NTP
National Toxicology Program

Toxicokinetic and Toxicological Based Geospatial Risk Mapping

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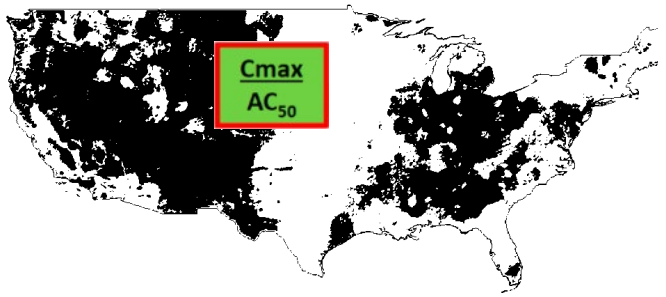
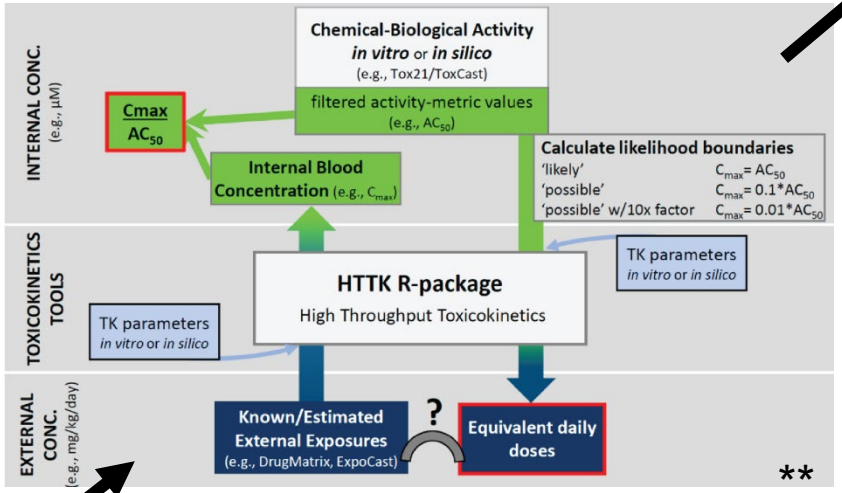
Translation of Toxicological Results

Toxicological-based Risk Assessment provides dose-response relationships and mechanistic understandings, but **does not allow for population impact or burden of disease assessments**

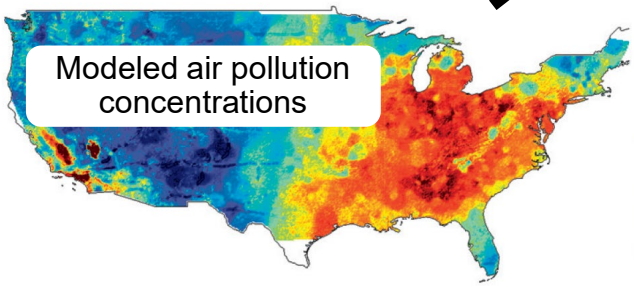
Human context from toxicological data

Risk characterization mapping with direct links to biological activity





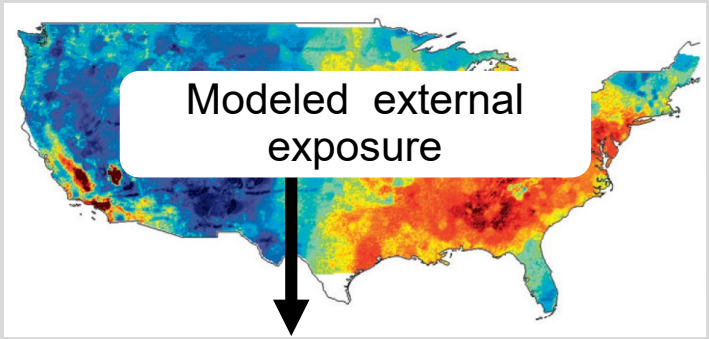
Sipes et al. An Intuitive Approach for Predicting Potential Human Health Risk with the Tox21 10k Library. *Environ. Sci. Technol.* **2017, *51* (18), 786–796.



Tox-Risk-Mapping

Toxicokinetic and Toxicological-based Risk Mapping

- ✓ Provides geographic translation from toxicological dose-response studies
- ✓ Risk characterization from toxicological data instead of epidemiological
- ✓ Flexible framework can include various targets (e.g. blood, liver, lung, etc.) and in-vivo (RfC) or in-vitro (C_{max}) results



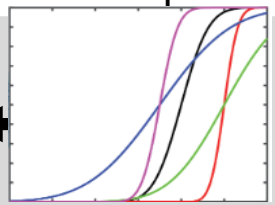
External Exposure

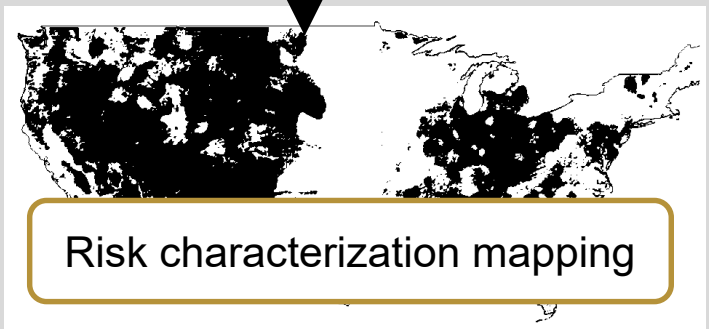
Toxicokinetic modeling

Internal Dose

$$\frac{dose}{dose/response}$$

In-vitro/In-vivo dose response





Data Needs

Spatiotemporal Exposure Predictions

- Ambient monitoring networks
- Geospatial model output

Spatiotemporal population characteristics

- Census Data
- Exposure Factors Handbook

Toxicokinetic information

- Toxicokinetic models such as httk
- TK parameters (e.g. intrinsic metabolic clearance)

Toxicological Dose-Response

- In vitro
- In vivo
- In-house experiments

Risk Assessment Discussion

Many ways to define risk

	Dose-Response	Health Impact
Epidemiological	• Odds Ratio • Relative Risk	• DALY • AF
Toxicological	• NOAEL • LOAEL • AC_{50}, EC_{50}	• RfD • RfC • HQ, RQ

Do we really need another risk assessment definition?

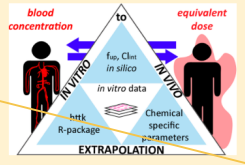
What Tox-Risk-Mapping Brings

- Spatial and population context
- Utilizes toxicological as opposed to epidemiological dose-response studies
  - [Number of tox dose-response substances] >> [Number of epi dose-response substances]
- Flexibility in dose-response type: *in vivo* vs *in vitro*
  - *In vitro* → any harm
  - *In vivo* → complex whole body disease
- Flexibility in biological target: blood plasma, liver, heart, etc.

Risk Assessment Discussion

Analogous to Pharma

ABSTRACT: In vitro–in vivo extrapolation (IVIVE) analyses translating high-throughput screening (HTS) data to human relevance have been limited. This study represents the first report applying IVIVE approaches and exposure comparisons using the entirety of the Tox21 federal collaboration chemical screening data, incorporating assay response efficacy and quality of concentration–response fits, and providing quantitative anchoring to first address the likelihood of human in vivo interactions with Tox21 compounds. This likelihood was assessed using a maximum blood concentration to in vitro response ratio approach (C_{max}/AC_{50}), analogous to decision-making methods for clinical drug–drug interactions. Fraction unbound in plasma (f_{up}) and intrinsic hepatic clearance (Cl_{int}) parameters were estimated in silico and incorporated in a three-compartment toxicokinetic (TK) model to first predict C_{max} for in vivo corroboration using therapeutic scenarios. Toward lower exposure scenarios, 36 compounds of 3925 unique chemicals with curated activity in the HTS data using high-quality dose–response model fits and ≥40% efficacy gave "possible" human in vivo interaction likelihoods lower than median human exposures predicted in the United States Environmental Protection Agency's ExpoCast program. A publicly available web application has been designed to provide all Tox21–ToxCast dose-likelihood predictions. Overall, this approach provides an intuitive framework to relate in vitro toxicology data rapidly and quantitatively to exposures using either in vitro or in silico derived TK parameters and can be thought of as an important step toward estimating plausible biological interactions in a high-throughput risk-assessment framework.



> "This likelihood was assessed using a maximum blood concentration to in vitro response ratio approach (C_{max}/AC_{50}), analogous to decision-making methods for clinical drug-drug interactions."

Tox-Risk-Mapping Options

- **Hazard or Risk Quotient** Analogs [Exposure / Toxicity]
  - e.g. C_{max}/AC_{50}
  - Safe < 1 < Dangerous
- **Population Impact**
  - [Exposure] x [Tox Dose-Response] x [Population]
- **Burden of Disease**
  - Attributable Fraction
  - DALY

Summary

Toxicokinetic and Toxicological Based Risk Mapping =
Tox-Risk-Mapping

Flexible approach that allows geospatial mapping of risk based on toxicological dose-response and risk estimates

Acknowledgements

- SACATM members
- SACATM organizers
- DNTP staff
  - Brian Berridge
  - Nisha Sipes

Thank you!