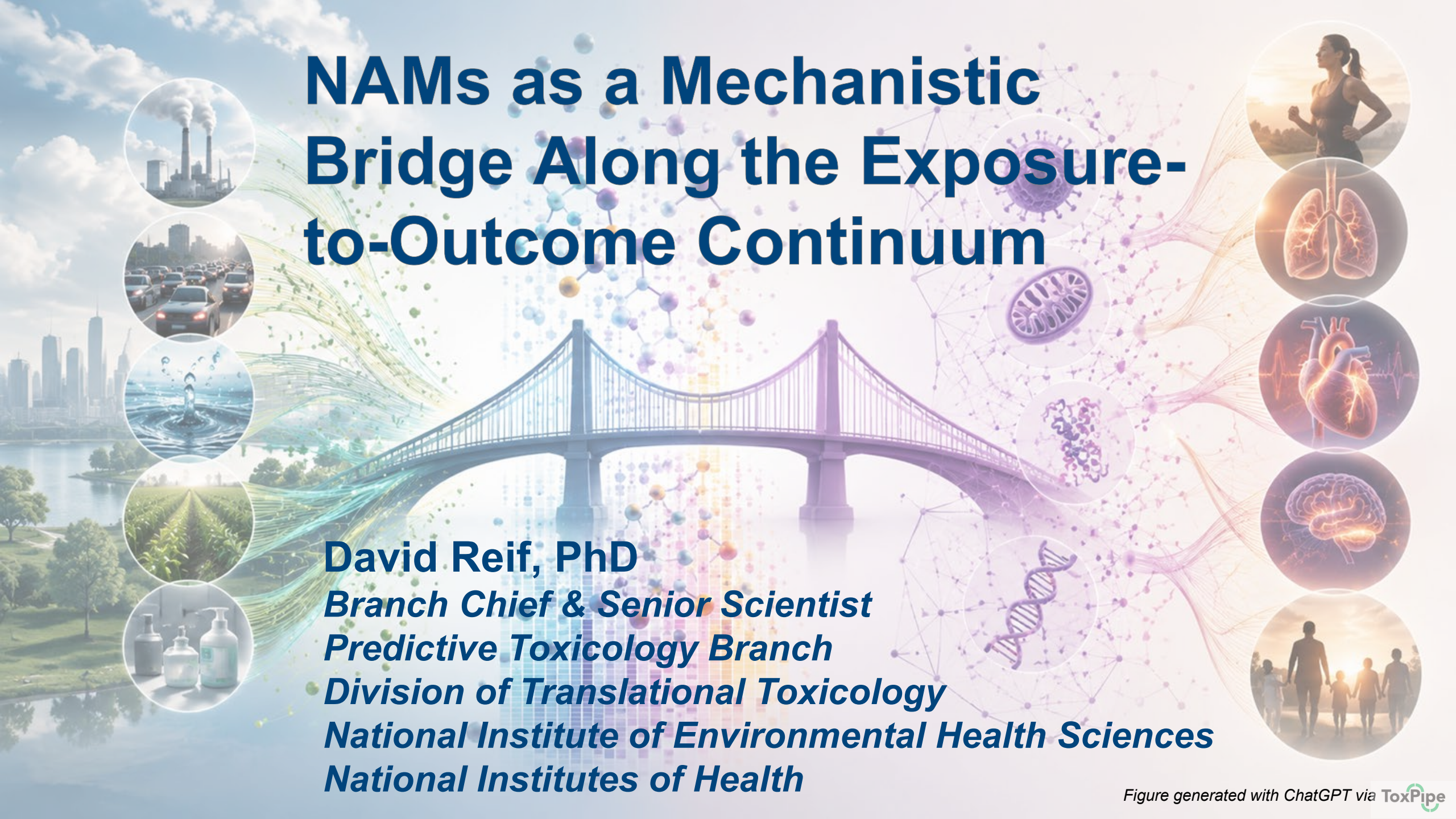


NAMs as a Mechanistic Bridge Along the Exposure-to-Outcome Continuum

David Reif, PhD
Branch Chief & Senior Scientist
Predictive Toxicology Branch
Division of Translational Toxicology
National Institute of Environmental Health Sciences
National Institutes of Health



What is the “exposure-to-outcome continuum”?

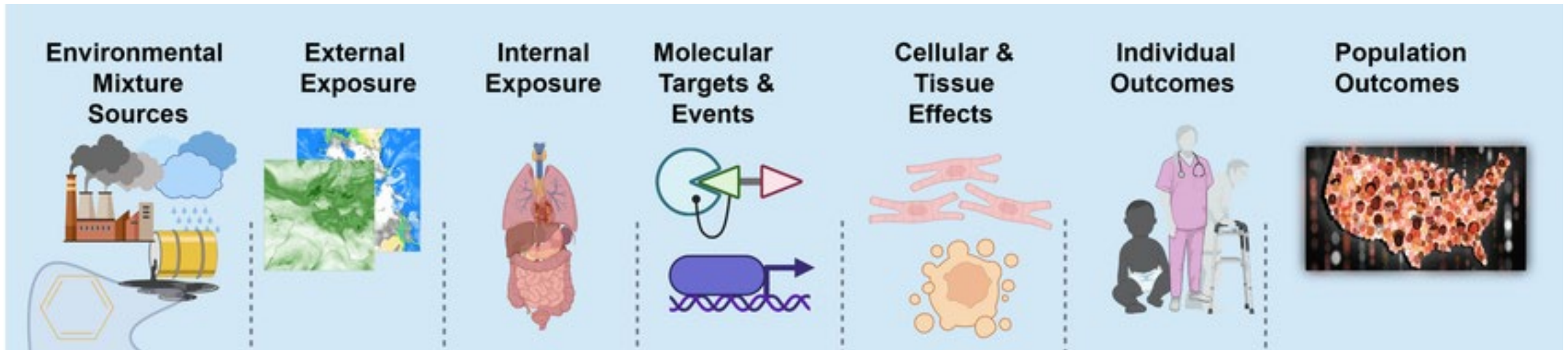
The series of events (*or interconnecting paths*) from introduction of a stressor into the environment and its movement through the environment via specific pathways to the receptor and the triggering of a biological response of potential regulatory concern

*National Academies of Sciences, Engineering, and Medicine. 2017.
Using 21st Century Science to Improve Risk-Related Evaluations.*

What is the “exposure-to-outcome continuum”?

The series of events (*or interconnecting paths*) from introduction of a stressor into the environment and its movement through the environment via specific pathways to the receptor and the triggering of a biological response of potential regulatory concern

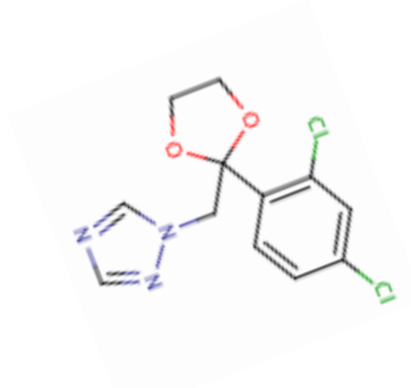
National Academies of Sciences, Engineering, and Medicine. 2017. Using 21st Century Science to Improve Risk-Related Evaluations.



Messier KP, Reif DM, Marvel SW. (2025). The GeoTox Package: open-source software for connecting spatiotemporal exposure to individual and population-level risk. Human Genomics.

Predictive Toxicology requires mechanistic knowledge of what's happening to receptors between exposures and outcomes

Exposure

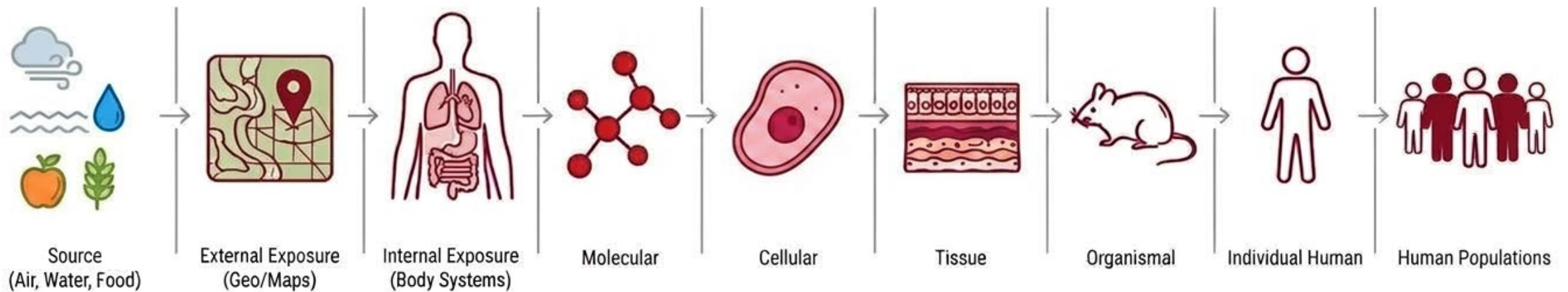


Receptor(s)

? ? ? ?

Outcome

**NAMs (*incl. assays + models + integrative approaches*)
provide a mechanistic bridge to advance predictive
toxicology at several points along the exposure-to-
outcome continuum**

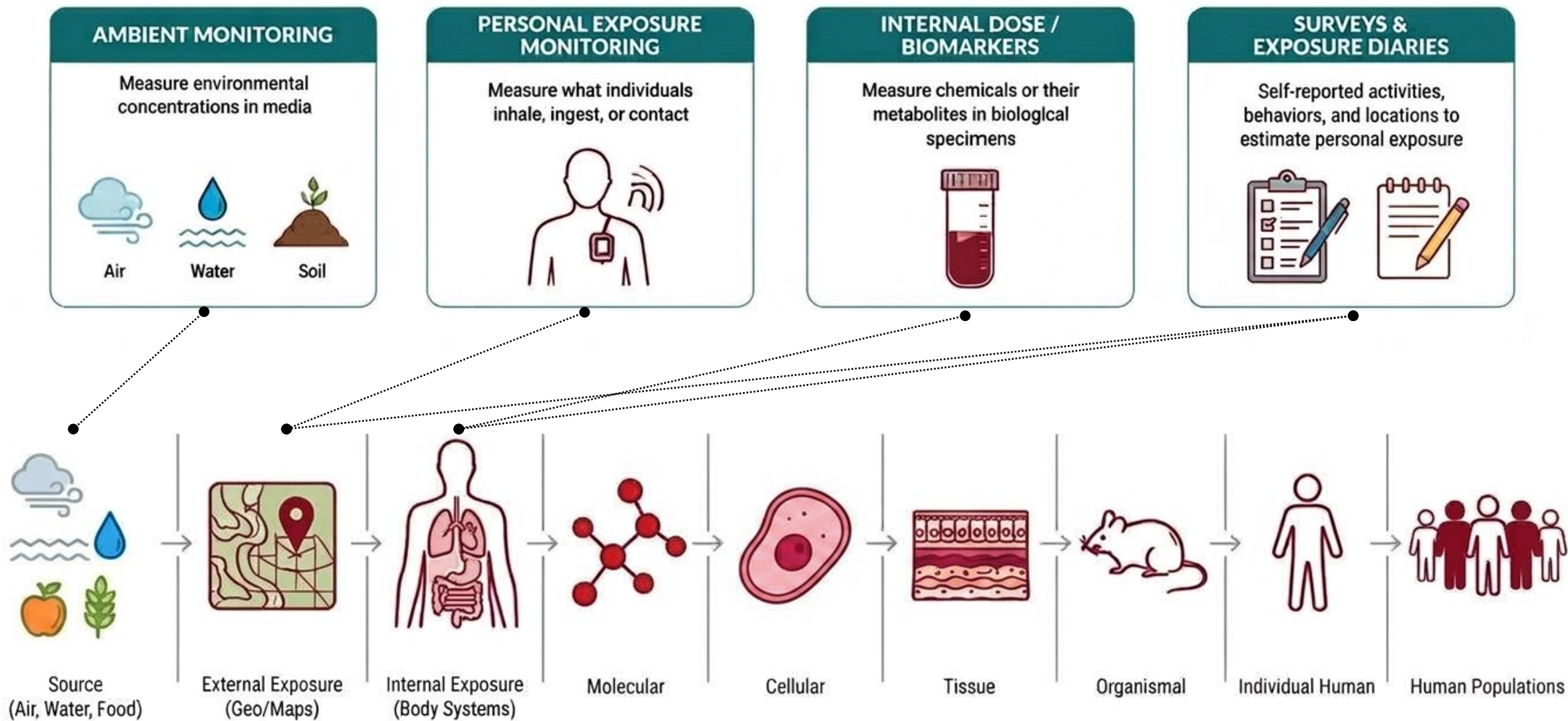




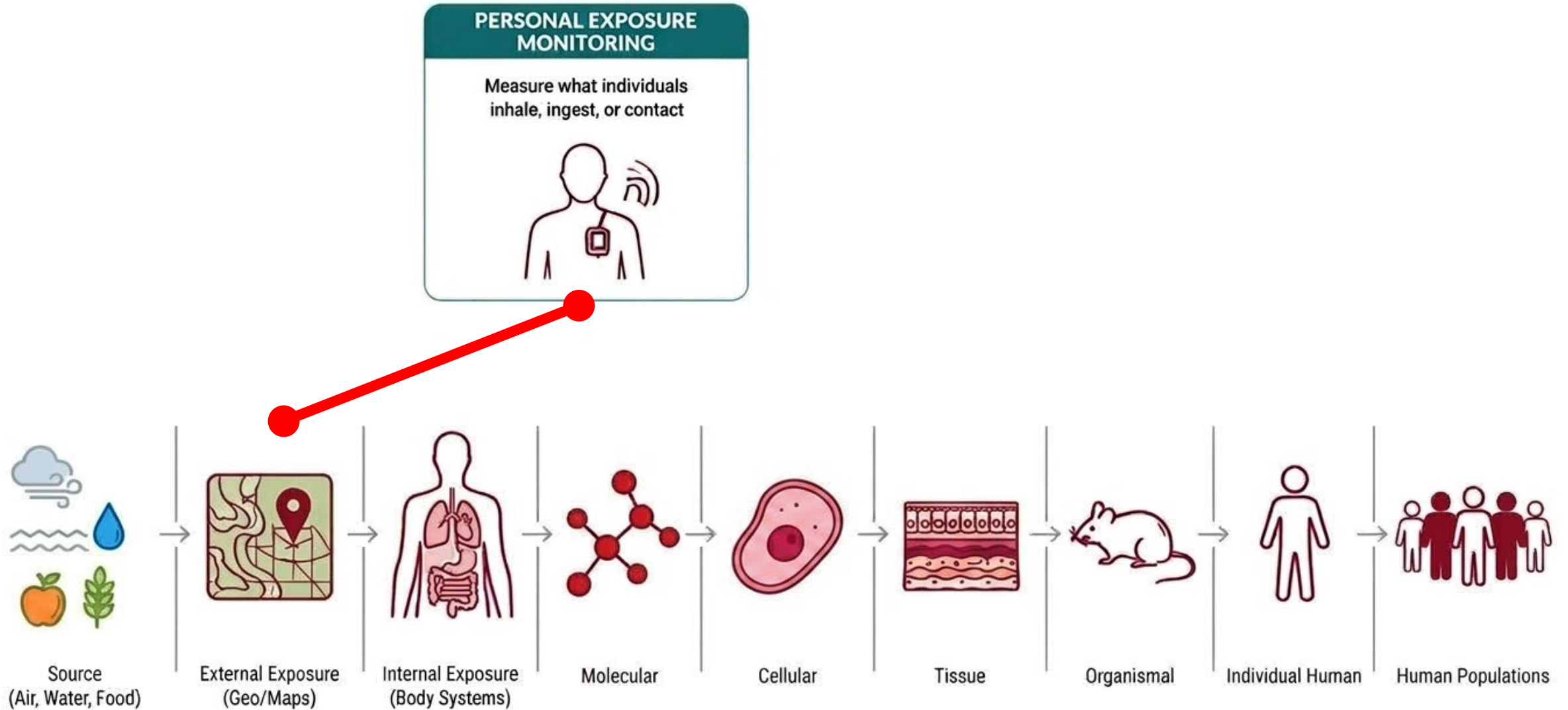
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**What kinds of exposure measures can NAMs help
bridge to outcomes?**

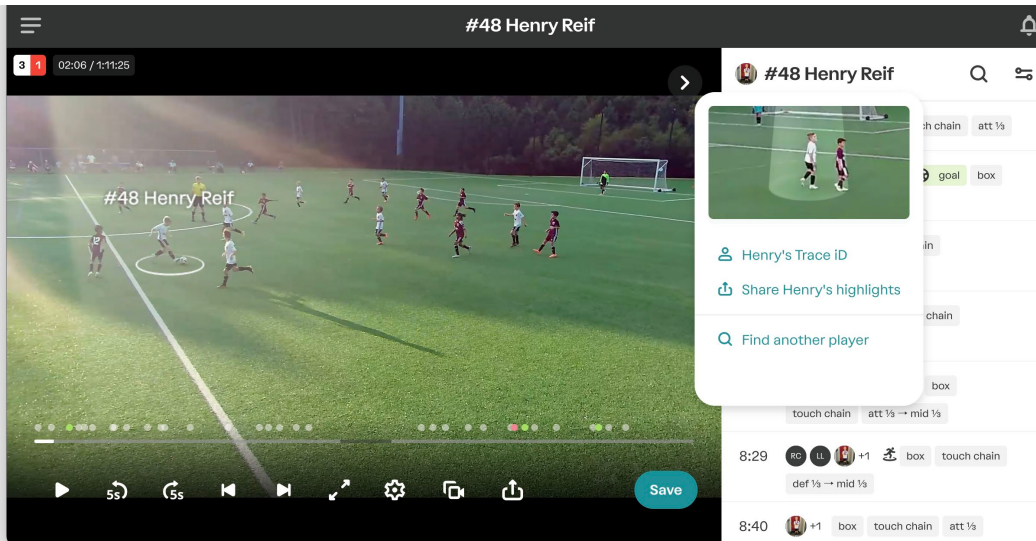
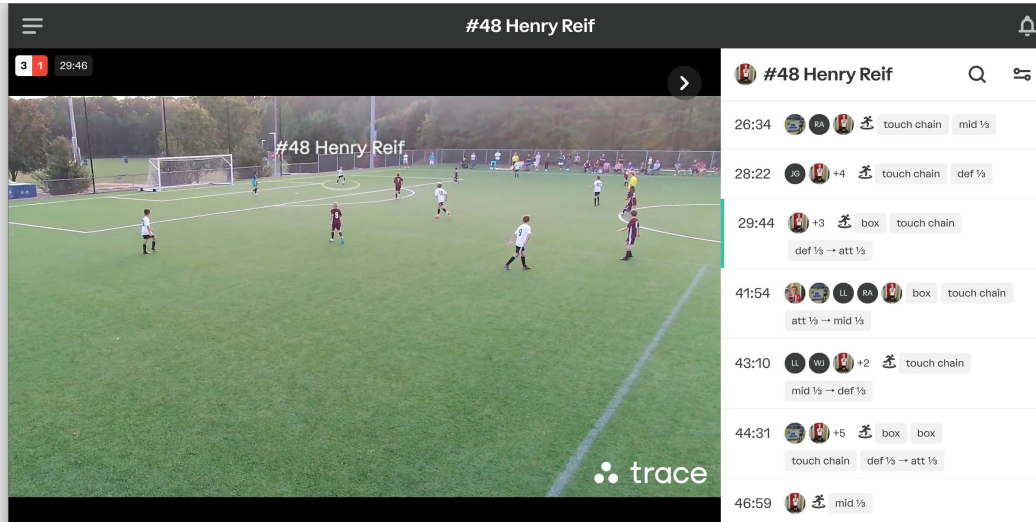
Typical exposure measurements across the continuum



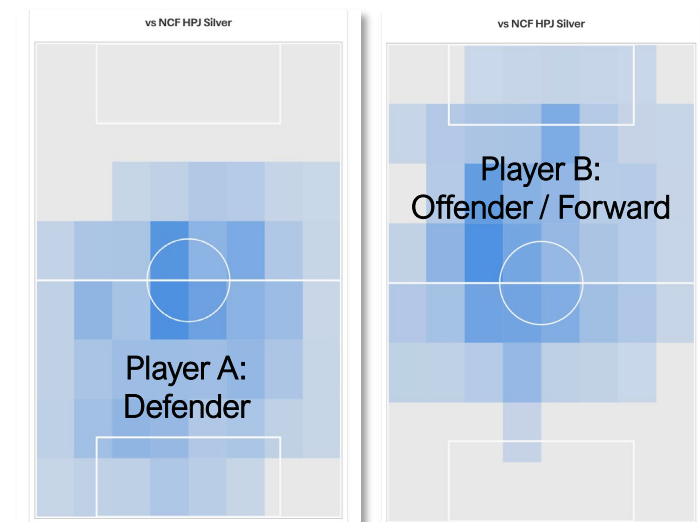
Typical exposure measurements across the continuum



Measurements via personal exposure monitoring (... And I'm still in a World Cup mood)



- For context on how sophisticated and widely-used AI personal exposure monitoring applications already are:
 - These screencaps are from tech used for youth soccer (The player highlighted here is my son, and he consented to this usage)
 - Tracking happens without wearing any external device → visual recognition AI tracks each player all over the field!
 - Player-specific highlights are automatically created by an AI engine within hours after each game!
- Think of the parallels to **tox / health** applications:
 - ( **top left**) What types/kinds of behavior do people engage in, and at what frequency?
 - (**lower right** →) Can we associate individual profiles/roles with differential exposure spaces?

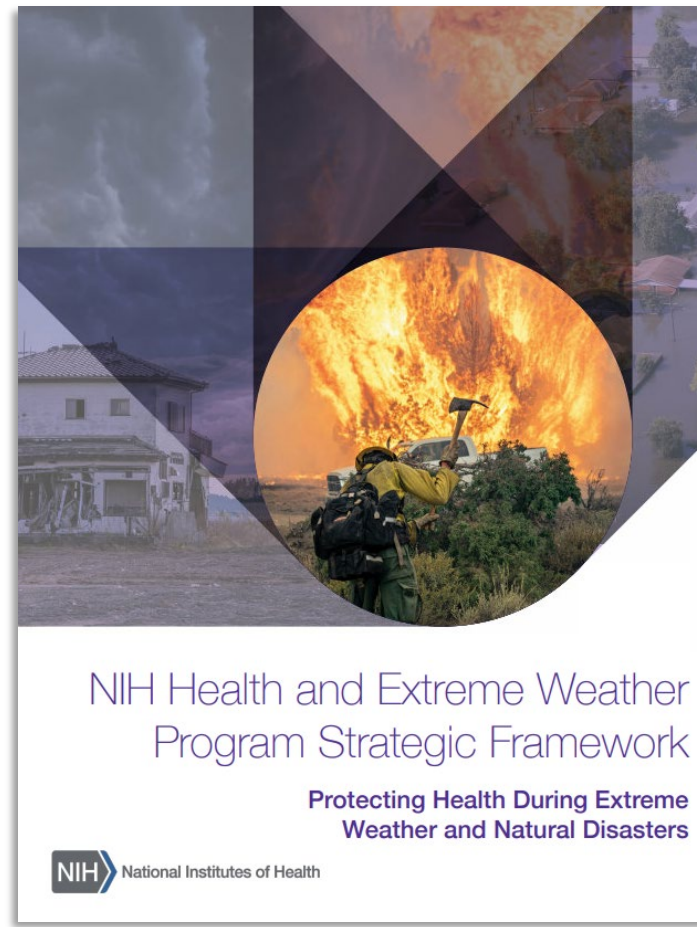
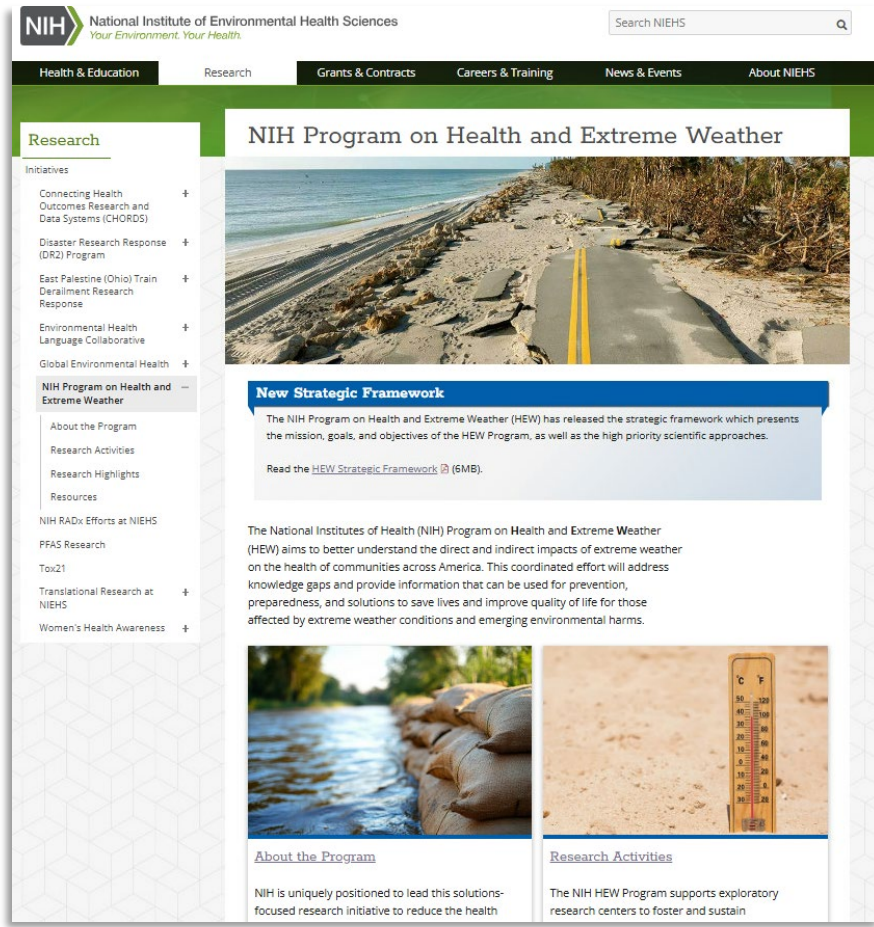




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What about complex, real-world exposure scenarios?

Health and Extreme Weather (HEW) program



Visit the HEW Webpage



Read the HEW Strategic Framework

(Slide created by Charles Schmitt, Ann Liu, and Aubrey Miller, on behalf of team @ <https://www.niehs.nih.gov/research/programs/chords/hew-data/navigator>)

HEW Data Accelerator for connecting real-world exposures with health data

A symphony of software tools to streamline complex analysis

 Amadeus repo status: Active Machine for Data, Environments, and User Setup for common environmental health datasets is an R package developed to improve and expedite users' access to large, publicly available geospatial datasets.	 Beethoven repo status: WIP Building an Extensible, Reproducible, Test-driven, Harmonized, Open-source, Versioned, Ensemble model for air quality is an R package developed to facilitate the development of ensemble models for air quality.	 Chopin repo status: WIP Computation of Spatial Data by Hierarchical and Objective Partitioning of Inputs for Parallel Processing.
 GeoTox repo status: Active GeoTox, or source-to-outcome, modeling framework with an S3 object-oriented approach. Facilitates the calculation and visualization of single and multiple chemical risk at individual and group levels.	 RGCA repo status: Active Implements Reflected Generalized Concentration Addition: A geometric, piecewise inverse function for 3+ parameter sigmoidal models used in chemical mixture concentration-response modeling.	 PrestoGP repo status: WIP Scalable penalized regression on spatio-temporal outcomes using Gaussian processes. Designed for big data, large-scale geospatial exposure assessment, and geophysical modeling.

Resources that address barriers and promote the ability to identify, access, integrate, and reuse environmental health data



[Data Navigator](#)

The Health and Extreme Weather (HEW) Data Navigator helps researchers find HEW data via artificial intelligence (AI) enhanced discovery services.

Research

Initiatives

- Connecting Health Outcomes Research and Data Systems (CHORDS)
- About CHORDS
- CHORDS Project Team
- Health & Extreme Weather (HEW) Data Accelerator
- About
- Data Commons
- Data Integration Resource
- Data Navigator
- Data Standards
- Highlighted Research
- Publications
- Software
- Training and Use Cases

NIH Health & Extreme Weather (HEW) Data Accelerator

Driving the ability to identify, access, harmonize, and use earth and atmospheric observations, environmental monitoring, and local data sources with health data.

Extreme weather and emerging environmental harms threaten the health and well-being of people in the U.S. and globally. In response to growing needs in this area, the NIH Data Accelerator aims to build cyberinfrastructure and sustainable extramural investments to empower the use of environmental health data to understand the 1) health impacts of environmental exposures and extreme weather and 2) critical value of interventions. An integral part to advancing this goal is to bolster an environmental health data savvy workforce that employs standardized environmental health data for research across the NIH portfolio and collaborates with the interdisciplinary community to advance new research capabilities.

[About](#)

The main components of the NIH Data Accelerator Program will address barriers and promote the ability to identify, access, integrate, and reuse environmental health data.

[Data Commons](#)

The HEW Data Commons aims to ensure all relevant HEW data assets are managed according to (Findable, Accessible, Interoperable, and Reusable) FAIR principles.

[Data Integration Resource](#)

The Health and Extreme Weather (HEW) Data Integration Resource provides geospatial-based datasets, software, and expert support to integrate health and extreme weather data.

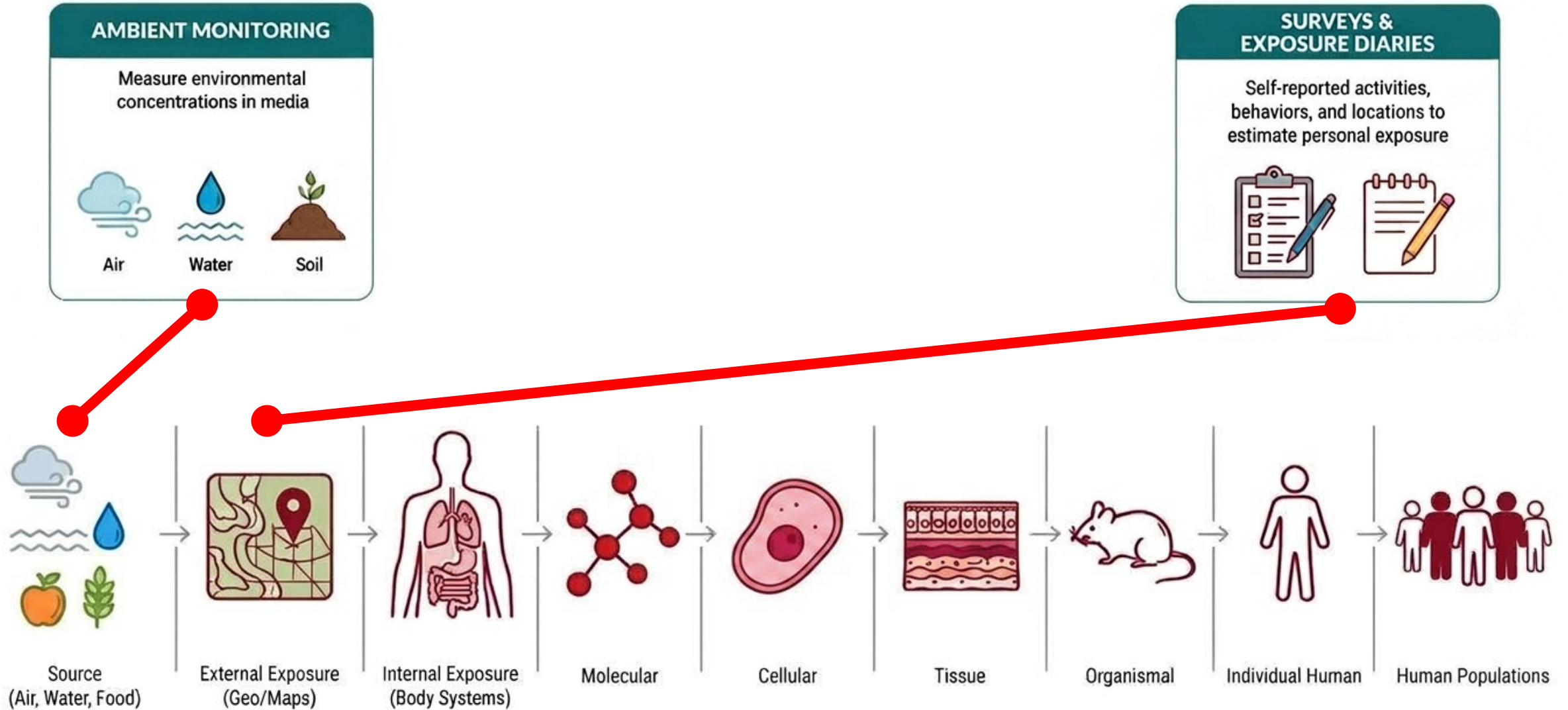
[Data Navigator](#)

The Health and Extreme Weather (HEW) Data Navigator helps researchers find HEW data via artificial intelligence (AI) enhanced discovery services.

[Data Standards](#)

These efforts will provide a dedicated and sustained focus on advancing Findable, Accessible, Interoperable, and Reusable (FAIR) practices, including the creation and adoption of environmental health data standards.

Can NAMs bridge from exposure to outcome with data from only the beginning of the continuum?



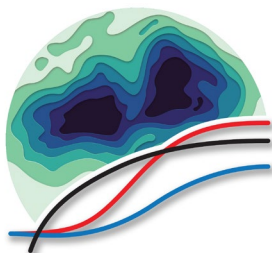


First, we need a modeling framework that can support modular integration across the source-to-outcome continuum

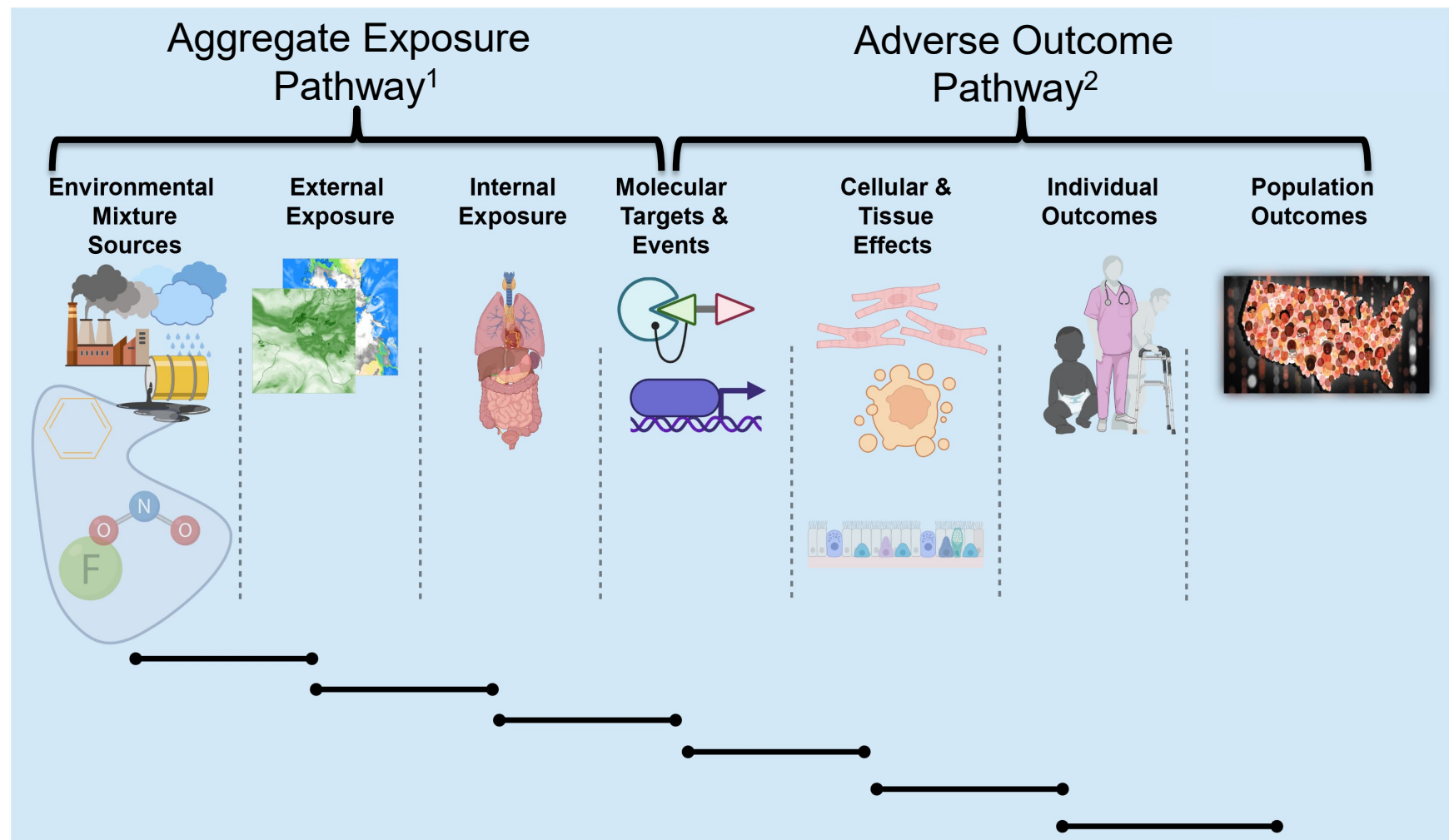
“GeoTox” framework



Kyle Messier



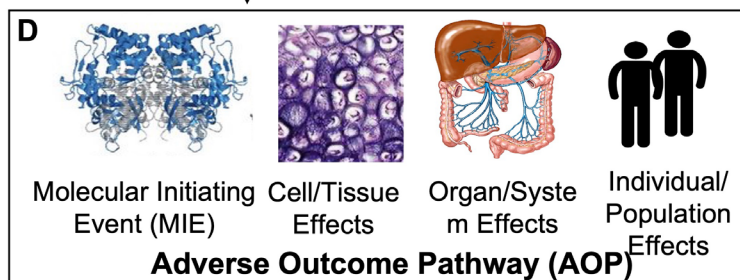
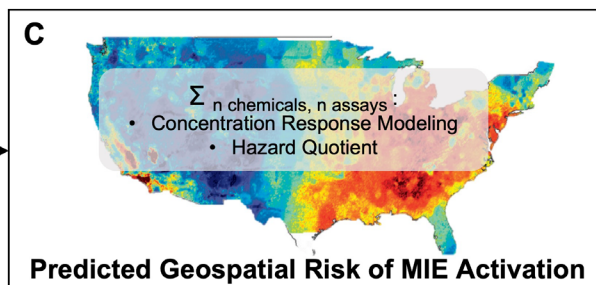
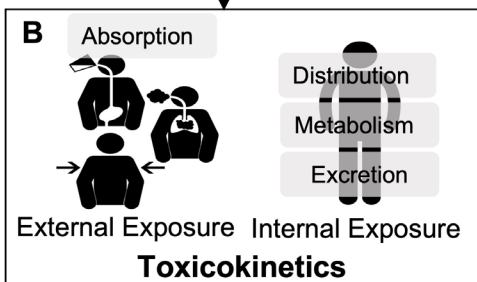
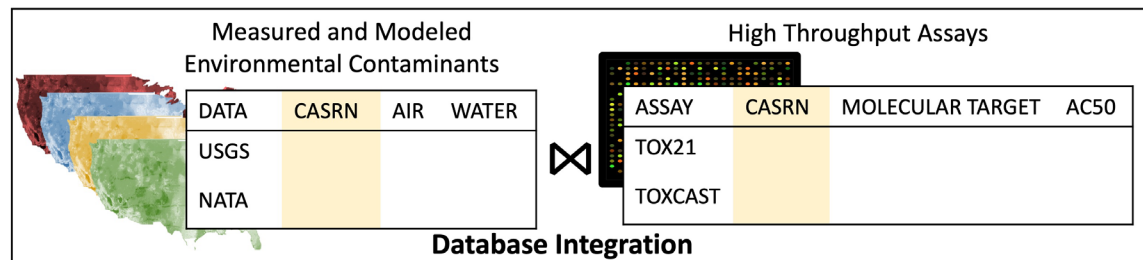
Spatiotemporal Exposures
and Toxicology (SET) Group



1. Teeguarden JG, Tan YM, Edwards SW, Leonard JA, Anderson KA, Corley RA, Kile ML, Simonich SM, Stone D, Tanguay RL, Waters KM. Completing the link between exposure science and toxicology for improved environmental health decision making: the aggregate exposure pathway framework.

2. <http://aop.wiki.org>; Society for the Advancement of Adverse Outcome Pathways

GeoTox: Modeling framework to connect data across the source-to-outcome continuum (2)



GeoTox

open-source R software package for characterizing the risk of perturbing molecular targets involved in adverse human health outcomes based on exposure to spatially-referenced stressor mixtures via the GeoTox framework - otherwise known as source-to-outcome-continuum modeling. The package, methods, and case-studies are described in Messier, Reif, and Marvel, 2024, medRxiv-Preprint.

The GeoTox framework was first described in Eccles et al. A geospatial modeling approach to quantifying the risk of exposure to environmental chemical mixtures via a common molecular target. Sci Total Environ. 2023 Jan 10;855:158905.

Installation

```
install.packages("GeoTox")
```

Development Version

The development version can be installed from GitHub.

```
#install.packages("pak")
pak::pak("NIEHS/GeoTox")
```

Overview

Figure 1 below shows the steps in the source-to-outcome-continuum or GeoTox modeling framework that is capable in the GeoTox package. blue text nodes represent an object and green text, rounded nodes represent a methodology or function required to go from one to the next. The GeoTox package uses R S3 object-oriented programming to create the GeoTox object. The GeoTox object is a list that contains all of the information required to run the analysis including tracking exposure, assays, dose-response, and geospatial referencing.

GeoTox R package and Analysis Framework

Geospatial Exposure

Geo-referenced exposure analysis is NOT part of the GeoTox package. The user is expected to bring an exposure model or data. The

Links

- [View on CRAN](#)
- [Browse source code](#)
- [Report a bug](#)

License

- [Full license](#)
- [MIT + file LICENSE](#)

Community

- [Contributing guide](#)
- [Code of conduct](#)

Citation

- [Citing GeoTox](#)

Developers

- Skylar Marvel
- Author

David Reif

- Author

Kyle Messier

- Maintainer, author
- [More about authors...](#)

Dev status

- repo status: Active
- R CMD check: passing
- pkgdown: passing
- coverage: 100%
- CRAN: 0.2.0



Skylar Marvel



David Reif



Kyle Messier

Messier, Reif, and Marvel (2025). *Human Genomics*.
Eccles et al. (2023). *Science of the Total Environment*.

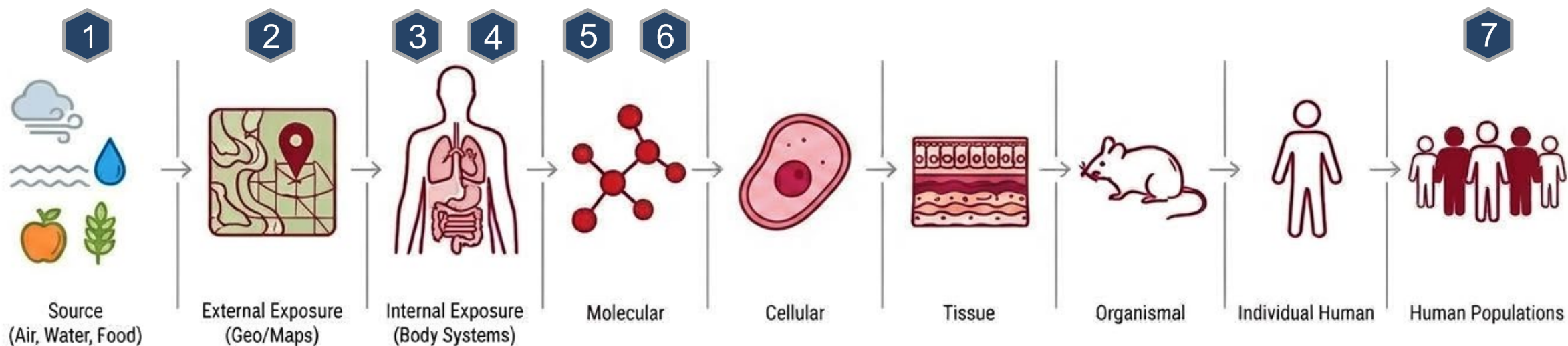
NAMs bridge from exposure (*PFAS mixture*) to outcome (*Risk*) in a human population cohort (*PEGS*) (2)



Danielle Demateis

GeoTox uses NAMs data (*httk* + *NICE* + *Tox21*) **to bridge** from exposure (*PFAS mixtures*) to outcome (*county-level risk*), parameterized by a human population cohort (*PEGS = Personalized Environment and Genes Study*)

→ Generates testable outcome hypotheses without requirement for new animal experimentation



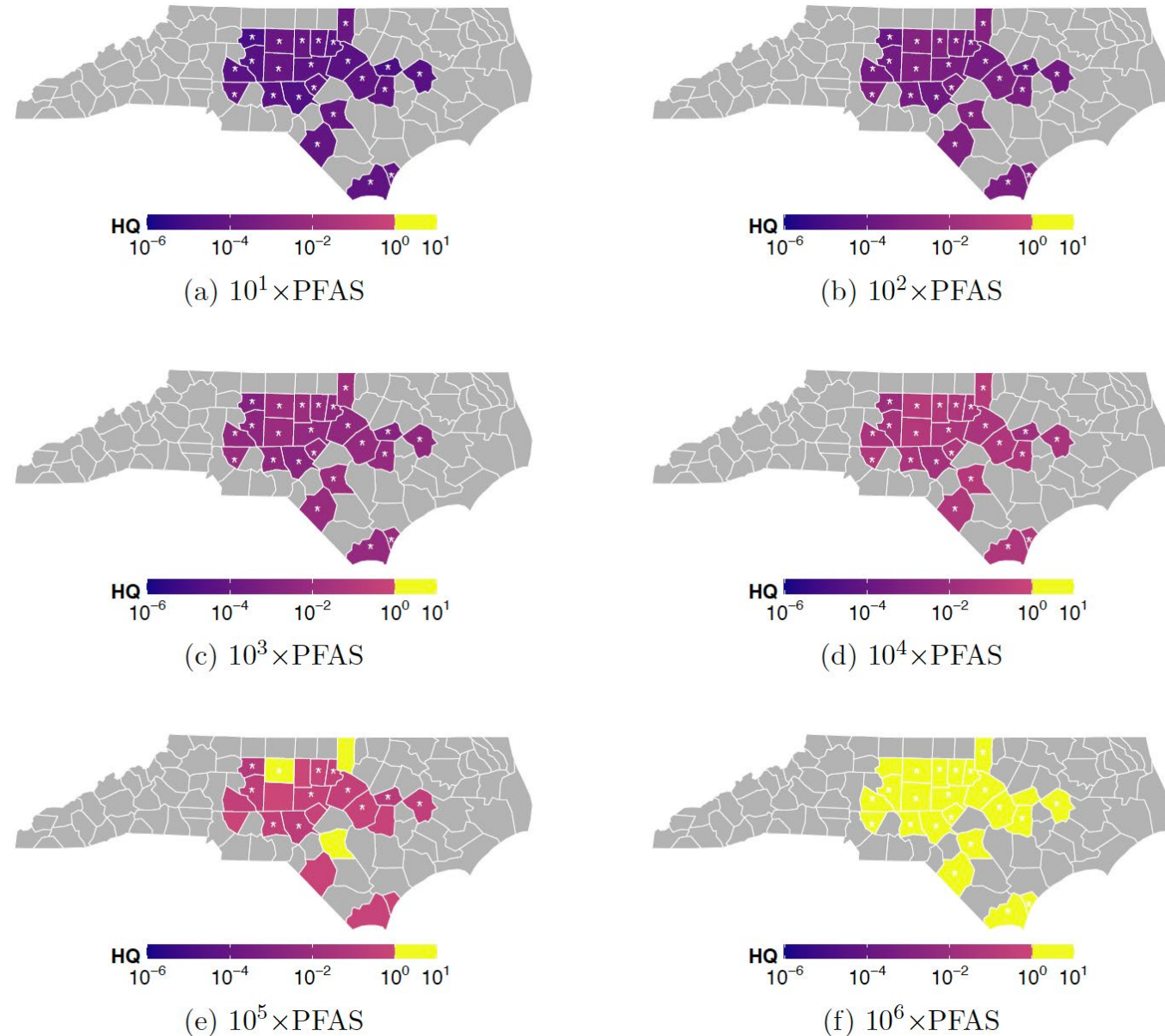
NAMs bridge from exposure (*PFAS mixture*) to outcome (*Risk*) in a human population cohort (*PEGS*) (5)

We can evaluate the uncertainty + sensitivity of our estimates and build baselines for predictive toxicology applications under different exposure scenarios.

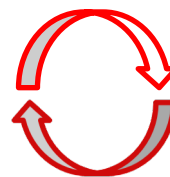
Figure: Estimated median hazard quotients (HQ) assuming the PFAS mixture of PFOS and PFOA exposure is more extreme than the observed PFAS concentration in the real data. The color scale is standardized across all panels, with yellow indicating an exceedance of the hazard threshold ($HQ \geq 1$).

Some counties may be more susceptible under certain scenarios.

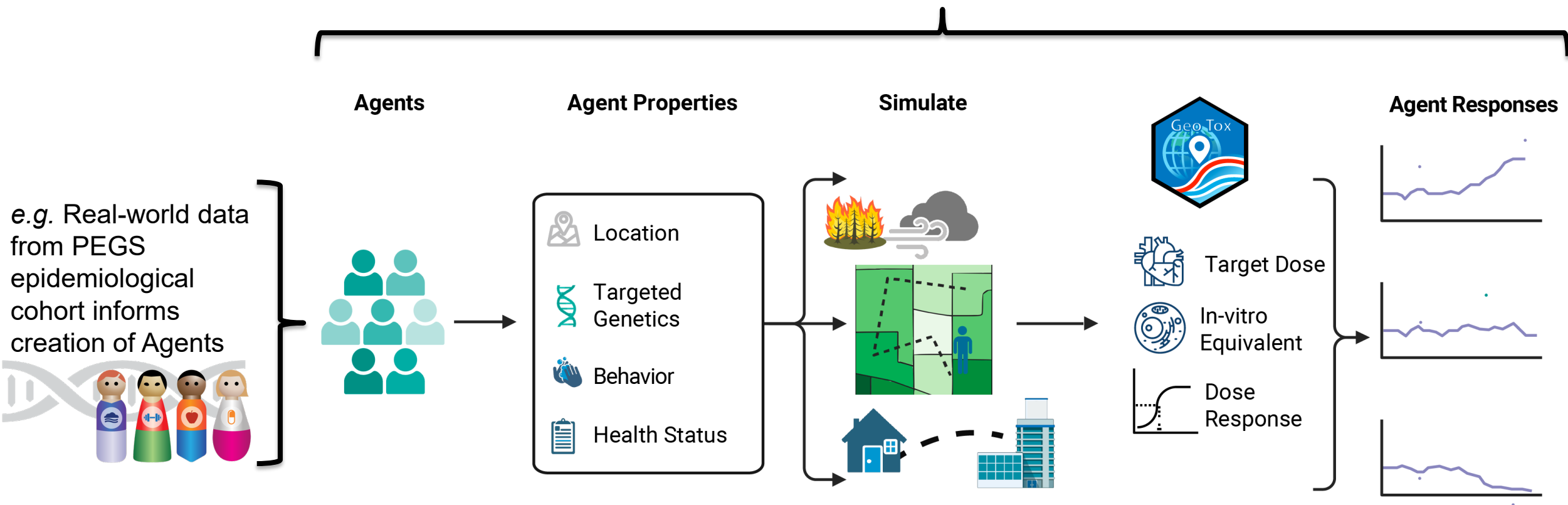
→ We could ask mechanistic plausibility questions from individual exposomics measured in biosamples ...



Predictive Toxicology workbench: Preparing for event/disaster scenarios using Agent Based Models



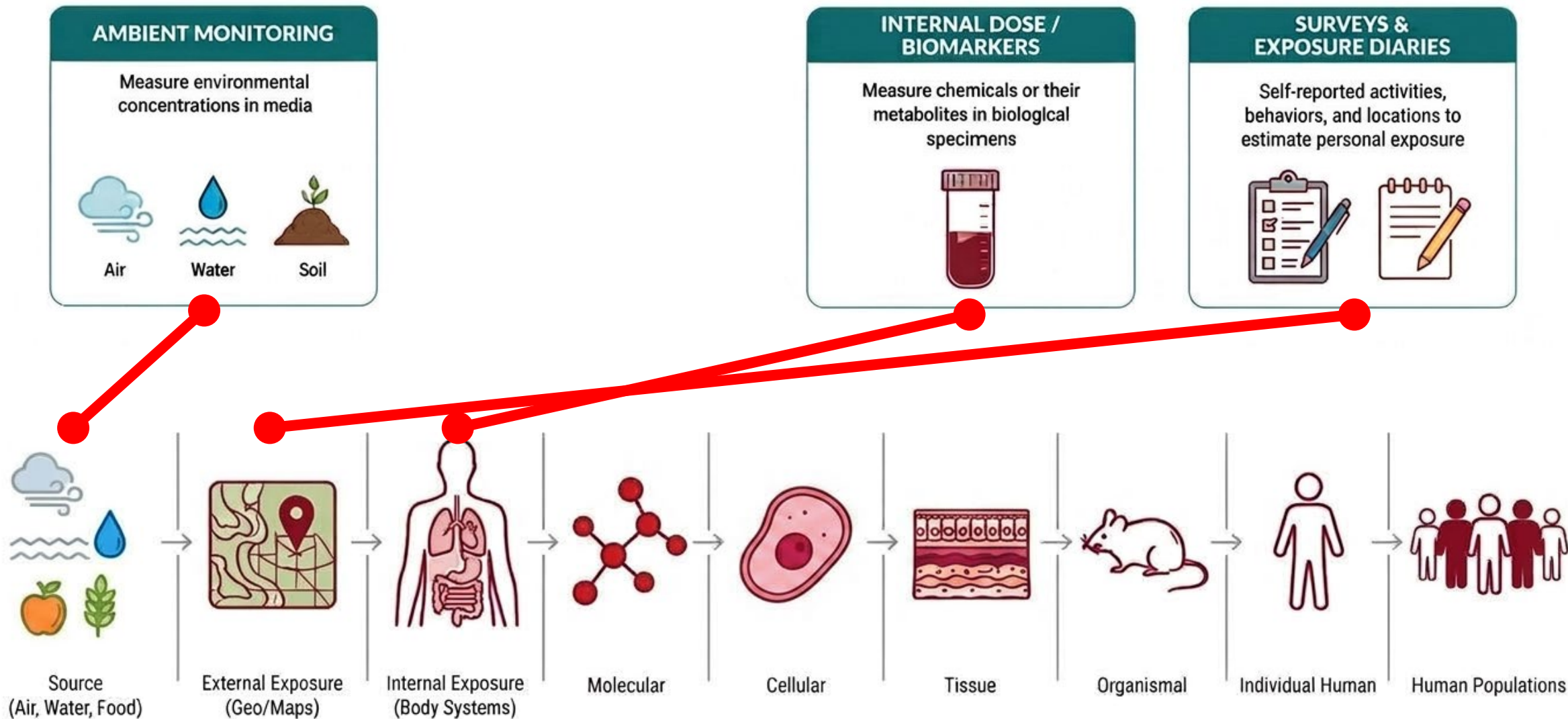
Predictivity can be tested, refined,
revised, reparameterized as needs arise
→ experimental-informatic feedback





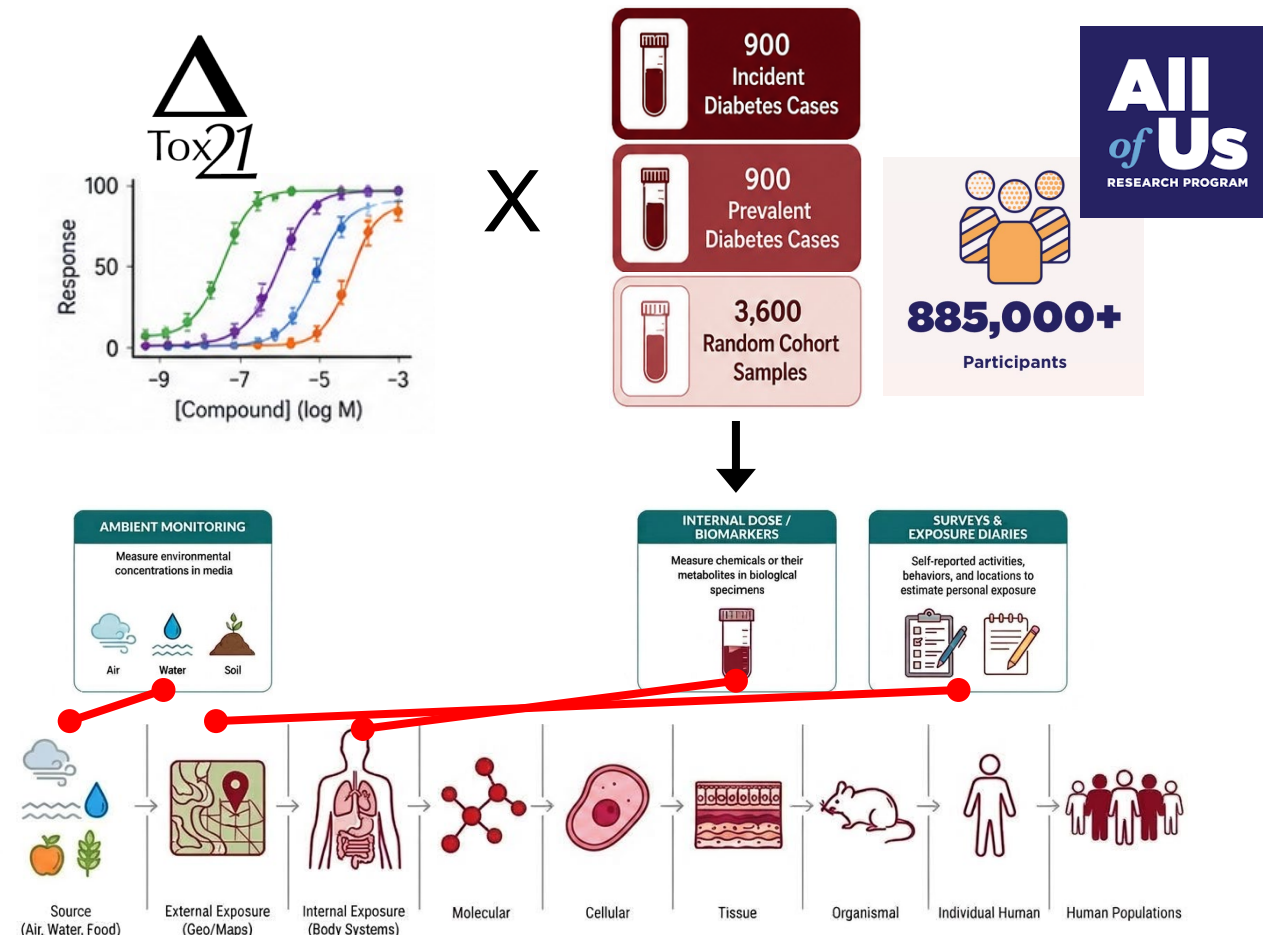
**What kinds of exposure measures can help
strengthen NAMs as a mechanistic bridge?**

What if we added personal exposomics from biosamples?

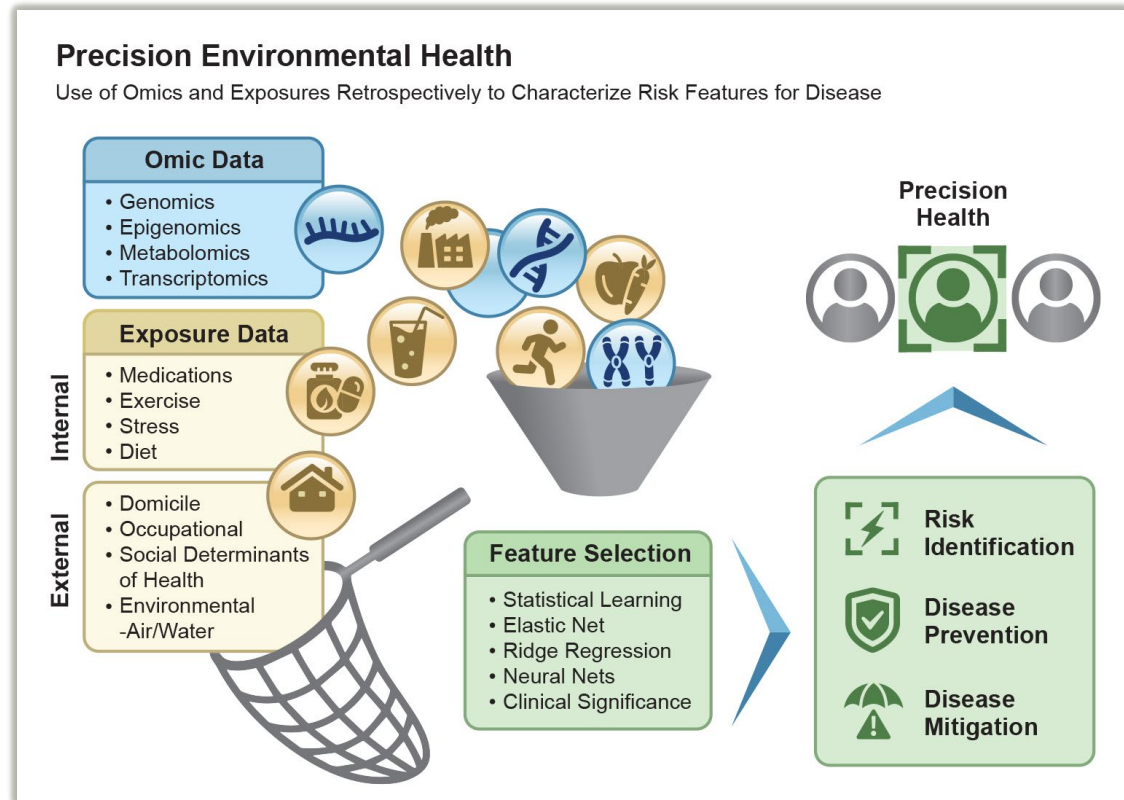


Metabolomics data from AllOfUs participants can be mapped to Tox21 profiling assays to **add direct mechanistic context**

Direct measurements of individual metabolomics are an opportunity to apply a precision environmental health framework



Current work-in-progress led by Alison Motsinger-Reif with All of Us research program



Motsinger-Reif AA, et al. Gene-environment interactions within a precision environmental health framework. Cell Genom. 2024 Jul 10;4(7):100591

So ... can we build bridges between exposures and outcomes?



Conclusions + Acknowledgements

NAMs (*incl. assays + models + integrative approaches*) **can provide a mechanistic bridge** to advance predictive toxicology at several points along the exposure-to-outcome continuum

- This ability is built on foundational data from traditional models as well as NAMs
→ emphasizes value of data reuse!
- Testable predictions can be generated from modular “pieces” along the continuum
→ confirming predictions will require new data generation/collection/analysis



National Institute of
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Health Sciences

Kyle Messier
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Danielle Demateis
Minoli Fernando
Charles Schmitt
Joe Breeyear

John House
Jonathon Fleming
Amlan Talukder
David Fargo
Parker Coombs
Trey Saddler
Scott Auerbach
Jeremy Erickson
Amlan Talukder
Heather Patisaul
Zach Stanfield

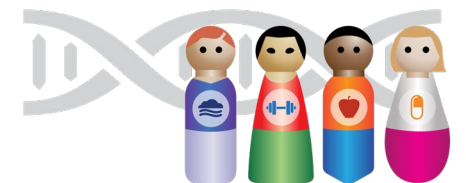
Ryan Campbell
Dillon Lloyd
Nat Macnell
Cristina Justice
Kwangmi An
Jui-Hua Hsieh
Ann Liu
Adam Burkholder
Aubrey Miller
Farida Akhtari
Alison Motsinger-Reif



Trang Do
Guojing Cong
Kazi Ashik Islam



All of Us leadership &
participants &
Metabolomics and
Clinical Assay Center



PEGS leadership &
participants