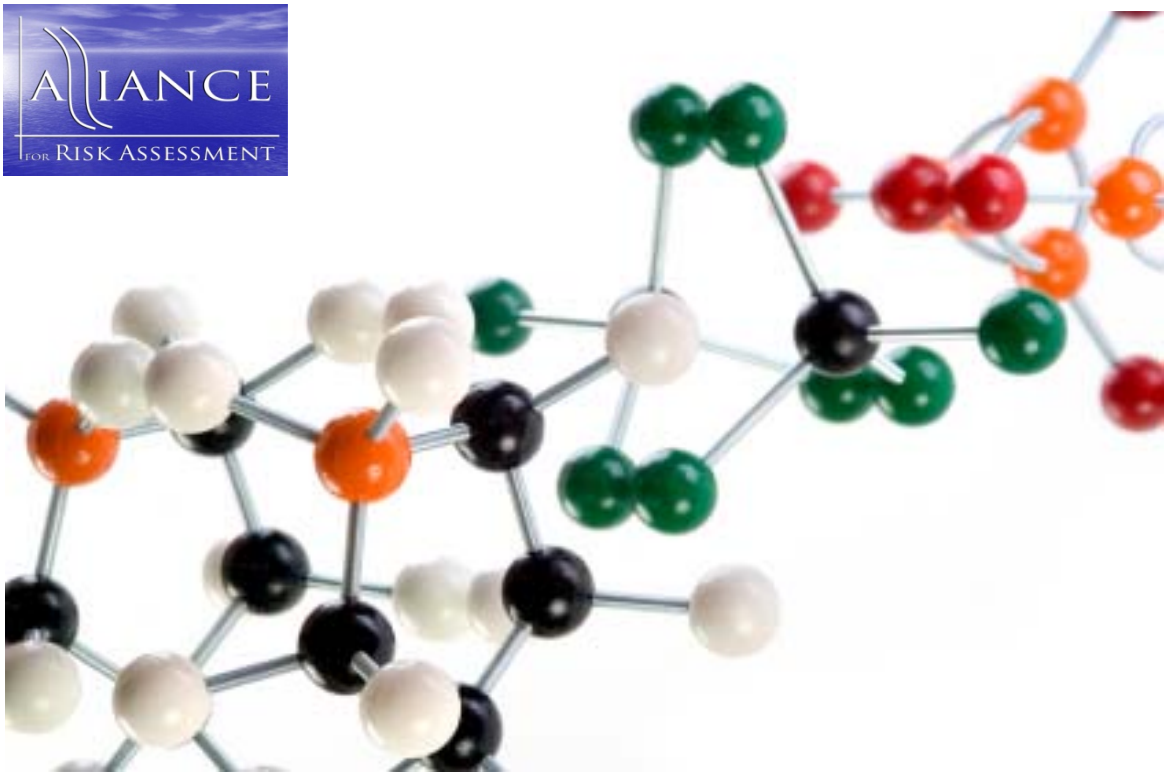

Beyond Science and Decisions:
From Problem Formulation to Dose-Response
Report from Workshop IV

Workshop Held:
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Austin, Texas
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Table of Contents

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

For Workshop IV, the *ARA* Steering Committee selected a standing Science Panel to serve for the next 2-3 years as discussants and to provide diverse scientific input on the utility of the case study methods to address specific problem formulations. The Panel was also asked to identify areas for additional development of case studies and/or methods. The Science Panel was designed to be balanced with a range of affiliations and perspectives, as well as types of expertise (biology, risk assessment, modeling). An open nomination process was used. Panel members from the initial workshop series were invited to self-nominate and announcements were widely distributed through a number of venues to invite additional nominations. The *ARA* Steering Committee carefully considered all the nominations and selected nine standing panel members and one alternate who can substitute for standing panel members in the case of scheduling conflicts. They also selected eight additional *ad hoc* members, providing additional specialized expertise for this workshop or on workshops in the future. Biographies for the Science Panel for Workshop IV are provided in Appendix 1; biographies for standing panel members, as well as the *ad hoc* and alternate panel members are provided at http://www.allianceforrisk.org/Workshop/Panel.htm. The Science Panel for Workshop IV consisted of the following, including all standing panel members and one ad hoc member:

- *Richard Beauchamp, Texas Department of State Health Services*
- *James S. Bus, The Dow Chemical Company*
- *Rory Conolly, U.S EPA National Health and Environmental Effects Research Laboratory*
- *Michael L. Dourson, Toxicology Excellence for Risk Assessment*
- *R. Jeffrey Lewis, ExxonMobil Biomedical Sciences, Inc.*
- *Bette Meek, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa*
- *Gregory Paoli, Risk Sciences International*[1]
- *Rita Schoeny, U.S. EPA Office of Water*
- *Alan Stern, New Jersey Dept of Environmental Protection*
- *Ad hoc Workshop IV member: Lorenz Rhomberg, Gradient*

Workshop IV 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 2) in consultation with the Science Panel. The sponsors of the workshop series are listed at http://www.allianceforrisk.org/ARA_Dose-Response_Sponsors.htm. Additional support for this workshop was provided by the Texas Commission on Environmental Quality, who hosted the workshop. The workshop included three types of presentations: (1) presentations on topics of interest to and requested by the Science Panel; (2) case studies being reviewed by the Science Panel; and (3) brief presentations on works in progress or other topics of interest. The workshop was open to the public for both in-person participation and participation via webcast. Participant comments were invited at selected times during the workshop. The list of participants is included in Appendix 3 of this report.

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

- Rusty Thomas, The Hamner Institutes for Health Sciences. *Keynote Talk: Incorporating New Technologies into Toxicity Testing and Risk Assessment: Moving from 21st Century Vision to a Data-Driven Framework*
- Lynne Haber, Toxicology Excellence for Risk Assessment. *Beyond Science & Decisions Dose Response Framework*
- Rita Schoeny, U.S. Environmental Protection Agency. *EPA's Response to NRC Framework Recommendation: Framework for Human Health Risk Assessment to Inform Decision Making*
- Bette Meek, University of Ottawa. *Combined Exposures Framework*

Much of the workshop was dedicated to review of case studies. Each review 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

[1] Member of the NAS *Science & Decisions* panel

and/or methods. The discussion was framed by the discussion questions in Appendix 4; one case study author also provided case study-specific discussion questions, which are also included in Appendix 4. The following case studies were presented:

- Chris Borgert, Applied Pharmacology Toxicology Inc. *Criteria Requirements for Data-Driven Carcinogenicity Mode of Action (MOA) Determinations as Exemplified by Chloroform*
- Roberta Grant, Allison Jenkins, and Joseph (Kip) Haney, Texas Commission on Environmental Quality. *Methods for Deriving Inhalation Effect Levels for Comparison to Health-Protective Values*
- Eric Ruder and Henry Roman, Industrial Economics, Incorporated. *A Decision Analytic Framework for Considering the Economic Value of Improved Risk Assessment Data (Value of Information)*
- Rick Becker, American Chemistry Council and Sean Hays, Summit Toxicology. *A Tiered Framework for Interpreting Human Biomonitoring Results*
- Chris Borgert, Applied Pharmacology Toxicology Inc. *The Human Relevant Potency Threshold: Reducing Uncertainty by Human Calibration of Cumulative Risk Assessments*

The following were briefer presentations with limited panel discussion:

- William Gulledge, American Chemistry Council. *Ethylene Oxide Mode of Action (MOA)*
- Jimmy Perkins, University of Texas Health Science Center. *The Occupational Alliance for Risk Science (OARS)*
- Lorenz Rhomberg, Gradient. *Naphthalene Mode of Action*
- Tiffany Bredfeldt, Texas Commission on Environmental Quality. *Structure Activity Relationships Applied to Short Term Exposures*

All presentations are available at http://www.allianceforrisk.org/Workshop/WS4/CaseStudiesWS4.html and recordings of presentations are available at http://www.texasadmin.com/tceqs.shtml (search for *ARA* workshop).

Panel Discussions of Presentations

Incorporating New Technologies into Toxicity Testing and Risk Assessment

Dr. Rusty Thomas of the Hamner Institute presented the keynote address on "Incorporating New Technologies into Toxicity Testing and Risk Assessment: Moving from 21st Century Vision to a Data-Driven Framework." In his evaluation of the utility and applicability of the ToxCast assays, he concluded that the assays are not useful for hazard identification at this point in time (in general, structure is a better predictor of hazard than the assays). He stated that the ToxCast assays are useful for mode of action (MOA) evaluation and for dose-response assessment, as a potentially conservative estimate of a point of departure. His team has also done work on prioritizing chemicals based on comparing estimated human exposure with *in vitro* bioactivity that has been adjusted for pharmacokinetics using reverse dosimetry. They have concluded that

the approach has potential utility for prioritizing chemicals and interpreting the results from the *in vitro* high-throughput screening studies, but is limited by the lack of exposure estimates. Dr. Thomas proposed a tiered risk assessment framework that incorporates 21st century methods. A key factor of this framework is the initial differentiation between weak, non-specific acting chemicals and potent, specific-acting chemicals.

In response to a panelist question about how the science can transition away from needing to be anchored to *in vivo* data, Dr. Thomas stated that he is not yet comfortable basing evaluations entirely on *in vitro* data. He has been working on designing studies to address why hazard is poorly predicted *in vitro*, an issue that he recommends be addressed prior to attempting better predictions of human response at relevant doses. He further noted that his proposed framework could be modified to include linear no-threshold dose-response extrapolation for cancer risk from mutagenic chemicals.

The panel discussed with Dr. Thomas why changes in gene transcription would reflect toxicity. Dr. Thomas noted that the transcriptome approach is feasible because both direct and indirect effects in target and non-target cells are being measured. Even if the mechanism of toxicity occurs via a direct effect (i.e., without requiring a transcriptional change), indirect transcriptional changes would be expected as part of compensatory or adaptive mechanisms in the cell. Thus, the transcriptome approach may not necessarily inform MOA (although it often does), but it can be used to identify the dose at which something is happening to the cell or tissue. Dr. Thomas also noted that his analysis of correlations between transcriptional perturbation of specific pathways and apical effects was adjusted for the maximal tolerated dose (MTD); this was done to account for the strong correlation between the MTD doses and various noncancer and cancer-related endpoints (e.g., the observed correlation between LD_{50} and cancer potency). Dr. Thomas also noted the need to consider the context of stress pathway activation, which will ultimately dictate how a cell or tissue will respond.

ARA Dose-Response Framework

Dr. Lynne Haber of TERA shared information on an interactive framework of risk methods that was developed by the Science Panel and interested workshop participants as part of earlier workshops in the series. She noted that key framework objectives include:

(1) guiding risk assessors to a variety of assessment methods relevant to a range of decision contexts and illustrated by case studies,
(2) aiding risk assessors in selecting among methods; and
(3) being a central access point for risk methods and guidance documents from a variety of agencies.

The *ARA* Dose-Response Framework is available at http://www.allianceforrisk.org/Workshop/Framework/ProblemFormulation.html). The framework is also posted on the National Library of Medicine's Enviro-Health Links, at http://sis.nlm.nih.gov/enviro/toxweblinks.html (under Associations and Societies). Discussion questions on the framework are included in Appendix 2. The panel considered ways to enhance the framework to achieve the goal of being a self-explanatory central resource for risk assessors

that aids in selecting "fit for purpose" risk methods. Panelist suggestions primarily fell into three categories:

(1) framing and explaining purpose of the framework;
(2) capturing panel feedback;
(3) developing aids to navigation.

Several recommendations for future development of the framework were also proposed. Individual panelist suggestions are listed here; however, the limited time precluded reaching consensus on priorities among this list.

(1) Framing objectives and explaining the purpose of the framework

- Explanatory text on the goals, objectives, and audience of the framework is needed; this could be written by current or former panel member(s).
- It would be useful to use the adverse outcome pathway diagram as an organizing frame, with links to methods addressing each step.
- It would be useful to formulate the question that each case study addresses.
- It is essential to show more clearly how each case study fits into the risk assessment process.

(2) Capturing panel feedback

- Flag case studies that are "testing" methods (e.g., from NRC 2009, or other methods) vs. those that the panel recommends for use.
  - Color coding could reflect panel recommendations based on "testing."
  - A scoring template could be provided for the panel.
  - It was also noted that authors of some case studies did not have the resources to address panel recommendations.
- Several panelists agreed that links to panel feedback discussion would be useful, but there was no decision regarding format.

(3) Aids to navigation

- Link to a video (e.g., on YouTube) that walks the user through how to use the framework.
- Improve user interface through, for example, inclusion of a list of key words that point to case studies.
- Have each page show an overall map/diagram of the tree with "you are here."
- Pop-up "hover boxes" could show explanations.
- Number case studies to provide consistency and make them easier to track. Consistent titles are also important.
- Organize based on minimal data needs for the method, or link to information on minimal data needs.
- Include a contact e-mail for questions.

(4) Other/future needs

- It would be useful for the framework to reflect the idea of using increasingly data-informed approaches, as needed in a tiered approach.

- Additional thinking is needed on how to organize the framework so that data-rich assessments can be used to inform data poor assessments. One example of such an output would be to assist in development of reasonable occupational exposure levels (OELs) for data-poor chemicals.
- It may be useful to engage someone with more communication and/or information technology expertise to help with the site design.
- Create a blog or other mechanism for user feedback on the framework and design.
- It may be useful to revisit case studies periodically, particularly in order to reflect the changing state of the science.
- Address how case studies can be used to facilitate good problem formulation for addressing future risk assessments.

EPA's Response to NRC Framework Recommendation

Dr. Rita Schoeny of the U.S. EPA gave a presentation entitled "EPA's Response to NRC Framework Recommendation: Framework for Human Health Risk Assessment to Inform Decision Making." Rather than a framework for risk assessment, this EPA product is a framework for assessment *to inform decision making*. Goals of the Framework are to improve transparency in risk assessments used in making choices among risk management options. The use of the risk assessment, or its "fit for purpose," needs to be considered throughout the process. To that end, the Framework document emphasizes the following: problem formulation; presentation of conceptual models and analysis plans; interaction with risk managers on fit for purpose; peer review as needed; and involvement of the public and stakeholders at various points of the process.

In response to a panel question, Dr. Schoeny stated that the *ARA* workshop process has informed the thinking of the EPA technical panel developing the Framework discussed in her presentation. Moreover, discussions from the *ARA* workshops have been relayed to other EPA work groups, such as the Risk Assessment Forum technical panel on cumulative risk assessment. An aim of the Framework technical panel has been to show explicitly how EPA plans, scopes, and conducts problem formulation. Therefore, this group is focusing on EPA examples, rather than using case studies from the *ARA* workshop series. Panel members noted additional considerations related to the EPA Framework presented by Dr. Schoeny. It would be useful to show options for risk management as part of the framing, since such options are often limited, restricting the scope of the risk assessment. "No action" is also one of the options to consider. Panel members noted that not all assessments have an iterative aspect, that many use "off-the-shelf" assessments from IRIS (EPA's Integrated Risk Information System) or other databases; this approach is appropriate and can be captured in a Framework. It was noted that in some cases, information may not be sufficient to make a decision. In response to an observer comment, Dr. Schoeny noted that EPA's work on cumulative risk and the impact of nonchemical stressors can include consideration of sustainability, including economic factors.

Combined Exposures Framework

Dr. Bette Meek of the University of Ottawa made a presentation entitled "WHO IPCS (World Health Organization International Programme on Chemical Safety) Framework: Combined Exposure to Multiple Chemicals." The framework considers the conditions under which it is appropriate to combine chemicals in a risk assessment, and presents a tiered approach for evaluating both the exposure and hazard components. An assessment needs to proceed down the tiering only as far as necessary to set the group aside (as not of concern) or to target it for further assessment and/or management. An international multi-sector multi-stakeholder working group is developing a plan for follow-on work, including additional case studies.

The panel discussed several issues related to the tiered approach. One advantage to tiering is that it allows one to identify and focus on refining the critical determinants for the assessment. Dr. Meek stated that exposure is more discriminating than hazard; the variation in estimates of exposure from the lower to higher tiers is many orders of magnitude greater for exposure than it is for hazard. This means that investment in improved exposure estimates, rather than the continuing (misplaced) focus on hazard, would afford much greater gains in efficiency. A panel member questioned whether the lower tiers (assuming dose additivity) are conservative, since this approach would not account for the potential for greater-than-additive responses. Dr. Meek noted the ILSI/HESI (International Life Sciences Institute/Health and Environmental Sciences Institute) project, which evaluated the literature on synergy at low doses. Based on the few relevant studies, available data indicated that if synergy occurred, the magnitude of the impact was in the range of 3-5 fold. An extra factor could be included at the early tier to account for the potential for synergy. A panel member suggested the human health implications of starting with lower-tier assessments could be evaluated with data-rich chemicals, such as pesticides. One could evaluate the implications of excluding various data sets or analytical approaches from the assessment. The utility of a qualitative uncertainty analysis was also noted.

Tiering for exposure considerations was also discussed. Noting that some exposure estimates are deliberately conservative, and represent exposures to which no individual is actually exposed, a panel member questioned whether such values should be termed exposure estimates. Dr. Meek noted the importance of distinguishing between priority setting (i.e., very crude, semi-quantitative estimates as in Tier 0) and exposure estimation. A panel member noted it would be useful to characterize the usual levels of conservatism resulting from adding together high-end estimates, comparing this approach with a more realistic estimate of the 95th percentile of exposure. With regard to the relevant tier of exposure estimate, Dr. Meek stated that the choice depends on the degree of precision necessitated by the problem formulation. Some understanding of the variability within the population and the critical determinants of outcome (based on qualitative uncertainty analysis) is also important.

Approaches for grouping chemicals were discussed. Dr. Meek noted that a rationale is needed for considering chemicals as part of a group. Typically chemicals are included in a group because co-exposures are expected (taking into account the respective metabolic profiles and half-lives). Unlike the approach in the U.S for pesticides under the Food Quality Protection Act, where grouping is restricted to MOA, grouping in Europe is based on broader similarity

considerations. More thought is needed on the best approaches for grouping. It may make sense to group based on shared target organ or tissue in early tiers.

Case Study Discussions

Four new case studies and one case study proposal/methods introduction were presented. Panel input was sought on the utility of the methods to address specific problem formulations, and on areas for additional development. Inclusion of a method or case study in the framework as an illustration of a useful technique does not imply panel acceptance of the chemical-specific outcome.

Table 1. Workshop IV-Summary of Case Study Discussions

New Case Studies	
Criteria Requirements for Data-Driven Carcinogenicity Mode of Action (MOA) Determinations as Exemplified by Chloroform	**Authored by: Borgert, C.**
This method provides a process and criteria for determining when a MOA has been sufficiently well established in an animal model that it may be applied in the hazard characterization or in determining the low-dose extrapolation approach. A key novel element of the approach is the use of counterfactual data in the weight of evidence (WOE) – evaluating the impact on the endpoint of interest when a key event is interrupted or reversed (e.g., evaluating necrosis and regenerative cell proliferation in a CYP2E1 knockout mouse). The method builds on the existing mode of action/human relevance framework (MOA/HRF) (IPCS, 2007), and provides a second layer of decision making. The MOA/HRF was designed to increase transparency, but did not specify criteria for sufficiency of data for chemical-specific approaches. The panel supported carrying this method forward, as providing a useful approach for weighing data in a consistent fashion with clear criteria. The use of counterfactuals was considered a meaningful addition, and the panel considered it advantageous to conduct such studies when feasible; however, the panel did not think that a counterfactual should be a requirement for demonstrating a MOA. The panel recommended that the case study be published, focused on generalizing from specifics and the utility of the method for enhancing transparency. There were several suggestions for improvement and enhancement of the case study. Panel members suggested that the evaluation be structured in terms of the overall WOE, rather than evaluating one key event at a time, though it is important that the key events in the hypothesized mode of action be clearly articulated at the outset of MOA analysis. Similarly, several panelists emphasized that the counterfactual evidence relates to the WOE for a hypothesized MOA, not for a hypothesized key event. However, two panelists suggested that it is important to look at key events individually, although the focus is on MOA. It was noted that the pattern of results of genotoxicity assays needs to be taken into consideration in interpreting weight of evidence for hypothesized modes of action, including the doses at which effects are seen, rather than as a binary yes/no issue. Interpreting genotoxicity data in the context of MOA analysis requires	

recognition that a mutagenic MOA implies that mutagenicity is an early initiating (key) event. This is distinguished from mutations occurring secondary to other effects, such as cytotoxicity. All of the data need to be arrayed in considering alternative MOAs. It was also suggested that the case study should conclude with the statement that no other sequence of key events is clearly superior as an alternative explanation of the MOA. A panel member stated that this case study is an example of a situation where an alternative assumption or approach is **"**clearly superior" to the default, as intended by NRC (2009)[2].

Panel members suggested some additional analyses that would be of interest. It would be useful to apply the same scheme to a chemical that acts via a clearly mutagenic MOA and to a chemical for which there the data are inconsistent regarding the MOA, in order to show that the results with this method are consistent with expectations for a broader range of chemicals. Structural equation modeling could be used to formally test which of several alternatives are best and evaluate the sensitivity of the model to key assumptions/choices.

Panel members also had several comments regarding the specific case study example. With regard to a threshold for cytotoxicity, it was noted that it is unlikely that a threshold exists for molecular damage, but a minimum level of damage (threshold) is needed to *kill* a cell, and a threshold level of dead cells is needed for compensatory hyperplasia. A quantitative description (model) of the dose-response implications of cytotoxicity and regenerative cell proliferation can provide additional insights beyond those of the qualitative description. Another panel member recommended that alternative hypotheses be analyzed further, such as incorporating duration adjustments when comparing toxicity at 3 weeks and tumor response at 2 years based on the Melnick et al. (1998) paper[3]. Panel members also recommended that the paper recognize the limitation that the chloroform reviews are not fully independent evaluations of the data.

Methods for Deriving Inhalation Effect Levels for Comparison to Health-Protective Values	**Authored by: Grant, R.; Jenkins, A.; Haney, J.**

The purpose of the method is to communicate to risk managers, the public, and other groups the air concentrations associated with effects levels based on available dose-response data and to put into context corresponding health-protective values (e.g., RfC). The presenters noted that the method is in the draft TCEQ guidelines which have been peer reviewed, but that the case study represents the first derivation of effect levels for individual chemicals. Furthermore, TCEQ does not yet have experience in using these values for public communication. The authors also noted that the effect levels should not be interpreted to mean that effects will not occur at lower concentrations, rather that dose-response data showing effects at lower concentrations are not available.

[2] NRC (2009) recommended that EPA adopt an alternative assumption in place of a default "when it determines that the alternative is 'clearly superior', that is, that its plausibility clearly exceeds the plausibility of the default."

[3] The Melnick paper concluded that noncancer toxicity did not preceed tumors in a dose-response comparison, based on comparison of the effect level for noncancer toxicity at 3 weeks and for tumor response at 2 years. The panel member recommended that the 3-week cytotoxicity effect level be divided by an uncertainty factor to extrapolate to chronic exposure prior to comparison with the tumor response data.

The panel supported carrying this method forward as a useful communication tool. Suggestions for improvement included: (1) include a graphic presentation to aid in communication; (2) be clear that the robustness of the effect level for a given chemical depends on that chemical's database; (3) focus groups can be useful for testing the effectiveness of the approach for risk communication; (4) clearly communicate data available and data gaps on potential sensitive groups; and (5) modify the term to something like "known effect level" or "observed effect level," to show the complementarity to safe doses and communicate that effects may occur at lower levels. While some panelists expressed concern about communicating the effect levels in the context of health-protective values, the panel as a whole considered the approach as generally aiding transparency, if done carefully. Panelists emphasized the importance of presenting appropriate context on why the health-protective value is lower, which the authors noted would be in the accompanying narrative. This context includes distinguishing information based on observation from that based on inference or extrapolation; predictive values are based on maximum likelihood estimates, while health-protective values are based on confidence limits. It should be stressed that health-protective values are population-based, not individual-based. It was noted that a useful area of research (not specific to this case study) could be an analysis of what the public thinks about how risk values are derived and what steps in the process account for what issues. Other useful aspects of risk communication to the public include the following concepts: (1) all chemicals are toxic at some dose; (2) the threshold is the lowest dose at which toxicity is observed; (3) health-protective values are designed to protect sensitive populations. With respect to the specific chemical examples, caution was expressed on the level of precision in uncertainty factors. It was also noted that some of the presented information (e.g., 1E-3 cancer risk level) is extrapolated, although wherever possible, human dose-response data from epidemiology studies are used directly.

Development of Screening Tools for the Interpretation of Chemical Biomonitoring Data	**Authored by:** Becker, R.A.; Hays, S.M.; Robison, S; Aylward, L.L.; Kirman, C.R.

The Biomonitoring Equivalent (BE) forward dosimetry method and the Framework for Developing Screening Values to Interpret Human Biomonitoring Data in a Risk Context provide a consistent and scientifically based approach for guiding the development of risk-based benchmarks to enable interpretation of human biomonitoring results in a health risk context. The BE forward dosimetry method converts an applied health standard (e.g., RfD, (NOAEL/AF[4]s), TTC) to an internal biomarker concentration that can then be used as a benchmark to compare to actual human biomonitoring results. Human biomonitoring biomarkers falling below the calculated health standard dose would be considered a low priority as a health concern. The Framework provides a path forward to address not only those substances with extensive toxicity data and solid toxicokinetic methods, but also guides the development of biomonitoring interpretation tools in cases where a substance has limited toxicity data and/ or limited toxicokinetic information.

The panel supported carrying this method forward, noting the strong utility of a tiered approach

[4] Abbreviations: AF = adjustment factor; TTC = threshold of toxicological concern

to BE development. Panel members noted that it is important to define the nature of the range of characteristics of the chemicals on which the class-based approaches are based. The case study authors noted that a number of different approaches are used for the forward dosimetry modeling and toxicokinetic analysis. Depending on the amount and nature of data available, the approaches range from chemical-specific models to class-based or generic 1-compartment models, to mass balance analyses of urinary metabolite, and use of internal dose measure at NOAEL/LOAEL. Sensitivity analyses were conducted on data-rich chemicals to determine the most important parameters. To aid in future work, a panel member recommended that toxicokinetic data be collected as part of toxicity studies in order to build a database that compares internal toxicokinetic biomarkers observed under conditions of animal toxicity (hazard) testing to similar biomarkers obtained from human biomonitoring studies .

The panel discussed a number of issues related to effective risk communication for the method. A key issue is developing simple descriptors for describing the nature of the underlying database for each type of BE (e.g., based on mass balance vs. physiologically-based pharmacokinetic (PBPK) modeling; generic vs. chemical-specific data). As part of the tiered approach, it is important to communicate the degree of conservatism at any particular level of assessment. Panel members stated that increasingly data-informed approaches decrease uncertainty and increase the confidence in the results. The panel noted that this case study method both aids in the interpretation of biomonitoring data, and encourages the risk assessment community to additionally consider- internal dose metrics.

The Human Relevant Potency Threshold: Reducing Uncertainty by Human Calibration of Cumulative Risk Assessments	**Authored by: Borgert, C.**

The Human-Relevant Potency-Threshold (HRPT) method provides a means for determining the dose levels at which it is justifiable, and yet still conservative, to assume the dose addition model of combined action for assessing risks of exposure to chemical mixtures. The evaluation is based on human data for the chemical of interest, or other chemicals or pharmaceuticals sharing an MOA (for example, interacting with the same receptor in the same way). The method compares potency to a benchmark from the human literature to determine whether dose additivity applies for a given exposure.

The panel supported carrying this method forward, as a second tier approach for combined exposures when margins of exposure for common adverse outcomes based on the assumption of dose additivity are inadequate. The case study illustrates an approach for maximally drawing on the available data, including information on chemicals acting via a similar MOA, rather than solely chemical-specific information. It demonstrates how consideration of human data can supplement results of animal studies in determining which exposures should be combined.

The panel made several recommendations for ways to enhance the utility of the case study for illustrating a method. A key aspect is the framing. Using the IPCS combined exposures framework (Meek et al., 2011), the NRC phthalates approach (NRC, 2008) can be thought of as an early tier, with the HRPT complementing the NRC report and exemplifying a later tier. The

case study is useful in bounding the exposures that can be combined realistically, but it would be useful to make the case study more generalizable.

A specific question for the method is what the magnitude of the potency threshold should be, that is, the dose levels (relative to an effect level) above which it is justifiable, and yet still conservative, to assume that dose addition should be applied. The initial case study suggested an HRPT of an order of magnitude for chemicals that meet TEQ criteria for similarity of MOA and structure-activity parameters with the model chemical (finasteride), based on comparable sensitivity of humans and rats to the effects of the model chemical. The case study also suggested that dose addition would be applied to chemicals whose potency is within an order of magnitude of that of the model chemical. Chemicals with lower potency would be assessed based on independent action (i.e., response addition), or by dose addition if the dose of that chemical was within 5-fold of the individual NOAELs/LOAELs. The case study author suggested that this could be evaluated pharmacologically, but he has not yet investigated that issue.

A panel member noted the distinction between science and science policy, observing that EPA has chosen to accept the Safe (1998) criteria for defining toxicity equivalence factors (TEFs). EPA has chosen to define TEFs as applying to all adverse endpoints that act through the same identified MOA; the classic example is for dioxins and dioxin-like compounds. EPA does choose to apply relative potency factor (RPF) when dose additivity is useful, but the Safe criteria are not completely met. An example of this is the application of RPFs for some polycyclic aromatic hydrocarbons only for carcinogenicity by the oral route. EPA does not use the Safe criteria to determine whether dose additivity is an appropriate method for evaluating combined exposure to chemicals. Another panel member noted that combining responses based on common endpoints can be challenging, because most assessments focus on the critical effect occurring at the lowest dose in an animal study, and data on effects on other targets at higher doses are often not available.

Panel members noted that a key challenge of evaluating effects from combined exposures is that it is very difficult to test the potential for an effect to occur when exposures to multiple chemicals, all below their respective effect levels, are combined. Because of the lack of data addressing this issue, it needs to be evaluated from multiple perspectives – including conceptual approaches and data-based approaches. Tiered approaches are useful, recognizing the degree of conservatism at each tier.

A panel member questioned whether dose additivity is truly a health-protective tier one approach, due to a concern about the potential for greater than additive effects at doses below effect levels. Using oxidative stress as a sample effect, the panel discussed the validity of the concern for synergy at doses below effect levels, and whether dose additivity should be applied when chemicals act via different MOAs, but have common effects. It was noted that multiple MOAs can result in decreased levels of reduced glutathione, but that the ultimate response in not determined solely by impacts on levels of reduced glutathione; glutathione re-synthesis rate should also be considered in evaluating the implications of combined exposures. The combined exposures that result in exceeding the re-synthesis rate could be evaluated in a higher tier as

described in Dr Meek's presentation. Panel members observed that it would be useful to have principles for interactions that occur at different levels of organization, focusing at the level of biomarker of effect, rather than at the level of apical effects. The panel noted that it would be useful to apply the approach for effects that are not receptor mediated, to test the generalizability of the approach.

A panel member also recommended that non-chemical stressors be considered. This is part of the problem formulation and consideration in the context of available risk management options.

Value of Information (VOI)	**Authored by: Ruder, E.; Roman, H.**

Value of Information (VOI) was discussed briefly at Workshop III, and the panel had expressed interest in learning more about the concept. The purpose of this presentation was to familiarize the panel with the approach, using some worked examples, rather than presenting a case study ready for inclusion in the *ARA* framework. VOI is a decision analytic framework that can be used to quantify the value of collecting additional information, or improving the data analysis before making a specific decision. VOI is best applied when there are a number of defined options, but substantial information is needed to apply VOI in a quantitative manner.

The panel expressed significant interest in including VOI as a method and future case study in the *ARA* framework. It was noted that, by evaluating the impact on the final decision of collecting additional data, the VOI approach shifts the focus from data collection *per se* to looking at the utility of additional data within the context of risk assessment and risk management.

Panel members had several comments and questions on specific aspects of the approach. With regard to the example on lead (Pb) in the presentation, a panel member noted that changes in VOI are predicated on a decreased value of the dollar with time, rather than the impact on human health; the panel member suggested that it would be useful to look at the impact of regulating earlier from the health benefit perspective. In response to a panelist question, the authors noted that one could conduct a retrospective analysis to validate the model with real-world data, addressing what the value would have been of addressing specific uncertainties for well-studied chemicals or pharmaceuticals. A panel member recommended that the authors explicitly communicate that the approach is a type of "expected value" decision making, which looks at the consequences of expected actions multiplied by probabilities. This approach does not take into account the risk aversion built into many regulatory approaches and agencies. For example, a regulatory action may *on average* have a lower dollar valuation than other potential decisions, but the action may be considered a rational choice in a regulatory context, because it removes (or reduces the probability of) a low-likelihood highly adverse outcome that regulators wish to avoid. To address the risk aversion desired in many regulatory contexts, the panelist asked if the approach can represent branches as distributions instead of single expected values, to facilitate evaluating tradeoffs. The case study authors replied that this could be done if sufficient data are available or if one is confident in the uncertainties.

The panel discussed possible case studies to illustrate the application of VOI. One possibility would be to use VOI to investigate the impact of obtaining refined exposure estimates for a scenario involving exposure to methylmercury from fish caught in waters off of Texas. Data from the case study by Gentry et al. (see http://www.allianceforrisk.org/Workshop/WS3/CaseStudiesWS3.html) could be used to characterize the dose-response for the Texas case study. The Gentry et al. work investigated four different methods for low-dose extrapolation as part of a case study on the use of biomarkers in the benchmark dose method, illustrated by application to methylmercury. A second suggestion for a case study would be to evaluate the VOI generically for conducting a chronic bioassay when a subchronic study is available. A default uncertainty factor of 10 is used to derive an RfD when extrapolation is needed from a subchronic assay, but the average value of the difference in the effect level between subchronic and chronic studies is 3. The VOI analysis could look at the cost of doing a chronic bioassay vs. the impact of having the RfD go up by a factor of 3 on average. Several panel members recommended that a generic, qualitative VOI analysis (such as the uncertainty factor topic) may be more useful than a chemical-specific case. A panel member suggested that it could be of interest to calculate what the stakes (i.e., minimum value added) would have to be in order to make a study worth doing; this could be done as a break-even analysis. It was also suggested that it would be useful to focus testing of the method on general case studies with hypothetical data so the panel can see how the "machine" works.

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