



Interagency Coordinating Committee on the Validation of Alternative Methods

Presentation Abstracts and Background Materials

SCIENTIFIC ADVISORY COMMITTEE ON ALTERNATIVE TOXICOLOGICAL METHODS

Session II: The Role of New Approach Methodologies (NAMs) in Improving Environmental Health Protection

Friday, September 22, 2023

Population Variability and Susceptibility: Using New Approach Methodologies to Address Variability and Susceptibility Across Populations – Report from the October 2022 Symposium/Workshop

Presenter: Dr. Helena Hogberg-Durdock, NIEHS

Human health risk assessment aims to characterize the potential harmful effects of chemical exposures to ensure the safety of broad populations. Among these broad populations are those with higher susceptibility to adverse effects from chemical exposures. Variation in response to chemicals is determined by a myriad of aspects such as life stage, sex, genomics, epigenomics, nutrition, microbiome, comorbidities, psychosocial stressors, co- and cumulative exposures.

NICEATM organized a public virtual symposium on October 26-27, 2022 on using NAMs to address variability and susceptibility across populations. The virtual event attracted over 250 attendees representing government, academia, and a diversity of industrial and nongovernmental sectors. An interdisciplinary group of over 50 members was invited to participate in a discussion session following the symposium. Some of the key points discussed and future recommendations will be shared in this presentation.

Background

- Sprankle C. Nonanimal testing experts connect with environmental justice community (article in NIEHS Environmental Factor newsletter, December 2022). <https://factor.niehs.nih.gov/2022/12/science-highlights/new-approach-methodologies>.
- Workshop presentation abstracts: https://ntp.niehs.nih.gov/sites/default/files/iccvam/meetings/popvar-2022/niceatm-popvar-abstracts_508.pdf.
- To et al. New approach methodologies to address population variability and susceptibility (editorial). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10308785/pdf/40246_2023_Article_502.pdf.

Population Variability and Susceptibility: Building Confidence in New Evidence Streams for Human Health Risk Assessment

Presenter: Dr. Weihsueh Chiu, Texas A&M University

New approach methods (NAMs) in toxicology offer opportunities to address several long-standing challenges. For instance, NAMs could potentially inform timely decision-making when no data are available from laboratory mammalian toxicity tests or epidemiological studies. NAMs may also characterize subtle health perturbations, better encompass genetic diversity, and account for nonchemical stressors, informing better protection of susceptible and vulnerable populations. Although the promise and need for NAMs is clear, many barriers to their use remain, and few concrete examples exist today of NAM data applications in hazard or risk assessment decisions. This report aims to bridge this notable gap between the potential of NAMs and their practical application in human health risk assessment.



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The report identified five common components of evaluating scientific confidence of NAMs: (1) intended purpose and context of use, (2) internal validity, (3) external validity, (4) experimental and biological variability, and (5) transparency. A key step towards integrating NAMs into risk assessment is the specification of the population, exposure, comparator, and outcomes (PECO) of the NAM in parallel with a “target human” PECO that specifies how the NAM would inform human health hazard identification or dose-response. This “parallel PECO” approach represents the interface by which NAMs can be considered as an evidence stream within modern systematic review-based best practices for risk assessment. The report envisions that the development and utilization of a framework that integrates these new evidence streams will enable NAMs both to address the lack of data for most chemicals in the environment and to better cover susceptible and vulnerable populations, and thus ultimately improve protection of public health.

Background

- National Academies of Science, Engineering, and Medicine. Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests. <https://nap.nationalacademies.org/catalog/26906/building-confidence-in-new-evidence-streams-for-human-health-risk-assessment>.

Population Variability and Susceptibility: Fruitflies for Precision Toxicology

Presenter: Dr. Brian Oliver, National Institute of Diabetes and Digestive and Kidney Diseases

PrecisionTox is a large international consortium exploring the replacement of traditional mammalian chemical safety testing by comparative toxicology in fruit flies, nematodes, water fleas, clawed frog and zebrafish embryos, and human cell lines. Following comparative toxicology data using more traditional terminal endpoints (primarily lethality), we are performing gene expression and metabolite profiling at low to subphenotypic dose to map the conserved adverse outcome pathways. The awesome power of fruitfly genetics is particularly important in the “precision” work, as we can easily test key human genes and allelic variants, as well as counteracting chemicals that might change susceptibility in people. These data are expected to provide mechanistic insight and feed predictive models useful for regulating groups of chemicals.

Background

- The PrecisionTox Consortium. The Precision Toxicology initiative. <https://doi.org/10.1016/j.toxlet.2023.05.004>.

Coordinated Responses to Contaminants of Emerging Concern: An Inter-Agency Initiative to Address Contaminants of Emerging Concern

Presenter: Dr. David Balshaw, NIEHS

In August of 2022, the U.S. National Science and Technology Council released a National Emerging Contaminants Research Initiative (NECRI, <https://www.whitehouse.gov/wp-content/uploads/2022/08/08-2022-National-Emerging-Contaminants-Research-Initiative.pdf>) outlining a vision for an Inter-Agency effort to speed the identification, risk characterization, and mitigation of contaminants of emerging concern (CECs) in the drinking water cycle. CECs can be newly identified or reemerging manufactured or naturally occurring materials and can cover a wide range of agents (e.g., chemical, biological, radiological), environmental media, and chemistries. They are most often identified and characterized contaminant-by-contaminant, an approach that does not consider their frequent occurrence in mixtures and limits generalization of research findings. Hence, decision makers are challenged with incomplete, diverse, and evolving data that make it difficult to systematically identify, monitor, and manage potential risks associated with CECs. With this complex CEC research landscape, an integrated strategic approach is needed to address data gaps and generate timely,



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actionable information for CECs. The NECRI, designed to meet this challenge, is based on the fundamental tenet that all people deserve access to clean and plentiful drinking water. This initiative outlines five central goals:

1. To decrease the time from CEC identification to risk mitigation
2. Promote technological innovation to discover, track, and mitigate CECs
3. Develop and deploy tools for CEC decision making
4. Coordinate transdisciplinary CEC research among partners
5. Foster transparency and public trust

Initial steps of implementation of the NECRI have focused on near-term efforts while identifying longer term activities for optimizing cross-governmental coordination and collaboration. The use of Non-Targeted Analysis (NTA) in conjunction with Effects Based Monitoring (EBM) to identify and prioritize potential CECs can now be implemented in cross-governmental projects. Combined with the use of cutting-edge risk characterization methods including New Approach Methodologies (NAMs) for hazard assessment, these techniques will soon be available to identify potential health impacts of CEC exposure to inform subsequent studies on risks, mitigation, and communication strategies.

Background

- Office of Science and Technology Policy. National Emerging Contaminants Research Initiative. <https://www.whitehouse.gov/wp-content/uploads/2022/08/08-2022-National-Emerging-Contaminants-Research-Initiative.pdf>.

Coordinated Responses to Contaminants of Emerging Concern: ICCVAM PFAS Work Group

Presenter: Dr. Natalia Vinas, Department of Defense

Per- and polyfluoroalkyl substances (PFAS) are a class of organofluorine chemicals that have been manufactured and used for decades. They have very specific properties that make them resistant to oil, water, and high temperatures. They are used in many products and applications, such as firefighting foams, food packaging, or stain- and water-resistant fabrics and carpeting. There is no consensus definition of PFAS, and depending on how they are defined, the number of compounds considered PFAS can differ by the thousands. The large number of compounds, structures, and properties makes PFAS hazard prediction extremely challenging. The newly formed PFAS Working Group will address some of the main concerns on the use of New Approach Methodologies to predict PFAS toxicity. Those will include definitions and categorization, specific properties, and translational challenges.

Background

- Office of Science and Technology Policy. Per- and Polyfluoroalkyl Substance (PFAS) Report. <https://www.whitehouse.gov/wp-content/uploads/2023/03/OSTP-March-2023-PFAS-Report.pdf>.