December 10-11, 2018
National Academy of Sciences (NAS) Building
2101 Constitution Avenue, NW | Washington, DC 20418

Lecture Room

Table of Contents

AGENDA

Monday, December 10, 2018	
8:30	**Welcome and Overview of the Workshop** *Ivan Rusyn*, Texas A&M University*
8:40	**Systematic Review: Best Practices and Special Considerations for Mechanistic Data** *Holger Schünemann*, McMaster University*
9:00	**The Systematic Review of Mechanistic Data in IRIS Assessments** *Catherine Gibbons, US Environmental Protection Agency*
SESSION 1: Problem Formulation for Evaluating Mechanistic Data	
9:20	**Principles of Problem Formulation and Approaches to Considering Mechanistic Data** *Julian Higgins, University of Bristol*
9:50	**Problem Formulation: Lessons and Tools from Practical Applications Involving Systematic Review of Mechanistic Data** *Daniele Wikoff, ToxStrategies*
10:20	**Panel Discussion:** *Moderator: Holger Schünemann*, McMaster University* *Discussants: Session 1 Speakers; Andrew Rooney*, National Toxicology Program; Maureen Gwinn, US Environmental Protection Agency*
11:30	**Poster Session** (East Court adjacent to Lecture Room)
12:30	*Lunch (Will not be provided. There is a cafeteria on Lower Level)*
SESSION 2: Approaches to Evaluating the Validity of Mechanistic Studies	
1:30	**Consideration of Internal and External Validity in Mechanistic Studies** *Andrew Rooney*, Office of Health Assessment and Translation, National Toxicology Program*
1:55	**Quality Assessment of Big and Complex Data in Pharmaceutical Target and Chemical Safety Assessment** *Matthew Martin, Pfizer Drug Safety Research & Development*
2:20	**OECD Good In Vitro Method Practices (GIVIMP) Guidance and Its Implementation** *Sandra Coecke, European Commission Joint Research Centre*
2:45	**The SciRAP Tool for Evaluating the Quality of In Vitro Studies** *Anna Beronius, Karolinska Institutet*
3:10	*Break*
3:30	**Panel Discussion:** *Moderator: Ivan Rusyn*, Texas A&M University* *Discussants: Session 2 Speakers; David Dorman, North Carolina State University; Julian Higgins, University of Bristol; Tala Henry, US Environmental Protection Agency*
4:30	**Poster Session** (East Court adjacent to Lecture Room)
6:00	*End of Day 1*

* Member of workshop organizing committee.

Tuesday, December 11, 2018

8:30	Welcome and Opening Remarks *Ivan Rusyn*, Texas A&M University*
	SESSION 3: Assimilating and Using Mechanistic Information to Support Evidence Synthesis and Integration
8:40	**Experiences with the Mode-of-Action Framework as an Organizing Framework for Mechanistic Data** *James Klaunig, Indiana University*
9:10	**Development and Use of Quantitative Adverse Outcome Pathways: Lessons Learned from Application to Cardiotoxicity** *Weihsueh Chiu, Texas A&M University*
9:40	**The Key Characteristics Approach to Evaluating Mechanistic Data in Hazard Identification and Risk Assessment** *Martyn T. Smith, University of California, Berkeley*
10:10	**GRADE Evidence-to-Decision Frameworks for Considering Mechanistic Data with Animal and Human Data to Support Evidence Synthesis and Integration** *Holger Schünemann*, McMaster University*
10:40	*Break*
11:00	**Panel Discussion:** *Moderator: Joyce Tsuji*, Exponent* *Discussants: Session 3 Speakers; David Dorman, North Carolina State University; Heather Lynch, Gradient Corporation; Elizabeth Méndez, US Environmental Protection Agency*
12:00	*Lunch (Will not be provided. There is a cafeteria on Lower Level)*
1:00	**Poster Session** (East Court adjacent to Lecture Room)
	SESSION 4: Practical Experience with Implementing Systematic Reviews of Mechanistic Evidence into Human Health Assessments
2:00	**Integrating Mechanistic Evidence into TCEQ Assessments** *Sabine Lange, Texas Commission on Environmental Quality*
2:30	**Approaches Used to Integrate Mechanistic Data into the Report on Carcinogens by the National Toxicology Program** *Amy Wang, Office of the Report on Carcinogens, National Toxicology Program*
3:00	**Implementing Systematic Review Methods and Approaches in TSCA Risk Evaluations** *Iris Camacho, US Environmental Protection Agency*
3:30	**Panel Discussion:** *Moderator: Katya Tsaioun*, Johns Hopkins University* *Discussants: Session 4 Speakers; Daniele Wikoff, ToxStrategies; Heather Lynch, Gradient Corporation; Andrew Kraft, US Environmental Protection Agency*
4:45	**Closing Remarks** *Ivan Rusyn*, Texas A&M University*
5:00	*Workshop Adjourns*

* Member of workshop organizing committee.

PRESENTATION ABSTRACTS

Systematic Review: Best Practices and Special Considerations for Mechanistic Data

Holger Schünemann, McMaster University

The presentation will cover key principles in the conduct of systematic review including a brief history and lessons learned across disciplines. I will briefly review the methodology and standards of the Institute of Medicine report on systematic review, Cochrane, the National Toxicology Program Office of Health Assessment and Translation (OHAT) and other authorities. This will include the topics initiating a systematic review, finding and assessing individual studies, synthesizing the body of evidence and reporting systematic reviews. Items that will be covered in more detail entail:

- Defining the purpose and review questions
- Describing criteria for inclusion and exclusion
- Developing protocols
- Considerations about conflicts of interest
- Assessing the certainty of the evidence
- Using ROBIS, AMSTAR and other tools to assess the credibility of a review

The session will conclude with how the lessons learned from other disciplines can be useful for systematic reviews of mechanistic data.

The Systematic Review of Mechanistic Data in IRIS Assessments

Catherine Gibbons, IRIS Program, National Center for Environmental Assessment, Office of Research and Development, US Environmental Protection Agency

US EPA's Integrated Risk Information System (IRIS) Program evaluates mechanistic data to inform hazard identification determinations regarding the biological plausibility of human and animal data, to identify susceptible populations or lifestages, and to inform low-dose-response relationships. Mechanistic studies, which include a variety of designs (i.e., in vitro, in vivo using various routes of exposure, ex vivo, and in silico), report measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects in both mammalian and non-mammalian model systems. Despite the importance of considering mechanistic data, incorporation of these studies within a systematic review framework remains challenging. Challenges include screening large numbers of diverse studies efficiently; developing transparent and reproducible criteria for identifying the most informative mechanistic studies; the lack of well-developed systematic review tools to assess internal validity of in vitro and in silico studies; and underdeveloped structured frameworks to guide integration of mechanistic information with human and animal health effects evidence. This presentation will provide an overview of the current approaches in the IRIS Program for the systematic review and integration of mechanistic information, describe challenges, propose options for addressing them, and seek feedback on these. [*The views expressed in this abstract are those of the author's and do not necessarily represent the views or policies of the US Environmental Protection Agency or other affiliations.*]

SESSION 1 – Problem Formulation for Evaluating Mechanistic Data

Principles of Problem Formulation and Approaches to Considering Mechanistic Data

Julian Higgins, University of Bristol

Systematic reviews have a privileged role in evidence-based guidelines, decision-making and policy. I will reflect on some of the advances in approaches to systematic review in the area of human health over the last three decades. I will consider their implications for reviews of mechanistic data, particularly in relation to problem formulation. I will explain how it is helpful to distinguish different types of reviews, and to be clear what is the purpose of any particular review at the outset. The planning stages of a review require careful attention to considerations of bias and of applicability. These influence both the choice of evidence to be collated and how the evidence will be synthesized and used to reach conclusions. I will discuss our experiences of translating the ROBINS-I tool for assessing risk of bias in non-randomized studies of health interventions into a new tool (ROBINS-E) for assessing credibility of causal claims about exposures. This has involved

careful articulation of the boundaries between bias and applicability, and lead to a greater degree of focus in a systematic review than has often been the case.

Problem Formulation: Lessons and Tools from Practical Applications Involving Systematic Review of Mechanistic Data

Daniele Wikoff, ToxStrategies

Problem formulation is a well-established component of systematic review (SR). However, in the practice of SR to support chemical assessments, this critical component is currently underappreciated – particularly for SRs involving mechanistic data. Decisions made when establishing the SR question (i.e., the output of problem formulation), as well as the context of the question, have significant impact on the scope, form, and conduct of a SR. Complexities in the utilization of mechanistic data in a SR are numerous. Determining the use or role of such data in the overall assessment is paramount, and is typically dependent on the extent of existing knowledge and assessment objectives. As part of such, it is important to consider how SR methods can be used to facilitate long-standing approaches for evaluating mechanistic data in chemical assessments. The often massive volume of available mechanistic is also important to consider during problem formulation. And specifically, if the underlying complexity and heterogeneity of an evidence base can be systematically assessed and integrated in a manner that is both practical and meaningful to assessment objectives. These and other elements are important to determining the utility and feasibility of conducting an SR of mechanistic data. Available tools and approaches for characterizing available evidence and making structured decisions in problem formulation for chemical risk assessments will be surveyed. Challenges encountered during the practice of systematically reviewing mechanistic data will be demonstrated via case studies; possible solutions that can be implemented during problem formulation will be offered.

SESSION 2 – Approaches to Evaluating the Validity of Mechanistic Studies

Consideration of Internal and External Validity of Mechanistic Studies

Andrew Rooney, Office of Health Assessment and Translation, National Toxicology Program

Abstract will be provided at a later date.

Quality Assessment of Big and Complex Data in Pharmaceutical Target and Chemical Safety Assessment

Matthew Martin, Pfizer Drug Safety Research & Development

The ability and capacity to generate big and complex data has created a tremendous promise with regards to advancing target and chemical safety assessments in the pharmaceutical industry as well as numerous challenges, including ensuring the quality of the data. Automation of analytical pipelines creates an opportunity to add systematic quality control procedures that can highlight, characterize or remove non-informative or bad data. For early target safety assessments, robust transcriptomic (RNA-Seq) tissue maps across human and preclinical species are available and used to characterize potential species-specific target liabilities and inform species selection decisions. In addition to standard RNA-Seq quality control metrics (e.g., % mapped reads), the large-scale and uniform nature of the tissue map dataset is leveraged to provide practical quality metrics that better characterize the true utility of any particular tissue or sample (e.g., biological replicate versus cross-tissue concordance). For early chemical safety assessments, high-throughput and high-content screening (HTS/HCS) has been deployed. For particular HTS/HCS assays, the toxcast data analysis pipeline (tcpl) has been deployed to automate the data analysis as well as provide systematic quality control metrics, including the flagging of bad data points and noisy concentration response profiles. The resulting data is then used in toxicity model predictions that rely on high quality data to make high quality predictions. Specific examples of practical steps to ensure big and complex data quality used in target and chemical safety assessment will be given as well as exemplifying how automation and systemization improve overall data quality.

OECD Good In Vitro Method Practices (GIVIMP) Guidance and Its Implementation

Sandra Coecke, European Commission Joint Research Centre

OECD Good In Vitro Method Practices (GIVIMP) Guidance and Its Implementation: There is a strong belief that in vitro methods are fast becoming a key tool for a new way of doing toxicology. However, their potential will not be fully realised

if they are not developed and applied in a way that scientific integrity and quality is assured. The data they produce will not be trusted by decision makers. A revealing paper (Nature 533, 452-454, 2016) showed that 70% of researchers have tried and failed to reproduce other scientists' experiment's, and more than half of the researchers failed to reproduce their own experiments. These dramatic results call for incentives for better practice. With the development of new high-throughput technologies, stem cells and new culture technologies (organo-typical cell cultures, organ-on-a-chip technologies) new challenges are presented for acceptance of such advanced test systems for regulatory assessment. Good In Vitro Method Practices (GIVIMP) for the development and implementation of in vitro methods for regulatory use in human safety assessment aims to reduce uncertainties in cell and tissue-based in vitro method derived predictions. The drafting of the OECD guidance document, GIVIMP, has been coordinated by the European Commission Joint Research Centre's EURL ECVAM and was approved at the OECD Working Group of the National Coordinators to the Test Guidelines Programme. GIVIMP tackles ten important aspects related to in vitro work: (1) Roles and responsibilities, (2) Quality considerations, (3) Facilities (4) Apparatus, material and reagents, (5) Test systems, (6) Test and reference/control items, (7) Standard operating procedures (SOPs), (8) Performance of the method, (9) Reporting of results, and (10) Storage and retention of records and materials. Since there are currently no validated thyroid in vitro methods, the Joint Research Centre's EURL ECVAM is coordinating a large-scale validation study of a set of 17 mechanistically informative alternative methods in collaboration with the European Union Network of Laboratories for the Validation of Alternative Methods (EU-NETVAL) and the developers of the methods. The methods cover the main possibilities of interaction with the thyroid signaling pathway. The validation study of the thyroid methods will comply with GIVIMP.

The SciRAP Tool for Evaluating *In Vitro* Studies

Anna Beronius, Institute of Environmental Medicine, Karolinska Institutet

The objective of the Science in Risk Assessment and Policy (SciRAP) initiative is to provide a systematic and transparent approach for evaluating individual (eco)toxicity studies to support hazard and risk assessment of chemicals. This presentation aims to present the SciRAP initiative and web-based platform (www.scirap.org), focusing on the SciRAP tool for evaluating the quality of *in vitro* studies and how it can be used for evaluation and integration of mechanistic data in chemical assessments. The tool is freely available on the SciRAP platform and includes criteria for evaluating reliability, addressing aspects of both reporting and methodological quality, as well as relevance of *in vitro* studies. The criteria were developed based primarily on requirements in OECD test guidelines and are currently being assessed for completeness and practical use by experts in the field of *in vitro* testing and health risk assessment. The SciRAP tool provides a summary of study evaluation in the form of a color profile and a numerical score. The color profile, especially, provides a transparent and qualitative overview of how the reviewer judged each criterion, which can be used for conclusions about study quality and to inform evidence integration in chemical assessments. The SciRAP tool for evaluating *in vitro* studies is currently being applied in several on-going studies, for example, case studies assessing the endocrine disrupting potential of chemicals according to the new European legislation. We are also conducting a study together with the US EPA exploring how the SciRAP tool can be adjusted for judging risk of bias domains. Preliminary results from these ongoing studies are presented here.

SESSION 3 – Assimilating and Using Mechanistic Information to Support Evidence Synthesis and Integration

Experiences with the Mode-of-Action Framework as an Organizing Framework for Mechanistic Data

James Klaunig, Indiana University

The Mode-of-Action Framework was created following the revision of the USEPA's cancer risk assessment guidelines in the early 2000s. Initial efforts in the development of the framework predominantly addressed the assessment of carcinogenic compounds. Subsequently, the framework has been applied to non-cancer endpoints. The mode of action frame work has proven to be very useful in performing a transparent and harmonized approaches to the risk assessment of chemicals and the relevance to humans. The first stage is to determine whether it is possible to establish a mode of action. This comprises a series of key events along the causal pathway to cancer, identified using a weight-of-evidence approach based on the Bradford Hill criteria. The key events are then compared first qualitatively and then quantitatively between the experimental animals and humans. Finally, a clear statement of confidence, analysis, and implications is produced. The framework provides an analytical tool to enable the transparent evaluation of the data, identification of

key data gaps, and the presentation of information that would be of value in the further risk assessment of the compound. Additional data on the shape of the dose-response curve, identification of any thresholds and recognition of susceptible subgroups (genetic or life-stage differences). Chemical carcinogens that function through activation of the PPAR alpha receptor have been extensively studied. Using our experience with the PPAR alpha activating compounds, a review of the approach used for determining the cancer mode of action in rodents and the relevance of the rodent findings to humans will be discussed.

Development and Use of Quantitative Adverse Outcome Pathways: Lessons Learned from Application to Cardiotoxicity

Weihsueh A. Chiu, Veterinary Integrative Biosciences, Texas A&M University

Adverse Outcome Pathways (AOPs) are commonly described as qualitative, conceptual constructs used to organize existing knowledge linking across multiple levels of biological organization, culminating in an adverse outcome at the individual or population level. Such qualitative constructs are particularly useful for risk assessment hazard identification, as they can inform biological plausibility, human relevance, as well as toxicity testing and assessment strategies. However, only limited progress has been made in converting such conceptual constructs into quantitative models that can inform dose-response assessment. Here we describe ongoing progress by the joint Texas A&M – North Carolina State University EPA STAR Center to develop a quantitative AOP (qAOP) for cardiotoxicity. Using QT prolongation as a case study, our approach integrates *in vitro* data from a population of induced pluripotent stem cell-derived cardiomyocytes, *in silico* pharmacokinetic and pharmacodynamic modeling, and clinically-based models for cardiovascular risk. We recently demonstrated that our model can accurately predict hazard, concentration-response, and the regulatory safety threshold for QT prolongation of 10 positive and 3 negative control drugs. These results demonstrate the potential for replacing a multi-million dollar clinical trial – the Thorough QT/QTc study – with an *in vitro-in silico* model. Moreover, because cardiotoxicity clinical trials are not performed for environmental chemicals, such a model could fill a critical gap in chemical toxicity testing. Additional applications we are pursuing include characterizing population variability, testing and analysis of a large screening set of >1000 chemicals, mixtures, and population risk prediction. A critical lesson of this work is that identification of a molecular initiating event is not necessary for developing a useful qAOP. Instead, focusing on clinical biomarkers may be a more fruitful avenue to pursue, as they provide a human-relevant anchor point at a “middle” level of biological organization that can be linked both “down” to cellular/molecular events and “up” to individual/population-level effects.

The Key Characteristics Approach to Evaluating Mechanistic Data in Hazard Identification and Risk Assessment

Martyn T. Smith, University of California, Berkeley

The key characteristics (KCs) of human carcinogens were recently introduced as the basis of a uniform approach for searching, organizing, and evaluating mechanistic evidence to support cancer hazard identification (Smith et al 2016; Guyton et al, 2018). The KCs comprise the properties of known human carcinogens, including their ability to, be genotoxic; be immunosuppressive; or modulate receptor-mediated effects. Established human carcinogens commonly exhibit one or more of these characteristics, and therefore, data on these characteristics can provide independent evidence of carcinogenicity when human data are lacking. Such data can also help in interpreting the relevance and importance of findings of cancer in animals and in humans. In its 2017 report on “Using 21st Century Science to Improve Risk-Related Evaluations”, the NRC recently opined that the KCs approach “avoids a narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence.” They further suggested that key characteristics be developed for other endpoints, such as endocrine disruption and reproductive toxicity, and efforts in this regard are approaching completion and publication. The KC approach therefore holds great potential to improve hazard identification and risk assessment, but still needs to be further developed especially in regard to its integration with the hallmarks of cancer and its potential for helping analyze the toxic effects of untested chemicals and chemical mixtures in cell culture and experimental animals. Unfortunately, the current Tox21 and Toxcast repertoire of assays are mostly lacking in relevance to the KCs, as are most clinical biomarkers. Approaches to developing a new set of high throughput tests and biomarkers (a CarciCAST) will be described along with a discussion of the use of the key characteristics approach in hazard identification and risk assessment instead of, or as well as, the current MOA/AOP approach.

GRADE Evidence-to-Decision Frameworks for Considering Mechanistic Data with Animal and Human Data to Support Evidence Synthesis and Integration

Holger Schünemann, McMaster University

Like other decisions about health, decisions about the environment are often concerned with balancing benefits for society against harms in individuals. Decision makers may accept exposures that can cause undesirable health effects in individual cases if desirable consequences for society are overall greater. This information can be difficult to convey to the public. Furthermore, decision-makers in environmental health (EH) often face challenges that require consideration of indirect, mechanistic data or modelling that do not provide estimates about harms in humans with high certainty.

Evidence about mechanisms and animal data provide indirect or supporting evidence for exposure effects on humans. For example, mechanistic evidence is evaluated to help understand potential causality between the exposure and outcome or to understand the shape of dose response below the observed range in animal or epidemiological studies. It is also possible that decisions on interventions that focus on reducing exposure to potentially toxic chemicals could result from a measured mechanistic impact. Thus, mechanistic data may inform the health related question.

Toxicology assessments should include such information to support evidence-based decisions. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to grading evidence and recommendations has been adopted by over 100 organizations worldwide. Much of GRADE's work is focusing on improving the process and increasing transparency of making health related decisions. Despite the work that has been invested for over 18 years, numerous conceptual questions remain unanswered. More recently, GRADE developed and tested Evidence to Decision (EtD) Frameworks for clinical, public health, coverage and policy decisions. EtD frameworks focus on key criteria when moving from evidence to decisions about health, which include the importance of the health problem, the certainty of the evidence, values and preferences (relative importance of the health outcomes), the balance of health harms and benefits, resource implications, equity, acceptability and feasibility. The EtDs have not been tested explicitly in questions about mechanistic data and in toxicology but the criteria should be applicable. This presentation will explore its potential.

SESSION 4 – Practical Experience with Implementing Systematic Reviews of Mechanistic Evidence into Human Health Assessments

Integrating Mechanistic Evidence into TCEQ Assessments

Sabine S. Lange, Joseph (Kip) Haney, Jessica Myers, and Heather Schaefer, Texas Commission on Environmental Quality

The Toxicology Division at the Texas Commission on Environmental Quality (TCEQ) develops toxicity factors, primarily for use in air monitoring and air permit review, but also for remediation of toxicants in water and soil. The TCEQ developed guidelines for derivation of toxicity factors in 2005 (updated in 2012, 2015), and recently has added systematic review guidance to ensure that our toxicity factor derivation is comprehensive and transparent. The TCEQ's guidelines for toxicity factor derivation specify that a mode-of-action (MOA) analysis should occur as the second step in the derivation process, after conducting a literature review for the chemical of interest. The MOA analysis can provide information about: the key and obligatory steps in cellular or organ function that lead to toxicity; the most appropriate dose metric for a dose-response assessment; whether a chemical has a threshold or non-threshold dose-response; the relevance of an adverse effect to humans; and sensitive subpopulations. Derivation of an oral toxicity factor for CrVI provides an example of how we have applied MOA and mechanistic information to our toxicity factor derivation (Haney, 2015, PMID 26493004). Haney used information about the mechanism of CrVI-induced carcinogenesis in animals (regenerative hyperplasia), and information about the sub-linear relationship between oral dose and internal dose to make an informed decision about low-dose extrapolation for CrVI oral carcinogenesis. We have also used mechanistic information during our ethylene glycol systematic review and toxicity factor derivation (Schaefer & Myers, 2017, PMID 29080853). In the ethylene glycol review, mechanistic studies provided important information about ethylene glycol metabolism and potential developmental effects. The TCEQ systematic review guidelines are still very new and we are continuing to develop them as we use the process for more chemical toxicity factor derivations. One future task is developing a more explicit framework for the use of mechanistic data.

Approaches Used to Develop the Report on Carcinogens by the National Toxicology Program

Amy Wang, Office of the Report on Carcinogens, National Toxicology Program

The Report on Carcinogens (RoC) is a cancer hazard identification document mandated by the US congress and prepared by the National Toxicology Program (NTP). Cancer mechanistic information in each assessment can be used to support the findings from cancer studies in humans and/or animals or as the primary rationale for listing (or not listing) a substance in the RoC.

The general approach for the literature-based evaluation of mechanistic information is consistent among substances. Mechanistic information for each agent, substance, mixture, or exposure circumstance (collectively referred to as "substance") is searched and selected via a systematic review approach. The information is organized based on ten key characteristics of carcinogens, and evaluated and synthesized using expert judgement. The approach is also tailored for each assessment based on key issues and available data. For example, in the assessment of antimony trioxide, we utilized available transcriptomic and Tox21 (including ToxCast) data to identify biological changes at the pathway level (rather than individual gene or target affected) and their potential contribution to carcinogenicity. Additionally, we attempt or use a read across approach to list a group or class of chemicals (e.g., haloacetic acids) rather than one distinctive chemical at a time when possible. In some cases, the mechanistic information may further define the exposure to be listed. Take night shift work assessment for example, the preliminary proposed listing is for "persistent night shift work that causes circadian disruption", based on the mechanistic studies in humans and animals, and cancer studies in humans.

We continue to refine the approach to evaluate cancer mechanisms for potential listings in RoC. Our ongoing efforts include developing a systematic approach to capture data from diverse genotoxicity studies and collaborating with other groups to improve text mining tools on cancer mechanisms.

Implementing Systematic Review Methods and Approaches in TSCA Risk Evaluations

Iris Camacho, US Environmental Protection Agency

The 2016 Lautenberg amendments to the Toxic Substances Control Act (TSCA) require EPA to develop fit-for-purpose risk evaluations to determine whether a chemical substance presents an unreasonable risk of injury to human health and/or the environment. The risk evaluation must integrate and assess available information on hazards and exposures for the conditions of use of the chemical substance, including information relating to potentially exposed or susceptible subpopulations. EPA is also required to meet the scientific standards under TSCA section 26, which require using the best available science and the weight of the scientific evidence when conducting risk evaluations. As part of fulfilling these science standards, EPA's Office of Pollution Prevention and Toxics (OPPT) is applying systematic review principles across various multi-disciplinary lines of evidence supporting the risk evaluation, including mechanistic evidence. EPA/OPPT plans to prioritize the evaluation of mechanistic evidence, instead of evaluating all the identified evidence upfront. This approach is anchored in the scoping/problem formulation step supporting each TSCA risk evaluation and has the advantage of conducting a focused review of those mechanistic studies that are most relevant to the hazards under evaluation. After conducting a systematic search of the mechanistic data, the prioritization approach is generally initiated during the data screening step. EPA/OPPT also developed an evaluation tool to assess the quality of *in vitro* toxicity data that uses a numerical scoring system intended to guide the analysis, synthesis and integration of the data in the human health hazard assessment. As EPA/OPPT gains experience assessing a large and diverse chemical space under TSCA, it is anticipated that the current evaluation tool will be refined to capture the heterogenicity of the mechanistic evidence beyond *in vitro* toxicity data. The presentation will discuss the current systematic review process under TSCA, the leverage of technology using systematic review tools and the evaluation tool to assess the quality of the *in vitro* toxicity data. It will also discuss ideas for developing and/or optimizing methods and approaches based on the lessons learned from the first ten TSCA risk evaluations.

POSTER ABSTRACTS

SESSION 1 POSTERS

#1 - Key Characteristics of Male Reproductive Toxicants: An Approach for Screening and Sorting Mechanistic Evidence

***Xabier Arzuaga*[1], Martyn T. Smith[2], Catherine Gibbons[1], Niels E. Skakkebæk[3], Erin Yost[1], Brandy Beverly[4], Andrew Hotchkiss[1], Russ Hauser[5], Rodrigo L. Pagani[6], Steve Schrader, Lauren Zeise[7], and Gail S. Prins[6,8]**

[1]U.S. Environmental Protection Agency, National Center for Environmental Assessment; [2]University of California, Berkeley, School of Public Health; [3]Department of Growth & Reproduction, University of Copenhagen; [4]National Institute of Environmental Health Sciences, National Toxicology Program; [5]Harvard University, T.H. Chan School of Public Health; [6]University of Illinois at Chicago, Department of Urology; [7]California Environmental Protection Agency; Office of Environmental Health Hazard Assessment; 8University of Illinois at Chicago, School of Public Health.

Since the introduction of ten key characteristics of carcinogens as a basis for organizing mechanistic data on carcinogenesis, the National Academy of Sciences has recommended that key characteristics approaches also be developed for noncancer hazards. The aim of this project was to identify a set of key characteristics that can be used for searching, screening, and sorting mechanistic evidence on chemical-induced toxicological responses in the male reproductive system. An expert workgroup was convened at the University of California-Berkeley in March 2018 to review the key characteristics approach and determine whether it can be applied to endocrine disruptors and male and female reproductive toxicants. For male reproductive toxicants, eight key characteristics were identified based on survey of established mechanisms, and include alterations in: 1) germ cell functions, 2) somatic cell functions, 3) reproductive hormone levels/production, 4) hormone receptors, 5) DNA damage, 6) epigenetic modifications, 7) oxidative stress, and 8) inflammation. As a proof of principle, this set of key characteristics was used to organize mechanistic evidence from in vivo and in vitro studies on the PCB mixture Aroclor 1254 and effects in the male reproductive system. The proposed key characteristics of male reproductive toxicants facilitates the systematic screening of mechanistic data from diverse research methods, models, and endpoints, as well as from a variety of known pathways for chemical-induced toxicity that can support hazard characterization. Disclaimer: The views expressed are those of the authors and do not necessarily represent the views or policies of the US EPA. *The views expressed in this abstract are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.*

#2 - Abstract Sifter: A Literature Informatics Tool for Chemical Safety Assessments

***Nancy C. Baker*[1] and Thomas Knudsen[2]**

[1]Leidos; [2]National Center for Computational Toxicology, Office of Research and Development, US Environmental Protection Agency

The biomedical literature contains an abundance of information about the activity of chemicals in biological systems. Literature informatics approaches applied to chemical toxicity research can help researchers make use of this vast literature in more effective ways, including the facilitation of systematic reviews. At the EPA's National Center for Computational Toxicology, we have developed a novel approach to article retrieval in our Abstract Sifter application. The Abstract Sifter is a document retrieval tool that integrates the richness of PubMed and other bibliographic sources with the powerful data-handling capabilities of Microsoft Excel. Results from searches are imported directly into an Excel sheet where the end-user can then use a novel "sifting" methodology for quick, agile relevance ranking of articles. The tool also enables article triage capabilities through easy tagging and noting functionality. Triaged citations can be exported to external software such as reference management tools. The Abstract Sifter can also provide a high-level view of a corpus of literature for a defined set of entities such as chemicals. This "landscape" view helps researchers assess the volume of literature in any given subject area to help with project scoping and chemical ranking and prioritization. Queries developed from the OECD Adverse Outcome Pathway (AOP) project connect key events in AOPs to the literature for chemicals on the Landscape sheet, offering evidence for inferring and investigating a chemical's mechanisms of action. The Excel format of the tool provides ease of use and facilitates collaboration. This abstract does not necessarily represent U.S. EPA policy.

#21 - Table Builder: A Content Management System for Carcinogenicity Health Assessments for the IARC Monographs and the NTP Report on Carcinogens

Andy Shapiro[1,*], Ruth Lunn[1], *Gloria Jahnke*[1], Pam Schwingl[2], Kate Guyton[3], Dana Loomis[3], and Neela Guha[3]
[1]National Toxicology Program, National Institute of Environmental Health Sciences; [*]Current affiliation: Infinia ML; [2]Integrated Laboratory Services; [3]International Agency for Research on Cancer (IARC) Monographs Programme, World Health Organization

The International Agency for Research on Cancer (IARC) Monographs Program and the NTP Report on Carcinogens (RoC) are tasked with evaluating evidence to determine whether agents, exposure scenarios, or mixtures pose a cancer hazard to humans. This process requires an extensive literature search and systematic review of the evidence. Evidence synthesis requires extracting and interpreting data in multiple domains, including 1) human exposure, 2) epidemiologic evidence, 3) animal evidence in test model systems, and 4) mechanistic evidence on key characteristics of carcinogenicity, such as genotoxicity. Standardized tables are necessary to synthesize and evaluate evidence in a transparent and systematic manner; they are included in final reports to summarize the strength of these findings. The Table Builder is a web-based content management system that was designed to capture data and facilitate analyses for human health assessments. This software allows collaborators to extract reported evidence, list potential covariates and confounders, and indicate study strengths and limitations. The data extraction fields are standardized for each evidence stream; this allows multiple collaborators to enter data in a consistent format in parallel. The software is reactive; whenever a user changes any data in the system, it is updated for all other users of the system in real-time (a feature that is indispensable during IARC Monograph meetings). Statistical analysis can be performed in the software (such as Cochrane Armitage trend test or pairwise tests for animal bioassay data). Data visualizations can be created (e.g. forest plots) and filtering of data by cancer site, which facilitate the interpretation and synthesis of data for report writing, especially when the number of extracted elements are large. Further, data can be managed in the software system and quality control (QA/QC) of data entry is integrated into the software. Finally, reports can be downloaded in Microsoft Word format, or data can be downloaded in Microsoft Excel. The Table Builder software was designed using the Meteor JavaScript web framework and uses a Mongo database, and is open-source and publicly available at https://github.com/shapiromatron/tblBuilder. To date, the Table Builder software has been used for 11 IARC and 4 NTP RoC Monographs (including monographs that are finalized and currently under development).

#3 - Implementing Machine Learning Methods in Literature Searching and Screening to Identify and Categorize Mechanistic Evidence for the Integrated Science Assessments

***Jennifer L. Nichols*, Ryan Jones, Michael J. Stewart, and Steven J. Dutton**
National Center for Environmental Assessment, US Environmental Protection Agency

The National Ambient Air Quality Standards (NAAQS) for criteria air pollutants are established by the EPA as mandated by the Clean Air Act to protect public health and welfare. A critical component in reviewing the NAAQS is the development of the Integrated Science Assessments that assess the state of the science informing the relationship between ambient exposures and a range of health and welfare effects. This requires that EPA scientists identify, evaluate, and integrate a broad range of scientific evidence, including mechanistic evidence that is an important aspect to understanding the nature of the relationship between exposure and effect. Because of the vast amount of evidence pertinent to ISAs from both observational and experimental studies, identifying and evaluating the relevant evidence in a comprehensive and efficient manner is a challenge. In the current review of the Ozone NAAQS, recently initiated under an accelerated timeline by directive from the EPA Administrator, methods and approaches for ISA development have been streamlined and modernized to further adopt systematic review methodologies, including for the identification and categorization of mechanistic evidence. As presented in this case study, a combination of machine learning and automated approaches in literature searching through the Health and Environmental Research Online database and the adoption of the SWIFT-ActiveScreener tool, have resulted in a substantially more efficient process to identify and categorize evidence. Ultimately, this streamlined workflow provides an easily adaptable process to effectively search and screen for mechanistic evidence that is a critical component to drawing conclusions in scientific assessments supporting key Agency policy decisions. *The views expressed in this abstract are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.*

#4 - HAWCPROJECT.ORG: A Content Management System for Human Health Assessments

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Decision-makers and researchers frequently conduct literature-based assessments of the potential for chemicals or other exposures to pose a threat to human health. Such assessments typically consist of a critical review of a literature corpus to identify adverse health effects, to extract data for exposure-response relationship modeling, and/or to elucidate toxicity mechanisms. The systematic review methodology increases the transparency and objectivity in an evaluation by using a pre-defined, multistep process to identify, critically assess, and synthesize evidence. In addition to extraction of data, systematic review may also include an assessment of potential bias in a body of literature. A clear and detailed presentation of problem formulation, analysis and outputs, as well as properly documented search strategies and intermediate decisions, are critical to ensure transparency of the process. We address these challenges by creating a modular, web-based content-management system to synthesize multiple data sources into overall human health assessments of chemicals. This free, open-source web-application, HAWC (Health Assessment Workspace Collaborative, https://hawcproject.org/), integrates and documents the overall workflow from literature search, literature screening, risk of bias assessment, data extraction, dose-response analysis using EPA benchmark dose modeling software (BMDS), and data synthesis by enabling creation of customizable visualizations of evidence and risk of bias. Each HAWC assessment can be composed of some or all of these steps, based on the goals of the assessment, and at the discretion of assessment owners. User access is assessment-specific; project-managers can create public or private assessments, and can share with their team during development and ultimately release publicly as supplemental information to final reports (e.g., the US National Toxicology Program (NTP) monograph of immunotoxicity associated with PFOA/PFOS exposure, or the National Academy of Science's report on low-dose toxicity from endocrine active chemicals). All data and figures are exportable in user-friendly formats. To date, nearly 500 assessments have been created by users, and has been adopted for use by the NTP, the US EPA, TCEQ, and 34 assessments to date by the WHO IARC Monographs program. Crucial benefits of such a system include improved integrity of the data and analysis results, greater transparency, standardization and consistency in data collection and presentation.

#9 - Lessons from Using Software Tools to Conduct Systematic Reviews

***Katya Tsaioun*[1], Andrew Rooney[2], Zebrafish Embryotoxicity Workgroup, and Tox21 Workgroup**
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In this presentation, we will present the processes and lessons learned for two case studies: a systematic review (SR) of the Zebrafish Embryotoxicity Test as a predictor of developmental toxicity, and a review of the predictability of the publicly available Tox21/ToxCast data for hepatotoxicity as determined in experimental animals and humans. We will show how the knowledge from the first SR influenced the approach to the second project and how it has affected time lines. The presentation will focus on capacity building, engaging multidisciplinary geographically distributed teams, highlighting the use of collaborative tools with text-mining capabilities that help facilitate and improve the quality of the systematic review process. Four programs were evaluated (Sciome Active Screener, Distiller SR, SysRev and HAWC) and three selected in these projects. Advantages and drawbacks will be presented. Directions for the continued development of such collaborative tools assisting in SRs will be proposed from the practitioner's perspective.

#5 - CRAB: Automatic Text Mining of PubMed for Cancer Mechanisms/Mode of Action (MoA)

***Amy Wang*[1], Ulla Stenius[2], Johan Högberg[2], Imran Ali[2], Simon Baker[3], Ruth Lunn[1], and Anna Korhonen[3]**
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Mechanistic information is often the diverse, challenging, and having-less-developed-approach-and-tool part of systematic review and cancer hazard identification. The CRAB project developed a public tool http://crab3.lionproject.net enabling users to enter a search term (e.g., a(n) substance, occupation, cancer) and immediately receive PubMed abstracts that are tagged according to scientific evidence, mode of action (MoA) of cancer, and toxicokinetics. In scientific evidence,

study design is tagged for subject (human, animal, cell, subcellular, microorganism), study length, and outcome types (biomarker, tumors, morphological effects, biochemical/cell biological effects etc.) In MoA, studies are tagged as genotoxic (include event types) or nongenotoxic with events of co-initiation, promotion (e.g., specific receptor/pathway activation), promotion, progression (e.g., immunosuppression), and multiphase (e.g., transcriptional modification, inflammation). Except electrophilicity and altered nutrient supply, all 10 characteristics of carcinogens are covered. Additionally, each sentence of the abstract is color-coded as describing the background, objective, method, result, conclusion, related work, or future work of the study. For example, searching "benzo(a)pyrene" lead to nearly 12,000 abstracts, among which over 4000 are on genotoxicity (with adducts, strand breaks and mutations being most common, each with over 1300 abstracts), 475 on epigenetics, 0 on angiogenesis, and 50 on toxicokinetic modeling. Users can also search by PubMed IDs to tag specific abstracts. This tool provides a great coverage of mechanistic information landscape and detailed and thoughtful tagging structure is effective and rapid. In the future CRAB will interface with other databases and software, providing even greater support to existing working practices in systematic review and cancer hazard identification.

SESSION 2 POSTERS

#6 - A Novel Approach to Screen for and Evaluate Mechanistic Data for Developmental Neurotoxicity

***Mamta Behl*[1], Kristen Ryan[1], Jui-Hua Hsieh[2], Frederick Parham[1], Andrew Shapiro[1], Bradley J. Collins[1], Nisha S. Sipes[1], Linda S. Birnbaum[1], John R. Bucher[1], Paul M.D. Foster[1], Nigel J. Walker[1], and Richard S. Paules[1]**
[1]National Toxicology Program, National Institute of Environmental Health Sciences; [2]Kelly Government Solutions

The National Toxicology Program (NTP) receives requests to evaluate chemicals for their potential to cause adverse health effects, including developmental neurotoxicity (DNT). Recent requests have included classes of chemicals such as flame retardants, polycyclic aromatic compounds, perfluoroalkyl substances, and bisphenol A analogs, all with approximately 20 – 50 compounds per class, many of which are commercial mixtures. However, all of the compounds within a class cannot be tested using traditional DNT animal testing guideline studies due to resource and limitations and the desire to be timely. Hence, a biologically relevant screening approach is required to rapidly prioritize compounds for further *in vivo* testing. Since neurodevelopment is a complex process involving multiple distinct cellular processes, it is unlikely that any one assay will be able to address the complexity. Hence, the NTP sought to characterize a battery of *in vitro* and alternative animal assays to quantify chemical effects on a variety of neurodevelopmental processes though a collaborative project. The NTP analyzed data from fourteen assays covering *in vitro* and alternate animal models that capture various aspects of neurodevelopment; results were compared using benchmark concentration (BMC) modeling to determine which assays may provide robust information to prioritize compounds for further studies in mammals. This poster highlights: 1) the overview and goals of the project, 2) strategies involved in compound selection 3) development of NTP's approach to evaluate utility of these assays for further prioritization 4) determine the validity of mechanistic data generated by these models, 5) evaluate data analysis strategies, and 6) present data visualization tools through an interactive web application. Finally, we discuss key issues with emphasis on the utility of this approach, some challenges associated with data handling, and highlight knowledge gaps that need to be addressed for its use in regulatory decision-making.

#7 - The SciRAP Tool for Evaluating *In Vitro* Studies for Use in Hazard and Risk Assessment of Chemicals

Anna Beronius **and Johanna Zilliacus**
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The objective of the Science in Risk Assessment and Policy (SciRAP) initiative is to provide a systematic and transparent approach to evaluating individual (eco)toxicity studies for chemical hazard and risk assessment. The SciRAP tools for evaluating ecotoxicity and in vivo toxicity studies were first published on a web-based platform in 2014 (scirap.org). The increasing interest in the integration of in vitro mechanistic data as evidence in hazard and risk assessment prompted us to also develop a SciRAP tool for evaluating in vitro studies. Criteria for evaluating reliability, addressing aspects of both reporting and methodological quality, as well as relevance of in vitro studies were developed based primarily on requirements in OECD test guidelines. This first version of the criteria are now available on the SciRAP platform and are being assessed for completeness and practical use by experts in the field of in vitro testing and health risk assessment.

The output of a study evaluation using the SciRAP method is a color profile, which provides a transparent overview of how the evaluator judged each criterion. These color profiles can be used as basis for evidence integration in hazard and risk assessment. Ongoing studies, using the SciRAP tool for evaluating in vivo studies, demonstrate how the SciRAP method can be adjusted for judging risk of bias domains when applying a systematic review approach. Future studies should illustrate how evaluations of in vitro studies using the SciRAP tool can be used to integrate mechanistic data in hazard and risk assessment.

#8 - OECD Good *In Vitro* Method Practices (GIVIMP) Guidance and Its Implementation

Sandra Coecke[1], **Gerard Bowe[1] and Patience Browne[2]**
[1]European Commission, Joint Research Centre; [2]Organisation for Economic Cooperation and Development (OECD)

OECD Good In Vitro Method Practices (GIVIMP) Guidance and Its Implementation: There is a strong belief that in vitro methods are fast becoming a key tool for a new way of doing toxicology. However, their potential will not be fully realised if they are not developed and applied in a way that scientific integrity and quality is assured. The data they produce will not be trusted by decision makers. A revealing paper (Nature 533, 452-454, 2016) showed that 70% of researchers have tried and failed to reproduce other scientists' experiment's, and more than half of the researchers failed to reproduce their own experiments. These dramatic results call for incentives for better practice. With the development of new high-throughput technologies, stem cells and new culture technologies (organo-typical cell cultures, organ-on-a-chip technologies) new challenges are presented for acceptance of such advanced test systems for regulatory assessment. Good In Vitro Method Practices (GIVIMP) for the development and implementation of in vitro methods for regulatory use in human safety assessment aims to reduce uncertainties in cell and tissue-based in vitro method derived predictions. The drafting of the OECD guidance document, GIVIMP, has been coordinated by the European Commission Joint Research Centre's EURL ECVAM and was approved at the OECD Working Group of the National Coordinators to the Test Guidelines Programme. GIVIMP tackles ten important aspects related to in vitro work: (1) Roles and responsibilities, (2) Quality considerations, (3) Facilities (4) Apparatus, material and reagents, (5) Test systems, (6) Test and reference/control items, (7) Standard operating procedures (SOPs), (8) Performance of the method, (9) Reporting of results, and (10) Storage and retention of records and materials. Since there are currently no validated thyroid in vitro methods, the Joint Research Centre's EURL ECVAM is coordinating a large-scale validation study of a set of 17 mechanistically informative alternative methods in collaboration with the European Union Network of Laboratories for the Validation of Alternative Methods (EU-NETVAL) and the developers of the methods. The methods cover the main possibilities of interaction with the thyroid signaling pathway. The validation study of the thyroid methods will comply with GIVIMP.

#10 – Systematic Literature Review of Available Tools to Critically Appraise In Vitro Studies

Katya Tsaioun[1], **Robert Wright[2], Rob de Vries[3], Paul Whaley[4], and Andrew Rooney[5]**
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In vitro studies are becoming an increasingly important source of evidence in chemical risk assessment. There are concerns, however, about the methodological quality of these studies and multiple interventions are being undertaken to improve them. These interventions to improve study quality can focus on three target groups: (1) researchers designing, conducting and reporting primary *in vitro* exposure studies, (2) peer reviewers of journals advising on whether to publish a submitted manuscript and (3) authors of systematic reviews aiming to assess the risk of bias/study quality of the primary *in vitro* studies included in their review. The systematic review presented here are part of a collaborative project between EBTC and NIEHS, with NIEHS focusing on target groups (1) and (3), and, EBTC focusing on target group (2).

The aim of the EBTC sub-project is to develop a tool, IV-CAT (InVitro Critical Appraisal Tool), which will help ensure comprehensive and exacting peer-review of *in vitro* toxicology studies, to increase the quality (understood as "fitness-for-purpose") of published *in vitro* research. The first step in the development of IV-CAT is a systematic review of existing critical appraisal tools and reporting standards for in vitro research in order to collect potential criteria, which could be included in IV-CAT. The extracted criteria will be used as input for a Delphi study to construct the tool.

In order to conduct this systematic review, a multi-stakeholder working group has been put together by EBTC and a protocol and search strategy have been developed. The search was designed in such a way as to be suitable for all three

sub-projects, with respective groups subsequently doing the screening for target group (1) and (3) (NIEHS) and target group (2) (EBTC). The screening and extraction of data are being done in Distiller SR. The protocol outline, search strategy and search results will be presented.

SESSION 3 POSTERS

#11 - Enhancing Evidence Interpretation and Database Integration via Semantic Matching

Michelle Angrish[1], **Sean Watford**[2,3], **Gail Hodge**[4], **George Woodall**[1], **and Anand Mudambi**[5]
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As part of implementing systematic review, the US Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) program extracts data from ~150 studies per year across 15–20 chemical assessments that are in the development phase. These data are stored in the Health Assessment and Workspace Collaborative (HAWC, https://hawcprd.epa.gov/about/) a free, open-source, and web-based application. Data extraction of author reported health findings have introduced a data consistency and semantic challenge because terms reported by authors are inconsistent (e.g. cytotoxicity, cell death, programmed cell death, cell viability). Inconsistent language may lead to duplication and/or misinterpretation of study findings, make it difficult to efficiently retrieve information from HAWC, and pose a significant barrier to data exchange across different databases used to store toxicity findings. To address these data inconsistencies, the author reported terms managed within EPA HAWC were matched to ontologies and ontology classes within Bioportal (https://bioportal.bioontology.org/ (a comprehensive repository of medical ontologies) to create a controlled vocabulary and ontology useful for expressing relationships between terms. The results (between the input [author term] and Bioportal ontology classes) were scored as: 1 = perfect match, 0.5 = synonym, and other values (0–1) for partial matches. The matching process returns other parameters (e.g. ontology, preferred name, synonym, class definition, class parent, parent definitions) that were used along with the numerical score to annotate author terms into a HAWC controlled vocabulary. The controlled vocabulary is critically important to unify study data managed by the HAWC database, whereas ontologies are used to query the database for relationships between those terms. The result is increased transparency and consistency in identifying and retrieving pertinent evidence during evidence synthesis. The EPA HAWC vocabulary and ontology are interoperable with other databases such as the Adverse Outcome Pathway (AOP) knowledge base and by class matching and ontology mapping can be integrated and used for advanced querying of potential relationships between exposure and outcome. *The views expressed in this abstract are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.*

#12 - Quantitative Weight of Evidence Integration to Compare Confidence in Hypothesized Modes of Action

Richard Becker[1], **Vicki Dellarco**[2], **and Rita Schoeny**[3]
[1]American Chemistry Council; [2]VL Dellarco Independent Consultant LLC; [3]Rita Schoeny LLC

The World Health Organization/International Programme on Chemical Safety mode of action (MOA) framework provides a structure for evaluating evidence in pathways of causally linked key events (KE) leading to cancer. Variability in use of the MOA framework has led to different interpretations of the sufficiency of evidence in support of hypothesized MOAs. To improve the incorporation of MOA knowledge in characterizing human health hazards and selecting dose-response extrapolation methods for specific chemicals, we have extended the MOA framework to enable scoring of confidence in the supporting data. This involves selecting hypothesized MOAs, and then, for each MOA, scoring the weight of evidence (WOE) in support of causality for each KE using evolved Bradford Hill causal considerations (essentiality, dose-response concordance, consistency, and analogy). The utility of this method for understanding and communicating the confidence in the evidence supporting selection of the likely operative MOA was documented in Becker et al., 2017 doi10.1016/j.yrtph.2017.02.017). Additional case examples that are under development will be presented: comparing mutagenic to cytotoxic MOAs for chromium VI, 1,4-dioxane and carbon tetrachloride; for dimethylarsinic acid, comparing a cyotoxicity/regenerative proliferation MOA, a mutagenic MOA, and a reactive oxygen species-induced clastogenicity MOA; for diethanolamine comparing a mutagenic MOA to a choline perturbation MOA; and scoring the confidence in the

WOE for AfB1, an agent that is considered an archetypal mutagenic carcinogen. This method improves the systematic and transparent evaluation of data and facilitates communication of the relative confidence in the evidence used to identify the likely operative MOA.

#13 - Systematic Evaluation and Integration of Data Relevant to Mechanisms of Carcinogenesis: Practical Experience in the Identification, Assessment, and Integration of Mechanistic Evidence in Human Health Assessments

Grace A. Chappell, **Susan J. Borghoff, Seneca Fitch, Candace L. Doepker, and Daniele S. Wikoff**
ToxStrategies, Inc.

Mechanistic data provide valuable information regarding characterization of carcinogenicity. However, the evaluation and integration of mechanistic data is particularly complex for a number of reasons, including heterogeneity of data collection and reporting, and understanding the human relevance of endpoints measured in animal and/or cell-based models, or even in silico approaches. Using a series of four case studies, we demonstrate the application of a systematic approach for the identification, assessment, and integration of mechanistic evidence in human health assessments of carcinogenicity. The approach utilizes a framework that builds upon the key characteristics of carcinogens (KCC) organizational concept by providing a quantitative integration of publicly available KCC-relevant data. For each agent in the series of case studies (collectively >1000 endpoints), data were subjected to three steps: (1) appraisal of individual studies and endpoints, (2) evaluation of the body of evidence for each KCC, and (3) evaluation of all of the KCC-relevant data relative to reported tumors and/or cancer types. Mechanistic data were evaluated and scored for reliability, strength, and activity. These elements were then quantitatively integrated to provide a weighted score for each KCC. The scores facilitate the assessment of the body of evidence in the context of observed tumorigenic responses in animals and humans. In addition to demonstrating how the KCC data can be systematically integrated with other evidence streams, the utility and challenges in the implementation of this approach are addressed.

#14 - Assimilation of Multiple Toxicity Endpoints to Identify and Prioritize Constituents of Concern in Oil and Gas Produced Water

Cloelle Danforth[1], **Ivan Rusyn**[2], **Weihsueh Chiu**[2], **and Elena Craft**[1]
[1]**Environmental Defense Fund;** [2]**Texas A&M University**

Produced water is the largest waste stream associated with oil and gas development. In the United States, onshore operations generate an estimated 900 billion gallons of produced water annually, and its efficient management and disposal is often challenging. While this wastewater is primarily deep-well injected for enhanced oil recovery and disposal, factors including drought and induced seismicity have led to the consideration of its use outside the oilfield. There remain significant gaps in our understanding of potential risks to human health or environmental impacts from such practices. We performed a comprehensive literature search, screening nearly 16,000 articles, to identify and aggregate chemicals detected in produced water. However, the dearth of information on toxicity of these chemicals limits our ability to design effective treatment and monitoring strategies for potential constituents of concern. This poster will present our method to assimilate mechanistic information on these chemicals and to generate data using in silico methods where lacking. This study not only recognizes and prioritizes which chemicals are of concern currently, but also identifies chemicals with no data that will require further study. This research effort will inform stakeholders and decision-makers on the risks that this complex waste stream may pose, and indicates research and regulatory improvements to reduce those risks.

#15 - Review of Environmental and Human Health Hazards from Alternative Applications of Produced Water

Fabian A. Grimm[1], **Karen P. Christensen**[1], **Karlene S. Lavelle**[1], **Silvia I. Maberti**[1], **Melannie S. Alexander**[1], **Thomas F. Parkerton**[1], **and Dennis J. Devlin**[2]
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Alternative applications of produced water (PW), the largest waste stream of the oil and gas industry, are currently being evaluated. While the benefits lie in reintroduction of a potentially valuable resource, especially in certain geographic regions, the risks associated with introducing onshore PW into the environment and impacts resulting from PW exposures to crops, wildlife, and humans are not well understood. The goal of this study was to identify scientific reports on environmental and human health impacts of PW with an emphasis on mechanistic data relating to endocrine activity and

mutagenicity. >2000 articles were identified through database searches and initially subjected to expert review. 300 of these publications were considered relevant to the topic of interest and were further evaluated using software-assisted evaluation in "Sciome Workbench for Interactive computer-Facilitated Text-mining" (SWIFT Review). SWIFT analysis revealed compositional, exposure and ecotoxicological studies as major focus areas in the PW literature. Consistent with increasing interest in alternative applications of PW, publication trends show a proportionally much stronger increase in the onshore PW literature compared to offshore PW. In order to identify mechanistic studies, search results were imported into "Health Assessment Workspace Collaborative" (HAWC) for subject matter expert review. Altogether, eighteen manuscripts relevant to endocrine disrupting potential and five papers evaluating mechanisms of mutagenicity and mutagenic potential of PW were identified. Hazard contextualization by consideration of published human health risk assessments and PW treatment prior to environmental release indicate low mutagenicity and overall cancer risk, especially when appropriate PW treatment strategies are being considered.

#16 - Incorporating Mechanistic Evidence and Systematic Review Tools to Assess the Biological Plausibility of Cardiovascular Effects in Integrated Science Assessments

Michael J. Stewart, ***Ellen Kirrane, Thomas Luben, Michelle Angrish, and Jennifer Nichols***
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National Ambient Air Quality Standards (NAAQS) are set for the six criteria pollutants: particulate matter (PM) ozone (O3), oxides of sulfur, oxides of nitrogen, lead, and carbon monoxide. Primary NAAQS are set to protect public health- including sensitive populations such as children, older adults and people with chronic diseases. The Integrated Science Assessments (ISAs) identify, evaluate, and synthesize the best available and most policy-relevant exposure and health evidence, and communicate critical science judgments regarding the extent to which a specific health effect is related to exposure to a specific criteria pollutant. In making causality determinations, it is important to provide evidence that can plausibly link the inhalation of a criteria pollutant to downstream health effects that are systemic in nature. In the 2018 ISA for PM, a new and innovative approach was taken to systematically assess the biological plausibility for epidemiologic results indicating positive associations between ambient PM2.5 concentrations and serious health outcomes such as ischemic heart disease, heart failure, and mortality. This approach leveraged mechanistic animal toxicology evidence along with human health endpoint data to create biologically plausible pathways by which inhalation exposure to PM2.5 could lead to these health outcomes. Here, we describe this approach and these biologically plausible pathways, placing emphasis on the role of mechanistic data in their construction. We also briefly describe how this process has been improved upon in the O3 ISA by incorporating elements of systematic review.*The views expressed in this abstract are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.*

#17 - Development of a Novel Evidence Integration Framework that Incorporates Human, Animal and Mechanistic Data

Sandra I. Sulsky[1], **Tracy Greene**[1], **Greg Mariano**[1], **Farah Chowdhury**[1], **Allison Franzen**[1], **P. Robinan Gentry**[1], **Donna C. Smith**[2], **and Willie McKinney**[2]
[1]**Ramboll US Corporation;** [2]**Altria Client Services**

To accurately characterize human health hazards, human, animal and mechanistic data must be integrated and the relevance to the research question of all three lines of evidence must be considered. Mechanistic data are often critical in fully integrating animal and human data and characterizing relevance and uncertainty. This novel Evidence Integration Framework (EIF) provides a method for synthesizing data from comprehensive, systematic, quality-based assessments of the epidemiological and toxicological literature, including in vivo and in vitro mechanistic studies. The data are organized using both a disease-based and mechanism-based scheme, providing a method for assimilating and using mechanistic information to support evidence synthesis. The disease-based scheme uses the evidence of human health outcomes studied in the best quality epidemiological literature to organize the toxicological data according to authors' stated purpose, with the pathophysiology of the disease determining the potential relevance of the toxicological data. The mechanism-based scheme organizes the data based on the proposed mechanisms of effect and mechanistic data supporting key events leading to each endpoint, with the epidemiological data providing corroboration or no corroboration of causality. The EIF includes a method to cross-classify and describe the concordance of the data, and to characterize its uncertainty. A case study with nicotine is presented focused on the integration of evidence related to

non-acute exposure and cancer. The results of the case study highlight knowledge gaps, demonstrate how different conclusions may be drawn depending on the organization of the data, and show the impact of uncertainties on the strength of causal inference.

SESSION 4 POSTERS

#18 - Building and Evaluating the Utility of an Adverse Outcome Pathway Network forArsenic-Induced Diabetes

***Ingrid L. Druwe*[1], J. Allen Davis[2], Jeff Gift[1], Ila Cote[1], and Janice S. Lee[1]**
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Arsenic exposure has been associated with numerous diseases including various cancers, adverse pregnancy outcomes, and metabolic diseases such as diabetes mellitus, however, the exact molecular events by which arsenic contributes to these diverse disease states is yet to be fully elucidated. In their recommendations to the IRIS Program regarding the inorganic arsenic assessment, the National Research Council (NRC) recommended conducting mode of action (MOA) analysis to facilitate understanding of exposure-response relationships and interindividual variabilities for health outcomes where dose response extrapolation to below the observed range may be necessary (NRC, 2013). The AOP framework (Villenueve et al., 2014) was used to organize and identify important key events and data gaps in the arsenic-induced diabetes MOA. To identify the key events leading to the AO, we performed a literature search in PubMed and identified peer reviewed medical reviews of idiopathic diabetes disease. We screened the results and included publications that described mechanisms and or molecular events in the onset of idiopathic diabetes mellitus disease. We assembled the AOP for idiopathic diabetes by binning the results into key events in the disease process. Next, we performed a targeted literature search for arsenic MOA and used clustering to identify and tag AOs using studies from the previous IRIS arsenic assessments as seeds. We took the information under the diabetes tag and overlaid the information onto the AOP for idiopathic diabetes disease. This allowed us to identify key events in the progression of iAs-induced diabetes. While this approach has been helpful in identifying key mechanistic steps and illustrates a process whereby mechanistic information can be systematically arrayed to help inform human health risk assessments, the analysis was not sufficient to dictate a dose-response shape. However, the results from this analysis helped to refine the scope of the assessment, focusing it on the relevant epidemiologic studies. *The views expressed in this abstract are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.*

#19 - The Key Characteristics of Carcinogens as an Organizing Principle for Mechanistic Evidence: Ethylene Oxide as a Case Study

***Jason M. Fritz*[1], Nagu Keshava[2], Suryanarayana V. Vulimiri[2], and Catherine Gibbons[3]**
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In 2016, the U.S. Environmental Protection Agency's Integrated Risk Information System Program finalized a cancer assessment of ethylene oxide (EtO), characterizing it as "carcinogenic to humans" following inhalation exposure. EtO induces lymphoid and breast cancers in both humans and rodents, as well as other tumors in rats and mice. While strong epidemiological evidence was instrumental in the human health hazard characterization process, evaluation of the animal and mechanistic data was also critically important. Core concepts from the key characteristics of carcinogens (KCCs) (Smith et al., 2016), a pragmatic means of categorizing and evaluating the weight of evidence for mechanisms of carcinogenesis, were adopted in the organization of the mechanistic data summary sections supporting the mode of action analysis. In subsequent work, the mechanistic evidence identified in the comprehensive literature search included in the IRIS assessment has been further reviewed and organized in a systematic manner using the KCCs as an organizing principle, coupled with a weight of evidence approach and integrated into adverse outcome pathways. Strong and consistent evidence indicates that EtO is both electrophilic and mutagenic, representing two of the 10 KCCs; however, evidence for oxidative stress, another KCC, was neither strong nor consistent. Evidence of coherence in genetic or genomic damage in similar tissues across rodents and humans provides further support, linking relevant associations across data streams. One significant challenge was a paucity of mechanistic data identified from the EtO assessment literature search to support

evaluation of 7/10 of the KCCs; specific supplemental literature searches have since been performed to locate published information pertinent to each KCC. In this case study of EtO, the evaluation and discussion of cancer mechanisms was facilitated by using the key characteristics of carcinogens as a central organizing principle to evaluate mechanistic data. *The views expressed in this abstract are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.*

#20 - Using Mechanistic Information to Support Evidence Integration and Synthesis: A Case Study with Formaldehyde

Robinan Gentry[1], **Tracy Greene**[1], **Allison Franzen**[1], **and Chad M. Thompson**[2]

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Formaldehyde is one of the most comprehensively studied chemicals, with over 30 years of research focused on understanding the development of cancer following inhalation. The extensive database has been reviewed by multiple authoritative bodies, focusing on upper respiratory tract cancer and leukemia to characterize the potential for carcinogenicity. Modes of action (MOA) have been proposed for each endpoint, with mechanistic data developed to help understand if these MOAs are operable in humans. When consistent with the problem formulation, proposed MOAs help to narrow the focus of literature search and review of mechanistic data. Formaldehyde is also produced endogenously, and therefore requires mechanistic considerations to understand the potential for health effects that can be attributed to exogenous exposure. An approach is presented to organize and integrate mechanistic data to evaluate the key events postulated for both upper respiratory tract cancer and leukemia. The approach utilizes pharmacokinetic data and existing MOA frameworks to assess evidence around the key events in proposed MOAs, considering modified Bradford Hill criteria, as well as evaluation of the quality and consistency of the mechanistic studies. Output from available tools, e.g. biologically-based dose-response models, are also considered in evaluating proposed cancer MOAs for formaldehyde. This case study demonstrates the utility of a mechanism driven approach for a chemical with extensive data to support an MOA for one endpoint and limited/no data to support another endpoint. These two contrasting examples show the role and value of mechanistic data in drawing conclusions from evidence integration and synthesis and reducing uncertainty.

#22 - Use of the Key Characteristics of Carcinogens and Read Across-Like Approaches for Cancer Hazard Evaluation: A Case Study with Haloacetic Acids

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The Report on Carcinogens (RoC) is a congressionally mandated public health report that identifies cancer hazards. It identifies agents, substance mixtures or exposure circumstances known or reasonably anticipated to be human carcinogens based on systematic evaluation of the scientific literature and application of specific listing criteria. These criteria include listings based on mechanistic evidence indicating that the agent either acts through relevant cancer mechanisms in humans or belongs to a structurally-related class of chemicals previously listed in the RoC. Thus, these criteria allow for the use of mechanistic data and read across-like approaches to evaluate chemical agents.

This RoC cancer hazard evaluation focuses on 13 haloacetic acids (HAAs) found as water disinfection by-products. HAAs are formed during the disinfection process when chlorine-based disinfectants react with organic matter naturally present in the source water resulting in by-products potentially affecting public health. Of the 13 HAAs, 6 have been tested for carcinogenicity in rodents and 5 were positive for cancer. A primary objective of this evaluation was to determine if read across-like techniques would enable listing HAAs as a class, subclass or individually. Mechanistic data based on the 10 characteristics of carcinogens along with disposition and toxicokinetic data were organized and clear trends were identified related to the halogen substitution pattern. Although these data were insufficient to propose listing haloacetic acids as a class, they supported NTP listing recommendations of *reasonably anticipated to be human carcinogen* for two haloacetic acids with no animal cancer data plus four haloacetic acids with animal cancer data.

#23 - An Approach for Assimilating and Applying Mechanistic Information in Human Health Assessment: A Case Study with Hexavalent Chromium

***Chad M. Thompson*, Mina Suh, Deborah M. Proctor, Laurie C. Haws, and Mark A. Harris**
ToxStrategies, Inc.

Mode of action (MOA) analysis is an exercise in structured integration of mechanistic data, but as risk assessment evolves toward using systematic review approaches, best practices for assimilating MOA data into risk assessment are still being explored. Two challenges to MOA analysis for carcinogens with large databases are i) focusing the analysis on the data most relevant for the risk assessment (informed by problem formulation), and ii) succinctly summarizing large amounts of literature into a coherent series of key events (as part of appraisal, synthesis, and integration). Herein, we demonstrate a two-phase approach that builds upon and/or refines two existing strategies for assimilating and applying mechanistic data in risk assessment. Specifically, Phase 1 adapts the most relevant factors Eastmond (2012) identified as influencing mutagenic MOA determinations by regulators—including the nature of the tumors of interest, properties of the chemical, pharmacokinetics, and in vivo genotoxicity. These factors/summaries provide critical information that subsequently feed into Phase 2, which is a formal MOA analysis using existing frameworks (e.g. IPCS or EPA) that consider weight of evidence, Hill criteria, and human relevance. We demonstrate this two-phase approach by retrospectively combining two published articles on the oral carcinogenicity of hexavalent chromium (one based on the Eastmond factors; one based on a MOA framework) into an integrated analysis. Phase 1 organizes critical information that is relatively judgement free (e.g. dosimetry data; in vivo genotoxicity results) such that MOA analysis in Phase 2 (which inherently involves more scientific judgment) is presented in a clearer and transparent manner.

#24 - Application of Mechanistic Data Quality Criteria in Assessment of the Relationship between Congenital Heart Defects and TCE Exposure—A Case Study

***Daniele Wikoff*, Jon Urban, Grace Chappell, and Laurie Haws**
ToxStrategies, Inc.

This case study examined the utility of USEPA OPPT's Draft TSCA Data Quality Criteria for mechanistic data. This work is part of a larger effort to assess and compare available study validity approaches for multiple evidence streams by building on a previous application of OHAT risk of bias criteria to the human and experimental animal data characterizing potential associations between gestational exposure to trichloroethylene and congenital heart defects. The mechanistic evidence base consisted of diverse study designs and endpoints. Application of the TSCA criteria resulted in a range of quality scores. Common differentiators across the mechanistic experiments included test design (e.g., lack of a relevant positive control), exposure characterization (e.g., inadequate reporting on substance preparation and/or storage; inappropriate exposure duration or staging), and data presentation (e.g., failure to report or describe exposure-related toxicities). Application of the TSCA quality metrics allowed for categorization of the quality of the mechanistic evidence base, including identification of studies that would better support development of conclusions with a greater degree of confidence, as well as those that are not sufficiently adequate. Challenges in application were also apparent, consistent with those commonly associated with assessing quality in a heterogenous dataset. Results highlight the need for continued refinement of available tools to ensure "fit for purpose" evaluation of both internal and external validity of mechanistic studies. Challenges in application, workflow, and subsequent integration of validity concepts with other types of evidence will be addressed.

#25 - A Case Study Approach to Systematically Review Mechanistic Information of the Thyroid Hormone Adverse Outcome Pathway

Andrea Kirk[1], *Kristan Markey*[2], Isabelle Lee[3], Pamela Noyes[4], Nancy Baker[5], Seema Schappelle[2], and Stanley Barone[2]
[1]Office of Land and Emergency Management, US Environmental Protection Agency, [2]Office of Chemical Safety and Pollution Prevention, US Environmental Protection Agency, [3]University of Pennsylvania, Perelman School of Medicine, [4]Office of Research and Development, US Environmental Protection Agency, [5]Leidos, Inc.

The US Environmental Protection Agency's (EPA) uses systematic review (SR) and systematic evidence mapping for multiple purposes including elucidation of biological pathways and identification of reference chemicals for model and test guideline evaluation. SRs use well-defined, transparent, consistently applied approaches to evaluate available

research on a topic. We have adapted and built upon standard systematic review frameworks (such as NAS/IOM, OHAT, and TSCA) to interrogate complex biological pathways and mechanisms. The proposed approach is expected to facilitate and further refine efforts to design SR approaches for interrogation of mechanistic lines of evidence. Early search strategies of the thyroid literature identified 1+ million potentially relevant articles across a broad range of biological complexity. These results prompted the need to adapt and develop workflows that integrate elements of evidence mapping together with data extraction, machine learning systems and natural language processing, and harmonization of ontologies for management and optimization of large scale pathway-based systematic reviews. Given the breadth and complexity of the literature space, key innovations include modularizing the workflows, inventorying the study elements and experiments rather than papers, and tracking data extraction against inventories. It is unlikely that the complete literature space could ever be surveyed by a single research entity. This adapted framework is being piloted to support the development of high throughput screening strategies to interrogate thyroid perturbations by:

-Identifying molecular mechanisms of xenobiotic disruption of thyroid hormone-related networks;
-Identifying new potential high and low throughput test methods for further development and evaluation of molecular initiating events of adverse outcome pathways; and
-Identifying diverse reference chemicals with a range of potencies.

We anticipate that this approach will generate evidence roadmaps of downstream adverse outcome key events. We present a conceptual model, adapted systematic review framework, and preliminary results of interrogating mechanistic information of thyroid hormone perturbation pathways.

The views expressed in this abstract are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

PROFESSIONAL BIOSKETCHES

WORKSHOP COMMITTEE

Ivan Rusyn, MD, PhD, Texas A&M University

Dr. Rusyn is a Professor in the Department of Veterinary Integrative Biosciences of the College of Veterinary Medicine and Biomedical Sciences of Texas A&M University. He is also chair of the Interdisciplinary Faculty of Toxicology at the university. His laboratory has an active research portfolio with a focus on the mechanisms of action of environmental toxicants, the genetic determinants of susceptibility to toxicant-induced injury, and computational toxicology. His studies on health effects of environmental agents have resulted in over 200 peer-reviewed publications. He is currently on the Board of Scientific Councilors of the National Institute of Environmental Health Sciences and is a member of the Research Committee of the Health Effects Institute. He has served on several committees of the National Academies, including the Committee on Incorporating 21st Century Science into Risk-Based Evaluations and the Committee on the Design and Evaluation of Safer Chemical Substitutions. Most recently, he chaired the Committee to Review Report on Long-Term Health Effects on Army Test Subjects. Dr. Rusyn received his MD from Ukrainian State Medical University in Kiev and his PhD in toxicology from the University of North Carolina at Chapel Hill.

Richard A. Corley, PhD, Greek Creek Toxicokinetics Consulting, LLC

Dr. Corley was a Laboratory Fellow at the Pacific Northwest National Laboratory operated by Battelle for the US Department of Energy. He specializes in the development of physiologically based pharmacokinetic models, real-time breath analysis, dermal and inhalation bioavailability, and the development of three-dimensional computational fluid-dynamic models of the respiratory system. He has published numerous peer-reviewed papers on oral, dermal, and inhalation toxicology; on modes of action of a variety of industrial and consumer chemicals; and on pharmacokinetic modeling and its applications in human health risk assessment. Dr. Corley has served on several National Academies committees, including the Committee to Assess the Health Implications of Perchlorate Ingestion, the Standing Committee on Risk Analysis Issues and Reviews, the Committee to Review EPA's Draft IRIS Assessment of Formaldehyde, the Committee to Review EPA's Draft State of the Science Paper on Nonmonotonic Dose Response, and the Committee to Review Advances Made to the IRIS Process. He received his PhD in environmental toxicology from the University of Illinois at Urbana-Champaign.

Ana Navas-Acien, MD, PhD

Dr. Navas-Acien is a Professor of environmental health sciences at Columbia University and director of the Columbia University Superfund Research Program. She is a physician-epidemiologist with a specialty in preventive medicine and public health. Her research interests are in cardiovascular and metabolic effects related to chronic exposure to arsenic and other metals in drinking water and food. She is involved in prospective cohort studies of arsenic exposure and metabolism in American Indian communities and in multi-ethnic urban adults. Other research interests include tobacco control research and the contribution of emerging tobacco products, including e-cigarettes to metal exposure and health effects. Her work for the National Academies includes past service on the Committee on Inorganic Arsenic and Committee on the Review of Health Effects of Electronic Nicotine Delivery Systems, among other committees. Dr. Navas-Acien received her MD from the University of Granada School of Medicine in Spain, her MPH from the National School of Health in Madrid, and her PhD in epidemiology from the Johns Hopkins University Bloomberg School of Public Health.

Andrew A. Rooney, PhD, Office of Health Assessment and Translation, National Toxicology Program

Dr. Rooney is the Acting Director of the Office of Health Assessment and Translation (OHAT) in the National Toxicology Program at the National Institute of Environmental Health Sciences (NIEHS). He has been developing risk assessment methods and guidance throughout his professional career and is a principal author of the 2012 World Health Organization/International Programme on Chemical Safety Guidance for Immunotoxicity Risk Assessment for Chemicals. Most recently, Dr. Rooney has been working on emerging issues in toxicology and environmental health, including methods to address study quality in terms of risk of bias for human, animal, and mechanistic studies and adaptation of

systematic review methods for addressing environmental health questions. He led the team that developed the OHAT approach to systematic review. Dr. Rooney was a member of the National Academies Committee Endocrine-Related Low Dose Toxicity. He has an MS and a PhD in zoology from the University of Florida.

Holger J. Schünemann, MD, PhD, McMaster University

Dr. Schünemann is Chair of the Department of Health Research Methods, Evidence, and Impact, Director of Cochrane Canada and co-chair of the GRADE working group who dedicates his research to knowledge synthesis and guideline development. Maintaining his internal medicine practice fulfills his passion for patient care and ensures his research is people-oriented. Dr. Schünemann received his MD from the Medical School of Hanover in Germany, and his MSc in epidemiology and PhD in epidemiology and community medicine from the University at Buffalo, State University of New York.

Peter S. Thorne, PhD, University of Iowa

Dr. Thorne is Professor and Head of the Department of Occupational and Environmental Health at the University of Iowa College of Public Health. He is Associate Director and co-founder of the Interdisciplinary Graduate Program in Human Toxicology. He also directs the NIH-funded Environmental Health Sciences Research Center. His research interests are in environmental risk factors for asthma, inflammatory lung diseases, endotoxin- and glucan-induced immunomodulation, and novel methods for exposure assessment and modeling. He is internationally recognized for his discoveries in the exacerbation of asthma associated with domestic and occupational exposures to bioaerosols. He was a co-investigator on a large study of exposure and health outcomes in Persian Gulf War veterans. He is a former Chair of the U.S. Environmental Protection Agency's Science Advisory Board. Dr. Thorne is currently a member of the National Academies Board on Environmental Studies and Toxicology and the Committee on Toxicology. He received his BS in chemical engineering, MS in biomedical engineering and PhD in toxicology from the University of Wisconsin-Madison and completed a postdoctoral fellowship in immunotoxicology at the University of Pittsburgh.

Katya Tsaioun, PhD, Johns Hopkins University

Dr. Tsaioun is the Director of Evidence-based Toxicology Collaboration at Johns Hopkins Bloomberg School of Public Health, where she leads international multi-stakeholder efforts to establish evidence-based methodologies and practices in translational research to inform regulatory decisions. The focus of her career has been on the translation of scientific innovations into policies and technologies enabling improvements in public health. She spent two decades in the pharmaceutical industry leading translational drug-discovery teams, subsequently founding her company, Apredica, which became a leader in commercializing innovative *in vitro* ADME and toxicity technologies. After a successful acquisition of Apredica by Cyprotex, PLC (now Evotec), she then served as CSO and Board member in the merged company. Dr. Tsaioun is serving on advisory boards of companies and non-profit organizations, and on scientific review committees at the NIH and private foundations. She earned her PhD in human nutrition science from Tufts University Friedman School of Nutrition Science and Policy and completed post-doctoral training in neurochemistry at Harvard Medical School.

Joyce S. Tsuji, PhD, Exponent, Inc.

Dr. Tsuji is a Principal Scientist at Exponent, where she is involved in assessing health risks associated with substances in the environment, foods, consumer and personal care products, and medical devices in the United States and internationally for industry, trade associations, the federal government, state agencies, municipalities, and private citizens. Her work has also involved environmental exposure studies and community programs involving health education and biomonitoring for populations potentially exposed to chemicals in the environment, including soil, water, and food-chain exposures. Dr. Tsuji is a board-certified toxicologist and a Fellow of the Academy of Toxicological Sciences. She has served on expert committees for EPA, the US Army, and the state of Washington. She is a former member of the National Academies Board on Environmental Studies and Toxicology and has served on a number of National Academies committees. Dr. Tsuji received her PhD focused in environmental physiology from the Department of Zoology at the University of Washington.

SPEAKERS

Anna Beronius, PhD, ERT, Karolinska Institutet

Dr. Beronius is a European Registered Toxicologist (ERT) and Assistant Professor at the Institute of Environmental Medicine, Karolinska Institutet, in Sweden. Dr Beronius' scientific activity primarily concerns methodologies that promote structure and transparency in hazard and risk assessment of chemicals, such as systematic review methodologies and adverse outcome pathways (AOP). Focus has specifically been on health risk assessment of endocrine disruptors and of combined exposures. She is one of the initiators and developers of the Science in Risk Assessment and Policy (SciRAP) web-based platform (www.scirap.org), which provides criteria and tools for the evaluation of individual toxicity and ecotoxicity studies for use in hazard and risk assessment of chemicals. Dr. Beronius is also involved in various expert assignments to support national and international agencies and organisations in the area of hazard and risk assessment. She also teaches at Karolinska Institutet and other institutions on the topics of endocrine disrupting chemicals and risk assessment methodologies, and is involved in organizing courses in health risk assessment, for example at Karolinska Institutet and at the European Food Safety Authority.

Iris A. Camacho, PhD, US Environmental Protection Agency

Dr. Camacho is a Toxicologist and Human Health Risk Assessor at the U.S. EPA's Office of Pollution Prevention and Toxics (OPPT), Risk Assessment Division. She is currently coordinating the efforts of implementing systematic review methods and approaches in chemical risk evaluations conducted under the new requirements of the Frank R. Lautenberg Chemical Safety for the 21st Century Act, which amends the Toxic Substances Control Act (TSCA). Prior to this role, Dr. Camacho provided technical and leadership support for various risk assessment activities including those related to trichloroethylene (TCE), dichloromethane (DCM) and N-methylpyrrolidone (NMP) as part of OPPT's chemical safety program under the TSCA Work Plan. She was also a member of the EPA's National Advisory Committee on Acute Exposure Guideline Levels (AEGLs), which in conjunction with the National Academies of Science, Engineering, and Medicine Committee on Toxicology, developed human health guidelines for emergency planning and response applications. Dr. Camacho received her BS in biological sciences from Virginia Tech and PhD in microbiology and immunology from the Virginia Commonwealth University Medical Center.

Weihsueh Chiu, Ph.D., Texas A&M University

Dr. Chiu is a Professor in the Department of Veterinary Integrative Biosciences in the College of Veterinary Medicine and Biomedical Sciences at Texas A&M University. Before joining the university, he worked at the US Environmental Protection Agency (EPA) for more than 14 years, most recently as chief of the Toxicity Pathways Branch in the Integrated Risk Information System (IRIS) Division of the National Center for Environmental Assessment. His research has focused broadly on human health risk assessment, including systematic review and meta-analysis methods, pharmacokinetic modeling, dose-response assessment, characterizing uncertainty, and addressing individual susceptibility to better protect sensitive subpopulations. He has served on several National Academies of Sciences, Engineering, and Medicine committees, including the Committee on Endocrine-Related Low-Dose Toxicity, which performed several systematic reviews as part of an overall strategy for evaluating low-dose toxicity from endocrine active chemicals. He is currently a member of the National Academies Committee to Review the Dietary Reference Intakes for Sodium and Potassium. Dr. Chiu received a PhD in physics from Princeton University.

Sandra Coecke, PhD, European Commission Joint Research Center's Chemicals Safety and Alternative Methods Unit hosting the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM)

Dr. Coecke established and manages the regulatory required European Union Network of Laboratories for the Validation of Alternative Methods (EU-NETVAL), which are 37 high quality *in vitro* testing laboratories across Europe. She has 30 years of experience in *in vitro* toxicology, in vitro method validation and running a GLP test facility. She has been involved in many international research-and-development and validation activities related to the development of new *in vitro* cell and tissue-based methods. She established international accepted quality principles related to cell culture and

in vitro method practices. She was one of the lead persons in the issuing of the OECD advisory document on *The Application of the Principles of GLP to in vitro Studies* (OECD, 2004). She coordinated, on behalf of the European Commission Joint Research Centre, the Good Cell Culture Principles (GCCP) document (2005) and the OECD Guidance Document on Good *In Vitro* Method Practices (GIVIMP) (OECD, 2018) recently approved by 36 OECD member states. With the involvement of EU-NETVAL and a network of international method developers and scientists, she is coordinating a validation study of a set of 17 mechanistically informative alternative methods covering the main possibilities of interaction with the thyroid signaling pathway. Dr. Coecke received her PhD in pharmaceutical sciences from the Free University of Brussels, Belgium.

Catherine Gibbons, PhD, US Environmental Protection Agency (EPA)

Dr. Gibbons is a biologist and genetic toxicologist with US EPA's IRIS Program. She is a contributing author on the IRIS Handbook that describes systematic review procedures being adopted by the IRIS Program, focusing on the systematic review of mechanistic information. She has a BA in biology from the University of Texas at Austin and a PhD in environmental toxicology from the University of California, Riverside.

Julian Higgins, PhD, University of Bristol

Dr. Higgins is Professor of Evidence Synthesis at the University of Bristol, UK, where he heads the Centre for Research Synthesis and Decision Analysis. He was previously Chair in Evidence Synthesis at the University of York, and Programme Leader at the MRC Biostatistics Unit in Cambridge, where he was also head of the UK Human Genome Epidemiology Network Coordinating Centre. Dr. Higgins' research interests span all areas of systematic review and meta-analysis. Among his research contributions are the Bayesian approach to network meta-analysis; the I-squared statistic to quantify inconsistency across studies in a meta-analysis; the simple prediction interval for random-effects meta-analysis; a general framework for individual participant data meta-analysis; and risk-of-bias assessment tools for clinical trials, observational studies and systematic reviews. Dr. Higgins is a past President of the Society for Research Synthesis Methodology and a long-term, active contributor to Cochrane. He has co-edited the *Cochrane Handbook for Systematic Reviews of Interventions* since 2003 and is also co-author of the Wiley 2009 textbook *Introduction to Meta-analysis*. With a Google Scholar H-index over 100, Julian has been named as a Highly Cited Researcher each year since 2015, and he has received lifetime achievement awards from the Campbell Collaboration and from the Society for Research Synthesis. He was appointed an NIHR Senior Investigator in 2018.

James E. Klaunig, PhD, Indiana University

Dr. Klaunig is Professor of Environmental Health in the School Public Health at Indiana University. Prior to joining the School of Public Health, from 1991 to 2010 he was Robert Forney Professor and Director of Toxicology at the Indiana University School of Medicine and concurrently held the position of State Toxicologist for the State of Indiana. In 2010, he joined the newly formed School of Public Health at Indiana University Bloomington. Dr. Klaunig's research has focused on understanding the toxicological and pathological effects of chemical agents including pharmaceuticals. Central to his research has been the application of the laboratory results to the further understanding and producing of scientifically based human risk assessment. His laboratory has been continually funded by extramural sources (including NIH, USEPA, DOD, State of Indiana and private sources) since 1984. He was identified in 2013, 2015, and 2017 as a highly cited author in pharmacology and toxicology by the Thomson Reuters (Web of Science). He has also served on numerous scientific advisory panels including for the USEPA, the NTP, the National Academies of Sciences, Engineering, and Medicine, the FDA and the WHO (IARC) as well as a member of several NIH study sections. He has served as Associate Editor of *Toxicological Sciences* and as Editor-in-Chief for *Toxicologic Pathology*. He received a BS from Ursinus College and a PhD in pathology from the University Of Maryland School Of Medicine.

Sabine S. Lange, PhD, DABP, Texas Commission on Environmental Quality

Dr. Lange is the Section Manager for the Toxicology Division at the Texas Commission on Environmental Quality (TCEQ). Dr. Lange's responsibilities include overseeing health effects risk assessments of air permit applications, ambient air monitoring projects, and hazardous waste sites; overseeing the development of chemical toxicity factors; and conducting and overseeing systematic reviews and independent analyses of risk assessments. Dr. Lange serves as a technical resource for the State and citizens of Texas for human health and environmental risk assessment, especially

related to air and water quality. Dr. Lange received a Bachelor's degree from the University of Western Ontario in Canada, and completed a PhD and post-doctoral training in biochemistry and molecular carcinogenesis at the University of Texas at Houston and MD Anderson Cancer Center. Dr. Lange is a Diplomate of the American Board of Toxicology.

Matthew Martin, PhD, Pfizer

Dr. Martin is Director and Computational Toxicology Domain Lead within Pfizer's Drug Safety Research & Development organization focusing on safety applications of predictive modeling, data infrastructure, bioinformatics and NGS data analysis. Prior to joining Pfizer last year, Dr. Martin was a Research Biologist (and proud Tar Heel) at the US EPA's National Center for Computational Toxicology leading ToxCast and ToxRefDB data analysis efforts with over 60 peer-reviewed publications. He received his PhD in environmental science and engineering with an emphasis on bioinformatics and computational biology from the University of North Carolina at Chapel Hill.

Martyn Smith, PhD, University of California at Berkeley

Dr. Smith is Professor of Toxicology and Kaiser Chair of Cancer Epidemiology in the Division of Environmental Health Sciences in the School of Public Health at the University of California at Berkeley. He is a laboratory scientist with expertise in molecular epidemiology, toxicology and genomics, and his research is aimed at finding the causes of chronic diseases, including cancer and diabetes. He has led the Superfund Research Program at Berkeley for over 30 years with continuous funding. He currently teaches classes in toxicology and health risk assessment and mentors graduate students and postdoctoral scholars in the Molecular Toxicology, Epidemiology and Environmental Health Science programs. Dr. Smith is a Fellow of the American Association for the Advancement of Science. He received the 2010 Children's Environmental Health Network Award, became an Elected Fellow of the Collegium Ramazzini in 2012, and received the Alexander Hollaender Award from the Environmental Mutagenesis and Genomics Society in 2014. He has served on the Scientific Council of the International Agency for Research on Cancer (IARC), and led the effort to establish the key characteristics of human carcinogens that are now used by IARC, NTP, EPA and CalEPA to evaluate mechanistic data in hazard identification. He received his Ph.D. in biochemistry from St. Bartholomew's Hospital in London in 1980 and did Post-Doctoral training in toxicology at the Karolinska Institute in Stockholm.

Amy Wang, PhD, National Toxicology Program

Dr. Wang has expertise in a broad range of toxicological topics, including cancer mechanisms, predictive and computational toxicology, systematic review, nanotoxicology, high-throughput screening, and comprehensive environmental risk assessment. She has been a health scientist in Office of the Report on Carcinogens, National Toxicology Program (NTP), National Institute of Environmental Health Sciences (NIEHS) in North Carolina since 2017. Dr. Wang's current research focuses on strategies to systematic review mechanistic information for cancer hazard identification. Her projects include exploring and refining the approaches and tools to search, evaluate, and synthesize diverse cancer mechanistic information, coordinating the development of data extraction approach of widely-varied genotoxicity studies, and collaborations to advance text mining tools for cancer mechanism assessment, and conducting cancer hazard assessment for possible listing in the Report on Carcinogens. The data and tools used in these projects include high-throughput screening results (e.g., Tox21, ToxCast), transcriptomics, read across, (Q)SAR, and various models. She is also interested in mentoring, data visualization, and emerging technologies.

Daniele Wikoff, PhD, ToxStrategies, Inc.

Dr. Wikoff is the Health Sciences Practice Leader at ToxStrategies, Inc. She specializes in evaluating human health hazards and risks associated with exposures to a wide variety of consumer products, food ingredients and additives, pharmaceuticals, and industrial chemicals. Her current focus is on systematic reviews in support of risk assessment applications, including development of health-based toxicity values. Dr. Wikoff has led the firm's initiatives to integrate evidence-based methods, and has been responsible for designing and implementing projects involving systematic review and systematic maps using a variety of frameworks, including those of the Institute of Medicine and the NTP's Office of Health Assessment and Translation. Most recently, she has been involved in exploring the utility of quantitative integration techniques (e.g., meta-analysis, Bayesian modeling) and tools to characterize confidence and/or uncertainty in hazard analyses, points of departure, estimate of relative potency, and dose-response relationships. Dr. Wikoff has particular interest in methods development related to the definition and evaluation of data quality, and how elements

of study validity can be used to transparently inform conclusions and provide critical information to decision makers. Dr. Wikoff is vice chair of the Science Advisory Council for the Evidence-Based Toxicology Collaboration (EBTC) and is on the editorial boards of *Toxicological Sciences* and *Toxicology Reports*. She received her PhD in toxicology from the University of North Carolina at Chapel Hill.

DISCUSSANTS

David C. Dorman, DVM, PhD, North Carolina State University

Dr. Dorman is Professor of Toxicology in the Department of Molecular Biosciences of North Carolina State University. The primary objective of his research is to provide a refined understanding of chemically induced neurotoxicity in laboratory animals that will lead to improved assessment of potential neurotoxicity in humans. Dr. Dorman's research interests include neurotoxicology, nasal toxicology, pharmacokinetics, and cognition and olfactory in military working dogs. He has served as a member or chair of several National Academies committees, including two Committees on Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, the Committee to Evaluate Potential Health Risks from Recurrent Lead Exposure to DOD Firing Range Personnel, the Committee to Review EPA's Draft IRIS Assessment of Formaldehyde, the Committee to Review the IRIS Process, and the Committee on Endocrine-Related Low-Dose Toxicity. He received his DVM from Colorado State University. He completed a combined PhD and residency program in toxicology at the University of Illinois at Urbana-Champaign and is a Diplomate of the American Board of Veterinary Toxicology and the American Board of Toxicology.

Maureen Gwinn, PhD, National Center for Computational Toxicology, Office of Research and Development, US Environmental Protection Agency

Dr. Gwinn has been with the US Environmental Protection Agency (EPA) since 2006 and is currently a Senior Science Advisor in the National Center for Computational Toxicology (NCCT) in the Office of Research and Development (ORD) focusing on research translation of alternative toxicity testing, particularly as it relates to hazard characterization and risk assessment for regulatory decision-making. Previously, she worked as Senior Science Advisor in the Immediate Office of the Assistant Administrator (IOAA), where she supported the senior leadership in ORD on key scientific activities. Dr. Gwinn also worked in the National Center for Environmental Assessment (NCEA) in ORD, where she worked on human health hazard assessments for the Integrated Risk Information System (IRIS) program, with a focus on better understanding the toxicity related to particles and fibers. During this time, she also worked on issues related to the risk assessment of nanomaterials, particularly related to the validation of toxicity testing for a variety of nanomaterials. Dr. Gwinn earned her BS degree in Biology at Bates College in Lewiston, Maine in 1994 and her MS and PhD in Oral Biology at the State University of New York in Buffalo, New York in 1997 and 2001, respectively. She became a Diplomate of the American Board of Toxicology in 2007 and was nominated into the Academy of Toxicological Sciences in 2014.

Tala R. Henry, Ph.D, Office of Pollution Prevention and Toxics, US Environmental Protection Agency

Dr. Henry is the Acting Deputy Director for Programs in the Office of Pollution Prevention and Toxics (OPPT) at the US Environmental Protection Agency. She has worked in a variety of programs at EPA including conducting research on the toxicity of chemicals, conducting risk assessments for hazardous waste sites, and developing Water Quality Criteria. Most recently, she was Director of the Risk Assessment Division in OPPT. She received her PhD in pharmacology from the University of Minnesota and completed a post-doctoral fellowship at the University of Wisconsin-Madison.

Andrew Kraft, PhD, National Center for Environmental Assessment, Office of Research and Development, US Environmental Protection Agency

Dr. Kraft currently serves as the Associate Director of Science in the Integrated Risk Information System (IRIS) Program at the US Environmental Protection Agency. He has worked at the EPA National Center for Environmental Assessment (NCEA, where IRIS is housed) since 2011. His research training is in neurotoxicology and pharmacology. Dr. Kraft leads the development of assessments on the potential human health risks of environmental pollutants. His responsibilities include the coordination and review of critical science and policy decisions in human health assessments, and he is

currently the co-chemical manager of the IRIS formaldehyde assessment and a lead developer of the forthcoming "IRIS Handbook" of standard operating procedures for developing NCEA assessments. For the past six years, Dr. Kraft has been an active developer and practitioner of the application of systematic review approaches to assessments in the field of environmental health, and he has represented the EPA at numerous national and international forums on this topic. Dr. Kraft received his PhD in pharmaceutical sciences at the University of Wisconsin-Madison and completed a postdoctoral fellowship at the National Institute of Environmental Health Sciences (NIEHS) Neurotoxicology Group.

Heather N. Lynch, MPH, Gradient Corporation

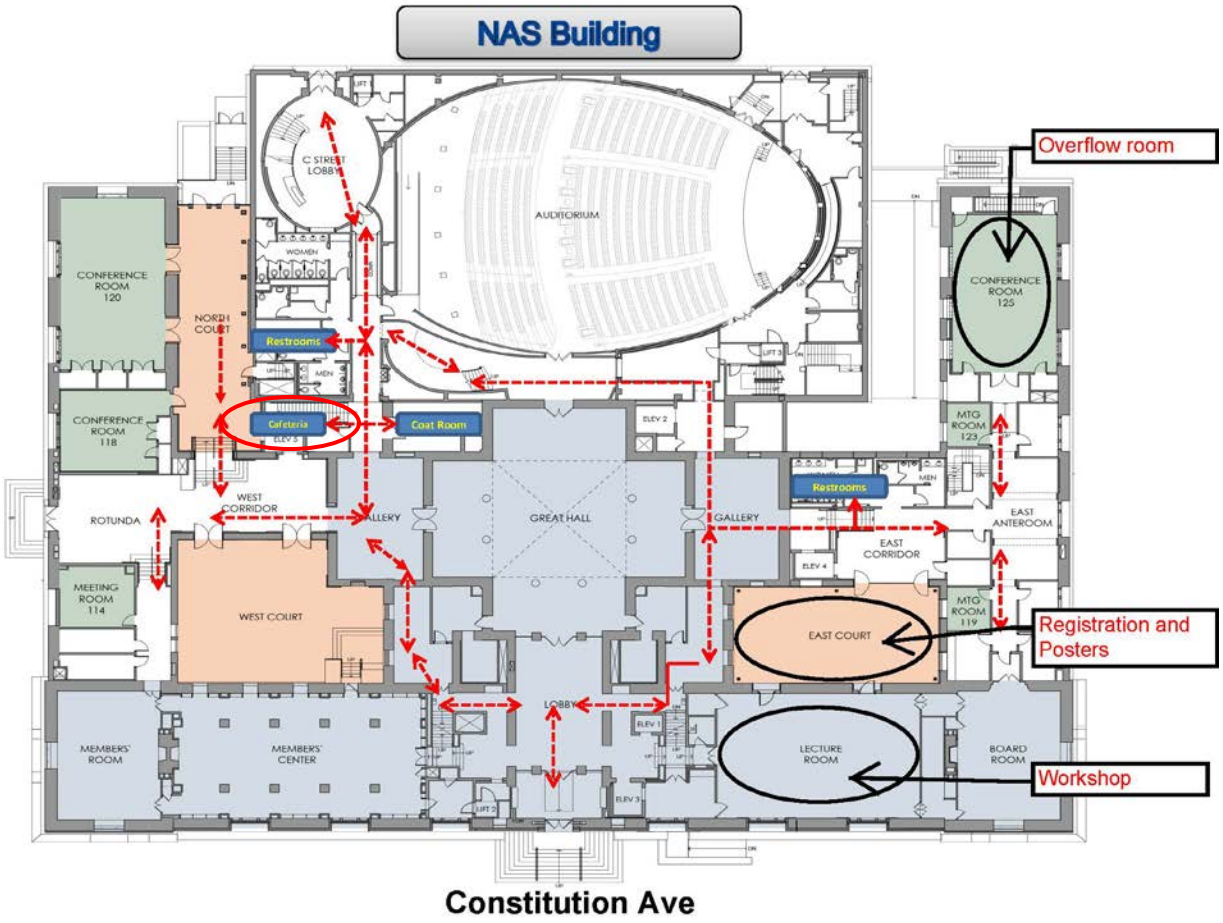
Ms. Lynch is a Senior Toxicologist and Senior Project Manager at Gradient, an environmental consulting firm in Cambridge, MA. Her areas of expertise include systematic review and weight-of-evidence methodologies, controlled human exposure study design, and the toxicology of heavy metals (e.g., arsenic and lead) and perfluoroalkyl substances. Ms. Lynch's primary responsibilities at Gradient include critically reviewing toxicology and epidemiology studies and managing multi-disciplinary human health risk assessments of chemicals in consumer products, the workplace, and the environment. Ms. Lynch has authored numerous peer-reviewed publications in collaboration with colleagues at Gradient, including several systematic reviews and weight-of-evidence analyses, and overviews of the use of mechanistic data in risk assessment. Prior to joining Gradient, Ms. Lynch was a toxicologist for the environmental consulting firm ICF International, working predominantly on large, and chemical-specific risk assessments for several programs within the US EPA National Center for Environmental Assessment. She also worked at the non-profit Center for Health, Environment, and Justice assisting with community outreach and scientific publications related to a wide range of environmental health and justice issues. She received an MPH in environmental health from the Boston University School of Public Health.

Elizabeth Méndez, PhD, Office of Pesticide Programs, Office of Chemical Safety and Pollution Prevention, US Environmental Protection Agency

Dr. Méndez is the Senior Scientist in the US EPA's Office of Pesticide Programs Health Effects Division (OPP/HED). She has 20 years of experience in regulatory toxicology overseeing a number of projects intended to advance the state of the science and risk assessments produced by the OPP. She works closely with staff scientists providing guidance on bridging, mode of action data analysis, hazard characterization, endpoint selection, identifying data gaps, and protocol reviews. She has served as Temporary Advisor to the World Health Organization's Joint Meeting on Pesticide Residues (JMPR), and co-chaired an Organization for Economic Cooperation and Development (OECD) Expert Group on Developmental and Reproductive Toxicology that developed a new OECD Test Guideline. She has also served in several OECD Review Panels on several proposed Adverse Outcome Pathways and co-chairs ICCVAM's Developmental and Reproductive Toxicology Workgroup.

NAS BUILDING MAP

1st Floor Conference Rooms Layout and Emergency Exits



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