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RED Project:
High Throughput Toxicokinetics (HTTK) and Systematic Empirical Evaluation of Exposure (SEEM)

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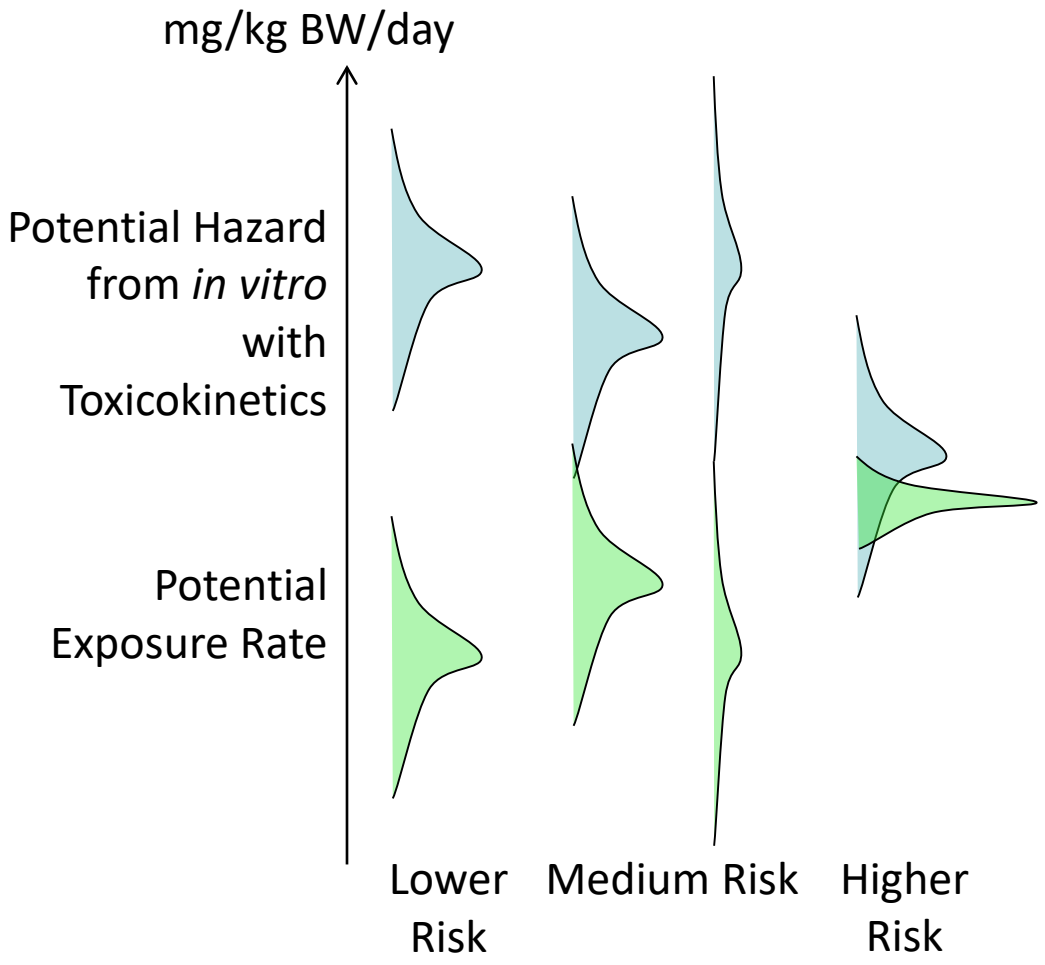
High-Throughput Risk Prioritization

The National Research Council (1983) identified chemical risk as a function of both inherent hazard and exposure

In order to address thousands of chemicals, we need to use "high throughput methods" to prioritize those chemicals most worthy of additional study

High throughput risk prioritization needs:

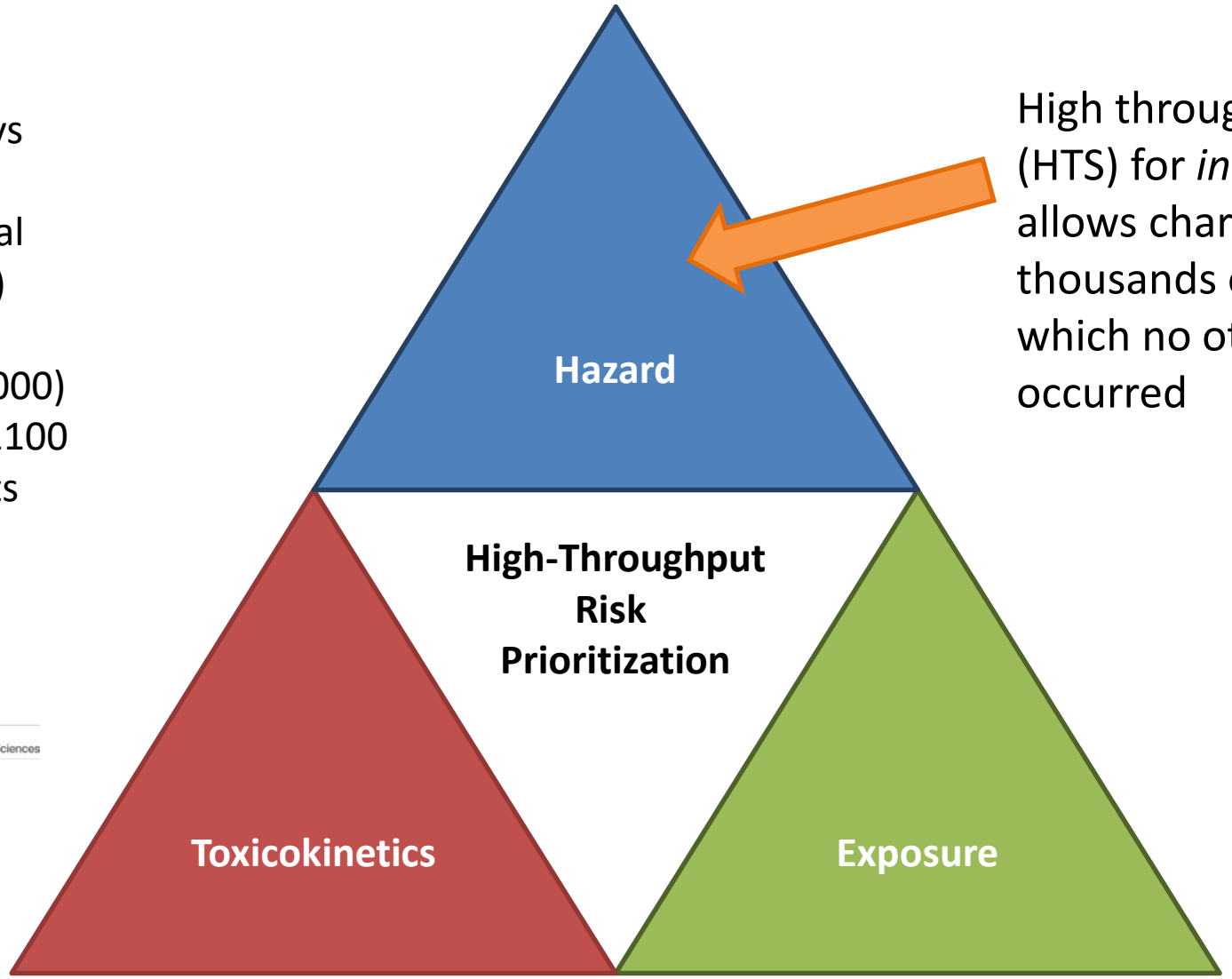
1. high throughput **hazard** characterization
2. high throughput **exposure** forecasts
3. high throughput **toxicokinetics** (*i.e.*, dosimetry)



High-Throughput Risk Prioritization

Tox21: Examining >8,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)

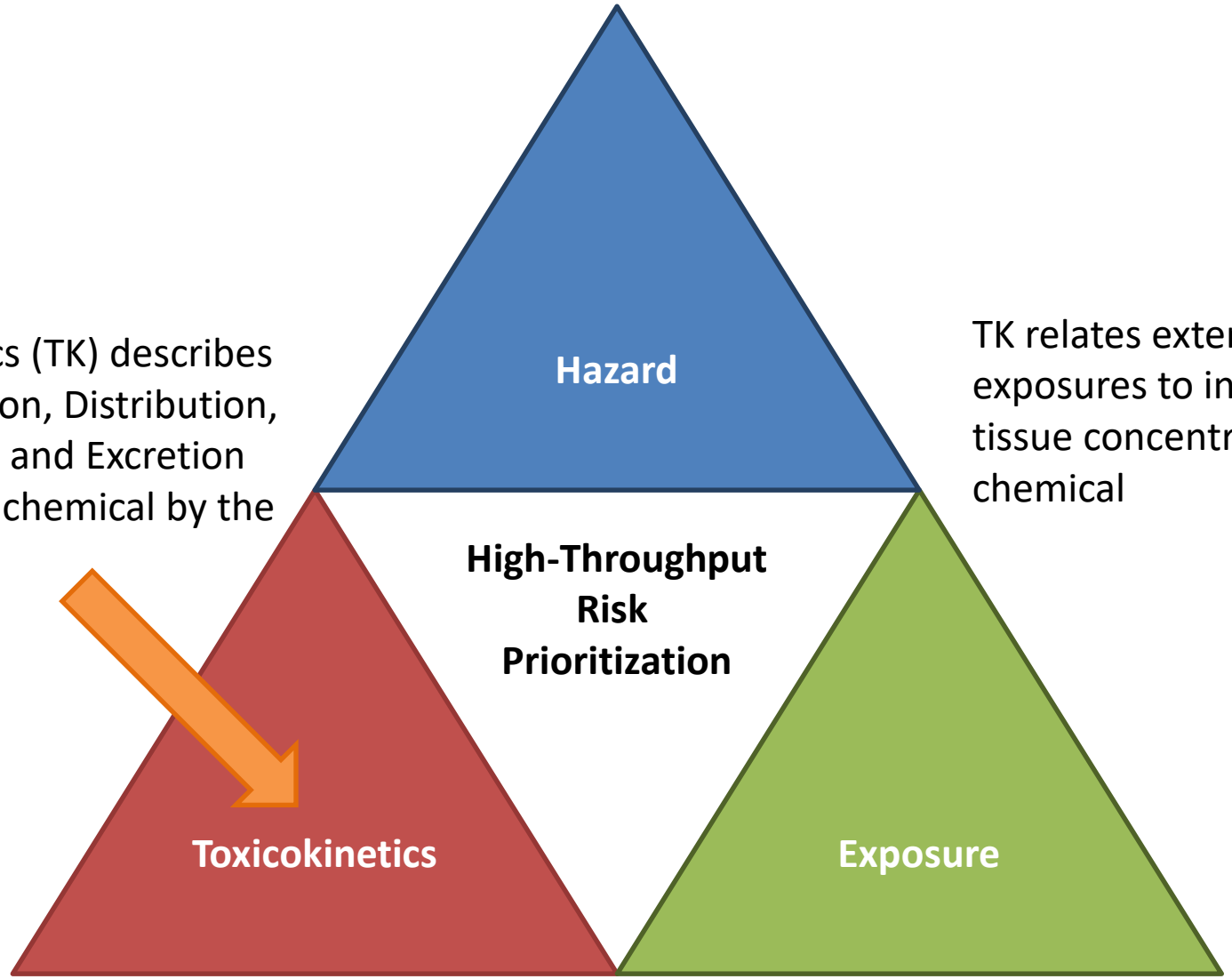
ToxCast: For a subset (>2000) of Tox21 chemicals ran >1100 additional assay endpoints (Kavlock *et al.*, 2012)



High throughput screening (HTS) for *in vitro* bioactivity allows characterization of thousands of chemicals for which no other testing has occurred

High Throughput Toxicokinetics (HTTK)

Toxicokinetics (TK) describes the Absorption, Distribution, Metabolism, and Excretion (ADME) of a chemical by the body



TK relates external exposures to internal tissue concentrations of chemical

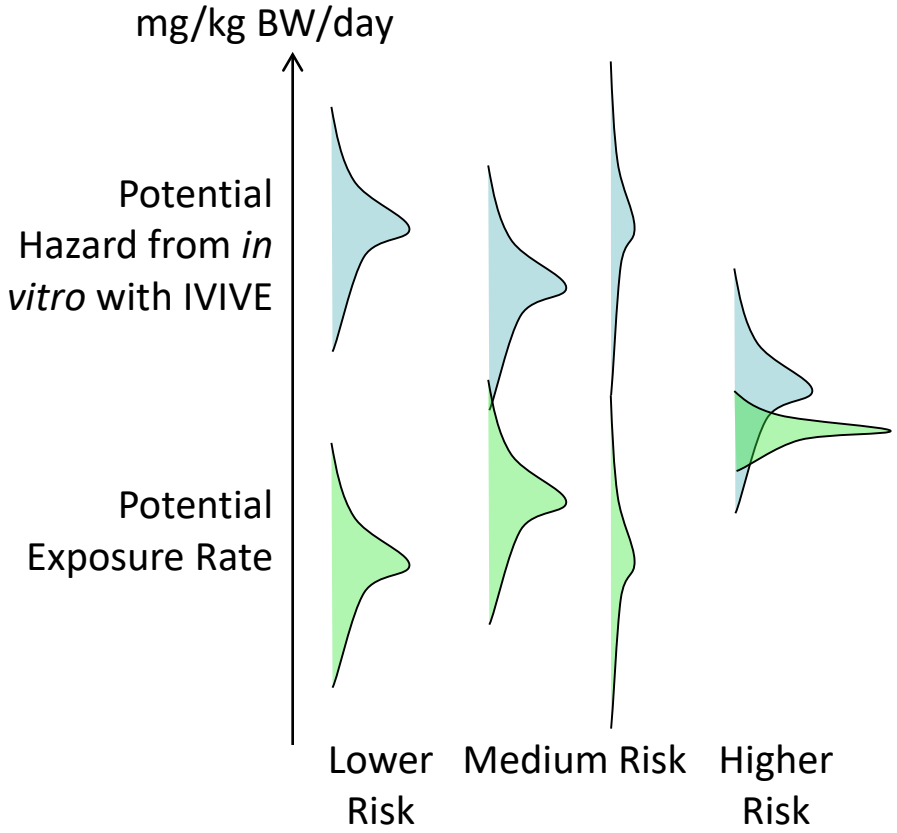
In Vitro - In Vivo Extrapolation (IVIVE)

Definition:
IVIVE is the utilization of *in vitro* experimental data to predict phenomena *in vivo*

- IVIVE-PK/TK (Pharmacokinetics/Toxicokinetics):
  - Fate of molecules/chemicals in body
  - Considers absorption, distribution, metabolism, excretion (ADME)
  - Uses empirical PK and physiologically-based (PBPK) modeling

- IVIVE-PD/TD (Pharmacodynamics/Toxicodynamics):
  - Effect of molecules/chemicals at biological target *in vivo*
  - Assay design/selection important
  - Perturbation as adverse/therapeutic effect, reversible/ irreversible

- Both contribute to predict *in vivo* effects



Slide from Barbara Wetmore

High-Throughput Toxicokinetics (HTTK)

- **Most chemicals do not have TK data** – we use *in vitro* HTTK methods adapted from pharma to fill gaps
- In drug development, HTTK methods estimate therapeutic doses for clinical studies – predicted concentrations are typically on the order of values measured in clinical trials (Wang, 2010)

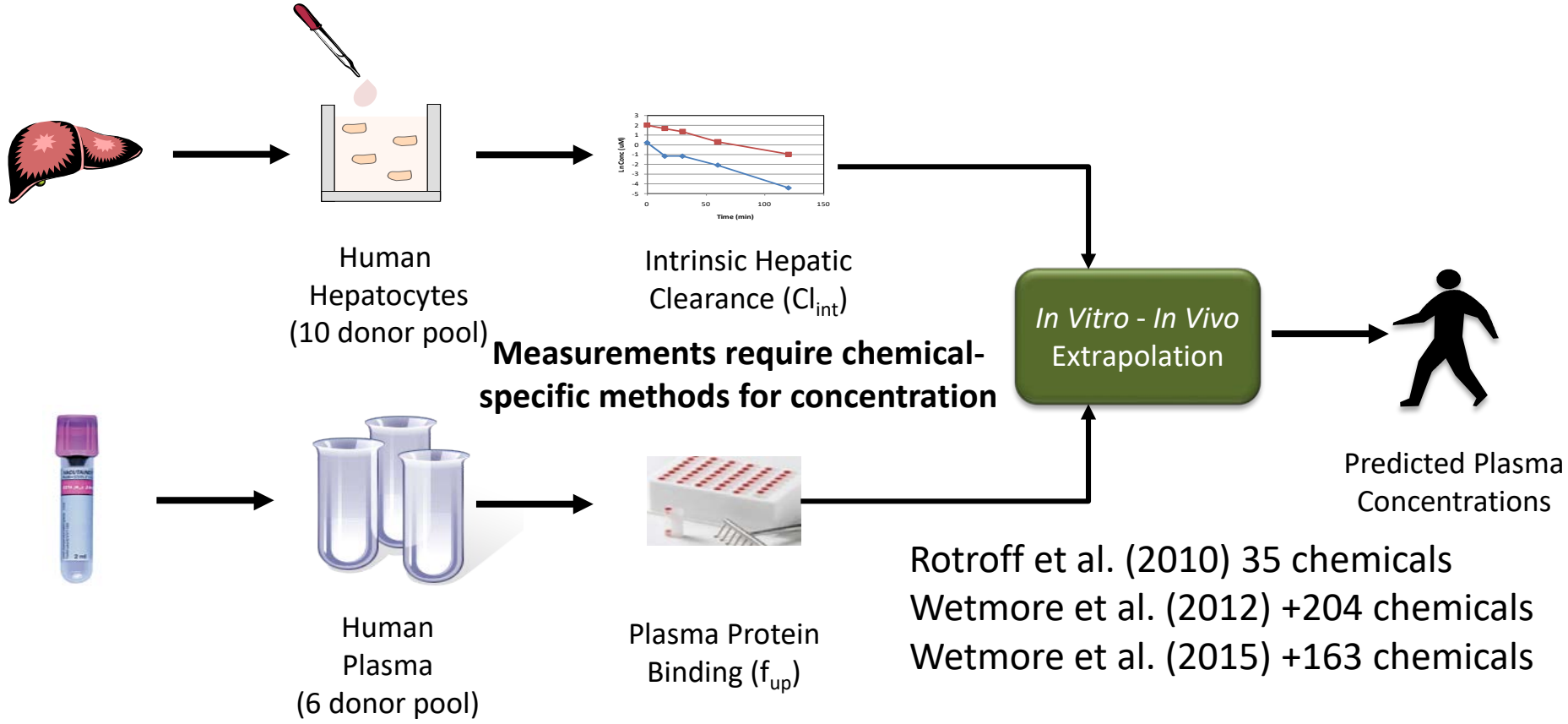


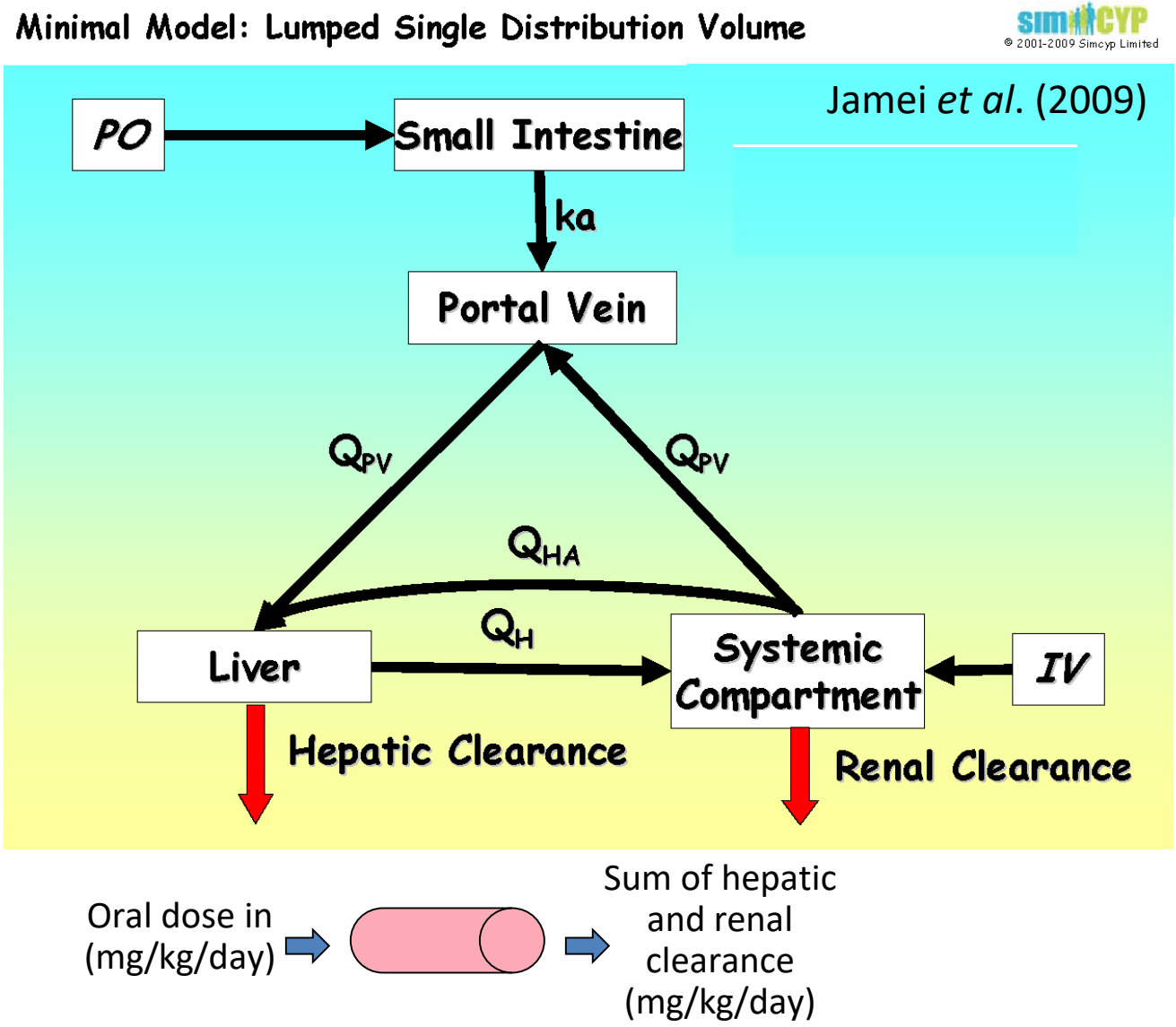
Figure from Barbara Wetmore

A Basic Model Allows HTTK

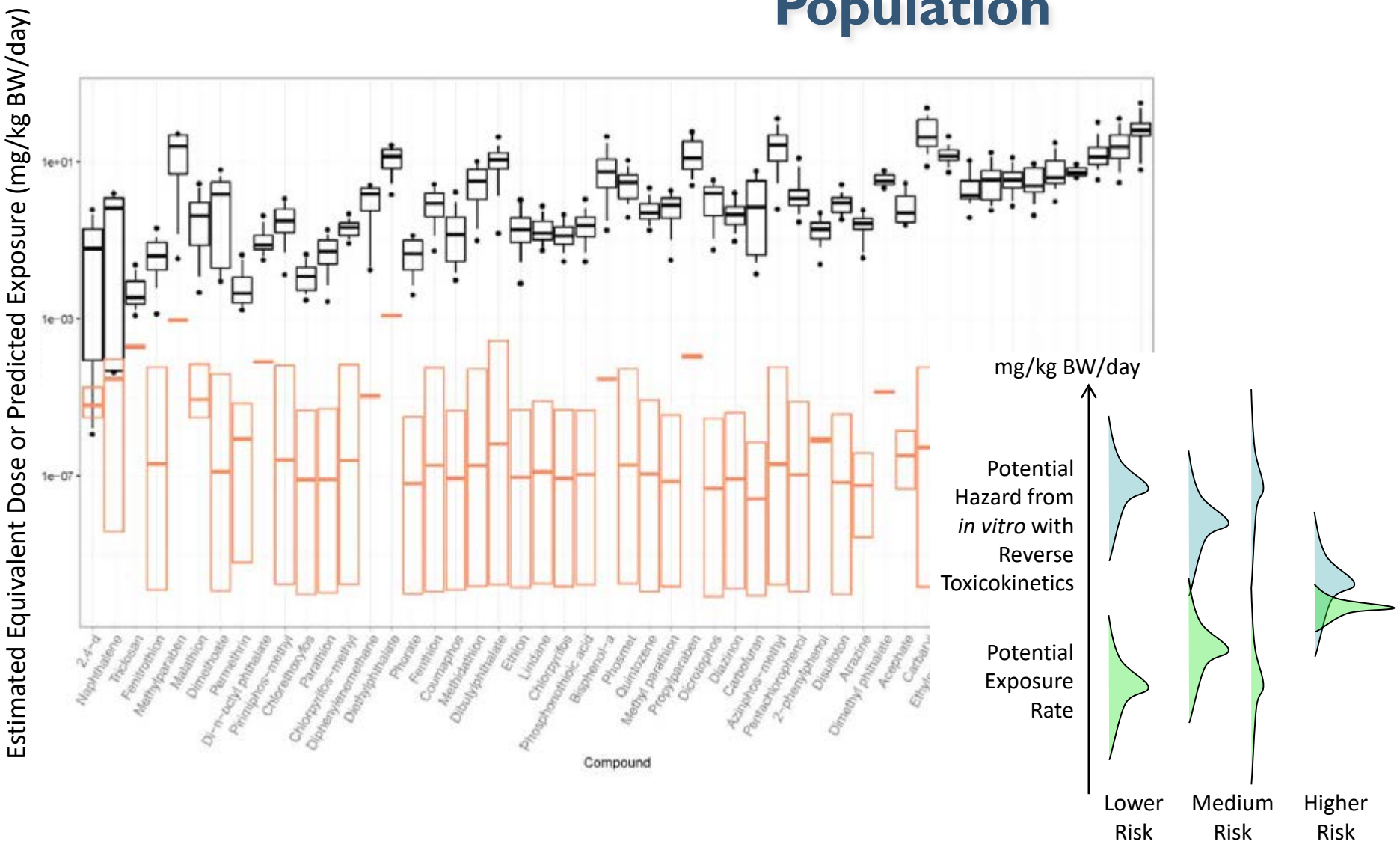
- *In vitro* plasma protein binding (fraction unbound in plasma – f_{up}) and intrinsic hepatic metabolic clearance (Cl_{int}) assays allow approximate hepatic and renal clearances to be calculated
- At steady state this allows conversion from concentration to administered dose
- 100% bioavailability assumed

$$C_{ss} = \frac{\text{oral dose rate}}{\left(\text{GFR} * \text{F}_{up}\right) + \left(\text{Q}_l * \text{F}_{up} * \frac{Cl_{int}}{\text{Q}_l + \text{F}_{up} * Cl_{int}}\right)}$$

GFR: Glomerular filtration rate (kidney)
Q_l: Liver blood flow



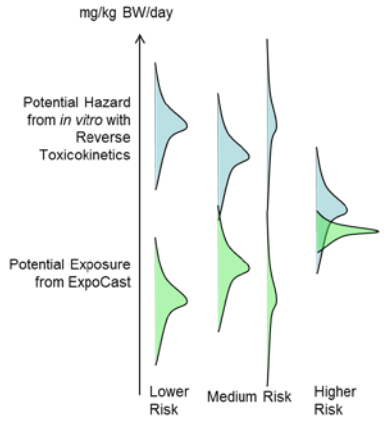
Risk-Based Ranking for Total NHANES Population

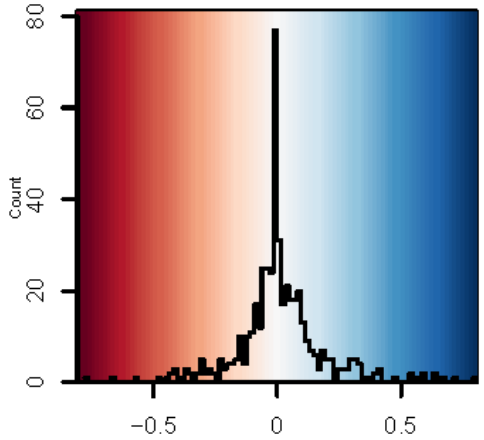


Ring *et al*. (2017)

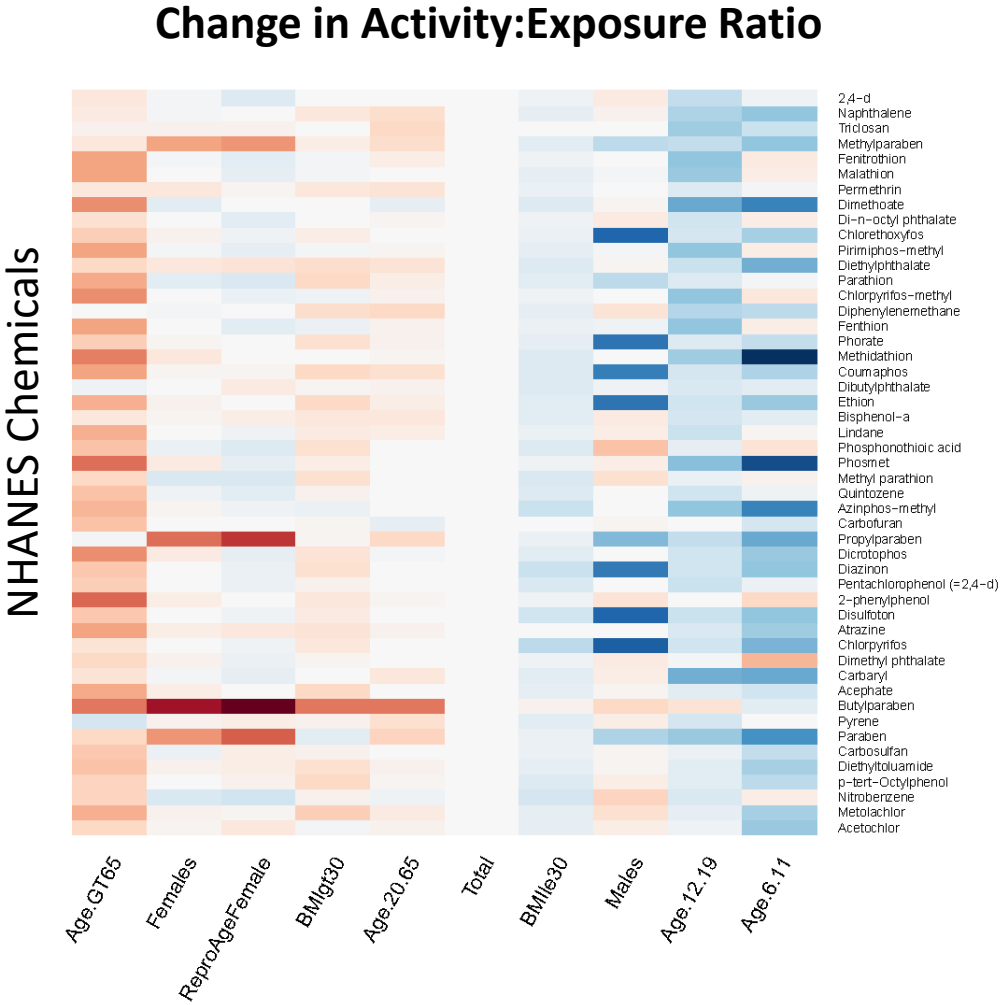
Life-stage and Demographic Specific Predictions

- Can calculate margin between bioactivity and exposure for specific populations





Change in Risk Relative to Total Population



Ring *et al*. (2017)

All Models and Data Open Source and Public

Download R:

https://www.r-project.org/

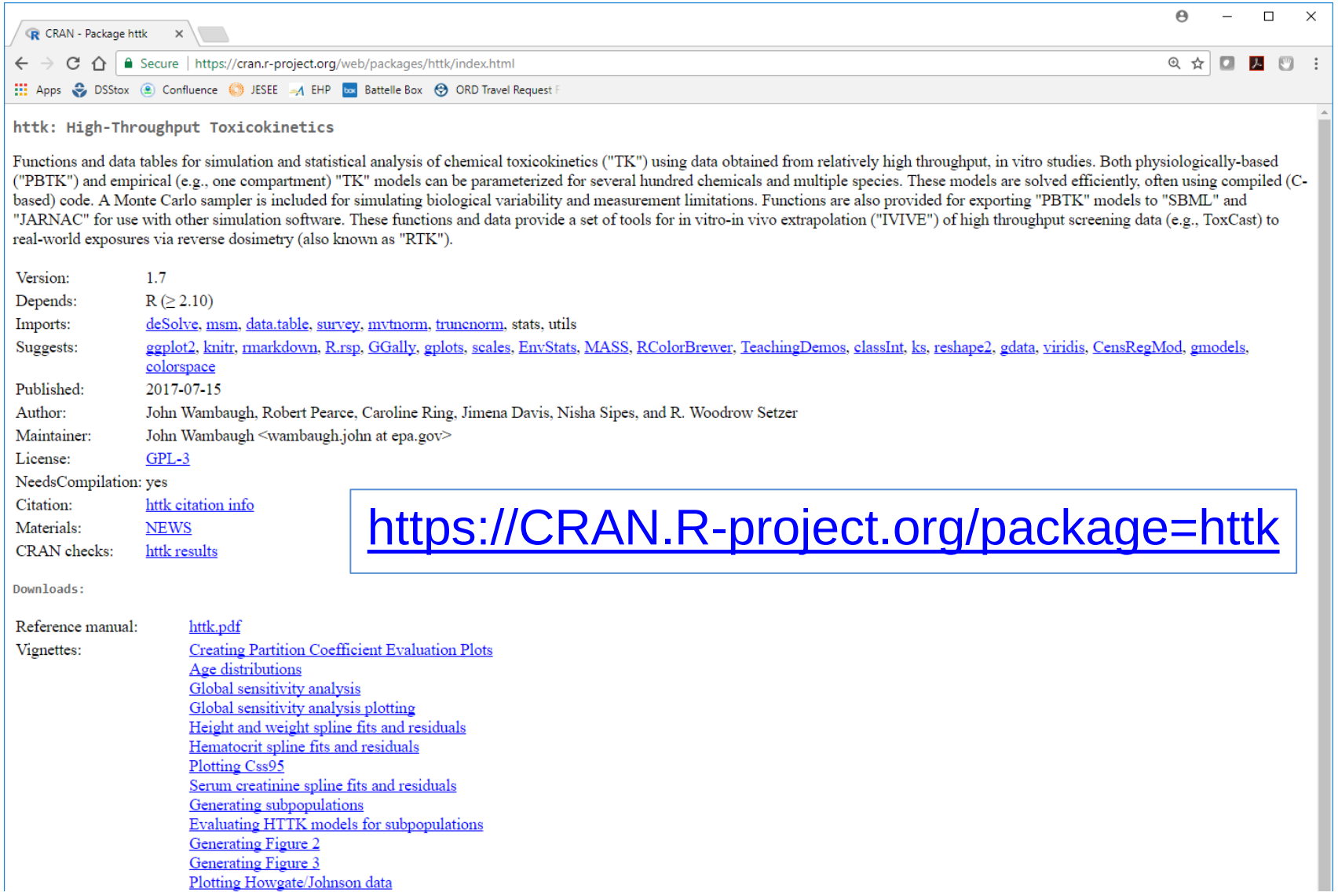
within R, type:

```
install.packages("httk")
```

Then

```
library("httk")
```

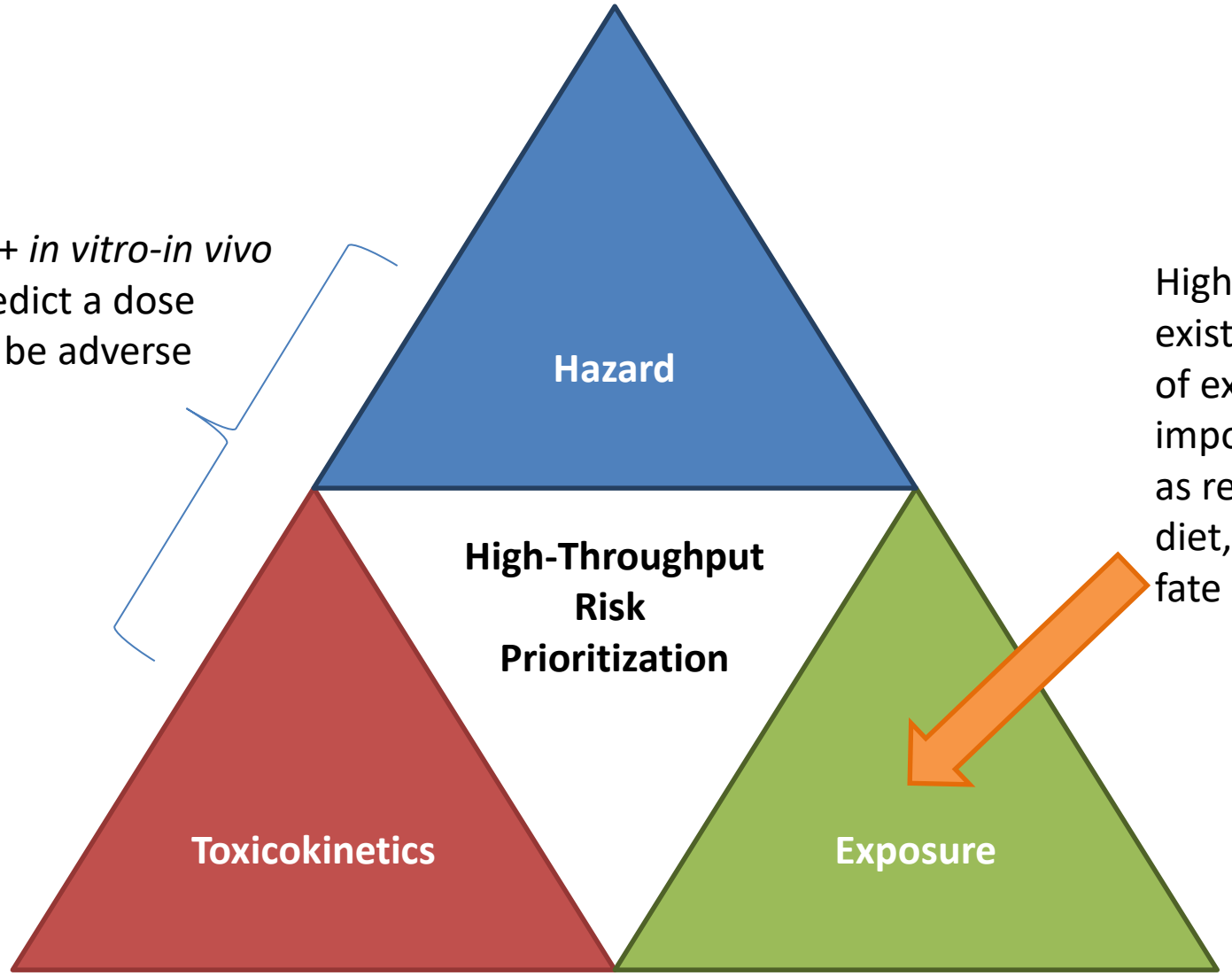
- "httk" R Package for IVIVE and **PBTK**
- 553 chemicals to date
- 100's of additional chemicals being studied
- Pearce *et al.* (2017a) provides documentation and examples
- Built-in vignettes provide further examples of how to use many functions



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

New Exposure Data and Models

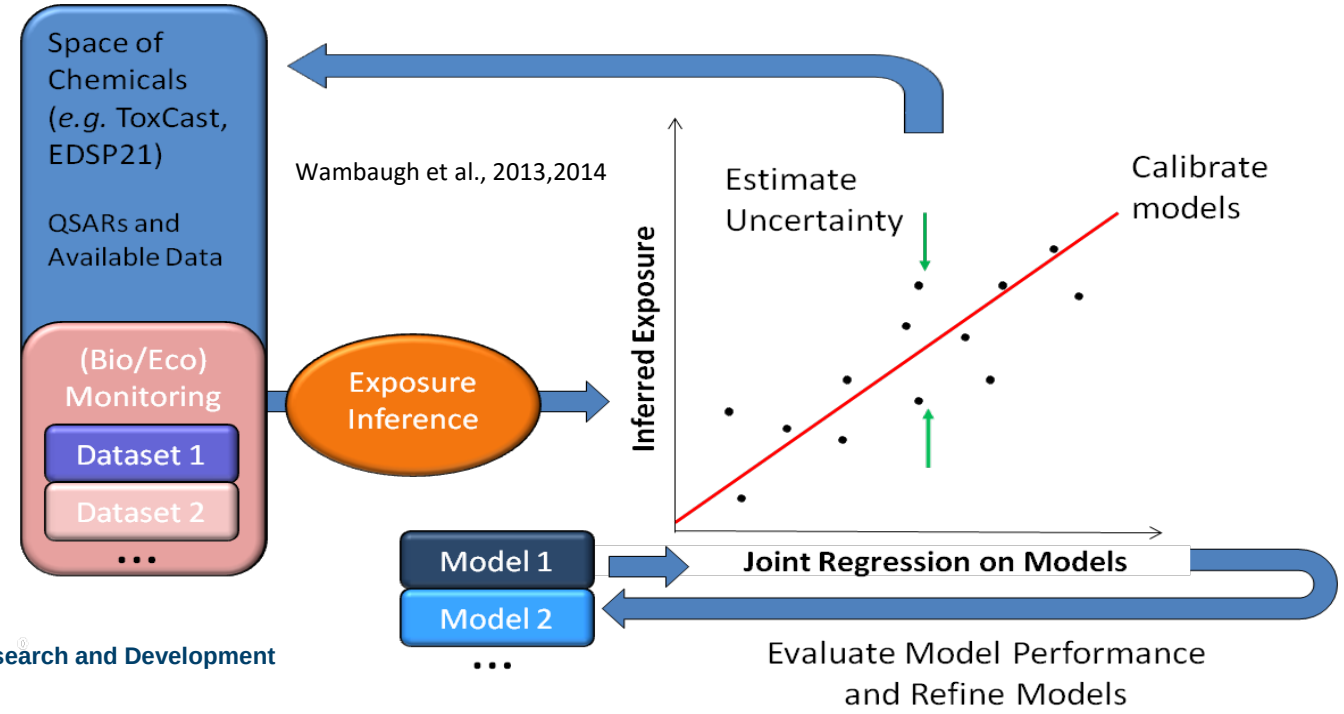
High throughput screening + *in vitro-in vivo* extrapolation (IVIVE can predict a dose (mg/kg bw/day) that might be adverse

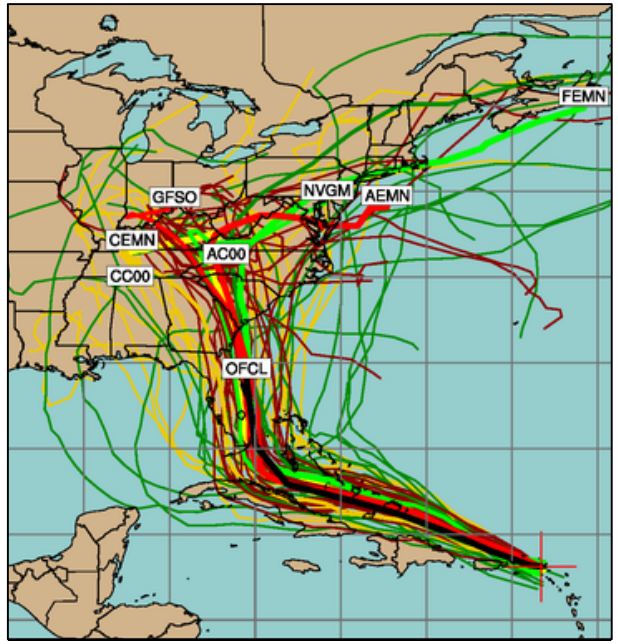


High throughput models exist to make predictions of exposure via specific, important pathways such as residential product use, diet, and environmental fate

Consensus Exposure Predictions with the SEEM Framework

- We incorporate multiple models (including SHEDS-HT, ExpoDat) into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM) framework**
- We evaluate/calibrate predictions with available monitoring data
- This provides information similar to a sensitivity analysis: What models are working? What data are most needed? This is an iterative process





Integrating Multiple Models

Exposures Inferred from NHANES

- Annual survey, data released on 2-year cycle.
- Different predictive models provide different chemical-specific predictions
  - Some models may do a better job form some chemical classes than others overall, so we want to evaluate performance against monitoring data
- Separate evaluations can be done for various demographics

National Health and Nutrition Examination Survey

Urinary Bisphenol A (2,2-*bis*[4-Hydroxyphenyl] propane)

Geometric mean and selected percentiles of urine concentrations (in µg/L) for the U.S. populatio and Nutrition Examination Survey.

	Survey years	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval) 50th	75th	90th
Total	03-04	2.64 (2.38-2.94)	2.80 (2.50-3.10)	5.50 (5.00-6.20)	10.6 (9.40-
	05-06	1.90 (1.79-2.02)	2.00 (1.90-2.00)	3.70 (3.50-3.90)	7.00 (6.40-
	07-08	2.08 (1.92-2.26)	2.10 (1.90-2.30)	4.10 (3.60-4.60)	7.70 (6.80-
Age group					
6-11 years	03-04	3.55 (2.95-4.29)	3.80 (2.70-5.00)	6.90 (6.00-8.30)	12.6 (9.50-
	05-06	2.86 (2.52-3.24)	2.70 (2.30-2.90)	5.00 (4.40-5.80)	13.5 (9.30-
	07-08	2.46 (2.20-2.75)	2.40 (1.90-3.00)	4.50 (3.70-5.50)	7.00 (6.30-
12-19 years	03-04	3.74 (3.31-4.22)	4.30 (3.60-4.60)	7.80 (6.50-9.00)	13.5 (11.8-
	05-06	2.42 (2.18-2.68)	2.40 (2.10-2.70)	4.30 (3.90-5.20)	8.40 (6.50-
	07-08	2.44 (2.14-2.78)	2.30 (2.10-2.60)	4.40 (3.70-5.50)	9.70 (7.30-
20 years and older	03-04	2.41 (2.15-2.72)	2.60 (2.30-2.80)	5.10 (4.50-5.70)	9.50 (8.10-
	05-06	1.75 (1.62-1.89)	1.80 (1.70-2.00)	3.40 (3.10-3.70)	6.40 (5.80-
	07-08	1.99 (1.82-2.18)	2.00 (1.80-2.30)	3.90 (3.40-4.60)	7.40 (6.60-

CDC, Fourth National Exposure Report (2011)

Chemical Use Identifies Relevant Pathways

- **The exposure event is unobservable**
  - But we can try to predict exposure by characterizing pathway
- Some pathways have much higher average exposures!
  - In home "Near field" sources significant (Wallace, *et al.,* 1987)
- Chemical-Product Database (https://actor.epa.gov/cpcat/) provides chemical use information (Dionisio et al., 2015)

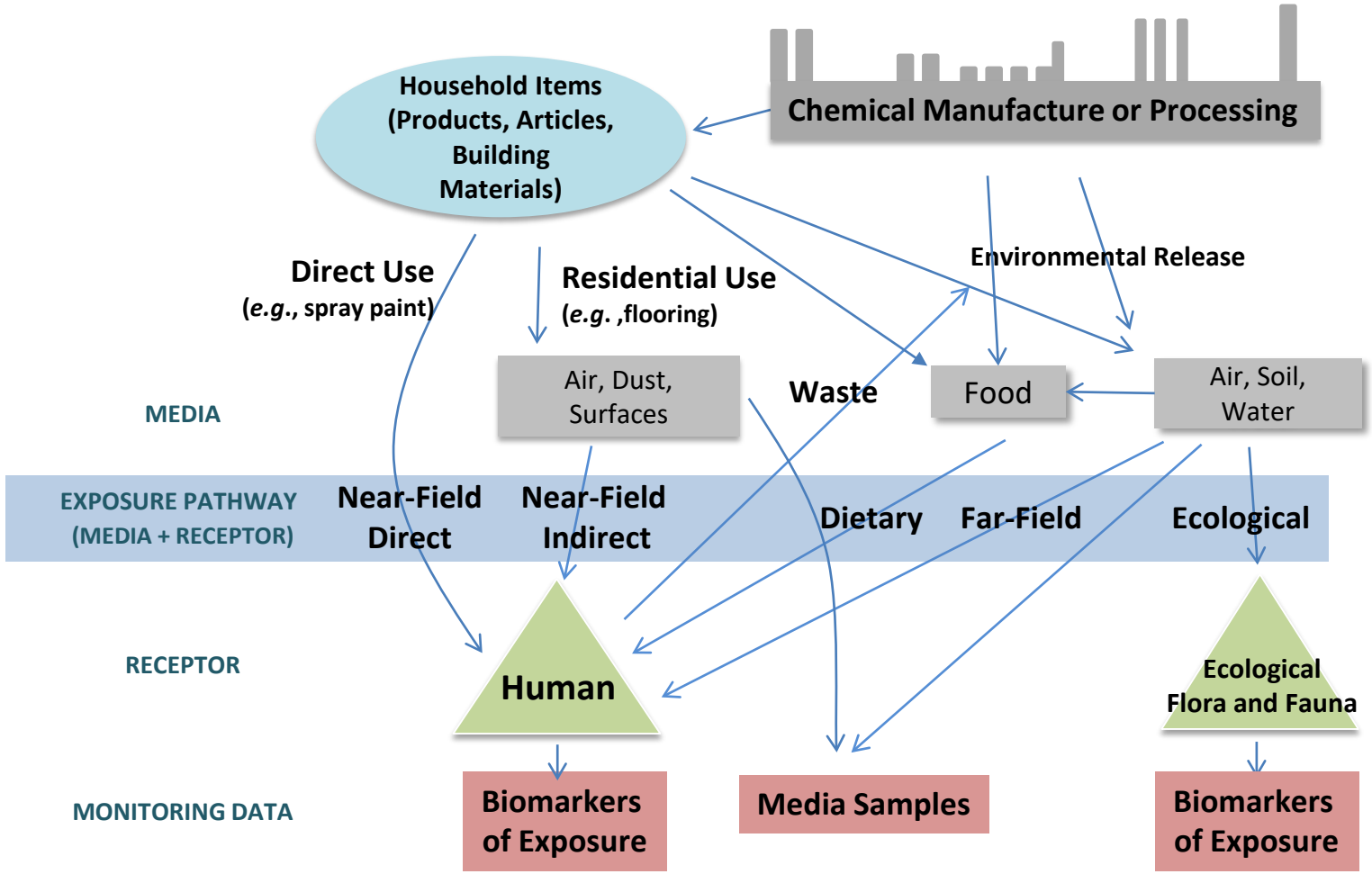
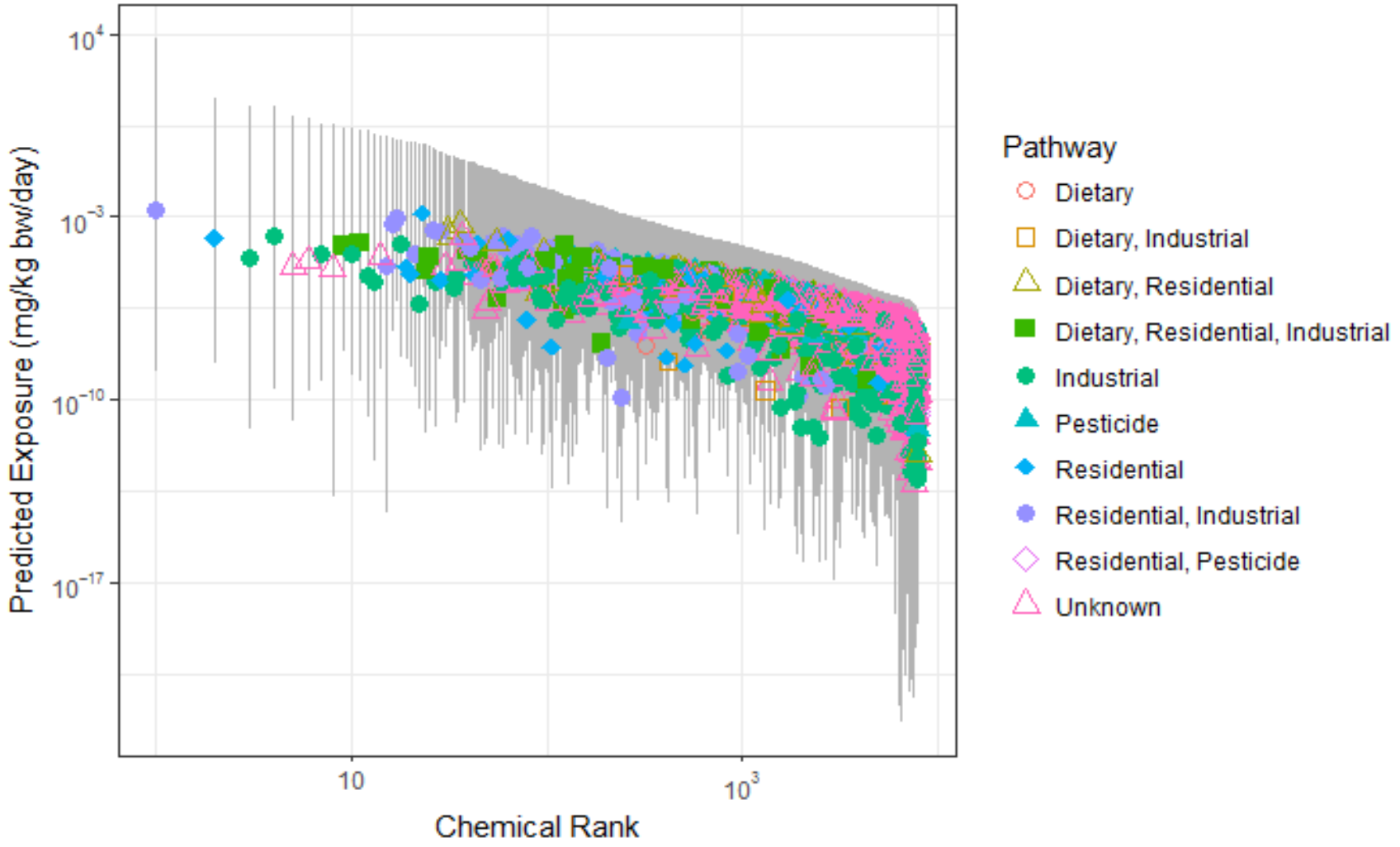


Figure from Kristin Isaacs

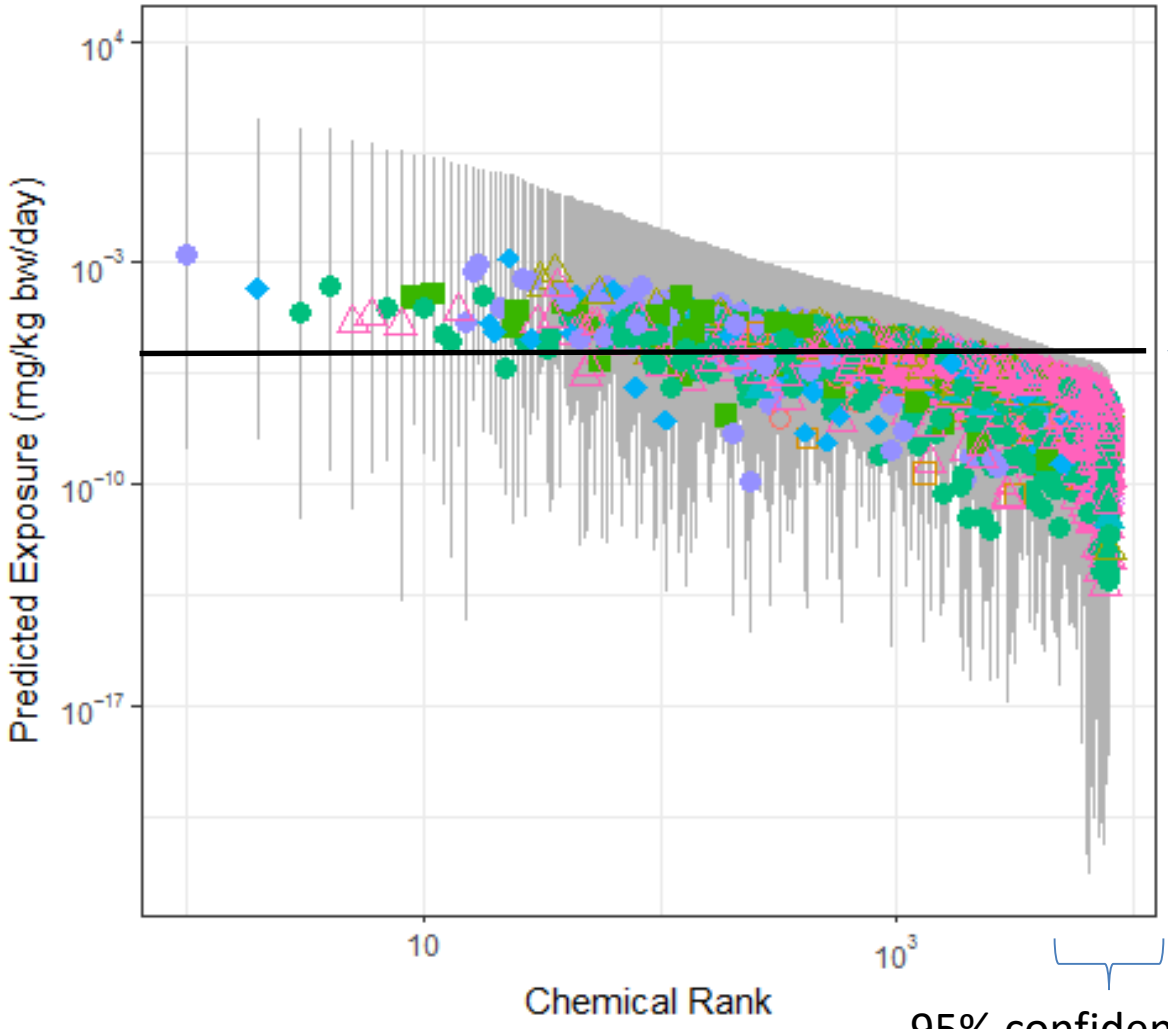
Human Exposure Predictions for 134,521 Chemicals



- Machine learning models were built for each four exposure pathways
- Pathway predictions can be used for large chemical libraries
- Use prediction (and accuracy of prediction) as a prior for Bayesian analysis
- Each chemical may have exposure by multiple pathways

Ring et al. (*in prep.*)

Human Exposure Predictions for 134,521 Chemicals

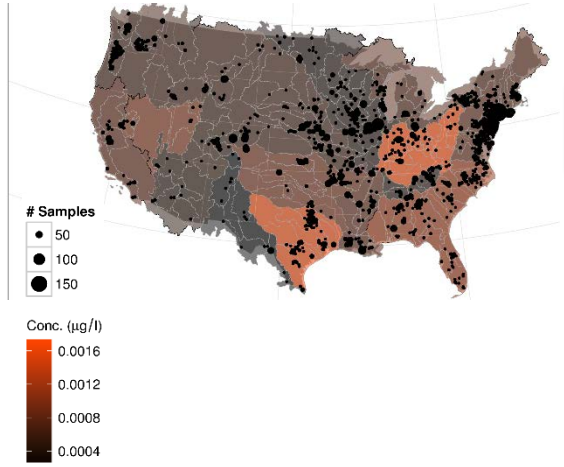


Lowest NHANES limit of detection (LOD) roughly corresponds to ~10^{-6} mg/kg BW/day

95% confident that median population would be <LOD for thousands of chemicals

Ring et al. (*in prep.*)

Ecological SEEM



Chemicals
n = 91

- Pesticides
- PAHs
- Solvents,…

Dataset
Setzer et al., (in prep)

Watersheds

- **1984 – 2014**
  Aggregated by season
- **3 Levels**
  - **National**
  - **Region**
    (HUC2)
    n = 18
  - **Sub-region**
    (HUC4)
    n = 196

HUC = hydrological unit

Fate and Transport Models

USETox (n = 82)	RAIDAR (n =74)	HT-EXAIR (n = 91)
Rosenbaum et al., 2008	Arnot et al., 2006	Barber et al., 2017