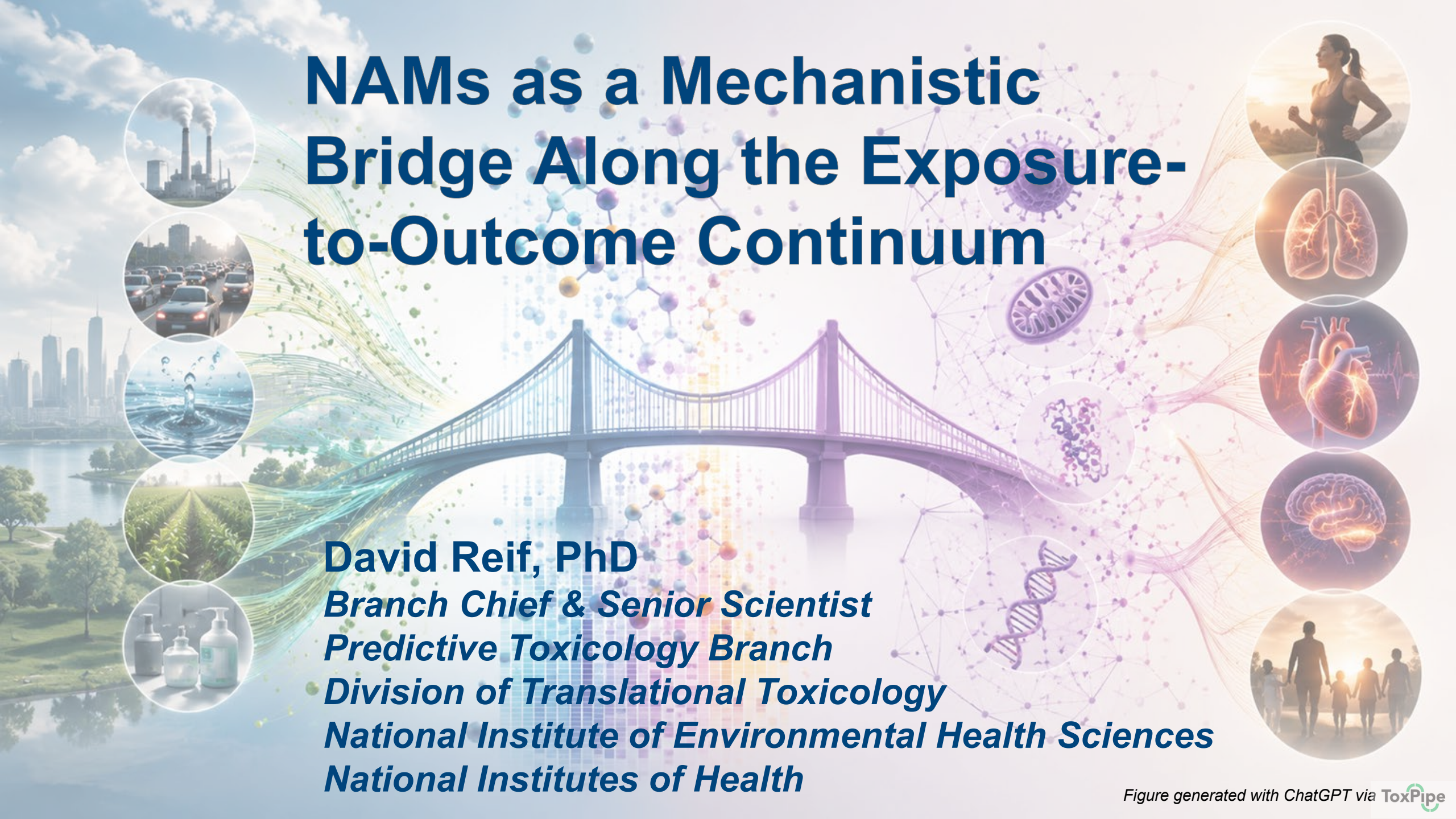
NAMs as a Mechanistic Bridge Along the Exposure-to-Outcome Continuum



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

Figure generated with ChatGPT via ToxPipe

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.

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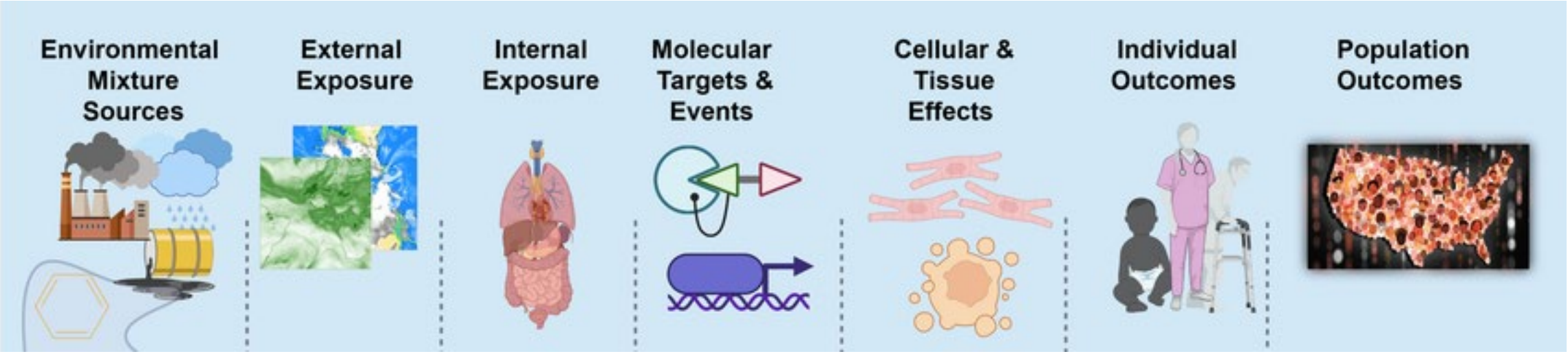
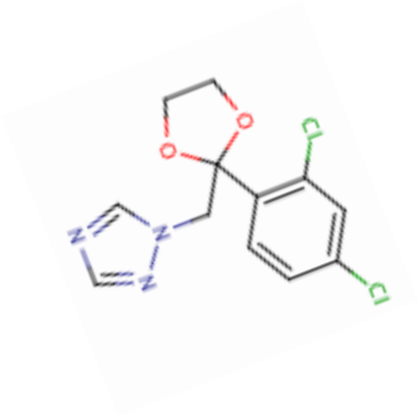


Messier KP, Reif DM, Marvel SW. (2025). The GeoTox Package: open-source software for connecting spatiotemporal exposure to individual and population-level risk. Human Genomics.

The need for mechanistic bridges

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

Exposure



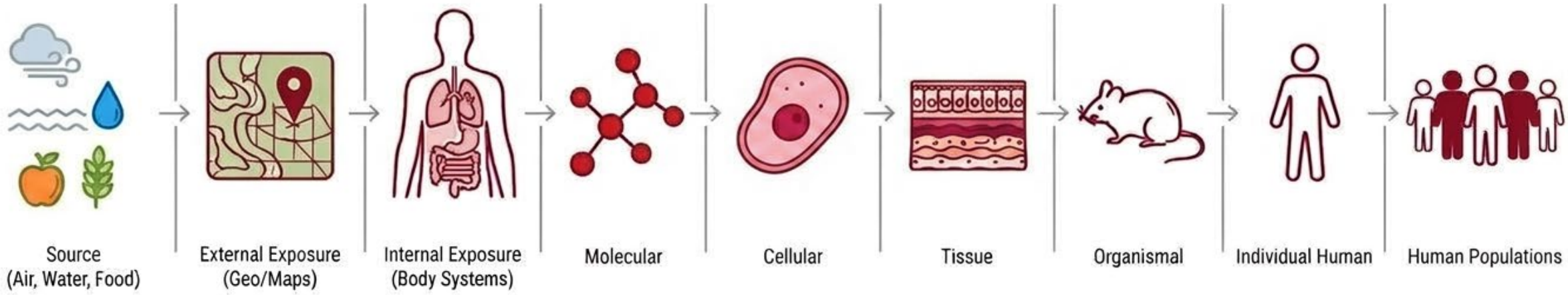
Receptor(s)

? ? ? ? ?

Outcome

Measurements available at different scales across the continuum

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



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

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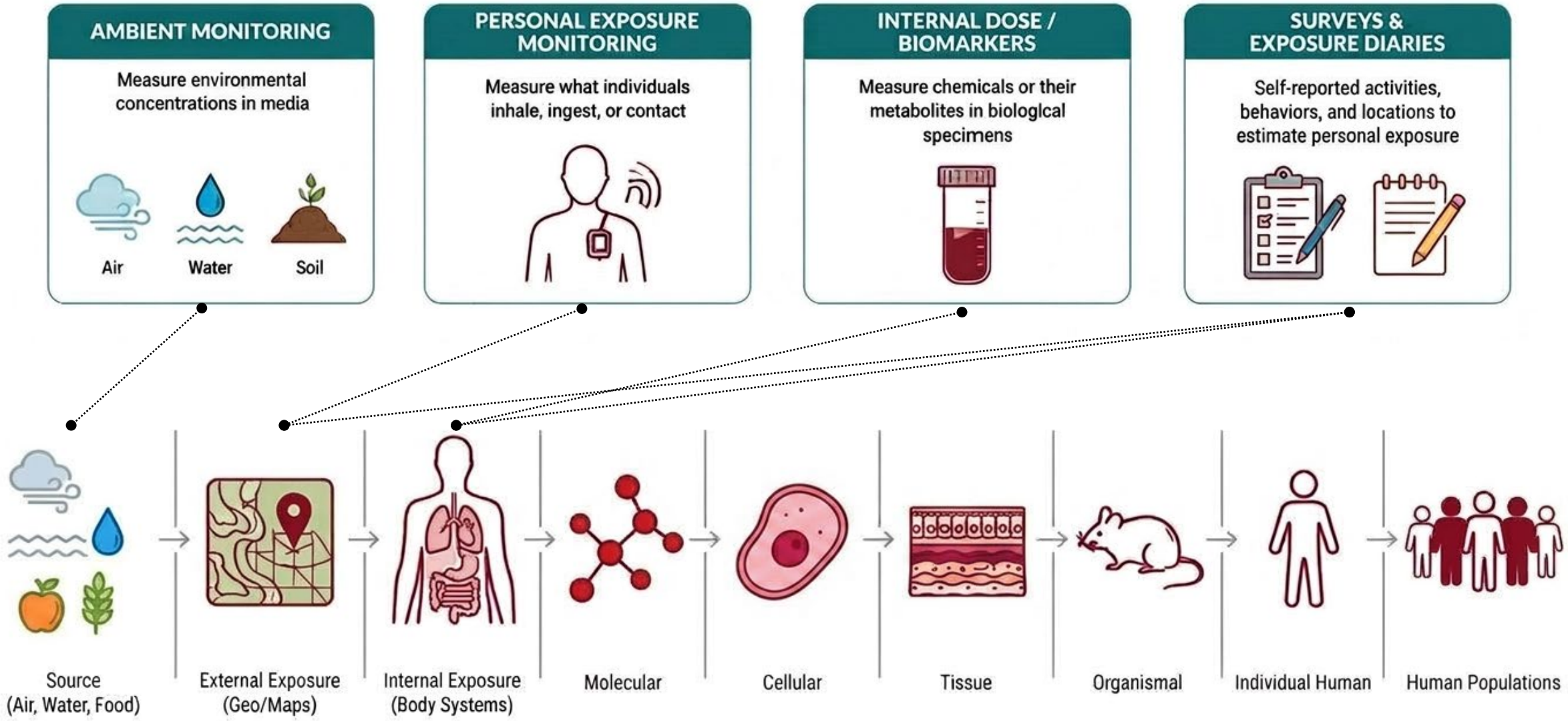
Typical exposure measurements across the continuum



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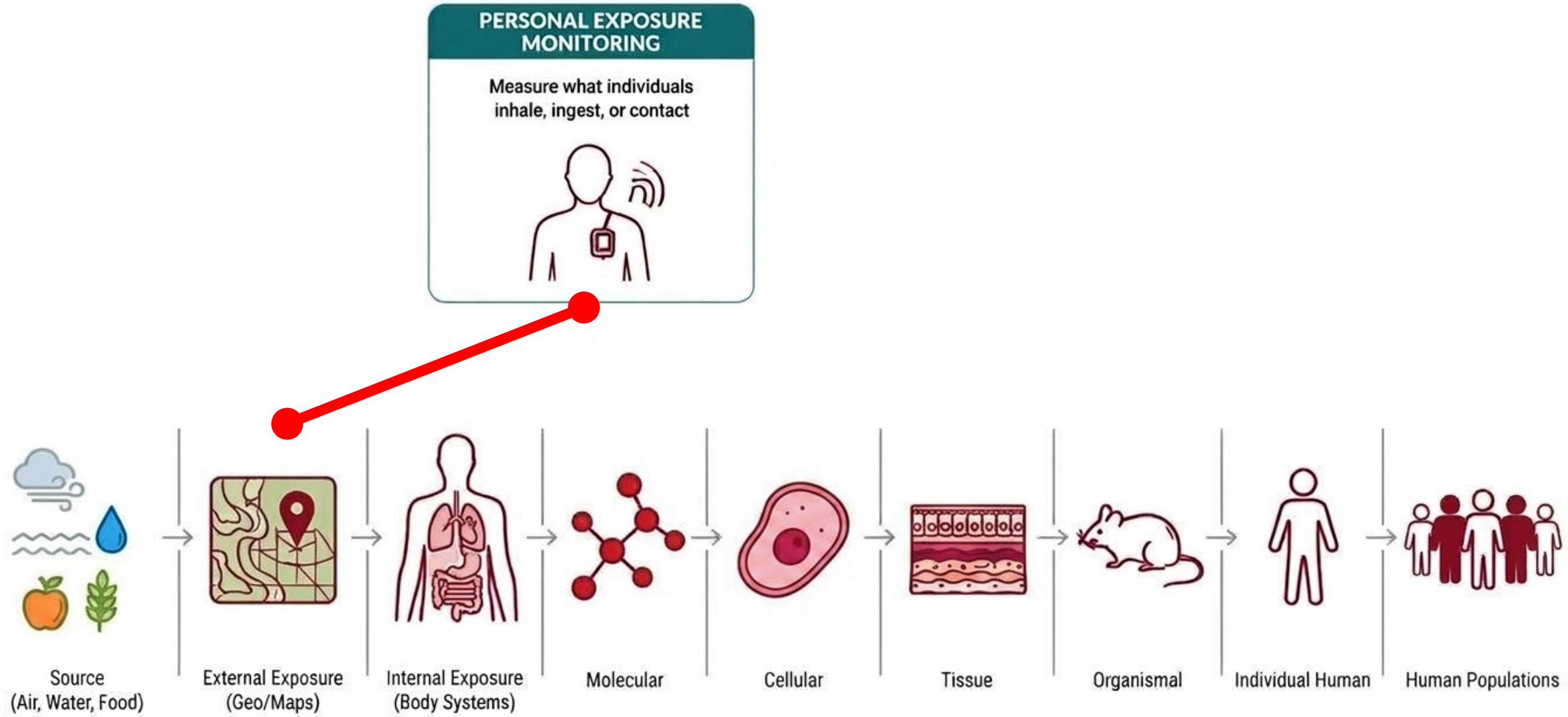
Typical exposure measurements across the continuum



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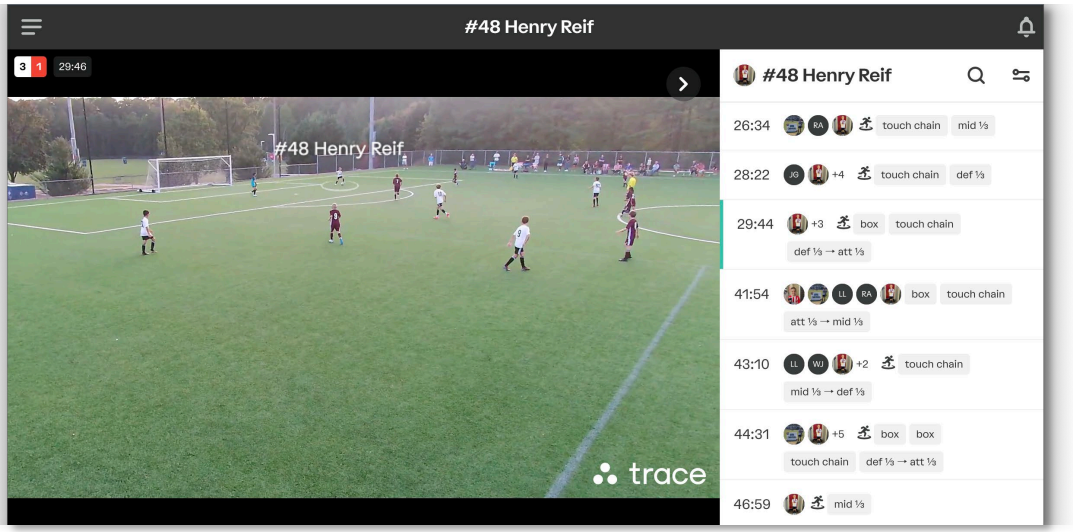
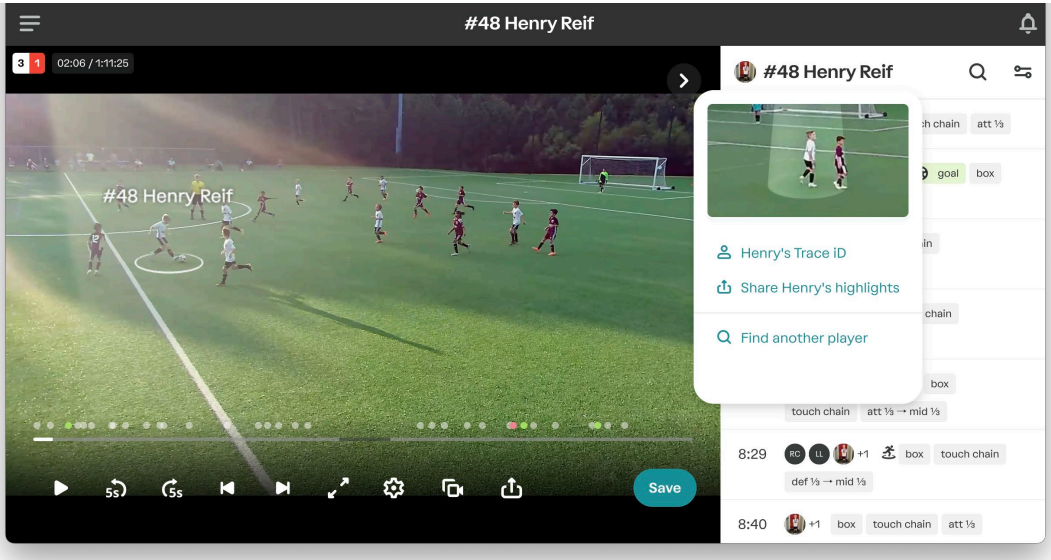
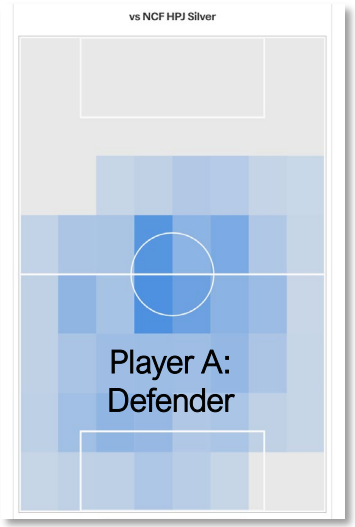
Measurements via personal exposure monitoring
(... And I'm still in a World Cup mood)



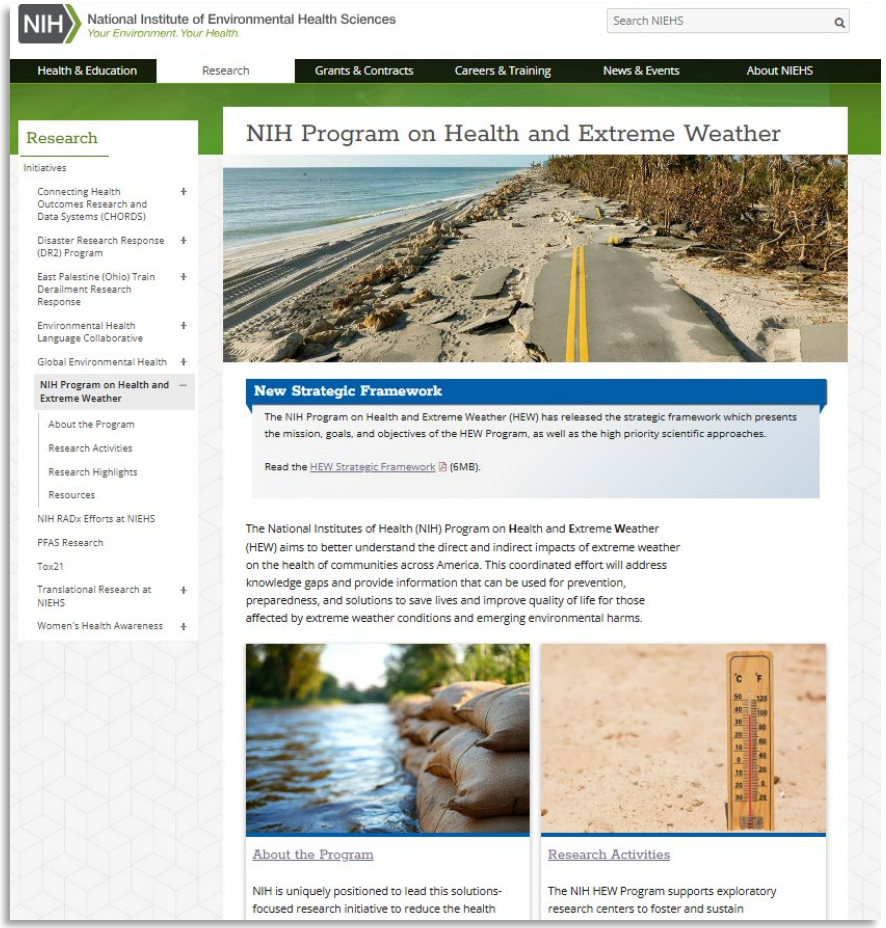


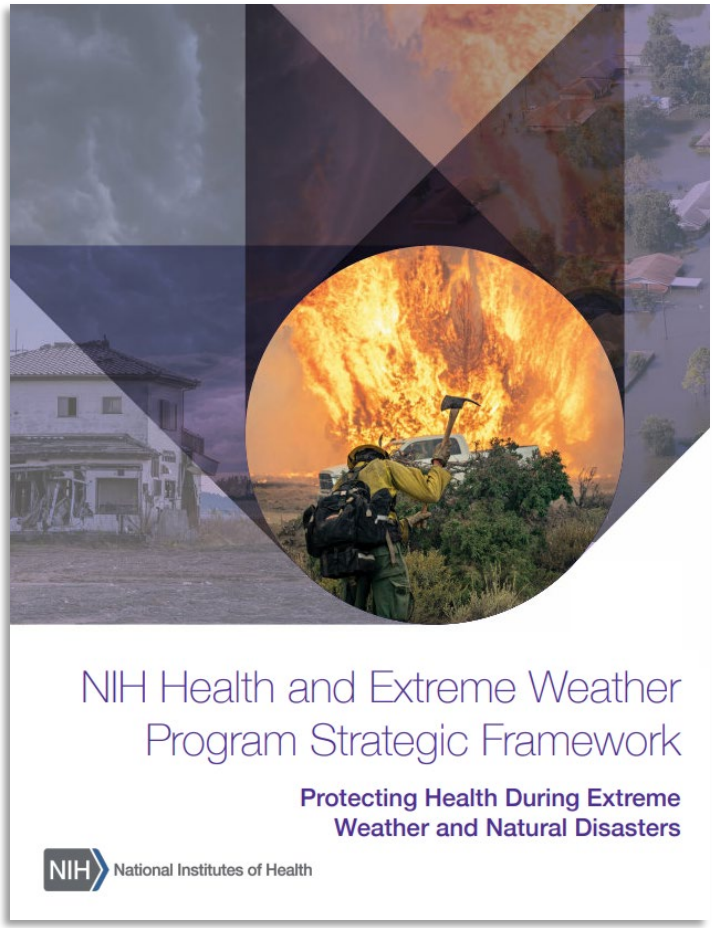
- For context on how sophisticated and widely-used AI personal exposure monitoring applications already are:
  - These screencaps are from tech used for youth soccer (The player highlighted here is my son, and he consented to this usage)
  - Tracking happens without wearing any external device → visual 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?



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)

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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

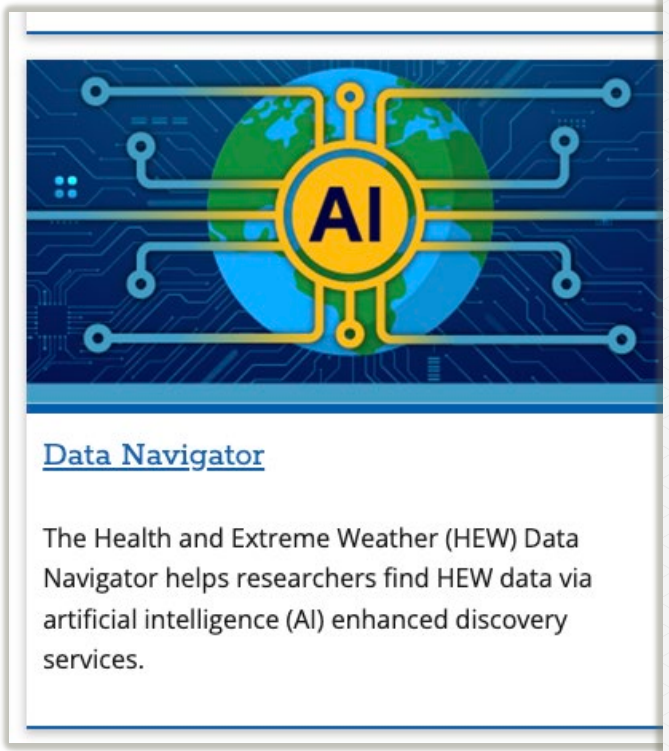
Implements Reflected Generalized Concentration Addition: A geometric, piecewise inverse function for 3+ parameter sigmoidal models used in chemical mixture concentration-response modeling.

PrestoGP

repo status WIP

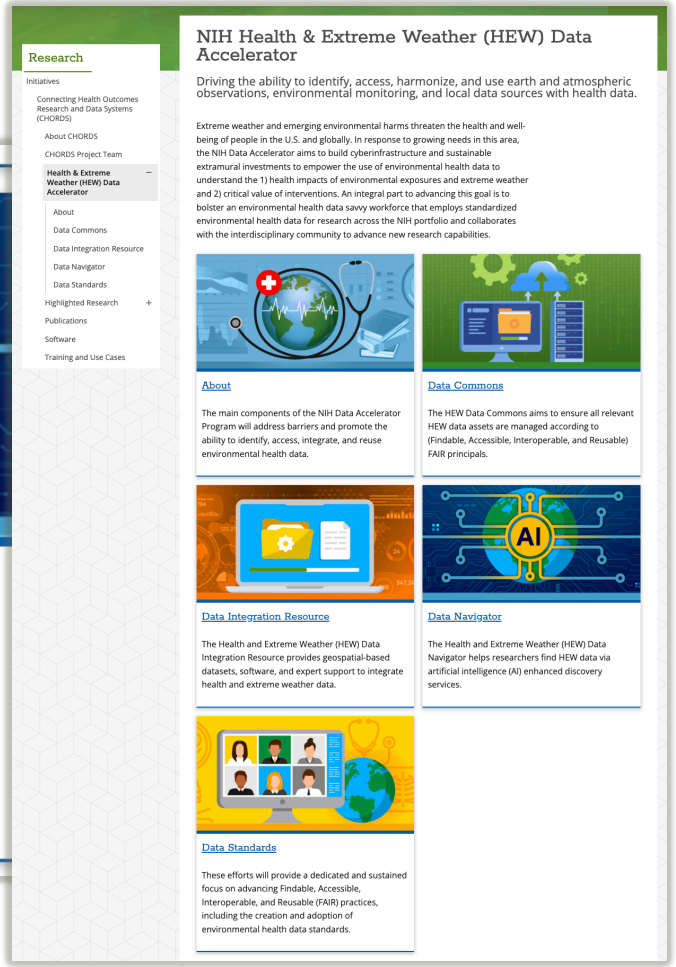
Scalable penalized regression on spatio-temporal outcomes using Gaussian processes. Designed for big data, large-scale geospatial exposure assessment, and geophysical modeling.

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.



https://www.niehs.nih.gov/research/programs/chords/hew-data

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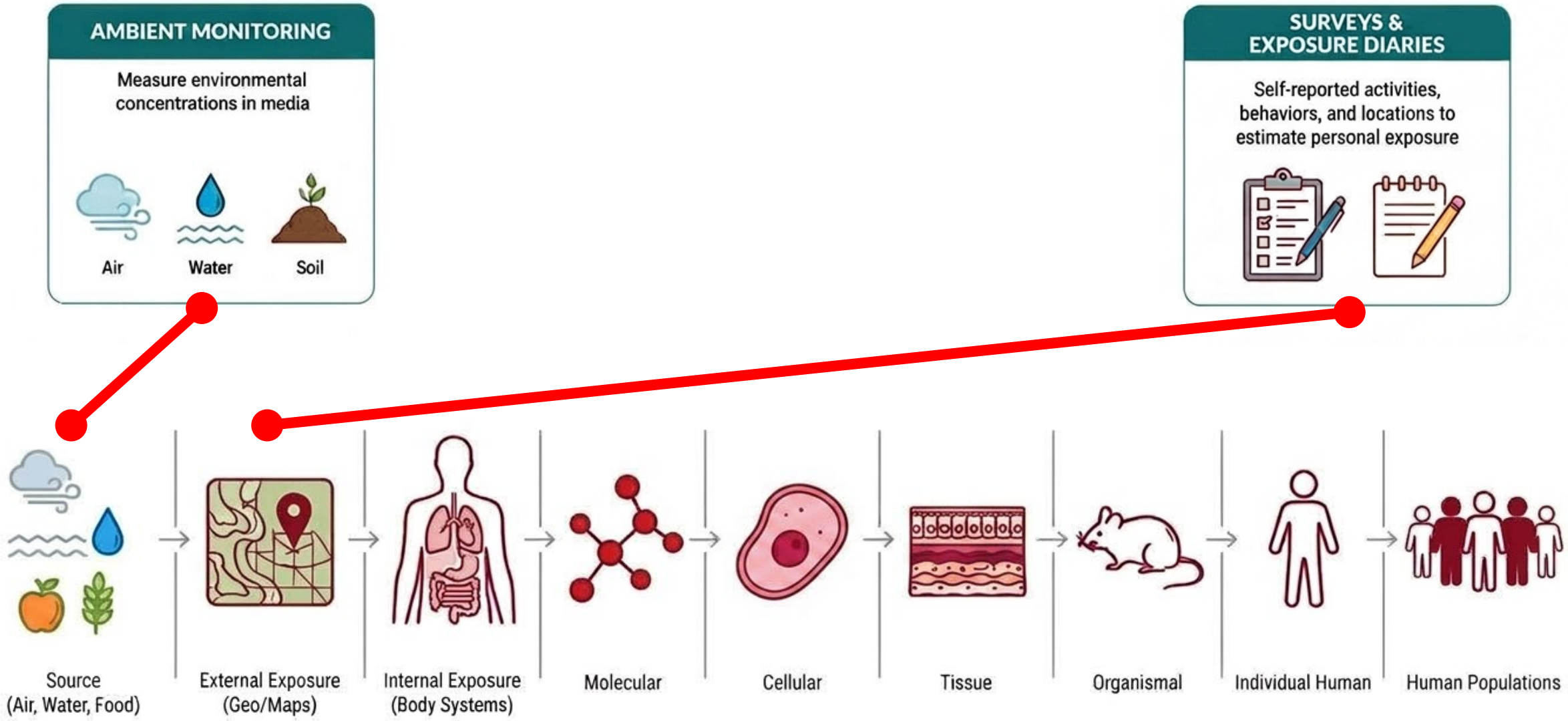
Can NAMs bridge from exposure to outcome with data from only the beginning of the continuum?



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

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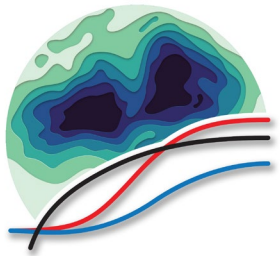
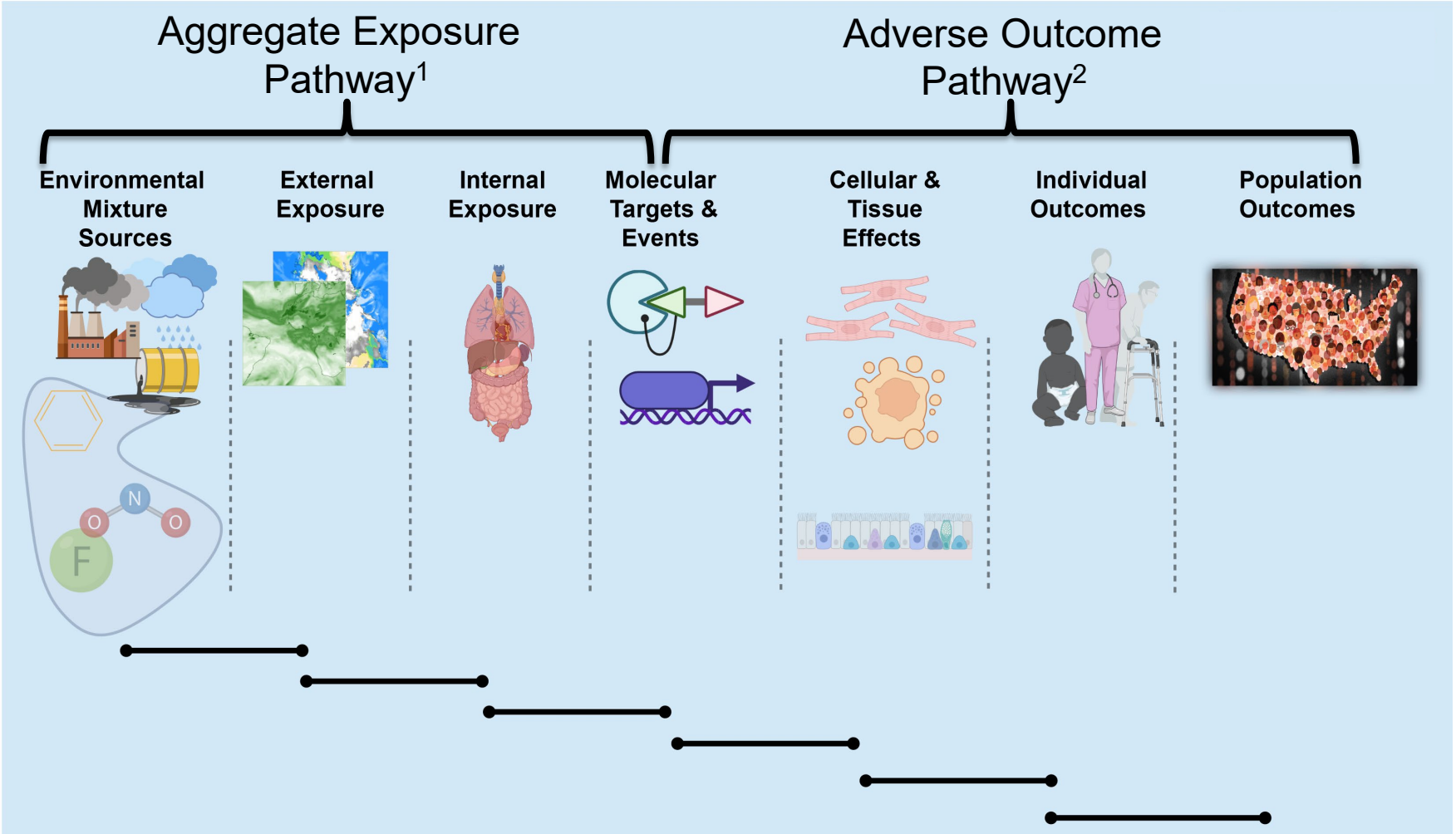
GeoTox: Modeling framework to connect data across the source-to-outcome continuum

"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

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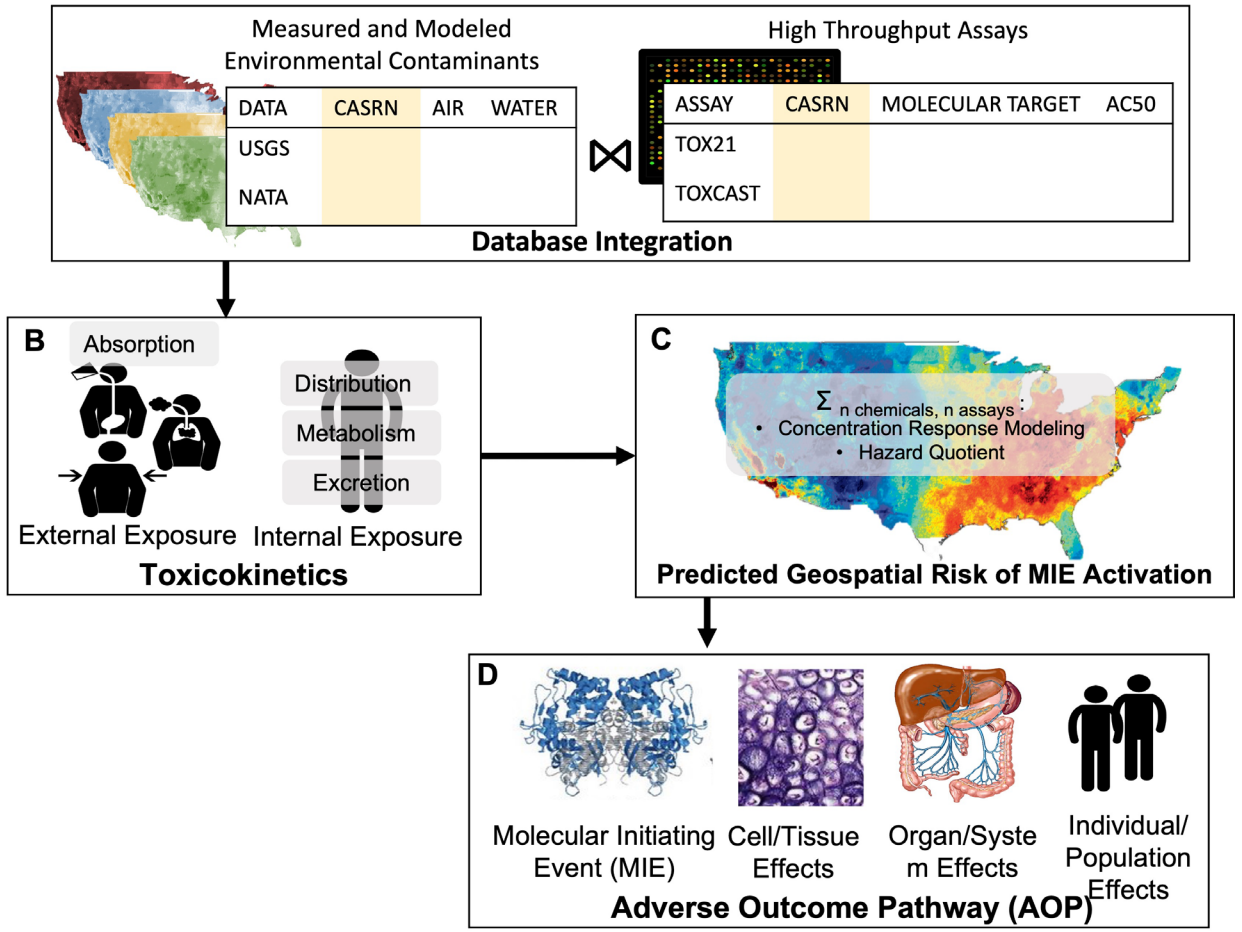
GeoTox: Modeling framework to connect data across the source-to-outcome continuum (2)




Skylar Marvel


David Reif


Kyle Messier

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

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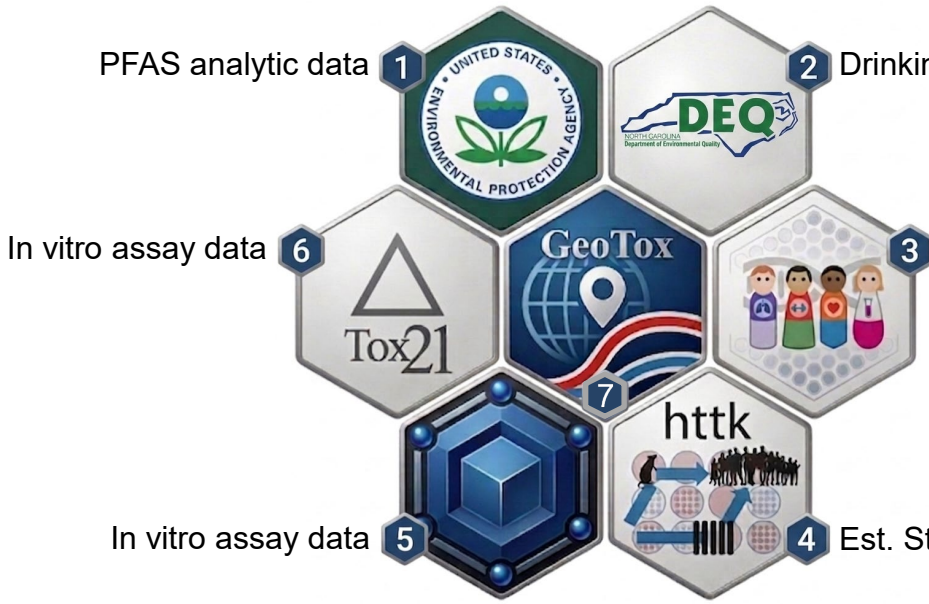
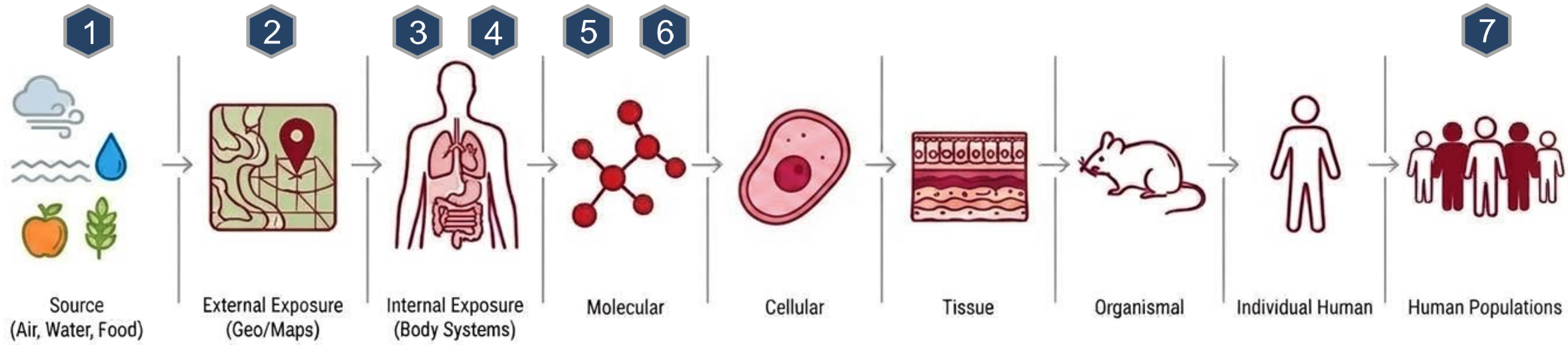
NAMs bridge from exposure (*PFAS mixture*) to outcome (*Risk*) in a human population cohort (*PEGS*) *(2)*

Danielle Dematteis

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





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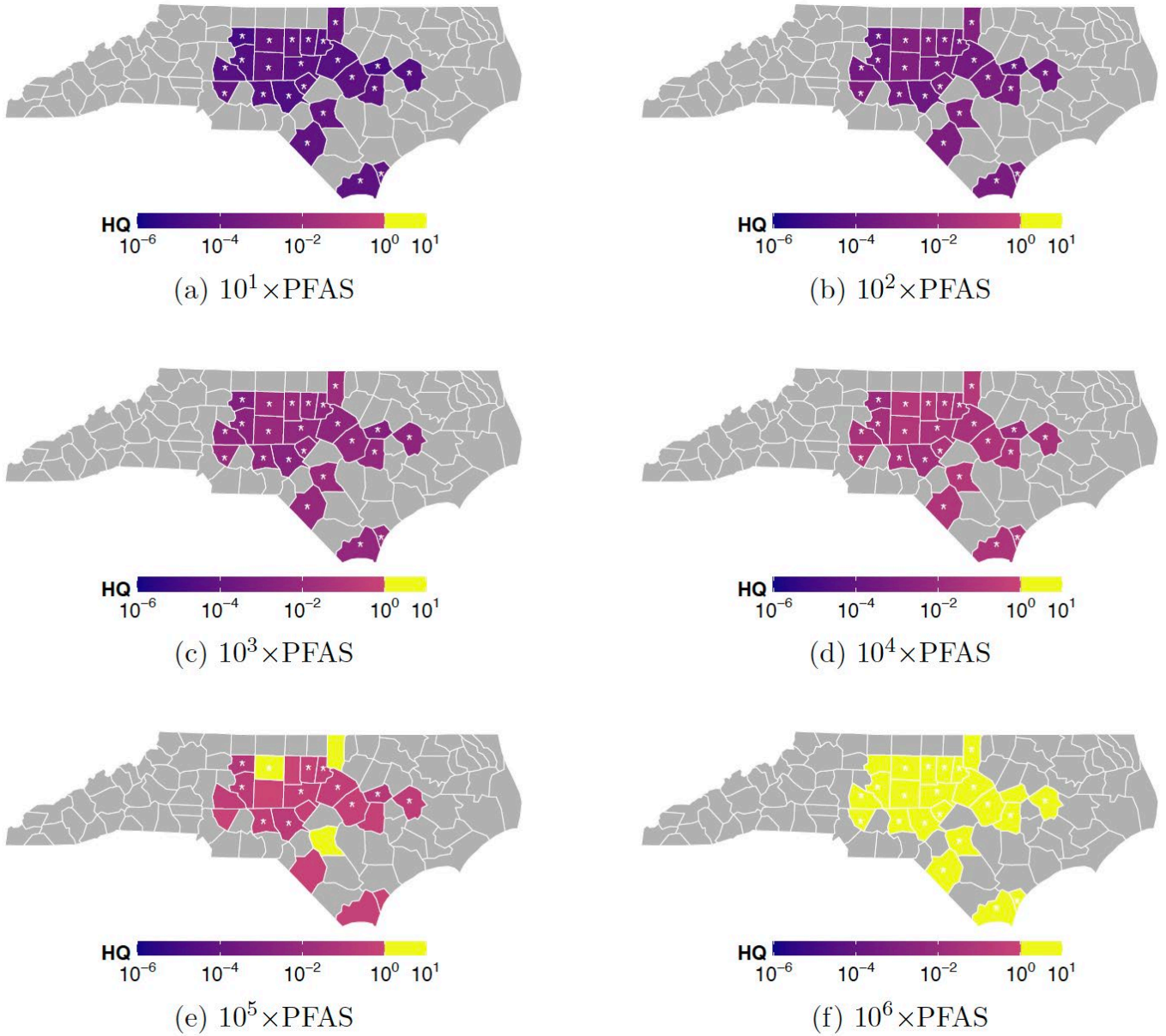
NAMs bridge from exposure (*PFAS mixture*) to outcome (*Risk*) in a human population cohort (*PEGS*) *(5)*

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 ≥ 1).



Some counties may be more susceptible under certain scenarios.

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

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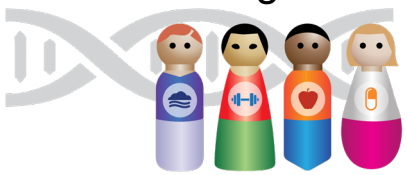
Predictive Toxicology workbench: Preparing for event/disaster scenarios using Agent Based Models

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

e.g. Real-world data from PEGS epidemiological cohort informs creation of Agents

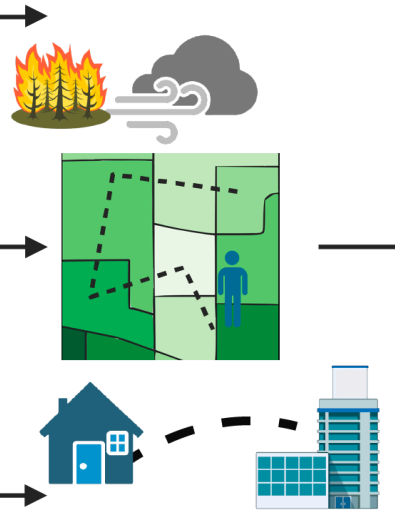


Agents

Agent Properties

- Location
- Targeted Genetics
- Behavior
- Health Status

Simulate



- Target Dose
- In-vitro Equivalent
- Dose Response

Agent Responses

Led by Kyle Messier (NIEHS) + Guojing Cong (ORNL)

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

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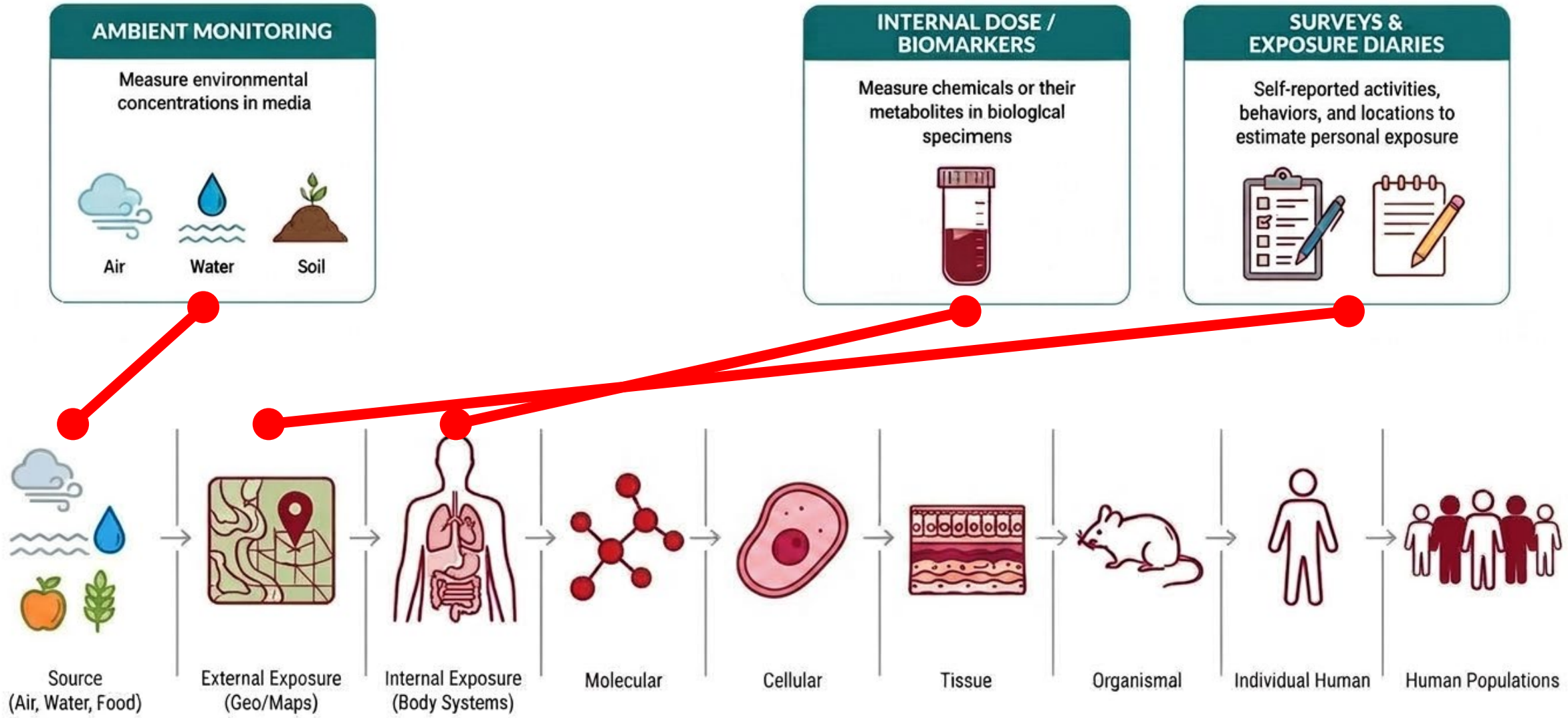
What if we added personal exposomics from biosamples?



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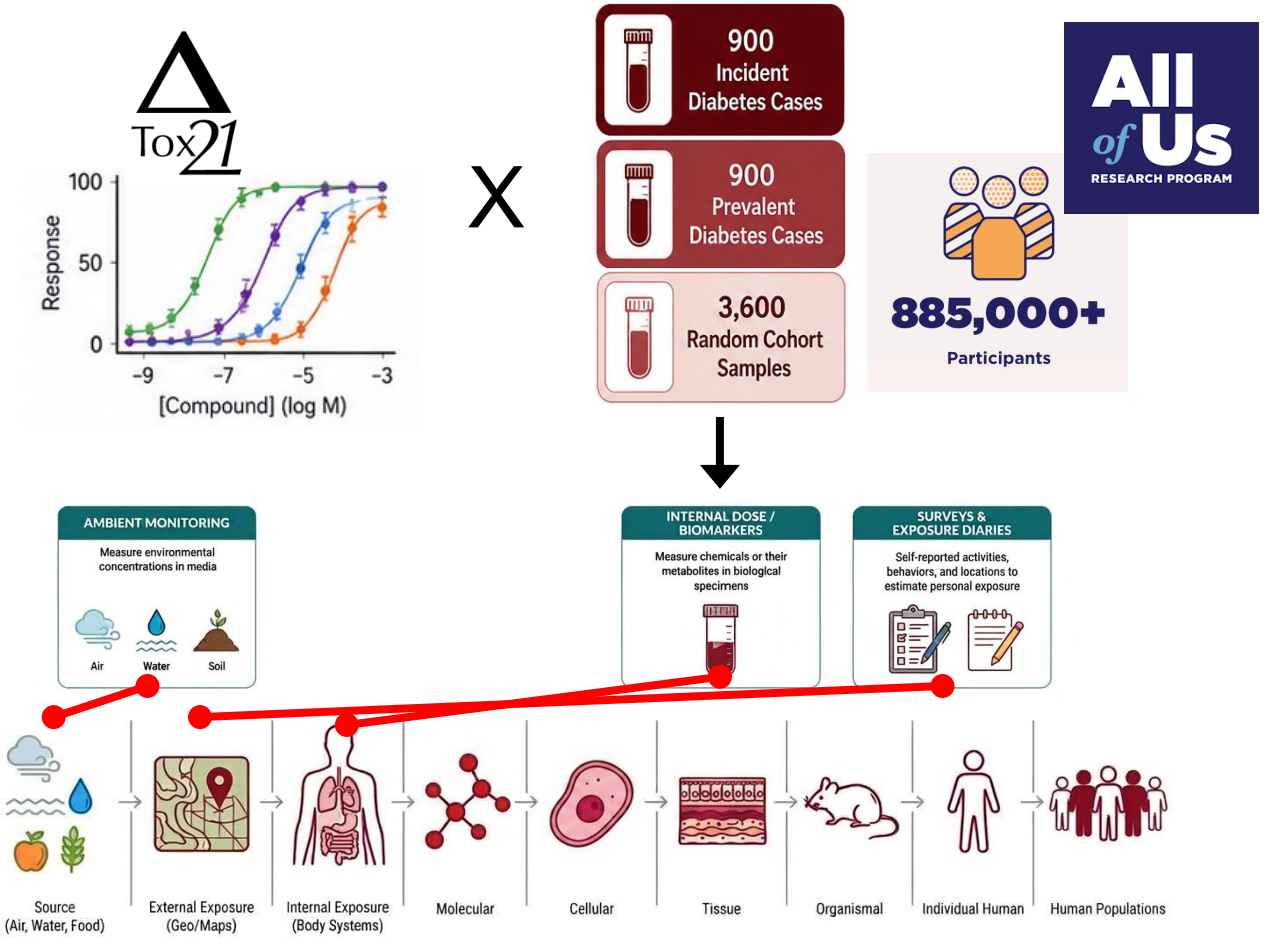
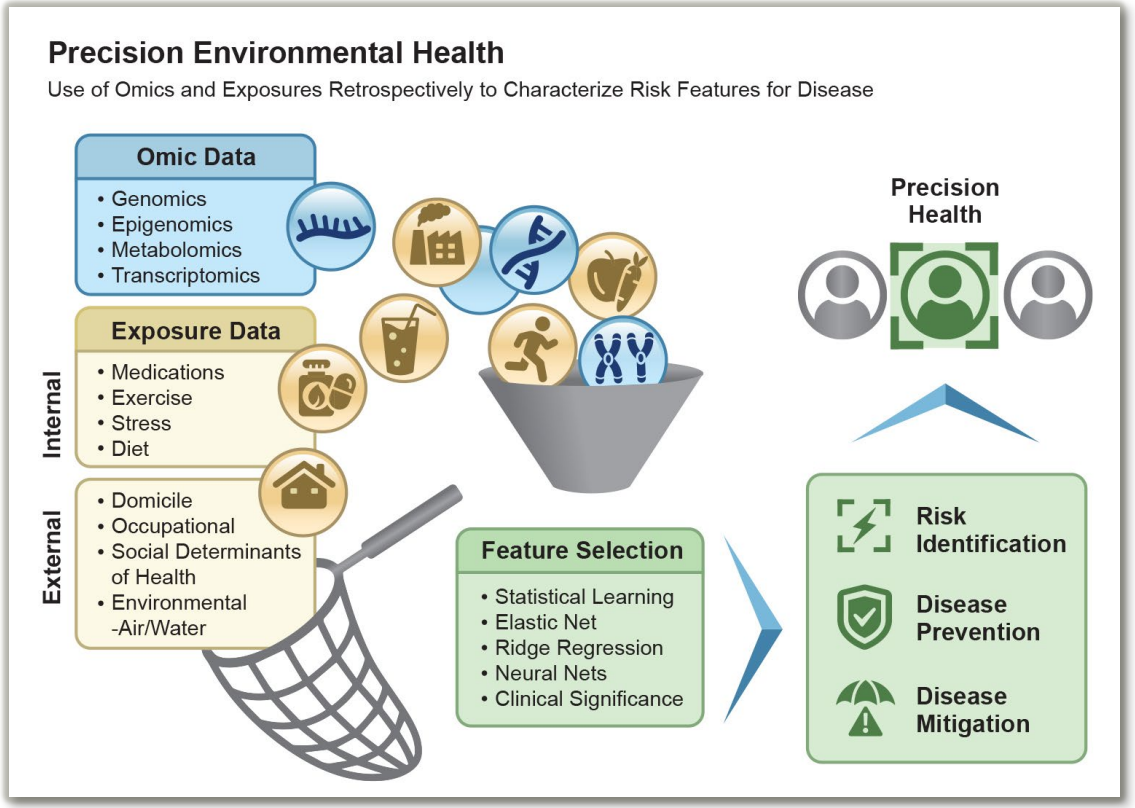
Tox21 x AllOfUs: NAMs x Metabolomics data as a mechanistic bridge connecting exposures to outcomes (3)

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



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

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



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?

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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

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Kyle Messier
Skylar Marvel
Danielle Dematteis
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

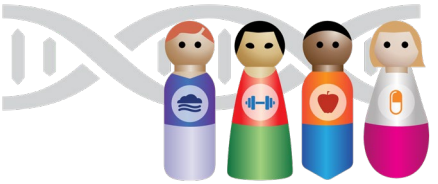
Ryan Campbell
Dillon Lloyd
Nat Macnell
Cristina Justice
Kwangmi An
Jui-Hua Hsieh
Ann Liu
Adam Burkholder
Aubrey Miller
Farida Akhtari
Alison Motsinger-Reif

OAK RIDGE National Laboratory

Trang Do
Guojing Cong
Kazi Ashik Islam

All of Us RESEARCH PROGRAM

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



PEGS leadership & participants