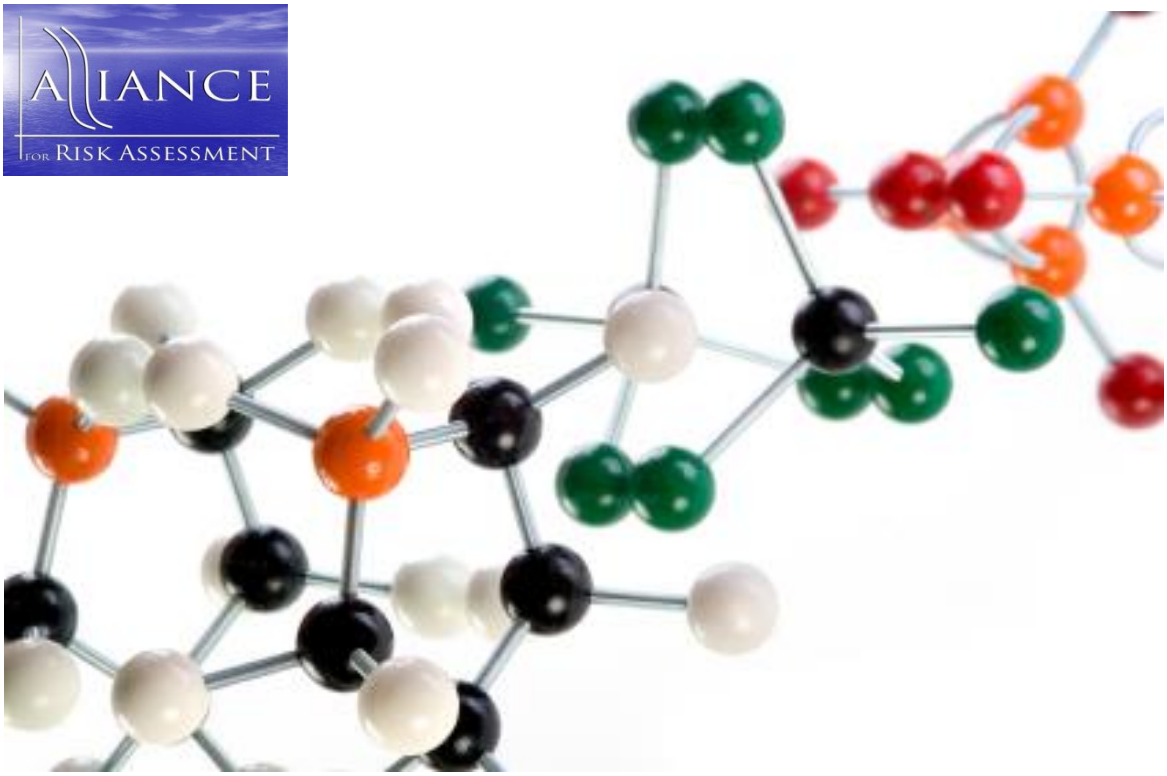


Beyond Science and Decisions:
From Problem Formulation to Dose-Response
Report from Workshop VIII

Workshop Held:
May 21-22, 2014
Austin, TX
Texas Commission on Environmental Quality

FINAL Report Prepared By:
Toxicology Excellence for Risk Assessment (TERA)
Lead Rapporteur and Report Author: Lynne Haber (haber@tera.org)

Supporting Rapporteur: Neeraja Erraguntla

August 18, 2014

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://chemicalriskassessment.org/methods/).

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

Most members of the standing Science Panel chosen by the *ARA* Steering Committee prior to Workshop IV continued their service for Workshop VIII; one individual left and one new member was chosen by the Steering Committee. Panel biographies are provided in Appendix 1, as well as at http://www.allianceforrisk.org/Workshop/Panel.htm. The Science Panel for Workshop VIII consisted of the following, including standing panel members and one *ad hoc* member:

- *Richard Beauchamp, Texas Department of State Health Services*
- *James S. Bus, Exponent, Inc.*
- *Michael L. Dourson, Toxicology Excellence for Risk Assessment*
- *Annie M. Jarabek, U.S. EPA, Office of Research and Development (unable to attend)*
- *R. Jeffrey Lewis, ExxonMobil Biomedical Sciences, Inc.*
- *Bette Meek, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa*
- *Moiz Mumtaz, Agency for Toxic Substances and Disease Registry (ATSDR) (ad hoc)*

- *Gregory Paoli, Risk Sciences International*[1]
- *Alan Stern, New Jersey Dept of Environmental Protection*

Workshop VIII 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 (TCEQ), who hosted the workshop. The workshop included both invited presentation on topics of interest to the Science Panel, and case studies being reviewed by the Science Panel. The workshop was open to the public for both in-person participation and participation via webcast. Public comments were invited at selected times during the workshop. The list of workshop 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.

- Rita Schoeny, U.S. EPA. *Plenary address - National Research Council: Risk Assessment Recommendations: EPA Response*
- Lynne Haber, Toxicology Excellence for Risk Assessment. *Beyond Science and Decisions Dose Response Assessment Framework*
- Gonçalo Gamboa da Costa, National Center for Toxicological Research. *Dose-response assessment of a mixture of melamine and cyanuric acid in rats: practical challenges and outcome.*
- Patricia Nance, Toxicology Excellence for Risk Assessment**.** *Kids and Chemical Safety: Risk Communication Challenges.*
- Nancy Beck, American Chemistry Council. *Understanding Uncertainties and Confidence in Hazard Databases: An Example Using IRIS.*
- Ellen Mihaich, *ER*[2]. *Lessons learned from the U.S. Endocrine Disruptor Screening Programs.*
- Moiz Mumtaz, Agency for Toxic Substances and Disease Registry. *Comparative risk assessment of mixtures in fish.*

Much of the workshop was dedicated to review of case studies. Each review began with a 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 refinement of methods. The following case studies were presented:

- Tiffany Bredfeldt, Texas Commission on Environmental Quality. *Weight of Evidence Approach for Chemicals with Limited Toxicity Data (silanes and siloxanes)*

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

- Ed Pfau, Hull and Associates; Rod Thompson, Alliance for Site Closure. *Practical guidance on the development of a non-cancer hazard range for effective risk assessment and risk management of contaminated sites: A case study with trichloroethylene and other chemicals.*

All presentations are available at http://www.allianceforrisk.org/Workshop/WS8/ws8casestudies.html. With the exception of the keynote talk, the abstracts for all invited talks were provided by the speakers, and the speakers have had the opportunity to review the summary of the discussions after their presentations.

Panel Discussions of Presentations

Keynote Talk: National Research Council Risk Assessment Recommendations: EPA Response, Dr. Rita Schoeny[2]

ABSTRACT:

Four recent major NRC reports addressed risk assessment at EPA. These were Phthalates and Cumulative Risk Assessment; Science and Decisions; Toxicity Testing in the 21st Century; and Exposure Science in the 21st Century. In response to these reports, EPA has developed an action plan that includes: (1) Framework for Human Health Risk Assessment to Inform Decision Making; (2) dose response assessment; (3) cumulative risk assessment; (4) uncertainty and variability assessment; and (5) capacity-building and training. The Framework for Human Health Risk Assessment to Inform Decision Making has been finalized and is available at http://www.epa.gov/raf/files/hhra-framework-final-2014.pdf. It includes an emphasis on planning and scoping, and doing "fit for purpose" assessments. With regard to defaults, technical guidances such as that for benchmark dose modeling have been updated to create improved default methods. Guidance and practices have been made more transparent about choices in analyses (including documenting assumptions) and the use of defaults. EPA regions have been using site specific information, when available, instead of defaults in exposure models. The use of mode of action (MOA)/adverse outcome pathways (AOPs) is now considered central to risk assessment at EPA. Work is ongoing on other issues, such as addressing prenatal exposures to carcinogens, unified dose-response, cumulative risk assessment, and addressing defaults.

DISCUSSION:

In response to a question from a member of the audience, Dr. Schoeny noted that the IRIS program and related processes are subjects of active discussion within EPA. Updates are posted on the IRIS web site. A major change is the initiation of meetings on broader-ranging topics (e.g., mouse lung tumors), not just on individual chemicals. IRIS now holds bimonthly meetings to increase transparency and opportunities for input. Another broad topic being addressed is

[2] The rapporteur's summary is provided, since no abstract was provided for Dr. Schoeny's talk.

additivity to background exposures. Vince Cogliano is the contact for specific changes to IRIS. In response to another question, Dr. Schoeny stated that the Human Health Risk Assessment strategy meeting that was taking place within EPA at the same time as the workshop was considering how dose-response is part of evaluation of causality. EPA scientists are doing work breaking adverse outcome pathways (AOPs) into steps, to aid in modeling and to improve the dose response assessment in support of quantitative cost-benefit analyses. In response to a question about how the Alliance for Risk Assessment can help EPA, Dr. Schoeny noted that the workshop series is providing useful input to the EPA process. Input to IRIS bimonthly meetings and EPA workshops would also be useful, as would publishing of additional case studies.

Beyond Science and Decisions Dose Response Assessment Framework, Dr. Lynne Haber

ABSTRACT:

The dose-response workshop series has resulted in the review of more than 30 case study methods. To aid in organizing the methods, and to make the methods and key information available to risk assessors, the case studies have been organized into a broader framework, http://www.chemicalriskassessment.org , also available on NLM's Enviro-Health Links http://sis.nlm.nih.gov/enviro/toxweblinks.html (see Associations). An open access manuscript describing the workshop series and pointing to the framework has also been published (Meek et al., 2013). The framework has been enhanced to make it more user-friendly and easier to browse the content by topic. Features include search capability, an overview synopsis of each method highlighting key information, and automatic translation to French, Spanish, German, and Mandarin Chinese.

DISCUSSION:

There were no comments or questions.

Dose-response assessment of a mixture of melamine and cyanuric acid in rats: practical challenges and outcome, Dr. Gonçalo Gamboa da Costa

ABSTRACT:

In 2007, the intentional adulteration of pet food ingredients with melamine and a number of its derivatives, including cyanuric acid, caused kidney failure and death of hundreds of cats and dogs in the USA. While a body of experimental evidence indicated that neither melamine nor cyanuric acid alone posed a significant toxicological risk in a number of animal species, further investigation revealed that co-exposure to these compounds can elicit nephrotoxicity due to the formation of highly insoluble melamine cyanurate crystals in the nephrons. In response to these events, and later events in China in 2008 involving the contamination of infant formula with melamine, it became apparent to regulatory agencies, including the US Food and Drug Administration (FDA), that further in-depth studies addressing the toxicity of melamine,

cyanuric acid, and their combination were warranted. We report the design and experimental challenges of a tiered series of dose-response studies conducted at the FDA on the combined toxicity of melamine and cyanuric acid, and critically discuss the results in light of low-level background exposure and food adulteration scenarios.

DISCUSSION:

Panel members commented on the unusual result that the toxicity of melamine plus cyanuric acid is 100-fold higher than that of melamine alone. Dr. Gamboa da Costa explained that the toxicity results from a physical effect, the crystallization of the melamine cynurate complex in the nephrons. There are some other cases of strong greater-than-additive responses, but in those cases the interaction is much smaller than for cyanuric acid/melamine (i.e., typically a few-fold). Another panel member noted that one of the first mode of action (MOA) analyses was about damage from crystallization illustrated by the case example of melamine, where a difference between rodents and humans related to key events was noted. The panel member wondered whether the interaction could have been predicted, based on the understanding of the MOA. Furthermore, in light of the physiological/anatomical differences between experimental animals and humans (different urine pH; horizontal vs. vertical anatomy), is it possible to predict the relative sensitivity in humans vs. rodents to the combined exposure? Finally, because it was not possible to quantitate the interspecies difference for melamine exposure alone at the time of the original MOA evaluation, it would be useful to go back to the earlier MOA analysis and determine whether the data are now adequate to characterize the quantitative dose-response implications associated with this potential MOA in humans. It was noted that asbestos (which has a physical MOA) and smoking also have a larger synergistic effect. Since most cases of a greater than additive response have a much smaller response (~4-5x effect), these cases suggest that physical MOAs may be more likely to have large synergistic response than other MOAs.

A panel member asked whether it would be possible to predict the level at which effects would be expected to occur in humans from the combined exposure to melamine and cyanuric acid, based on the physical differences between animals and humans. Dr. Gamboa da Costa replied that the literature indicates that the NOAEL values for a co-exposure to melamine and cyanuric acid seem to be well conserved across species, from fish to rodents and pigs, and it is thus reasonable to expect that these values should translate well to humans too. Dr. Gamboa da Costa further noted that it was fortunate that the China incident involved children exposed to clean melamine, because the highest dose that the children received was several times higher than a near-lethal dose of the melamine:cyanuric acid mixture in rats.

Kids and Chemical Safety: Risk Communication Challenges, Ms. Patricia Nance

ABSTRACT:

Kids + Chemical Safety is a website (www.KidsChemicalSafety.org) for scientific outreach to parents that strives to provide up-to-date health information on chemical hazards and safe use of chemicals around children. Children's exposure to chemicals in their environment and the

possible effects of these chemicals on childhood growth and development is a paramount social concern. A key challenge in developing this website is to rapidly communicate independent, scientifically accurate information. The communication needs to be understandable and applicable to a broad user audience. Other similar websites are available, but they tend to not provide the needed information in a clear and concise manner. The media also create challenges communicating the science to the public, due to the rapidity of the news cycle and the focus of the news cycle on human health scares. Together, these factors can result in poor communication of the underlying science. With today's social media frenzy, bloggers can spread unbalanced and biased stories to stir up controversy. We have developed an approach to reduce these challenges, enabling us to provide accurate and unbiased scientific information to the public by developing a collaboration among diverse organizations (Cincinnati Drug & Poison Control Center, Harvard Superfund Research Program, and NSF International), conducting basic community outreach and establishing media relations. Website content is reviewed by collaborating team members prior to posting, to ensure the website provides balanced and unbiased information.

DISCUSSION:

In response to questions from panel members, Ms. Nance noted that the collaborators are working on outreach to additional poison control centers, including involvement with the Association of Poison Control Centers, and efforts are underway to have additional poison control centers join the collaborating group. The group has also done informal outreach to the National Library Medicine (NLM), but no formal effort has been made yet. An audience member noted that the NLM has information geared to the general public that could be a resource. Others suggested that pediatricians and obstetricians/gynecologists could be enlisted to provide this information to the parents they serve, and collaboration with the National Institutes of Environmental Health Sciences (NIEHS) would also be useful.

Understanding Uncertainties and Confidence in Hazard Databases: An Example Using IRIS, Dr. Nancy Beck

ABSTRACT:

Hazard and risk assessment programs often provide a single estimate as a final work product. These point estimates of human health hazard/risk associated with environmental exposures are regularly used by risk managers in regulatory decision-making in setting standards, determining emissions controls, setting occupational standards, and mitigating exposures to pollutants both nationally and internationally. Methodologies used to derive these point estimates vary, and may rely on upper bound or worst case assumptions. Additionally, transparency in the attendant uncertainties of the components of these assessments and how they impact the estimates is often limited, particularly in the summary information that is provided. Thus risk assessors, risk managers and stakeholders are often challenged to understand and communicate all of the assumptions and uncertainties embedded in a hazard characterization. Increased transparency

and communication can help to fully convey the plausible range of risk estimates to risk managers.

This talk presented four distinct and independent approaches that could be used to improve the transparency and clarity related to the way in which uncertainties and confidence are presented in hazard databases. Using IRIS as an example, and recognizing that there is no 'right' way to communicate this type of information, the four approaches provide a diverse set of options for improving the presentation of information in IRIS or other hazard summaries. These methods use a variety of tabular and graphical approaches to describe different aspects of uncertainty and variability in the assessments.

DISCUSSION

Panel members expressed appreciation for the range of communication tools, noting that different tools and different levels of detail will be needed for different audiences (e.g., one tool for the public and one for communicating with risk assessors). One panel member suggested it would be useful to put cancer and noncancer assessments together on the same arrow graph. Another panel member commented that one method used at the Texas Department of State Health Services is a "thermometer diagram" superimposed on a human figure. The numerical scale would represent concentrations (or dose) and points along the scale could be labeled with adverse health effects seen at those levels of exposure. Dr. Beck noted that the team had initially used red, yellow, and green, but risk communicators said that such color-coding communicates bright line distinctions and are problematic for people who are color-blind.

One panel member who is involved in the project described by Dr. Beck noted some key aspects of the final method (see Figure 1, below, summarizing EPA's acrylamide assessment on IRIS; Table 1, providing a detailed analysis of the IRIS acrylamide assessment; and the summary of confidence and importance of the decisions in Table 2). The panel member noted that these key aspects were proposed to more robustly capture the true uncertainty and variability in the assessment, rather than relying on the "bright line" RfD construct. The RfD construct is a default approach based on the nature of the dose-response and hazard data that have been collected historically in animal studies. This approach also highlights important information that is often not reported in assessments (e.g., some elements have not been explicitly addressed in the IRIS assessment used as a case study). The uncertainty or range of variability bars capture the concept that some elements are more important than others. This approach allows one to identify uncertainties in the hazard part of the assessment, and increases transparency to aid in identifying which factors are the most important. It could easily be extended to exposure but this would take some thought and would permit consideration of relative uncertainty/variability across both hazard and exposure. A key issue is the degree of confidence in how well the animal model represents what is happening in humans, an issue that is not well addressed with standard default uncertainty factors. Another panel member noted that some of the range in Figure 1 refers to the degree of protectiveness, not only confidence. If one wanted to be absolutely certain that all of the population is covered, one might always choose an extreme value for the intraspecies uncertainty factor. This panelist recommended that uncertainty and discretion be differentiated in the communication tools; discretion is currently labeled as science policy. Additional discussion among the project participants is needed regarding the scaling and the

choice of the value used for normalizing (i.e., the "1" in Figure 1). Although Figure 1 shows the direction of conservatism, it was noted that the inconsistency of this direction could be confusing. The project team is also considering using color coding to differentiate science-based from policy-based decisions. An audience member stated that the presentation in Figure 1 and the shading approach are useful for public communication, and recommended that such tools also be included in documents aimed at risk assessors, such as on IRIS.

A panel member noted that a standardized approach for communication will be useful. The panelist also suggested that rather than only subjecting the risk assessment to peer review, it would be useful to have peer review of the communication tools. Dr. Beck stated that the project team is aiming to publish their work by the end of the year. The final product could be brought back to the Dose-Response workshop next year. The project team also plans to present the work at the Society of Toxicology (SOT) and Society for Risk Analysis (SRA) annual meetings. In response to a question about comparing risk values from different organizations, Dr. Beck noted that risk values from multiple organizations are presented on ITER (https://iter.ctc.com/publicURL/pub_search_list.cfm) or http://toxnet.nlm.nih.gov/). The project did include a comparison of risk values from different organizations, and one team member is looking at differences in the underlying decision points.

Lessons learned from the U.S. Endocrine Disruptor Screening Programs, Dr. Ellen Mihaich

ABSTRACT:

Fifty-two chemicals were recently screened using some or all of the 11 US EPA Endocrine Disruptor Screening Program (EDSP) Tier 1 assays and the data have been submitted to the EPA for review. EDSP Tier 1 was designed as a battery of screens to identify the potential of a chemical to interact with the estrogen, androgen, thyroid, and steroidogenic pathways. Tier 2 tests are then used to identify and characterize adverse effects on reproductive function and development and the exposures required to produce them. EDSP Tier 1 was supposed to be rapid and inexpensive but it was neither. Taking over 2 years to complete at a cost of $175,000 to $1 million per chemical, the EDSP Tier 1 screens are resource intensive and many of them are challenging to perform and interpret. Given the completion of the screening of the first list of chemicals and the availability of a significant amount of data on the performance of the screens, over 240 scientists participated in a workshop on the EDSP in April 2013 (http://www.altex.ch/resources/WR_Juberg_epub.pdf) to share scientific learnings and experiences with the EDSP and identify opportunities to inform ongoing and future efforts to evaluate the endocrine disruption potential of chemicals. In addition, the FIFRA Scientific Advisory Panel held 4 meetings in 2013 to review progress and results from the US EPA programs, including their work with prioritization, Tier 1 screens, Tier 2 tests, and weight of evidence (WoE) (http://www.epa.gov/scipoly/sap/meetings/2013/index.html).

Concerning the conduct and performance of the 11 Tier 1 assays, many challenges in conducting the assays have been noted. Solutions developed by the laboratories, as well as issues relevant to data interpretation were proposed at both the workshop and during the SAPs. For example,

experience has shown that appropriate dose-setting is key, as overt toxicity may overwhelm normal physiological function, thus confounding the interpretation of the response. Another challenge is how to apply relevant information from the current Tier 1 battery to identify potential modes of action. A transparent, consistent, and quantitative weight of evidence (WoE) assessment for evaluating potential interactions with endocrine pathways was identified as a key step in the process (e.g. Borgert et al. 2011 Reg Tox Pharm 61:185; Borgert et al., 2014, Birth Defects Res, Part B, 10:90). Presentations and discussions at both the workshop and the SAP explored the development of a systematic evaluation of existing data prior to implementation of Tier 2 testing, and the application of alternative and/or supplemental data to replace Tier 1 assays. Perspectives on the future of endocrine screening, including *in vitro* high-throughput analyses, toxicity pathways, and prediction models were given at both venues. A number of common themes emerged from the extensive discussions, including that a critical review and update of current Tier 1 screening guidelines is needed, reducing the number of animals used in testing should be a goal, and the use of a robust WoE approach to align available Tier 1 data with potency and exposure information to better inform decisions on Tier 2 testing is needed. Alternative high-throughput methods and adverse outcome pathway development were seen as promising tools providing that the methodology is transparent and systematic, and that they are fit for their intended purpose.

DISCUSSION:

In a response to a panelist question, Dr. Mihaich stated that the registrant (for pesticides and some drinking water contaminants) is responsible for testing chemicals found in drinking water. A challenge is that there are a number of chemicals present in drinking water that are "orphans," i.e., they are no longer being produced. It appears that EPA is not doing testing for the orphans. In response to another panelist question, Dr. Mihaich stated that some natural chemicals would be considered endocrine disruptors using the screening approach; dose is important. Another panel member noted that dosimetry and dose selection are also important, and that doses tested should be considered in the context of human exposures. This recognition has been institutionalized for some Tier 2 tests. For example, the Organization for Economic Cooperation and Development (OECD) guideline for the Extended One-generation Reproduction Study now states that testing does not need to be done in dose ranges where toxicokinetics is nonlinear and doses are well above human exposure. The default highest concentration tested in the in vitro EDSP tests is 1 mM, but if toxicokinetic studies are available in animal toxicity studies, the highest dose (concentration) can be limited to the inflection point for in vivo nonlinear toxicokinetics. Another panel member asked about discussion at the workshop regarding using 1000x the human serum levels in the National Health and Nutrition Examination Survey (NHANES) as the top dose for in vitro testing, but Dr. Mihaich did not recall additional details. Dr. Mihaich also noted that the fish Tier 1 assay had been suggested as a "gatekeeper assay," together with the rat Tier 1 assay as a screening assay for endocrine activity. (In other words, this proposal suggests that limiting EDSP screening solely to the fish and male rat "gatekeeper" studies would adequately identify endocrine disruption potential, and other screening tests may not be necessary.) Both tests appear to include sensitive indicators of endocrine activity, e.g., vitellogenin in fish. A panel member noted that the Tier 1 assays are being used in developing

Quantitative Structure Activity Relationships (QSARs) and in evaluating AOPs for priority setting and reducing the amount of testing needed.

Comparative risk assessment of mixtures in fish, Dr. Moiz Mumtaz and Dr. Michael Dourson

ABSTRACT:

People living on the Faroe Islands are exposed to a unique combination of toxic chemicals, seafood being their main food source. Fish and pilot whale consumption constitutes 44% and 9.5% of their daily meals, respectively. These types of seafood are not only contaminated with methyl mercury, but also with polychlorinated biphenyls (PCBs) and dichlorodiphenyl-trichloroethane (DDT). The Faroese population has been studied extensively and several studies have been published on developmental neurobehavioral effects in children born to mothers living on these islands. The U.S. EPA has established individual risk values, reference doses (RfDs), for exposures to methyl mercury, PCBs or DDT. However, the Faroese population is co-exposed to these three chemicals in their diet. The U.S. EPA's current guidance for mixtures risk assessment recommend three approaches, that is, the component based, target organ toxicity dose (TTD), or the whole mixture approach (U.S. EPA, 2000). The goal of this project was to see if the published data lend themselves to derivation of a 3-component mixture RfD through the development of target organ toxicity doses (TTDs). We used all three approaches to derive safe levels for the combined exposure. The results of this analysis indicate that it is important to estimate a combined exposure-based RfD for the critical effect. Neurobehavioral toxicity has been studied in this population as a critical effect i.e. the most sensitive effect. Our analysis shows that immunotoxicity might actually be its critical effect. Additional data are needed to confirm these findings. The determination of immunotoxicity for this mixture will become even more important as the levels of these contaminants start going down as a consequence of advisories and restrictions in seafood intake of this population.

DISCUSSION:

Dr. Mumtaz noted that there is now a pilot whale consumption advisory, so population exposures are going down. In response to a panelist question, Dr. Mumtaz stated that the approach of acceptable exposure levels being based on the target organ or system is an initial screening approach; if health concerns are found, a more refined approach can be used. Consistent with the EPA methods and WHO framework, the chemicals are grouped together based on the nature of effects; an assumption of common MOA is not needed. This approach can allow one to identify the key drivers for exposure and toxicity. In this case, blubber is identified as the key driver of exposure, and therefore of risk. In general, the TTD approach characterizes the risk better than the approach of ignoring a chemical if no RfD exists, although RfDs exist for all of the chemicals in the current case example. Meek et al. (2011) describe a tiered approach to combined exposures that can aid in addressing the issue. Dr. Meek stated that that tiered assessments are useful when sorting large numbers of chemicals. Such assessments do not need to be based on MOA, but a rationale does need to be provided for why chemicals are grouped together (e.g., based on common target organ, chemical similarity, or other reasons). One approaches the

problem by doing just enough analysis to support a risk management decision or to set the exposure aside as not being an issue. Crude sensitivity analyses can be useful in determining what is driving the assessment, and therefore where data gathering should be focused. The assessment described by Dr. Mumtaz presents a nice example of proactive assessment based on limited data

Dr. Dourson noted that one lesson from the analysis is that the controversy of whether to use the data from either the Faroe Islands or Seychelles for the determination of a methyl mercury RfD is misguided. These are two different studies investigating two different exposure scenarios. For the Faroe Island children, exposure to PCBs in pilot whale blubber was driving the neurological effects. In response to a suggestion from a member of the audience that some of the observed effects could have been related to a unique genetic profile in a small population, Dr. Mumtaz noted that the effects did reverse as exposure went down. Dr. Dourson also noted that the studies on the Faroes population primarily focused on neurological effects, but the highest hazard index was for immune effects, so investigators may not have analyzed the most sensitive endpoint.

Case Study Discussions

Two new case studies 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. All case study presentations are available at http://www.allianceforrisk.org/Workshop/WS8/ws8casestudies.html.

Table 1. Workshop VIII-Summary of Case Study Discussions

New Case Studies	
Case Study: Weight of Evidence Approach for Chemicals with Limited Toxicity Data (silanes and siloxanes)	**Authored by: Tiffany Bredfeldt, Jong-Song Lee, Ross Jones, Roberta Grant**
During the air permit review process, the Toxicology Division (TD) from the Texas Commission of Environmental Quality (TCEQ) frequently generates an effects screening value (ESL) for chemicals with limited toxicity data (LTD chemicals) in order to regulate those chemicals. This case study presents a systematic approach and framework for choosing among several different approaches for deriving an ESL for LTD chemicals. Possible approaches include the use of surrogates, a category approach such as threshold of concern (TOC), a threshold of regulation approach, NOAEL-to-LC_{50} (N:L) ratio, route-to-route extrapolation, and relative toxicity/potency. The panel supported carrying this method forward into the framework, and recommended that the authors publish the method in a peer-reviewed journal. They supported the idea of tiering to match the strengths and limitations of the available data and to identify what additional data would be needed to move to a different tier. Using this weight of evidence approach could assist in more clearly explaining the nature of the data and approach upon which an ESL is based.	

Because TCEQ does not have the option of *not* developing an ESL, it is important to have an approach for dealing with chemicals with limited toxicity data; the issue is how to choose the best approach using what is now available. A panelist noted that it is important to clarify that because an ESL must be developed, the approach addresses comparative strengths and weaknesses among the methods, not the strengths and weaknesses of a specific data set with regard to whether the data are adequate to develop an ESL.

The TCEQ approach is labeled as a weight of evidence (WOE) approach, but panelists questioned the use of the WOE term, noting that it is used and defined in many different ways and its use here may impede communication. These panelists suggested that if the WOE term is retained, then TCEQ should more clearly define what is meant by the term in this context; "comparative weight of evidence" may be a better description. More explicit use of the modified Bradford Hill criteria (and description of how the criteria are used), rather than the use of the term "WOE," would be useful.

The authors noted that the results of the more data-poor methods to derive generic ESLs are meant to be conservative. The ESL program itself is a screening program that purposely uses conservative approaches; further evaluation is conducted if exceedances are found. A panelist suggested testing the approach by selectively removing data from data-rich chemical sets, and then running the limited data through the framework to see how well it predicts the known toxicity. This may provide a quantitative estimate of the degree of conservatism that is inherent in the specific methods. It may be useful to do this analysis separately for chemicals that act at the portal of entry and for systemic toxicants.

The authors noted that under the TCEQ guidelines, a company can conduct additional toxicity testing if it chooses and can even derive its own ESL if there is only an interim ESL available. Panel members suggest that it would be helpful to show how new toxicology studies can be used might supplant LTD approaches. Panelists suggested that if additional toxicity testing is conducted, that over time there might be sufficient data to develop a generic tier-based hierarchy of chemical tests. By identifying the most important drivers of the ESLs, this hierarchy could indicate the most important tests to conduct to refine the ESL; a similar approach has been used to develop targeted testing strategies for occupational exposure limits. It was also suggested that data gaps be explicitly identified.

Additional suggestions to improve transparency were suggested. It is not clear how the adequacy of health protectiveness is weighed in the evaluation. The method documentation should also explain the nature of any reality checks that TCEQ does on its analysis. Panelists found the term N:L ratio confusing, since many thought it meant NOAEL:LOAEL ratio. Panelists recommended that a different term or the full phrase be used, and that the method clarify how and whether additional extrapolations and adjustments (e.g., animal:human, human variability) are considered in the adjustment factor used. Although the N:L ratio is a published methodology, the method for the case study needs to be understandable as a stand-alone document. It would also be useful for the method documentation to describe the nature of the data that are being relied on for each approach. Furthermore, it would be useful to document the rules of thumb that are being identified as experience is gained with applying the systematic

framework. Communication with other groups using a TOC-type approach (also known as threshold of toxicological concern – TTC) for the inhalation route would be useful. Panelists suggested including a discussion of how exposures to multiple chemicals are considered within the approach.

Practical guidance on the development of a non-cancer hazard range for effective risk assessment and risk management of contaminated sites: A case study with trichloroethylene and other chemicals	**Authored by: Ed Pfau, Rod Thompson, Bernard Gadagbui, David Gillay, John Lowe** **Panel Advisor: Michael Dourson**

Within the process of chemical risk assessment, risk characterization of non-cancer endpoints lacks an established method to account for the uncertainties associated with a point value estimate of the non-cancer hazard. The purpose of the case study is to describe such a method, establishing a hazard range by defining floor, midpoint and ceiling values.

The panel concluded that the case study method addressed a clear risk assessment need, but saw the current method as a work in progress and recommended that the guidance be further developed before including it on the ARA dose response framework. Panelists thought that the method has value in that it contributes to better communicating what the RfD[3] is based on, and the potential range of variability associated with an otherwise brightline value. The authors of the case study partially deconstructed the RfDs using their best scientific judgment; the result of their analysis is useful for communicating to risk managers that the range varies by chemical. The panel recommended a number of areas for revision and further development. A more systematic approach to deconstruction of the RfD is needed, rather than presuming the RfD is the floor of the range. Panel members recommended connecting this case study approach to one of the methods presented by Nancy Beck in the previous day of the workshop, which describes how values or approaches chosen for key decision points in an RfD assessment relate to the overall range of uncertainty for that decision element (Figure 1). This would allow the authors to systematically deconstruct the RfD and identify its key elements. In other words, the approach would evaluate the uncertainty and variability related to each element, and consider how that uncertainty and variability quantitatively affect the final RfD. A better understanding of the RfD is obtained by decoupling uncertainty and variability, and describing the uncertainty related to variability (e.g., the uncertainty in describing human variability, and the variability in estimates of human variability – i.e., range of the relevant parameter estimates). This sort of approach has been used with great success in the physiologically-based pharamacokinetic (PBPK) modeling community to conduct sensitivity analyses and determine which parameters in models are key drivers; further model refinements can then focus on those key parameters. It is also important to increase the transparency regarding what are science policy decisions vs. what are science-based judgments. Finally, it would be useful to have a template for the approach to aid in systematic analysis and transparency.

The panel discussed whether the problem formulation for this method appropriately describes the

[3] The term RfD is used generically here, to also include RfCs and risk values developed by other agencies.

real world situation and if a hazard range (i.e., a range focusing on the hazard characterization and dose-response portions of the risk paradigm) is helpful. Panel members suggested that the approach is overly narrow by focusing on the RfD alone and not also addressing uncertainty in the exposure estimate. An author agreed that it would be useful to address exposure for scenarios where a specific population is being evaluated. However, for long-term remediation objectives, screening level exposure equations and default assumptions generally are used, and those exposure estimates (when compared with brightline RfDs) become the drivers for closure decisions. For the TCE example, the author group has chosen to address the toxicity evaluation first, but their ultimate goal is to address exposure as well. Emphasizing the importance of uncertainty in exposure, a panelist noted that exposure is often more discriminating than hazard. In other words, as assessments are refined from lower tier to higher tier analyses, the exposure estimate tends to change much more than the toxicity value does. Another panelist noted that it is useful to determine whether the people who are most sensitive toxicologically are also the most heavily exposed. Typical assessments may assume that the 99^{th} percentile exposed individual is also the most sensitive, which can lead to unreasonable compounding conservatism; it is unlikely that both parts will be at extremes at the same time.

While this case study draws an analogy to the 10^{-4} to 10^{-6} cancer risk range commonly used in the US for site cleanup decisions, the method does not provide probabilities of risk, but only speaks to qualitative certainty or confidence that a concentration or dose will be protective. A panel member observed that this approach is helpful for risk management, but it is not something that could be used for cost-benefit analyses, as envisioned by NAS (2009). That committee had envisioned a probabilistic approach that would allow quantification of risk and associated uncertainty bounds, in a manner similar to the Hattis method (see next paragraph). Use of chemical-specific adjustment factors/data-derived extrapolation factors (CSAFs/DDEFs) based on a probabilistic analysis of the components of uncertainty would also provide a sense of the portion of the population that would be protected.

The Hattis strawman case study presented by Dale Hattis, Meghan Lynch and Sue Greco at the May 2011 workshop (see http://www.allianceforrisk.org/Workshop/WS3/CaseStudiesWS3.html) discussed a probabilistic definition of the RfD that may be relevant to the current case study. In that case study, Hattis and colleagues used information on the distributions underlying uncertainty factors to characterize the level of population protection associated with RfD values, and the degree of confidence in that level of protection. The issue of how much of a population is protected is a key part of the discussion. It is also important to differentiate what is happening at the ceiling - are more people affected or are the toxic effects more serious?

A panel member expressed additional concerns that the RfD is a blunt instrument intended to get the population into a safe area of exposure. An important area of uncertainty is that concordance of effects between animals and humans cannot be assumed, and this needs to be recognized in these approaches. However, mode of action information is often helpful as a basis to identify relevant critical effects in humans and/or degree of uncertainty in the relevance of the animal model.

The panel asked how the range captures the level of confidence in the critical effect, noting the

importance of risk managers understanding any relevant controversies and uncertainties related to the choice of a critical effect. A panel member suggested that for the TCE example, low confidence in the critical effect for the study used for the ceiling might suggest the need for a larger ceiling:floor ratio. The authors noted that there was a desire for the generic method to follow a defined approach, but for the TCE case study, this issue was addressed by using the studies with higher confidence as the basis of the floor and midpoints, and then using the lower-confidence study for the ceiling.

Panel members had several thoughts on what would be an adequate scientific basis for a hazard range for non-cancer endpoints. One thought that the range should transparently reflect confidence in the critical study, and that the contradictions in the underlying body of science should be captured and communicated to the risk manager. Another suggested that, rather than thinking in terms of a range, one should identify the two to three critical elements that are most important in describing uncertainty and variability, and develop a range for each of those factors. Sensitivity analyses can help to identify those elements in a transparent manner, and they can be communicated using a graphic such as the slider bars in Figure 1.

The imprecision of the RfD as defined by EPA was discussed. In particular, the panel addressed the meaning of "an estimate (with uncertainty spanning perhaps an order of magnitude…,". A panel member involved in the initial EPA definition discussions explained that the EPA definition of an RfD was written in the 1980s by a committee. The phrase was designed to convey that the imprecision around the RfD is on either side of the RfD, but the uncertainty is nearly all above the RfD, since each uncertainty factor is protective from the perspective of the behavior of the average chemical, and use of multiple uncertainty factors compounds this protectiveness. A panel member noted that there are several wiggle words in the RfD definition ("likely to be without appreciable risk of deleterious effect..."). It would be useful to define those terms, to clarify which terms change if the RfD is changed.

Panel members noted that the human variability uncertainty factor is intended to capture both human variability and the existence of sensitive subpopulations, but does not protect *all* individuals (e.g., those who have idiosyncratic responses or exposures/habits, such as a pica child). However, when one has a bimodal population distribution, it is important to make sure that the uncertainty factor captures the full population distribution, rather than just using a factor from the literature that describes the primary part of the distribution. Panel members noted that efforts are underway to try to quantitate the portion of the population protected by RfDs. It would also be useful to ground truth the degree of uncertainty associated with RfDs by looking at robust human data sets and pharmaceutical data sets. For example, Bruce Naumann and others have used pharmaceutical data to identify distributions of interspecies uncertainty factors, and Michael Dourson and colleagues have compared RfDs based on animal data with those based on human data as part of ground truthing extrapolations. Acquiring pharmaceutical data for such analyses has been a challenge in the past, but recent collaboration between the pharmaceutical and environmental chemical communities (such as for ToxCast^{TM}) suggest future similar collaborations may be fruitful.

There was considerable discussion about the purpose and utility of the "midpoint." It was

suggested that "midpoint" may not be an appropriately descriptive term. A panel member suggested that the "midpoint" is really intended as a best estimate, or "best judgment value." The authors noted that they have considered other terms, including "intermediate value." The authors' intent for the "midpoint" was to identify a value that will protect sensitive populations, based upon greater understanding of the relevant uncertainty factors. An audience member countered that the midpoint, as applied by the authors, may be a concentration that protects the general population, but sensitive populations may not be protected. This audience member suggested that, based on the approach used, the midpoint is not a middle or best estimate of the RfD, but an estimate of the exposure at which one expects to begin seeing effects in people – an "effect level." If the desire is to identify an effect level, TCEQ has developed a method for estimating such an exposure (TCEQ, 2012), but the TCEQ approach is less conservative than the "ceiling" approach in the case study. The approach used by TCEQ does include dosimetric adjustments, but not a subchronic to chronic uncertainty factor or other uncertainty factors. The authors responded that the midpoint is intended to protect sensitive subpopulations, based on a refinement of the point of departure and uncertainty factors to provide a central tendency estimate (rather than a conservative estimate) of the safe dose.

An audience member suggested that when greater uncertainty exists, one would want the "midpoint" to be closer to the RfD, rather than farther from the RfD. The authors replied that greater uncertainty in the RfD tends to mean a larger total uncertainty factor, which would mean there is already a larger range between the floor and the ceiling. Regardless of the term used, it is important to clearly communicate that the value is a judgment. In light of the overall recommended changes, the panel did not discuss the specifics of the method for identifying the midpoint/intermediate value.

With regard to the ceiling, the authors clarified an error in the case study summary – the calculation of the ceiling does *not* include the uncertainty factor for human variability. The range (ratio) between the floor and ceiling differs among the case study chemicals, although it is 100 for most of the case study chemicals. A member of the audience suggested it would be useful to report the ratio of ceiling:floor and intermediate value to floor, to aid in comparing chemicals. A panel member noted that the case study method does not set all parameters to the extremes, suggesting that the "floor" and "ceiling" are not bright line values. Instead, the edges can be considered fuzzy (as in Figure 1**).**

As a broader overall recommendation, a panel member suggested that both this method and the method described by Nancy Beck would benefit from cognitive research into the mental models of the RfD developer and the risk manager. This would help in understanding what each is trying to achieve and where there may be misunderstandings in meaning. Part of the challenge in problem formulation is increasing understanding of risk managers of the constraints on communicating risk due to limitations of available dose-response methods.

References

ARA (Alliance for Risk Assessment). (2012). ARA Dose-Response Framework, Draft. Phase I: Problem Formulation and Scoping. Available online at: http://chemicalriskassessment.org/methods/.

Borgert, C.J., E.M. Mihaich, L.S. Ortego, K.S. Bentley, C.M. Holmes, S.L. Levine, R.A. Becker. 2011. Hypothesis-driven weight of evidence framework for evaluating data within the US EPA's Endocrine Disruptor Screening Program. Reg Toxicoland Pharmacol, Volume 61, Issue 2, November 2011, Pages 185-191

Borgert, C.J. L.D. Stuchal, E.M. Mihaich, R.A. Becker, K.S. Bentley, J. M. Brausch, K. Coady, D.R. Geter, E. Gordon, P.D. Guiney, F. Hess, C.M. Holmes, M.J. LeBaron, S. Levine, S. Marty, S. Mukhi, B.H. Neal, L.S. Ortego, D.A. Saltmiras, S. Snajdr, J. Staveley and A. Tobia. 2014. Relevance Weighting of Tier 1 Endocrine Screening Endpoints by Rank Order. Birth Def Res. Part B. Volume 101, Issue 1, February 2014, Pages: 90–113,

Meek, M.E., M. Bolger, J.S. Bus, J. Christopher, R.B. Conolly, R.J. Lewis, G. Paoli, R. Schoeny, L.T. Haber, A.B. Rosenstein, M.L. Dourson. 2013. A Framework for Fit-for-Purpose Dose Response Assessment. Regul. Toxicol. Pharmacol. 66(2):234-40. Doi: 10.1016/j.yrtph.2013.03.012 Open Access/

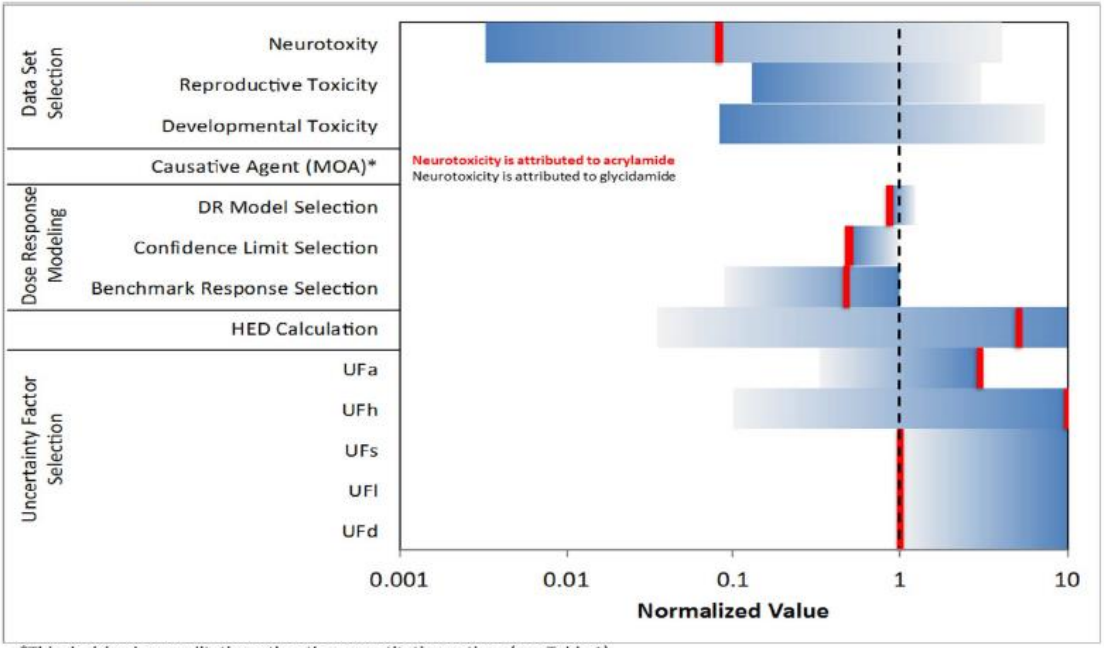
Meek, M.E., Boobis, A.R., et al., 2011. Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. Regul. Toxicol. Pharmacol. 60, S1–S14.

NRC (National Research Council of the National Academy of Science). (2009). Science and decisions: Advancing risk assessment. National Research Council, National Academies Press, Washington, DC. AKA, "Silverbook".

TCEQ (Texas Commission on Environmental Quality). 2012. TCEQ Guidelines to Develop Toxicity Factors. Revised RG-442. Available at http://www.tceq.texas.gov/publications/rg/rg-442.html

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.

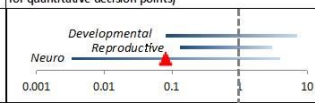
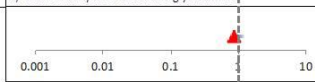
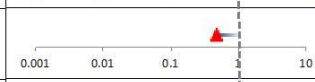
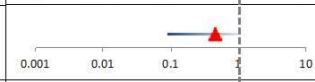
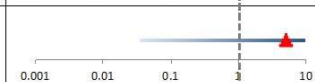
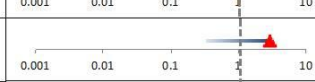
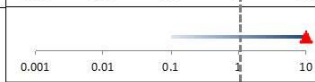
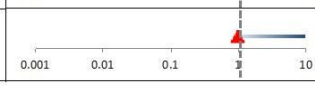
Figure 1. Summary of Decisions Made for the Acrylamide Oral RfD Assessment



*This decision has qualitative rather than quantitative options (see Table 1)

The solid red lines indicates the "selected" option or value (column 4 in Table 1). The dashed line indicates the normalizing value (column 3 in Table 1). The shading gradient of the bars indicates the direction of higher or lower conservatism. Values in the dark blue region result in lower RfDs than the light blue region.

Table 1. Summary of Decisions in EPA's IRIS Assessment for the Acrylamide Oral RfD

Decision Point	Range of Options[a] Fraction of Central Tendency Value (indicated by dashed line for quantitative decision points)	Range Reflects Uncertainty or Variability	Basis for Normalizing Values (e.g., central tendency or highest confidence value)	Decided Option	Confidence in Decision (Science- or Policy-based)
Data Set/Endpoint Selection[b]		Variation in the effective chronic NOAEL values (minimum and maximum values calculated from EPA Table 5-1)[c]	Mean effective chronic NOAEL value across candidate studies (6.1 mg/kg-day, based on data provided in EPA Table 5-1)	NOAEL for peripheral nerve effects (0.5 mg/kg-day; Johnson et al., 1986)	Medium/High confidence in key study. Selection of a sensitive endpoint and study reflects a policy decision to be protective
Causative Agent Determination (MOA)[b]	1) Neurotoxicity is attributed to acrylamide 2) Neurotoxicity is attributed to glycidamide	Uncertainty in MOA regarding causative agent	NA	Neurotoxicity is attributed to acrylamide	Not explicitly stated by EPA
Dose-Response Model Selection[b]		Variation in POD across models, based on minimum (1.2 mg/kg-day) and maximum (1.8 mg/kg-day) for alternative BMD values	Mean POD of acceptable models (1.4 mg/kg-day; EPA Table C-2)	Log-logistic model (1.2 mg/kg-day; EPA Table C-2)	High confidence (EPA Section 5.3.1.3). Selecting the best fitting model reflects a science-based decision to be predictive
Confidence Limit Selection		Uncertainty in model parameters for log-logistic model, based on BMDL10 (0.57 mg/kg-day) and BMD10 (1.2 mg/kg-day) from EPA Table C-2	POD = BMD (1.2 mg/kg-day; central tendency)	POD = BMDL (0.6 mg/kg-day; 95% lower confidence limit)	Not explicitly stated by EPA, however selecting lower confidence limit reflects a policy-based decision to be protective
Benchmark Response Rate Selection		Uncertainty in POD response, based on range defined by the BMDL01 (0.05 mg/kg-day) and BMDL10 (0.57 mg/kg-day) from EPA Table 5-3	BMR = 10% (BMDL10 = 0.57 mg/kg-day) for the default response rate for dichotomous data	BMR = 5% (BMDL05 = 0.27 mg/kg-day)	Not explicitly stated by EPA, however selecting a BMR value (5%) that is below the default value (10%) appears to reflect a policy-based decision to be protective
Interspecies Extrapolation (rat dose:HED)[b]		Variation across measured/ estimated adduct rates in rats and humans, based on the range rat dose:HED ratios for acrylamide (0.035-16.4) from EPA Table 5-6	Based on assumption of equivalent dose (i.e., rat dose:HED = 1)	Based on relative rates of AAVal formation in rats (27.4 uM-hr per mg) and humans (140.1 uM-hr per mg) the rat dose:HED = 5.1	Not explicitly state by EPA
Interspecies Variation (UFa)		Variation across species, based on a default range for toxicodynamics (3-fold in each direction, or 0.33-3)	UFa=1 (assume humans and rats are equally sensitive)	3 (assume that humans are 3x more sensitive than rats based on toxicodynamic factors)	Not explicity states by EPA, however selecting a value greater than 1 reflects a policy decision to be protective
Intraspecies Variation (UFh)		Variation across individuals, based on a default range of for toxicokinetics and toxicodynamics (10-fold in each direction, or 0.1-10)	UFh=1 (for average individual)	10 (assume some individuals are 10x more sensitive)	Not explicity states by EPA, however selecting a value greater than 1 reflects a policy decision to be protective
Duration Extrapolation (UFs); LOAEL-to-NOAEL Extrapolation (UFl); Database Uncertainty		Uncertainty in additional factors, based on default range (1-10)	UFs=1; UFl=1; UFd=1	1 for each (key study is chronic; BMD methods used; database is complete)	Medium/High confidence places in the toxicity database
Results			***Central Tendency Value = 3 mg/kg-day***	***RfD = 0.002 mg/kg-day***	***Medium/High confidence in RfD***

[a] The shading gradient of the lines indicates the direction of higher or lower conservatism. Values in the dark blue region result in lower RfDs than the light blue region.

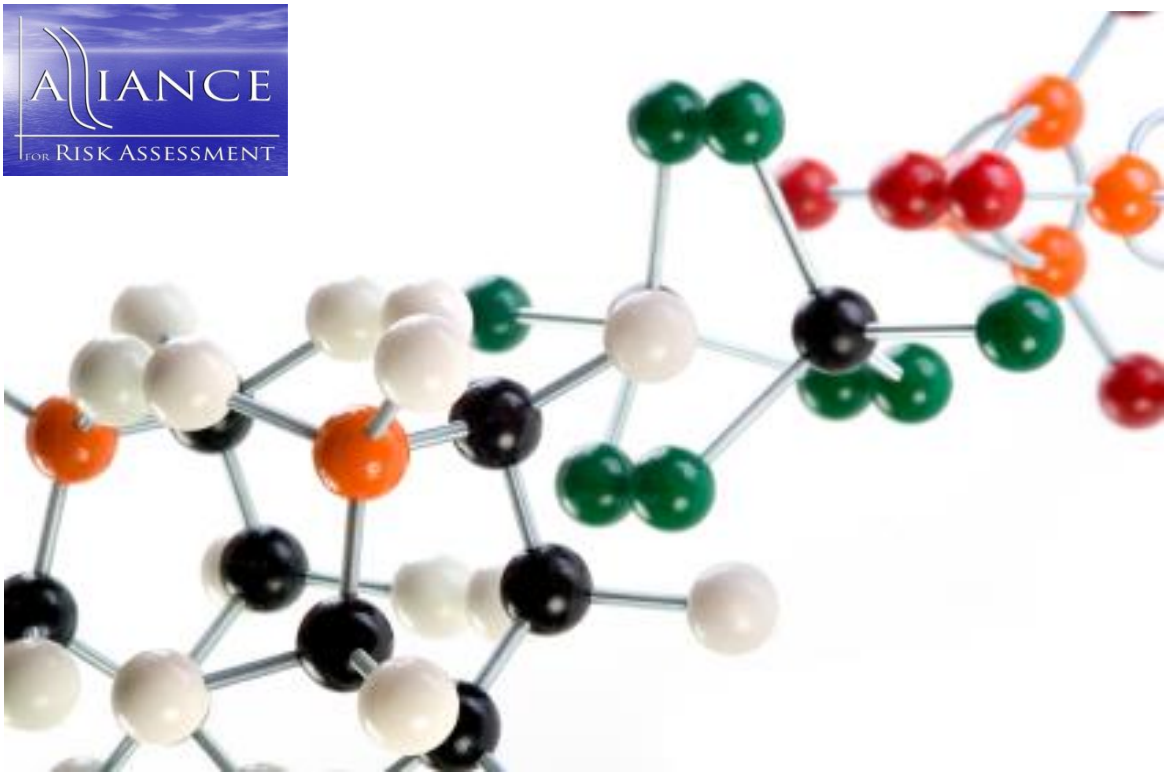
[b] Decision points that are impacted by MOA conclusions are designated with an "*". Adopting of a different MOA conclusion may yield alternative results for these decision points

[c] Range of effective chronic NOAEL values for each endpoint: neurotoxicity (0.02-25 mg/kg-day); reproductive (0.79-18.7 mg/kg-day); developmental (0.5-45 mg/kg-day). Effective chronic NOAEL values reflect that application of default uncertainty factors of 10 each for use of a LOAEL and/or subchronic study for comparison purposes.

Table 2. Summary of Confidence and Importance of the Decisions Made in EPA's IRIS RfD Assessment fo Acrylamide

		Confidence in Decision[b]				
		High	Medium	Low	Not Specified in EPA (2010)	Prioritization of Data Needs (Section Discussed)
Importance of Decision to Assessment[a]	High	*Data set/endpoint selection*			*Causative agent determination (MOA)* *Interspecies extrapolation (rat dose:HED)* *Intraspecies variation (UFh)*	*1) Causative agent determination[c] (EPA Section 4.7.3.1.4)* *2) Data set (EPA Section 5.3.1.1)* *3) Interspecies extrapolation (EPA Section 5.3.1.4)*
	Medium				*Benchmark response rate selection* *Interspecies variation (UFa)* *Addition uncertainty factors (UFs, UFl, UFd)*	None identified by EPA
	Low	*Dose-response model selection*			*Confidence limit selection*	Not applicable

[a]Relative importance of decision to the assessment characterized using the range of options defined in Table 1, Column 2: High (>10-fold range defined by min and max); Medium (3- to 10-fold range); Low (<3-fold range).
[b]Confidence based on the designation in the last column of Table 1.
[c]Considered high since this decision impacts multiple steps in the assessment.
Shaded region of the table can be used to identify priority data needs for additional research/refined assessment



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

Workshop Held:
May 21, 22, 2014
Austin, Texas
at the Texas Commission on Environmental Quality

Appendices

August 18, 2014

Table of Contents

Appendix 1. Biographies for Standing Panel Members

Science Panel

Richard Beauchamp, Texas Department of State Health Services

Richard A. Beauchamp is the Senior Medical Toxicologist for the Texas Department of State Health Services (DSHS) with responsibility for providing advanced toxicological and risk assessment support for the Exposure Assessment, Surveillance, and Toxicology (EAST) Group. As cooperative agreement partners with the Agency for Toxic Substances and Disease Registry (ATSDR), Dr. Beauchamp and other EAST Group members are tasked with conducting Public Health Assessments at abandoned hazardous waste sites that are proposed and added to the Environmental Protection Agency's (EPA's) National Priority List (NPL) of Superfund sites in Texas. Dr. Beauchamp is also involved with conducting other medical and toxicological Public Health Consultations involving exposures to environmental hazardous substances.

After earning his medical degree at the University of Texas Health Science Center at San Antonio (1973-1977), Dr. Beauchamp completed a three year pediatric residency with the Austin Pediatric Education Program at Brackenridge Hospital in Austin, Texas (1977-1980) and began working at the Texas Department of Health as a Public Health Physician Epidemiologist (1980). Early in his career at the health department, he was tasked with developing risk assessment expertise that would be essential for the newly-formed Environmental Epidemiology Program in the evaluation of environmental and chemical exposures. With an undergraduate degree in Electrical Engineering (U.T. Austin) and a strong background in mathematics and computer sciences, Dr. Beauchamp has applied the knowledge gained through participation at numerous risk assessment conferences, symposia, and seminars (sponsored by EPA, NGA, CDC, ASTHO, NIOSH, and others) to the development of his so-called "Risk Assessment Toolkit." Dr. Beauchamp's toolkit consists of a series of Excel® spreadsheets designed for the flexible and rapid evaluation of cancer and non-cancer risks resulting from exposures to a wide variety of environmental contaminants through all of the common exposure pathways. Risks are calculated incrementally using age-specific exposure parameters, including body weights, body surface areas, respiratory daily volumes, and EPA's early-life exposure factors. Risks are integrated over the exposure duration, using up to 46 different age intervals, to insure that childhood exposures are appropriately addressed.

James S. Bus, Exponent

James S. Bus is a Senior Managing Scientist in the Center for Toxicology and Mechanistic Biology in the Health Sciences Group of Exponent, a leading global consulting firm (May 2013-present). His primary responsibilities at Exponent are to provide toxicology expertise for addressing client product stewardship and regulatory needs associated with industrial and pesticide chemicals. Prior to joining Exponent, Dr. Bus retired from The Dow Chemical Company as Director of External Technology, Toxicology and Environmental Research and Consulting (1989-2013). He also previously held positions as Associate Director of Toxicology and Director of Drug Metabolism at The Upjohn Company (1986-1989), Senior Scientist at the Chemical Industry Institute of Toxicology (CIIT, 1977-1986), and Assistant Professor of Toxicology, University of Cincinnati (1975-1977). Dr. Bus currently serves on the Boards of Directors of The Hamner Institutes (formerly CIIT) and the ILSI Research Foundation. He has also has served as Chair of the American Chemistry Council and International Council of Chemical Associations Long-Range Research Initiatives; the Board of Directors of ILSI-HESI; the USEPA Office of Research and Development Board of Scientific Counselors (1997-2003) and Chartered Science Advisory Board (2003-2009); the National Toxicology Program Board of Scientific Counselors (1997-2000); the FDA National Center for Toxicological Research Science Advisory Board (2004-2010); and the National Academy of Sciences/National Research Council Board on Environmental Studies and Toxicology (BEST; 2005-2011). He has served as an Associate Editor of *Toxicology and Applied Pharmacology*, and on the Editorial Boards of *Environmental Health Perspectives* and *Dose Response*. Dr. Bus is a member of the Society of Toxicology (serving as President in 1996-97), the American Society for Pharmacology and Experimental Therapeutics, the American Conference of Governmental and Industrial Hygienists, and the Teratology Society. He is a Diplomate and Past-President of the American Board of Toxicology and a Fellow of the Academy of Toxicological Sciences (member of Board of Directors, 2008-present; President, 2010-2011). Dr. Bus received the Society of Toxicology Achievement Award (1987) for outstanding contributions to the science of toxicology; the Society of Toxicology Founders Award (2010) for leadership fostering the role of toxicology in improving safety decisions; Rutgers University Robert A. Scala Award (1999) for exceptional work as a toxicologist in an industry laboratory; and the K.E. Moore Outstanding Alumnus Award (Michigan State University, Dept. Pharmacol. And Toxicol.). He received his B.S. in Medicinal Chemistry from the University of Michigan (1971) and Ph.D in pharmacology from Michigan State University (1975) and currently is an Adjunct Professor in the Dept. Pharmacology and Toxicology at that institution. His research interests include mechanisms of oxidant toxicity, chemical and pesticide modes of action, defense mechanisms to chemical toxicity, relationships of pharmacokinetic and exposures information to expression of chemical toxicity, and general pesticide and industrial chemical toxicology. He has authored/co-authored over 100 publications, books, and scientific reviews.

Mike Dourson, Toxicology Excellence for Risk Assessment

Mike Dourson is the President of Toxicology Excellence for Risk Assessment (TERA), a nonprofit corporation dedicated to the best use of toxicity data in risk assessment. Before founding TERA in 1995, Dr. Dourson held leadership roles in the U.S. Environmental Protection Agency as chair of US EPA's Reference Dose (RfD) Work Group, charter member of the US EPA's Risk Assessment Forum and chief of the group that helped create the Integrated Risk Information System (IRIS). Dr. Dourson received his Ph.D. in Toxicology from the University of Cincinnati. He is a Diplomate of the American Board of Toxicology and a Fellow of the Academy of Toxicological Sciences. Dr. Dourson has served on or chaired numerous expert panels, including peer review panels for US EPA IRIS assessments, US EPA's Risk Assessment Forum, TERA's International Toxicity Estimates for Risk (*ITER*) independent peer reviews and consultations, FDA's Science Board Subcommittee on Toxicology, the NSF International's Health Advisory Board, and SOT's harmonization of cancer and non-cancer risk assessment. He served as Secretary for the Society for Risk Analysis (SRA) and has held leadership roles in specialty sections of SRA and SOT. He is currently on the editorial board of three journals. Dr. Dourson has published more than 100 papers on risk assessment methods, has co-authored over 100 government risk assessment documents, and has made over 100 invited presentations.

Annie M. Jarabek, U.S. EPA, Office of Research and Development

Annie M. Jarabek is a senior toxicologist in the immediate office of the National Center for Risk Assessment (NCEA) within the US EPA's Office of Research and Development (ORD). Annie is the principal author of the US EPA's Methods for Derivation of Inhalation Reference Concentrations (RfC) and Application of Inhalation Dosimetry, which introduced dosimetry and physiologically-based pharmacokinetic (PBPK) model structures and reduced forms into the RfC methods for interspecies adjustment. She has worked on several high-priority and interdisciplinary Agency assessments including the risk characterization of perchlorate ingestion and the inhalation of particulate matter (PM); and has served in an advisory capacity on other methods and assessments, including the guidance on body-weight scaling for harmonizing noncancer and cancer approaches for the interspecies adjustment of ingested chemicals. Her current research efforts focus on multi-scale modeling of dose-response and decision analysis. Annie has twice received awards for best manuscript in risk assessment application from the Risk Assessment Specialty Section (RASS) of the Society of Toxicology (SOT), along with several best abstract awards. She has also received the Lifetime Achievement Award from the University of Massachusetts, the Risk Practitioner of the Year award from the Society of Risk

Analysis (SRA), the Superfund National Notable Achievement Award, and several award medals (1 gold, 1 silver and 5 bronze) and "S awards" for scientific leadership from the Agency for her various contributions. Annie has served as an elected Councilor to the Society for Risk Analysis and as the vice-president/president of the SOT RASS. Annie has also served the SOT on its awards, communications, nominations, and scientific program committees. She is currently on the editorial board of the international journal "Dose-Response."

R. Jeffrey Lewis, ExxonMobil Biomedical Sciences, Inc.

Dr. R. Jeffrey Lewis is currently Section Head of the Epidemiology, Health Surveillance and Quality Assurance group at ExxonMobil Biomedical Sciences, Inc (EMBSI). In this position, Dr Lewis is responsible for managing EMBSI's Epidemiology and Health Surveillance group, the company's laboratory quality assurance program, and for providing support to ExxonMobil scientific programs related to 1,3-butadiene, naphthalene, asphalt, legislative/regulatory affairs and regulatory impact analysis (e.g., benefit-cost analysis). He has served on a number of industry trade association scientific committees (e.g., the American Chemistry Council's 1,3-butadiene Work Group), external science advisory boards (e.g., the Alliance for Risk Assessment Expert Science Panel) and is a member of the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) Committee. Dr. Lewis also has an adjunct faculty appointment at the University of Texas School of Public Health and is Past Treasurer for the Society for Risk Analysis. Dr. Lewis received his Bachelor of Science degree in biology from the University of Kansas in 1985 and a M.S. and Ph.D. in Epidemiology from the University of Texas School of Public Health in 1987 and 1990, respectively. In addition, he earned a Master of Business Administration degree from Rutgers University in 1997.

Bette Meek, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa

Bette Meek has a background in toxicology receiving her M.Sc. in Toxicology (with distinction) from the University of Surrey, U.K. and her Ph.D. in risk assessment from the University of Utrecht, the Netherlands. She is currently the Associate Director of Chemical Risk Assessment at the McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, completing an interchange assignment from Health Canada. She has extensive experience in the management of chemical assessment programs within the Government of Canada, most recently involving development and implementation of process and methodology for the health

assessment of Existing Substances under the Canadian Environmental Protection Act (CEPA) and previously, programs for contaminants in drinking water and air.

With colleagues within Canada and internationally, she has contributed to or led initiatives to increase transparency, defensibility and efficiency in health risk assessment, having convened and participated in initiatives in this area for numerous organizations including the International Programme on Chemical Safety, the World Health Organization, the International Life Sciences Institute, the U.S. Environmental Protection Agency, the U.S. National Academy of Sciences and the U.S. National Institute for Environmental Health Sciences. Relevant areas have included frameworks for weight of evidence analysis including mode of action, chemical specific adjustment factors, physiologically-based pharmacokinetic modeling, combined exposures and predictive modeling. She has also authored over 175 publications in the area of chemical risk assessment and received several awards for contribution in this domain.

Moiz Mumtaz, Agency for Toxic Substances and Disease Registry (ad hoc)

Dr. Moiz Mumtaz, MSc, MS, PhD, FATS, is Science Advisor, Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry (ATSDR), Centers for Disease Control and Prevention (CDC) and an Associate Professor (adjunct), Emory University, Department of Environmental Health, Atlanta, Georgia, USA. He obtained his Ph.D. in toxicology from the University of Maryland and received his M.S. in chemistry/entomology from Oregon State University. Dr. Mumtaz started his professional career as a chemist after completing his M.Sc. in analytical chemistry from Osmania University, India.

Dr. Mumtaz is the ATSDR's principal representative on the Department of Health and Human Services (DHHS) Interagency Coordinating committee on the validation of alternative methods (ICCVAM), and member of the Society of Toxicology (SOT) Toxic Substances Control Act subcommittee, SOT Government Liaison Group, and Oregon State University Superfund Center External Advisory Committee. He has served on several national and international workgroups/committees including the CDC's Cigarette Ingredients Toxicology Analysis Working Group, U.S. EPA Board of Scientific Counselors (BOSC) Computational Toxicology Subcommittee, EPA Guidelines Work Group for the Health Risk Assessment of Chemical Mixtures, the NIOSH Mixed Exposures Work Group, National Occupational Research Agenda, Research Working Group of Military and Veterans Health Coordinating Board, the Health Impact of Chemical Exposures during the Gulf War, Research Working Group of the Persian Gulf War Coordinating Board, Health Assessment Work Group of the Interagency Air

Assessment Team on Kuwaiti Crude Oil Fires. Dr. Mumtaz is a member of the Society of Toxicology, and the past- president of the SOT Mixtures Specialty Section.

In 2013, he was elected a Fellow of the Academy of Toxicological Sciences (FATS) and won the Society of Toxicology (SOT) Lehman award for major contributions to risk assessment and the regulation of chemical agents. During the past three decades, Dr. Mumtaz has actively published his research findings in several peer-reviewed journals. These publications have covered a wide range of research areas pertinent to medicine and human health including dopamine metabolism and mental health; comparative toxicology; chemical analysis of xenobiotics and environmental chemicals; health risk assessment of chemical mixtures and environmental stressors.

Greg Paoli, Risk Sciences International

Greg Paoli serves as Principal Risk Scientist and COO at Risk Sciences International, a consulting firm specializing in risk assessment, management and communication in the field of public health, safety and risk-based decision-support. Mr. Paoli has experience in diverse risk domains including toxicological, microbiological, and nutritional hazards, air and water quality, climate change impacts, medical and engineering devices, as well as emergency planning and response for natural and man-made disasters. He specializes in probabilistic risk assessment methods, the development of risk-based decision-support tools and comparative risk assessment. Mr. Paoli has served on a number of expert committees devoted to the risk sciences. He was a member of the U.S. National Research Council committee that issued the 2009 report, *Science and Decisions: Advancing Risk Assessment*. He serves on the Canadian Standards Association Technical Committee on Risk Management, advisory committees of the National Roundtable on the Environment and the Economy, a US NRC Standing Committee on the Use of Public Health Data at the U.S. Food Safety and Inspection Service, and has served on several expert committees convened by the World Health Organization. Mr. Paoli completed a term as Councilor of the Society for Risk Analysis (SRA) and is a member of the Editorial Board of *Risk Analysis*. Recently, Mr. Paoli was awarded the Sigma Xi – SRA Distinguished Lecturer Award. He has provided training in risk assessment methods around the world, including the continuing education programs of the Harvard School of Public Health and the University of Maryland. Greg holds a Bachelors Degree in Electrical and Computer Engineering and a Master's Degree in Systems Design Engineering from the University of Waterloo.

Alan Stern, New Jersey Department of Environmental Protection

Dr. Alan H. Stern is the Section Chief for Risk Assessment in the Office of Science of the New Jersey Department of Environmental Protection; Adjunct Associate Professor in the Department of Environmental and Occupational Health of the University of Medicine and Dentistry of New Jersey-School of Public Health. He received a bachelor's degree in biology from the State University of New York at Stony Brook (1975), a master's degree in cellular and molecular biology from Brandeis University (1978), a master of public health degree (1981) and a doctorate in public health from the Columbia University School of Public Health (1987). Dr. Stern is board-certified in toxicology by the American Board of Toxicology (Diplomate of the American Board of Toxicology). Dr. Stern's areas of expertise include risk assessment and exposure assessment including the application of probabilistic techniques to quantitative estimation of exposure and risk. His research interests have focused on heavy metals including lead, mercury, chromium and cadmium. Dr. Stern was a member of the National Research Council/National Academy of Sciences Committee on the Toxicology of Methylmercury (1999-2000) and a member of the recent USEPA Science Advisory Board panel for the National-Scale Mercury Risk Assessment for Coal- and Oil-Fired Electrical Generating Units (June-July 2011) as well as the USEPA Science Advisory Board Panel for Peer Review of the All-Ages Lead Model (Oct. 27-28, 2005). He has also served on numerous USEPA-IRIS review panels including Toxicological Review of Urea (Dec. 13, 2010, Panel Chair), Toxicological Review of Trichloroacetic Acid (Dec. 10, 2009, Panel Chair), Toxicological Review of 2-Hexanone (May 22, 2008, Panel Chair), Toxicological Review of Toluene (Feb. 5, 2004, Panel Chair). Other panels, committees and workshops include, ATSDR Toxicological Profile Review of Revised Minimal Risk Levels (MRLs) for 1,4-Dioxane (March-April, 2010), ATSDR Toxicological Profile Review of Revised Inhalation MRL for 1,4-dioxane (Sept. 2011),.USEPA Panel for the Review of Draft Exposure Factors Handbook (March 3-4, 2010), USEPA Workshop on Cardiovascular Toxicity of Methylmercury (Jan. 12-13, 2010), USEPA Panel for Review of ―Draft Child-Specific Exposure Factors Handbook (Sept. 19-20, 2007). Dr. Stern has authored numerous articles in peer-reviewed journals, and contributed a book chapter on Exposure Assessment for Neurotoxic Metals in ―Human Developmental Neurotoxicology - D. Bellinger, ed. (Taylor & Francis, New York, 2006.), and the article on *Environmental Health Risk Assessment‖ in the Encyclopedia of Quantitative Risk Assessment and Analysis*. John Wiley and Sons Ltd., 2008.

Appendix 2. Meeting Agenda

Workshop VIII Agenda

Agenda

Date: May 21 & 22, 2014

Location: Texas Commission on Environmental Quality, Austin, Texas

Purpose: To advance the recommendations of NAS (2009) and subsequent framework of *ARA* (2013) on problem formulation and dose-response analysis, through review of illustrative case studies for further development of methods

All times are Central Daylight Time.

Wednesday May 21st

Welcome (8:30 am)

- **Richard Hyde, P.E., Executive Director of the Texas Commission on Environmental Quality**

- Introduction and Opening Remarks (8:40 to 8:50)
  - **Members of the Advisory Committee and Science Panel**

- Keynote Talk: EPA's Risk Assessment Forum activity related to the Science and Decisions Report (8:50 to 9:35)
  - **Rita Schoeny, U.S. Environmental Protection Agency**

Morning Break (9:30 to 10:00)

Review of Case Study: Weight of Evidence Approach for Chemicals with Limited Toxicity Data (silanes and siloxanes) (10:00 to noon)

- **Tiffany Bredfeldt, Texas Commission on Environmental Quality**
- **Science Panel discussion**

Lunch (noon to 1:00)

Beyond Science and Decisions Dose Response Assessment Framework (1:00 to 1:30)

- **Lynne Haber, Toxicology Excellence for Risk Assessment**

Dose-response assessment of a mixture of melamine and cyanuric acid in rats: practical challenges and outcome (1:30 to 2:15)

- **Gonçalo Gamboa da Costa, National Center for Toxicological Research**

Kids and Chemical Safety (2:15 to 3:00)

- **Patricia Nance, Toxicology Excellence for Risk Assessment**

Afternoon Break (3:00 to 3:30)

Understanding Uncertainties and Confidence in Hazard Databases: An Example Using IRIS (3:30 to 4:15)

- **Nancy Beck, American Chemistry Council**

Observer Comments (4:15 to 5:00)

Reception (dinner portion hors d'oeuvres, 6:30 to 9:00)

Thursday, May 22nd

Review of Case Study: Practical guidance on the development of a non-cancer hazard range for effective risk assessment and risk management of contaminated sites: A case study with trichloroethylene and other chemicals. (8:00 to 10:00)

- **Ed Pfau of Hull and Associates and Rod Thompson of Alliance for Site Closure**

Morning Break (10:00 to 10:30)

Practical Guidance … (continued) (10:30 to noon)

- **Science Panel discussion**

Lunch (noon to 1:00)

Lessons learned from the U.S. Endocrine Disruptor Screening Programs (1:00 to 1:45)

- **Ellen Mihaich, *ER*^{2}**

Case Study Proposal: Comparative risk assessment of mixtures in fish (1:45 to 2:30)

- **Michael Dourson, Toxicology Excellence for Risk Assessment**
- **Coauthor: Moiz Mumtaz, Agency for Toxic Substances and Disease Registry**

Observer Comments and Closing remarks (2:30 to 3:00)

Adjourn

Appendix 3. List of Workshop Participants

In-Person Attendees

Mr. Michael Alpin
Texas Commission on Environmental Quality
mike.aplin@tceq.texas.gov

Dr. Janet Anderson
US Air Force
janet.anderson.5@us.af.mil

Mr. Eric Barefoot
AFCEC CZR
eric.barefoot.1@us.af.mil

Dr. Richard Beauchamp
Texas Dept of State Hlth Srvc
Richard.Beauchamp@dshs.state.tx.us

Dr. Nancy Beck
American Chemistry Council
nancy_Beck@americanchemistry.com

Dr. Tiffany Bredfeldt
Texas Commission on Environmental Quality
tiffany.bredfeldt@tceq.texas.gov

Dr. James Bus
Exponent, Inc.
jbus@exponent.com

Dr. Varley Catharine
AFCEC
Catharine.Varley.Ctr@us.af.mil

Dr. Shanna Clark
HQ Air Force (Civil Engineer Center)
shanna.clark@us.af.mil

Ms. Angela Curry
Texas Commission on Environmental Quality
angela.curry@tceq.texas.gov

Dr. Michael Dourson
TERA
dourson@tera.org

Dr. Neeraja Erranguntla
Texas Commission on Environmental Quality
neeraja.erraguntla@tceq.texas.gov

Dr. Shannon Ethridge
Texas Commission on Environmental Quality
shannon.ethridge@tceq.texas.gov

Dr. Goncalo Gamboa da Costa
FDA NCTR
goncalo.gamboa@fda.hhs.gov

Dr. Roberta Grant
Texas Commission on Environmental Quality
roberta.grant@tceq.texas.gov

Shannon Garcia
AFCEC/CZTE
shannon.garcia.3@us.af.mil

Dr. Lynne Haber
TERA
haber@tera.org

Mr. Joseph Haney
Texas Commission on Environmental Quality
joseph.haney@tceq.texas.gov

Mr. John Hinz
Self / USAFSAM - retired
jphinz@sbcglobal.net

Michael Honeycutt
Texas Commission on Environmental Quality
michael.honeycutt@tceq.texas.gov

Dr. Richard Hyde
Texas Commission on Environmental Quality

Allison Jenkins
Texas Commission on Environmental Quality
allison.jenkins@tceq.texas.gov

Sabine Lange
Texas Commission on Environmental Quality
Sabine.Lange@tceq.texas.gov

Dr. Jong-Song Lee
Texas Commission on Environmental Quality
jong-song.lee@tceq.texas.gov

Dr. R. Jeffrey Lewis
ExxonMobil Biomedical Sciences, Inc.
r.jeffrey.lewis@exxonmobil.com

Dr. Rodriguez Mark
AFCEC/CZTE
mark.rodriguez.2@us.af.mil

Darrell McCant
Texas Commission on Environmental Quality
Darrell.McCant@tceq.texas.gov

Dr. Bette Meek
University of Ottawa
bmeek@uottawa.ca

Dr. Ellen Mihaich
ER2
emihaich@nc.rr.com

Vesna Milovanovic
Student
vesna.milovanovic@gmail.com

Dr. Moiz Mumtaz
ATSDR/NCEH
mgm4@cdc.gov

Dr. Jessica Myers
Texas Commission on Environmental Quality
jessica.myers@tceq.texas.gov

Ms. Patricia Nance
TERA
nance@tera.org

Chris Saranko
Geosyntec Consultants
csaranko@geosyntec.com

Mr. Gregory Paoli
Risk Sciences International, Inc.
gpaoli@risksciences.com

Dr. Kelly Scanlon
Noblis
kelly.scanlon@noblis.org

Ms. Camerie Perry
ToxStrategies
cperry@toxstrategies.com

Dr. Stephanie Shirley
Texas Commission on Environmental Quality
stephanie.shirley@tceq.texas.gov

Mr. Edward Pfau
Hull & Associates, Inc.
epfau@hullinc.com

Rod B. Thompson
Physicians Mutual
rodbthompson@comcast.net

Dr. Lynn Pottenger
The Dow Chemical Company
lpottenger@dow.com

Anthony Tweedale
R.I.S.K Consultancy
ttweed@base.be

Ms. Heather Reddick
Texas Commission on Environmental Quality
Heather.Reddick@tceq.texas.gov

Milovanovic Vesna
University of Belgrade, Faculty of Pharmacy
vesna.milovanovic@gmail.com

Dr. Fred Reitman
Shell
fred.reitman@shell.com

Dr. Lisa Westbrook
Texas Commission on Environmental Quality
lisa.westbrook@tceq.texas.go

Webinar Participants

Dr. Dan Arrieta
Chevron Phillips Chemical Company LP
arriede@cpchem.com

Dr. Wafaa Ayad
Church&Dwight Inc
wafaa.ayad@churchdwight.com

Dr. Ambuja Bale
Drug Enforcement Administration
Ambuja.S.Bale@usdoj.gov

Dr. Patrick Beatty
American Petroleum Institute
beattyp@api.org

Dr. John Bell
Halogenated Solvents Industry Alliance
jbell@hsia.org

Dr. Christopher Bevan
CJB Consulting LLC
cbevan@cinci.rr.com

Peter Beyrouty
PCB
peter_c_2007@yahoo.com

Dr. Janice Britt
ToxStrategies
jbritt@toxstrategies.com

Mr. Ron Brown
Food and Drug Administration
ronald.brown@fda.hhs.gov

Dr. Patience Browne
US EPA
browne.patience@epa.gov

Mrs. Ashley Burt
North Texas Municipal Water District
aburt@ntmwd.com

Dr. Stuart Cagen
Shell Health
stuart.cagen@shell.com

Erik Carlson
General Electric Company
carlson@ge.com

Ms. Patricia Kablach Casano
General Electric Company
pat.casano@ge.com

Ms. Diana Effio
URS Corporation
diana.effio@urs.com

Mr. Chris Kirman
Summit Toxicology
ckirman@summittoxicology.com

Mr. Jarrod Case
USAF
jarrod.case@us.af.mil

Dr. Tsu-Fan Cheng
FDA/CFSAN
tsu-fan.cheng@fda.hhs.gov

Ms. Rena Chung
Public Health Ontario
rena.chung@oahpp.ca

Dr. Kimberly Ehman
WuXi Apptec
kimberly.ehman@wuxiapptec.com

Caroline English
NSF International
jenglish@nsf.org

Dr. Mingzhu Fang
Rutgers, The State University of New Jersey
mzfts13@gmail.com

Dr. Penelope Fenner-Crisp
Independent Consultant
pfennercrisp@aol.com

Robert Fensterheim
RegNet
rfensterheim@regnet.com

Dr. Suzanne Fitzpatrick
Food and Drug Administration
suzanne.fitzpatrick@fda.hhs.gov

Ms. Julie Fitzpatrick
US EPA/Risk Assesment Forum
fitzpatrick.julie@epa.gov

Dr. William Frez
The Lubrizol Corp.
william.frez@lubrizol.com

Dr. Doug Fuhrer
Wuxi Apptec
douglas.fuhrer@wuxiapptec.com

Dr. Bernard Gadagbui
TERA
gadagbui@tera.org

Mrs. Olga Grabovska
MOE
olga.grabovska@ontario.ca

Ms. Sarah Grossi
AECOM
sarah.grossi@aecom.com

Dr. Ruth Hummel
US EPA OPPT
Hummel.Ruth@epa.gov

Dr. Elizabeth Furukawa
FDA
elizabeth.furukawa@fda.hhs.gov

Dr. Amlan Ghosh
Corona Environmental Consulting
aghosh@coronaenv.com

Dr. Zach Guerrette
ToxServices LLC
zguerrette@toxservices.com

Dr. Lance Hallberg
UTMB
lmhallbe@utmb.edu

Dr. David Halliday
TCEQ
David.Halliday@TCEQ.Texas.gov

Ali Hamade
State of Alaska
ali.hamade@alaska.gov

Maria Hegstad
Risk Policy Report
mhegstad@iwpnews.com

Dr. Martin Hoagland
US FDA
martin.hoagland@fda.hhs.gov

Razelle Hoffman-Contois
Vermont Department of Health
razelle.hoffman@state.vt.us

Annie Jarabek
US EPA NCEA & HHRA
jarabek.annie@epa.gov

Dr. Elke Jensen
Dow Corning
elke.jensen@dowcorning.com

Sophie Jia
Chevron Phillips Chemical
jiasz@cpchem.com

Dr. Tom Johnson
New York State Department of Health
tbj01@health.state.ny.us

Mr. Tom Jonaitis
Intertek
tomas.jonaitis@intertek.com

Dr. Rhonda Kaetzel
Public Health Seattle & King County
rhonda.kaetzel@kingcounty.gov

Mr. David Kang
MicroBioTest Division of Microbac Labs
David.Kang@microbac.com

James Kim
OMB
james_h_kim@omb.eop.gov

Dr. April Kluever
Food and Drug Administration
april403@gmail.com

Mr. Gary Kolesar
Dow Corning
gary.kolesar@dowcorning.com

Mr. Gopala Krishna
Supernus Pharmaceuticals
gkrishna@supernus.com

Ms. Kavya Krishna
Supernus Pharmaceuticals
kkrishna@supernus.com

Mr. Oliver Kroner
TERA
kroner@tera.org

Dr. Catherine Lazaro
Merck Consumer Care
catherine.lazaro@merck.com

Mrs. Doreen Lehner
State of Michigan Dept of Environmental Quality
lehnerd@michigan.gov

Dr. Betina Lew
Church & Dwight
betina.lew@churchdwight.com

Dr. Yu-Sheng Lin
US EPA
Lin.Yu-Sheng@epa.gov

Mr. John Lowe
CH2M HILL
john.lowe@ch2m.com

Dr. Angela Lynch
American Chemistry Council
amalinlynch@gmail.com

Dr. Elaina MacIntyre
Public Health Ontario
elaina.macintyre@oahpp.ca

Mr. Sidney Marlborough
Noble Energy Inc
smarlborough@nobleenergyinc.com

Ms. Jerri Martin
Kentucky Dept. Environmentla Protection
Jerri.Martin@ky.gov

Dr. Jeanelle Martinez
US EPA
martinez.jeanelle@epa.gov

Dr. Elizabeth Maull
NIEHS
maull@niehs.nih.gov

Dr. Tami McMullin
Dow Corning
t.mcmullin@dowcorning.com

Ms. Anita Meyer
Army Corps of Engineers
anita.k.meyer@usace.army.mil

Dr. Steven Mog
FDA-CFSAN
steven.mog@fda.hhs.gov

Mrs. Heidi Murray-Smith
National Research Council
hmurray-smith@nas.edu

Mr. Michael Musso
HDR, Inc.
michael.musso@hdrinc.com

Ms. Tania Onica
Ontario Ministry of the Environment
tania.onica@ontario.ca

Dr. Sharon Oxendine
US EPA
oxendine.sharon@epa.gov

Ms. Laura Owens
AECOM
LAURA.OWENS@AECOM.com

Dr. Kalaiselvan P
syngene
drpkalai@gmail.com

Brian Pachkowski
NJ Department of Environmental Protection
brian.pachkowski@dep.state.nj.us

Dr. Norka Paden
Idado Department of Health and Welfare
padenn@dhw.idaho.gov

Dr. Xiao Pan
Michigan State University
panxiao@msu.edu

Sang Ki Park
FDA
Sang-ki.Park@fda.hhs.gov

Dr. Jin-Young Park
FDA/Center for Food Safety and Applied Nutrition
jinyoung.park@fda.hhs.gov

Mrs. Deval Patel
Amway Corporation
deval.patel@amway.com

Dr. Donald Patterson
Exponent
dpatterson@exponent.com

Dr. Geoff Patton
Food and Drug Administration
geoffrey.patton@fda.hhs.gov

Dr. John Piper
Celanese
john.piper@celanese.com

Christy Powers
US EPA
powers.christina@epa.gov

Dr. Resha Putzrath
Toxicologist and Risk Assessor
Resha.Putzrath@med.navy.mil

Dr. Bonnie Ransom Stern
Consulting in Health Sciences & Risk Assessment
br.stern@yahoo.com

Dr. Jennifer Rayner
SRC Inc
jrayner@srcinc.com

Mrs. Maria Remmert
Maria Remmert and Associates
maremmert@aol.com

David Reynolds
Inside EPA newsletter
dreynolds@iwpnews.com

Dr. Lorenz Rhomberg
Gradient
lrhomberg@gradientcorp.com

Dr. Mark Rigby
Parsons
mark.rigby@parsons.com

Mrs. Sue Robinson
Golder Associates
scrobinson@golder.com

Ms. Pamela Rodgers
Battelle
rodgersp@battelle.org

Dr. Chester Rodriguez
The Coca-Cola Company
chester.rodriguez@coca-cola.com

Dr. Dojin Ryu
University of Idaho
dryu@uidaho.edu

Dr. Reena Sandhu
Toxicology Excellence For Risk Assessment
sandhu@tera.org

Dr. Barbara Schmitt
Dow Corning Europe SA
barbara.schmitt@dowcorning.com

Dr. Rita Schoeny
ORD/ EPA
schoeny.rita@epa.gov

Ms. Angela Sederquist
Booz Allen Hamilton
sederquist_angela@bah.com

Dr. Mary Shackelford
Food and Drug Administration
mary.shackelford@fda.hhs.gov

Dr. Ted Simon
Ted Simon LLC
ted@tedsimon-toxicology.com

Dr. Alan Stern
New Jersey Dept of Environmental Protection
Alan.Stern@dep.state.nj.us

Dr. Bola Taiwo
WuXi AppTec
bola.taiwo@wuxiapptec.com

Mr. Samuel Taiwo
Texas Commission on Environmenral Quality
mails2samtaiwo@gmail.com

Dr. Michael Taylor
NiPERA
mtaylor@nipera.org

Dr. Scott Thurmond
Food and Drug Administration
Scott.Thurmond@fda.hhs.gov

Mr. Shen Tian
Bayer
shen.tian@bayer.com

Mr. Anthony C. Tweedale
R.I.S.K. Consultancy
ttweed@base.be

Julia Varshavsky
UC Berkeley
juliav@berkeley.edu

Mr. Brad Venman
NTH Consultants,
Ltd. bvenman@nthconsultants.com

Ms. Vonnie Rodarte
AECOM
vonnie.rodarte@aecom.com

Dr. Zemin Wang
Indiana University
zemwang@indiana.edu

Dr. Teresa Wegesser
Chevron
twegesser@chevron.com

Dr. Jeffrey Wickliffe
Tulane University
jwicklif@tulane.edu

Dr. Al Wiedow
Environmental Resources Management
al.wiedow@erm.com

Mr. Justice Williams
Georgia Environmental Protection Department
Justice.Williams@gaepd.com

Mr. Brian Wong
Multiquip Inc.
bwong@multiquip.com

Ms. Tracy Wright
US EPA
wright.tracy@epa.gov

Ms. Melanie Young
US EPA
young.melanie@epa.gov

Gary Zeiders
City of Lubbock
gzeiders@mylubbock.us

Yuzhao Zhou
WuXi AppTec
zhouyuzhao@hotmail.com

Dr. Tong Zhou
Food and Drug Administration
tong.zhou@fda.hhs.gov

Meegan Zimmerman
AECOM
meegan.zimmerman@aecom.com