

Alliance for Risk Assessment (ARA): Beyond Science and Decisions XV

Location: Virtual Workshop

Dates: November 19 and 20, 2025

Workshop Report





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Virtual Workshop XV

November 19 and 20, 2025

Purpose & Agenda

To advance the recommendations in the NAS (2009) report concerning issue identification (problem formulation) and all aspects of risk assessment and management, through selection of illustrative research case studies for further development

Day 1: Wednesday, November 19, 2025
(all times are US EST)

Chair: Tracie Phillips, member of the ARA Advisory Panel

Welcome: (8:30 to 9:00)

- **Sabine Lange**, Texas Commission on Environmental Quality
- **James Bus**, member of the ARA Advisory Panel
- **Michael Dourson**, Member of the Science Panel

Keynote Talk: The Design of Risk Assessments: Updates on Methods for Problem Formulation, Causality Determinations and Value-of-Information Analyses (9:00 to 9:45)

- **Greg Paoli**, Risk Sciences International

Morning Break (9:45 to 10:00)

Case Study 1. Are glyphosate and/or its formulations carcinogenic? A technical debate (10:00 to noon)

- **Yes: Michael Dourson**, Toxicology Excellence for Risk Assessment
- **No: Gary Burin**, Independent Consultant
- Discussion by the Science Panel
 - o **James Bus**, Exponent
 - o **Michael Dourson**, Toxicology Excellence for Risk Assessment
 - o **Bette Meek**, University of Ottawa
 - o **Greg Paoli**, Risk Sciences International
 - o **Tracie Phillips**, Texas Commission on Environmental Quality
 - o **Pamela Williams**, E Risk Sciences

Lunch (noon to 12:30)

Case Study 1 Continued... (12:30 to 2:00)



- Discussion by the Science Panel
- Comments from Observers

Case Study 2. The safe dose range of perfluorooctane sulfonate (PFOS): An International Collaboration (2:00 to 3:00)

- **Laura Green and Edmund Crouch**, Green Toxicology LLC

Afternoon Break (3:00 to 3:15)

Case Study 2 continued (3:15 to 5:00)

- The safe dose range of perfluorooctane sulfonic acid (PFOS)
- Discussion by the Science Panel
- Comments from Observers

Chair's Summary

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Day 2: Thursday, November 20

Chair: Pamela Williams, member of the ARA Advisory Panel

Case Study 3. Fit-for-purpose systematic review guidelines for toxicity factor derivation, using vanadium as a case study (8:30 to 10:00)

- **Nnamdi Nnoli & Stony Lo**, Texas Commission on Environmental Quality

Morning Break (10:00 to 10:15)

Case Study 3 continued: (10:15 to noon)

- Discussion by the Science Panel
- Comments from Observers
- Chair's Summary

Lunch (noon to 12:30)

Updates on Risk Assessment Methods (12:30 to 2:00)

- RIFM Safety Assessment of Inhalation Exposure to Fragrances - Current Practices and Future Direction
 - o **Nikaeta Sadekar**, Research Institute for Fragrance Materials
- Framework for Pre-Manufacturing Notification for Electrocoat Polymers
 - o **Britt McAtee**, PPG
- Transforming the Evaluation of Agrochemical Safety and Risk Assessment: Human Health Risk Example
 - o **Douglas Wolf**, Independent Consultant



Afternoon Break (2:00 to 2:15)

Updates continued (2:15 to 3:45)

- Fish Consumption Benefits and PFAS Risks
 - o **Ali Hamade**, Oregon Health Authority
- Application of the threshold of toxicological concern (TTC) in the evaluation of drinking water contact chemicals
 - o **Brad Lampe**, NSF International
- Setting Performance Expectations for New Approach Methods in Toxicity Testing: Moving from Intuition to Hard Data
 - o **Rusty Thomas**, Chemical Insights Research Institute (ULRI)

Open Discussion: All Participants (3:45 to 4:30)

Summary of the Workshop: (4:30)

- **Tracie Phillips, Pamela Williams, and Michael Dourson**, members of the ARA Advisory Panel



Meeting Summary for ARA Workshop XV Day 1 Morning

Virtual ARA Workshop Overview

The 15th ARA Beyond Science and Decisions Workshop began with opening remarks from Sabine Lange, Jim Bus, and Michael Dourson. Tracie Phillips, the day 1 workshop chair, outlined the agenda and housekeeping rules. The 2-day workshop, originally planned as an in-person event in Texas, was hosted virtually due to funding constraints. Jim Bus explained the role of the science advisory committee in identifying topics for discussion and updates in risk assessment. Michael Dourson provided an overview of the workshop's history, including the number of case studies and participating groups. He also announced that the International Society for Regulatory Toxicology and Pharmacology (IS RTP) has endorsed this workshop, specifically the glyphosate debate. The upcoming Society for Risk Analysis (SRA) meeting in Washington, D.C. was highlighted, along with a roundtable discussion on "Is Hazard the New Risk?" and a book review of Dennis Paustenbach's 3rd edition of *Human and Ecological Risk Assessment: Theory and Practice* by Pamela Williams.

Keynote Talk

Greg Paoli presented a keynote address on the design of risk assessments including updates on methods for problem formulation, causality determinations, and value-of-information (VOI) analysis. In emphasizing the importance of clear problem formulation in risk assessment, Greg described how the "APRIO framework" that he and colleagues recently developed helps identify the following key components: agents, pathways, receptors, interventions, and outputs. He also discussed the need for a common language in risk assessment to facilitate communication across different scientific disciplines.

Greg then introduced the concept of VOI analysis, which systematically assesses the economic value of information in terms of dollars. He explained that VOI differs from traditional scientific evaluation by focusing on decision-making impact rather than scientific value and emphasized the importance of considering both cost and timeliness of information. Greg demonstrated how VOI analysis can be applied to compare different testing methods, using a case study of transcriptomic methods versus animal studies, which showed that less expensive and more timely methods often provide sufficient value for regulatory decision-making.

Next, Greg presented a comprehensive overview of a Bayesian network tool developed for Health Canada, which quantifies causality determinations and integrates Bradford Hill considerations. He demonstrated how the tool uses conditional probability tables to provide transparent, auditable, and reproducible weight-of-evidence assessments, starting from individual study characteristics and propagating to overall causality conclusions. Greg highlighted that while the tool is still a work in progress and needs case studies to validate its effectiveness, it shows promise as an augmentation to the traditional human-based weight-of-evidence process, particularly in its ability to handle new evidence and hypothetical scenarios.



Meeting Summary for ARA Workshop XV Day 1 Morning

Case Study 1: Are Glyphosate and/or its Formulations Carcinogenic? A Technical Debate

Michael Dourson and Gary Burin presented two competing perspectives on the carcinogenicity of glyphosate. Michael began with a portrayal of IARC's (International Agency for Research on Cancer) perspective, highlighting some (albeit limited) human evidence, positive animal trends, and genotoxicity and acknowledging recent studies that support these findings. Gary followed with an opposing view, where he presented a comprehensive review of glyphosate's safety profile, highlighting that despite being one of the most widely used herbicides, the U.S. Environmental Protection Agency (U.S. EPA) has never had concerns about its carcinogenicity. He explained that while one study showed an increased incidence of rare tumors in mice, subsequent studies and regulatory reviews have not confirmed these findings, leading U.S. EPA and other agencies to conclude that glyphosate is not carcinogenic.

The case study was then opened to the Science Panel for discussion. Bette Meek noted that while the gene toxicity data raised some concerns, the key characteristics approach would require more detailed dose-response analysis and mechanistic data to fully evaluate the potential pathways to tumors. The group discussed the IARC classification of glyphosate as a probable carcinogen, with Gary and Jim Bus explaining that IARC's approach focuses on hazard identification rather than dose-response considerations. They noted that in vitro studies often use much higher concentrations than those found in human exposure, with Jim highlighting that real-world glyphosate exposure is typically around 0.5 micrograms per kilogram per day. The discussion also covered the lack of dermal absorption of glyphosate due to its charged nature, and Bette raised questions about the structure-activity relationship analyses which showed no carcinogenic potential.

Jim and Gary further noted that despite IARC's concerns, glyphosate's unique physical-chemical properties, including its charged nature and limited dermal absorption, make it unlikely to cause tumors at relevant exposure levels. They noted that human biomonitoring studies show low levels of exposure worldwide, and an agricultural health study with 89,000 farmers found no increased cancer risk despite real-world formulation exposure. Michael raised questions about dose-response relationships and the need to better understand the implications of high-dose animal studies relative to human exposure levels.

The group also discussed statistical significance and multiple comparisons in regulatory agency evaluations, particularly regarding glyphosate and cancer studies. Michael and Gary debated the use of Bonferroni corrections for multiple endpoints, with Michael noting that U.S. EPA typically applies such corrections. The discussion then shifted to genotoxicity studies, where Bette highlighted the distinction between genotoxicity and mutagenicity, and the need to consider dose-response relationships in cancer risk assessment. Jim raised concerns about the U.S. EPA guidelines' reliance on genotoxicity for defaulting to linear models, suggesting a need for reorientation in how genotoxicity databases are evaluated.



Meeting Summary for ARA Workshop XV Day 1 Afternoon

Case Study 1 Continued

The afternoon session continued with the Science Panel discussion of Case study #1 and opened to comments from observers (who are not named here). The discussion touched on the evolution of toxicity methods, with a consensus that the hazard identification step may need redefinition due to advancements in measuring contaminants at low levels and the ability to find perturbations. Jim Bus raised concerns about the relevance of chronic hazard assessments in the absence of real-world dosimetry, suggesting a need for context-specific guidelines. One observer discussed a statistical approach to multiple comparisons in bioassays, while another observer inquired about the value of going beyond statistics to consider preneoplastic lesions and dose-response relationships. A third observer shared insights on the IARC Monographs program, suggesting that the genesis of efforts to classify glyphosate as a carcinogen may have been driven by a desire to protect French agriculture.

The group further discussed the role and relevance of IARC classifications in the current regulatory landscape. Michael Dourson and others noted that while IARC's hazard-based approach differs from risk-based approaches used by regulatory agencies like U.S. EPA, the legal implications can vary significantly, particularly in litigation. One observer shared insights from her time on the U.S. EPA Science Advisory Board (SAB) regarding glyphosate, suggesting that IARC's continued focus on carcinogen identification may stem from organizational needs to justify its existence. Bette Meek raised questions about the current utility of IARC classifications, given that many governments now use risk-based assessments and highlighted how different jurisdictions use IARC classifications in various ways, such as California's Prop 65 program.

The group also discussed the challenges and limitations of current chemical classification systems, particularly focusing on IARC and Proposition 65. They explored how these systems often rely on linear extrapolation for carcinogenicity assessments, which can lead to overclassification of chemicals. Jim Bus and Michael debated the interpretation of U.S. EPA guidelines regarding linear extrapolation, with Jim emphasizing the difficulty of demonstrating an alternative mode of action and Michael suggesting that negative mutation data could justify non-linear extrapolation. The discussion highlighted the need for more efficient and scientifically sound methods of chemical assessment, with Bette advocating for focusing on replacing hazardous chemicals with non-hazardous alternatives.

Additional group discussion focused on challenges with the IARC monograph program's approach to evaluating well-studied and regulated chemicals, with one observer and Bette highlighting that such assessments can create confusion and duplicate efforts across different regulatory bodies. They agreed that IARC should focus on chemicals with limited information and potential human carcinogenic hazards, rather than well-regulated substances like pesticides and glyphosate. The observer shared insights from his experience with pesticide toxicology, noting that while registration submissions address specific questions, they often don't cover all relevant toxicological concerns, particularly regarding metabolites and formulated products.



Meeting Summary for ARA Workshop XV Day 1 Afternoon

Lastly, the group discussion focused on pesticide regulations and toxicology, with Gary Burin explaining that pesticides are strictly regulated by the U.S. EPA Office of Pesticide Programs and can be tested for various toxicities. One observer raised concerns about the Key Characteristics of Carcinogens (KCCs), which Bette responded to by sharing a cross-mapping study by herself and Daniele Wikoff, explaining how KCCs can be useful in systematic reviews when properly understood and applied. Michael then used a coin-flipping analogy to demonstrate statistical significance and its relevance to glyphosate assessments, emphasizing the importance of considering the totality of data, including dose-response relationships and mode of action, when evaluating chemical risks.

Case Study 2: The Safe Dose Range of Perfluorooctane Sulfonate (PFOS): An International Collaboration

Laura Green and Edmund Crouch presented a second case study on the safety of perfluorooctane sulfonate (PFOS), highlighting its persistence and bioaccumulation in the environment and human body. Laura discussed the decline in PFOS exposure levels in the U.S. population over the past two decades, contrasting it with higher exposures in Chinese workers and fishermen. She noted that there was no reliable epidemiological evidence of PFOS-induced health effects in highly exposed groups, including workers and consumers of contaminated fish. She also highlighted the World Health Organization's inability to establish a health-based drinking water limit for PFOS due to lack of clear evidence of harm.

Laura and Edmund discussed a particular study on the toxicological effects of PFOS in laboratory animals, focusing on liver weight changes as a sensitive endpoint. They analyzed data from two studies: one in cynomolgus monkeys and another in Sprague-Dawley rats, using blood serum concentrations to determine points of departure. They applied conservative uncertainty and safety factors to estimate a maximum contaminant level (MCL) for drinking water, suggesting it could be as high as 140 to 700 nanograms per liter, which is more achievable and less costly than the current U.S. EPA standard of 4 parts per trillion.

Edmund presented a Benchmark Dose Software (BMDS) analysis showing a quantilinear dose-response curve for serum concentrations across different dose groups, with significant overlap in serum concentrations between high and low dose groups. He discussed studies on neonatal effects, parental toxicity, and the half-life of PFAS in humans, noting that a 2022 study by Lai et al. was not mentioned in U.S. EPA's 2024 evaluation, despite providing updated information on half-life estimates. The analysis revealed no significant differences in half-life distributions between males and females in a highly exposed population, with a median half-life of 2.88 years.

The discussion by Edmund and Laura then focused on comparing safe dose estimates for PFOS between independent scientific groups and regulatory agencies like the U.S. EPA. Laura explained that three groups of 29 scientists estimated safe daily doses of PFOS to be between 20 to 100 nanograms, which were more generous than U.S. EPA's estimate of 0.1 nanogram. She highlighted several reasons for the discrepancy, including the lack of clear epidemiological evidence, different regulations, and the absence



Meeting Summary for ARA Workshop XV Day 1 Afternoon

of public or political pressures among the groups of scientists. The discussion also touched on the differences between PFOA and PFOS compounds, as well as the role of epidemiological data in toxicological assessments.

The case study was then opened to the Science Panel for discussion. Members of the panel discussed the reliability of data on PFOS (and PFOA), with Laura emphasizing that these compounds are not immunotoxic and that rodent models may not be suitable for studying their effects. They debated the value of epidemiological studies versus toxicological data, with Bette Meek suggesting that mechanistic data could help integrate different types of studies.

In particular, the group discussed the U.S. EPA's approach to PFOS toxicity, which is based on developmental and cardiovascular effects rather than immune effects. Bette raised concerns about relying on immunotoxicity endpoints without clear mechanistic evidence. Michael Dourson and Laura suggested conducting studies in China where PFOS exposure levels are much higher, and Laura proposed using cyclosporine as a positive control in animal studies to better understand PFOS's immunosuppressive effects. The group agreed that mechanistic data should be considered when interpreting epidemiological studies, and Bette emphasized the need to integrate mechanistic inference with epidemiological and toxicological data.

The group discussed the challenges of interpreting epidemiological data, particularly for PFOS (and PFOA) studies, noting the difficulty in accessing and verifying underlying data. Laura again emphasized the need for new epidemiological studies in China and mechanistic studies using guinea pigs, as current rodent models may not be relevant. Bette highlighted the value of systematic reviews in improving transparency and reproducibility, while Michael and Laura agreed on the freedom and flexibility of their current work compared to regulatory agencies. The discussion touched on the political constraints faced by U.S. EPA regarding PFOS standards and the potential for Health Canada to operate without similar constraints.

The case study discussion was then opened to comments from observers. The group discussed PFOS, focusing on confounding factors in epidemiological studies, safe dose values, and regulatory challenges. Michael highlighted the need for a head-to-head comparison of PFOS with cyclosporine to clarify immune suppression concerns. Laura and Michael noted that IARC classified PFOS as a Group 2B carcinogen, while Bette suggested engaging the thoughts of an observer who was a former U.S. EPA genetic toxicologist, to discuss IARC's key characteristics. The observer shared insights on nitrate and nitrite standards, emphasizing the need for reliable data and alternative approaches to current regulations. The first day concluded with the group agreeing to continue the workshop series, including case studies, and to revisit risk assessment practices.



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Workshop Day 2 Overview

The workshop series continued with Case Study 3 and some follow-up presentations on previous workshop topics, focusing on risk assessment methods and improvements. Pamela Williams, the day 2 workshop chair, provided an overview of the workshop's purpose and format, emphasizing its role in providing feedback on new risk assessment methods without a lengthy review process. The morning session included a case study on systematic review guidelines for toxicity factor derivation using vanadium as an example, presented by Nnamdi Nnoli and Stony Lo from the Texas Commission on Environmental Quality (TCEQ). They outlined the steps for conducting systematic reviews to develop toxicity factors, highlighting the importance of transparent and structured frameworks. The afternoon session included six update presentations on risk assessment methods, with participants discussing challenges and solutions in their respective areas of expertise.

Case Study 3: Fit-for-purpose Systematic Review Guidelines for Toxicity Factor Derivation, Using Vanadium as a Case Study Example

The case study presented a systematic review and evidence integration process for evaluating vanadium and vanadium compounds, focusing on the adverse health effects in humans and animals. Nnamdi and Stony outlined their search strategy, inclusion and exclusion criteria, and data extraction methods, which were conducted using specialized software to ensure transparency and reproducibility. After screening 2,659 citations, 41 studies were included for data extraction, with 13 epidemiological studies and 28 animal bioassay studies. The review aimed to inform the development of toxicity factors for TCEQ's risk assessment process.

The case study first focused on the topic of study liability and quality evaluation. Nnamdi and Stony discussed the assessment of internal validity, sensitivity, and overall study quality for both epidemiological and animal studies, using the U.S. EPA Health Assessment Workspace Collaborative (HAWC) study evaluation matrix. The presentation included examples of quality ratings and heat maps for various studies. They also explained the evidence integration and synthesis process, which involves compiling data from different studies to support or inform toxicity factors. They compared the results of an approach to developing a Development Support Document (DSD) for vanadium with the systematic review process, highlighting the potential benefits of using systematic reviews when appropriate.

Nnamdi and Stony further highlighted the strengths of systematic reviews, including transparency, reproducibility, and the ability to identify broader literature and future research topics. However, they also acknowledged limitations such as time and resource consumption, publication bias, and language bias. They emphasized the importance of having multiple reviewers with expertise, a clear research question, and a comprehensive search strategy. They also discussed the need for data collection and analysis plans, risk of bias assessment, and transparent documentation of the review process. They described how the goal of the presentation was to obtain input from the Science Panel about using the systematic



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review approach in study selection for toxicity factor development and potential improvements to the process.

The case study discussion was opened to the Science Panel, with Pamela Williams and Nnamdi discussing the challenges and potential improvements in evaluating study outcomes. Nnamdi discussed conducting sensitivity analyses using a broader range of studies, including previously excluded ones, to validate the findings. Bette Meek raised concerns about the current assessment process, emphasizing the need for better integration of evidence across studies and the importance of considering mechanistic data early on. She also suggested exploring additional tools for evaluating toxicological studies. The group agreed on the need for more robust integration steps and the use of crude uncertainty analysis in future reviews.

The group further discussed the approach to systematic reviews, with Bette emphasizing the need for a more integrative method and Nnamdi explaining that mechanistic studies are kept as context while focusing on data for air monitoring. Michael Dourson raised questions about exclusion criteria and the fit-for-purpose approach, while Greg Paoli questioned the exclusion of certain studies and the use of PICO/PECO frameworks.

The discussion continued with Nnamdi emphasizing the importance of defining the purpose of a systematic review and highlighting the need to customize the process based on that purpose. Sabine Lange, also with TCEQ, discussed the challenges of balancing systematic review principles with the practical needs of TCEQ's chemical risk assessments. Jim Bus raised questions about the natural occurrence of vanadium and its therapeutic benefits, emphasizing the need to consider these factors in the context of risk assessments. The group agreed on the necessity of conducting an in-depth study to determine accurate toxicity values for vanadium, as current interim values are based on limited data.

The group discussed the value and limitations of systematic reviews in chemical risk assessment, with Sabine explaining that reviews serve three main purposes: ensuring accurate outcomes through study quality evaluation, providing transparency in methodology, and allowing for future review of past decisions. Michael suggested that systematic reviews serve as a training framework for younger staff, while Bette emphasized the need to adapt the PICO (Population, Intervention, Comparator, Outcome) framework to better suit their needs. This part of the discussion concluded with Bette highlighting the importance of systematic evidence maps and AI tools for mechanistic data, while questioning the criteria for when not to conduct a systematic review.

The group further discussed the use of systematic evidence mapping and systematic reviews in chemical risk assessment. Nnamdi explained that systematic reviews are not always necessary when existing studies already provide known effects but should be conducted when new chemicals with unknown effects are evaluated. Sabine highlighted the importance of transparency and confidence in the review process, while Bette suggested that existing systematic review tools may need modification for chemical risk assessment purposes. Greg proposed a new approach to systematic reviews in this context, focusing



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on comparing current assessments to existing standards rather than following strict inclusion and exclusion criteria.

Lastly, the group discussed the role and limitations of systematic reviews in risk assessment, with Jim expressing concerns that requiring systematic reviews could undervalue existing robust risk assessments and potentially harm public health. Nnamdi and Sabine agreed that systematic reviews should complement rather than replace existing assessment methods, noting that TCEQ has conducted two such reviews so far. Michael shared an anecdote about a senior risk assessor's critique of systematic reviews, highlighting the danger of younger assessors using them as a "club" without full understanding of the context. The discussion concluded with a detailed explanation from Nnamdi about the qualitative nature of systematic review ratings, which require at least two reviewers and a third to resolve conflicts, rather than a purely quantitative approach.

The discussion was opened to comments from observers and centered on whether to prioritize animal studies over human studies, with participants debating the quality assessment criteria and the relevance of controlled human exposure studies. The Science Panel raised concerns about the systematic review methodology, suggesting that it may not be well-suited for regulatory purposes due to its origins in medical research. The panelists agreed that while systematic reviews have value, they may not be necessary in every case, and there's a need to develop a more streamlined approach that considers resource constraints and regulatory decision-making needs.



Meeting Summary for ARA Workshop XV Day 2 Afternoon

Updates on Risk Assessment Methods

The afternoon session consisted of 6 presentations on updates of topics that have previously been presented at workshops.

1) RIFM Safety Assessment of Inhalation Exposure to Fragrances – Current Practices and Future Direction

This update was presented by Nikaeta Sadekar with the Research Institute for Fragrance Materials (RIFM).

Key Points and Decisions:

- Developed a framework to assess inhalation exposure and local respiratory toxicity for fragrance ingredients
- Prioritized use of existing data, read-across, and exposure-based waiving to inform safety assessments
- Established criteria for evaluating natural complex substances. Highlighted an example of applying *in vitro* and *in silico* respiratory models to evaluate local respiratory effects from inhalation exposure to fragrance ingredients.

Next Steps:

- Enhance the inhalation threshold of toxicological concern (TTC) by refining existing threshold values
- Support the advancement of scientific knowledge in respiratory sensitization through a dedicated research program

2) Framework for Pre-Manufacturing Notification for Electrocoat Polymers

This update was presented by Britt McAtee with PPG.

Key Points and Decisions:

- Developed a tiered risk assessment framework to facilitate new chemical notifications under the Toxic Substances Control Act (TSCA)
- Tier 1 involves literature review, analog data, *in silico* modeling, and qualitative exposure assessment
- Tier 2 includes quantitative exposure assessment and *in vitro* toxicology testing
- Tier 3 may involve *in vivo* animal testing as a last resort.

Next Steps:

- Continue to refine and improve the tiered risk assessment framework



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- Explore opportunities to automate data entry and validation with U.S. EPA to reduce duplication of effort

3) Transforming the Evaluation of Agrochemical Safety and Risk Assessment: Human Health Risk Example

This update was presented by Douglas Wolf, an independent consultant.

Key Points and Decisions:

- Focused on using existing knowledge and data to inform the evaluation of new agrochemicals
- Leveraged read-across, in silico models, and exposure assessment to reduce animal testing
- Demonstrated that hazard endpoints derived from read-across were adequately protective for the chemicals evaluated in the examples presented.

Next Steps:

- Publish the outcomes of the research project, including the harmonized and curated dataset
- Explore opportunities to expand the approach to other chemical sectors beyond agrochemicals

4) Fish Consumption Benefits and PFAS Risks

This update was presented by Ali Hamade with the Oregon Health Authority.

Key Points and Decisions:

- Compared PFAS studies used by U.S. EPA to derive reference doses with meta-analyses of PFAS effects and fish intake studies
- Found that maternal fish intake is associated with increased birth weight and improved birth outcomes, contrasting with adverse PFAS effects
- Found that adult fish intake is associated with beneficial cardiovascular outcomes with exceptions related to fish type, preparation, and contaminant profiles, as compared to both small increases in serum cholesterol and potential increase in risk of higher cholesterol concentrations associated with PFAS exposure.

Next Steps:

- Advocate for a more thoughtful assessment of PFAS risks that considers the benefits of fish consumption
- Encourage collaboration between healthcare professionals and the public to educate on the balance of risks and benefits



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5) Application of the Threshold of Toxicological Concern (TTC) in the Evaluation of Drinking Water Contact Chemicals

This update was presented by Brad Lampe with NSF International.

Key Points and Decisions:

- Incorporated the Threshold of Toxicological Concern (TTC) approach into NSF's qualitative risk assessment framework for drinking water chemicals
- Developed a process to determine if a chemical is appropriate for TTC evaluation, assess genotoxicity, assign Kramer class, and derive a comparative point of departure.

Next Steps:

- Continue to monitor developments in TTC approaches, such as the recent revisions proposed by FDA, and evaluate their fit for purpose
- Explore opportunities to further automate and streamline the TTC evaluation process

6) Setting Performance Expectations for New Approach Methods in Toxicity Testing: Moving from Intuition to Hard Data

This update was presented by Rusty Thomas with Chemical Insights Research Institute of UL Research Institutes (ULRI).

Key Points and Decisions:

- Conducted a study comparing rodent, human clinical, and in vitro new approach method (NAM) points of departure
- Found moderate quantitative concordance between rodents/humans and NAMs/humans, but limited concordance between rodents and NAMs
- Demonstrated that rodent low effect levels tend to be higher than human low effect levels, requiring larger uncertainty factors for protection.

Next Steps:

- Advocate for the use of data-driven performance expectations, rather than intuition, when evaluating the application of NAMs
- Explore opportunities to leverage pharmaceutical data to further inform benchmarking of NAMs against human toxicity

Overall Next Steps and Considerations

The workshop concluded with a robust discussion of next steps and considerations pertaining to the presentation updates as well as future case study ideas. The following recommendations were made:



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- Continue to explore and develop new approach methods (NAMs) to reduce animal testing, while ensuring they provide adequate protection of human health
- Advocate for a risk-benefit perspective that considers the known benefits of fish consumption alongside PFAS and other chemical risks
- Promote the use of systematic, transparent, and data-driven approaches for problem formulation, literature review, and decision-making
- Leverage existing data and knowledge, such as read-across and TTC, to streamline chemical evaluations and reduce the need for new animal testing
- Encourage collaboration and data sharing across industry, academia, and government to advance the science and application of NAMs and other innovative approaches

As noted by many panelists and workshop participants, the presentations and discussions from this workshop highlighted the ongoing transition in the field of toxicology and risk assessment, with a focus on moving away from traditional animal testing towards more modern, human-relevant methods. The group agreed that the key is to ensure these new approaches provide adequate protection of human health while also considering the broader context of exposure, benefits, and decision-making needs.