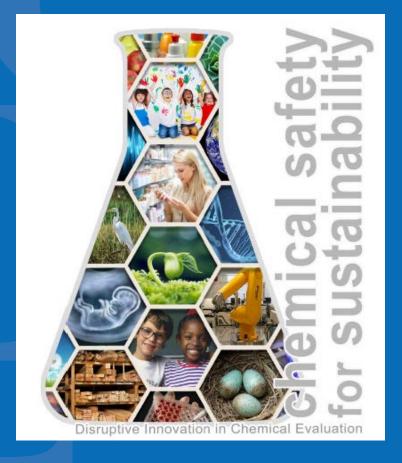
National Center for Computational Toxicolog Office of Research and Developmen U.S. Environmental Protection Agenc





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

January 23, 2018

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA

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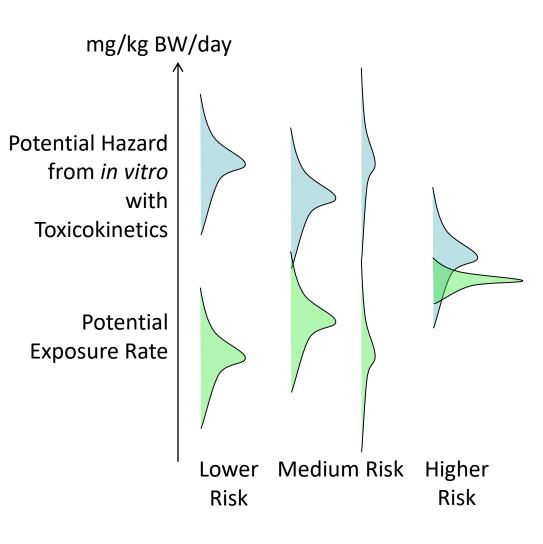
High-Throughput Risk Prioritization

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)

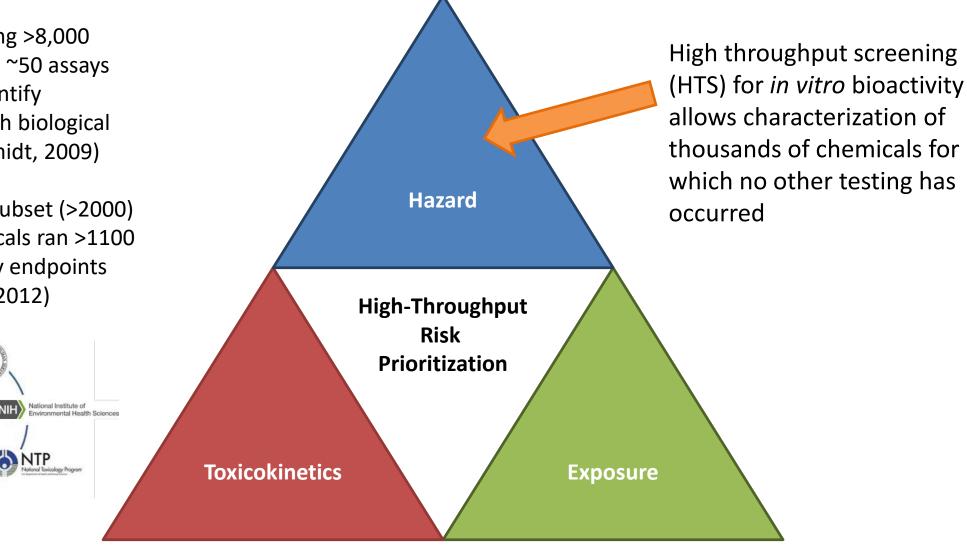




High-Throughput Risk Prioritization

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)

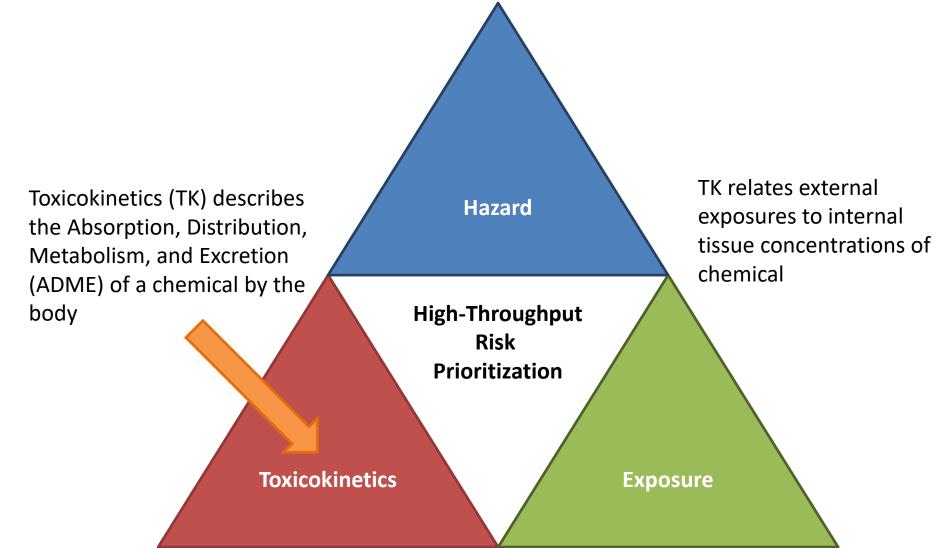


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High Throughput Toxicokinetics (HTTK)



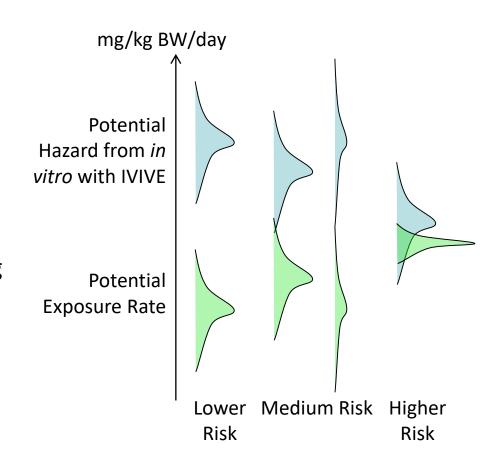


In Vitro - In Vivo Extrapolation (IVIVE)

Definition:

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

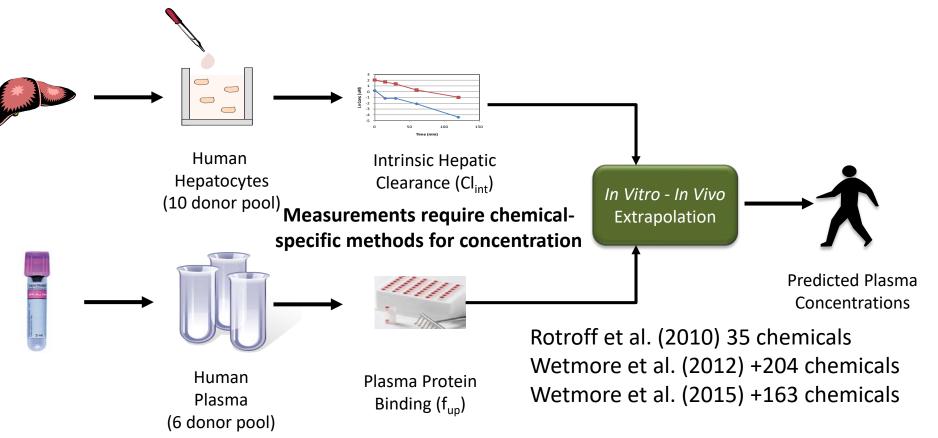
- IVIVE-PK/TK (Pharmacokinetics/Toxicokinetics):
 - Fate of molecules/chemicals in body
 - Considers absorption, distribution, metabolism, excretion (ADME)
 - Uses empirical PK and physiologically-based (PBPK) modeling
- IVIVE-PD/TD (Pharmacodynamics/Toxicodynamics):
 - Effect of molecules/chemicals at biological target in vivo
 - Assay design/selection important
 - Perturbation as adverse/therapeutic effect, reversible/ irreversible
- Both contribute to predict *in vivo* effects





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)



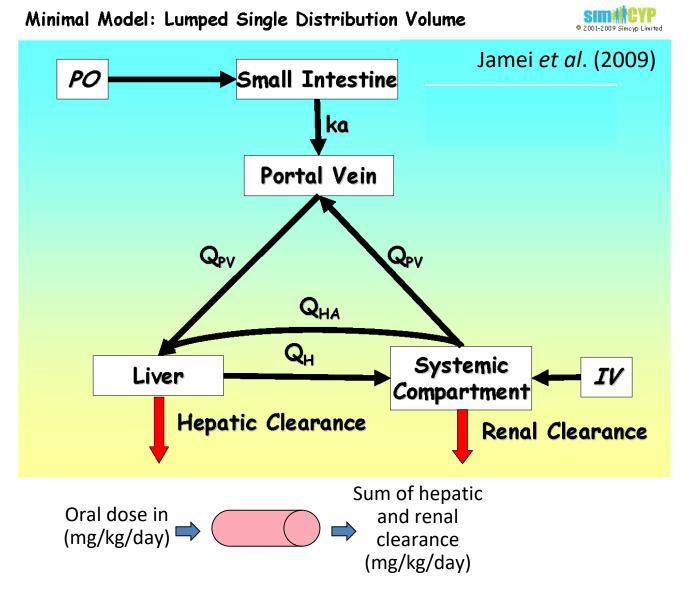


A Basic Model Allows HTTK

- 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

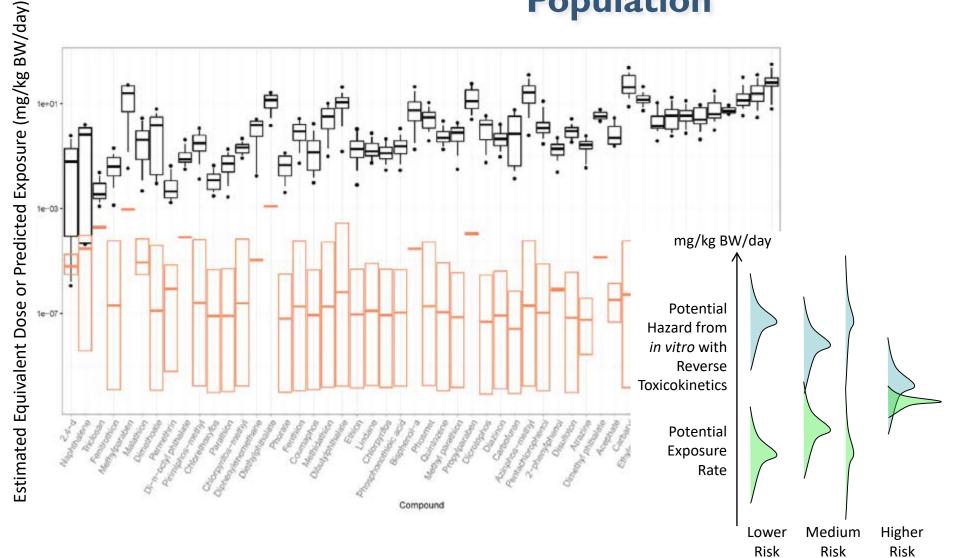
$$C_{ss} = \frac{\text{oral dose rate}}{\left(\text{GFR} * F_{up}\right) + \left(Q_1 * F_{up} * \frac{Cl_{int}}{Q_1 + F_{up} * Cl_{int}}\right)}$$

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





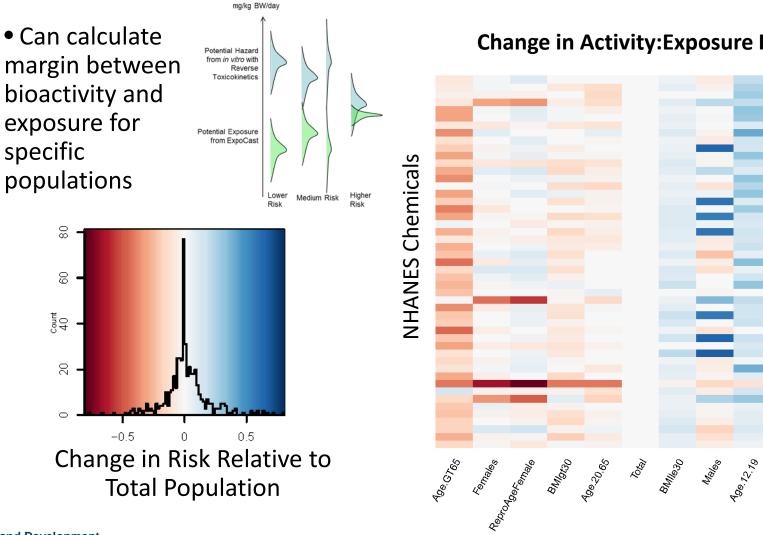
Risk-Based Ranking for Total NHANES Population



Ring et al. (2017)



Life-stage and Demographic Specific Predictions



Change in Activity: Exposure Ratio

Ring *et al*. (2017)

196.6.17

2,4-d

Naphthalene Triclosan Methylparaben Fenitrothion

Malathion Permethrin

Dimethoate

Parathion Chlorpyrifos-methyl Diphenylenemethane Fenthion

Phorate

Ethion Bisphenol-a Lindane Phosphonothioic acid

Phosmet Methyl parathior

Diazinon

Carbaryl Acephate Butylparaben Pyrene Paraben Carbosulfan

Diethyltoluamide p-tert-Octvlphenol Nitrobenzene

Metolachior Acetochlor

Pentachlorophenol (=2,4-d) 2-phenviphenol Disulfoton Atrazine Chlorpyrifos Dimethyl phthalate

Quintozene Azinphos-methy Carbofuran Propylparaben Dicrotophos

Methidathion Cournaphos Dibutylphthalate

Chlorethoxyfos Pirimiphos-methyl

Diethylphthalate

Di-n-octyl phthalate



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

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("PBTK") and en based) code. A M "JARNAC" for u	mpirical (e.g., one compartment) Monte Carlo sampler is included :	istical analysis of chemical toxicokinetics ("TK") using data obtained from relatively high throughput, in vitro studies. Both "TK" models can be parameterized for several hundred chemicals and multiple species. These models are solved efficiently for simulating biological variability and measurement limitations. Functions are also provided for exporting "PBTK" model re. These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of high throughput screening known as "RTK").	, often usin s to "SBMI	ig coi _" an	npile d	d (C		
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httk.pdf Creating Partition Coefficient Evaluation Plots Age distributions Global sensitivity analysis Global sensitivity analysis plotting Height and weight spline fits and residuals Hematocrit spline fits and residuals Plotting Css95 Serum creatinine spline fits and residuals Generating subpopulations Evaluating HTTK models for subpopulations Generating Figure 2 Generating Figure 3 Plotting Howgate/Johnson data

Reference manual:

Vignettes:



New Exposure Data and Models

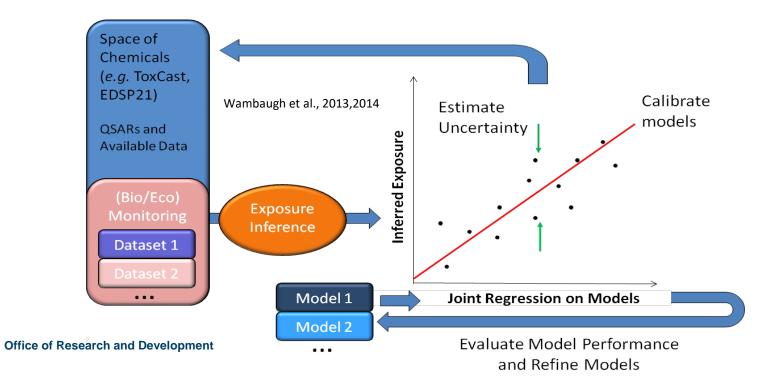
High throughput screening + *in vitro-in vivo* High throughput models extrapolation (IVIVE can predict a dose exist to make predictions (mg/kg bw/day) that might be adverse Hazard of exposure via specific, important pathways such as residential product use, diet, and environmental **High-Throughput** fate Risk **Prioritization Toxicokinetics Exposure**

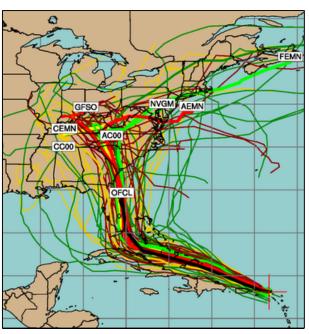


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Consensus Exposure Predictions with the SEEM Framework

- 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 chemicalspecific 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

<u>National Health and Nutrition Examination Survey</u>

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

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

		Geometric		Selected percentile		
	Survey	mean		(95% confidence interval)		
	years	(95% conf. 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 (<u>https://actor.epa.gov/cpcat/</u>) provides chemical use information (Dionisio et al., 2015)

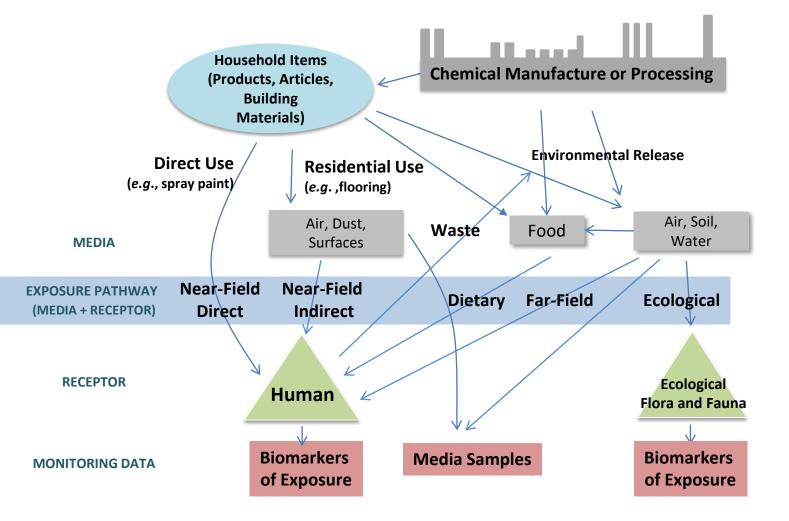
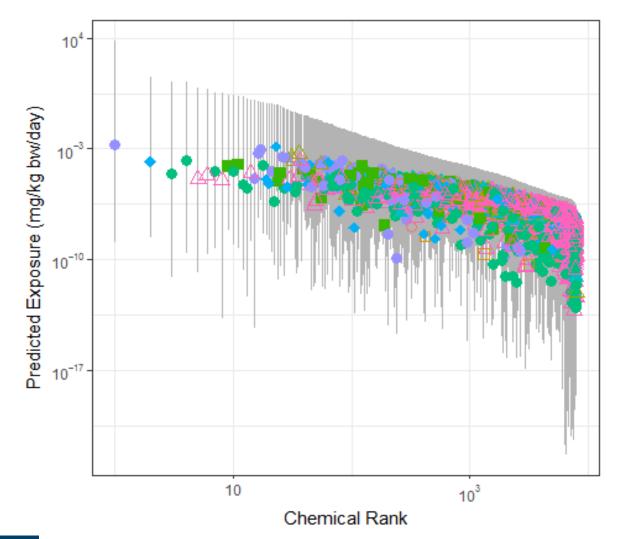


Figure from Kristin Isaacs



Human Exposure Predictions for 134,521 Chemicals



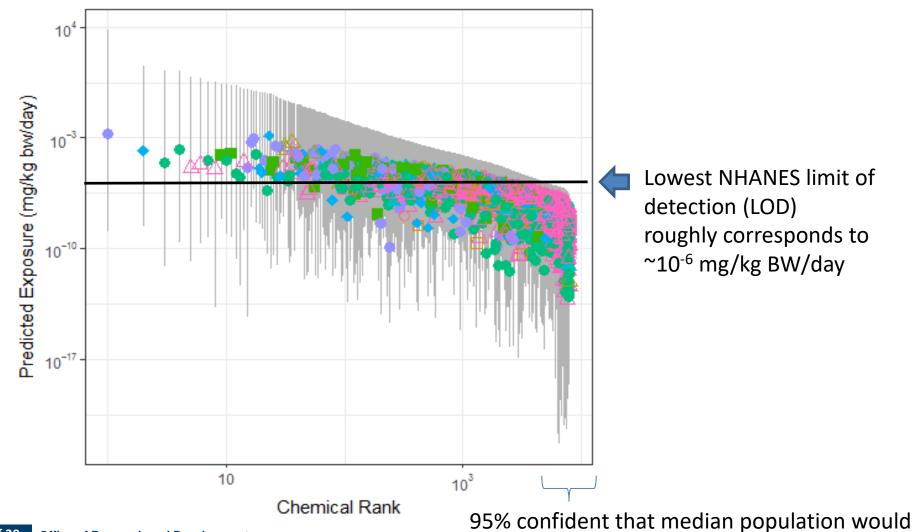
Pathway

- Dietary
- Dietary, Industrial
- 🛆 Dietary, Residential
- Dietary, Residential, Industrial
- Industrial
- 🔺 Pesticide
- Residential
- Residential, Industrial
- 🛇 Residential, Pesticide

- 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



Human Exposure Predictions for 134,521 Chemicals



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

Ring et al. (in prep.)

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be <LOD for thousands of chemicals



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Ecological SEEM

