



National Institute of
Environmental Health Sciences
Division of Translational Toxicology

Mapping a Path to Disease: Quantifying the risk of exposure to environmental chemical mixtures via a common molecular target using a geospatial modeling approach

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**National Institute of Environmental Health Sciences
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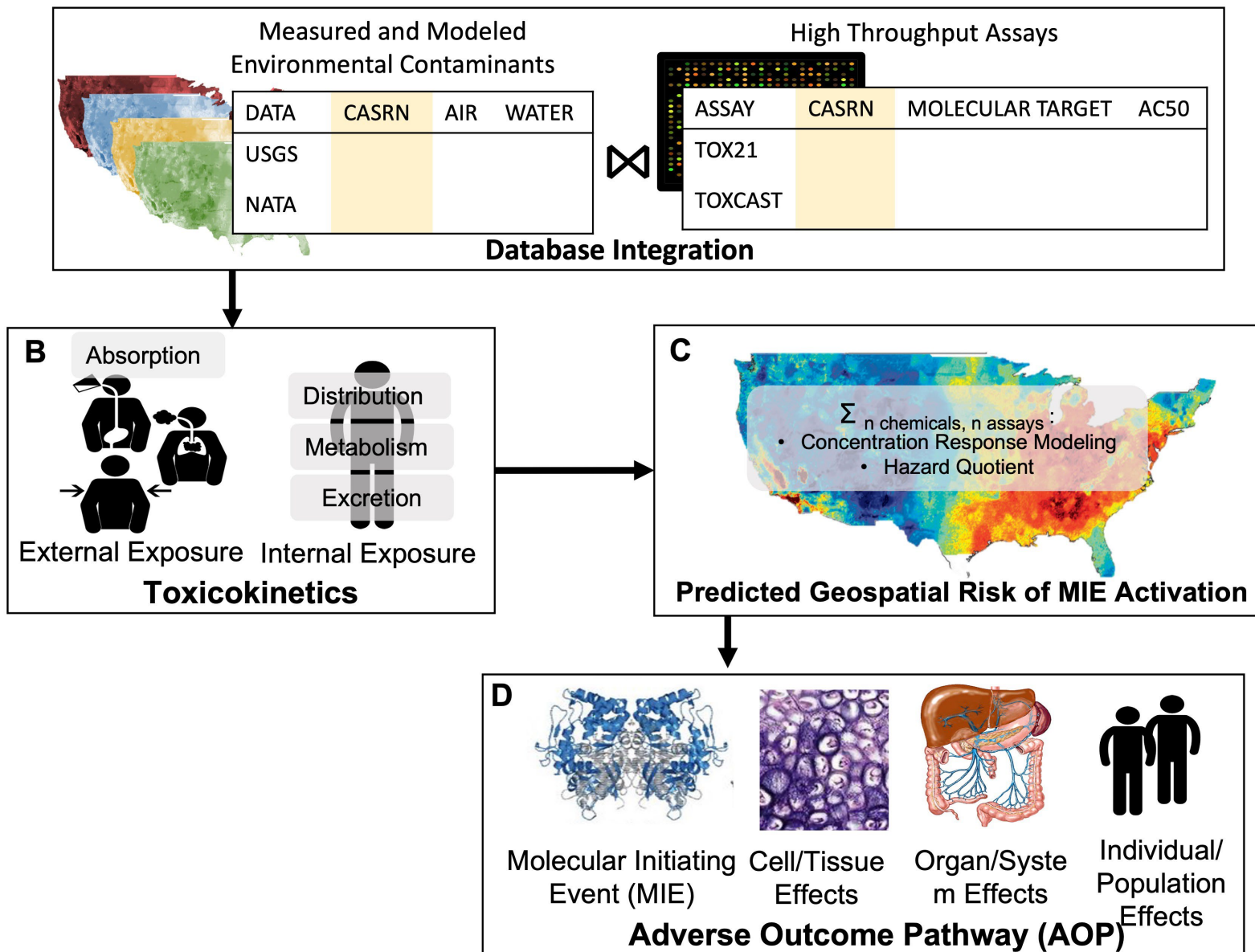
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Introduction

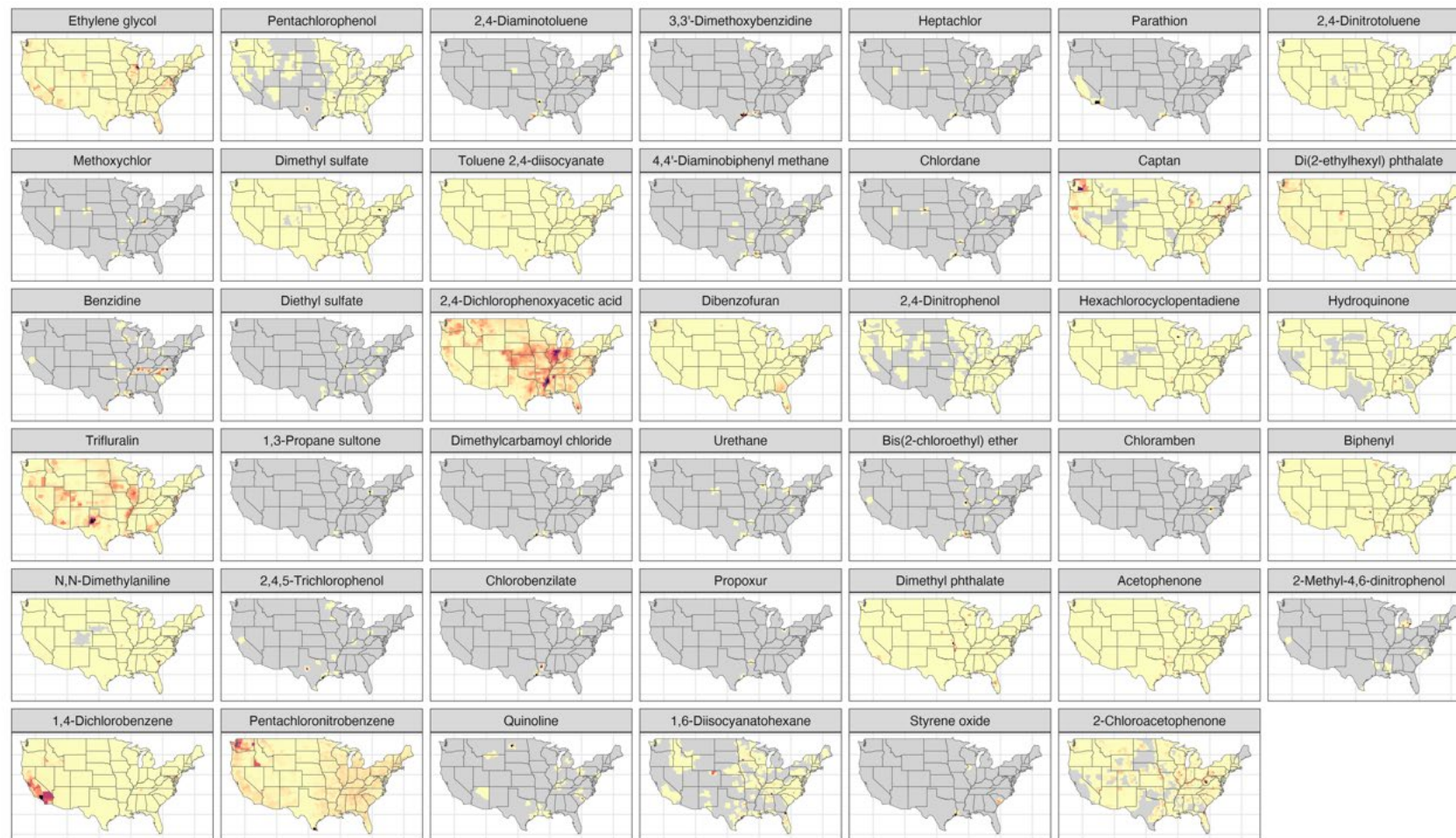
- Real-world chemical exposures are complex mixtures heterogeneously distributed across space.
- Traditional risk assessments use a chemical-by-chemical approach and apical disease endpoints.
- New methods for toxicity testing, such as high throughput screening (HTS) assays, can quantify chemical hazards
- HTS data inform on molecular level changes that act on a biological pathway
 - Multiple exposures can be integrated based on chemicals that act on the same pathway.





Chemical Data: National Air Toxics Assessment (NATA)

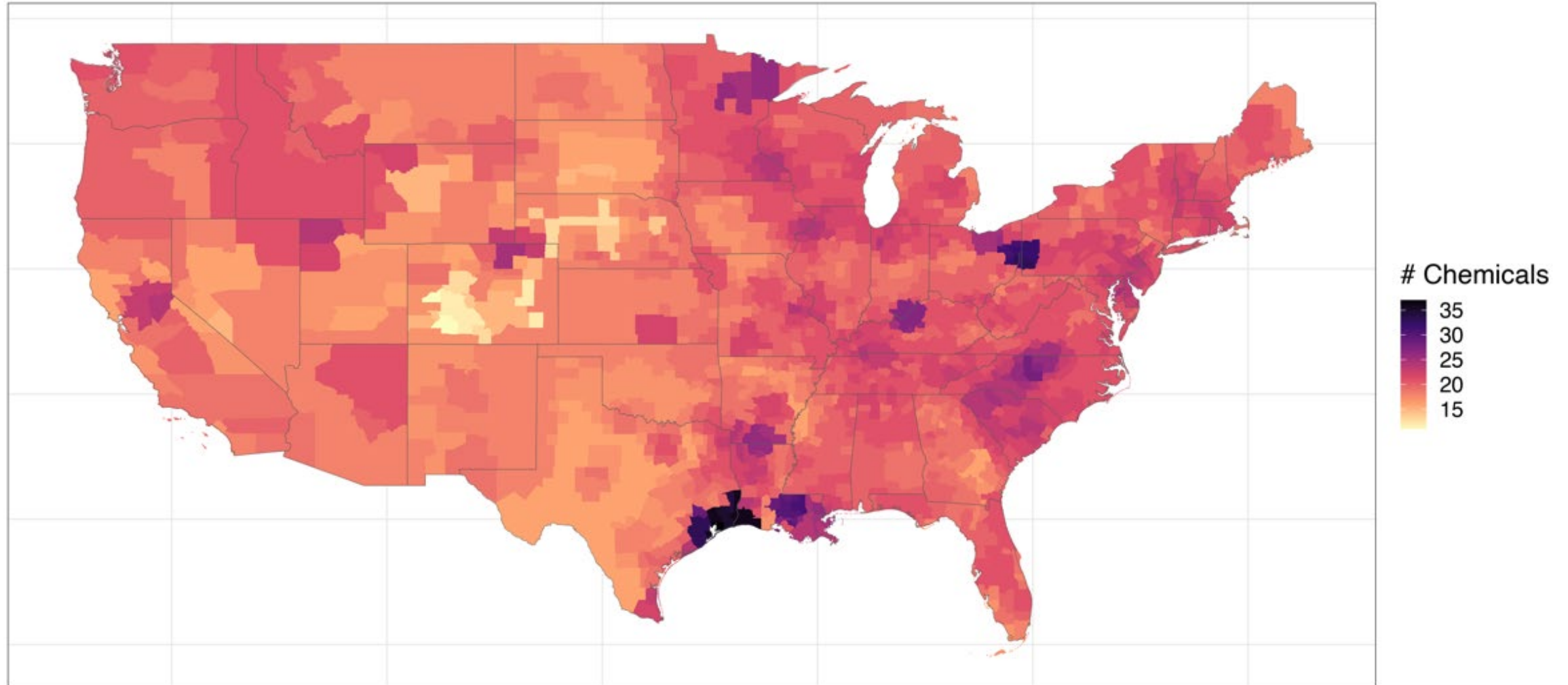
- Chemical transport model
 - Emissions
 - Chemistry
 - Meteorology
- Average annual chemical concentration in 2014 by census tract
- n chemicals in NATA = 188
- n chemical activate CYP1A1_Up = 41



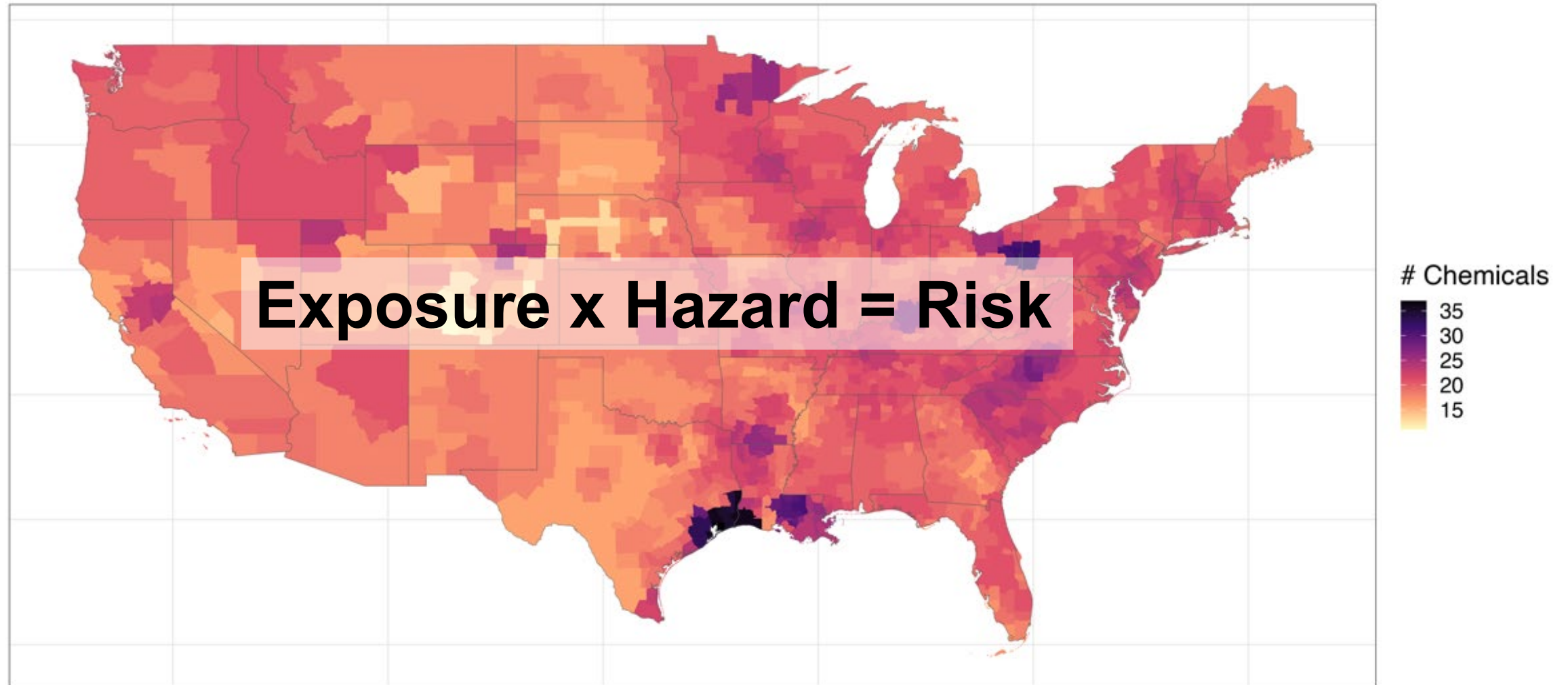
Normalized Concentration 

 0.00 0.25 0.50 0.75 1.00

Chemical Co-occurrence

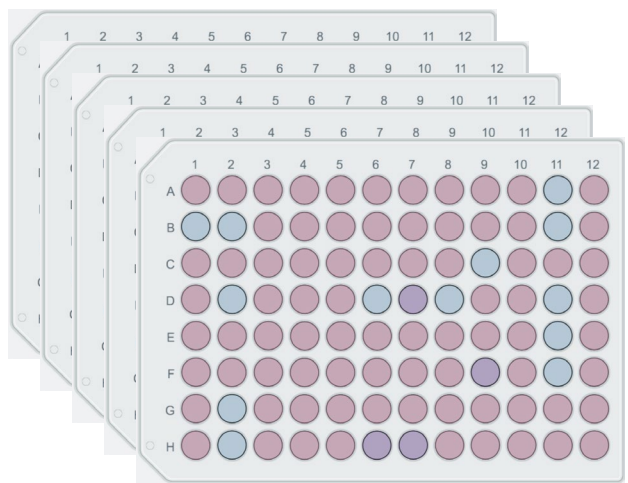


Chemical Co-occurrence



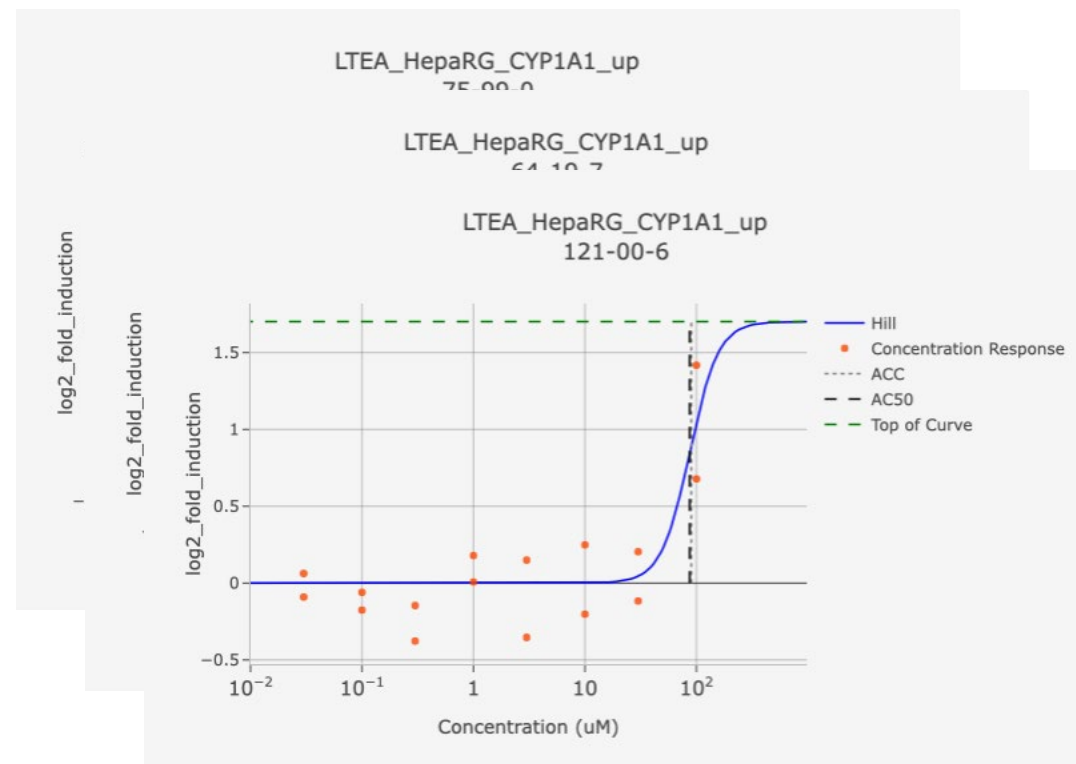
Hazard Data: Curated TOX21 High Throughput Assay Data

- **Hazard Data:** Exposure response parameters from the EPA developed pipeline (n assays=1457, n chemicals=9298)
 - EPA data is then curated with additional QA/QC by the NIEHS/NTP Integrated Chemical Environment



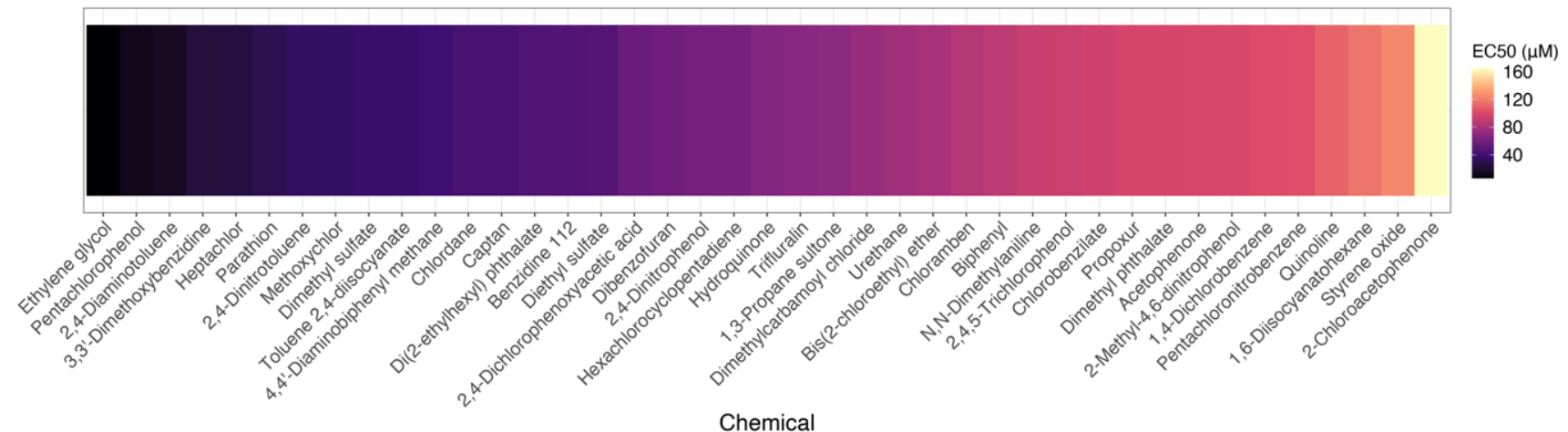
High Throughput
Screening Assays

R: tcpl pipeline



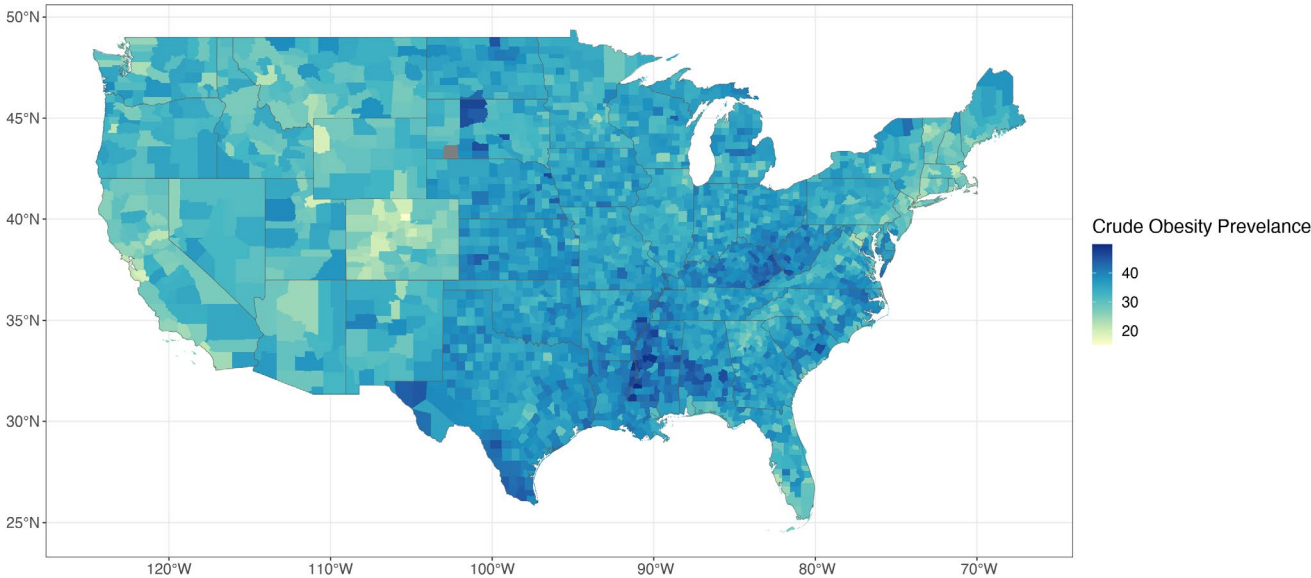
Hazard Data: High Throughput Assay

- Increase transcription factor expression of CYP1A1 (LTEA_HepaRG_CYP1A1_up)
- The gene encodes for one of the cytochrome P450 superfamily of enzymes
 - Responsible for Phase I metabolism → can results in carcinogenic intermediates
 - Also necessary for metabolic functions (e.g., steroidogenesis)
- Expression is induced by exposure to some polycyclic aromatic hydrocarbons
 - E.g., cigarette smoke

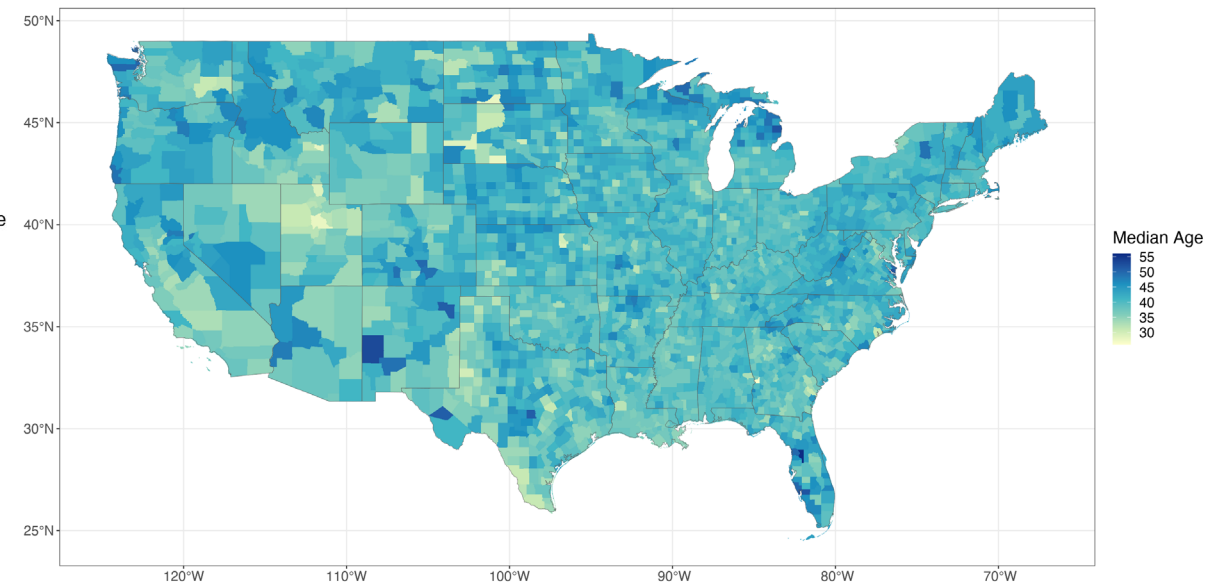


Population Data by County

Crude Obesity Prevalence



Median Age

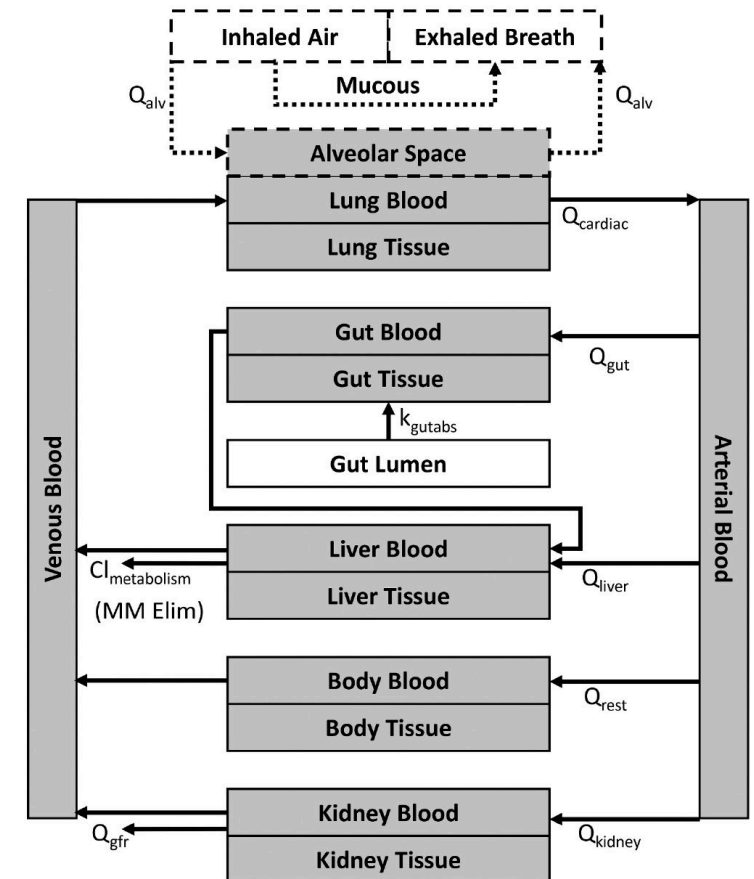


Key for estimating spatial variation of:

- Internal exposure via rate of inhalation
- Steady State Plasma (Blood) Concentration via hepatic clearance

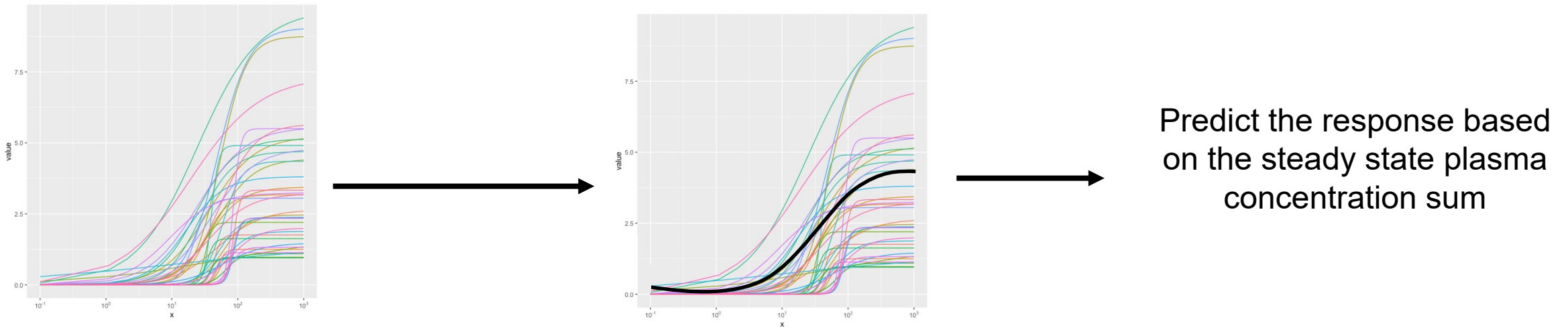
External concentration → Internal dose → Steady state plasma concentration

1. Inhalation rate by county
 - Affected by age and obesity status
2. Physiologically based toxicokinetic (PBTK) modeling links inhaled dose to a plasma concentration
 - *httk*: 3 compartment model (lung, liver, blood)
 - ADME controlled by: Chemical parameters and Hepatic Clearance
 - Affected by age and obesity status
 - E.g., Younger age = higher metabolic clearance = Lower steady state plasma concentration



Steady state plasma concentration → Combined risk of molecular perturbation

1. Generalized Concentration Addition/ Response Addition: Predicting the Log2 Fold Change in mRNA Expression



2. Hazard Index

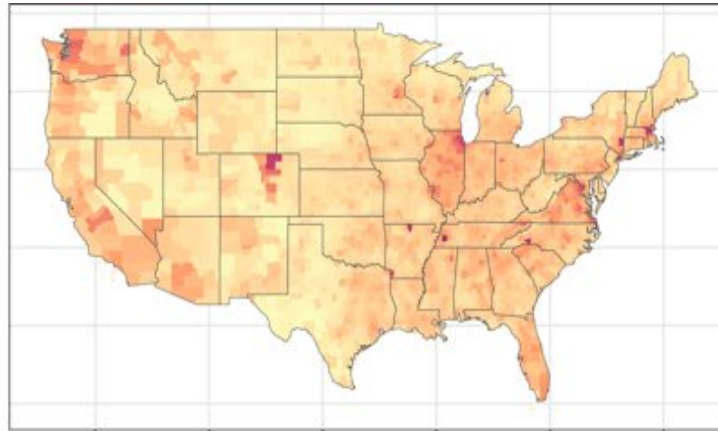
$$HI = \sum_n \frac{\text{Steady State Plasma Concentration}}{\text{Concentration at 10\% Activity (AC10)}}$$

Mapped Risk of Molecular Perturbation

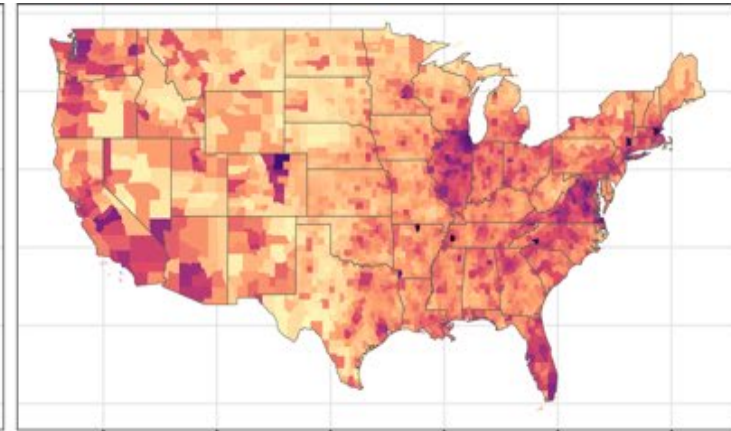
5th Percentile



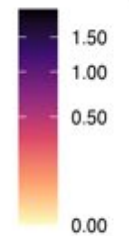
Median



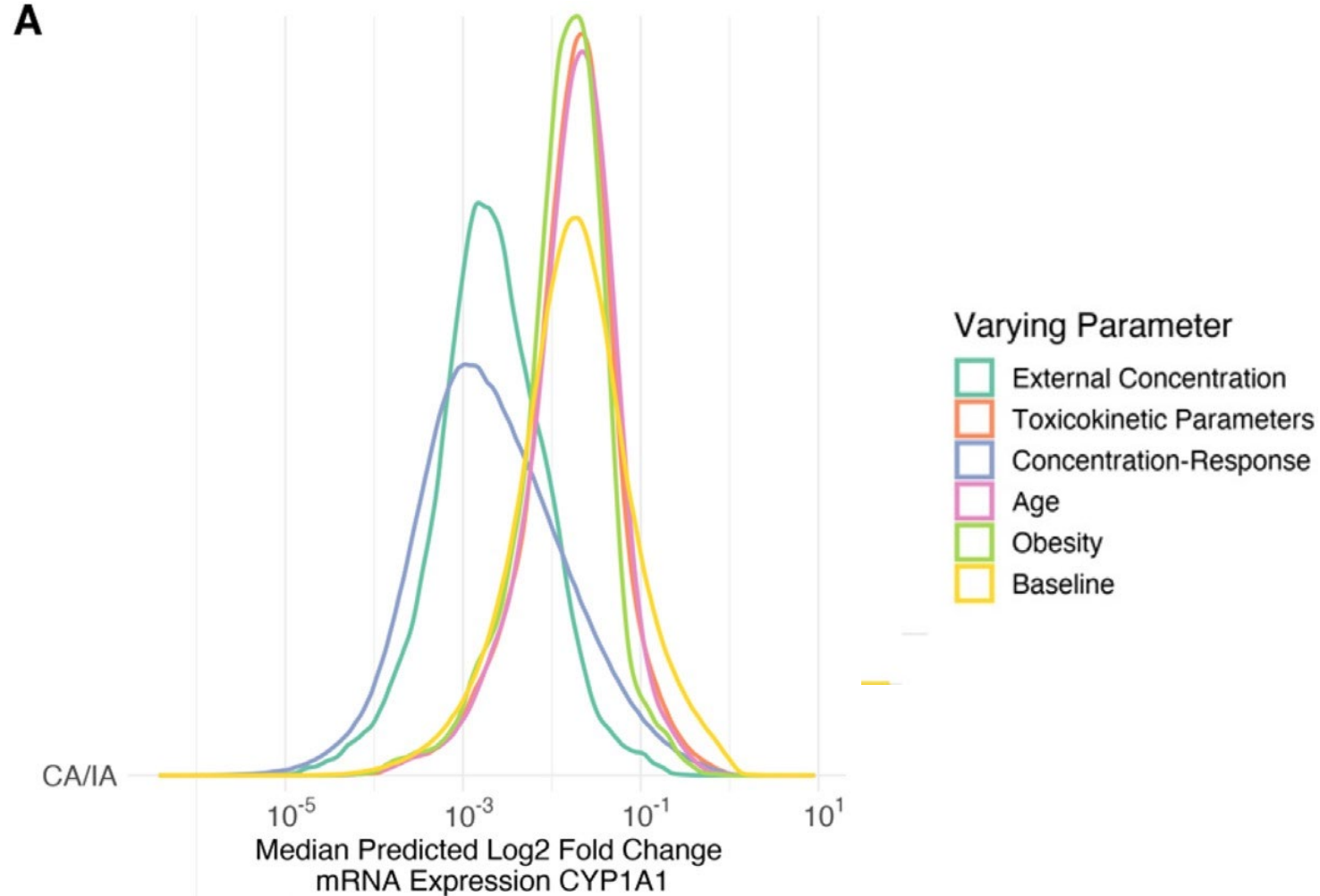
95th Percentile



Predicted Response
Log2 Fold Change
mRNA Expression

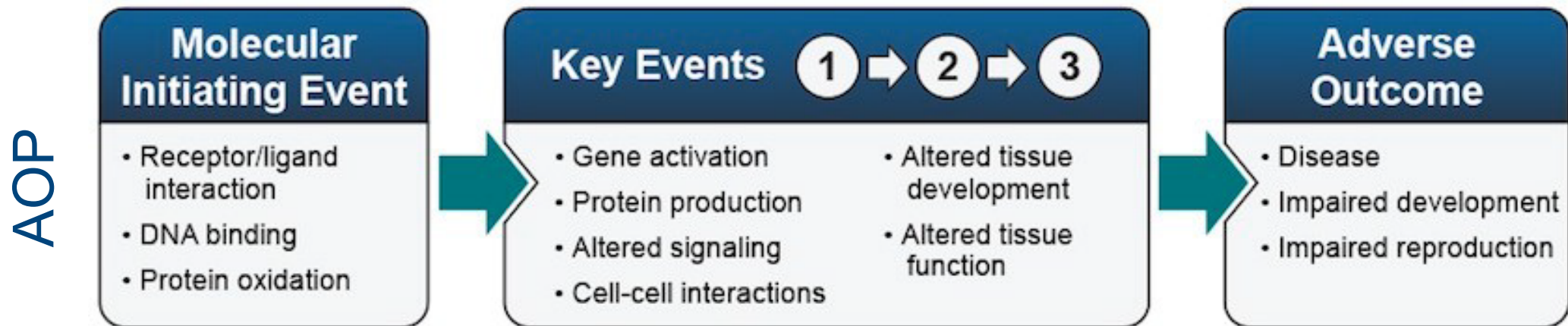


Monte Carlo Uncertainty Analysis



Conclusions

- This method integrates multiple geospatial chemical exposures with chemical potency, for chemicals that act on the same molecular target
- Can be expanded to other chemical, assays, geographic extents
- Ongoing work: use this workflow to link molecular level perturbations with adverse cardiovascular outcome data
- Build a weight of evidence linking environmental exposures to health outcomes





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Thank you

Questions

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