National Institute of Environmental Health Sciences
Division of Translational Toxicology

Using NAMs to Address Variability and Susceptibility Across Populations

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Introduction

- In October 2022, National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) organized a **state-of-the-science** symposium focused on **population variability and susceptibility (PopVS)** in the context of chemical risk assessment and **new approach methodologies (NAMs)** .
  - Characterizing **population-level variability** and the factors that influence **heterogeneity of response** will help build a comprehensive understanding of chemical risk that is inclusive and protective of **broad populations**.
  - **NAMs** have the potential to characterize or integrate **PopVS** to provide human-relevant toxicity predictions.
- The symposium connected **government, scientific experts on NAMs, and the environmental justice (EJ) community** for discussions on the state-of-the-science.
- Symposium presentations and discussions described **ongoing research and opportunities** to address factors that can affect variability such as genetics, sex, life stage, or co- and cumulative exposures.
- Common themes among the panel and breakout discussions were the varying perspectives on **building confidence in NAMs** and the need **for community engagement** when planning and conducting research that aims to address EJ concerns.

Symposium Objectives

1. **Review NAMs** that have been developed to address PopVS to environmental chemicals
2. **Understand** environmental health **challenges** around PopVS and how NAMs could address them
3. **Identify knowledge gaps** in PopVS and the feasibility of using NAMs to fill them; prioritize future research initiatives
4. **Foster connections** between NAMs researchers and the environmental justice community

Presentations

View symposium presentations, panel discussion, related materials

https://ntp.niehs.nih.gov/go/popvar

View the pre-symposium webinars

https://www.pcrm.org/popvars

Symposium Panel Questions

1. **What NAMs are ready to be used now** to model PopVS and for what specific applications?
2. What are the **technical or logistical challenges** to understanding PopVS using NAMs?
3. What are the **research areas to prioritize** NAM development to better represent PopVS?
4. **What priorities have susceptible populations expressed** in relation to NAMs, and how have these priorities been addressed?

Symposium Breakout Questions

1. **What is needed to build confidence** in models that aim to address susceptibility and variability?
2. **How can NAMs developers and users interact with communities** in a productive way to ensure that the needs of sensitive subpopulations are being met?
3. What are the **barriers and opportunities to apply NAMs** to issues of susceptibility and variability in toxicology?

Research and Opportunities

Microphysiological Systems (MPS)

- The NIH Clinical Trial on a Chip program has developed MPS such as the **fetal-maternal-interface-on-a-chip** and **human-kidney-on-a-chip** model to inform design and execution of clinical trials for rare and common diseases in susceptible populations.
- **Reconstructed human epidermis** models are being used to screen skin tone modulators within different phototypes.

In Vitro Assay Battery

- The OECD has published a draft guidance document for evaluating data from a **developmental neurotoxicity in vitro battery**.
- **Air-liquid interface** exposure models have been used to characterize interindividual variability in ozone response gene expression.

Induced Pluripotent Stem Cells (iPSC)

- **IPSCs** have been sourced from mapping populations such as the Mouse Collaborative Cross that are designed to be genetically diverse to model heterogenous human responses.
- **Human iPSCs** are used to study gene-by-environment neurotoxicant vulnerabilities across life stage.

Small Model Organisms

- **Zebrafish** are being used to study the role of environmental exposures on heightened incidence of chronic kidney disease of unknown etiology in tropical farming communities.
- The Precision Tox project aims to implement **comparative genomics** across **fruit flies, water fleas, round worms, zebrafish embryos, frog embryos, and human cell lines** to model toxicity pathways across species.

Integrating Existing Data with NAMs

- Exposure data from biobanks, climate and air pollution data, and census data have been leveraged in **exposome-wide association studies** to characterize intrinsic and extrinsic factors affecting disease phenotypes.
- **Probabilistic Bayesian approaches** have been integrated with **physiologically based pharmacokinetic models** for risk assessment of per-and polyfluoroalkyl substances.

Building Confidence

Types of Confidence

Scientific	Regulatory	Community
• Technical characterization • Human relevance • Data • Limitations	• Fit-for-purpose • Reproducibility • Scalability • Comprehensive documentation	• Transparency • Early engagement • Bidirectional communication • Observable impact

- **Scientific confidence** is influenced by **technical characterization**, which helps to build an understanding of the usability and **limitations** of a NAM.
  - An ongoing challenge is defining metrics for determining how to measure sufficient representation of human population variability.
- **Regulatory confidence** is dependent on reliability, **reproducibility**, and **scalability** of a NAM. **Fit-for-purpose** models overcome uncertainties regarding human relevance in comparison to animal-based tests.
  - Regulators need **comprehensive guidance documents** that clearly define how a NAM should be used in a regulatory decision context.
- At the **community** level, building confidence in NAMs will require **building trust in both the science and scientists**.
  - The EJ community will have more confidence in NAMs if there is **concrete evidence** of scientific results translating into policy change.

Community Engagement and Building Trust

Direct and open dialogue with communities will inform NAM implementation.

- **Extrinsic factors** such as social stressors or historic redlining lead to **cumulative impacts** that disproportionately burden minority and low-income communities.
- Community-level **issues, exposures, and health disparities** are known but **persist** despite existence of relevant data and tools.
- **NAMs** may be viewed as a **barrier to action** on regulatory decisions by certain stakeholders while the scientific support for the NAM is being developed.
- **Transparent communication** and ongoing engagement with EJ communities during NAM development will **build trust** in the scientific process.

NAMs research should center on real-world outcomes and solutions.

- **Long-term, results-oriented collaborations** between researchers and impacted communities could help focus research toward **high-priority issues.**
  - As a first step toward reaching this goal, the development of **additional workshops and working groups** would provide opportunities for NAMs researchers to engage with community leaders and advocates.
- Scientists and regulators that actively engage with communities should be **educated in EJ issues** to build trust and avoid harm.
  - Institutional Review Boards, ethics offices, and community and Tribal liaisons should be leveraged to facilitate effective communication and meaningful relationships.
- **Models and algorithms** should be evaluated to ensure that they are characterizing **relevant variation** and are not biased against vulnerable groups.

Call for Papers

Human Genomics invites contributions to the recently launched research collection “New Approach Methodologies to Address Population Variability and Susceptibility in Human Risk Assessment”. Papers are encouraged to deal with human health risk assessment and feature research developing, refining, or implementing NAMs with consideration of population variability or susceptibility.

Read more about the collection
https://www.biomedcentral.com/collections/NAMAPVS

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