Methodological details for quantifying the risk of exposure to environmental chemical mixtures via a common molecular target using a geospatial modeling approach

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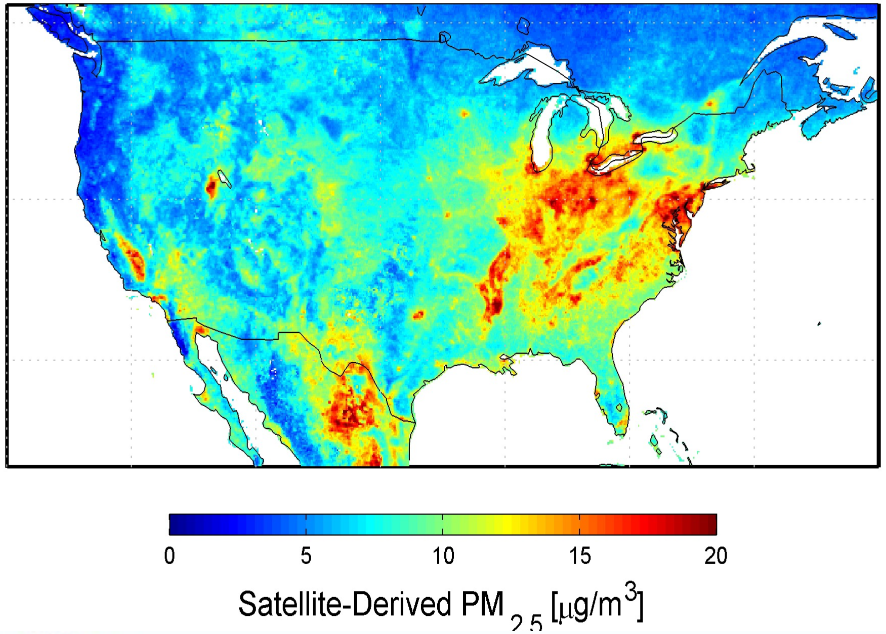
EPA

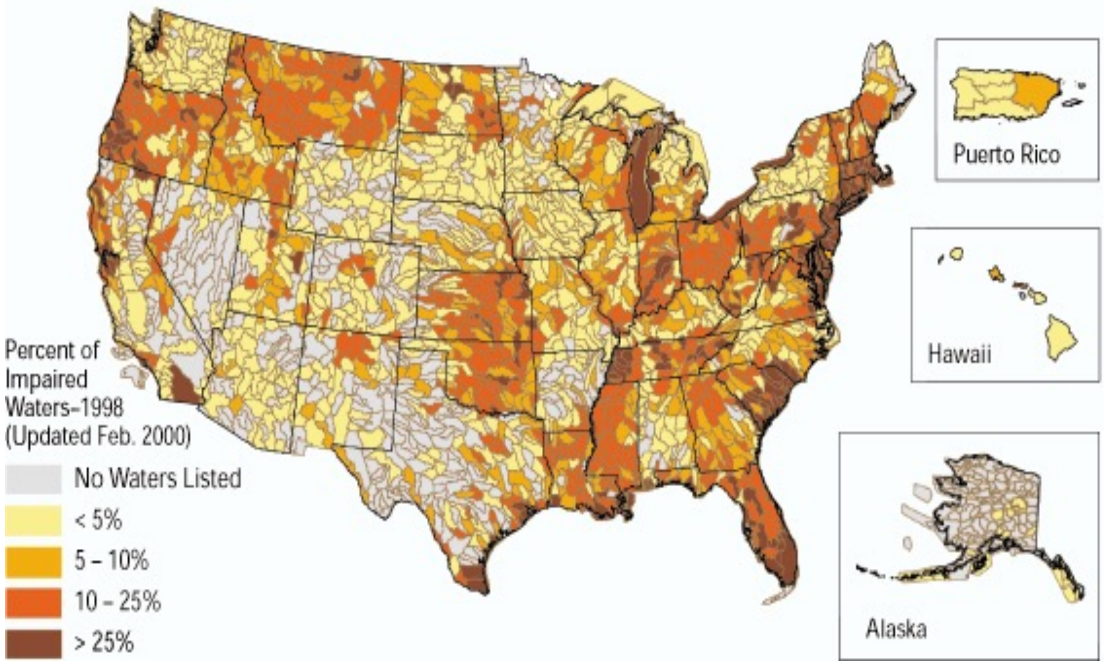
Disclaimer

I declare that I have no conflicts of interest. The contents reflect the opinions and views of the author and do not represent the official views of the NIH, EPA, or Health Canada.

Background

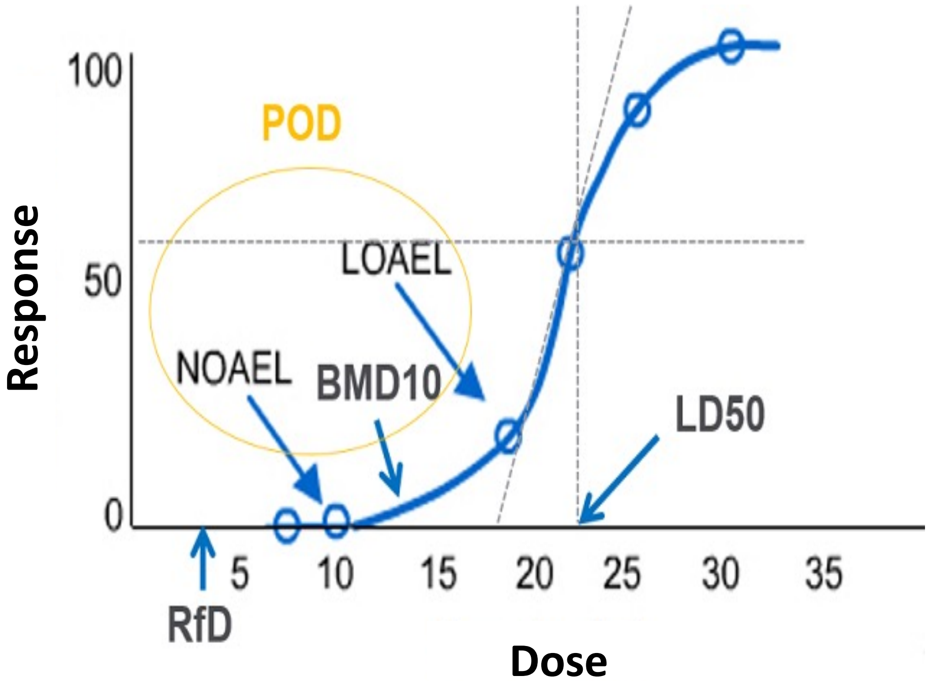
- Chemical exposures are plentiful and ubiquitous
- Real-world chemical exposures are complex mixtures heterogeneously distributed across space
- Geospatial exposures are rarely considered in chemical risk assessment





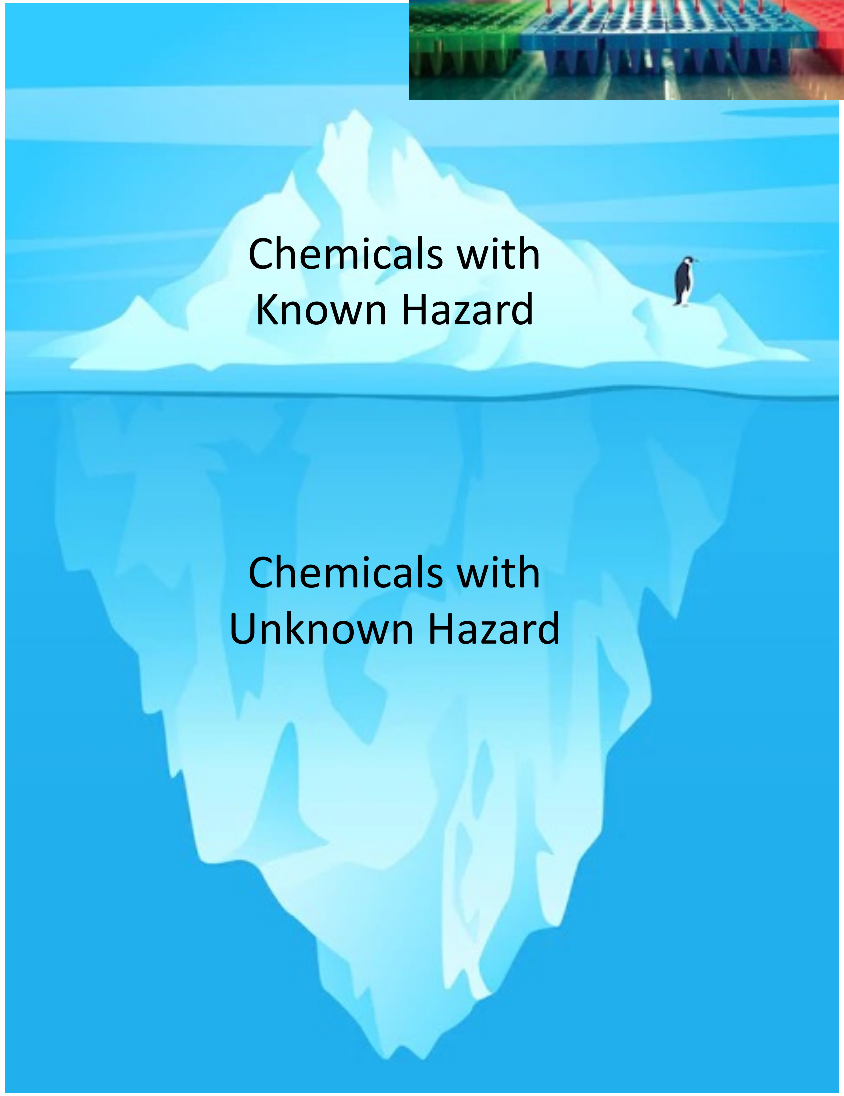
Background

- Traditional risk assessments use a chemical-by-chemical approach and apical disease endpoints
  - Reliance on animal data can be problematic
  - Leaves gaps in our understanding of the progression of disease
- Something from nothing (Silva et al., 2002, *Environ. Sci. Technol.*)
  - Some chemicals when combined at concentrations below their NOECs can produce significant effects



Background

- New approach 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 molecular target



Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

A geospatial modeling approach to quantifying the risk of exposure to environmental chemical mixtures via a common molecular target

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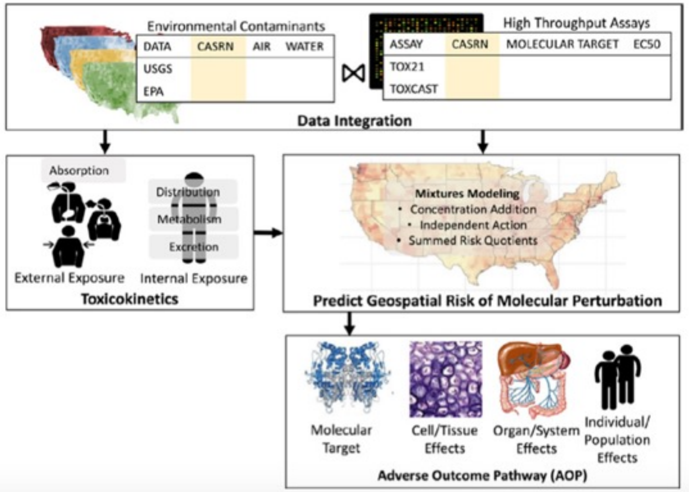
HIGHLIGHTS

- We assess the geographic variation for the joint effect of many chemical exposures.
- This example workflow integrates NAMs with chemical exposure data.
- The biological perturbations were heterogeneously distributed across space.
- Exposure concentrations, demographics, and toxicokinetics influence variability.
- We provide methods for modeling the source-exposure-effect continuum.

GRAPHICAL ABSTRACT



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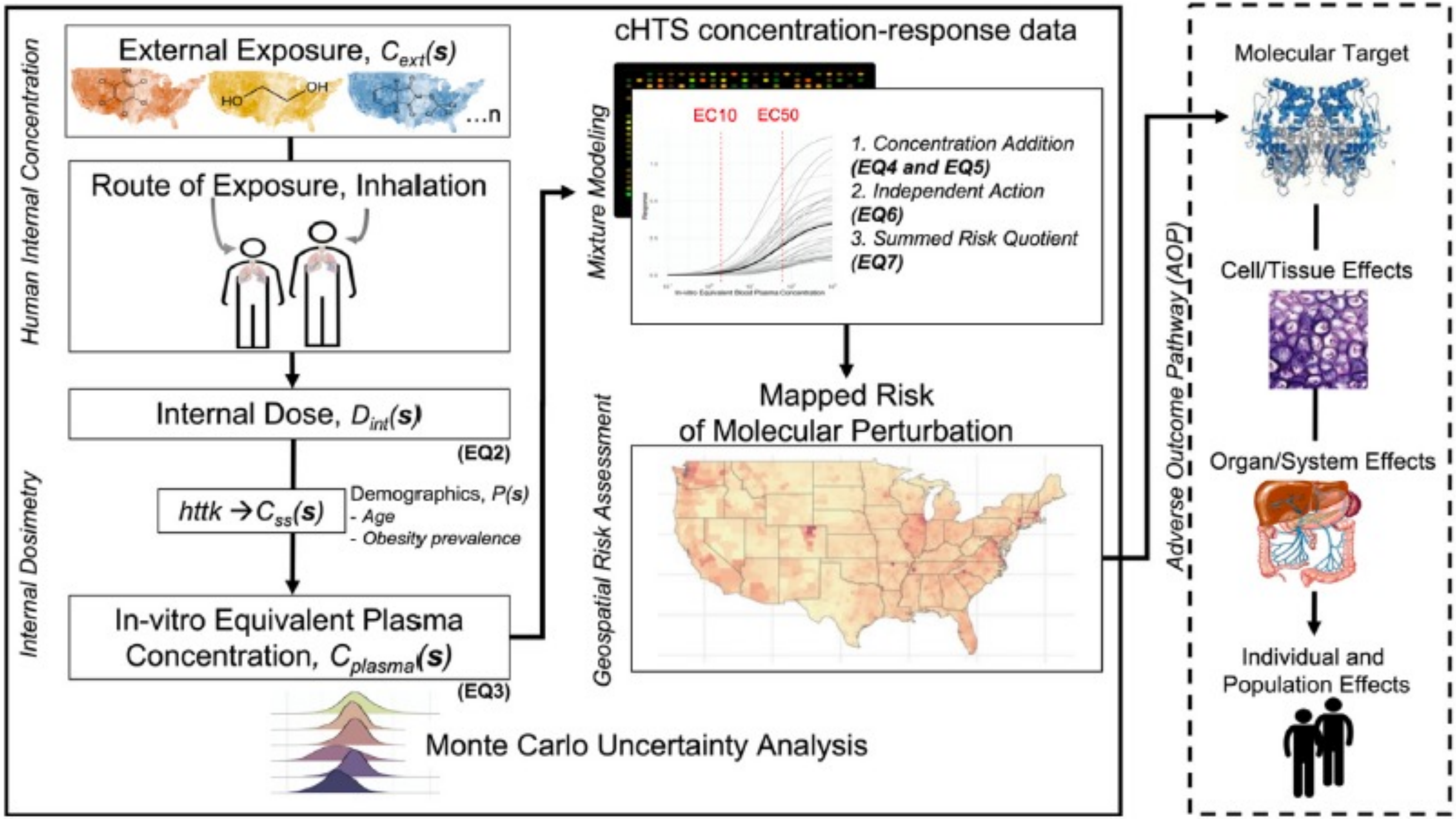
Overview



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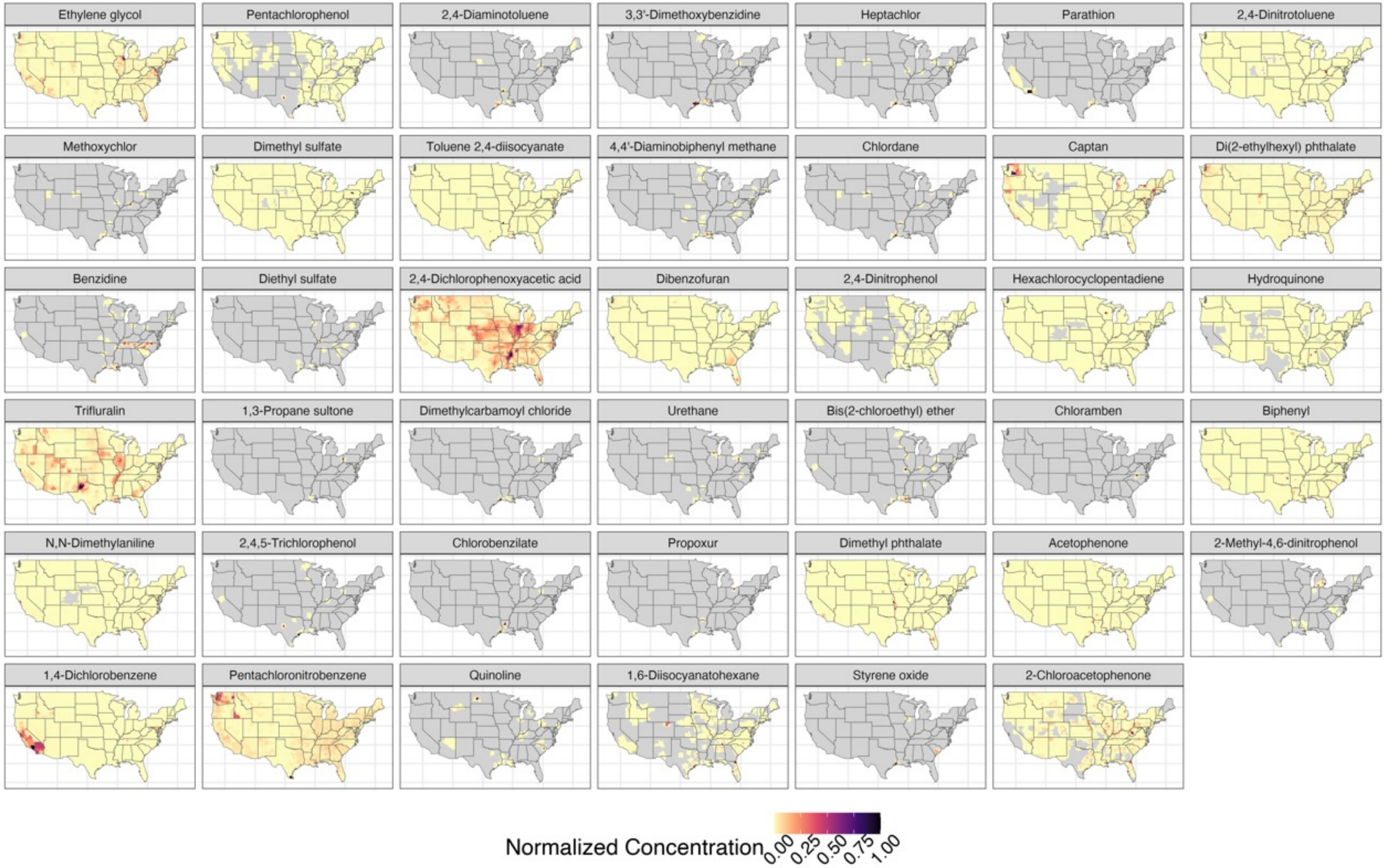
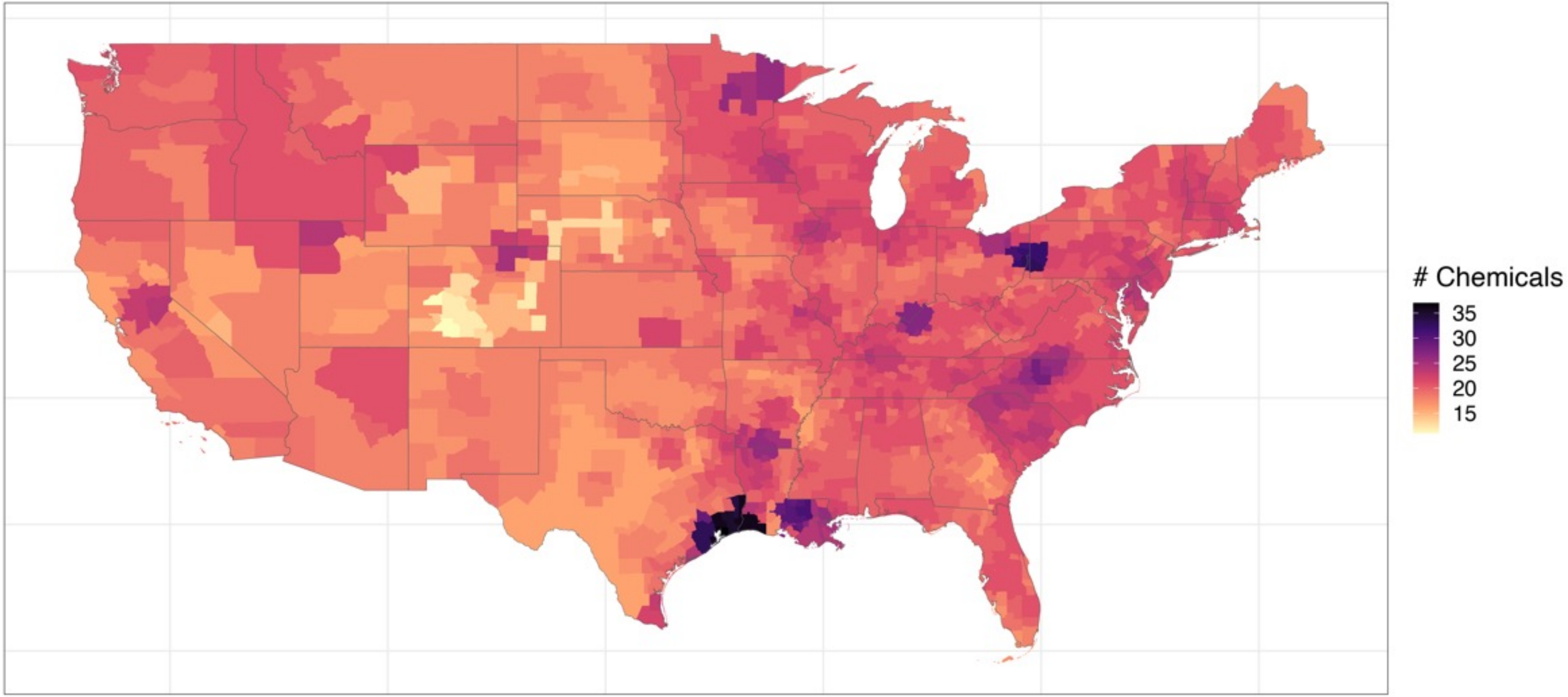
Data

Chemical Data: National Air Toxics Assessment (NATA)

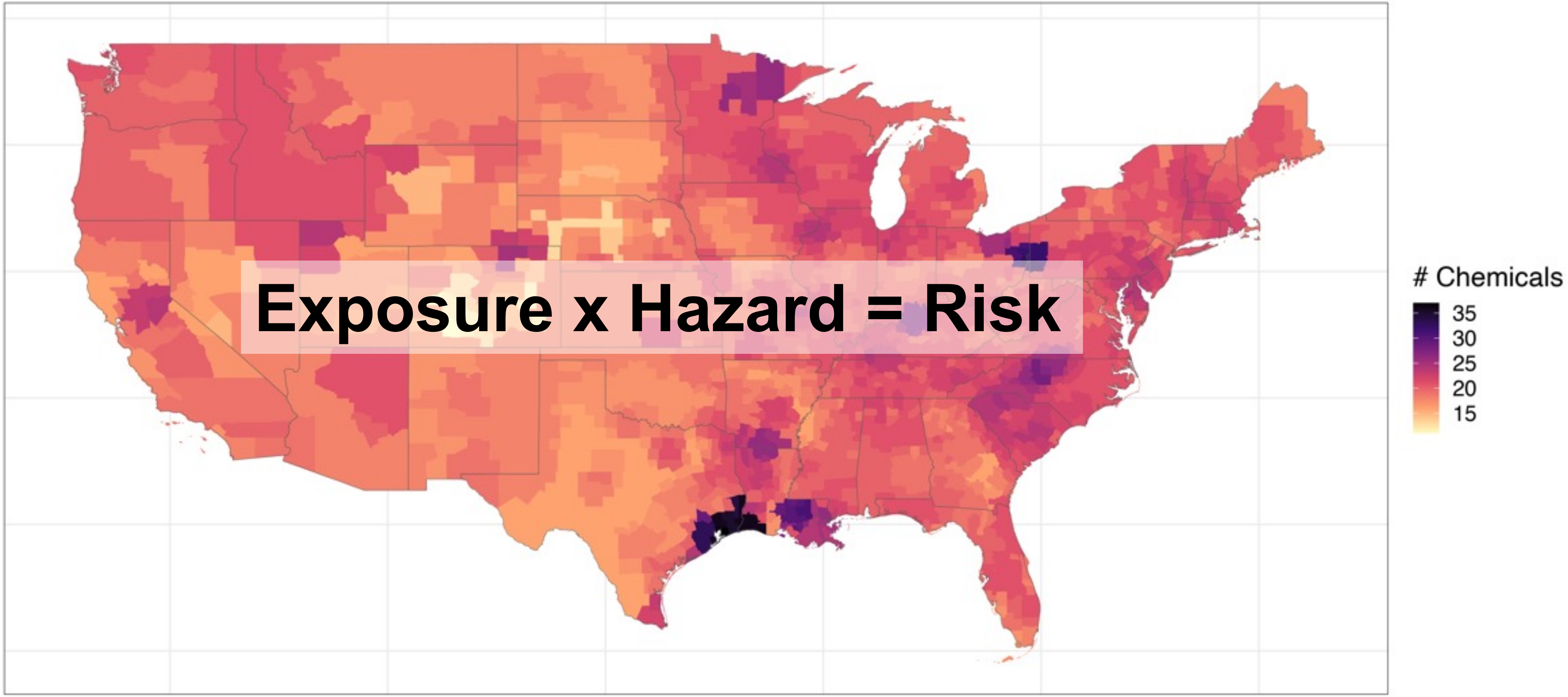
- Chemical transport model
  - Emissions
  - Chemistry
  - Meteorology
- Average annual chemical concentration in 2014 by census tract
- n chemicals in NATA = 188
- n NATA chemical that activate CYP1A1_Up = 41



Chemical Co-occurrence



Chemical Co-occurrence

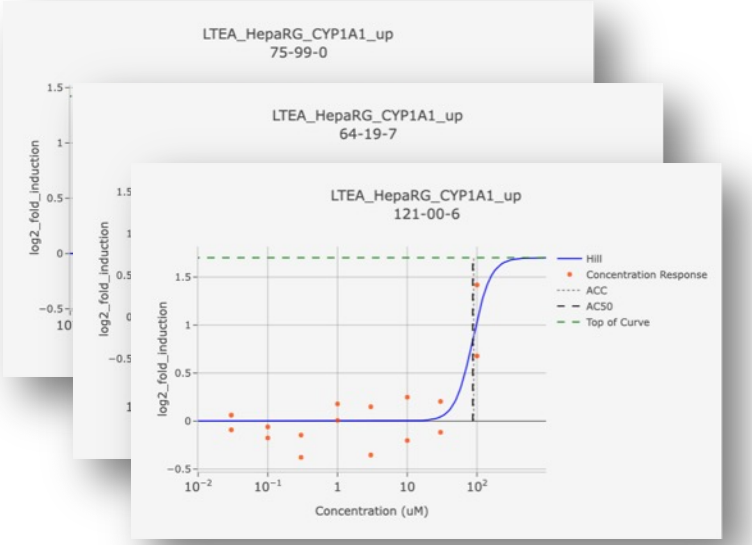


Hazard Data: Curated Tox21 and ToxCast High-Throughput Assay Data

- **Hazard Data**: Bioactivity response parameters from the EPA's tcpl pipeline (assays = 1457, chemicals = 9298)
  - Curated with additional QA/QC by NICEATM, retrieved from the webtool ICE (Integrated Chemical Environment; ice.ntp.niehs.nih.gov)

High-Throughput Screening Assays

R: tcpl pipeline



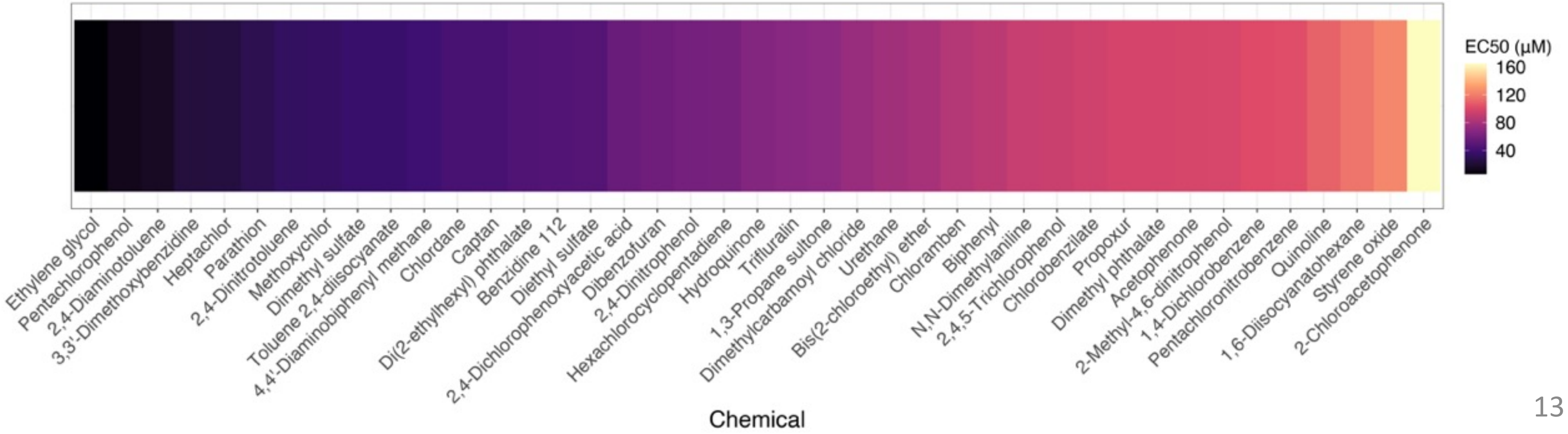
Concentration-Response Modelling

curation pipeline

Search and Download Curated cHTS Data

Hazard Data: High-Throughput Assay

- Increased expression of CYP1A1 mRNA transcripts (LTEA_HepaRG_CYP1A1_up)
  - The gene encodes for one of the cytochrome P450 superfamily of enzymes
  - Responsible for Phase I metabolism and can results in carcinogenic intermediates
  - Also necessary for metabolic functions (e.g., steroidogenesis)
- Expression is regulated by the Aryl Hydrocarbon Receptor
- Expression is induced by exposure to some polycyclic aromatic compounds
  - E.g., cigarette smoke, air pollutants



Chemical Overlap between NATA and Curated Tox21 and ToxCast

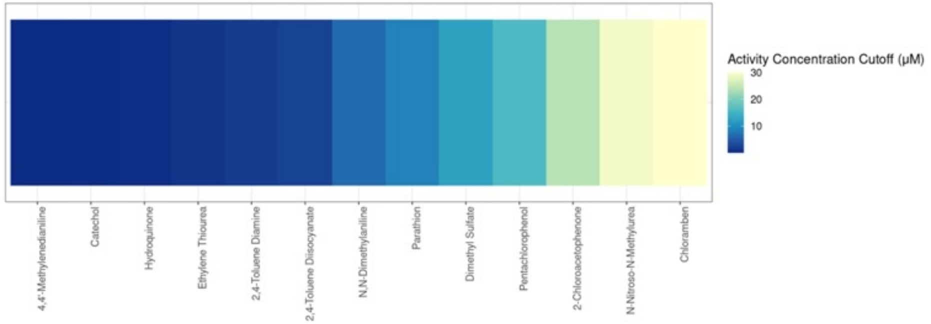
Risk of Molecular Target Activation From Exposure to Chemical Mixtures

Calculate the cumulative hazard quotient maps for chemical mixtures acting on molecular targets

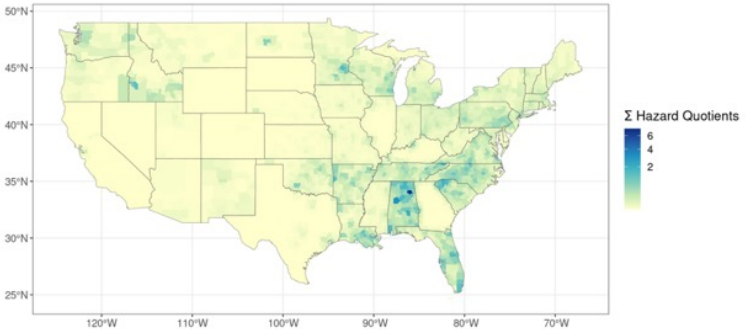
Exposure Data: National Air Toxics Assessment (NATA)
Hazard Data: TOX21 High Throughput Screening Assays

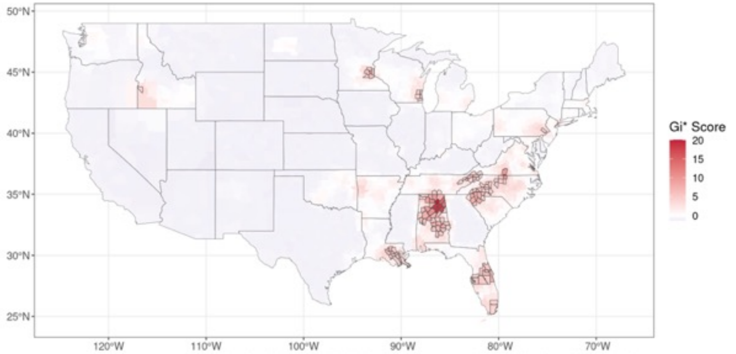
Select an assay:

NCCT_TPO_AUR_dn



Mixtures data: 83 NATA chemicals activate 493 assays

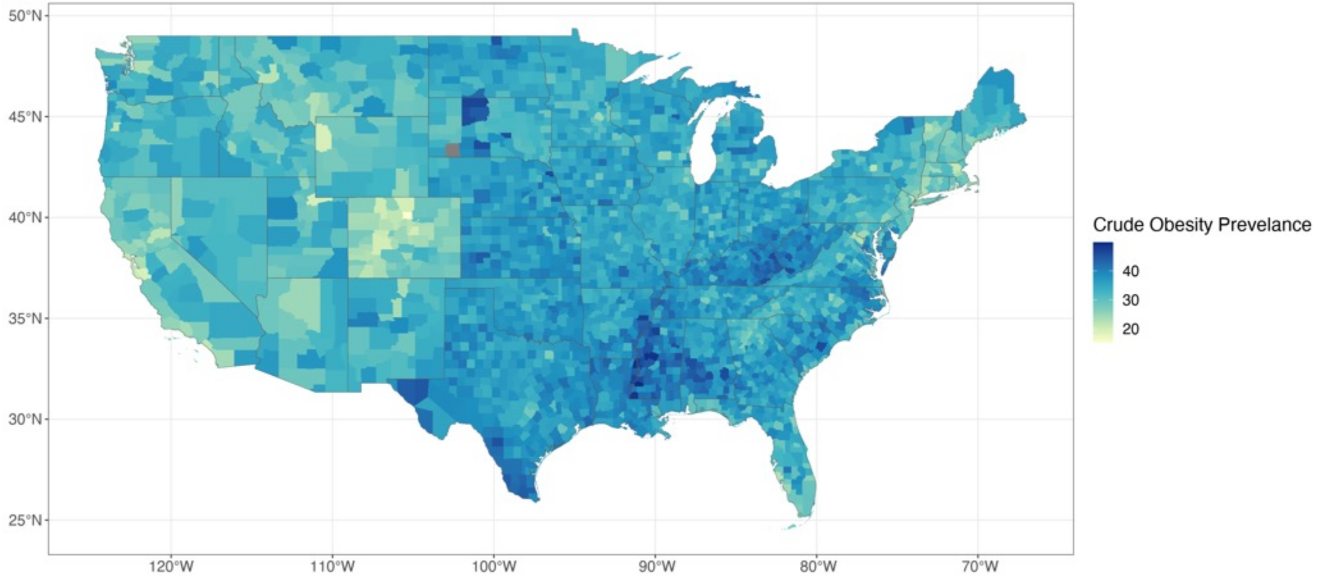




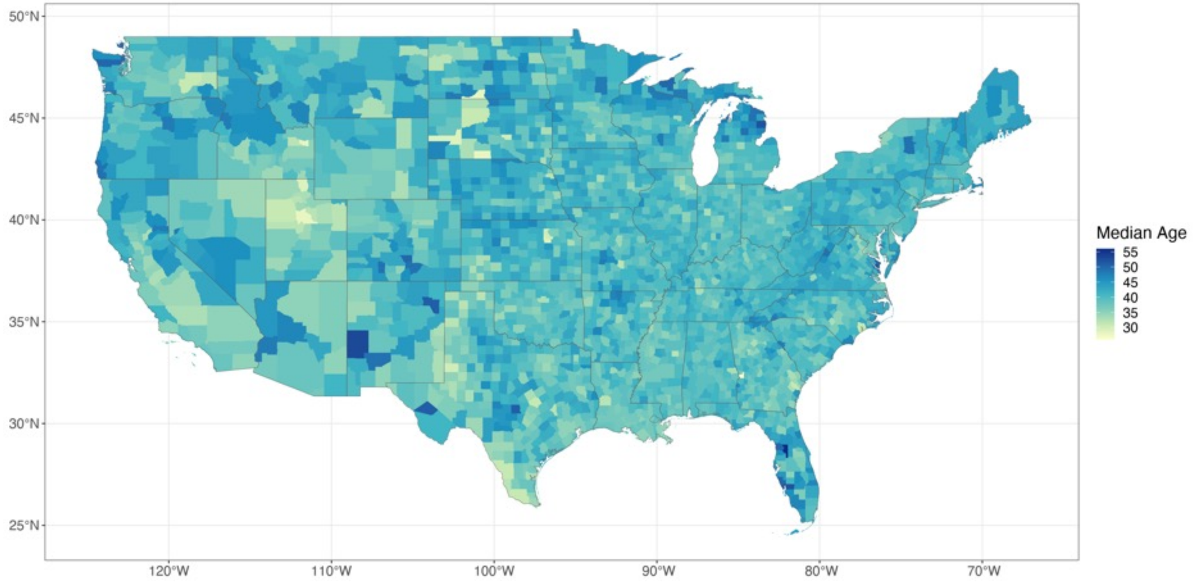
Counties with a dark outline indicate s cluster $p < 0.05$, after correcting for multiple comparisons.

Population Data

Crude Obesity Prevalence



Median Age



Key for estimating county specific spatial variation of:

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

Data Integration

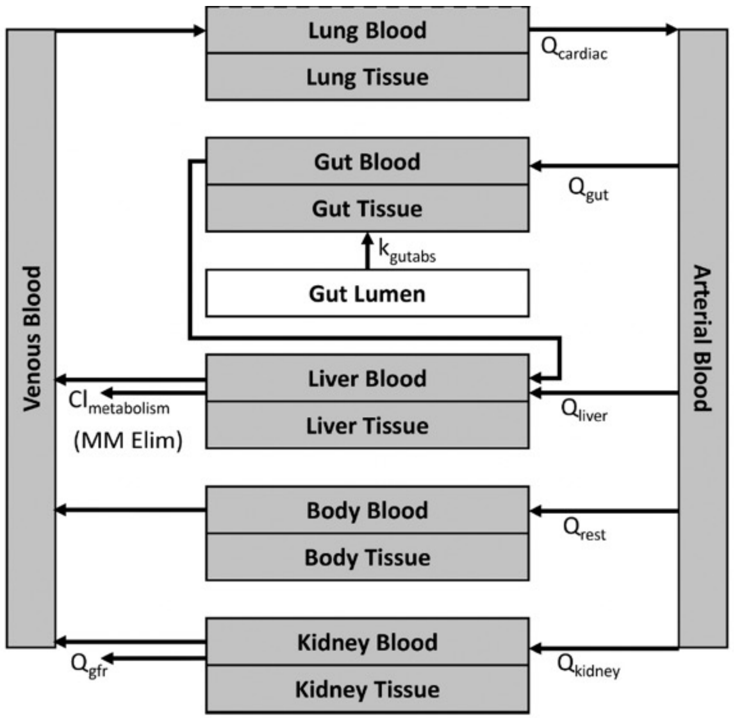
1. External concentration → Internal dose

- Route of Exposure: Inhalation
- Dose in a human (mg/kg) to obtain an internal chemical dose
- Rates of Inhalation (IR) are controlled by age and body weight (BW)
  - Vary by county
- Exposure over 1 year (t)

$$D_{int}(\boldsymbol{s}) = \frac{C_{ext}(\boldsymbol{s}) \times IR(\boldsymbol{s}) \times t}{\mathrm{BW}(\boldsymbol{s})}$$

2. Internal dose → Steady-state plasma concentration

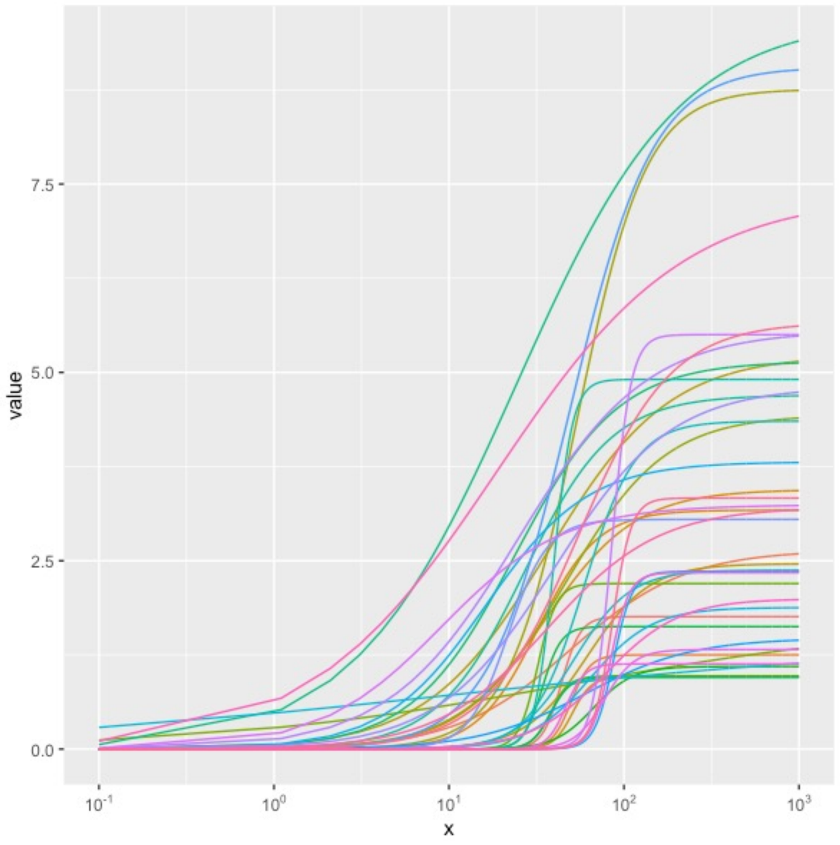
- Physiologically based toxicokinetic (PBTK) modeling links inhaled dose to a steady state plasma concentration
  - *httk:* 3 compartment model (lung, liver, blood)
  - ADME controlled by: Chemical parameters and Clearance parameters
    - Affected by age and obesity status

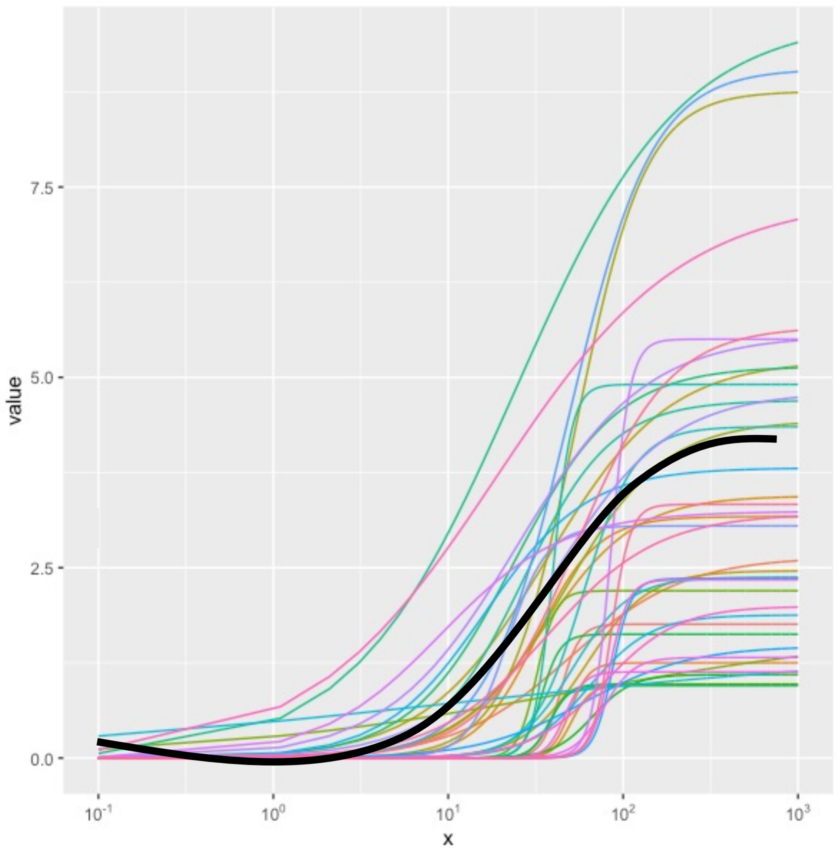


$$C_{plasma}(\boldsymbol{s}) = C_{ss}(\boldsymbol{s}) \times D_{int}(\boldsymbol{s})$$

3. Steady state plasma concentration → Combined risk of molecular perturbation

Concentration- response curve from the cHTS data





Predict the response based on the steady state plasma concentration sum

Mixture Modeling

1. Generalized Concentration Addition (Howard and Webster, 2009)

$$ECx_{mix}(\boldsymbol{s}) = \left(\sum_{i=1}^{n} \frac{p_i(\boldsymbol{s})}{ECx_i}\right)^{-1} \qquad 1 = \Sigma_{i=1}^{n(s)} \frac{C_i(\boldsymbol{s})}{f_i^{-1}(R(\boldsymbol{s}))}$$

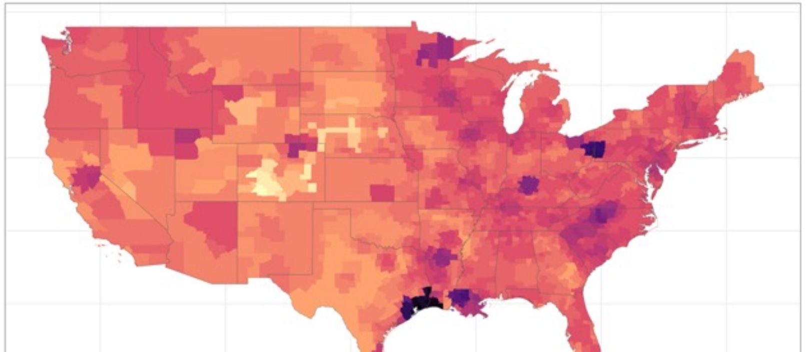
2. Response Addition (Bliss, 1939)

$$R(\boldsymbol{s}) = \alpha_{max}\left(1 - \prod_{i=1}^{n(s)}\left(1 - \frac{f_i[X]_i}{\alpha_{max}}\right)\right)$$

3. Risk Quotient

$$RQ(\boldsymbol{s}) = \Sigma_{i=1}^{n(s)} \frac{C_i(\boldsymbol{s})}{EC_{10,i}}$$

Results

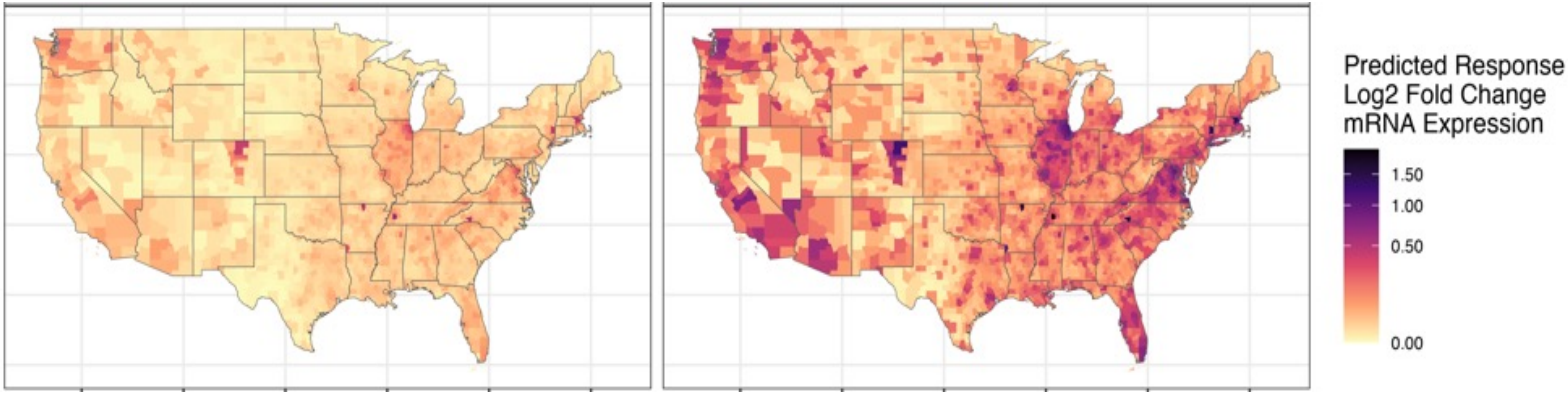


Co-occurrence

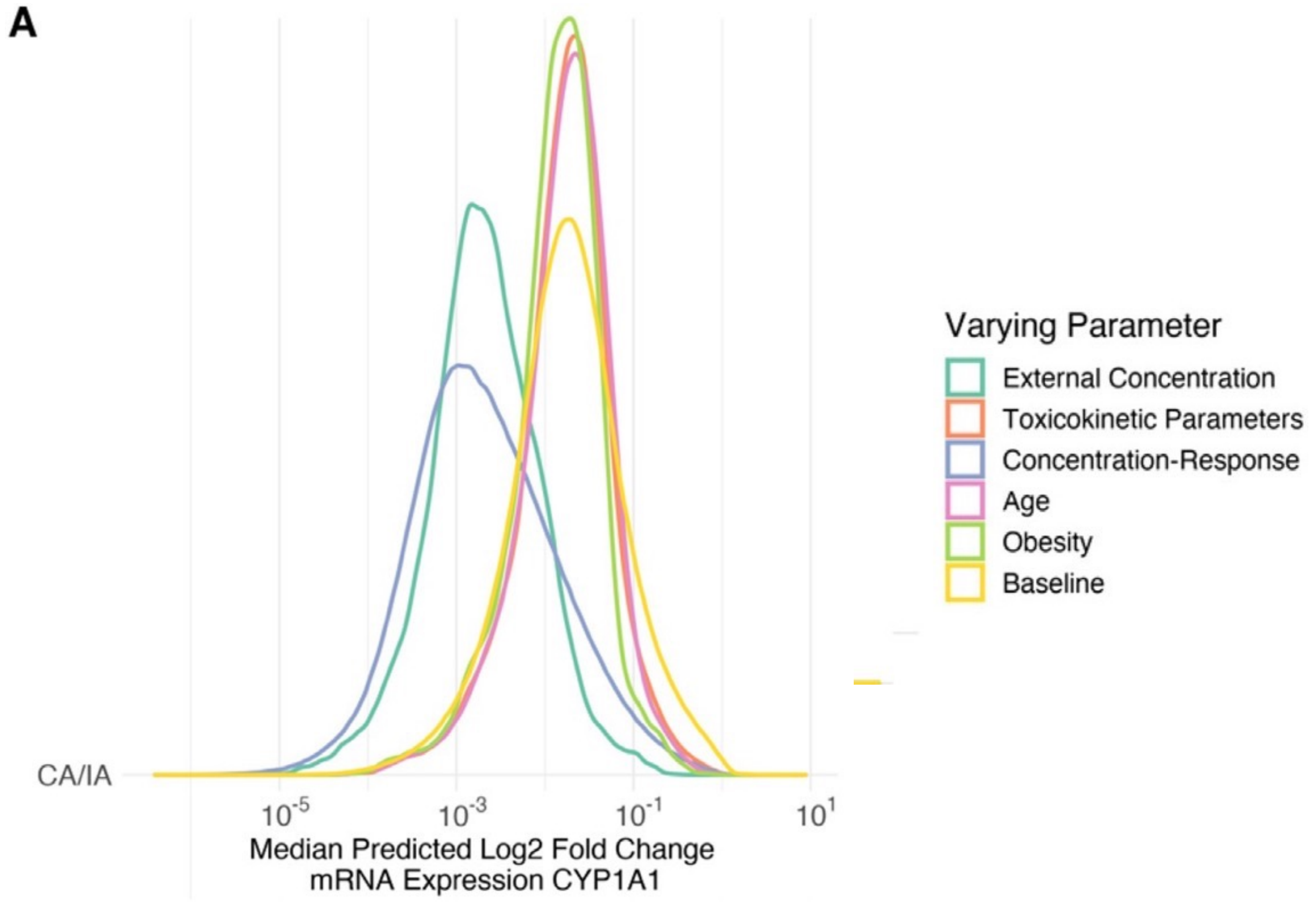
Mapped Risk of Molecular Perturbation

50th Percentile

95th Percentile



Monte Carlo Uncertainty Analysis



Workflow flexibility

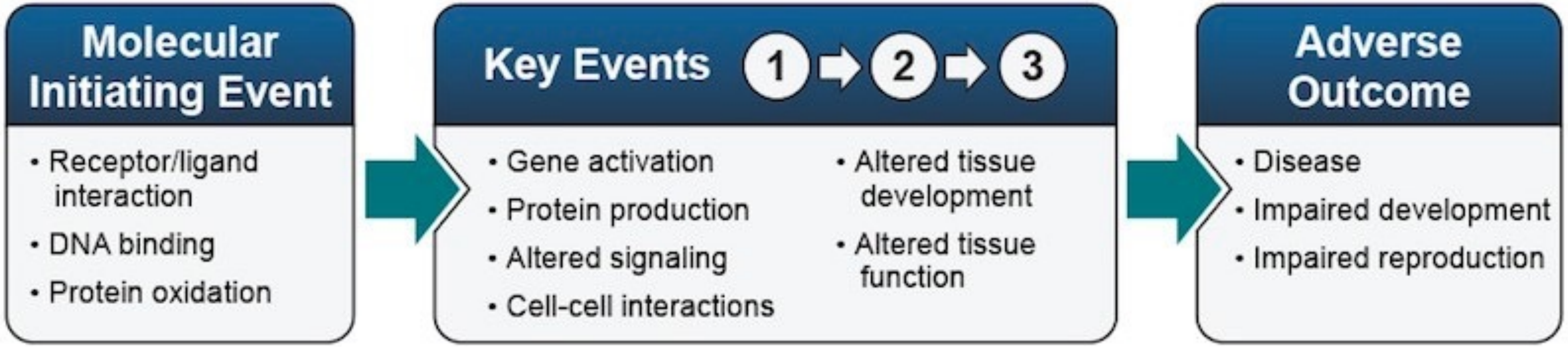
Table 2
Summary of flexibilities in different workflow steps to design a fit-for-purpose geospatial risk assessment of exposure to environmental chemical mixtures via a common molecular target.

Workflow steps	Possible variations	Details
Geographic extent	Local, Regional, National	- Selected based on available geospatial data and region of interest
Molecular target	Assay system	- Selected based on the molecular target, system, or adverse outcome pathways of interest - Selection constrained based on overlap with relevant and available external exposure data - Alternatively, this can be selected to match an apical outcome of interest
External exposure	Geospatial model Environmental measurements	- Selected based on available geospatial data
Route of exposure/internal concentration	Population parameters Route of exposure Internal exposure calculation Human biomonitoring data	- The route of exposure (e.g., oral, dermal, inhalation) and population (e.g., adults vs. children) of interest can be selected, and internal concentrations can be calculated based on equations specific to that population using the US EPA Exposure Factors Handbook (U.S. EPA, 2011) - Exposure factors like absorption can be taken into consideration at this step - Alternatively, geotagged biomonitoring data can be used instead of estimates

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
- Future 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 for improved chemical risk assessment

AOP



Thank you

Questions

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