June 3-4, 2019

National Academy of Sciences (NAS) Building

2101 Constitution Avenue, NW | Washington, DC 20418

Lecture Room

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* Member of workshop organizing committee.

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1:00	**Poster Session** (East Court adjacent to Lecture Room)
SESSION V. Practical Approaches to Expedited Evidence Integration	
2:00	**A Streamlined, Scientifically Rigorous Approach to Categorize Health Hazards [NASEM 2018: Review of Report and Approach to Evaluating Long-Term Health Effects in Army Test Subjects]** *Ivan Rusyn*, Texas A&M University*
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4:30	**Closing Remarks** *Holger Schünemann*, McMaster University*
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* Member of workshop organizing committee.

PRESENTATION ABSTRACTS

SESSION I: Lessons Learned from Recent International Workshops on Evidence Integration in Risk Assessment

Combining Apples and Oranges: Lessons Learned and Advances Made through International Collaboration

Katya Tsaioun, Johns Hopkins University

Systematic reviews, developed as a methodology of evidence synthesis in clinical research, has become the basis of evidence-based practice. Systematic review (SR) methodology's transparency, reproducibility and rigor are compelling for use in other areas, where public health questions have significant amount of published literature. Thus, in the last decade a number of government agencies, most notably, European Food Safety Authority (EFSA), Office of Health Assessment and Translation (OHAT) at the National Toxicology Program and US Environmental Protection Agency (US EPA) have developed tools for their specific hazard and risk assessment needs and started incorporating SRs into their processes in the field of environmental health, chemicals and food safety assessment. In this presentation you will hear a brief introduction to the evidence-based methods and systematic review, challenges of applying SR to chemicals risk assessment, with a particular emphasis on the evidence integration within and across evidence streams. The field has matured over the last decade with a number of agency-specific tools that have been developed and applied. Now the focus is on addressing the biggest challenges: development of qualitative methods for integration of diverse evidence streams, integration of mechanistic *in vitro* evidence (addressed in the December 10-11, 2018 NASEM workshop) and international harmonization of methodologies. This work is progressing via a number of international collaborations and workshops and resulting publications, with the leadership of EFSA, OHAT and US EPA, and with the input from academic, industry and non-government organizations, which are crucial for wider adoption of any new methodologies. The presentation will conclude with the summary of recent international collaborations and workshops in moving the field forward and open the floor for a panel discussion.

SESSION II: Best Practices in Evidence Integration

Perspectives on Common Elements for Evidence Integration

Weihsueh Chiu, Texas A&M University

Unlike clinical medicine, where the evidence usually consists of randomized controlled trials of the specific intervention of interest, human health assessments of environmental agents usually require integration of broad and heterogeneous bodies of evidence. Although this need was recognized even in the aspects of causality articulated by Sir Bradford Hill in 1965, there has been considerable evolution over time in the structure and formality of evidence integration approaches. Most current approaches have three common elements. Typically, the available studies are first separated into three broad "bodies of evidence": human data, experimental animal data, and mechanistic or mode-of-action data. Second, evaluations are typically conducted by integrating data within a body of evidence, taking into consideration individual study strengths and limitations. Third, the evidence across bodies of evidence are integrated, taking into consideration how the bodies of evidence inform each other. A key recent development for integrating within a body of evidence is the increasing use of quantitative meta-analysis. With respect to integrating across bodies of evidence, there has been an increasing emphasis on mechanistic or mode-of-action data, particularly given the dearth of human and experiment animal studies for many agents.

Emerging Strategies for Evidence Integration

Bette Meek, University of Ottawa

Mode of Action (MOA) and Adverse Outcome Pathways (AOPs) organize hazard-based knowledge as a sequence of measurable key events at different levels of biological organization. As such, they facilitate the integration of data from a broad range of sources including structure activity analysis, *in vitro* assays, toxicity tests in animals and observational or clinical studies in humans based on mechanistic hypotheses and/or understanding. Structured analysis of the extent of supporting data across these various lines of evidence in international frameworks for MOA/AOP analysis derives from

considerations developed originally by Bradford Hill (B/H) to assess causality in epidemiological studies. Modified considerations address the broader context of integration across lines of evidence as a basis to characterize relative confidence in the extent of the supporting data for supporting a range of regulatory applications. The considerations for integrated weight of evidence across levels of biological organization in MOA/AOP analysis have been refined and rank ordered based on increasing experience in their application, most recently in guidance and templates for an Organization for Economic Cooperation and Development (OECD) public knowledge base on AOP development. Evolution of the considerations balances simplicity to permit wide scale adoption ("codification") with the extent of expert informed prescription of the methodology to ensure adequate transparency. This promotes early focus of both the assessment and research communities on important aspects of evidence integration including, for example, patterns of dose-response between and among key events in assessment and research strategies. Implications of this experience for data integration in assessment planning are considered, taking into account "metrics" for selection of relevant methods to assess weight of evidence both within and across lines of evidence proposed in a recent initiative of the French Agency for Food, Environmental and Occupational Health and Safety (ANSES).

Experience with Incorporating GRADE-Based Evidence Integration Frameworks into Environmental Health Evaluations

Kris Thayer, US Environmental Protection Agency

There is increasing use in environmental health of structured frameworks that help document the expert judgements made during the process of evidence integration. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework is the most commonly used structured framework. GRADE has been applied successfully to areas of clinical medicine, public health, and health policy, but experience with GRADE in environmental and occupational health is just beginning. Although GRADE offers many advantages, including its wide usage (over 100+ organizations) and methodological rigor, there are features of the different sources of evidence used in environmental and occupational health that will require further consideration to assess the need for method refinement. Specific issues include methods for assessing confidence in observational studies of exposure, application of GRADE to animal and mechanistic evidence, and development of an approach(es) for integrating evidence from human, animal, *in vitro*, and *in silico* (computer modeling) studies when determining whether an environmental factor represents a potential health hazard or risk. This presentation will provide an overview of experience to date in applying GRADE to environmental health topics and highlight current areas of methods development.

SESSION III. Approaches for Using Mechanistic Data to Integrate Evidence from Animal and Human Studies: General Considerations

Practical Challenges in Assessing Indirectness and the Implications for Integrating Multiple Streams of Evidence in Systematic Reviews

Paul Whaley, Lancaster University

In this presentation, systematic review (SR) is defined as a research project which tests a hypothesis using pre-existing evidence instead of conducting a novel experiment, and evidence integration as the process of synthesizing across different streams of evidence. SR is contrasted with traditional evidence review methods in terms of how it seeks to explicitly ground interpretation of scientific evidence in (a) the textual record of the research, and (b) evidence for the validity of judgements made when interpreting that record. In this context, systematic approaches to evidence integration should be similarly grounded. An approach to this, based on mapping implicit Population-Exposure-Comparator-Outcome (PECO) statements derived from studies included in a SR onto the formal PECO statement which defines the parameters of a SR project, is presented. The potential contribution of Adverse Outcome Pathways to grounding this approach to integration in existing knowledge of biological systems is highlighted. Recognizing the challenges which data volume and the operational complexity of this approach presents to successful conduct of the evidence integration step in a complex SR, an explicitly algorithmic approach to evidence integration is outlined for discussion.

Investigating the Causality of Adverse Effects: Mechanistic Toxicology Meets Epidemiology

Jean-Lou Dorne and Marios Georgiadis, European Food Safety Authority

In food safety, human risk assessment of environmental contaminants aims to protect public health through deriving safe levels in food commodities. The integration of mechanistic, toxicological and epidemiological information can be used to investigate the causality of adverse effects with regards to Mode of Action (MoA) and Adverse Outcome Pathways (AOPs). A harmonized weight of evidence framework providing a range of qualitative and quantitative methods to assemble, weight and integrate such complex lines is presented. The framework allows to assess the strength, consistency and the biological relevance of the evidence as well as variability and uncertainty when availability of data allows. Historical examples at EFSA include meta-analysis of epidemiological studies and biomarkers of exposure and effects for dose response modelling of cadmium in humans. Currently, a guidance to integrate epidemiological data in chemical risk assessment is under development. Future perspectives to move towards integration of mechanistic toxicology and epidemiological data in human risk assessment are highlighted. These include models integrating quantitative *in vitro in vivo* extrapolation at the individual level to quantify effects in populations. In this context, the impact of risk factors such as human polymorphisms in key enzymes and target receptors constitute a key challenge that needs to be addressed from both a mechanistic and epidemiological perspective. Open source databases providing data to depict MoA and AOPs (e.g. *in vitro*, *in vivo* and OMICs data) as well as exposure patterns and epidemiological information, will contribute to further refine our understanding of the causality and the likelihood of human adverse effects from exposure to environmental contaminants.

SESSION IV. Systematic Review-Enabled Evidence Integration: Case Studies

Case Study 1: Systematic Review-Enabled Evidence Integration for Predictive Modeling of Endocrine Disruption Pathways

Nicole Kleinstreuer, National Toxicology Program

The U.S. Environmental Protection Agency (EPA) is considering computational methods to evaluate the endocrine bioactivity of environmental chemicals, such as the estrogen receptor (ER) pathway model based on Tox21/ToxCast high-throughput screening assays. Multiple assays covering key biological events from receptor binding to ER-dependent cell proliferation were integrated into a computational model that can discriminate bioactivity from assay-specific interference and cytotoxicity. A multistep, performance-based validation was implemented to demonstrate that these new tools are sufficiently robust to be used in the Endocrine Disruptor Screening Program (EDSP). Comprehensive literature reviews were conducted to identify and evaluate data from rodent uterotrophic animal studies, to determine study quality and analyze sources of variability. Study descriptors, such as species/strain, route of administration, dosing regimen, lowest effect level, and test outcome, were captured in a database and studies were assessed for adherence to protocol criteria from regulatory test guidelines. Chemicals with reproducible results in high-quality *in vivo* studies were identified as reference compounds and used to determine the performance of the high throughput assays and associated computational model. Based on the ability of these methods to correctly classify active and inactive reference chemicals, and rapidly identify chemicals with potential endocrine bioactivities for additional screening and testing, EPA is now accepting Tox21/ToxCast model data for EDSP Tier 1 testing.

Case Study 2: Integrating Evidence across Multiple Exposures: Applying the OHAT Framework to Traffic-Related Air Pollution and Hypertensive Disorders of Pregnancy

Brandy Beverly, National Toxicology Program

The adaptation of systematic review to address environmental health questions is an ongoing process to develop and refine methods to address key challenges in evaluating environmental health data as needs arise. For example, individuals are exposed to a large number of environmental chemicals that may be associated with adverse health effects, yet systematic review frameworks for environmental health still often provide guidance for evaluating single chemicals. While systematic review methods are becoming the gold standard, the need to develop guidance on how to reach conclusions on multiple exposures represents a critical gap in addressing "real world" multiple-chemical exposures, mixtures, or cumulative exposures. The NTP's Office of Health Assessment and Translation (OHAT) is addressing a multiple exposure question in the evaluation of potential effects of traffic-related air pollution (TRAP) on hypertensive disorders of

pregnancy. This evaluation follows the OHAT Approach to Systematic Review and Evidence Integration to evaluate health effects evidence for individual components of TRAP in a stepwise manner. Evidence is first grouped into focused exposure-outcome pairs. Then, the evidence is integrated, along with consideration of the independence of the datasets, independence of the mechanisms to elicit an effect on the outcome(s) of interest, and other relevant information, to reach hazard conclusions that inform the broader exposure of TRAP. The case example from the NTP Systematic Review of Traffic-Related Air Pollution and Hypertensive Disorders of Pregnancy will illustrate how hazard conclusions can be developed across multiple exposures using OHAT's systematic review framework.

Case Study 3: Use of Mechanistic Data for Evidence Integration across PCBs as a Chemical Class

Larry Robertson, University of Iowa

Polychlorinated biphenyls (PCBs) are an iconic class of contaminants. Industrially produced for about 5 decades in the United States and other countries and commercially sold as mixtures, they were employed in both closed-systems and in open sources, leaking into the environment and resulting in human exposure, which continues to this day. Given the wide range of chlorination, from 1 to 10 chlorine atoms per biphenyl, the chemical and physical properties (lipophilicity, volatility, flame retardancy and many others) of the homologues in these mixtures vary widely. This broad spectrum of chemical and physical properties is reflected in the varying ability of individual PCB congeners to be transported in the environment, to move among inorganic media (e.g. air, water and soil/sediment), and to persist in biological environments. PCBs can be divided into groups, reflecting their susceptibility to chemical and biological transformation. The lower chlorinated biphenyls, less than 5 chlorines per biphenyl, are more volatile, less stable/persistent, and more susceptible to metabolic transformation to compounds that are in some cases much more toxic. Higher chlorination renders the PCB more stable, less susceptible to metabolic change, and more likely to produce biologic/toxic changes that are due to the unaltered parent compound interacting with cellular and nuclear receptors. The mechanistic data considered by the International Agency for Research on Cancer (IARC) subgroup that I chaired, supported the concept that lower chlorinated biphenyls may be activated to potent mutagens, clastogens, and cause strand breaks and DNA adducts, while higher chlorinated biphenyls promote carcinogenesis through other mechanisms. Each of the 209 congeneric PCBs elicits an individual spectrum of effects. However, humans are not exposed to only one PCB congener but rather to a mixture. Animal studies and human cohort studies support the conclusion that mixtures of PCBs are carcinogenic, reflecting the combination of the many individual PCBs possessing differing toxic properties. (LWR is supported by P42 ES013661)

SESSION V. Practical Approaches to Expedited Evidence Integration

A Streamlined, Scientifically Rigorous Approach to Categorize Health Hazards [NASEM 2018: Review of Report and Approach to Evaluating Long-Term Health Effects in Army Test Subjects]

Ivan Rusyn, Texas A&M University

The NASEM 2018 report: *Review of Report and Approach to Evaluating Long-Term Health Effects in Army Test Subjects* proposed a strategy for evaluating many compounds for a range of health outcomes under conditions of tight deadlines and limited resources. This strategy was based on best practices in hazard identification and systematic review, which can be tailored to the circumstances. Six steps are followed in this strategy. The first step involves prioritizing the agent evaluations. In Step 2, problem formulation, the scope of the evidence available to evaluate an agent-and outcome-specific association is determined. During this step, a determination is made about whether an independent evaluation is required or whether it is possible to rely on a previous credible assessment from an authoritative source. Steps 3-5 cover the evaluations necessary to do an independent evaluation, including literature searching and screening, data analysis and synthesis, and evidence integration. The final step is drawing a hazard conclusion. This presentation will provide an overview of the strategy, with a particular focus on an evidence integration approach that has the flexibility to be applied to a disparate set of test agents with varying sets of data.

Elk River Chemical Spill Assessments

Michael Dourson, Toxicology Excellence for Risk Assessment

An independent expert panel met on March 31, 2014 in Charleston, WV, to review and discuss available toxicity data on chemicals released to the Elk River in January 2014 from a Freedom Industries facility. The expert panel and meeting were organized by Toxicology Excellence for Risk Assessment (TERA) under contract to Corona Environmental Consulting for the West Virginia Testing Assessment Project. The panel discussed the initial screening value of 1 ppm (or 1,000 ppb) for 4-methyl-1-cyclohexanemethanol (MCHM), which was developed by the US Centers for Disease Control and Prevention (CDC) for the State of West Virginia. The panel evaluated the currently available data and developed short-term health advisories for MCHM, propylene glycol phenyl ether (PPH) and dipropylene glycol phenyl ether (DiPPH). They also identified data gaps and made recommendations for additional studies and analyses to reduce uncertainty. For MCHM, the panel recommended a short-term health advisory of 120 ppb (120 µg/L). The panel determined that the development of a lifetime Reference Dose (RfD) or similar chronic duration toxicity value for MCHM would be difficult at the present time, because the longest duration toxicology study was only 4 weeks. The panel also recommended a short-term health advisory of 880 ppb (880 µg/L) for PPH, and of 260 ppb (260 µ/L) for DiPPH.

Clinical Research Applications: Influenza Virus Drugs

Holger Schünemann*, McMaster University

The potential exists that the field of evidence integration in chemical risk assessment could build on experiences and lessons learned of other health fields. This presentation will describe the use of different streams of evidence (*in vitro*, animal and human) to provide an evidence synthesis that was used to make decisions about antiviral drugs at the World Health Organization (WHO). It will further describe how such information may be summarized for different levels of urgency with decision-making. Specifically, avian influenza was a potential public health emergency and rapid guidance was requested from WHO. An evidence review team synthesized existing systematic reviews of human data, searched for animal and *in vitro* research (e.g. to identify evidence about mechanisms of action and drug resistance) and compiled all of this evidence to support decision-making by a WHO guideline panel within two months after initiation of the work. Animal and *in vitro* data influenced judgments about indirectness of the evidence (all human data were obtained from people exposed to a similar but not identical virus) and to understand if similar mechanisms of action and resistance development would plausibly exist in the related virus (e.g. by looking at receptors in the avian influenza virus). Recommendations were developed and approved within three months. Thus, the presentation will also lay out a framework for how to do a structured evidence assessment for informing decisions within a short timeline.

POSTER ABSTRACTS

#1 - Visualizing the Evidence: Exploring and Explaining Your Data via Interactive Methods

***Courtney Skuce*, Alessandria Schumacher, George Agyeman-Badu, Pam Hartman, and Kim Osborn**
ICF

Technological and methodological advancements in systematic review allow us to gather, screen, and characterize increasingly larger literature bases. Properly assessing, interpreting, and integrating these data and presenting them to the public in a transparent and easily understood manner is crucial as the risk assessment process faces increased scrutiny from scientific, political, and public communities. Evidence maps are helpful tools to visually represent these systematic review databases and communicate characteristics of the integrated evidence. Recently, more government agencies are leveraging these visualizations in public reports, some of them web-based and interactive, allowing audiences more access to underlying data and results. Here, we explore and compare visualization software and packages like Tableau, R Shiny, and Qlik which facilitate creation of interactive dashboards and how they can be used to build evidence maps, providing viewers direct access to the literature base and underlying data and the ability to manipulate the visual to 'zoom in' on specific parameters relevant to specific interests. We present recommendations for the use and display of these maps, including key features and examples, and lessons learned from using them in risk assessment, with a focus on how incorporating interactivity into these visualizations is a highly effective method for use in two contexts: 1) Exploring data - allowing risk assessors to examine and analyze complicated systematic review datasets, and 2) Explaining data - increasing the transparency and clarity with which data and analyses are presented to risk managers and the public.

#2 - SyRF: Systematic Review Facility

***Jing Liao* and Malcolm Macleod**
University of Edinburgh

Research synthesis in toxicology is a complex and time-consuming process. SyRF (Systematic review facility: app.syrf.org.uk) is designed to facilitate the entire pipeline of a systematic review from publication searching, screening, data extraction, data visualization to meta-analysis. Chemical evidence collection demands can be very diverse. The unique tree structure annotation design of SyRF enables researchers to customize the annotation questions for each project. With the cutting edge text-mining and machine learning techniques, SyRF leverages validated external services to assist reference selection and automatic annotation, expediting systematic review processes, with the potential to automatically authored enable curated contents. SyRF is constantly developing through the testing and implementation of new tools and methodological developments. SyRF also supports crowdsourcing to engage geographically distributed research teams, accelerating systematic review and engaging young researchers. Coupling with the flexible training application LearnToSyRF (learn.syrf.org.uk) and live data summarization and visualization, SyRF allows the training and engagement of unlimited reviewers and at the same time providing project owners with tools to monitor the project progress and quality in fine details. The SyRF enabled meta-analysis shiny app promotes researchers to use appropriate statistical methods.

#3 - Evaluating the Consistency of Heterogeneous Results: Important Determinants of Inconsistency

***Barbara S. Glenn*, Elizabeth Radke, and Andrew Kraft**
Office of Research and Development, US Environmental Protection Agency

Background/Aim: The evidence on exposure-health associations for chemicals with an extensive research history often includes studies with heterogeneous results. The heterogeneity may stem from differing study designs examining varying outcome and exposure definitions and be influenced to varying degrees by sources of bias and other factors that affect the magnitude, direction, and precision of effect estimates.

Methods: The impact of bias and other aspects of studies that could influence associations with health effects are discussed, and an approach to analyzing their impact is illustrated using examples from systematic reviews conducted in the IRIS Program. The evaluation of study results across a set of studies is a powerful tool that can help with decisions about whether a potential bias is an important concern for an individual study, and to illuminate a pattern within apparently inconsistent effect estimates. Influential aspects include potential bias (e.g., selection, information,

confounding) and other quality aspects (e.g., sensitivity, precision). This type of analysis also should include factors, such as exposure levels, that affect the sensitivity of a study to detect an association if one exists. Examples to illustrate the value of conducting these analyses are presented. The consistency of a set of results is examined via forest plots presenting effect estimates (e.g., risk ratios, odds ratios) stratified by ratings for the domains that comprise the IRIS study evaluation tool including participant selection, exposure, outcome, confounding, analysis and sensitivity. Additional factors are analyzed including exposure (low vs high) and overall study confidence.

Results: The case examples include studies from a variety of exposure settings (i.e., population-based and occupational studies) that appear to have considerable heterogeneity across studies for specific outcomes. However, when the effect estimates are stratified by exposure level and setting, and overall confidence in the exposure-outcome association, a more consistent pattern emerges. Generally, limitations in multiple domains contribute to the low confidence ratings for individual study results, potentially with opposing influence on the direction of bias, but stratification by some of the ratings for individual domains clarifies some of the greater heterogeneity observed among these exposure-outcome associations. Specifically, some results from studies rated deficient for potential confounding remain within the range of other results with an adequate rating, alleviating concern for this potential bias. However, in some cases, if a result received a rating of deficient for confounding due to co-exposures that were not adequately controlled for, the magnitude of the effect estimates is higher relative to the results overall, consistent with a prediction that the direction of bias is away from the null.

Conclusions: While the specific determinants may vary, sensitivity analyses that examine potential determinants of heterogeneity in study results are essential to analyses of evidence consistency as part of the integration of evidence in systematic reviews.

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

#4 - Semi-Automated Data Extraction Workbench for Environmental Health

B. Howard, A. Maharana, A. Tandon, and *Ruchir Shah*
Sciome, LLC

Systematic review, already a cornerstone of evidence-based medicine, has recently gained significant popularity in several other disciplines including environmental health and evidence-based toxicology. One critical and time-consuming process that must occur during systematic review is the extraction of relevant qualitative and quantitative raw data from the free text of scientific documents. The specific data types extracted differ among disciplines, but within a given scientific domain, certain data points are extracted repeatedly for each review that is conducted. To that end, Sciome has begun research and development of a semi-automated data extraction workbench for use in this context. We are focusing our research on three specific goals. First, we are using deep learning to build novel data extraction models to extract data elements of interest to those conducting systematic reviews in the domain of environmental health. Second, we are building a web-based data extraction software platform specifically designed for usage in the domain of systematic review. And finally, we plan to introduce new protocols to standardize the inputs and outputs for data extraction software components. Here we report our results so far, including the performance of more than 20 novel data extraction components of relevance to environmental toxicology, created and tested on an annotated dataset from NTP. Performance varied widely among data types with some tasks inherently more difficult than others. For certain simple data types, like sex of the experimental animal, we achieved F-scores in excess of 95%; for more difficult entities, we were still often able to achieve an F-score of 65% or more, given sufficient training data. Because accurate data extraction can be a challenging problem, and given that current methods rarely achieve 100% accuracy, we are integrating our methods into a “human-in-the-loop” system that combines machine and human intelligence in a manner that is superior to using either in isolation. The system will: highlight extracted terms in a pdf; automatically populate extraction forms with extracted data; allow humans to intervene and correct the results; and learn from the corrections to continually update the model. The resulting system will make systematic reviews both more efficient to produce and less expensive to maintain, greatly accelerating the process by which scientific consensus is obtained in a variety of health-related disciplines having great public significance.

#5 - Evidence Synthesis and Integration in the IRIS Program

Xabier Arzuaga **and Andrew Kraft**
Office of Research and Development, US Environmental Protection Agency

Systematic reviews conducted as part of developing Integrated Risk Information System (IRIS) assessments consist of structured processes for identifying, evaluating, and summarizing relevant evidence (i.e., evidence synthesis), and arriving at summary conclusions regarding the overall body of evidence (i.e., evidence integration). These approaches were developed through discussions within EPA and informed by multiple reviews by the National Research Council (2011; 2014; 2018). In addition, IRIS assessments include quantitative toxicity values based on the evidence identified as most informative during the systematic reviews. The standard operating procedures, including frameworks and considerations for developing the different parts of the systematic reviews, are outlined in an internal document. For each potential human health hazard, the evidence synthesis builds from the outcome-specific evaluations of individual studies and discusses additional considerations across the sets of pertinent studies. Thus, the available evidence is summarized in a manner that informs an evaluation of the body of evidence during evidence integration. A primary goal of the evidence synthesis is to evaluate potential sources of heterogeneity across the study results, which informs evaluations of each Hill criterion. Evidence integration is a two-step process based on structured, example-based frameworks for applying an adapted set of considerations described by Sir Bradford Hill (1965), first to each line of evidence, and then across all evidence. This process also informs the selection of studies and the derivation of toxicity values. This process also informs the selection of studies and the derivation of toxicity values.

Disclaimer: The views expressed are those of the authors and do not represent the views or policies of the US EPA.

#6 - Research Update: Using SWIFT-Active Screener to Reduce the Expense of Evidence Based Toxicology

B. Howard, A. Tandon, J. Phillips, A. Maharana, and *Ruchir Shah*
Sciome LLC

Systematic review is a formal process used widely in evidence-based toxicology and environmental health research to identify, assess, and integrate the primary scientific literature with the goal of answering a specific, targeted question in pursuit of the current scientific consensus. We recently received Phase I SBIR funding to conduct research and development to enhance our web-based, collaborative systematic review software application, SWIFT-Active Screener. By employing a machine learning methodology called “Active Learning”, and through a novel statistical method that can accurately estimate the percentage of relevant studies screened, Active Screener can significantly reduce the overall screening burden compared to traditional approaches. We first investigated several improvements to our statistical algorithms used for article prioritization and recall estimation (Aim 1 – Improved Statistical Models). The resulting refinements further improve the performance of our algorithms and address critical technical issues that previously limited the applicability of our methods. Secondly, we explored ways in which our models and methods can be improved to handle the scenario in which an existing systematic review is updated with new data several years after its initial publication (Aim 2 – New Methods for Systematic Review Updates). Finally, in order to ensure that our software is capable of supporting the full demand from our many users, we have reengineered the system to support hundreds to thousands of simultaneous screeners (Aim 3 - Software Engineering for Scalability, Usability). During this research, our methods and software have been rigorously tested on 26 different systematic review datasets, demonstrating robust performance of Active Screener’s prioritization and recall estimation methods in a variety of real-world scenarios. For reviews with 5,000 or more documents, we report an average reduction in screening burden of 61% (to obtain 95% recall). Active Screener has been used successfully to reduce the effort required to screen articles for systematic reviews conducted at a variety of organizations, including NIEHS, EPA, USDA, TEDX, and EBTC. These early adopters have provided us with an abundance of useful data and user feedback, and we have identified several areas where we can continue to improve our methods and software. Several new features have been planned for the software, and it will be developed, improved and maintained for the foreseeable future.

#7 - Role of Semantics, Ontologies, and Adverse Outcome Pathways as a Point of Integration in Chemical Assessments

Michelle Angrish[1], **George Woodall**[1], **Sean Watford**[2], **and Paul Whaley**[3]
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The quality and utility of literature based chemical assessments has been improved by leveraging the power of systematic review (SR) and systematic mapping (SM) approaches to aggregating and evaluating evidence of health risks posed by exposure to environmental chemicals. Successful conduct of SRs and SMs is currently impeded by linguistic inconsistencies resulting from different communities using different vocabularies to describe common study characteristics, requiring the systematic reviewer to anticipate all the concepts, relationships, and words related to a science question when developing a search string sensitive enough to locate all potentially relevant studies. The state-of-the-art approach, to use dictionaries and thesauruses are useful for ensuring all semantically related terms are included in a search, but they do not offer the context necessary to capture relationships between concepts, e.g. according to biological organization, such as gene expression versus biomarker measurement. We are therefore exploring the use of ontologies and semantic mapping as a point of evidence integration in literature based chemical assessments. An ontology is a controlled vocabulary of precisely-defined terms and the specified relationships between them, interpretable by both humans and machines. Here we give an example of how thyroid health outcome data extracted from human and animal literature studies can be matched to ontology concepts that serve as a point of integration in a semantic framework bounded by a structured Adverse Outcome Pathway (AOP) framework. When implemented, this ontological approach solves the problem of a researcher needing perfect *a priori* knowledge of all relevant terms and relationships in order to query a database for comprehensive information about mechanisms of thyroid toxicity: this information is already provided in the database ontology.

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#8 - Strengthening the Evaluation of Mechanistic Evidence Categorized by the IARC 10 Key Characteristics of Carcinogens

Kirsten Zu, *Julie E. Goodman*, Robyn L. Prueitt
Gradient

The International Agency for Research on Cancer (IARC) developed a framework for evaluating mechanistic evidence on carcinogenicity that emphasizes 10 key characteristics of carcinogens. While this framework is useful for organizing mechanistic evidence, it does not provide sufficient guidance for implementation, and thus has limited utility for evaluating carcinogenic potential in humans. In addition, it does not include explicit criteria for evaluating the biological significance of mechanistic endpoints, inter- and intra-individual variability, or study quality and relevance. It also does not explicitly address how mechanistic evidence should be integrated with other realms of evidence. Because mechanistic evidence is critical to understanding human cancer hazards, systematic and detailed guidelines for the use of this framework are warranted so that mechanistic evidence can be evaluated in a robust manner and properly integrated with other realms of evidence, to reach an appropriate conclusion regarding cancer hazards in humans. We propose that the IARC 10 key characteristic framework be used as a system to categorize studies, and other established frameworks that address biological significance, study quality, and relevance be used to evaluate and integrate mechanistic evidence in systematic reviews of potentially carcinogenic substances.

#9 - Evidence Integration in Integrated Science Assessments

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The National Center for Environmental Assessment (NCEA) develops Integrated Science Assessments (ISAs) as a key part of the Clean Air Act mandated reviews of the National Ambient Air Quality Standards (NAAQS), which are set for the six criteria pollutants: particulate matter (PM), ozone, oxides of nitrogen, sulfur oxides, lead, and carbon monoxide. EPA establishes primary NAAQS to protect public health- including sensitive life stages or populations, such as children or

people with pre-existing disease, and secondary NAAQS to protect against adverse ecological and welfare effects. The ISAs identify, evaluate, synthesize, and integrate the comprehensive body of scientific evidence, often including hundreds to thousands of peer-reviewed studies spanning epidemiology, controlled human exposure, animal toxicology, dosimetry, exposure science, atmospheric science, welfare effects, and ecology. NCEA employs systematic review methodology and a weight of evidence framework in developing ISAs, integrating findings from the various lines of evidence and drawing conclusions on causality. More specifically, ISAs use a five-level hierarchical causal framework, incorporating aspects of the Hill criteria to assess causality (e.g., consistency, coherence, biological plausibility, temporality, etc.) to classify whether evidence is sufficient to conclude a "causal relationship", "likely to be a causal relationship", "suggestive of, but not sufficient to infer, a causal relationship", "inadequate to infer a causal relationship", or "not likely to be a causal relationship". Each level of the hierarchy represents the extent to which we can rule out chance, confounding or other biases. In ISAs, these causality determinations are presented both in a narrative form and in summary tables delineating the rationales and key evidence supporting the conclusion, reflecting the application of the framework and characterization of the evidence. In this case study, an example from the draft PM ISA is presented, demonstrating the evaluation and integration of multiple lines of evidence underlying the conclusion that there is a "causal relationship" between short-term $PM_{2.5}$ exposure and cardiovascular effects.

#10 - Systematically Evaluating and Integrating Evidence in National Ambient Air Quality Standards (NAAQS) Reviews

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As part of the review process for National Ambient Air Quality Standards (NAAQS), the US Environmental Protection Agency (EPA) assesses causal relationships between air pollutant exposures and health effects using a framework it developed specifically for this purpose. Here, we discuss how this framework could be improved by adding detailed methods for integrating studies in a way that fully and systematically considers individual study quality and relevance, and the coherence of results across studies within and across scientific disciplines. For example, the framework should include not just a list of study quality aspects for evaluating human and animal studies, but also aspects for evaluating *in vitro* studies, and it should specify the criteria that must be met to demonstrate that an aspect has been fully addressed. In addition, these aspects should be considered in a transparent and systematic fashion for each individual study, with the quality evaluations forming the basis for weighing evidence as it is integrated within and across disciplines, and ultimately for conclusions regarding causality. We will also specifically address the human relevance of mechanistic evidence, with a particular focus on studies that evaluate upstream events *vs.* apical effects, and how informative they are for interpreting the results of epidemiology and toxicity studies. Incorporating the suggestions discussed here will make NAAQS causality assessments more transparent and reflective of the weight of scientific evidence, and will allow for scientifically defensible decision-making

#11 - Modeling Mechanistic Processes from Source to Outcome to Support Evidence Integration and Inform Risk Assessment

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Mechanistic models can inform ontologies and evidence maps by providing an organizing framework that describes the causal relationships among key events, biological endpoints, and Adverse Outcomes (AOs). A mechanistic understanding of exposure pathways, physicochemical properties, Absorption, Distribution, Metabolism, and Elimination (ADME), and toxicity pathways can provide key advantages for risk assessors because it highlights knowledge gaps, informs inferences, and supports mechanistic evidence integration along a source-to-outcome continuum, thereby increasing the confidence in risk assessment results. This work develops a quantitative approach for integrating mechanistic exposure and toxicity data for human health and ecological endpoints using the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks. We demonstrate this approach using a hypothetical case study of a geographical site that is affected by contaminated surface water, groundwater, and atmospheric deposition. Perchlorate (ClO_4^-), a molecule that competitively inhibits iodide uptake into the thyroid at the sodium-iodide symporter (NIS) and thus affects established AOPs for developmental neurotoxicity, was used as the contaminant

for this demonstration. External exposure pathways were quantified in an AEP fate-and-transport model describing chemical movement through the site. This model was used to predict NIS-inhibitor exposure and source apportionment for humans, fishes, and small herbivorous mammals under three contamination scenarios. External exposures were linked to a previously published multi-species AOP network for NIS inhibition using physiologically based pharmacokinetic models, then combined with mechanistic dose-response data to calculate a hazard index (HI) for each potential AO in each species. Thus, we demonstrate how a source-to-outcome mechanistic model allows for the display of exposure pathways and key events into a process model of pathways to characterize pathogenesis. The source apportionment analysis predicted that surface water contamination was the largest contributor to exposure in fishes, while groundwater contamination was the largest contributor in humans and small herbivorous mammals; additionally, changes in these apportionments were quantified across scenarios. HI results showed how quantitative evaluation of mechanistic exposure and toxicity pathways facilitated the evaluation of relative risk of AOs in each species across scenarios. This work demonstrates how the AEP-AOP construct can link environmental transport and transformation, exposure, toxicokinetics, and toxicodynamics; as well as inform cumulative risk assessment, by 1) organizing mechanistic data, 2) identifying data gaps, 3) quantifying uncertainties, and 4) facilitating simultaneous evaluation of risk in human health and ecological endpoints. We show how mechanistic models can inform the construction of process models, the assembly and integration of data from systematic review, and the use of ontologies.

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#12 - Application of the EFSA/ECHA Endocrine Disruption Guidance as a Framework for Evidence Integration in a Weight-of-Evidence (WoE) Analysis for Oxybenzone (BP-3)

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ECHA/EFSA guidance provides an evidence-to-decision framework for determining if a substance is considered to have endocrine disruptor (ED) properties. The approach involves integration of lines-of-evidence (LoE) that characterize modulation of endocrine pathways relative to adverse effects. This guidance was used to assess the ED potential of BP-3, a common ultraviolet light filter, in humans. An ongoing systematic review identified 63 epidemiological, experimental animal, and *in vitro* studies. >200 endpoints evaluating activity across the estrogen, androgen, thyroid, and steroidogenesis pathways were extracted from these studies via EFSA/ECHA templates modified to accommodate epidemiological and *in vitro* assay data including ToxCast/Tox21. Each endpoint was assigned a study level (1-5), representing an increasing order of biological complexity used to evaluate strength of evidence for ED. For BP-3, the number and level of assays varied; most of the evidence base consisted of level 2 (e.g., receptor binding and transactivation assays) through level 4 assays (e.g., repeated dose studies spanning life stages). Subsequently, evidence integration involves organization via an adverse outcome pathway construct which facilitates the WoE assessment by pathway with considerations for assay level, reliability, and dose relevance to determine the plausibility of an endocrine mode of action (MoA). For example, the WoE across LoE for the thyroid pathway shows no activity in level 2 assays used to evaluate possible initiating events and no consistent histopathology changes in the thyroid in level 4 methods. Use of the ECHA/EFSA guidance in WoE analyses allows for transparent integration of heterogenous data in characterizing ED potential for BP-3.

#13 - Using *In Vitro* ToxCast Assays to Evaluate Mechanistic Plausibility and Build Confidence in the Selection of Analogues for Quantitative Read-Across: A Case Study on *p,p'*-Dichlorodiphenyldichloroethane n

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Deriving human health assessment values for environmental chemicals has traditionally relied on toxicity data from humans and/or experimental animals. In the absence of *in vivo* toxicity data, new approach methods, such as read-across have the potential to fill data gaps. This case study applied an expert-driven read-across approach to assist in screening-level assessment of non-cancer oral toxicity for *p,p'*-dichlorodiphenyldichloroethane (*p,p'*-DDD), a data-poor chemical known to occur at contaminated sites in the United States. The read-across approach relies on the evaluation and

integration of evidence across three primary similarity contexts (structure, toxicokinetics and toxicodynamics). Briefly, structural analogues with existing health reference values were identified for the target, *p,p'*-DDD, using two publicly available similarity search databases (ChemIDplus and DSSTox). Available information for the target and identified analogues on structural and physicochemical properties, toxicokinetics (Absorption, Distribution, Metabolism and Excretion) and toxicity was analyzed for consistency and coherence to select the most suitable source analogue(s) for quantitative read-across. Once the structural analogues were identified, *in vitro* high-throughput screening assays from ToxCast were evaluated for evidence in support of the similarity justification for read-across. Analysis of ToxCast assays revealed similarities in *in vitro* bioactivity for the target and analogues with respect to cell-specific responses and target gene pathways that provide mechanistic plausibility for the primary health effects for this group of chemicals (*i.e.* liver and reproductive toxicity). Coherence across toxicity and *in vitro* bioactivity similarity comparisons helped reduce uncertainties associated with toxicity data gaps for the target, increasing overall confidence in the read-across approach. The concept of consistency is captured in existing systematic review structured frameworks for integrating evidence, such as GRADE. However, approaches to describe an increase in confidence based on observing coherence from indirect lines of evidence are not well operationalized. This case study can serve as an example to help foster discussions on how to elaborate or expand on current systematic review best practice to address the complex evidence integration scenarios encountered in environmental health.

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#14 - Targeted Mechanistic Evidence Synthesis to Inform Evidence Integration Decisions on the Potential Human Carcinogenicity of Naphthalene Exposure

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Animal and *in vitro* studies published over the past 20 years on naphthalene have provided mechanistic information implicating several biological processes in the development of naphthalene-induced tumor formation. Multiple modes of action (MOAs) for naphthalene-induced carcinogenesis have been proposed, including genotoxicity, cytotoxicity, and sustained regenerative cell proliferation. While these proposed MOAs may differ in specific key events, the formation of naphthalene toxic metabolite and the biological relevance of these toxic metabolites to humans has emerged as a key component in answering the question of applicability of carcinogenic risk to humans. Here, concurrent with the broad systematic review of health effects related to naphthalene exposure, specific aims within the mechanistic analysis were used to (1) integrate the available evidence for the formation of each toxic metabolite in human, and (2) determine the biological plausibility that each of these key metabolites could be generated in human tissue and increase human oncogenic risk. Mechanistic studies were identified by tagging studies during screening of the broad literature search focused on the potential human health impacts associated with napthalene exposure. There is a great deal of similarity between the rodent and human naphthalene metabolism pathways; however, the activity of the enzymes involved in naphthalene metabolism and therefore the number of metabolites and stereoisomers of the produced metabolites may differ between rodents to humans. For the specific question of metabolic relevance, we used a well-established metabolic pathway for napthalene as a scaffold and then evaluated the availability of studies that addressed the applicability of this metabolic pathway to humans. Studies that had deficiencies in reporting critically important study details (e.g., missing experimental exposure details) were excluded. The evidence for each study was summarized in a tabular format that described study details, supporting evidence, and opposing evidence. Using the metabolic pathway as a framework, results from included studies were then integrated to determine the human relevance of each naphthalene metabolite. This case study is useful to highlight approaches for conducting a targeted mechanistic analysis to answer key questions during evidence integration in a systematic review. In addition, this case study can help identify strategies to present the concept of biological plausibility in structured frameworks for evidence integration.

The findings and conclusions in this abstract have not been formally disseminated by the US EPA and should not be construed to represent any agency determination or policy.

#15 - Three-Tiered approach to Integrating Evidence Streams Assessing Gestational Trichloroethylene Exposure and Congenital Heart Defects (TCE-CHD)

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The systematic evaluation of animal data supports lack of association for TCE-CHD with a high level of confidence. There is very low confidence in the epidemiological data to assess a potential association. The objective herein is to identify, appraise, and integrate the mechanistic evidence stream to assess TCE-CHD. Twenty-two studies were identified, relating to 71 heterogenous mechanistic experiments. Following critical appraisal, mechanistic evidence was integrated using a three-tiered approach: hazard-based, risk-based, and adverse outcome pathway (AOP)-based integration. For hazard, although some *in vitro* and *in ovo* studies suggest TCE as a potential CHD hazard, these data are contradicted by other evidence streams, and limited in their validity (e.g., non-mammalian models). Using the risk-based approach, none of the mechanistic studies were considered appropriate for extrapolating a quantitative toxicity value. For the AOP approach, evidence was considered in context of a previously proposed putative AOP for relevant CHDs and an independent assessment of events associated with a dual pathway (inhibition of cardiomyocyte differentiation and disruption of calcium mobilization). For both, considerable data gaps and limitations in study validity make these pathways incomplete and/or invalidated. Regardless of the integration tier, the same result is achieved: available evidence does not support the association of gestational TCE exposure and increased risk of CHD. Mechanistic data would have been more informative to the assessment had more relevant experiments (e.g., established cardiac development gene targets, phenotypical anchoring of gene expression data, etc.) been utilized, thereby filling data gaps and reducing uncertainties related to human health risk assessment.

#16 - Evidence Integration in Deriving Toxicity-Based Benchmarks for Trichloroethylene

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An important public health function within the Army is balancing the critical mission of national defense with the risks associated with exposure to various substances by Soldiers, workers, and their families. Developing toxicity-based benchmarks for risk assessment requires the integration of evidence from human, laboratory animal, and mechanistic studies, each with varying study designs that are collected independently and often by disparate means. Here, we use the development of an occupational exposure level (OEL) for trichloroethylene as an example of a process for assessing the weight of evidence of various toxicity endpoints. Following collection of relevant studies via a systematic literature search, we developed a quantitative process for evaluating the controlled animal data with respect to study quality, strength of effects, relevance, data consistency, and risk of bias. Studies were then graphically compared within each non-cancer health effect domain (neurological, kidney, liver, immunological, reproductive, and developmental) to establish points of departure (PODs) for each class of health effects based on data that is robust and relevant. An iterative process was then used to incorporate human health data and mechanistic data that considered mode of action, plausibility, and human relevance of these PODs. Physiologically-based pharmacokinetic (PBPK) modeling was then used to estimate human equivalent concentrations (HECs), and uncertainty factors were employed using a Bayesian approach to establish an OEL for each health effect domain. Potential cancer risks were also evaluated and this dose-response was estimated at various risk levels for the purpose of comparison to the non-cancer OEL.

#17 - A Fit-for-Purpose Framework for Use of Systematic Methods in Risk Assessment

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A lack of ability to be adaptive when applying systematic review in the practice of risk assessment has been cited as one of the many challenges, particularly related to integration of mechanistic data. To address such, we propose a framework for using evidence-based methods to facilitate the risk assessment process in a "fit for purpose" manner to determine hazard, develop toxicity values, and characterize uncertainty. The framework relies on three key components: problem formulation, systematic mapping, and systematic review(s). Applied using a decision-tree type of approach, each component consists of multiple elements (e.g., protocol, critical appraisal, integration, etc.). By employing systematic maps, subsequent systematic reviews can have narrow scopes that can be implemented efficiently. Unique to this

framework is the consideration of exposure, thus allowing for prioritization as well as context important to selection and appraisal of individual studies (e.g., dose-relevance, routes of exposure, etc.). For outcomes carried forward to systematic review, critical appraisal involves consideration of both internal and external validity for individual studies (from all streams), directly facilitating transparent selection of candidate studies. Pending assessment objectives, decision criteria are included for three integration approaches: (1) hazard characterization, (2) mode of action assessment, and (3) dose-response. Each approach integrates evidence from human, animal, and mechanistic streams, utilizes existing risk assessment techniques, and is directly linked to uncertainty assessment. The proposed framework allows for an assessment to be adaptive to the needs of a practitioner of risk assessment while still adhering to the principles of evidence-based methodology.

#18 - Evidence-Based Dose-Response Assessment for Thyroid Tumorigenesis from Acrylamide

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Acrylamide is commonly found in various foods. Cancer studies in rodents have reported increases in tumors of the thyroid, mammary tissues, tunica vaginalis of the testis, and sometimes tumors at other sites. We review relevant studies on acrylamide's DNA toxicity, tumor formation, and the manner of its tumor formation. We find, as do others, that glycidamide (a metabolite of acrylamide) causes point mutations, but acrylamide does not. We also find that thyroid tumors are most consistently sensitive in rats, being evoked in each of six experiments. We evaluate the common manners of thyroid tumor formation, including both mutagenicity and thyroid growth-stimulation. Consistent with the overall weight of the evidence, we conclude that both manners or modes of action may be occurring. We conservatively assume that the mutagenic mode of action determines the low-dose response and conclude that growth stimulation likely dominates the response at higher doses. Following US EPA guidelines, we determined that the probit model best reflects the overall data set; this model is also preferred because it better reflects the underlying ''decoupled'' biology of two modes of action. We use the probit model to identify a health-protective, linear cancer slope factor (SF) of 0.02 to 0.03 (mg/kg-day) $^{-1}$ for the low area of the dose-response curve associated with possible mutagenicity. We also identify a Reference Dose (RfD) in the range of 0.05 to 0.02 mg/kg-day for the higher dose-response associated with growth stimulation. This dose-response assessment is briefly summarized in light of other work.

#19 - Evidence Integration Using AOP Networks: Assessing Human Health Risks Associated with Hydrogen Sulfide Exposure

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Although effects of exposure to high concentrations of hydrogen sulfide (H_2S) are clear, effects associated with chronic, low-level exposure in humans is under debate, leading to uncertainty in the critical effect used in regulatory risk assessments. This study integrates experimental animal, observational epidemiology, and occupational exposure evidence by applying a pathway-based approach. A hypothesized Adverse Outcome Pathway (AOP) network was developed from 24 animal studies, comprised of five AOPs sharing two molecular initiating events (MIEs) and five adverse outcomes. A comparative dose assessment of subchronic animal data identified AOP1 (nasal lesions at 30 ppm) as the most sensitive pathway compared to other outcomes (neurological effects, >125 ppm; pulmonary edema, >80 ppm; cardiovascular related mortality, >500 ppm; mortality via central nervous system depression, >500 ppm). Strong dose-temporal concordance occurs among the four proposed key events: cytochrome oxidase inhibition (>10 ppm), neuronal cell loss (>30 ppm), olfactory nasal lesions (defined as both neuronal cell loss and basal cell hyperplasia; >30 ppm), and rhinitis (80 ppm). The weight of evidence strongly supports this biological pathway based on the human experience and consistency across chemical space. We conclude that AOP1 leads to the critical effect in animals (olfactory nasal lesions). According to the human relevance framework, this biological pathway (or, mode of action) is both qualitatively possible in humans and likely manifests as olfactory paralysis. This approach provides a basis to link the known observations in humans with the subchronic animal data, reducing the overall uncertainty of the human health risk assessment of H_2S.

#20 - Complex Evidence Integration Using Evidence-Based Tables: A Case Study Using the NTP Cancer Hazard Assessment of Night Shift Work and Light at Night Related to Circadian Disruption

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Complex cancer hazard evaluations face numerous challenges, including accounting for the breadth of data, assessing multiple intermediate exposure-response relationships, and integrating evidence from different evidence streams (i.e., human, animal, and mechanistic studies). We highlight the NTP cancer hazard assessment of both night shift work and light at night (LAN) to illustrate an approach using evidence-based figures and tables to visually collate and compare all relevant evidence across studies in the relationships between two interconnected exposure scenarios (night shift work and/or LAN) related to circadian disruption (CD) and cancer. First, an established framework defined (a) the exposure scenarios (shift work, LAN), (b) key intermediates (CD, the key characteristics of carcinogens [KC]), and (c) the outcomes (types of cancer). Next, for each exposure scenario, we evaluated evidence from animal, human and mechanistic studies for multiple exposure-intermediate-outcome relationships, including exposure-->CD, exposure-->KC, exposure--> breast cancer, CD-->KC, and KC-->cancer. Due to the complexity of the carcinogenicity pathway, multiple data types must be integrated prior to consideration of toxicology and epidemiology data. Finally, the assessments of the various types of evidence are brought forward to the overall cancer hazard evaluation. Overall, use of evidence-based tables allows for a collaborative, multi-disciplinary approach that identifies potential areas of bias, strengths and weaknesses across evidence streams, and a broader picture of the complex exposure- response pathways, allowing for a comprehensive and transparent method to help reach an overall weight-of-evidence hazard conclusion.

#21 - Mechanistic Evidence Integration Case Study: Using Ten Key Characteristics of Carcinogens and a Systematic Review Approach for Antimony Trioxide (Sb_2O_3) Cancer Hazard Identification

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The key characteristics of carcinogens (KCs) offer a way to identify and organize diverse mechanistic information. Systematic review (SR) is an approach aimed at answering a specific question while minimizing bias by using a predefined protocol to search, evaluate, and synthesize all relevant studies. We used KCs and SR to synthesize cancer mechanistic information for Sb_2O_3 and selected other compounds containing trivalent antimony (SbIII). First, references were identified using systematic literature searches and inclusion/exclusion criteria. Second, mechanistic studies were evaluated for quality and relevance. Factors relating to test substance (e.g., purity), model system (e.g., animals, cell lines), method (e.g., consistency with current guidelines), relevance (e.g., direct measurements, indirect indicators), and others were considered. Unlike our evaluation of cancer studies in humans and experimental animals, no pre-defined risk of bias questions were used for mechanistic studies because of the intensive resources needed to develop risk of bias criteria for such diverse studies. Third, information from all studies was organized by KCs and then by test substances and measured endpoints with consideration of the study quality and relevance. We found that Sb_2O_3 increases oxidative stress and is genotoxic, and the SbIII ion released from Sb_2O_3 is electrophilic. Other compounds containing SbIII impair DNA repair and induce receptor-mediated effects. Based on sufficient evidence of carcinogenicity from experimental animal studies and this supporting mechanistic information, the National Toxicology Program recommends Sb_2O_3 be listed in the Report on Carcinogens as reasonably anticipated to be a human carcinogen.

#22 - Using Study Evaluation to Inform Evidence Integration: Application in a Systematic Review of Hexavalent Chromium Male Reproductive Outcomes

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Study evaluation is used in systematic reviews to identify the strengths and weaknesses of the evidence base in a consistent and transparent manner. This can be used to inform evidence integration by identifying factors that may affect the reliability and interpretability of the results. Here, we describe how this principle was applied in a systematic review

of the male reproductive effects of hexavalent chromium [Cr(VI)]. A literature search identified 23 animal toxicology studies that examined effects of Cr(VI) exposure on the male reproductive system. These studies were evaluated by at least two independent reviewers for reporting quality, risk of bias, and sensitivity using a domain-based approach, and were rated as *high* confidence, *medium* confidence, *low* confidence, or *uninformative*. Of these, eight were considered *uninformative* due to serious flaws and were excluded. Four studies had no notable concerns and were considered *high* confidence, and eleven had significant concerns across multiple study evaluation domains and were considered *low* confidence. Whereas the *high* confidence studies found that the male reproductive system appeared unaffected by Cr(VI) exposure, the *low* confidence studies found a range of effects including decreased sperm quality and quantity and altered hormone levels. It was concluded that the evidence for Cr(VI)-induced male reproductive effects in animal models was slight, as the reliability of the observed effects was compromised by risk of bias and sensitivity concerns.

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

#23 - Systematized Review Approaches in the Assessment of Tobacco Toxicants: Acrolein as a Case Study

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Research questions in tobacco science, such as understanding the biological effects of smoke toxicants like acrolein, benefit from rapid, transparent, and reproducible methods of evidence synthesis and integration. A systematized review for acrolein toxicity, conducted in approximately seven months, analyzed, synthesized, and integrated scientific evidence using a more-rapid approach over a traditional systematic review, while still addressing a specific research question. The key question of interest was whether acrolein is a major driver of tobacco smoke-related toxicity, especially that associated with noncancer respiratory disease resulting from exposure to cigarette smoke. A search strategy using publicly available databases was executed initially, employing pre-specified selection criteria to extract data from reviews and regulatory documents, from which a preliminary mode of action was built. Data from primary research articles were then evaluated to better inform the assessment of acrolein toxicity relevant to toxic endpoints, dose-response relationships, mechanisms or modes of action, with information from different streams of evidence integrated to support the role of acrolein in tobacco smoke-related respiratory diseases. Key cellular processes in the proposed MOA for acrolein toxicity, inflammation and necrosis, were presented as narrative summaries, with accompanying graphical and tabular representation. This serves as an example of how scientific evidence can be evaluated, integrated, and presented in a timely yet reproducible and rigorous, stepwise manner.

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#24 - Accelerating Chemical Assessments: A Case Study in Automatic Evidence Extraction from Text

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Motivation: The manual processes used to extract mechanistic evidence from studies is one of the most time consuming steps of a chemical assessment. Automated evidence extraction could reduce the time to conduct a review and/or increase the scope of a review.

Method: Explicit claims (Blake 2010) were identified from abstracts (n=3,078) collected in a previous study (Korhonen et al. 2012). Prior mode of action (MOA) annotations were used to identify keywords using Shannon's measure of entropy and expert review. We report the number of supporting claims, where the MOA has increased (e.g., improve, extend), where there was some effect but the claim is neutral (e.g., change, effect), and where the MOA has decreased (e.g., reduce, inhibited). For example, a decrease in cell death be recorded for the sentence "These studies suggest that DCA has the ability to down-regulate apoptosis in murine liver."

Results: Of the 342 cell proliferation changes, 156 (45.61%) claims negated, were neutral, or refuted the premise that cell proliferation had increased and 30% of the claims made directly contradicted this premise. Of the 668 cell death changes, 231 (34.58%) claims negated, were neutral, or refuted the premise that cell death had increased and 23% of claims directly contradicted this premise.

Conclusion: Results show that simply reporting a MOA should not be interpreted as evidence that the MOA has increased; moreover, that the claim framework provides the granularity necessary to differentiate between supporting, neutral, and refuting MOA evidence.

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Korhonen, A., et al., Text mining for literature review and knowledge discovery in cancer risk assessment and research. PLoS One, 2012. 7(4): p. e33427.

#25 - Exposure Evidence Integration in Systematic Review

***Kevin Hobbie*, A. Williams, T. Feiler, C. Henning, H. Hubbard**
ICF

Systematic review has grown out of the fields of healthcare and toxicology to become a standard practice in risk assessment. As such, best practices in systematic review and evidence integration are now required to be adapted to the field of exposure assessment. Exposure studies and data are frequently more heterogeneous in nature than toxicology data and differ in structure and format from epidemiological studies. This requires new methodologies for systematically extracting, evaluating, and integrating exposure data. This poster presents a methodology for using a flexible extraction form in ICF's litstream™ systematic review management application that can be quickly and easily customized to accommodate the capture of differing streams of exposure data, ranging from environmental monitoring data; biomonitoring data; data generated from laboratory experiments; and modeling data estimates for media concentrations, intake, and dose. Also presented is a methodology for integrating exposure data collected in litstream™ into a visual presentation that considers media (biological such as serum, urine, or animal receptor; environmental such as air, soil, dust) as well as salient details such as date and location of sample collection, species, tissue type, weight fraction, or microenvironment. The proposed integration output is useful for quickly assessing the breadth of exposure data available for a given chemical and can be used with estimates of hazard in conducting risk assessments. Additionally, the format of the visualization is flexible and can be adapted to specific research needs.

#26 - Technological Tools for Evidence Integration

***Shane Thacker*, Jennifer Nichols, and Ryan Jones**
Office of Research and Development, US Environmental Protection Agency

At the EPA's National Center for Environmental Assessment, the team supporting applications of the Health and Environmental Research Online Database (HERO) and Health Assessment Workplace Collaborative (HAWC) develops web-based and desktop computer tools to facilitate evidence integration in science assessment products. We have three new tools in current development/testing that will aid researchers during various steps in the systematic review and evidence integration process. The Evidence Mapping tool allows researchers to create heat maps to visualize and overlay characteristics (e.g., discipline, exposure, concentration, etc.) of the reviewed literature, making it easy to visualize the available evidence. The Evidence Inventory tool facilitates data extraction and portrayal by providing researchers a template to collect and categorize data from the relevant literature and then create summary tables of the extracted information. Finally, the Evidence Profile Table allows researchers to build an overview table based on the strength of the evidence, creating greater transparency about the body of evidence by illuminating the rationale behind the assessment findings. These tools are integrated into the existing HERO and HAWC applications, making data collected as part of the systematic review and evidence integration process available to users.

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

PROFESSIONAL BIOSKETCHES

WORKSHOP COMMITTEE

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

Dr. Rusyn is a University 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 Texas A&M. 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 230 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 is a principal at Greek Creek Toxicokinetics Consulting and Emeritus 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 currently serves as a member of the National Academies Committee to Review DoD's Approach to Deriving an Occupational Exposure Limit for TCE. His previous service on National Academies committees includes 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. Dr. Corley 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 is a former Chair of the US 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

Brandiese Beverly, PhD, National Toxicology Program

Dr. Beverly is a health scientist with the Office of Health Assessment and Translation (OHAT) in the National Toxicology Program at NIEHS. She conducts literature-based human health assessments, evaluating effects of environmental exposures on cardiovascular and pregnancy-related outcomes using systematic review methodologies. Dr. Beverly is an active participant in the GRADE (Grading, Recommendation, Assessment, Development and Evaluation) Working Group and is currently serving as a co-chair for the GRADE Project Group for Environmental Health. Her expertise and areas of interest include disease outcomes and underlying molecular mechanisms related to reproduction and development, emerging issues related to addressing environmental health questions, and global efforts to harmonize systematic review methodologies. Dr. Beverly worked in the Integrated Risk and Information Systems (IRIS) Program within the National Center of Environmental Assessment at the US Environmental Protection Agency (EPA), using her reproductive and developmental toxicology expertise to draft chemical assessments prior to joining OHAT in 2017. She earned a PhD in molecular medicine from the University of Maryland, Baltimore, where she investigated endocrine and cardiovascular adaptations to pregnancy. She received her postdoctoral training in toxicology at EPA's National Health and Environmental Effects Research Laboratory where she evaluated effects of environmental toxicants and pharmaceutical agents on reproductive and developmental outcomes.

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 committees, including the Committee on Endocrine-Related Low-Dose Toxicity and the Committee to Review the Dietary Reference Intakes for Sodium and Potassium, both of which utilized systematic review, meta-analysis, and evidence integration approaches to address key public health issues. Dr. Chiu received a PhD in physics from Princeton University.

Jean-Lou Dorne, PhD, European Food Safety Authority

Dr. Dorne has been a senior scientific officer in the Scientific Committee and Emerging Risks Unit at the European Food Safety Authority (EFSA), since 2006. His current focus areas include EFSA chemical hazards database (openfoodtox), the development of harmonized methodologies applied to human health, animal health and ecological risk assessment of chemicals including chemical mixtures, the use of metabolism and toxicokinetic data, PBPK modelling and QIVIVE models in risk assessment, and integration of modern animal free methods and models (QSAR, OMICs and DEB models). His other topical areas include the refinement of uncertainty factors, taxa specific-traits in risk assessment, international scientific cooperation, and the development of training programs in the risk assessment area. Dr. Dorne has contributed to more than 150 EFSA scientific opinions, guidance documents, and scientific reports in the chemical risk assessment area, as well as 100 peer-reviewed papers. He is a senior lecturer in the MSc Toxicology Programme at the University of Birmingham and is an active member of EUROTOX and SETAC. Dr. Dorne received a PhD in toxicology from Southampton University.

Michael Dourson, PhD, Toxicology Excellence for Risk Assessment

Dr. Dourson is the Director of Science at Toxicology Excellence for Risk Assessment (TERA), which is a 501(c)(3) nonprofit organization. Previously, he was Senior Advisor in the Office of the Administrator at the US Environmental Protection Agency (EPA). Before that, he was a professor in the Risk Science Center at the University of Cincinnati, College of Medicine and worked at TERA and EPA. Dr. Dourson received the Arnold J. Lehman award from the Society of Toxicology, the International Achievement Award from the International Society of Regulatory Toxicology and Pharmacology, and four bronze medals from EPA. He is a fellow of the Academy of Toxicological Sciences and a fellow of

the Society for Risk Analysis. He has co-published more than 150 papers on risk assessment methods or chemical-specific analyses, and co-authored well over 100 government risk assessment documents, many of which provided risk assessment guidance. Dr. Dourson has made over 150 invited presentations to a variety of organizations, and has chaired over 150 sessions at scientific meetings and independent peer reviews. He is a board-certified toxicologist (DABT) and has been elected to multiple officer positions in the American Board of Toxicology (including its President), Society of Toxicology (including the presidency of three specialty sections), and Society for Risk Analysis (including its Secretary). He is currently the President of the Toxicology Education Foundation, a nonprofit organization with a vision to help our public understand the essentials of toxicology. In addition to numerous appointments on government panels, such as EPA's Science Advisory Board, he is a current member on the editorial board of Regulatory Toxicology and Pharmacology and Human and Experimental Toxicology. Dr. Dourson received a PhD in toxicology from the University of Cincinnati, College of Medicine.

Marios Georgiadis, DVM, MPVM, PhD, European Food Safety Authority

Dr. Georgiadis is a scientific officer and epidemiologist in the Assessment and Methodological Support Unit at the European Food Safety Authority (EFSA), since 2011. He is also a leader of the EFSA Knowledge and Innovation Community on Epidemiology. In addition, he is a Diplomate of the European College of Veterinary Public Health. Previously, Dr. Georgiadis was an assistant professor in epidemiology within the Faculty of Veterinary Medicine of the Aristotle University of Thessaloniki, and he was a lecturer in biostatistics within the Faculty of Biochemistry and Biotechnology of the University of Thessaly in Greece. He has presented numerous national and international workshops and invited talks on epidemiology-related subjects. Dr. Georgiadis received a DVM from the Aristotle University of Thessaloniki, an MPVM and a PhD in epidemiology from the University of California at Davis, and a diploma from the European College of Veterinary Public Health.

Nicole C. Kleinstreuer, PhD, National Toxicology Program

Dr. Kleinstreuer began her role as Deputy Director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) at the National Institute of Environmental Health Sciences (NIEHS) in early 2016, leading domestic and international efforts to develop novel testing and analysis strategies that provide more rapid, mechanistic, and human-relevant predictions of potential environmental chemical hazards. She has a secondary appointment in the NIEHS Division of Intramural Research Biostatistics and Computational Biology Branch, and holds adjunct faculty positions in the Yale School of Public Health and the Eshelman School of Pharmacy at UNC-CH. Dr. Kleinstreuer's research focuses on mathematical and computational modeling of biological systems and their susceptibility to perturbations that result in adverse health outcomes. Prior to joining NIEHS, she worked for Integrated Laboratory Systems, Inc., as director of the ILS computational toxicology group. She is the recipient of numerous prestigious awards including the 2008 B.H. Neumann Prize from the Australian Mathematical Society, 2012 Impact Award from the US Environmental Protection Agency's (EPA's) Office of Research and Development, 2016 F. Clarke Fraser New Investigator Award from the Teratology Society, 2016 Young Researcher Americas Lush Prize, and the 2019 Society of Toxicology Achievement Award. Dr. Kleinstreuer received a PhD in bioengineering from the University of Canterbury, and she completed her postdoctoral training at the EPA National Center for Computational Toxicology.

M.E. (Bette) Meek, PhD, University of Ottawa

Dr. Meek is an Associate in Chemical Risk Assessment at the McLaughlin Centre for Risk Science, Faculty of Medicine, University of Ottawa. Previously, she managed several chemical risk assessment programs within Health Canada. With colleagues internationally, she has contributed to or led initiatives in developing methodology in chemical risk assessment, including mode of action, chemical specific adjustment factors, physiologically-based pharmacokinetic modeling, combined exposures, and predictive modeling. These initiatives have involved collaborations with a range of international organizations and national agencies, including the World Health Organization International Programme on Chemical Safety; Organization for Economic Cooperation and Development; US Environmental Protection Agency; and European Joint Research Centre and the Agency for Food, Environmental and Occupational Health and Safety of France (ANSES). She has authored approximately 200 publications in this area and received several awards for contribution in this domain. Dr. Meek received a PhD in risk assessment sciences from the University of Utrecht.

Larry W. Robertson, PhD, MPH, University of Iowa

Dr. Robertson is Professor of Toxicology in the Department of Occupational and Environmental Health, College of Public Health at the University of Iowa. He is the founding Program Director of the Iowa Superfund Program, entitled, "Semi-volatile PCBs: Sources, Exposures, Toxicities" which was funded in 2006 and has been renewed through 2020. Dr. Robertson is also the Director of the Interdisciplinary Graduate Program in Human Toxicology, a toxicology training program with more than 20 full-time doctoral students and more than 30 faculty. Earlier in his career, Dr. Robertson received an Alexander von Humboldt Research Fellowship and took a post-fellowship position as a Project Leader in SFB 302 Early Stages in Carcinogenesis at the University of Mainz in Germany. Dr. Robertson's primary research focus is the mechanism(s) of toxicity of polyhalogenated aromatic hydrocarbons, including the polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), and related persistent organic pollutants. He has published more than 290 articles in this area. Dr. Robertson organized, and obtained funding for, 10 International PCB Workshops, the last of which took place in Kraków, Poland, in August 2018. He is the recipient of the John Doull lifetime achievement award of the Central States Chapter of the Society of Toxicology and the Research Faculty Award of the College of Public Health at the University of Iowa. He is a fellow of the Academy of Toxicological Sciences. Dr. Robertson received a PhD in environmental health sciences and an MPH from the University of Michigan.

Kristina Thayer, PhD, US Environmental Protection Agency

Dr. Thayer is the Integrated Risk Information System (IRIS) Division Director, located within the US Environmental Protection Agency's (EPA's) National Center for Environmental Assessment (NCEA). IRIS assessments identify the potential for a chemical to cause cancer or non-cancer health effects in people. Those assessments are considered to be the top-tier source of toxicity information used by EPA and other agencies to inform decision-making concerning national standards, clean-up levels at local sites, and advisory levels. IRIS uses systematic review methods to conduct assessments. Prior to joining EPA, Dr. Thayer was Deputy Division Director of Analysis at the National Toxicology Program (NTP) and Director of the NTP Office of Health Assessment and Translation (OHAT), located on the campus of the National Institute for Environmental Health Sciences (NIEHS). She is considered an expert on the application of systematic review methods to environmental health topics and the use of specialized software and automation approaches to facilitate conducting reviews. Dr. Thayer received a PhD from the University of Missouri, Columbia.

Paul Whaley, MLitt, Lancaster University

Paul Whaley is a researcher and academic editor specializing in systematic review methods for environmental health research and chemical risk assessment. He is based at the Lancaster Environment Centre of Lancaster University, UK, and is a Research Fellow of the Evidence Based Toxicology Collaboration. His work focuses on developing frameworks for systematic mapping and review of scientific evidence in support of assessing and managing human health risks posed by exposure to environmental challenges. This includes the development of best-practice standards for conducting and reporting systematic reviews and maps, critical appraisal tools for evaluating research, and editorial workflow interventions to assure the quality of manuscripts published in scientific journals. Recognizing the challenge which a large and heterogeneous evidence base poses to successful, timely conduct of systematic reviews in environmental health, Mr. Whaley has begun research into how computational approaches can support complex systematic review projects. He has a MLitt in philosophy from the University of St Andrews and is pursuing a PhD in research synthesis methods in environmental health.

DISCUSSANTS

Stanley Barone, Jr, PhD, US Environmental Protection Agency

Dr. Barone is the Deputy Director of the Risk Assessment Division of the Office of Pollution Prevention and Toxics (OPPT) in the US Environmental Protection Agency's (EPA's) Office of Chemical Safety and Pollution Prevention (OCSPP). His key responsibilities include overseeing risk assessment activities related to both new chemicals and existing chemicals programs, as well as administrative and resource functions for the entire division. Dr. Barone's health and ecological assessment activities include developing and implementing systematic review approaches in risk evaluations for Toxics Substances Control Act (TSCA). Since he came to EPA in 1990, Dr. Barone has held several positions within the Office of

Research and Development, including Assistant Center Director for Human Health Risk Assessment at the National Center for Environmental Assessment (NCEA) and National Program Director for the Human Health Risk Assessment Program. He has published more than 75 peer reviewed papers, technical reports, and book chapters. Dr. Barone has served on peer review panels for numerous government and nongovernmental funding organizations and government advisory panels. He received a PhD in neurobiology from East Carolina University School of Medicine.

Samuel Cohen, MD, PhD, University of Nebraska Medical Center

Dr. Cohen is Professor of Pathology and Microbiology and Havlik-Wall Professor of Oncology at the University of Nebraska Medical Center, Omaha, and a member of the Buffett Cancer Center. He continues to be active as a surgical pathologist and in basic research, and teaches medical and graduate students, pathology residents and fellows. His research has been in chemical carcinogenesis, toxicology, and pathology, with an emphasis on extrapolation from animal models to humans. He has published over 400 peer reviewed articles and book chapters, and has served on numerous national and international panels and committees, including for the National Institutes of Health, National Academy of Sciences, Environmental Protection Agency, Food and Drug Administration, International Programme on Chemical Safety, International Agency for Research on Cancer, National Comprehensive Cancer Network, and the Expert Panel of the Flavor and Extract Manufacturers Association. He also has served on the Boards of Scientific Counselors of the National Toxicology Program and the National Institute of Environmental Health Sciences, and has been on the Board of Trustees of the International Life Sciences Institute (ILSI) and Health and Environmental Sciences (HESI). His research is funded from the NIH, Arsenic Science Task Force, Sumitomo Chemical Company, and Kumiai Chemical Company. He has received numerous awards, including the Lehman and Merit Awards from the Society of Toxicology, the Lifetime Achievement Award from the Society of Toxicologic Pathology, and the Distinguished Scientist Award from the American College of Toxicology. He is a fellow of the Academy of Toxicological Sciences and the International Academy of Toxicologic Pathology. He received his MD and PhD (Experimental Oncology) from the University of Wisconsin-Madison, residency training in anatomic and clinical pathology at St. Vincent Hospital, Worcester, MA, and is board certified in anatomic and clinical pathology.

Jennifer McPartland, PhD, Environmental Defense Fund

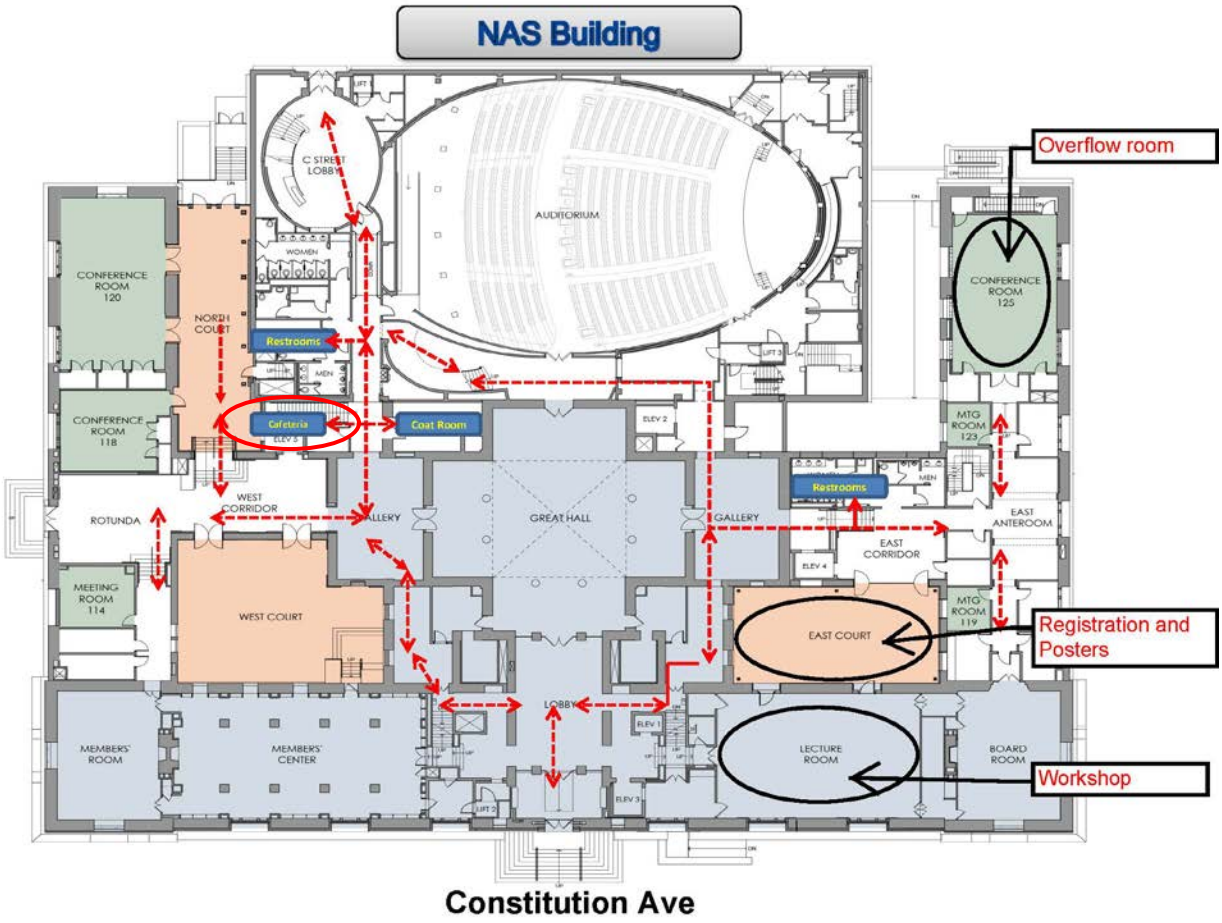
Dr. McPartland is a senior scientist in the Health Program at the Environmental Defense Fund (EDF), where she focuses on advancing science, policy, and market solutions to protect human health and the environment from harmful chemical exposures. She supports EDF's efforts to ensure public health protective implementation of the Toxics Substances Control Act. Dr. McPartland is the primary technical advisor for EDF corporate partnerships, focused on improving supply chain chemicals management and in this capacity has worked with major businesses to develop corporate chemicals policies and management plans. She leads EDF's engagement in federal efforts to apply systematic review in chemical assessment and to advance new chemical testing approaches. She also works closely with EDF's Energy program to address emerging issues associated with alternative reuse of produced water, including through various research initiatives and multi-stakeholder dialogue. Dr. McPartland currently serves on the steering committee for the National Academies' Environmental Health Matters Initiative, US EPA's Board of Scientific Counselors Chemical Safety for Sustainability Subcommittee, and on the GreenScreen for Safer Chemicals Steering Committee. She earned her PhD in microbiology from the University of Chicago.

Tracey Woodruff, PhD, University of California, San Francisco

Dr. Woodruff is a Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of California in San Francisco. Her research seeks to advance understanding of how environmental chemicals exposures affects early development and contributes to infant and child disease and health disparities and translates scientific findings to improve clinical care, community engagement, and policies to prevent harmful chemical exposures. Her research program uses innovative multidisciplinary approaches that 1) integrate research on understanding exposures of pregnant women and fetuses to environmental contaminants and the impact of these exposures on health and fetal development; and 2) translate these scientific findings to healthcare providers, policy makers and community groups in order to improve clinical care and promote policies that prevent prenatal exposures to harmful chemicals. Dr. Woodruff received a PhD in bioengineering from a joint program of the University of California, Berkeley and San Francisco.

NAS BUILDING MAP

1st Floor Conference Rooms Layout and Emergency Exits



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