High Throughput Exposure Science for Chemical Decision Making

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Total Exposure Health 2018: "Bridging Human Exposure & Precision Medicine"
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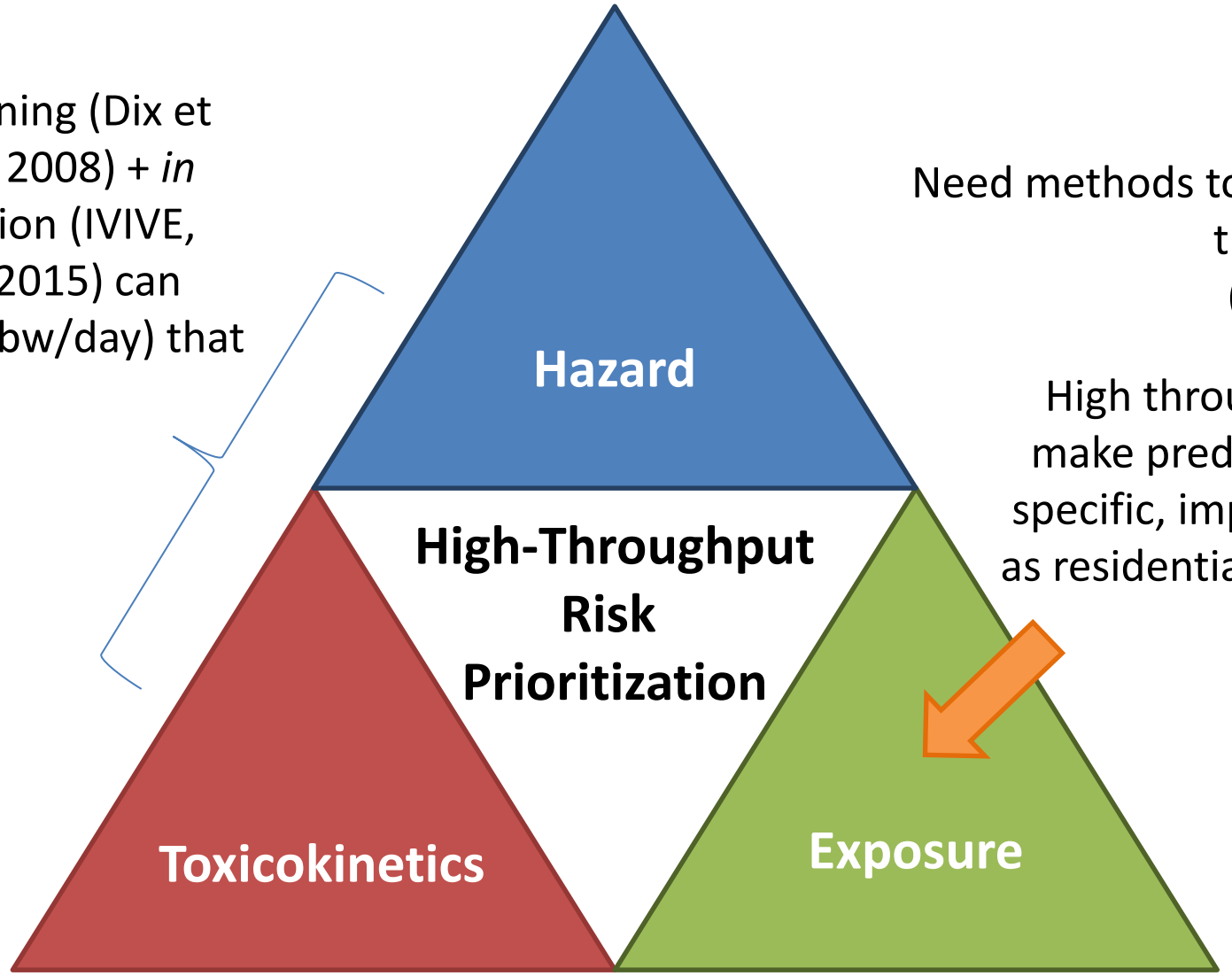
Risk = Hazard x Exposure

High throughput screening (Dix et al., 2007, Collins et al., 2008) + *in vitro-in vivo* extrapolation (IVIVE, Wetmore et al., 2012, 2015) can predict a dose (mg/kg bw/day) that might be adverse



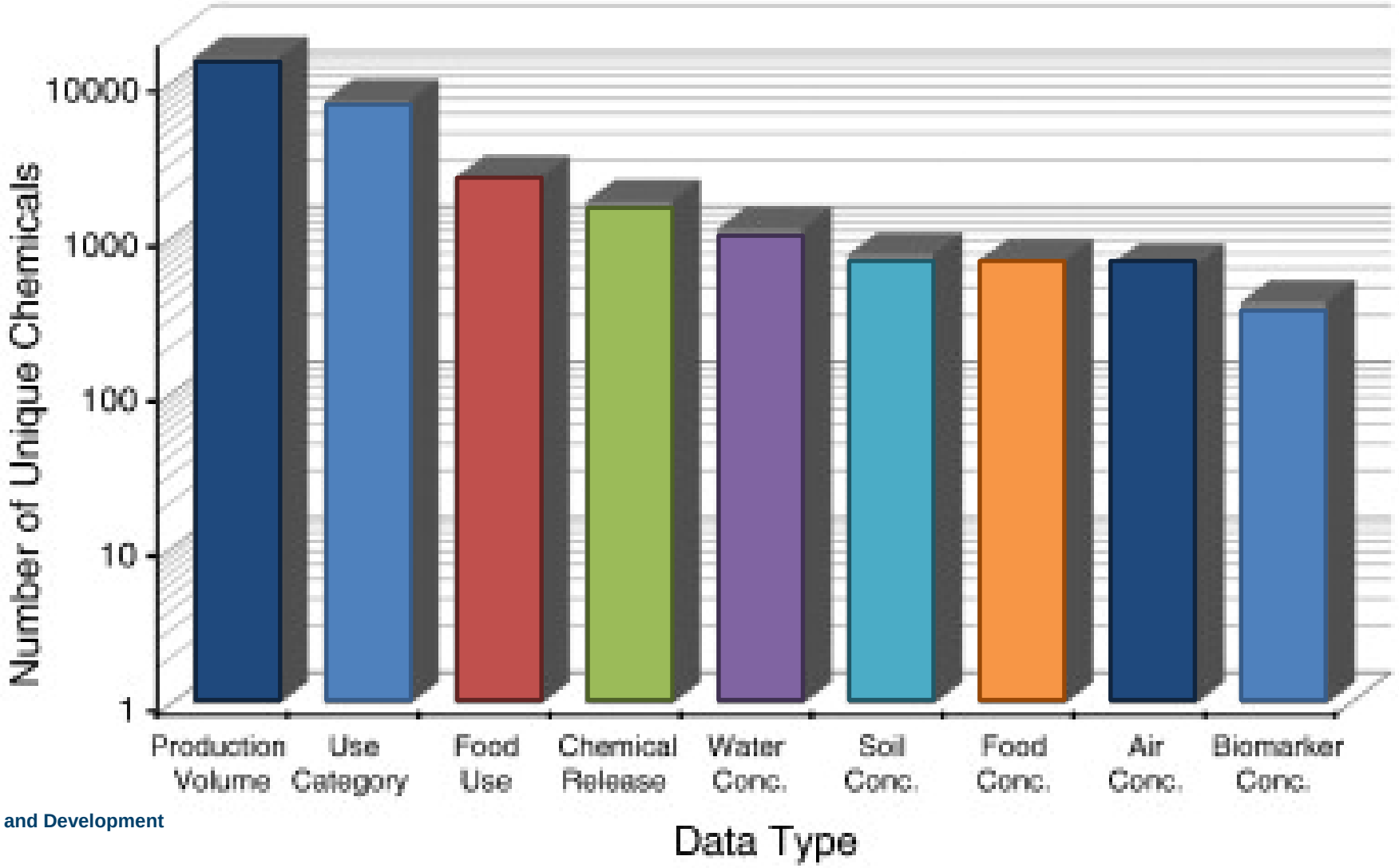
Need methods to forecast exposure for thousands of chemicals (Wetmore et al., 2015)

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

NRC (1983)

Limited Available Data for Exposure Estimation

Most chemicals lack public exposure-related data beyond production volume (Egeghy et al., 2012)



Biomonitoring Data

The National Health and Nutrition Examination Survey (NHANES) provides targeted biomonitoring data of chemicals and metabolites in human blood and urine

Chemicals in the *Fourth Report: Updated Tables, March 2018*

CDC (2018)

CDC's *Fourth National Report on Human Exposure to Environmental Chemicals: Updated Tables* provides exposure data on the following chemicals or classes of chemicals. The *Updated Tables* contain cumulative data from national samples collected beginning in 1999–2000 and as recently as 2015-2016. Not all chemicals were measured in each national sample. The data tables are available at http://www.cdc.gov/exposurereport. An asterisk (*) indicates the chemical has been added since publication of the *Fourth Report* in 2009.

Phthalate and Phthalate Alternative Metabolites

Mono-benzyl phthalate (MBzP)
Mono-3-hydroxybutyl phthalate (MHBP)*
Mono-n-butyl phthalate (MnBP)
Mono-2-methyl-2-hydroxypropyl phthalate (MHiBP)*
Mono-isobutyl phthalate (MiBP)
Mono-cyclohexyl phthalate (MCHP)
Mono-ethyl phthalate (MEP)
Mono-2-ethylhexyl phthalate (MEHP)
Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)

Organophosphorus Insecticides: Dialkyl Phosphate Metabolites

Diethylphosphate (DEP)
Dimethylphosphate (DMP)
Diethylthiophosphate (DETP)
Dimethylthiophosphate (DMTP)
Diethyldithiophosphate (DEDTP)
Dimethyldithiophosphate (DMDTP)

Pyrethroid Metabolites

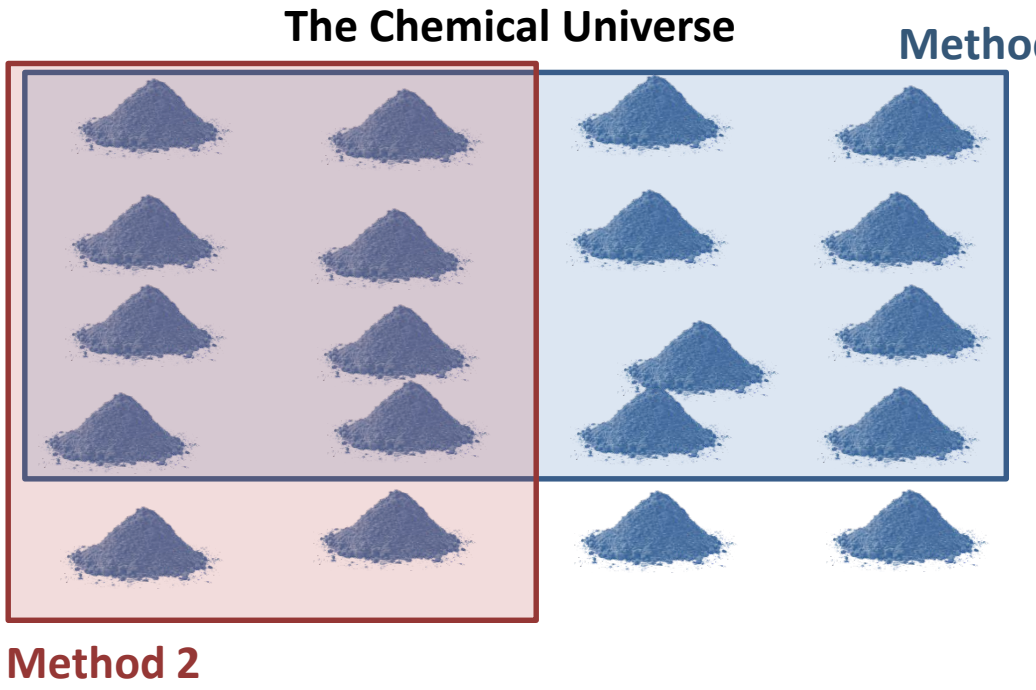
trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (trans-DCCA)
cis-3-(2,2-Dibromovinyl)-2,2dimethylcyclopropane carboxylic acid (cis-DBCA)
4-Fluoro-3-phenoxy-benzoic acid*
3-Phenoxybenzoic acid*

There are hundreds of chemicals, and yet Park *et al.* (2012) and others have seen evidence for many others

EPA's Non-Targeted Analysis Collaborative Trial (ENTACT)

Suspect screening / Non-targeted analyses (SSA/NTA) present opportunities for new exposure data

What NTA methods are available? What is the coverage of chemical universe and matrices? How do methods differ in their coverage?



Led by Jon Sobus and Elin Ulrich (EPA/NERL)

Phase 1:

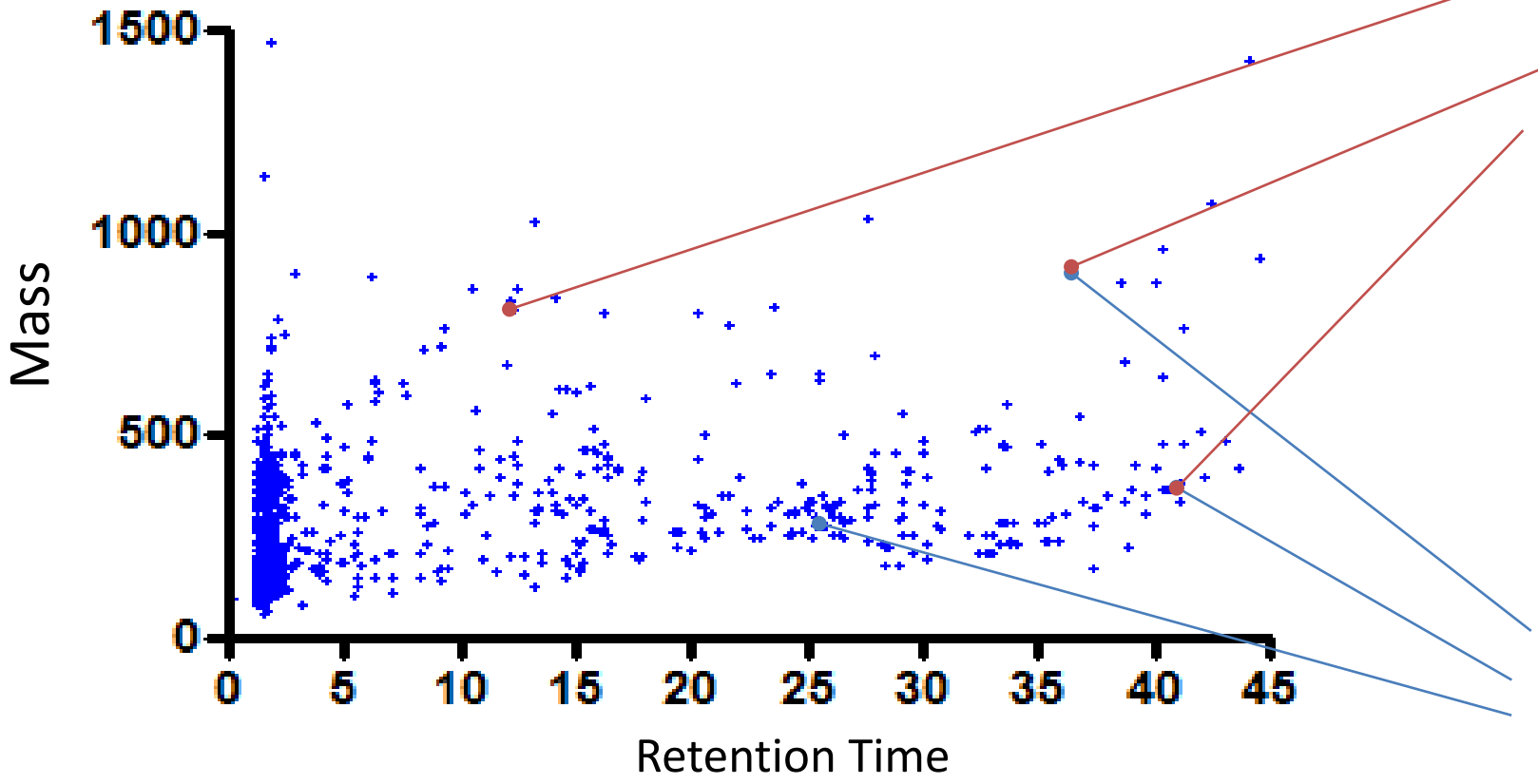
- Collaborators provided 10 mixtures of 100-400 ToxCast chemicals each
- MS vendors provided with individual chemical standards

Phase 2: Fortified reference house dust, human serum, and silicone wristbands

Sobus et al. (2017)

What We Learned from Suspect Screening in House Dust

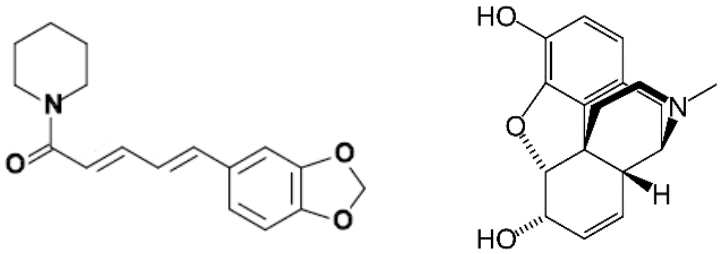
947 Peaks in an American Health Homes Dust Sample



Liquid chromatography peaks corresponds to a chemical with an accurate mass and predicted formula:

$C_{17}H_{19}NO_3$

Multiple chemicals can have the same mass and formula:

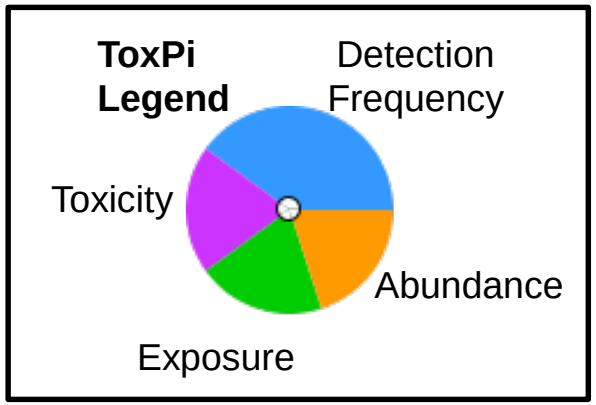


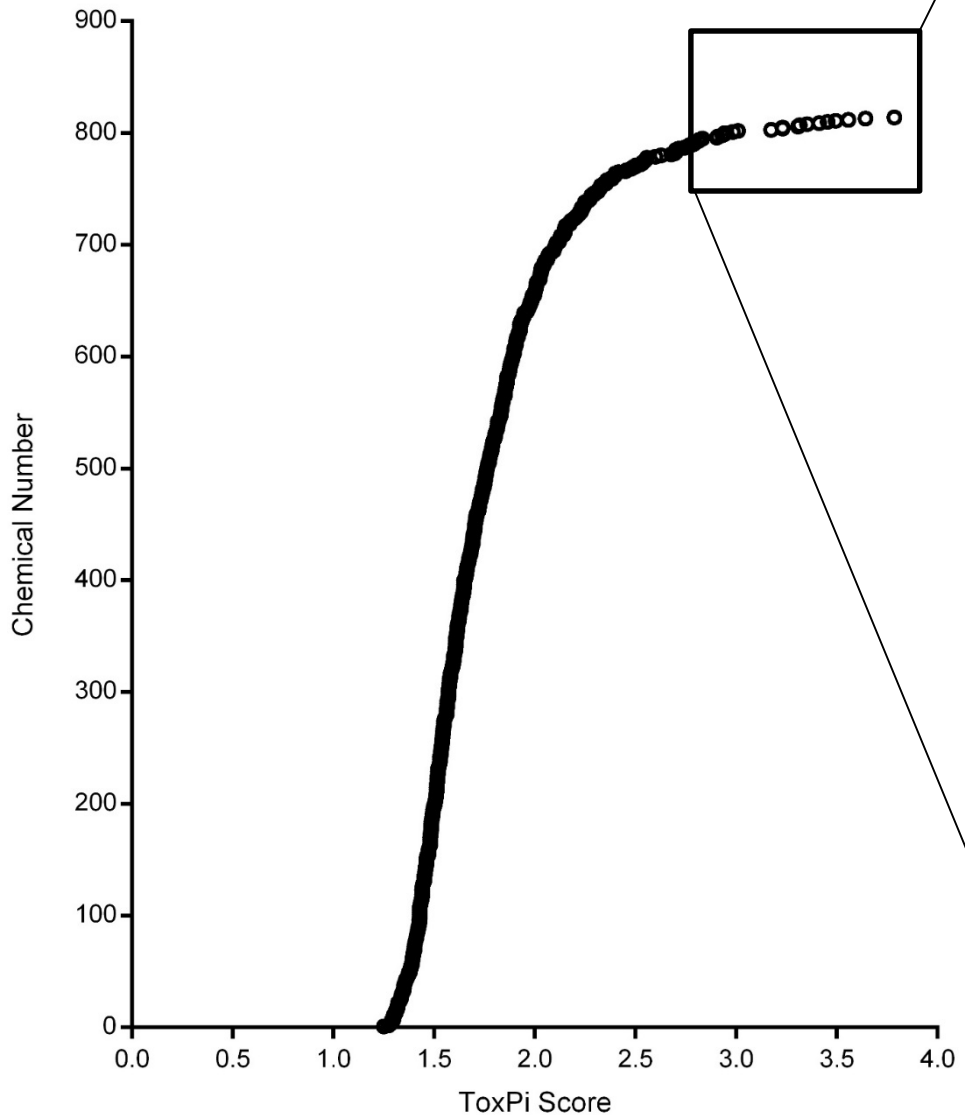
Is chemical A present, chemical B, or both?

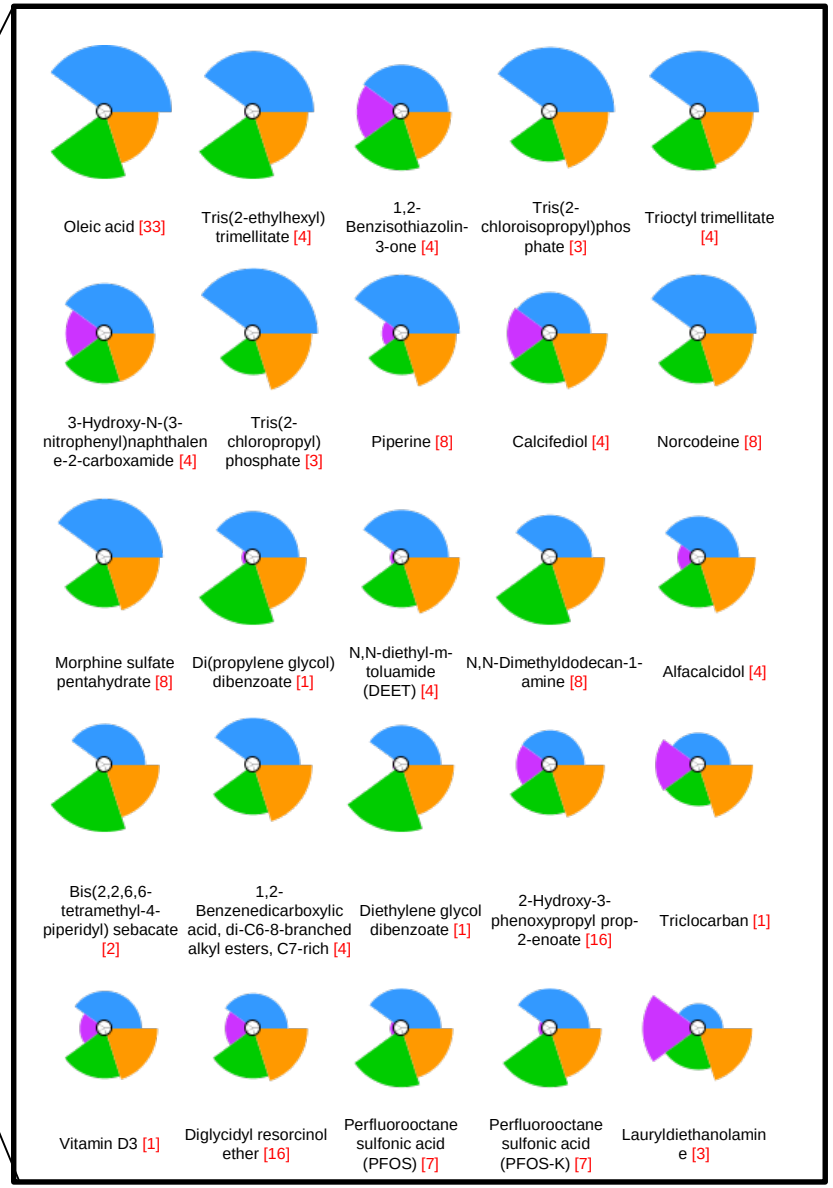
Rager et al. (2016)

Prioritizing Chemical Matches

United States Environmental Protection Agency



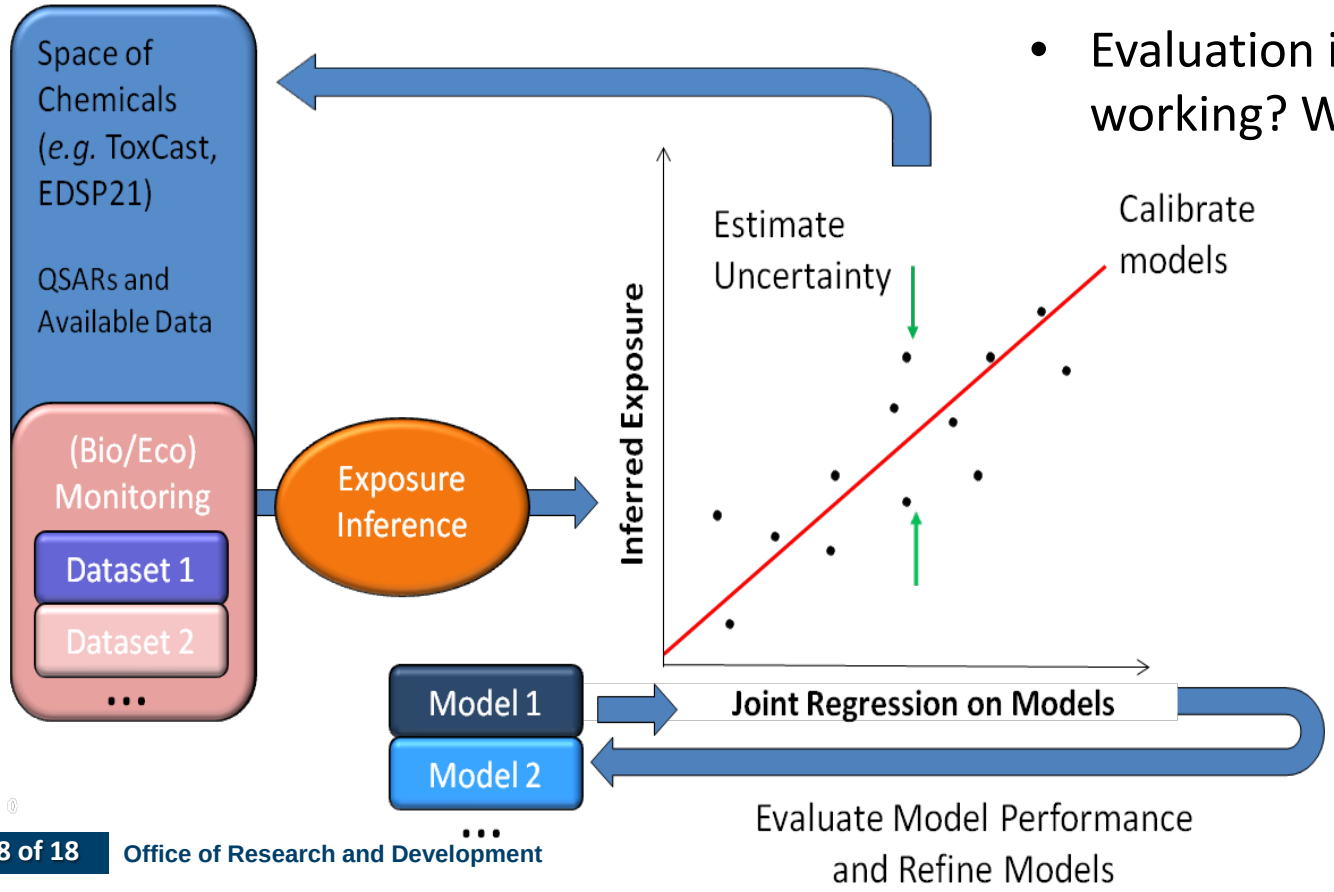




Rager et al. (2016)

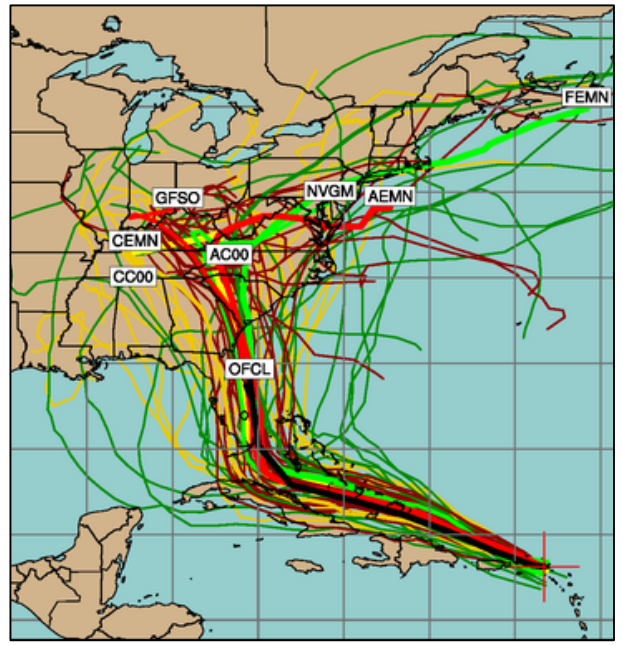
Consensus Exposure Predictions with the SEEM Framework

- Different exposure models incorporate **knowledge**, **assumptions**, and **data** (MacLeod et al., 2010)
- We incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)** (Wambaugh et al., 2013, 2014)

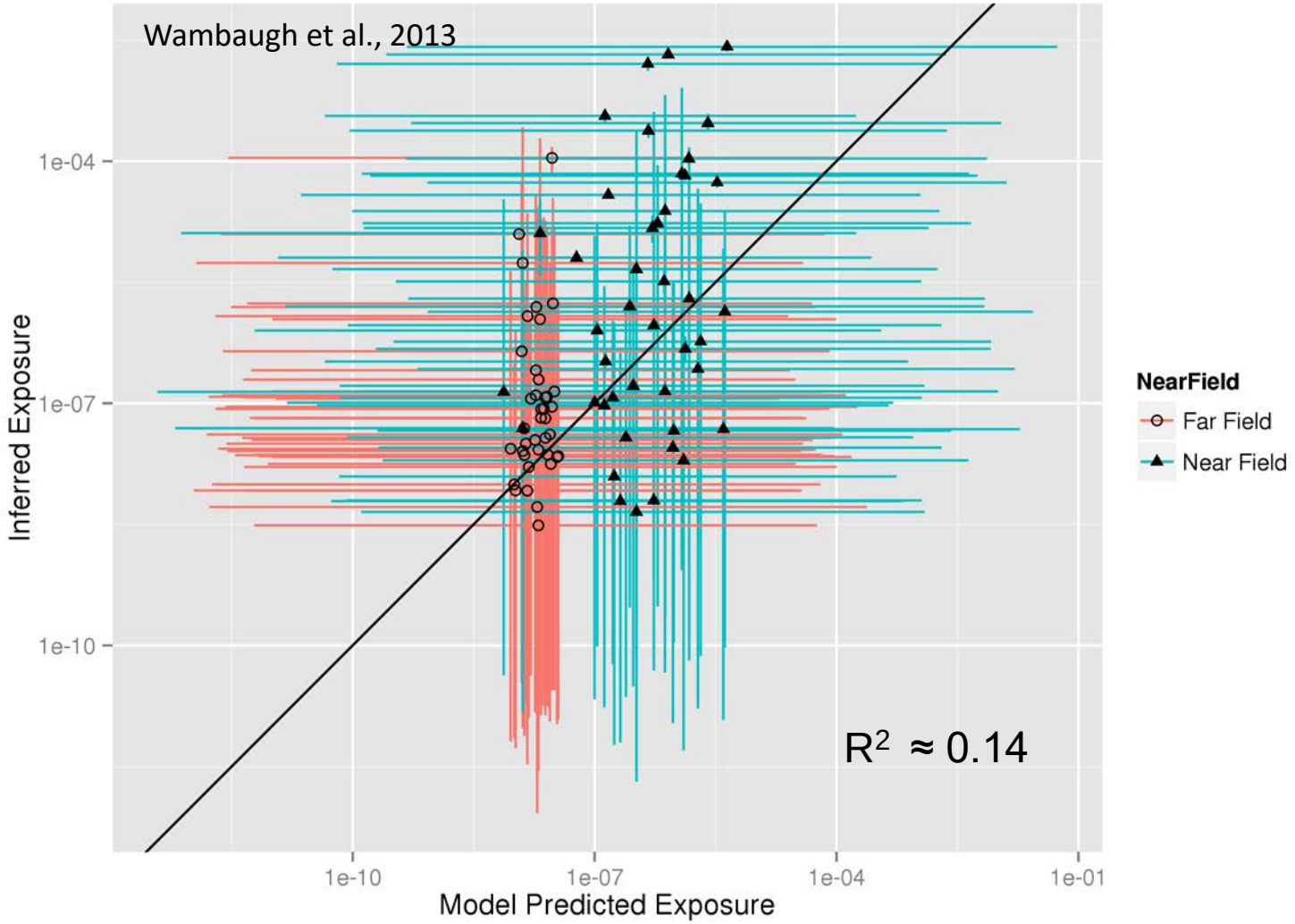


- Evaluation is similar to a sensitivity analysis: What models are working? What data are most needed?

Hurricane Path Prediction is an Example of Integrating Multiple Models

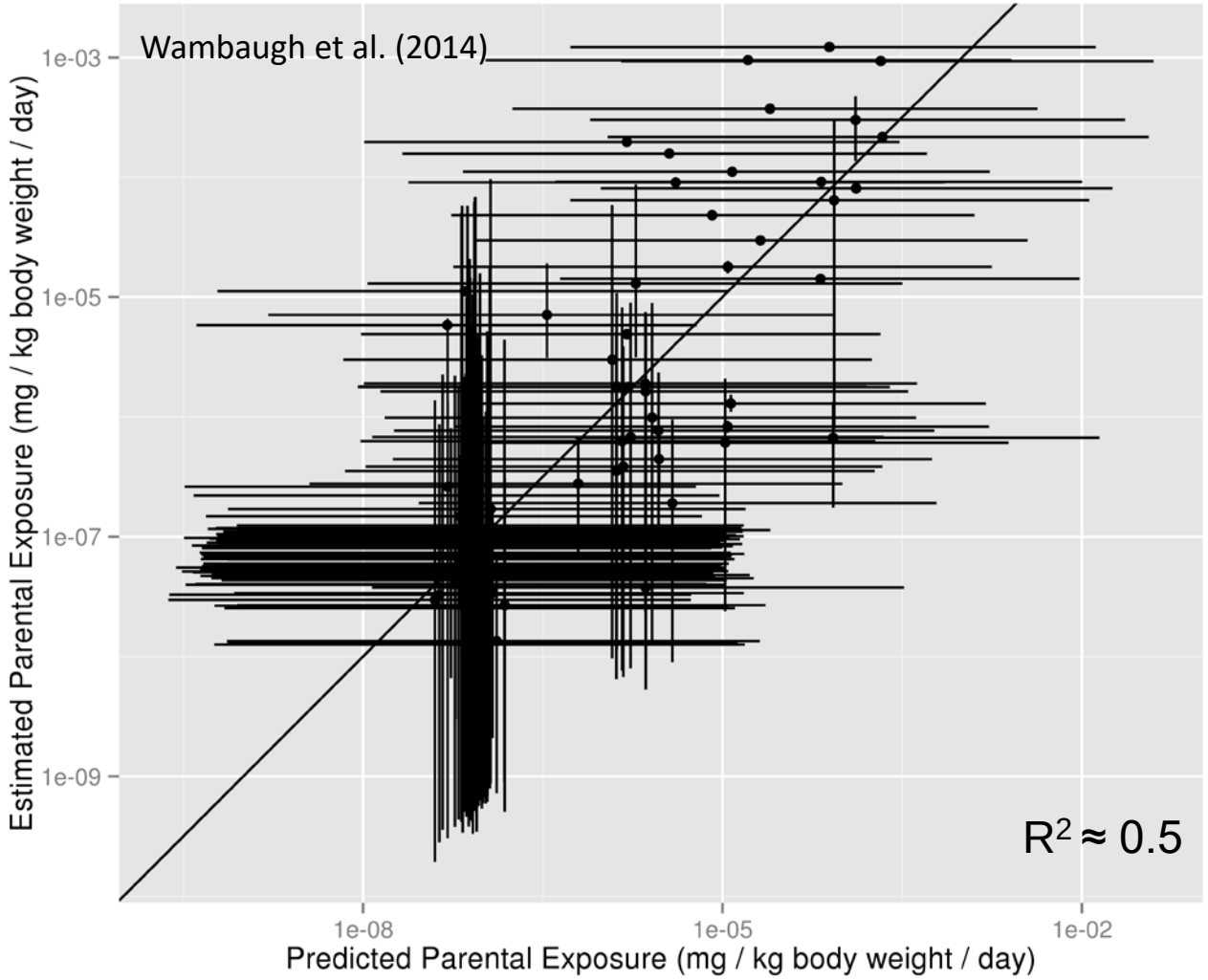


First Generation SEEM



- Those chemicals with "near-field" – proximate, in the home, sources of exposure – had much higher rates of exposure than those with sources outside the home (Wallace et al., 1986)
- The only available "high throughput exposure models in 2013 were for far-field sources

Second Generation SEEM

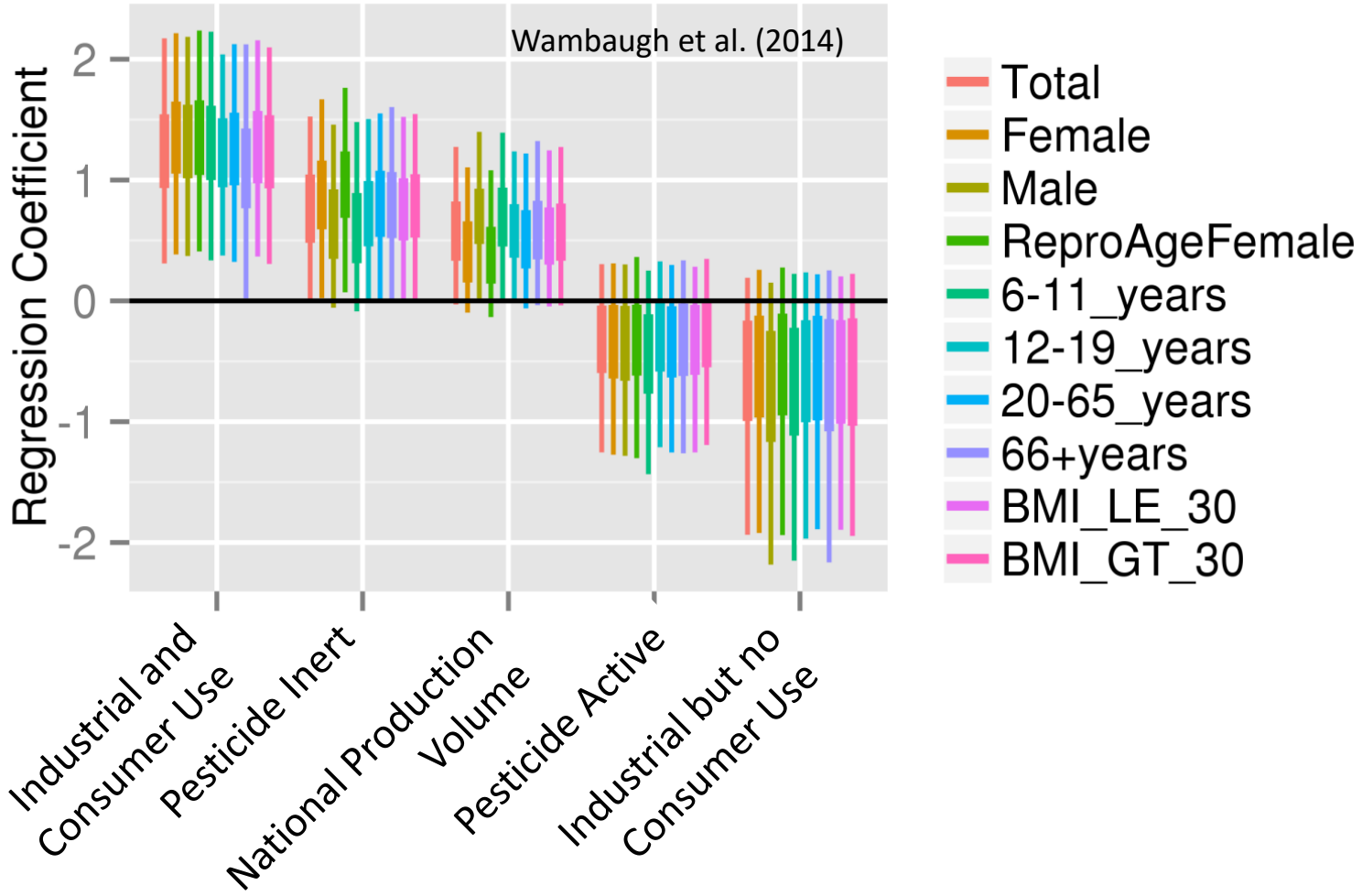


$R^2 \approx 0.5$ indicates that we can predict 50% of the chemical to chemical variability in median NHANES exposure rates

Same five predictors work for all NHANES demographic groups analyzed – stratified by age, sex, and body-mass index:

- Industrial and Consumer use
- Pesticide Inert
- Pesticide Active
- Industrial but no Consumer use
- Production Volume

Heuristics of Exposure



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- Industrial and Consumer use
- Pesticide Inert
- Pesticide Active
- Industrial but no Consumer use
- Production Volume

Knowledge of Exposure Pathways Limits High Throughput Exposure Models

"In particular, the assumption that 100% of [quantity emitted, applied, or ingested] is being applied to each individual use scenario is a very conservative assumption for many compound / use scenario pairs."

Environmental Science & Technology

Article

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Risk-Based High-Throughput Chemical Screening and Prioritization using Exposure Models and in Vitro Bioactivity Assays

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Supporting Information

ABSTRACT: We present a risk-based high-throughput screening

Predicting Exposure Pathways

We use the method of Random Forests to relate chemical structure and properties to exposure pathway

	NHANES Chemicals	Positives	Negatives	OOB Error Rate	Positives Error Rate	Balanced Accuracy	Sources of Positives	Sources of Negatives
Dietary	24	2523	8865	27	32	73	FDA CEDI, ExpoCast, CPDat (Food, Food Additive, Food Contact), NHANES Curation	Pharmapendium, CPDat (non-food), NHANES Curation
Near-Field	**49**	1622	567	26	24	74	CPDat (consumer_use, building_material), ExpoCast, NHANES Curation	CPDat (Agricultural, Industrial), FDA CEDI, NHANES Curation
Far-Field Pesticide	**94**	1480	6522	21	36	80	REDs, Swiss Pesticides, Stockholm Convention, CPDat (Pesticide), NHANES Curation	Pharmapendium, Industrial Positives, NHANES Curation
Far Field Industrial	**42**	5089	2913	19	16	81	CDR HPV, USGS Water Occurrence, NORMAN PFAS, Stockholm Convention, CPDat (Industrial, Industrial_Fluid), NHANES Curation	Pharmapendium, Pesticide Positives, NHANES Curation

Ring et al., submitted

Ring et al., submitted

Collaboration on High Throughput Exposure Predictions

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

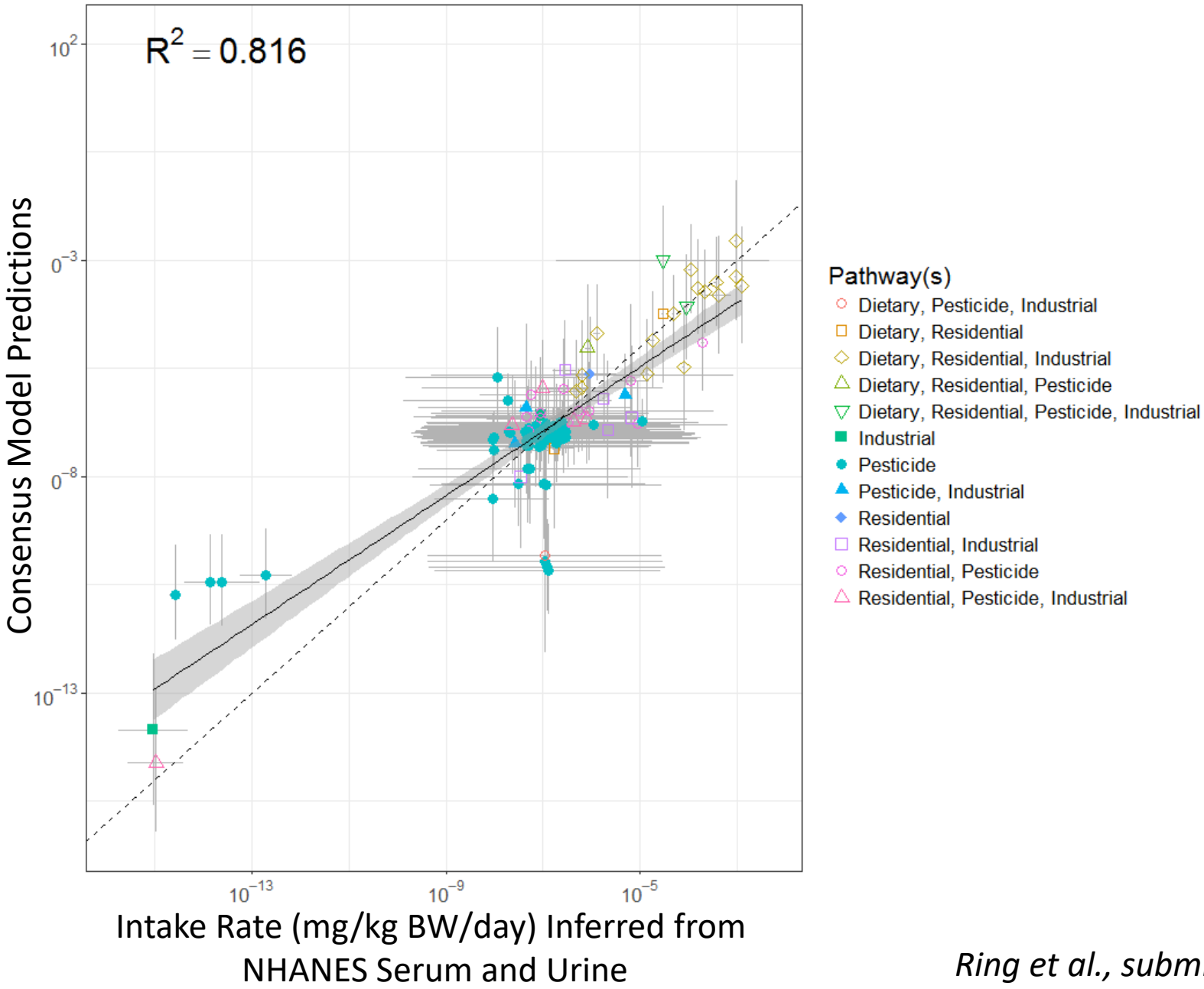
Predictor	Reference(s)	Chemicals Predicted	Pathways
EPA Inventory Update Reporting and Chemical Data Reporting (CDR) (2015)	US EPA (2018)	7856	All
Stockholm Convention of Banned Persistent Organic Pollutants (2017)	Lallas (2001)	248	Far-Field Industrial and Pesticide
EPA Pesticide Reregistration Eligibility 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

Pathway-Based Consensus Modeling of NHANES

- New machine learning tools provide improved high throughput exposure estimates by matching chemicals to exposure pathways and associated calibrated exposure models.

- Exposure predictors (data and models) have been grouped into four pathways (residential, dietary, pesticidal, and industrial) and calibrated via Bayesian multivariate regression using human intake rates inferred for 114 chemicals from a large bio-monitoring survey.

- We have evaluated and calibrated the models using NHANES biomonitoring data



Ring et al., submitted

Consensus Modeling of Median Chemical Intake

- New machine learning tools provide improved high throughput exposure estimates by matching chemicals to exposure pathways and associated calibrated exposure models.

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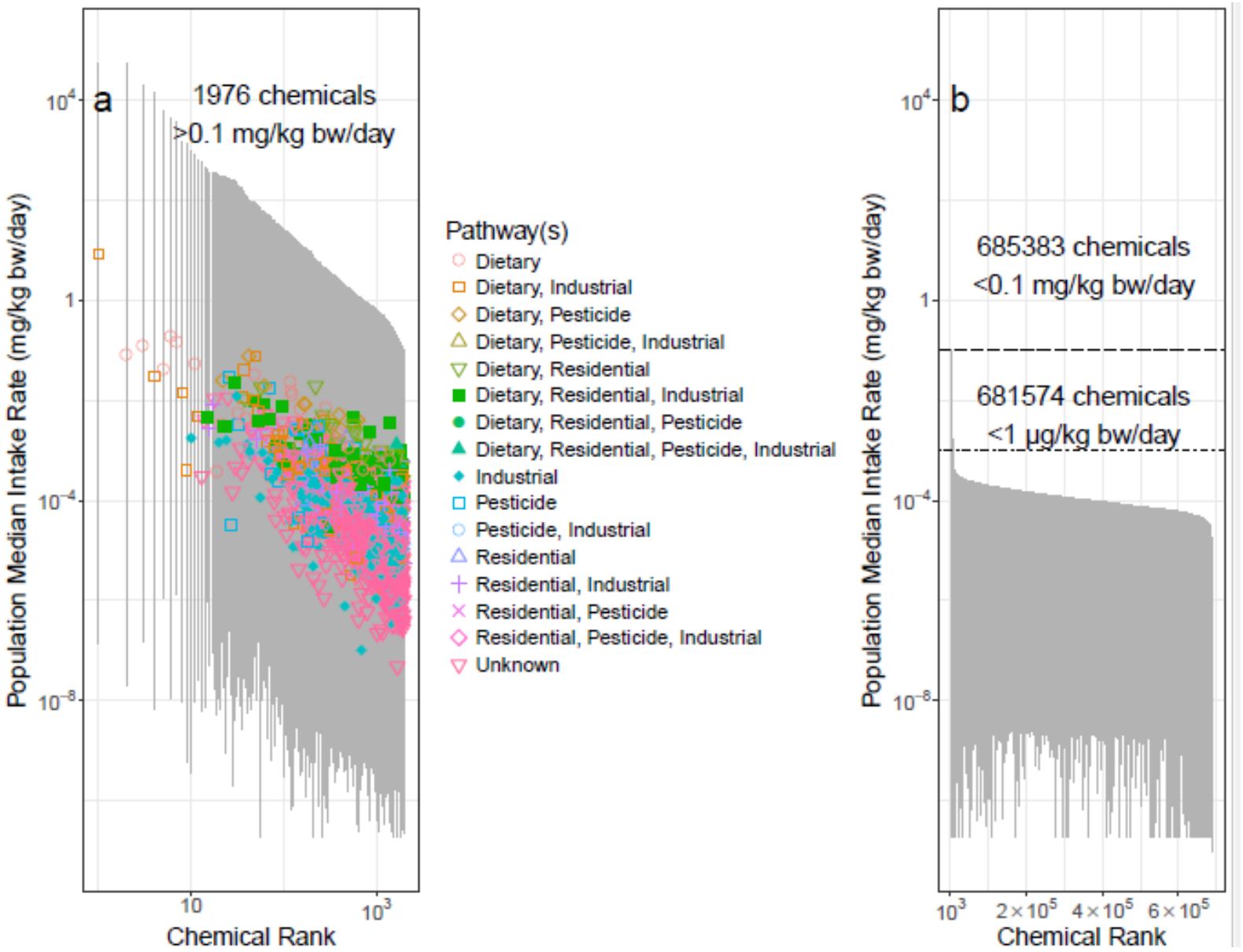
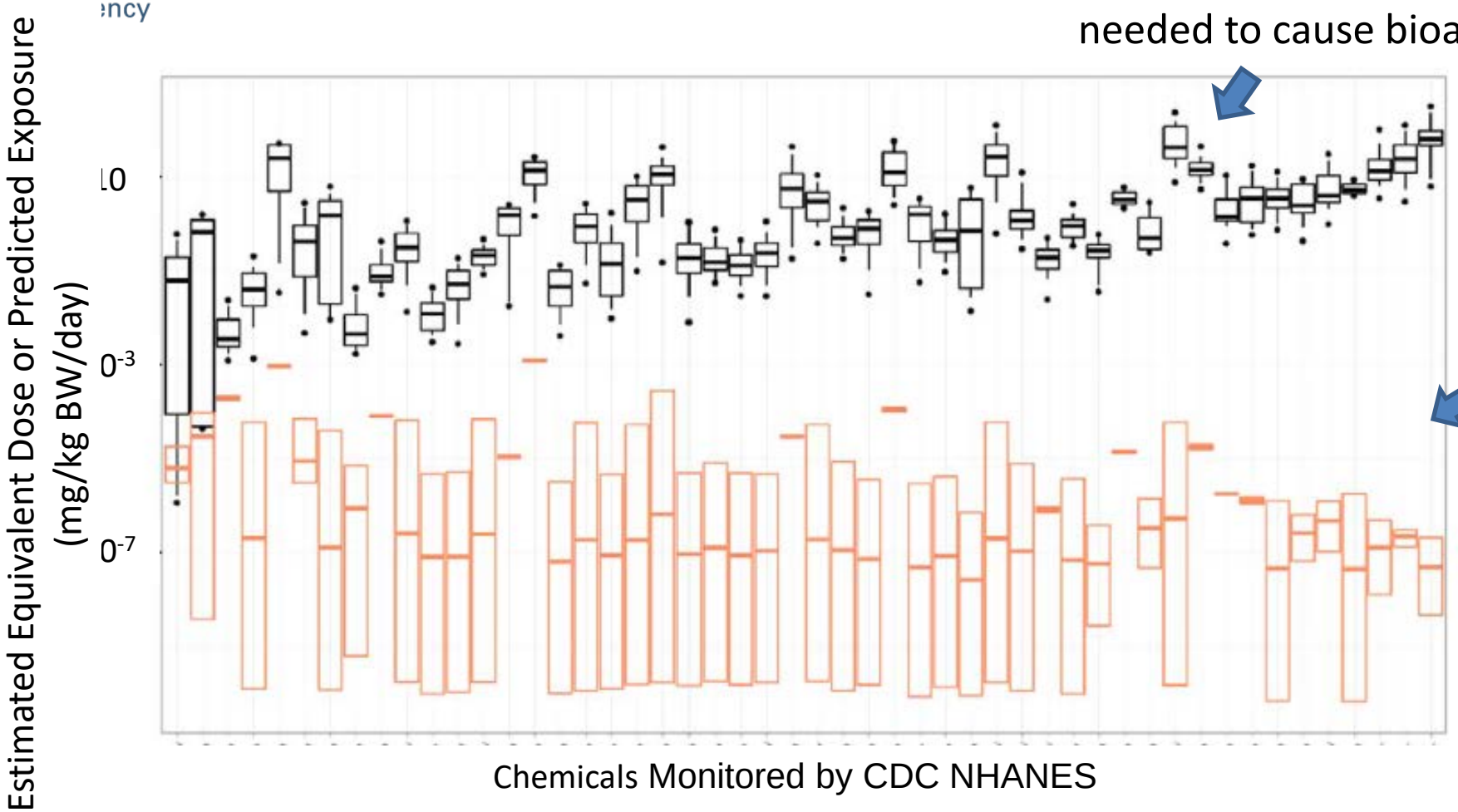


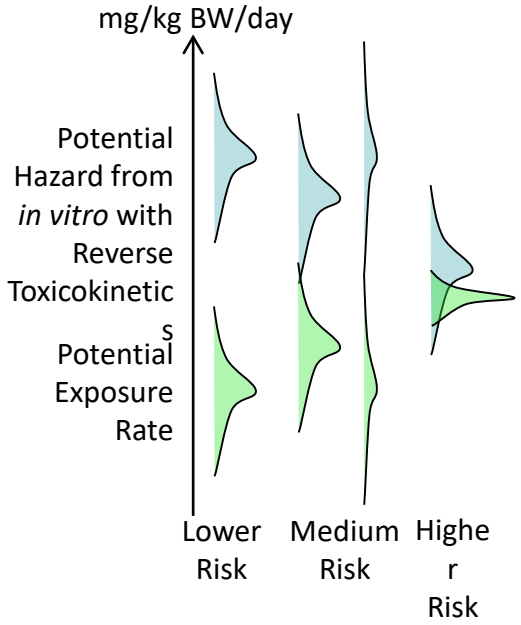
Ring et al., submitted

Selecting Candidates for Prioritization

ToxCast + HTTK can estimate doses needed to cause bioactivity



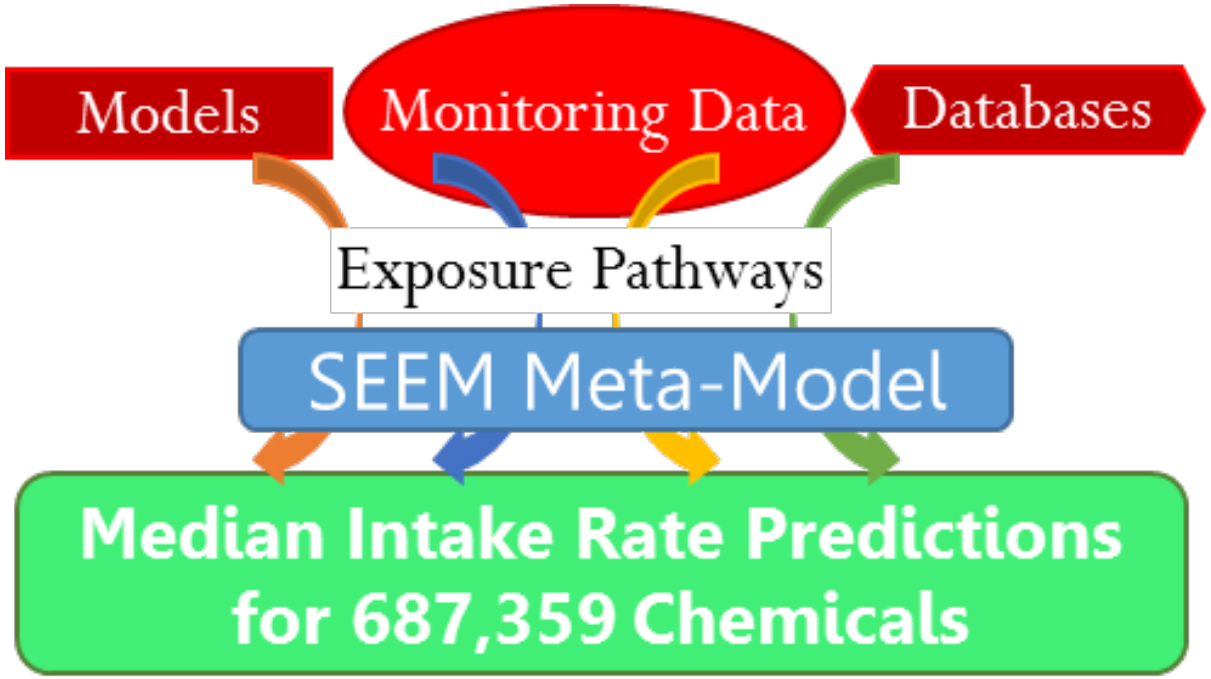
Exposure intake rates can be inferred from biomarkers (Wambaugh et al., 2014)



Ring *et al*. (2017)

Conclusions

- A tapestry of laws covers the chemicals people are exposed to in the United States (Breyer, 2009)
- Most other chemicals, ranging from industrial waste to dyes to packing materials, are covered by the recently updated Toxic Substances Control Act (TSCA) and administered by the EPA
- New approach methodologies (NAMs) are being developed to prioritize these existing and new chemicals for testing
- New machine learning tools provide improved high throughput exposure estimates by matching chemicals to exposure pathways and associated calibrated exposure models.



- Machine learning models based on chemical structure and physico-chemical properties predict whether or not each pathway is relevant to a library of over 680,000 chemicals, allowing an exposure estimate for each chemical based on the calibrated predictors.

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EPA's Chemical Safety for Sustainability (CSS) Research Program

Rapid Exposure and Dosimetry (RED) Project

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