Overcoming Challenges in Use of NAMs to Inform Population Variability and Susceptibility in Regulatory Decision-Making

Using New Approach Methodologies to Address Variability and Susceptibility Across Populations
A State of the Science Symposium Webinar

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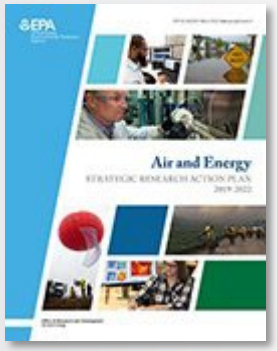
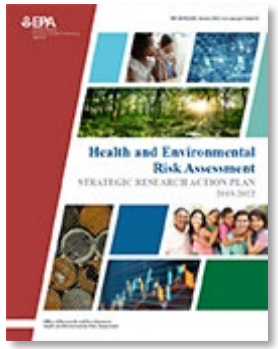
The views presented are those of the author and do not necessarily reflect the views of the US EPA.

Strategic Research Action Plans (StRAPs)

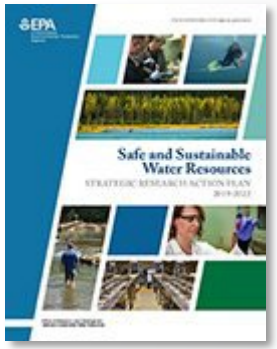
ORD just completed a long-term research planning cycle, developing Fiscal Years 2023-2026 Strategic Research Action Plans (StRAPs) for each National Research Program



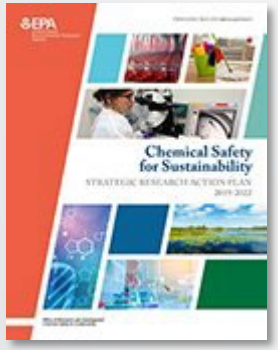
Air, Climate and Energy (ACE)



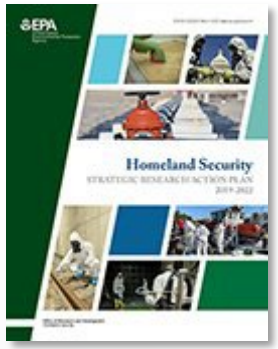
Health and Environmental Risk Assessment (HERA)



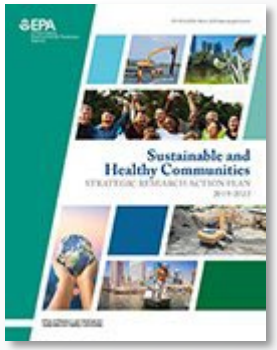
Safe and Sustainable Water Resources (SSWR)



Chemical Safety for Sustainability (CSS)



Homeland Security (HS)



Sustainable and Healthy Communities (SHC)

FY 2023-2026 StRAPs available: epa.gov/research/strategic-research-action-plans-fiscal-years-2023-2026

Integrating Efforts Across Programs

Cross-Cutting Research Priorities

ORD is working on joint and targeted engagement activities with key Agency partners and external partners and stakeholders to ensure ORD's research portfolio appropriately addresses key topic areas

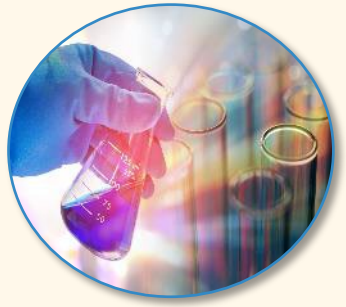
Environmental Justice

Cumulative Impacts

Climate Change

Community Resiliency

Children's Environmental Health



Contaminants of Immediate and Emerging Concern

Cumulative Impacts and Equity/Environmental Justice

Equity/Environmental Justice (EJ) is a priority of the Biden Administration

- President Biden signed two Executive Orders on EJ in January 2021:
  - EO 13985: Advancing Racial Equity and Support for Underserved Communities Through the Federal Government
  - EO 14008: Tackling the Climate Crisis at Home and Abroad
- EPA Administrator Regan issued an Agency-wide directive to better serve historically marginalized communities using cumulative impact assessment

ORD is working to ensure its research portfolio aligns with these priorities

Cross-Cutting Research Priorities

Where appropriate, EPA's six National Research Programs (NRPs) will work together through joint and targeted engagement activities with key Agency partners and external partners and stakeholders to ensure that ORD's research portfolio appropriately addresses key topic areas.

Environmental Justice

Will integrate research efforts to identify, characterize, and solve environmental problems where they are most acute, in and with communities that are most at risk and least resilient.

Cumulative Impacts

Cumulative Impacts are defined as the totality of exposures to combinations of chemical and non-chemical stressors and their effects on health, well-being, and quality of life outcomes.

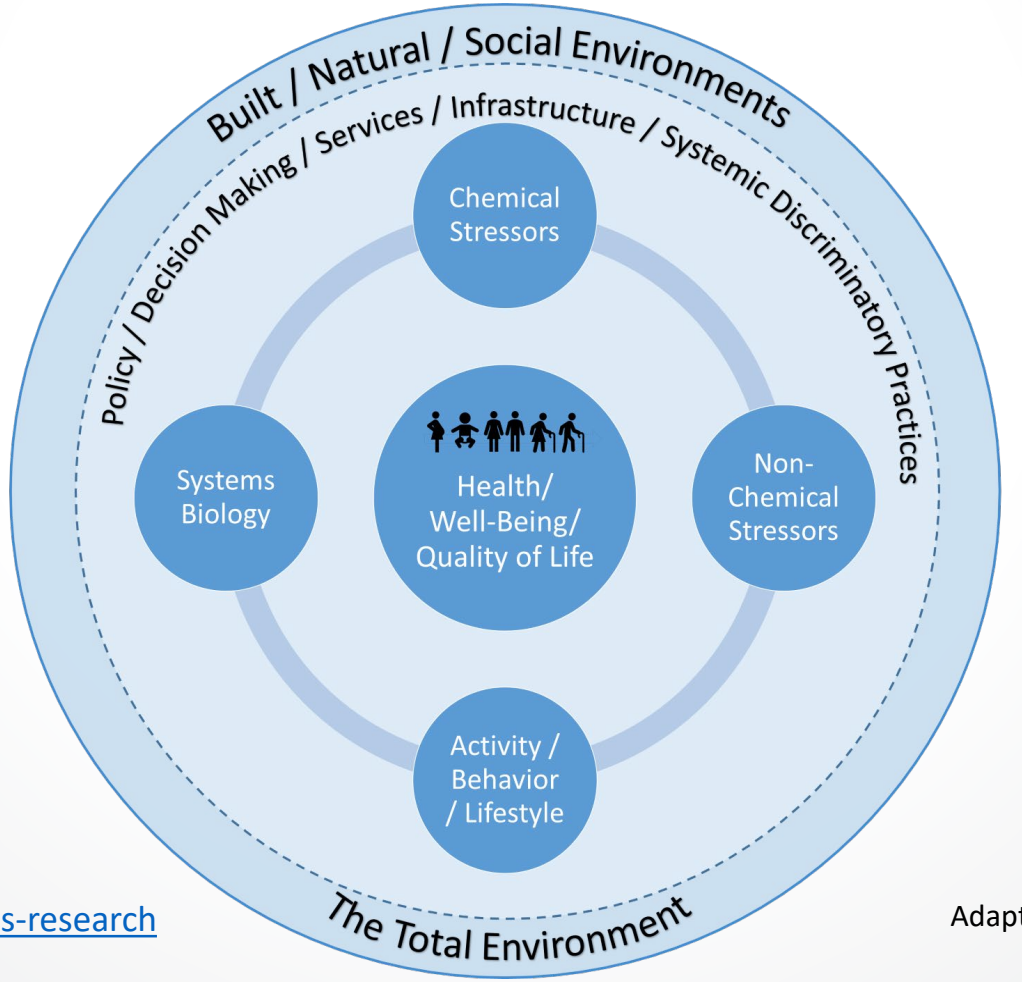
Cross-Cutting Research Priority

Cumulative Impacts

- Communities that have long been overburdened face cumulative impacts from:
  - chemical stressors in environmental media (air, water, land); and
  - non-chemical stressors, including social determinants of health
- Changing climate is exacerbating many of these cumulative impacts
- It is critical to bolster the scientific basis for identifying actions to improve community health and well-being, and to select, implement, and evaluate such actions

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

Definition(s) of New Approach Methods (NAMs)

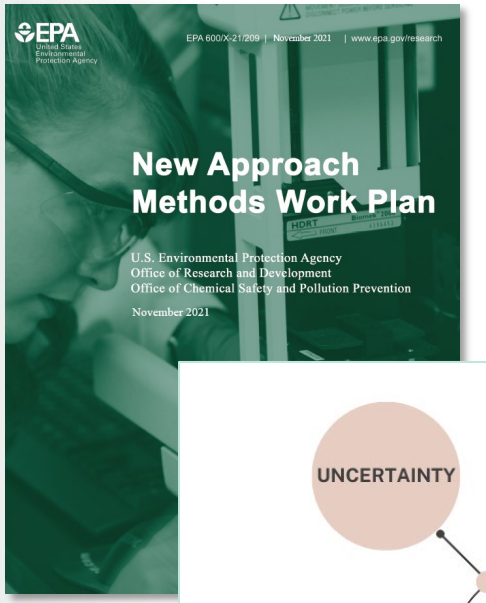
- Commonly defined to include *in silico* approaches, *in chemico* and *in vitro* assays, as well as the inclusion of information from the exposure of chemicals in the context of hazard assessment.

- Defined in the EPA's TSCA Alternative Toxicity Strategy as:
  - a broadly descriptive reference to any technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment that avoids the use of intact animals.

https://echa.europa.eu/documents/10162/22816069/scientific_ws_proceedings_en.pdf

https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/alternative-test-methods-and-strategies-reduce

EPA NAMs Work Plan



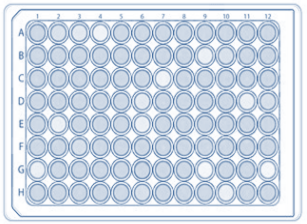
- Five objectives for achieving the reduction goals while ensuring that Agency decisions remain fully protective of human health and the environment
  - Evaluate regulatory flexibility
  - Develop baselines and metrics
  - Establish scientific confidence and demonstrate application
  - Develop NAMs to address information gaps
  - Engage and communicate with stakeholders

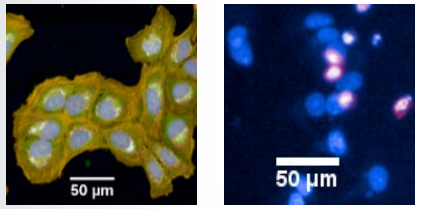
Changes in 2021 updated work plan:

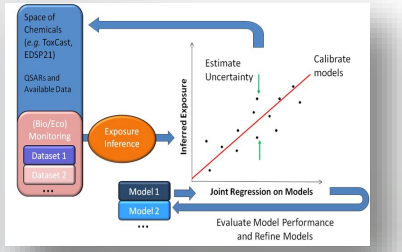
- Modified timelines & deliverables through 2024; two case studies
- Covered species now includes all vertebrate animals, consistent with TSCA
- Pilot study to develop NAMs training courses for a broad range of stakeholders

https://www.epa.gov/nam

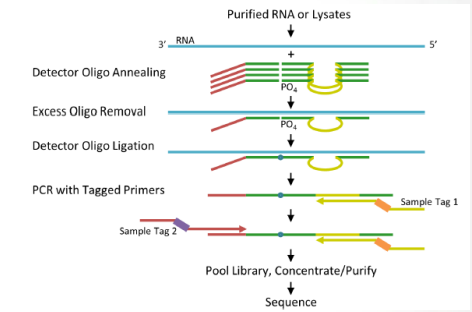
NAMs Today

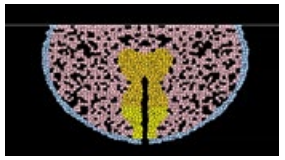


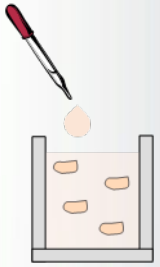


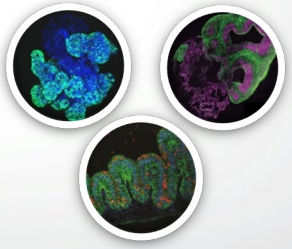


- In silico (e.g. QSAR and Read-across)
  - Estimate effects and doses
  - Consensus exposure modeling
- In vitro assays
  - Broad / screening (transcriptomics, cell painting)
  - Targeted (receptors, enzymes)
  - Organotypic models
  - In vitro PODs, modes / mechanisms of action
- In vitro Toxicokinetics
  - Allow conversion of an in vitro POD to in vivo (IVIVE)
- High-throughput Exposure Measurements
  - To fill data gaps in monitoring data
- Computer models
  - Hazard models to integrate multiple in silico and in vitro data streams
  - Exposure models to increase information on different pathways of exposure





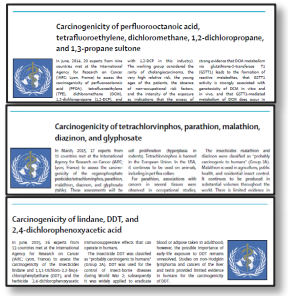




NAMs in Risk Assessment to Date

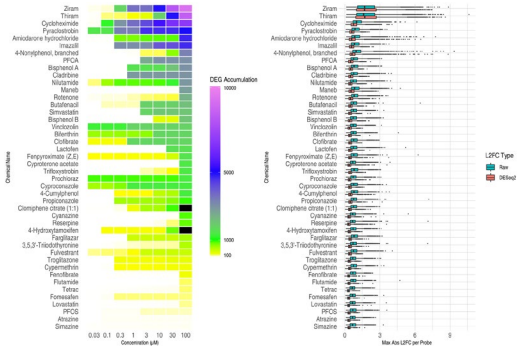
- Hazard characterization
- Dose-Response
- Exposure assessment

Provide Mechanistic Support for Hazard ID



IARC Monographs
110, 112, 113

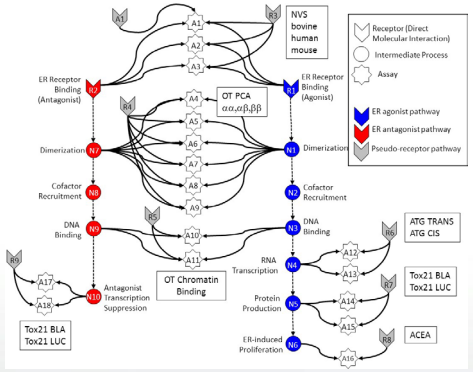
Tiered testing with High-throughput screening



Harrill et al 2021

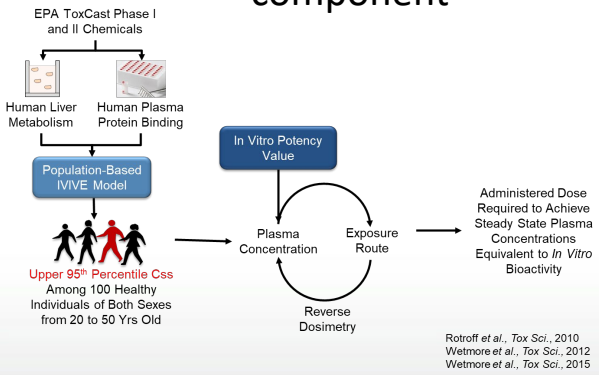
…and more!

Prioritization of Chemicals for Further Testing



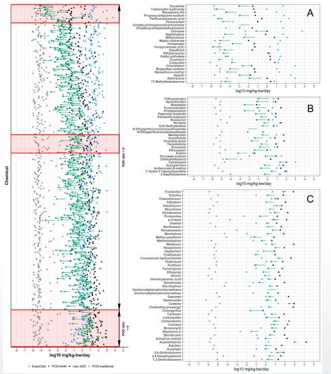
Judson et al., 2015

High-throughput toxicokinetic component



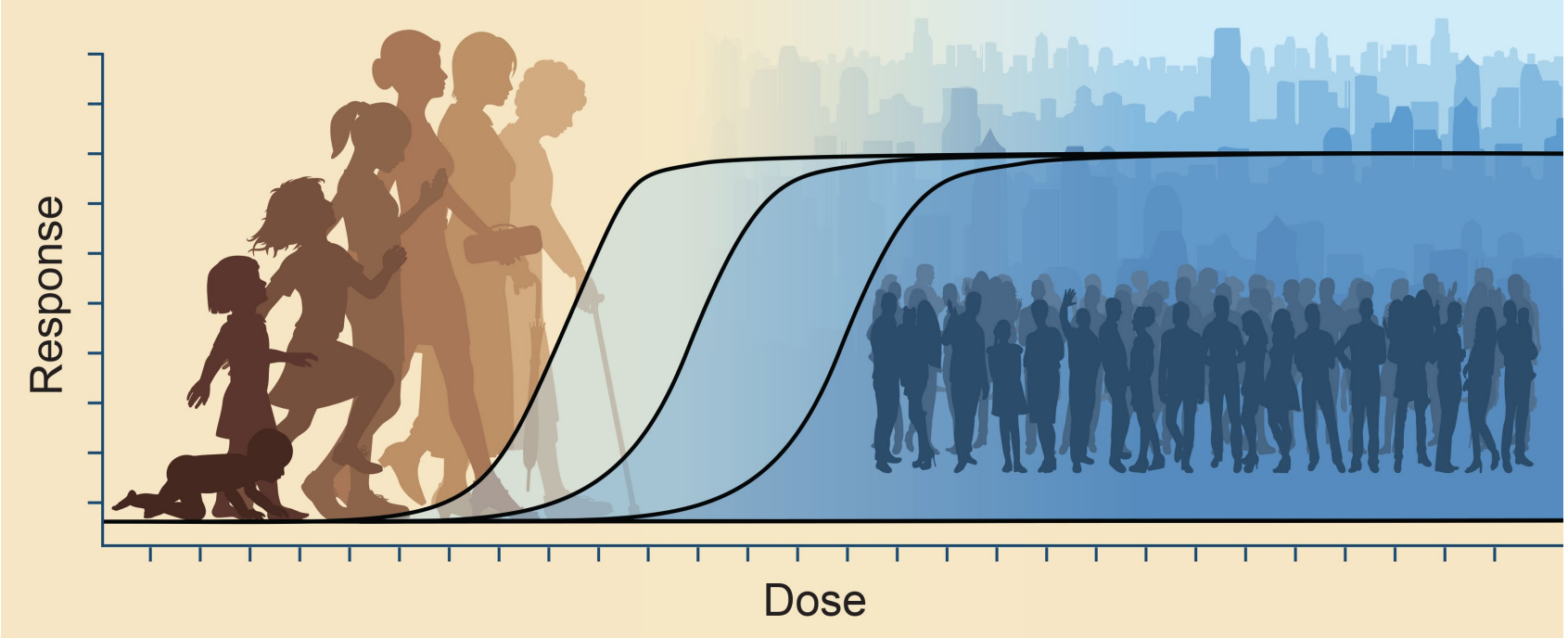
Rotroff *et al.*, *Tox Sci.*, 2010
Wetmore *et al.*, *Tox Sci.*, 2012
Wetmore *et al.*, *Tox Sci.*, 2015

In vitro point-of-departure development from NAMs



Paul Friedman et al, 2020

Variability and Susceptibility



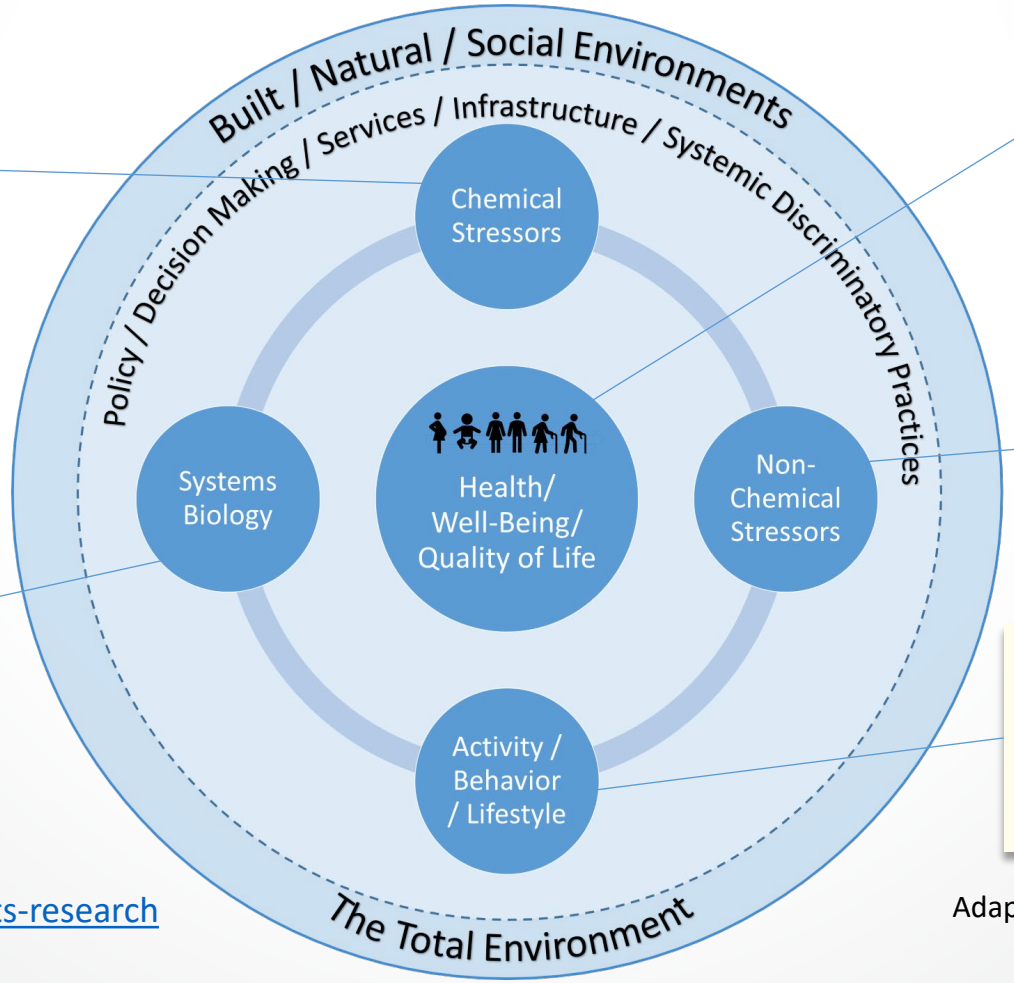
- **Susceptibility:**
  - **Life stage (ex. DNT NAMs test batteries; TK)**
  - **Exposure (ex. Community proximity to chemical sources)**
- **Variability:**
  - **Cell type & organ specificity of bioactivity (ex. HTPP and HTTR in a variety of cell types)**
  - **Screening in genetically diverse population models**

Cumulative Impacts Conceptual Diagram

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

Hazard characterization: *Highthroughput screening using genetically diverse cell lines*

Systems approach: *Computational modeling*



Interindividual variation: *Organotypic models with diverse tissues*

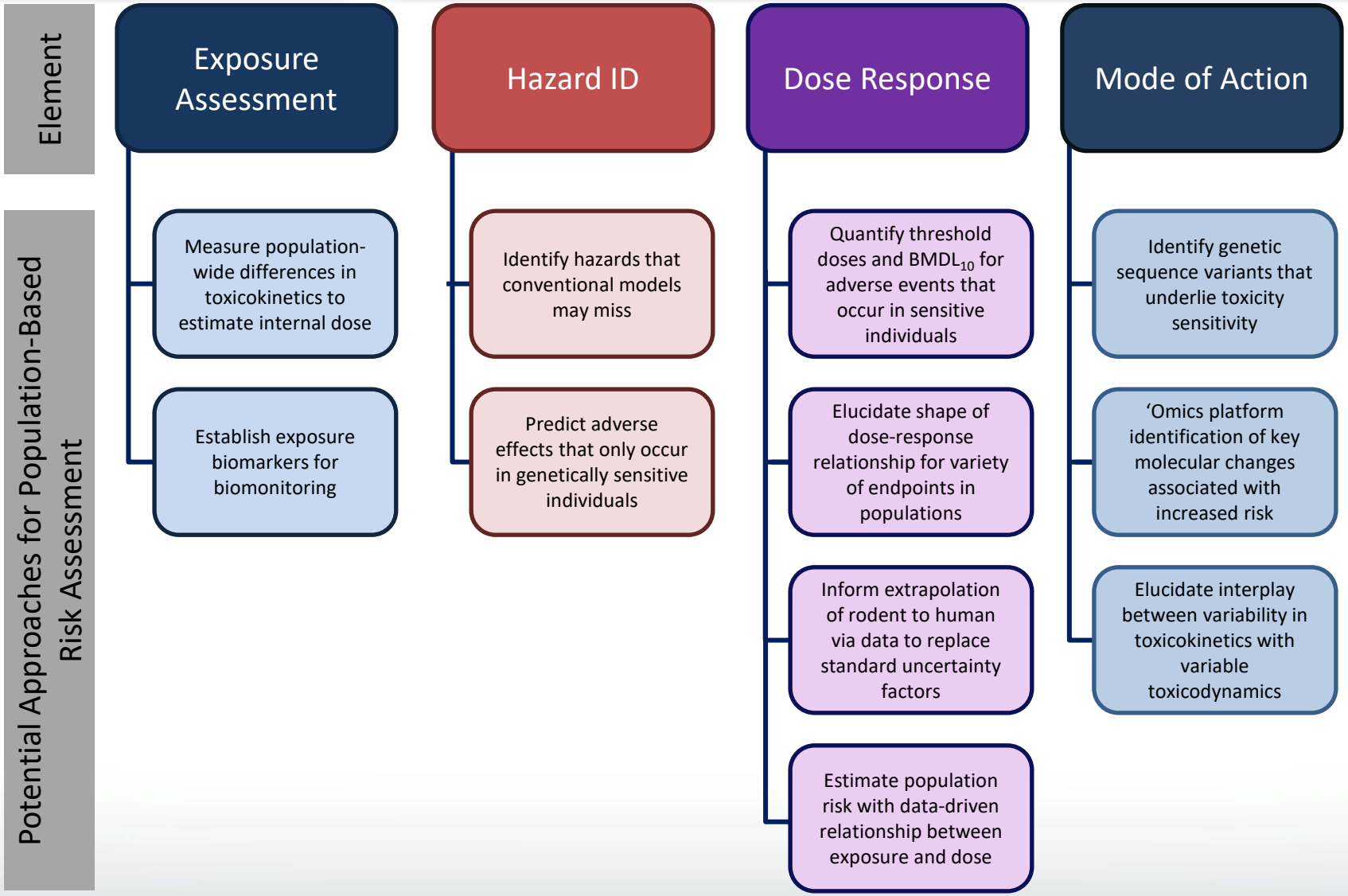
Biomarkers of exposure/bioindicators of stressors: *stay tuned!*

Exposure: *Non-targeted monitoring and/or structure-based QSAR models to predict exposure*

epa.gov/healthresearch/cumulative-impacts-research

Adapted from Tulve et al., 2016

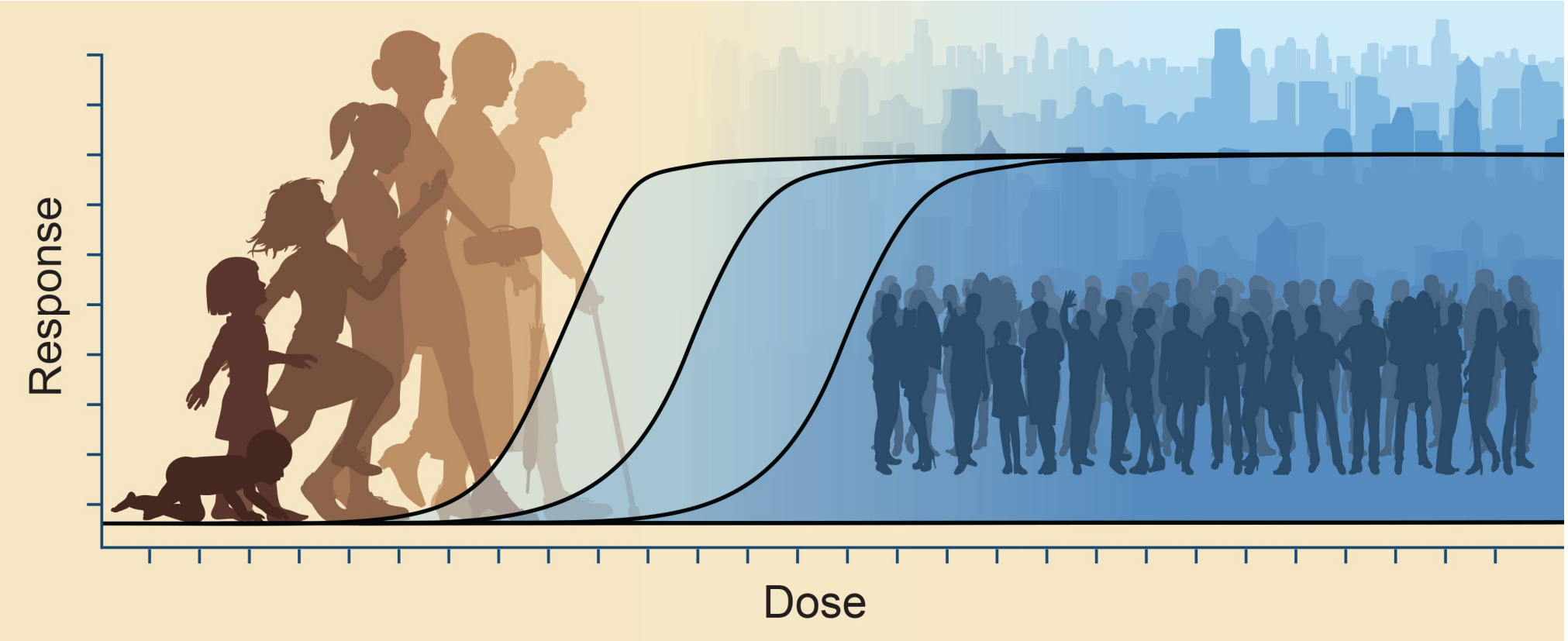
Population Models Potential in Toxicology



Harrill and McAllister, *Environmental Health Perspectives* 2017

Workshop Goals:

Identify opportunities and needs for NAMs to provide relevant information on population variability and susceptibility to xenobiotics



Specific information on the workshop and links to register are available at https://ntp.niehs.nih.gov/go/popvar

Thank you for your attention!

Cumulative Impacts Report

The purpose of the report was to inform ORD's strategic research planning to expand ORD's cumulative impacts research portfolio (Link Here)

- The recommendations are already informing actions within ORD to advance the state of the science on cumulative impacts
- Input was critical to developing these recommendations –
  - Listening sessions with 65 Tribes, 62 state agencies, 35 local agencies, and 9 national associations
  - Workshop with EPA Programs and Regions and community member panels to gather different perspectives
  - Science Advisory Board Consultation