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

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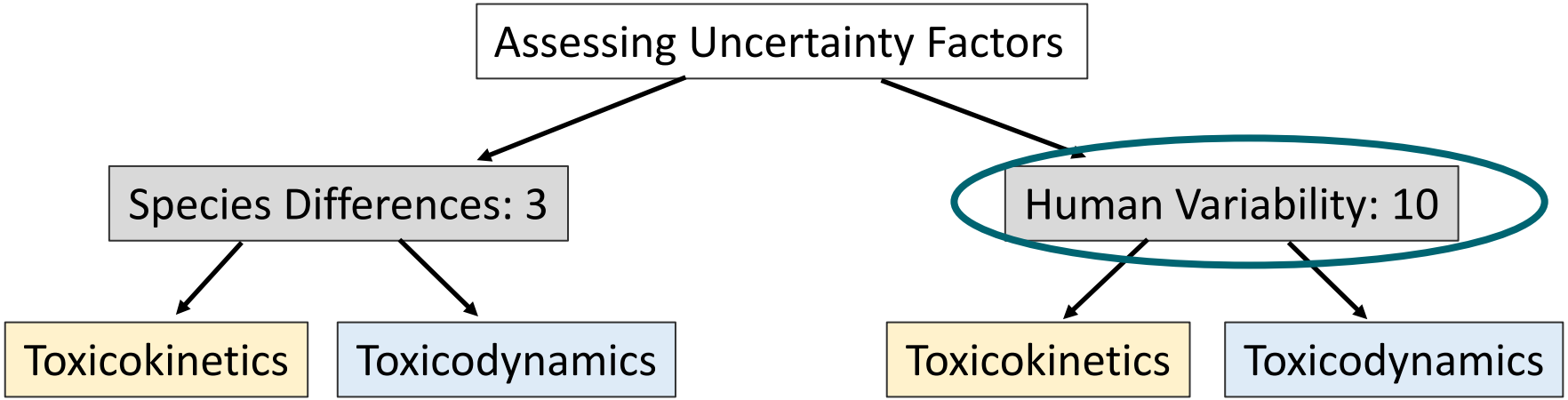
Risk Assessment Aims to Protect Very Broad Populations

Different people exhibit response variability and differing levels of susceptibility to toxic effects from chemical exposure, presenting a complex challenge for chemical risk assessment

NAMs may be able to provide or complement data to better predict which individuals or communities are most at risk of certain outcomes stemming from environmental exposures

Traditional Approach to Address Uncertainty Around Human Variability



Protective, overprotective, or not protective enough?

When sufficient data are available (perhaps from models/NAMs representing susceptible subpopulations), an intraspecies UF either less than or greater than 10× may be justified (US EPA IRIS Handbook, 2020).

Examples of Factors That Can Contribute to Population Variability and Susceptibility

Extrinsic

- Co-morbidities
- Nutrition
- Co- and Cumulative exposures
- Psychosocial stressors
- Microbiome

Intrinsic

- Genetic polymorphisms
- Epigenetics
- Sex
- Life stage

A State of the Science Workshop on October 26-27, 2022

Pre-webinars to highlight recent NAMs to examine PopVS (co-hosted by PCRM)

- Skin Models
- Clinical Trials on Chips
- Chemical Exposure

https://www.pcrm.org/popvars

More than 250 attendees
The symposium brought together scientific experts from government, industry, academia, and NGOs and community advocates

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

Interactive Panel Discussion

Followed by breakout group discussions with 50+ participants from Europe and US that represented various stakeholders and with diverse expertise

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Symposium Objectives

1) **Review NAMs** that have been developed to address population variability and to address susceptible subpopulations (PopVS)

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

Federal Government Prioritization of Equity/Environmental Justice

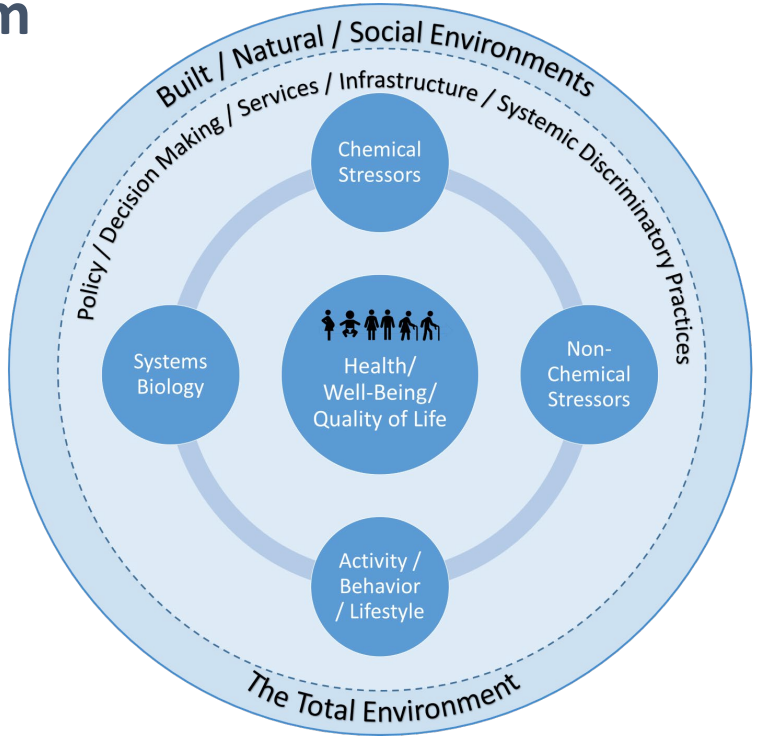
Several U.S. federal agencies have invested in research initiatives that aim to address health disparities and inequities

- National Center on Minority Health and Health Disparities (NCMHD) by NIH (2000)
- Office on Minority Health and Health Equity (OMHHE) by FDA (2010)
- Biden Administration signed two executive orders that prioritize Equity/Environmental Justice (2021)

However, there is need to integrate efforts to identify, characterize and solve environmental problems where they are most acute and with communities that are most at risk and least resilient

Cumulative Impacts Conceptual Diagram

Combined influences on the total (built, natural, social) environment for individuals, geographically defined communities, or definable population groups



epa.gov/healthresearch/cumulative-impacts-research

Adapted from Tulve et al., 2016

Chemical Exposures and Impacts at the Local Public Health Level

- “I thought everything on the market was tested and well-regulated, why isn’t it?”
- “It has become a luxury to buy healthy food, have the education, and not be exposed to toxic chemicals”
- Vulnerable and sensitive populations are falling through the cracks
- Hazardous chemical exposures affect lives → developmental impacts are life-long and require resources and knowledge to address
- The burden to deal with exposures should not fall on the communities or individuals affected
- Ultimate goal – address and mitigate exposures upstream before communities are exposed to harmful levels

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?

NAMs to Address Population Variability and Susceptibility

In vitro assays

- An OECD endorsed battery of in vitro assays for developmental neurotoxicity – **life stage**
- Human primary cells for respiratory toxicity – **genetics, sex**

MPS

- NCATS, NIH Clinical Trial on Chip for rare diseases – **comorbidities and life stage**
- Reconstructed human epidermis – **phototypes, sex, age, disease**

iPSCs

- Mouse iPSCs from Diversity Outbred mice – **genetic polymorphisms that modulate susceptibility**
- Human iPSCs for neurotoxicity – **genetic polymorphisms, epigenetics and life stage (development and age), sex, chronic exposure**

NAMs to Address Population Variability and Susceptibility

Small model organisms

- Zebrafish to study environmental exposures – **life stage, genetic variation, co- and cumulative exposures**
- Precision Tox project compare pathways across species (fruit flies, nematode, frog embryos, Zebrafish embryos, human cells) – **genetic variation, sex, age, disease**

Integrating existing data with NAMs

- Exposure data from biomonitoring, climate and air pollution – **co- and cumulative exposures**
- Probabilistic Bayesian approaches integrated with PBK models – **genetic polymorphisms, age, co- and cumulative exposures**

Technical and Logistical Challenges

- Enough sample size and broad enough to provide reasonable representation of factors affecting human variability
  - Costly, challenging to identify and get access to the right cohorts
- Even banked biological data has relatively limited variation, because donors and study participants are “self-selected” and may not reflect real population variability
- Models and algorithms should be evaluated to ensure that they are characterizing relevant variation and are not under-representing specific groups
- Differentiate between reproducibility vs variability for regulatory use

Research Areas to Prioritize in NAMs Development

- Develop NAMs to address information gaps related to population variability and susceptibility outside of genetic and epigenetic variation
- Cumulative impacts beyond chemical stressors, e.g., social stressors, systemic racism, physical stress, nutrition, access to high quality products and health care are desirable to include and may present a challenge to NAMs researchers
- Find ways to leverage obtained information into regulatory decision making
- Identify biomarkers of who might be most susceptible
- Integrate human exposure biomarker data with existing toxicity data

Priorities Expressed by Susceptible Populations

- Engage in dialogue with and understand the concerns of communities with exposure and environmental justice concerns
- More effort to engage with populations and communities who are impacted to get their input and guidance on what their priorities are
- Historical failures and challenges in engagement between researchers and communities need to be addressed in order to establish confidence
- Develop new strategies to prevent and mitigate harmful exposures

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?

What is needed to build confidence in NAMs for PopVS?

Types of Confidence

Scientific

- Technical characterization
- Human relevance
- Data
- Limitations

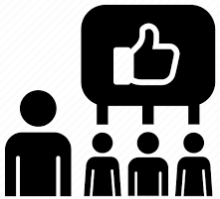
Regulatory

- Fit-for-purpose
- Reproducibility
- Transferability
- Comprehensive documentation

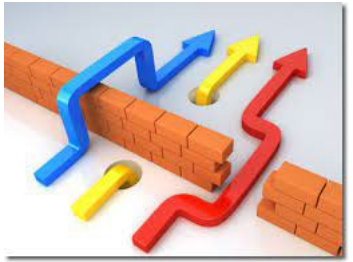
Community

- Transparency
- Early engagement
- Bidirectional communication
- Inform decisions

How can NAMs developers and users interact with communities?



- Scientists and regulators that actively engage with communities should be educated in EJ issues to build trust and avoid harm
- Involve EJ advocates & community representatives, social scientists, and bioethicists in the process from the beginning
- Transparent communication about timelines, results and capabilities of NAMs
- Acknowledge that community-level concerns exist regarding existing socioeconomic and/or health disparities and ongoing chemical exposures
- Clear communication that we have a common goal - to understand and improve human health



Barriers and opportunities to apply NAMs

- Funding is necessary for larger and more interdisciplinary projects
- Consider including more probabilistic risk assessment practices
- Still not enough knowledge about susceptibility factors and co- and cumulative exposures and their resulting health effects
- NAMs can provide evaluation of sensitive/susceptible populations
- Can be further connected with existing data on health disparities
- NAMs might generate new information about variability and susceptibility in ways that *in vivo* animal studies do not

Conclusion and Future Directions

- 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
- **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

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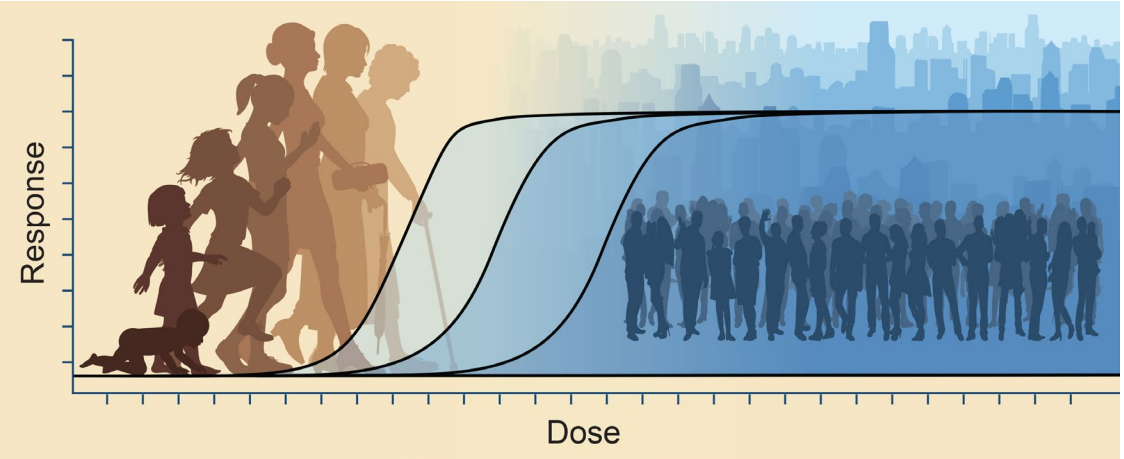
Human Genomics Call for Papers
New Approach Methodologies to Address Population Variability and Susceptibility in Human Risk Assessment

Guest Editors: Helena Hogberg, Nicole Kleinstreuer and Kim To



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

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Breakout group participants
50+ international, stakeholder and expert diverse group

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