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Modeling Exposure to Chemicals in Indoor Air

Emerging Science on Indoor Chemistry
A Virtual Information-Gathering Workshop

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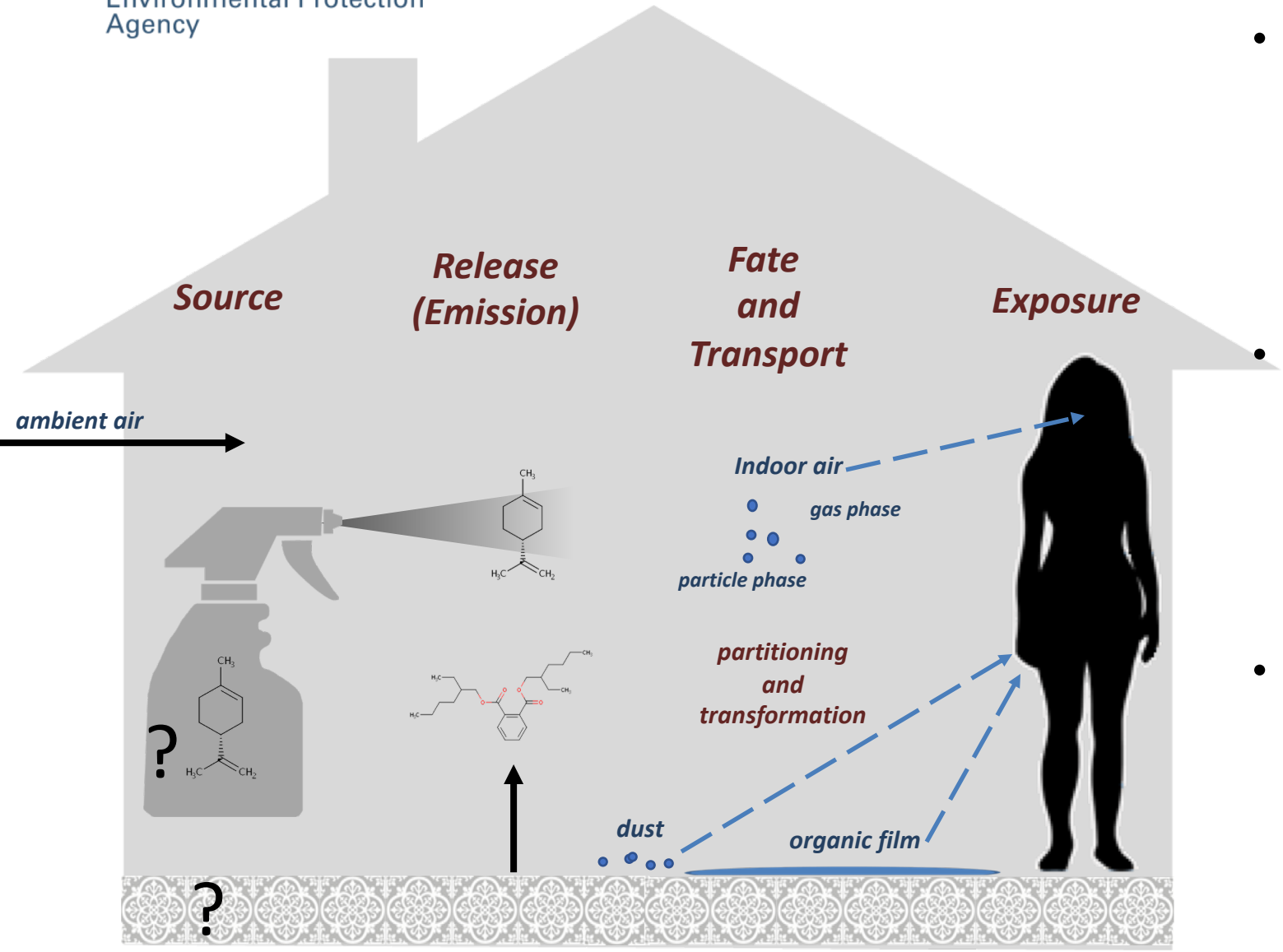
Overview

- Modeling exposures in the indoor (near-field) environment
  - Challenges
  - Strategies and recent advances
- From exposure to risk
  - Integrating near-field exposure predictions with other pathways
  - Tools for predicting internal exposures
  - Risk-based prioritization

From Source to Exposure Indoors



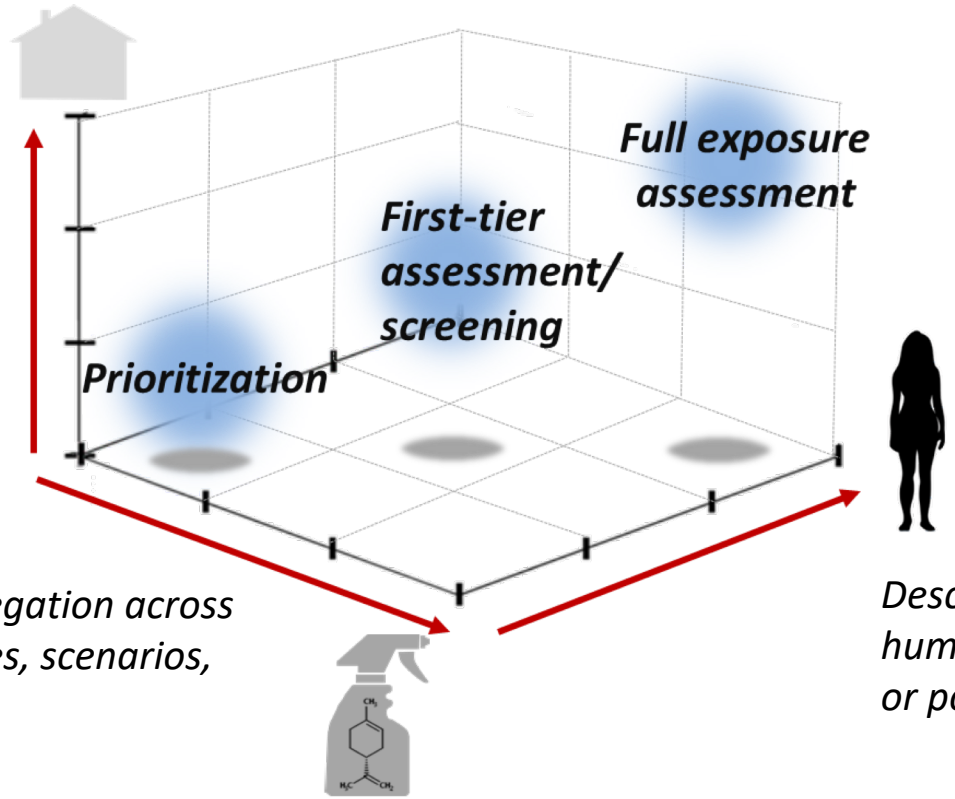
- Exposure is the ***contact*** between a receptor (human) and a chemical (carried by an environmental medium)
  - Many exposure metrics that describe the ***duration***, ***intensity, and pattern*** of contact
- Modeling exposure requires some estimate of concentrations in indoor media (e.g., air)
  - Function of source, release, and fate and transport (as discussed in many other talks today)
- Exposure is also dependent on ***human behaviors*** and housing characteristics
  - Exposure factors
  - Consumer habits and practices (product use patterns)

Fit-for-Purpose Exposure Modeling Frameworks

United States Environmental Protection Agency

Increasing Complexity

Mechanistic description of the built environment and exposure processes, including temporal variability



Level of aggregation across sources, routes, scenarios, chemicals

Description of human behavior or population

Fit-for-Purpose Exposure Modeling Frameworks

Increasing Complexity

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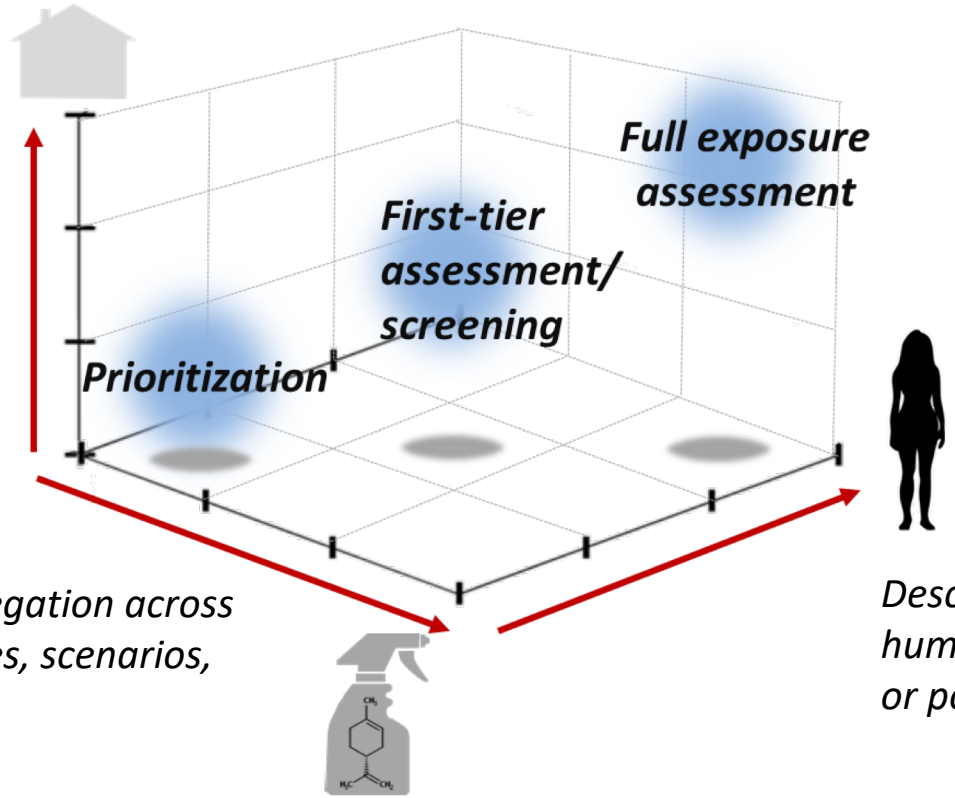

Level of aggregation across sources, routes, scenarios, chemicals

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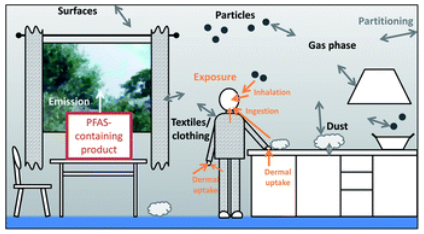
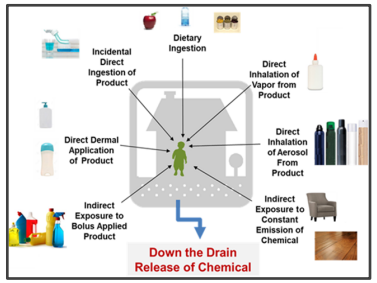
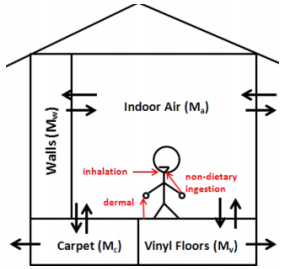


Eichler and Little, 2020



SHEDS-HT, Isaacs et al., 2014

Li et al., 2018



FINE, Shin et al., 2015

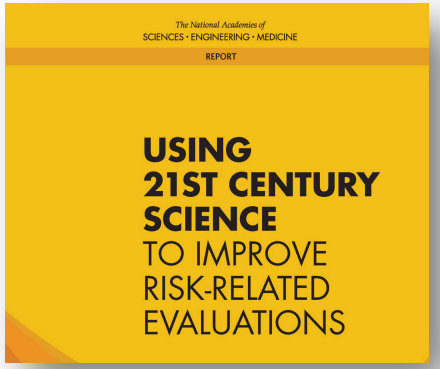
EPA, 2019

- Models of different levels of complexity have **overlapping data needs**
- They also share some **universal challenges**

Challenges and Data Gaps Associated with Modeling Exposure

2012

2017



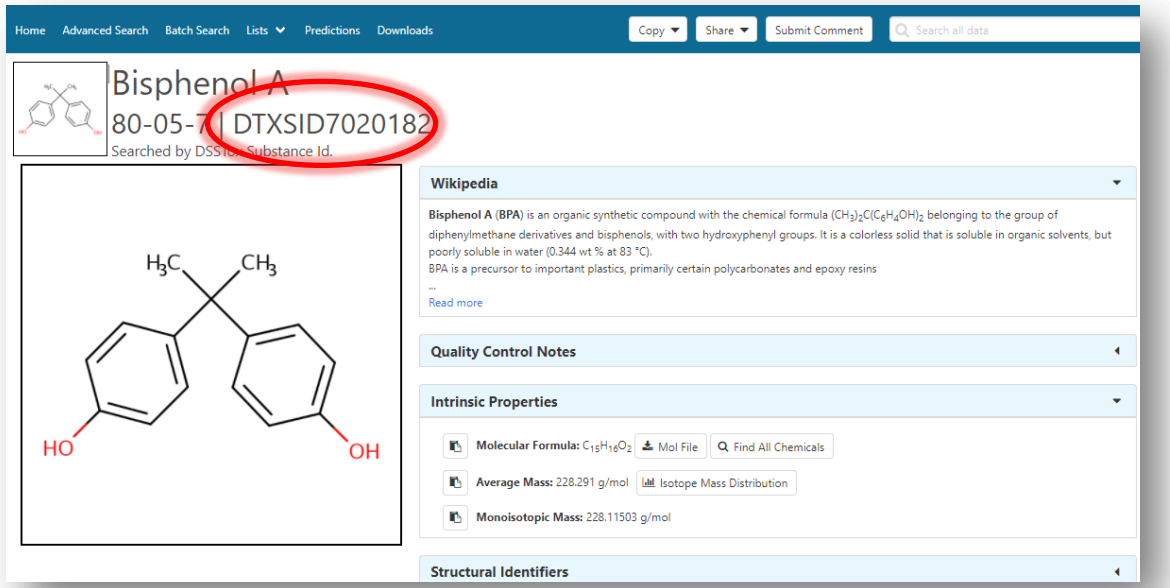
- **What are additional challenges beyond the inherent gaps associated with source, emission, and fate and transport characterization?**
- **Data accessibility**
  - It is difficult to identify existing data relevant to a given exposure scenario
  - NAS 2017: "*...most information is fragmented, incompletely organized, and not readily available or accessible …the full potential of the existing and emerging information for exposure-based and risk-based evaluations cannot be realized.*"
- **Population variability**
  - Human behavior is complex, and surveys and field studies are expensive
  - NAS 2012: Recommendation to "e*xplore options for using data obtained on individuals and populations through market-based and product-use research to improve exposure information*"
- **Mixtures or co-Exposures**
  - NAS 2017: Assessing cumulative exposure and exposure to mixtures is a high-value activity, and "*computational exposure methods will help to identify chemical mixtures to which people are exposed*."
- **Model validation**
  - Data for validating predictions are often limited
  - NAS 2017: *Continued efforts to measure and estimate concentrations in multimedia sources—such as indoor air, indoor surfaces, dust, and consumer products—are required to address uncertainty in near-field exposures and pathways.*

Frameworks for Improving Data Organization and Model Parameterization

4,4'-(Propane-2,2-diyl)diphenol
Phenol, 4,4'-(1-methylethylidene)bis-
80-05-7
BPA
4,4'-Propane-2,2-diyldiphenol
Phenol, 4,4'-(1-methylethylidene)bis-
4-06-00-06717
(4,4'-Dihydroxydiphenyl)dimethylmethane
2,2-Bis(4'-hydroxyphenyl) propane
2,2'-Bis(4-hydroxyphenyl)propane
2,2-BIS-(4-HYDROXY-PHENYL)-PROPANE
2,2-Bis(4-hydroxyphenyl)propane
2,2-Bis(p-hydroxyphenyl)propane
2,2-Di(4-Hydroxyphenyl) Propane
2,2-DI(4-HYDROXYPHENYL)PROPANE
2,2-Di(4-phenylol)propane
4,4'-(1-Methylethylidene)bisphenol
4,4'-Bisphenol A
4,4'-DIHYDROXYPHENYL-2,2-PROPANE
4,4'-isopropilidendifenol
4,4'-Isopropylidendiphenol
4,4'-Isopropylidene bisphenol
4,4-ISOPROPYLIDENE DIPHENYL
4,4'-Isopropylidenebis[phenol]
4,4'-isopropylidenediphenol
4,4'-Methylethylidenebisphenol
Bis(4-hydroxyphenyl)dimethylmethane
Bis(p-hydroxyphenyl)propane

+100 more

https://comptox.epa.gov/dashboard



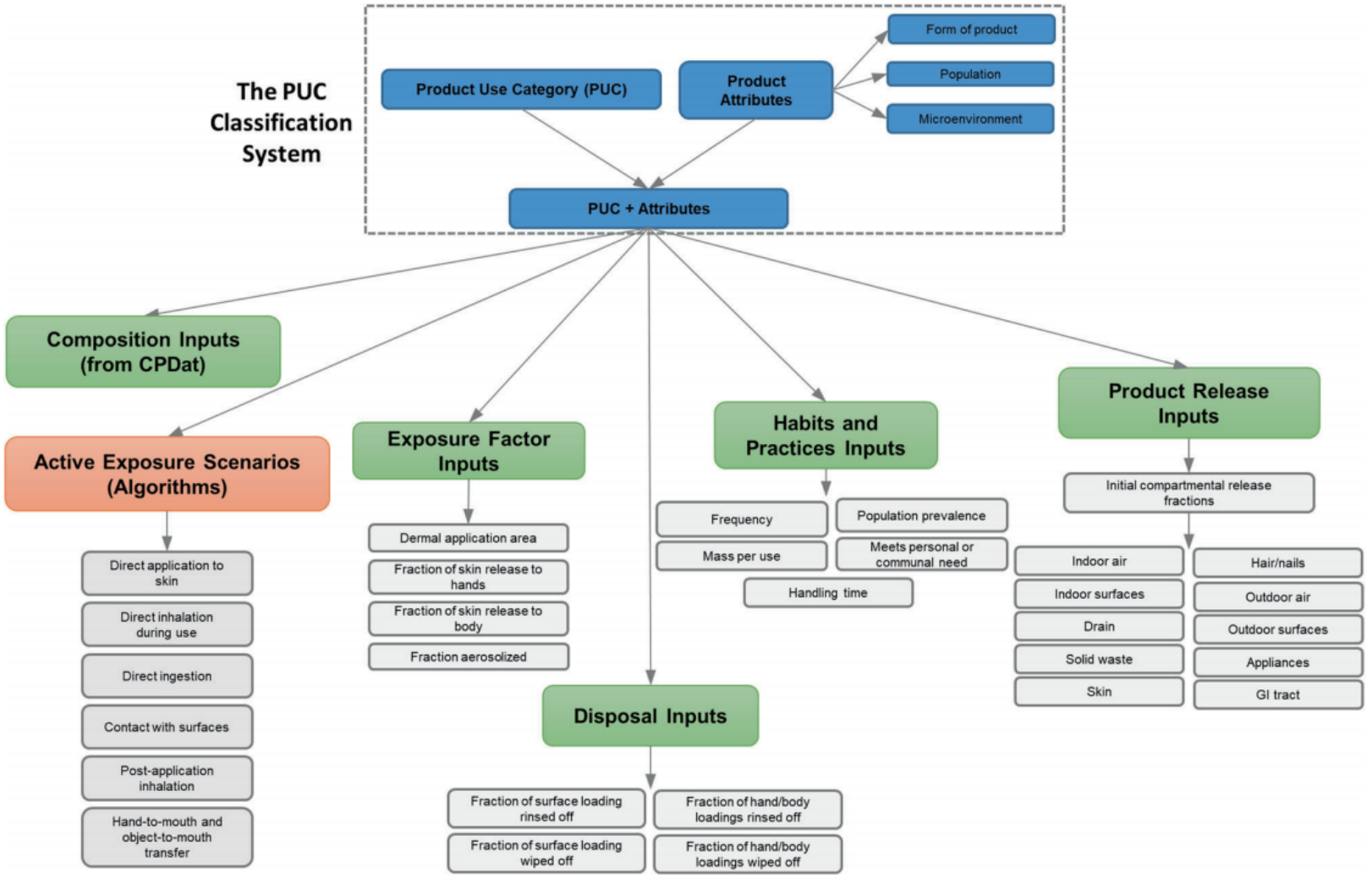
- Chemical frameworks

DSSTox Substance Identifier (DTXSID) ⟷ DSSTox Chemical Identifier (DTXCID)

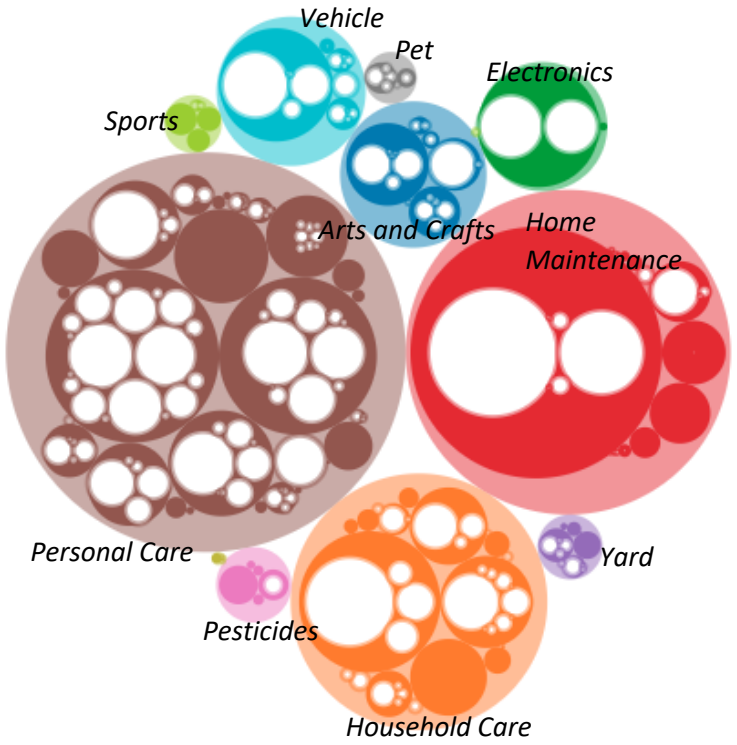
Substance can be any single chemical, mixture, polymer

Unique chemical structure

Frameworks for Improving Data Organization and Model Parameterization



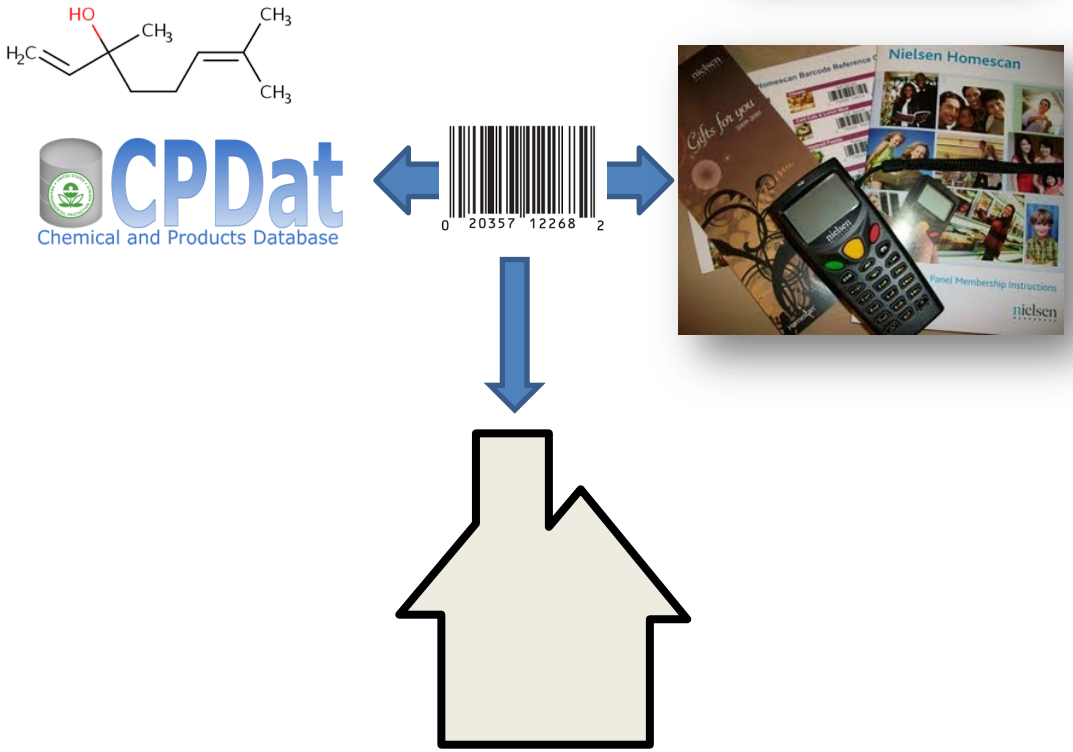
- Chemical frameworks
- Product frameworks



Isaacs et al., 2020

Addressing Challenges with Novel Data Streams

- EPA Office of Research and Development entered a collaboration with the Nielsen company
- Nielsen provided consumer product purchasing data for 60,000 U.S. households from their National Consumer Panel Study ("Homescan")
- Purchasing data were integrated with CPDat ingredient data by Universal Product Code
- Analyses informed **co-exposures** and **demographic differences in habits and practices**



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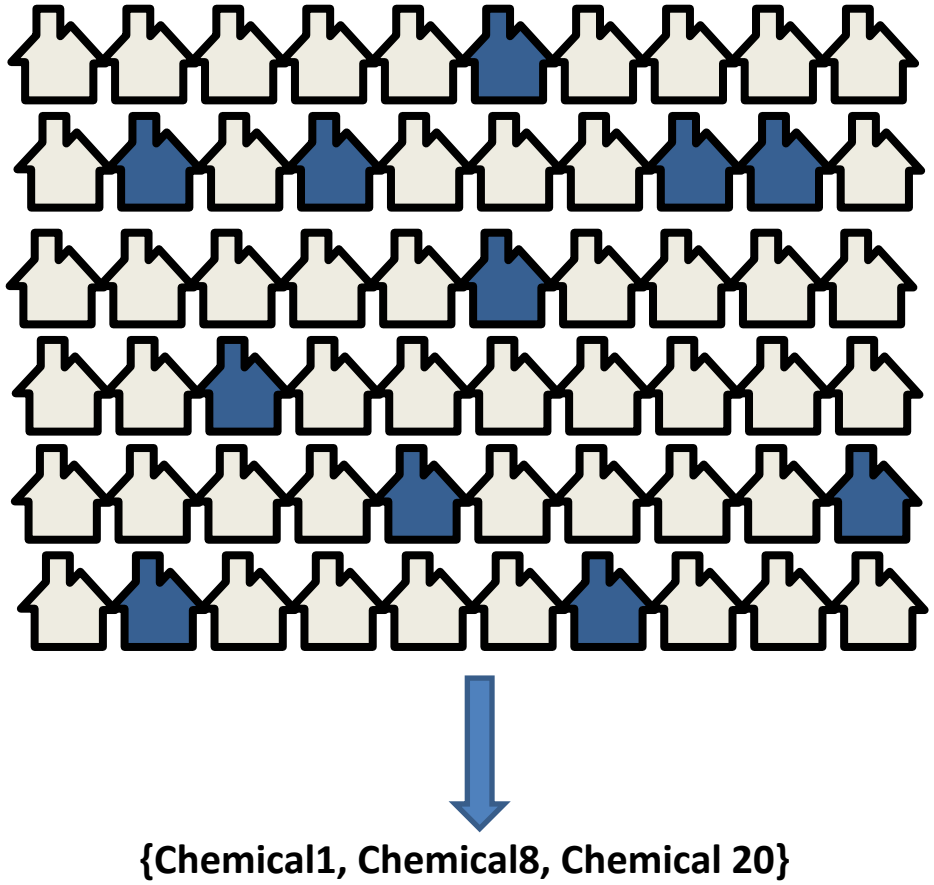
- Purchasing data were integrated with CPDat ingredient data by Universal Product Code
- Analyses informed **co-exposures** and **demographic differences in habits and practices**
- We identified all chemicals being introduced into homes within the same month (and thus had potential co-exposure)
- Used a data-mining technique (Frequent Itemset Mining) to identify frequently-occurring combinations of chemicals across households (broad group of chemicals and potential endocrine-active chemicals)
- Were able to examine impact of demographics (race, household size, income, education) on frequent combinations

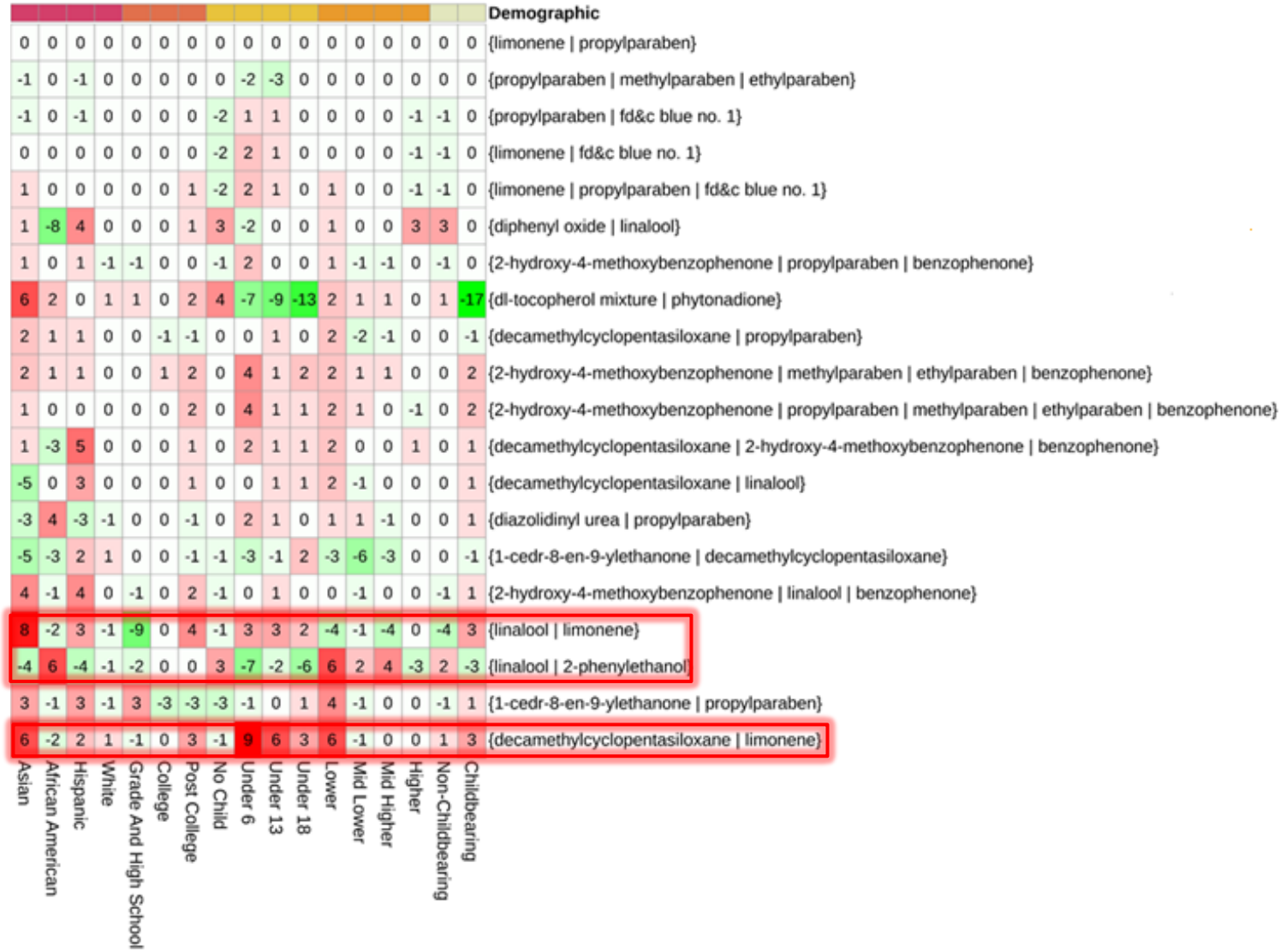


Addressing Challenges with Novel Data Streams

United States Environmental Protection Agency

- Here demographics and chemical sets are clustered to indicate the similarity of rankings of chemical combinations
- Cell color reflects relative prevalence of the chemical combination (rank across all prevalent combinations) for the demographic versus total population
- We could identify patterns in chemical co-occurrence
- Examples of rank departures for certain demographics are highlighted
- Results can be used to prioritize chemicals for testing in *in vitro* systems

Potential Endocrine Active Chemicals

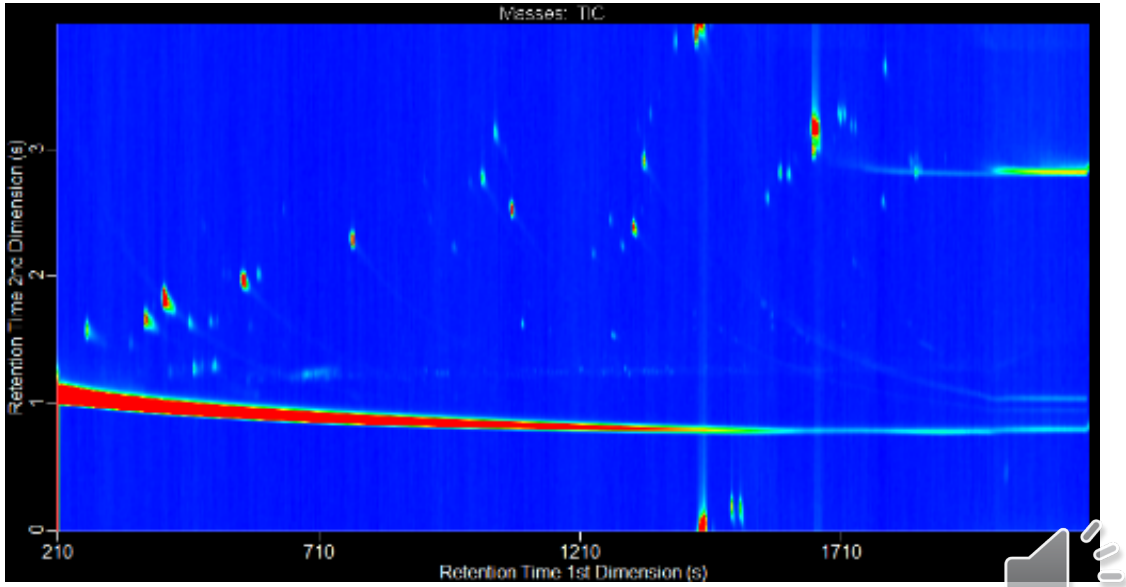


Stanfield et al., submitted

Non-Targeted Analysis: Increasing the Data Available for Model Evaluation

- Targeted Analysis:
  - We know exactly what we're looking for
  - 10s – 100s of chemicals
- Non-Targeted Analysis (NTA) or Suspect Screening Analysis (SSA)
  - We have no preconceived targets
  - 1,000s – 10,000s of chemicals
- Can supplement and evaluate predicted concentrations in sources (e.g., consumer products), in indoor media, and human receptors (e.g., blood concentrations)
  - Occurrence
  - Prioritization of confirmation with standard targeted methods

High Resolution Mass Spectrometry



Published and Ongoing NTA Studies in the ExpoCast Project

United States Environmental Protection Agency

Source and Release

Pilot: 20 Consumer Product Categories

Phillips *et al., Env. Sci. Tech*. 2018

Recycled Consumer Materials

Lowe *et al., Submitted*

Consumer Product Emissions from Different Substrates

Fate and Transport

Residential Air

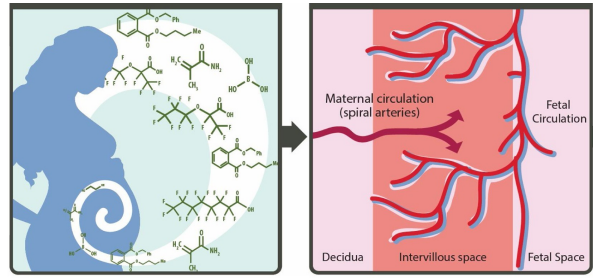
Residential Dust

Rager *et al., Env. Int.,* 2016

Exposure

Pooled Human Blood

Human Placenta

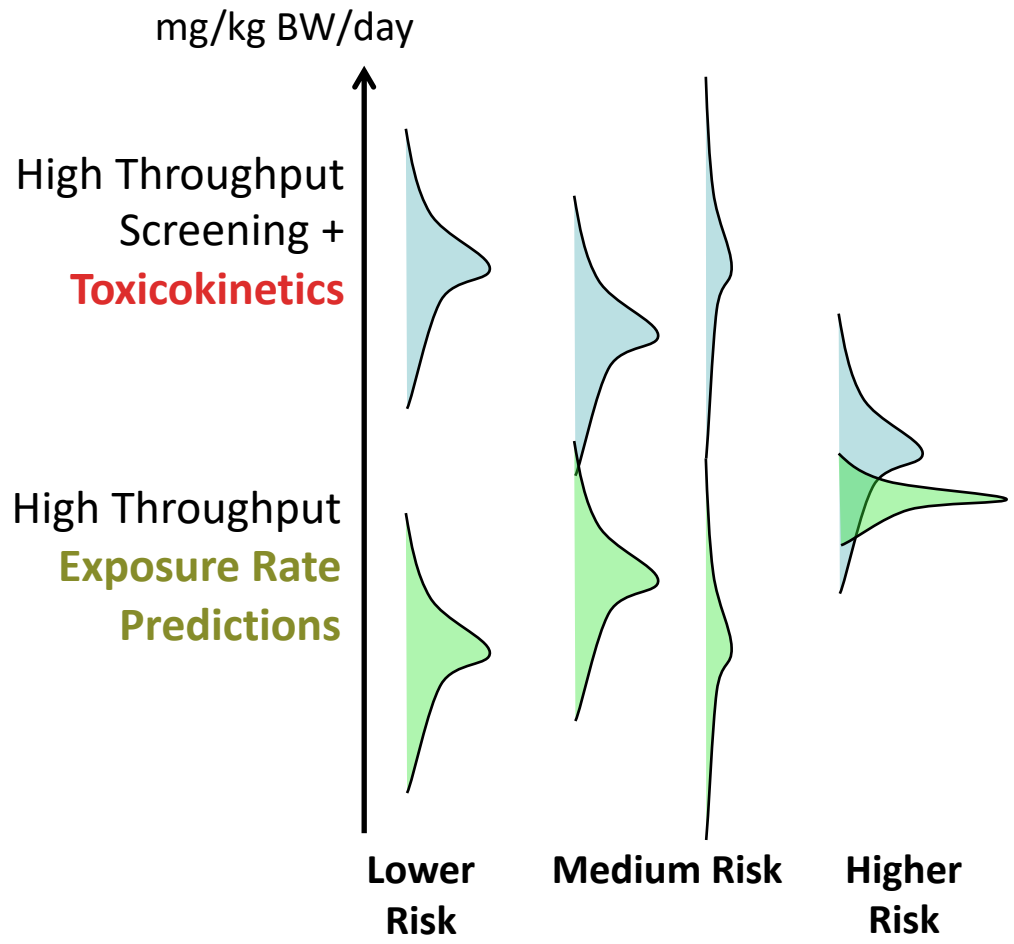


Rager *et al., Repro. Tox. ,* 2020

Emerging Science: How can we **quantify** concentrations of chemicals in media using NTA?

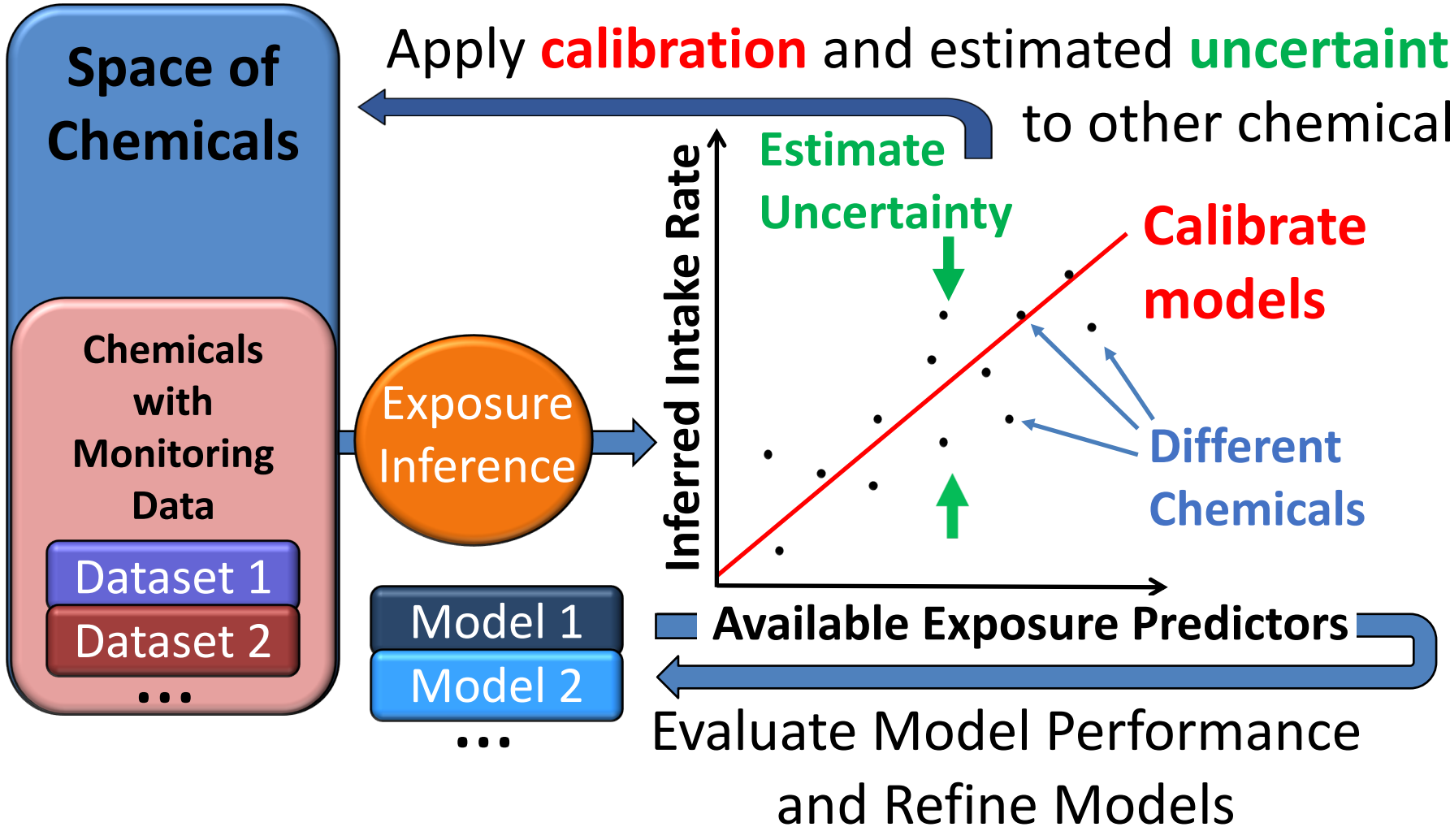
Chemical Risk = Hazard x Toxicokinetics x Exposure

- We have applied the same general philosophy to both **exposure rate prediction** and **toxicokinetics**:
- The fun part of science is building models – quantitative theories of how the world works
- The tough part is evaluating models – we collect evaluation data where we can
- This allows us to estimate uncertainty and potentially extrapolate to new circumstances
- We identify modeling gaps – places where we need new models
- More than anything we identify data gaps – need more data to better evaluate model



Evaluating Exposure Models with the SEEM Framework

- We use Bayesian methods to incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)** (Wambaugh et al., 2013, 2014; Ring et al., 2018)



Wambaugh et al., 2018

SEEM3 Collaboration

Jon Arnot, Deborah H. Bennett, Peter P. Egeghy, Peter Fantke, Lei Huang, Kristin K. Isaacs, Olivier Jolliet, Hyeong-Moo Shin, Katherine A. Phillips, Caroline Ring, R. Woodrow Setzer, John F. Wambaugh, Johnny Westgate

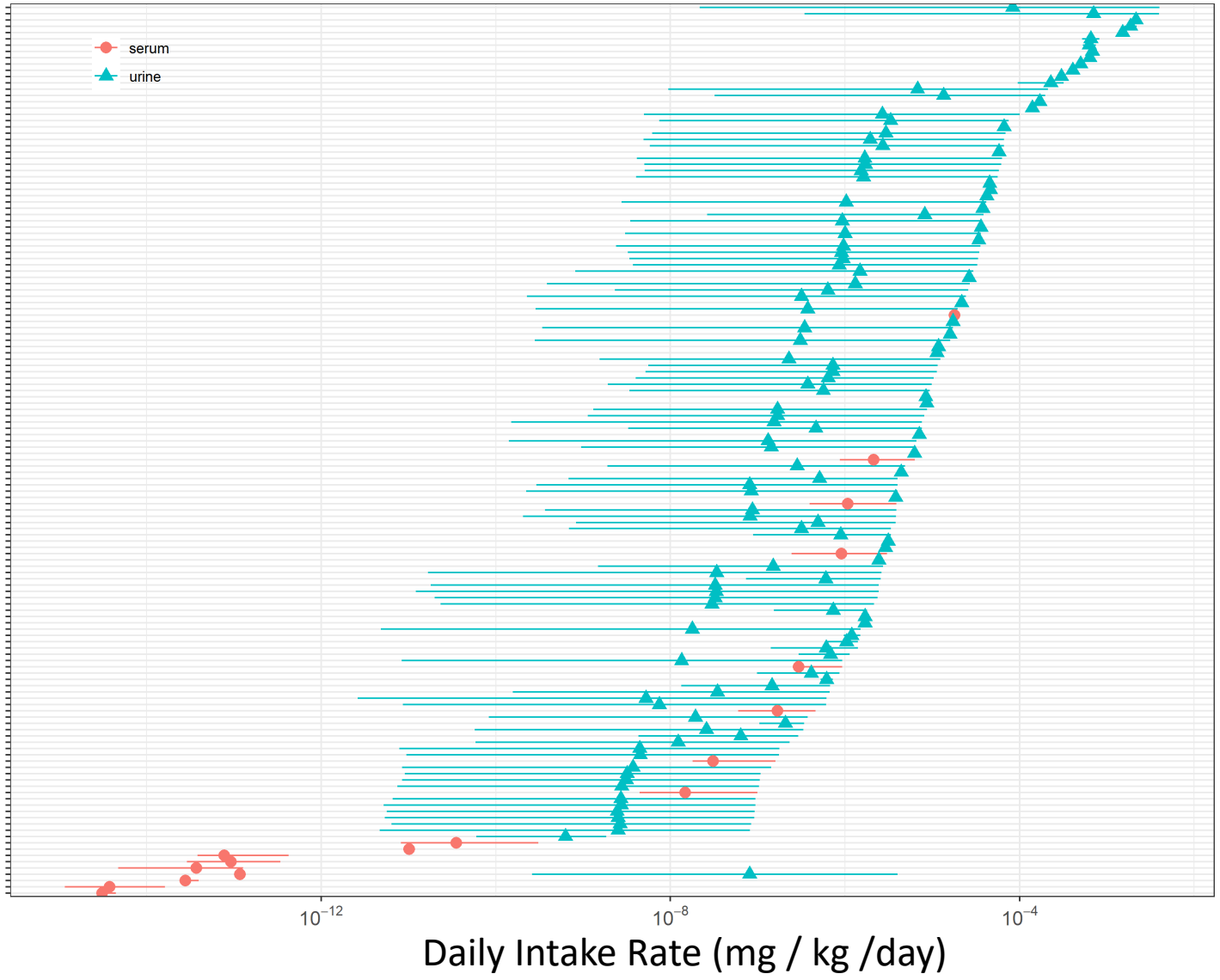
Predictor	Reference(s)	Chemicals Predicted	Pathway(s)
EPA Inventory Update Reporting and Chemical Data Reporting (CDR) (2015)	US EPA (2018)	7856	All
Stockholm Convention of Banned Persistent Organic Pollutants (2017)	Lallas (2001)	248	far field Industrial and Pesticide
EPA Pesticide Reregistration Eligibility Documents (REDs) Exposure Assessments (Through 2015)	Wetmore et al. (2012, 2015)	239	far field Pesticide
United Nations Environment Program and Society for Environmental Toxicology and Chemistry toxicity model (USEtox) Industrial Scenario (2.0)	Rosenbaum et al. (2008)	8167	far field Industrial
USEtox Pesticide Scenario (2.0)	Fantke et al. (2011, 2012, 2016)	940	far field Pesticide
Risk Assessment IDentification And Ranking (RAIDAR) far field (2.02)	Arnot et al. (2008)	8167	far field Pesticide
EPA Stochastic Human Exposure Dose Simulator High Throughput (SHEDS-HT) near field Direct (2017)	Isaacs (2017)	7511	far field Industrial and Pesticide
SHEDS-HT near field Indirect (2017)	Isaacs (2017)	1119	Residential
Fugacity-based INdoor Exposure (FINE) (2017)	Bennett et al. (2004), Shin et al. (2012)	645	Residential
RAIDAR-ICE near field (0.803)	Arnot et al., (2014), Zhang et al. (2014)	1221	Residential
USEtox Residential Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016,2017)	615	Residential
USEtox Dietary Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016), Ernstoff et al. (2017)	8167	Dietary

Ring et al., 2018

Inferred Exposure Rates from CDC NHANES

- Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) provides an important tool for monitoring public health

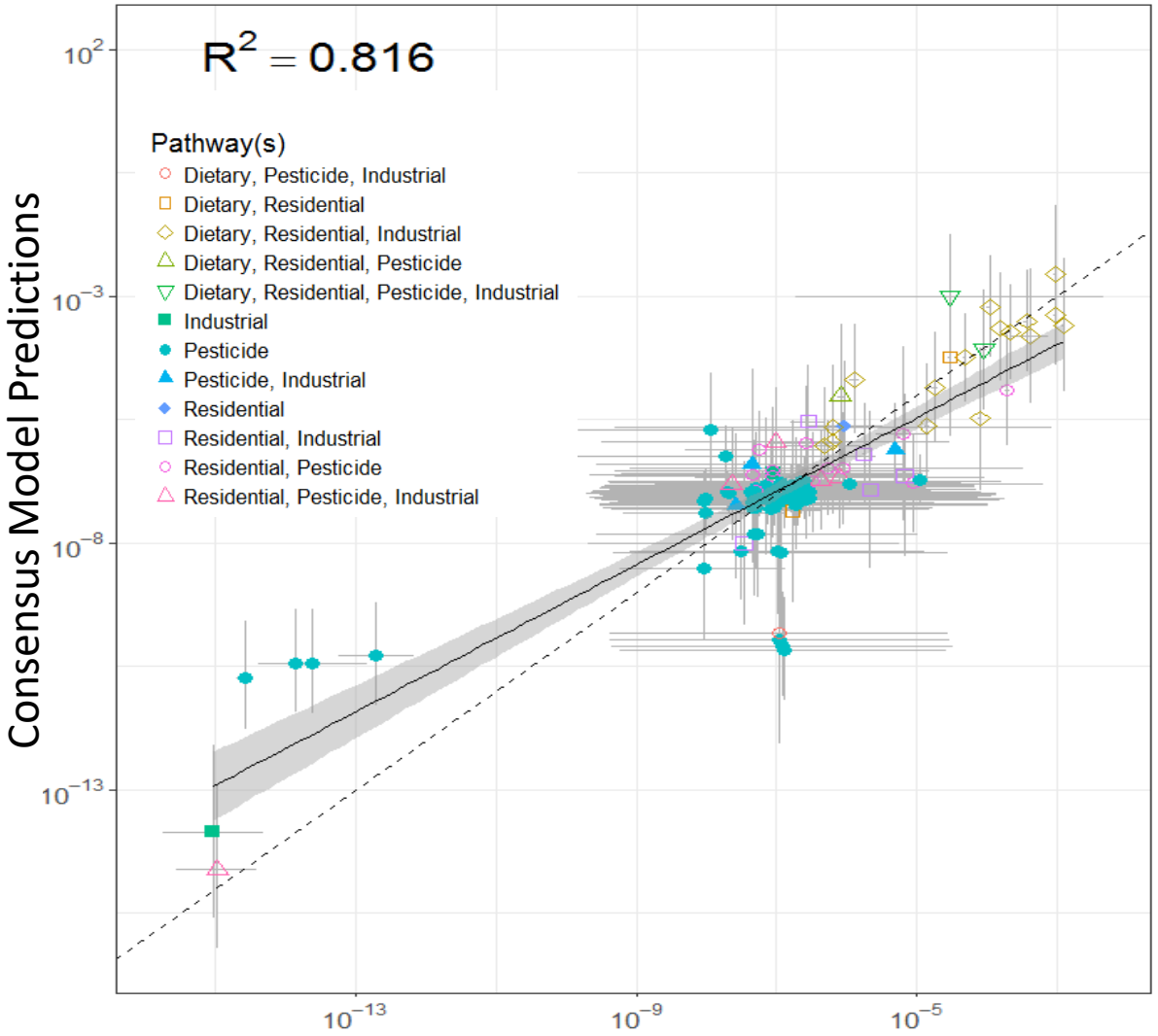
- Large, ongoing CDC survey of US population: demographic, body measures, medical exam, biomonitoring (health and exposure), …



National Health and Nutrition Examination Survey

Work by Miyuki Breen and Zach Stanfield (Breen et al. and Stanfield et al. both in preparation)

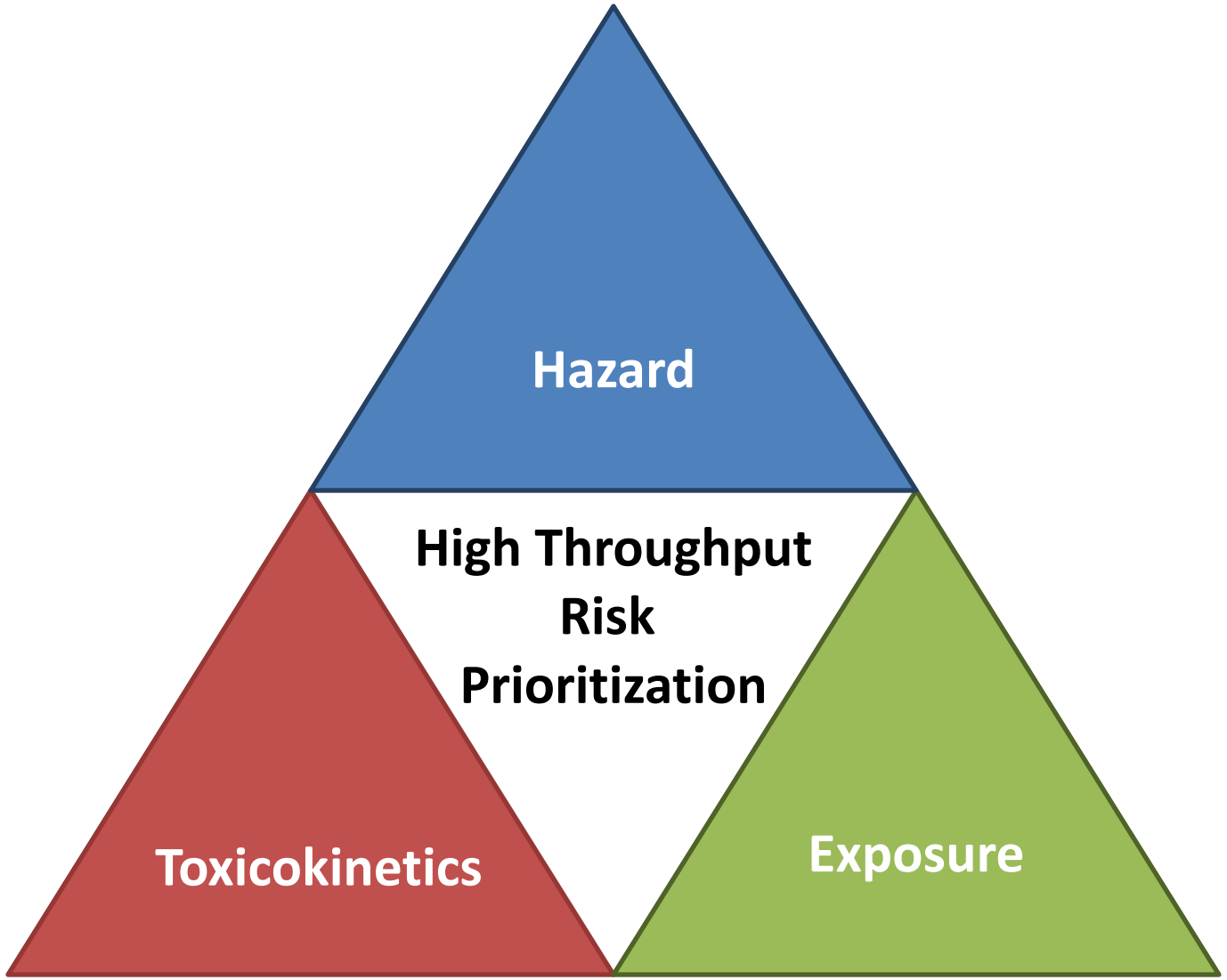
SEEM3: Pathway-Based Consensus Modeling



- SEEM3 consensus model provides estimates of human median intake rate (mg/kg/day) for nearly 500,000 chemicals via the CompTox Chemicals Dashboard (http://comptox.epa.gov/dashboard)
- SEEM3 first predicts relevant exposure pathways from chemical structure – model predictions are then weighted according to the models' abilities to explain NHANES data
- We rely on pathway determinations from Cpdat
- We rely on NHANES biomonitoring data
  - 2014 FIFRA Scientific Advisory Panel identified need for broader sets of evaluation data

Ring et al., 2018

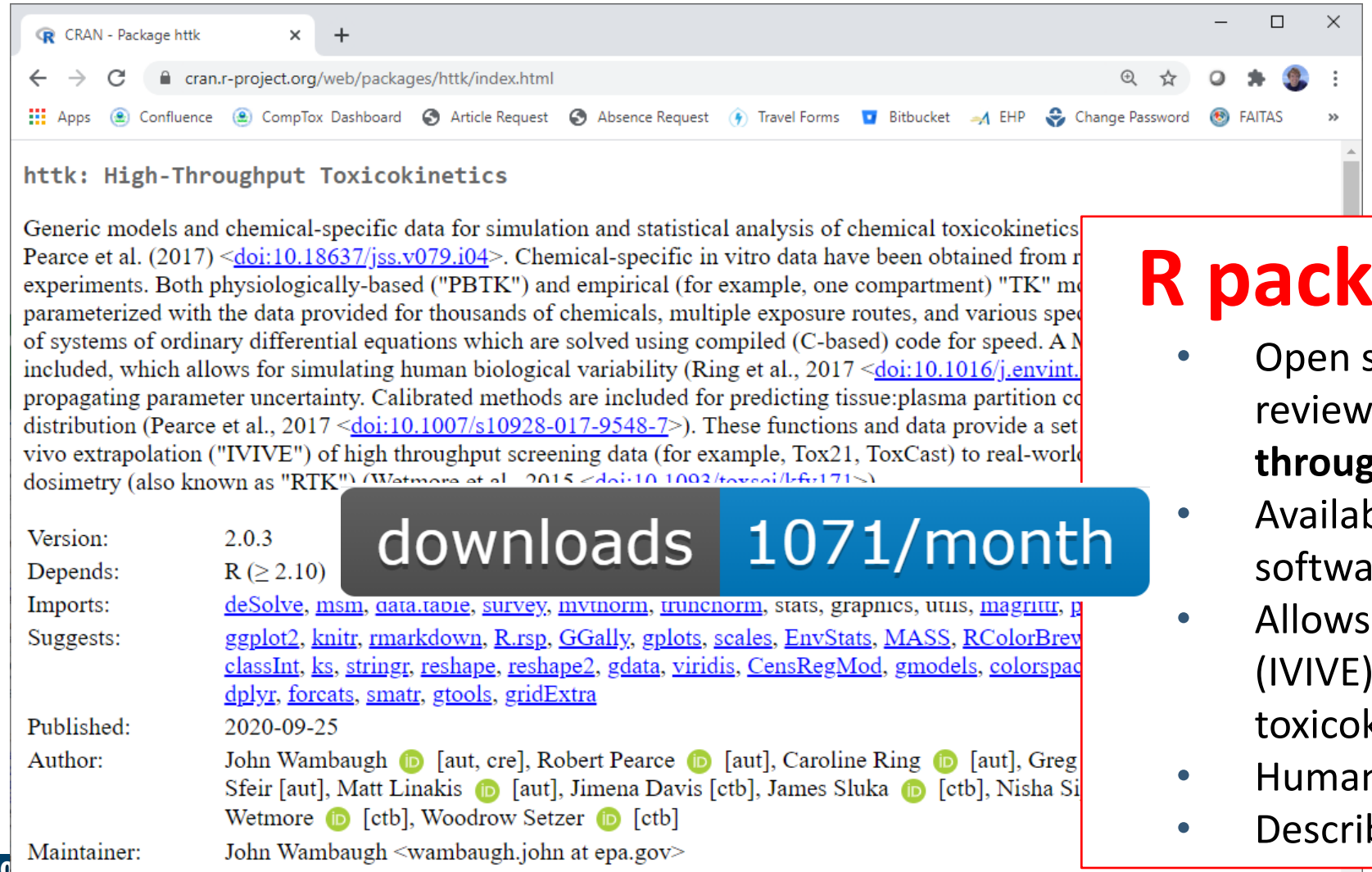
Risk = Hazard x Toxicokinetics x Exposure



NRC (1983)

Open-Source Tools and Data for HTTK

https://CRAN.R-project.org/package=httk



downloads 1071/month

R package "httk"

- Open source, transparent, and peer-reviewed tools and data for **high throughput toxicokinetics (httk)**
- Available publicly for free statistical software R
- Allows *in vitro-in vivo* extrapolation (IVIVE) and physiologically-based toxicokinetics (PBTK)
- Human-specific data for 987 chemicals
- Described in Pearce et al. (2017)

In Vivo TK Database

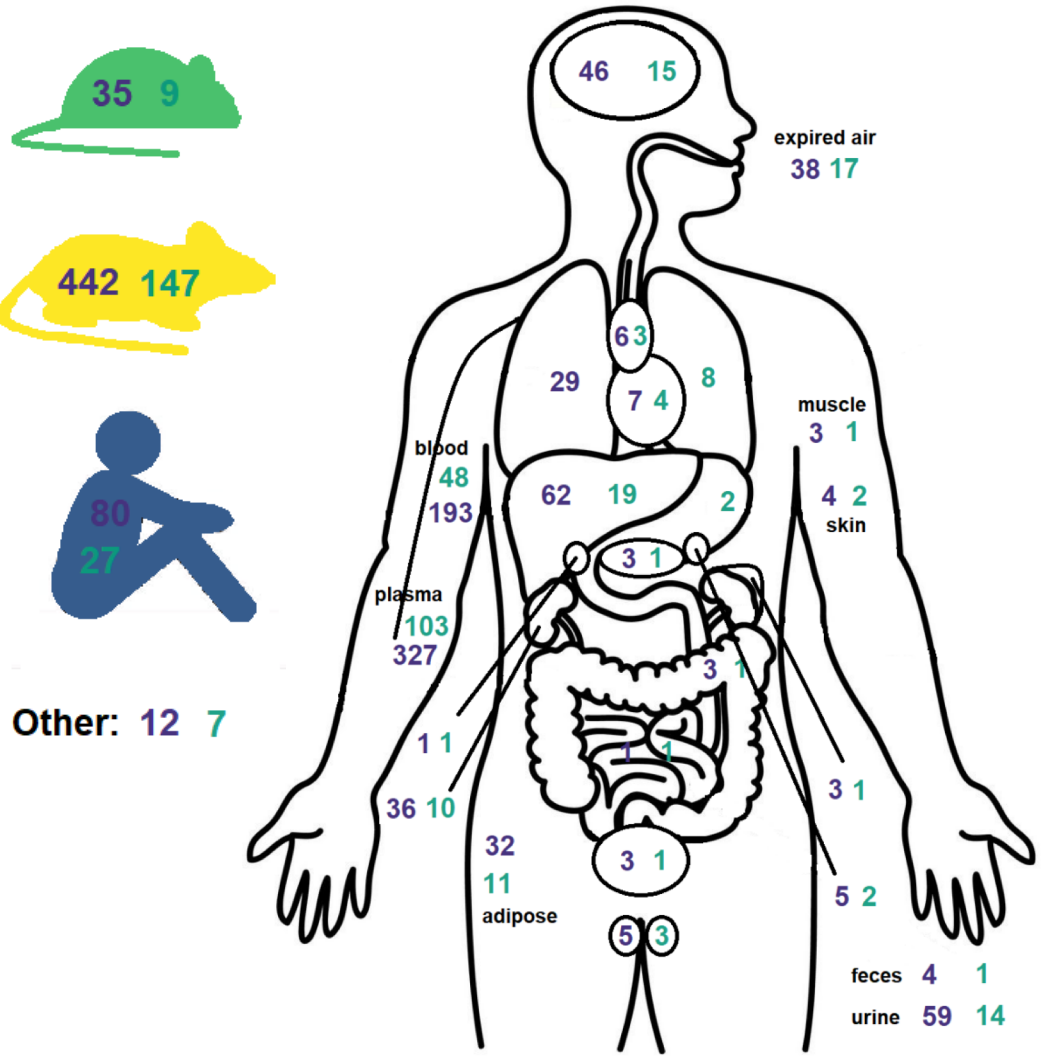
https://github.com/USEPA/CompTox-PK-CvTdb

- EPA has developed a **public database** of **concentration vs. time data** for building, calibrating, and evaluating TK models

- Curation and development ongoing, but to date includes:
  - 198 analytes (EPA, National Toxicology Program, literature)
  - Routes: Intravenous, dermal, oral, sub-cutaneous, and inhalation exposure

- Standardized, open source curve fitting software invivoPKfit used to calibrate models to all data:

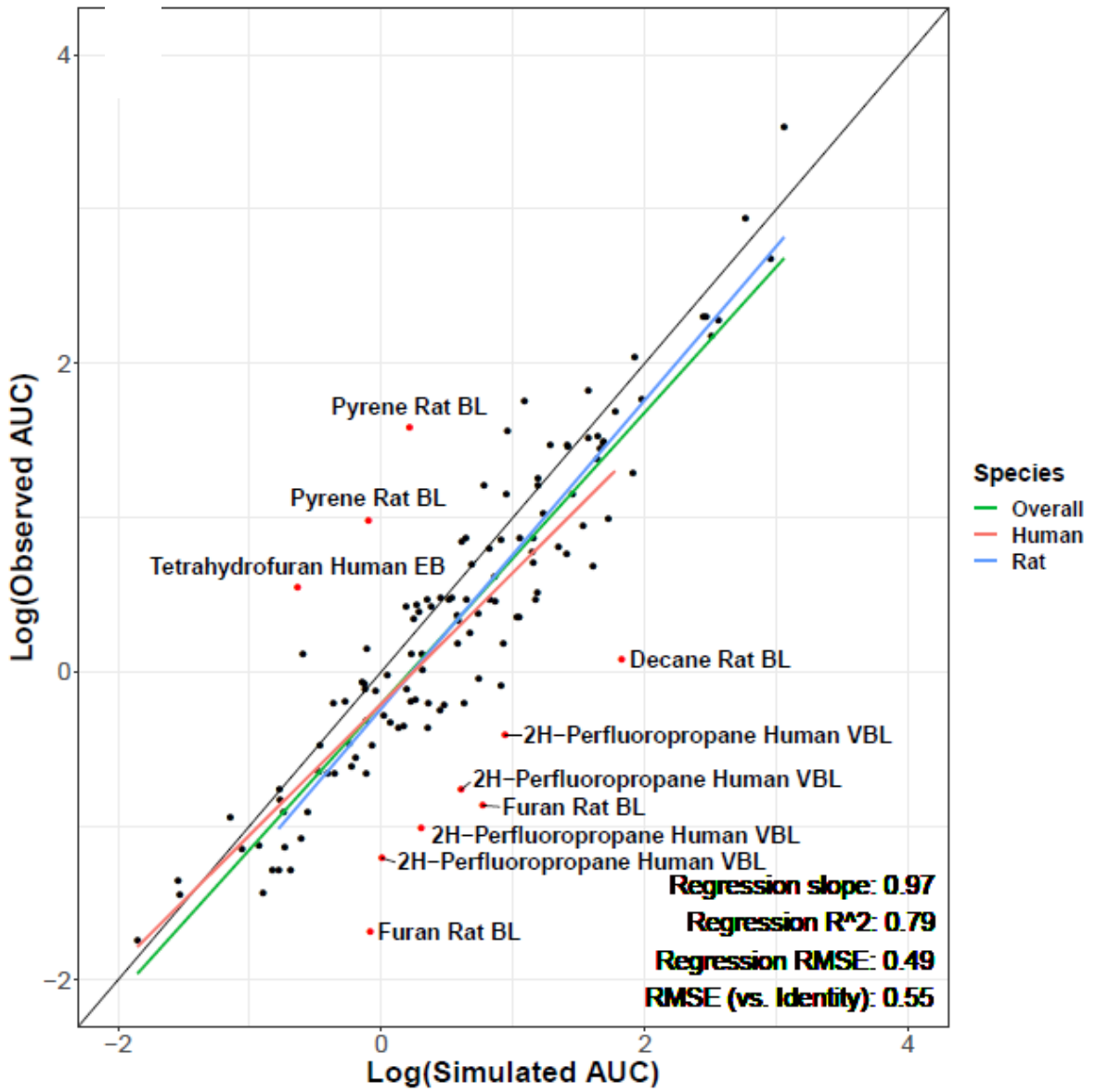
  https://github.com/USEPA/CompTox-ExpoCast-invivoPKfit



Sayre et al. (2020)

Developing Models with the CvT Database

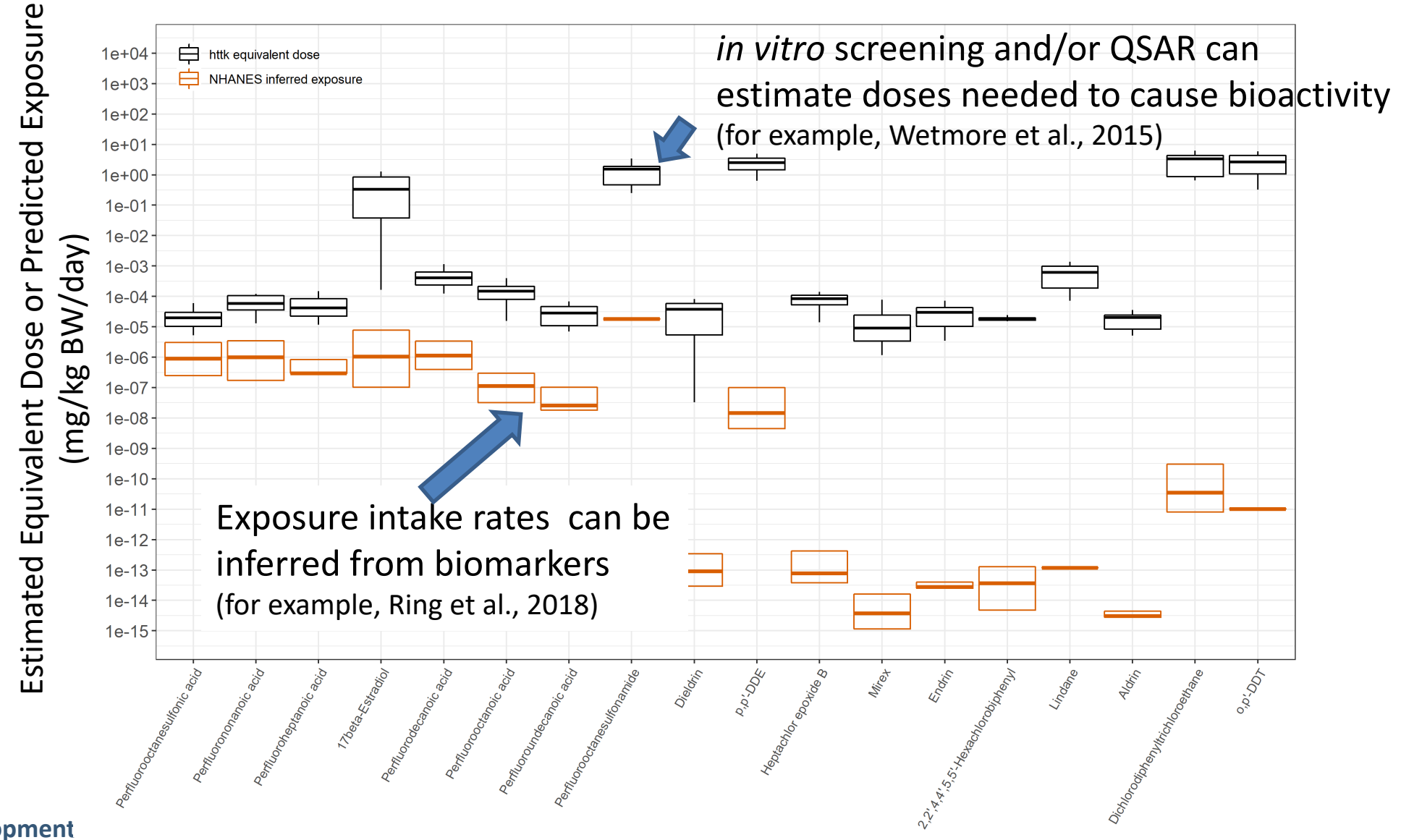
- USAF and EPA developed generic gas inhalation physiologically-based toxicokinetic (PBTK) model
- Evaluated HTTK with CvTdb: 142 exposure scenarios across 41 volatile organic chemicals were modeled and compared to published *in vivo* data for humans and rat
- Overall RMSE was 0.69, R^2 was 0.54 for full concentration time-course across all chemicals and both species
- R^2 was 0.69 for predicting peak concentration
- R^2 was 0.79 for predicting time integrated plasma concentration (Area Under the Curve, AUC)



Linakis et al. (2020)

Risk-based Chemical Prioritization

- We can use HT-PBPTK gas inhalation model to infer exposures consistent with NHANES data for volatile chemicals
- Can compare those intake rates with doses predicted to cause toxicity:
- Bioactivity:Exposure Ratio (BER) allows risk-based prioritization



Summary

- We need to know chemical hazard, exposure, and toxicokinetics to assess risk posed to the public health
- At EPA we build consensus models and evaluate them to estimate uncertainty – relies on available data
- Data Needs for Exposure:
  - Expanded monitoring data
    - NTA will need for semi-quantitative methods
    - We must also catalog the chemicals that should be present
  - Models for formulation-dependent emission rates from household products
- Data needs for Toxicokinetics:
  - USAF and EPA developing aerosol exposure PBTK model but we need a particle dissolution model
  - Need additional chemical concentration vs. time in tissue (CvT) data – studies exist in the literature but must be made machine-readable
- All models to date focus on chemicals with well-defined structures
  - What do we do about chemicals of unknown, variable composition, or biologicals (UBCBs)?

ExpoCast Project (Exposure Forecasting)

Center for Computational Toxicology and Exposure

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United States Environmental Protection Agency

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