EPA United States Environmental Protection Agency

Predicting Exposure Pathways Allows Risk-Based Prioritization

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EPA Office of Research and Development

- The Office of Research and Development (ORD) is the scientific research arm of EPA
  - 655 peer-reviewed journal articles in 2016
- Research is conducted by ORD's three national laboratories, four national centers, and two offices
  - Includes **National Center for Computational Toxicology** and **National Exposure Research Laboratory**
- 14 facilities across the country and in Washington, D.C.
- Six research programs
  - Includes **Chemical Safety for Sustainability**
- Research conducted by a combination of Federal scientists; contract researchers; and postdoctoral, graduate student, and post-baccalaureate trainees

ORD Facility in Research Triangle Park, NC

Chemical Regulation in the United States

- Park *et al.* (2012): At least 3221 chemicals in pooled human blood samples, many appear to be exogenous
- A tapestry of laws covers the chemicals people are exposed to in the United States (Breyer, 2009)
- Different testing requirements exist for food additives, pharmaceuticals, and pesticide active ingredients (NRC, 2007)

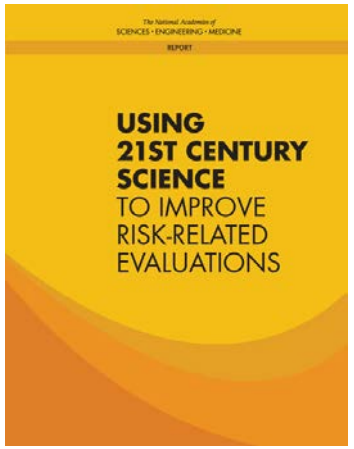
November 29, 2014

Chemical Regulation in the United States

- Most other chemicals, ranging from industrial waste to dyes to packing materials are covered by the recently updated Toxic Substances Control Act (TSCA)
  - Thousands of chemicals on the market were either "grandfathered" in or were allowed without experimental assessment of hazard, toxicokinetics, or exposure
  - Thousands of new chemical use submissions are made to the EPA every year
  - **Methods are being developed to prioritize these existing and new chemicals for testing**

November 29, 2014

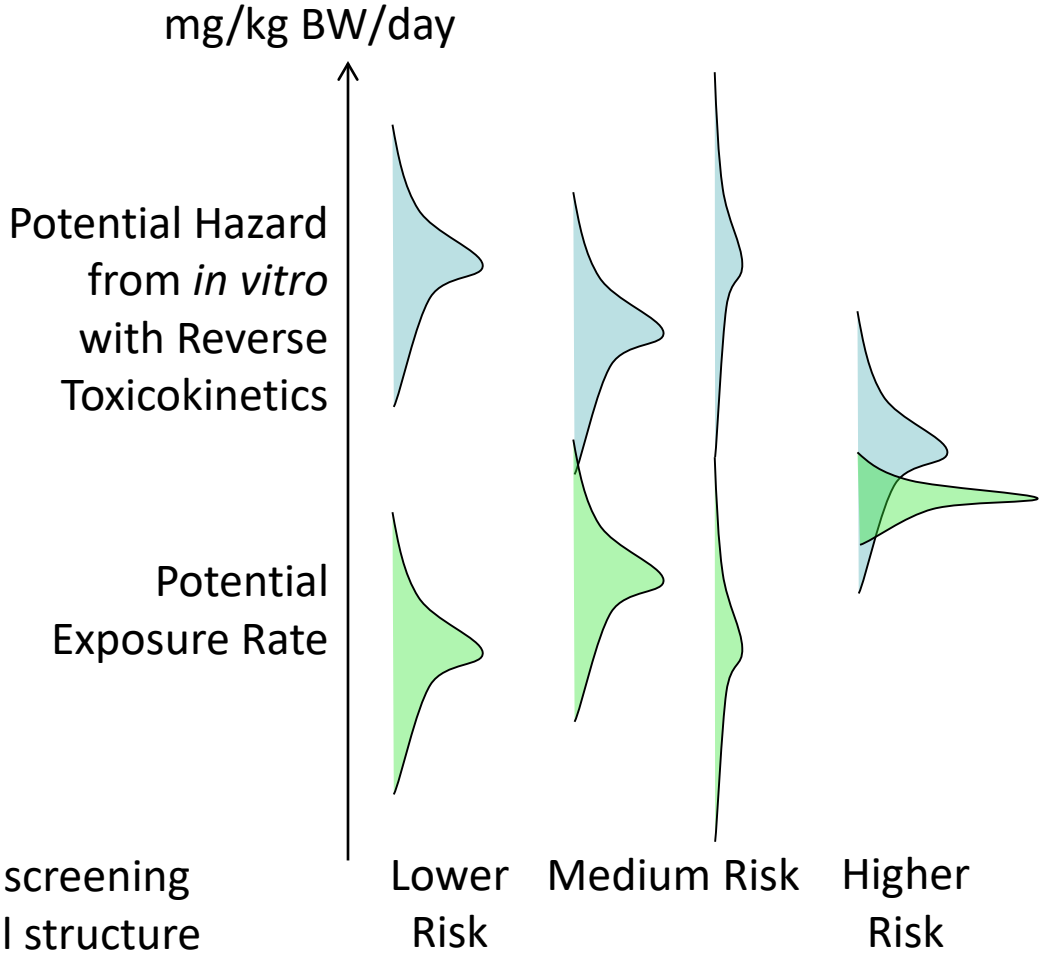
High-Throughput Risk Prioritization



National Academy of Sciences, January, 2017:
"Translation of high-throughput data into risk-based rankings is an important application of exposure data for chemical priority-setting. Recent advances in high-throughput toxicity assessment, notably the ToxCast and Tox21 programs… and in high-throughput computational exposure assessment… have enabled first-tier risk-based rankings of chemicals on the basis of margins of exposure…"

High throughput risk prioritization needs:

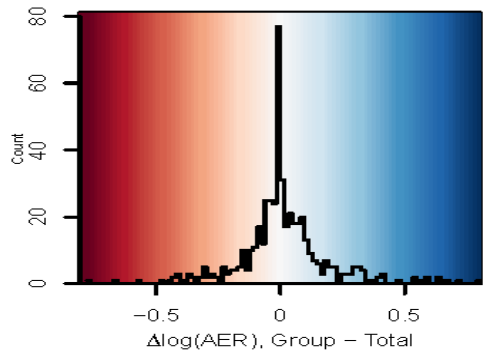
1. high throughput **hazard** characterization
2. high throughput **exposure** forecasts
3. high throughput **toxicokinetics** (*i.e.*, dosimetry)

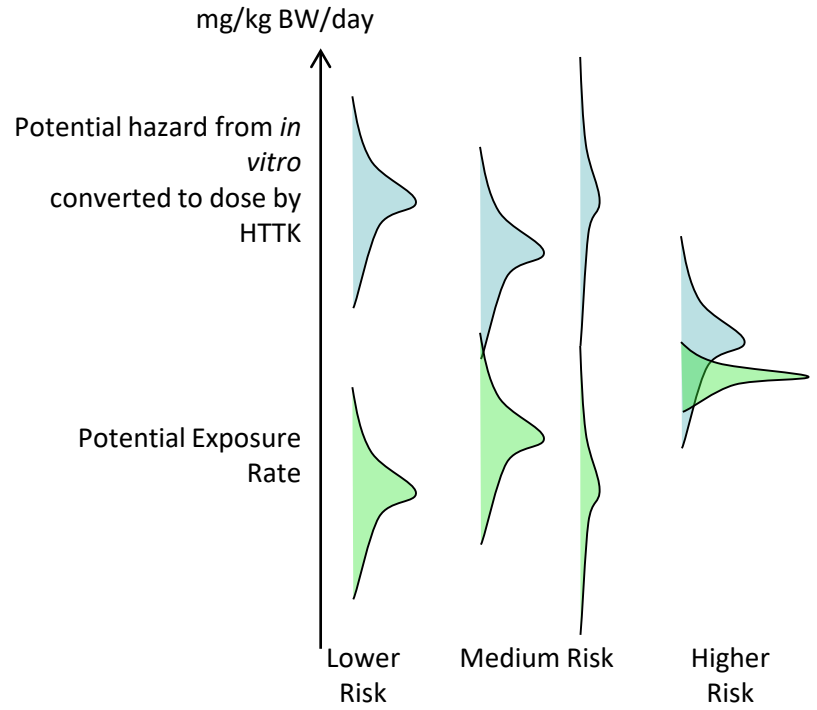


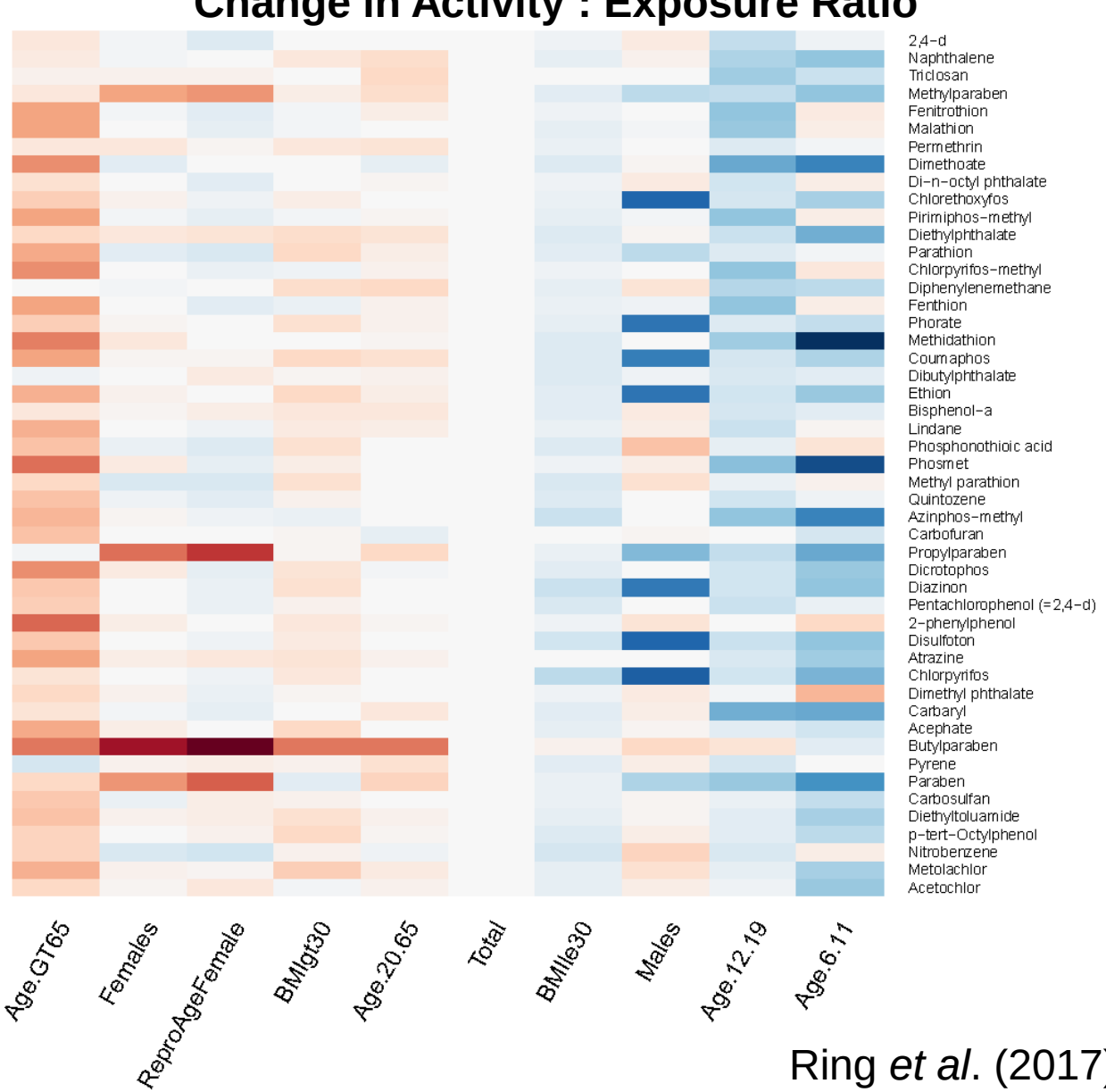
Providing predictions for novel compounds will need to rely on screening massive chemical libraries and drawing inference from chemical structure (*e.g.*, quantitative structure activity relationships, QSAR)

Life-stage and Demographic Specific Predictions

We use toxicokinetics to calculate margin between bioactivity and exposure for specific populations

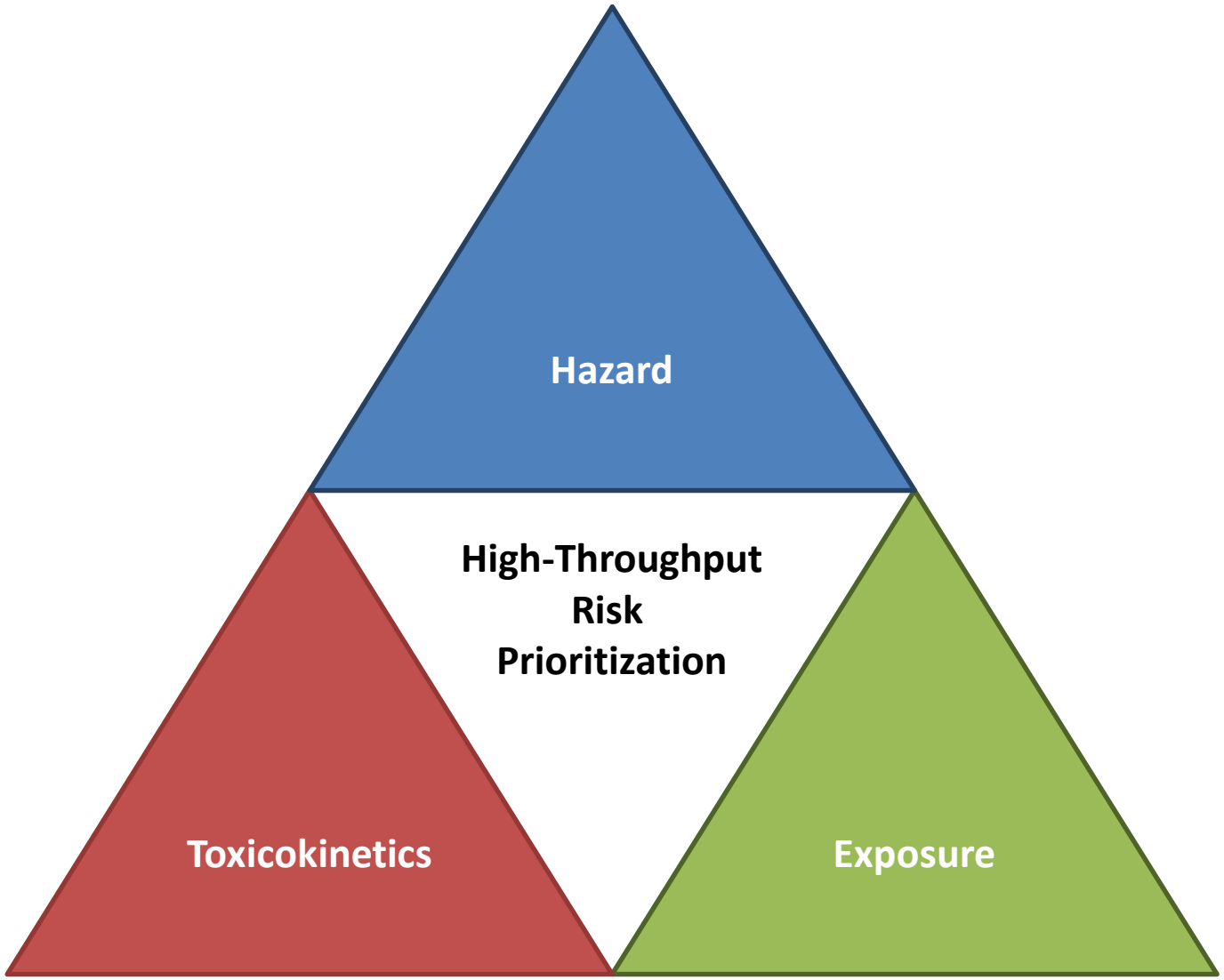






Ring *et al*. (2017)

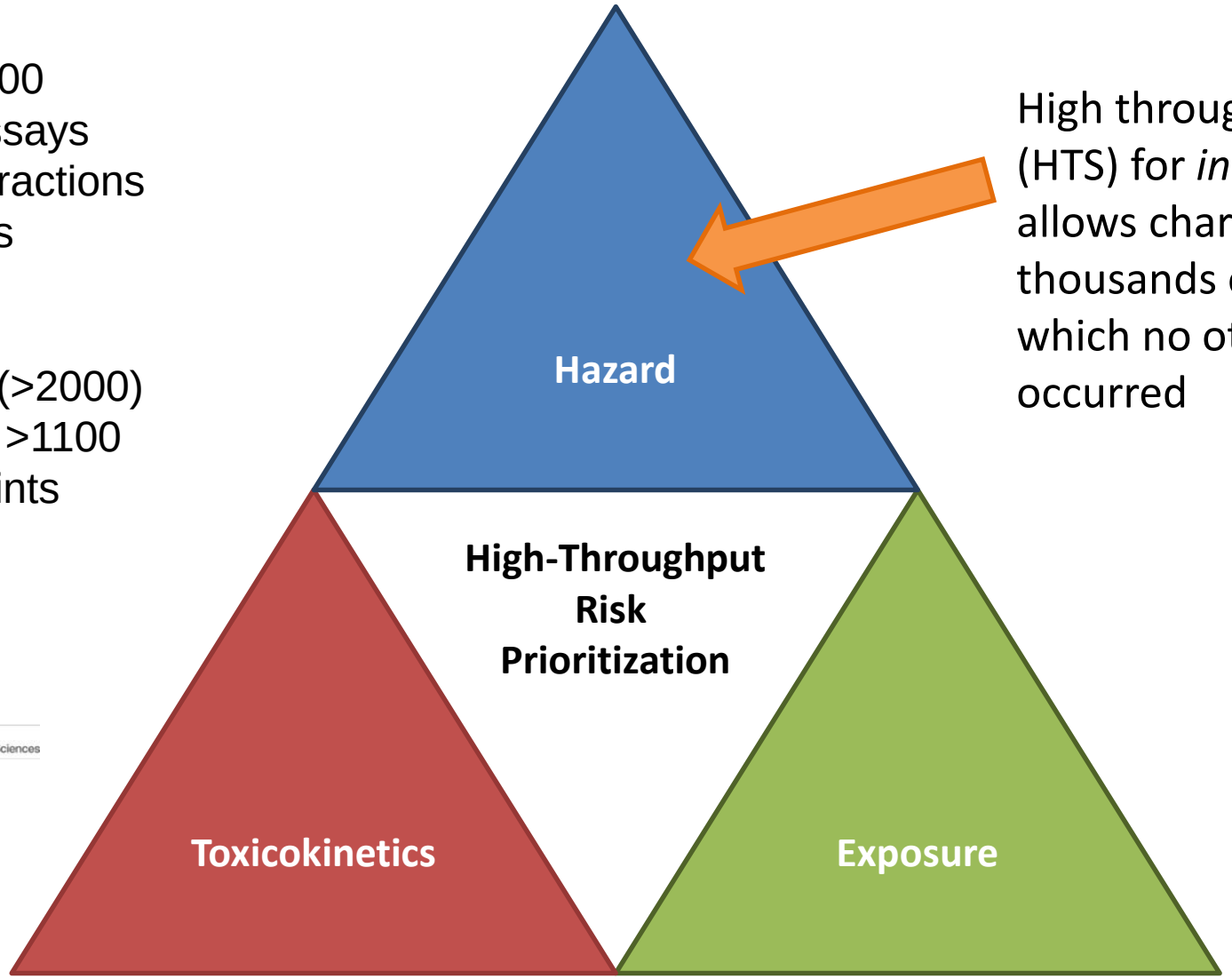
High-Throughput Risk Prioritization



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)

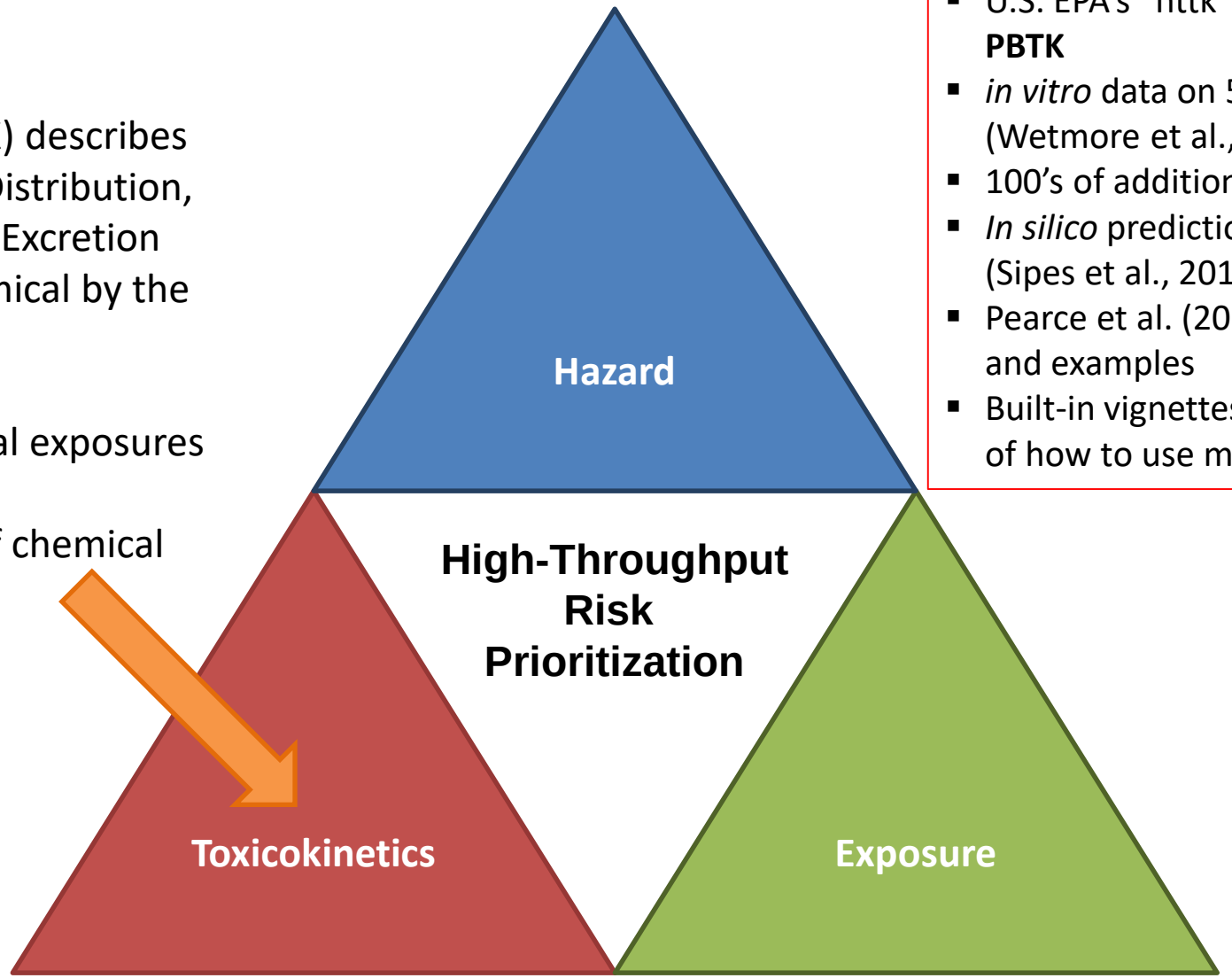


High throughput screening (HTS) for *in vitro* bioactivity allows characterization of thousands of chemicals for which no other testing has occurred

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

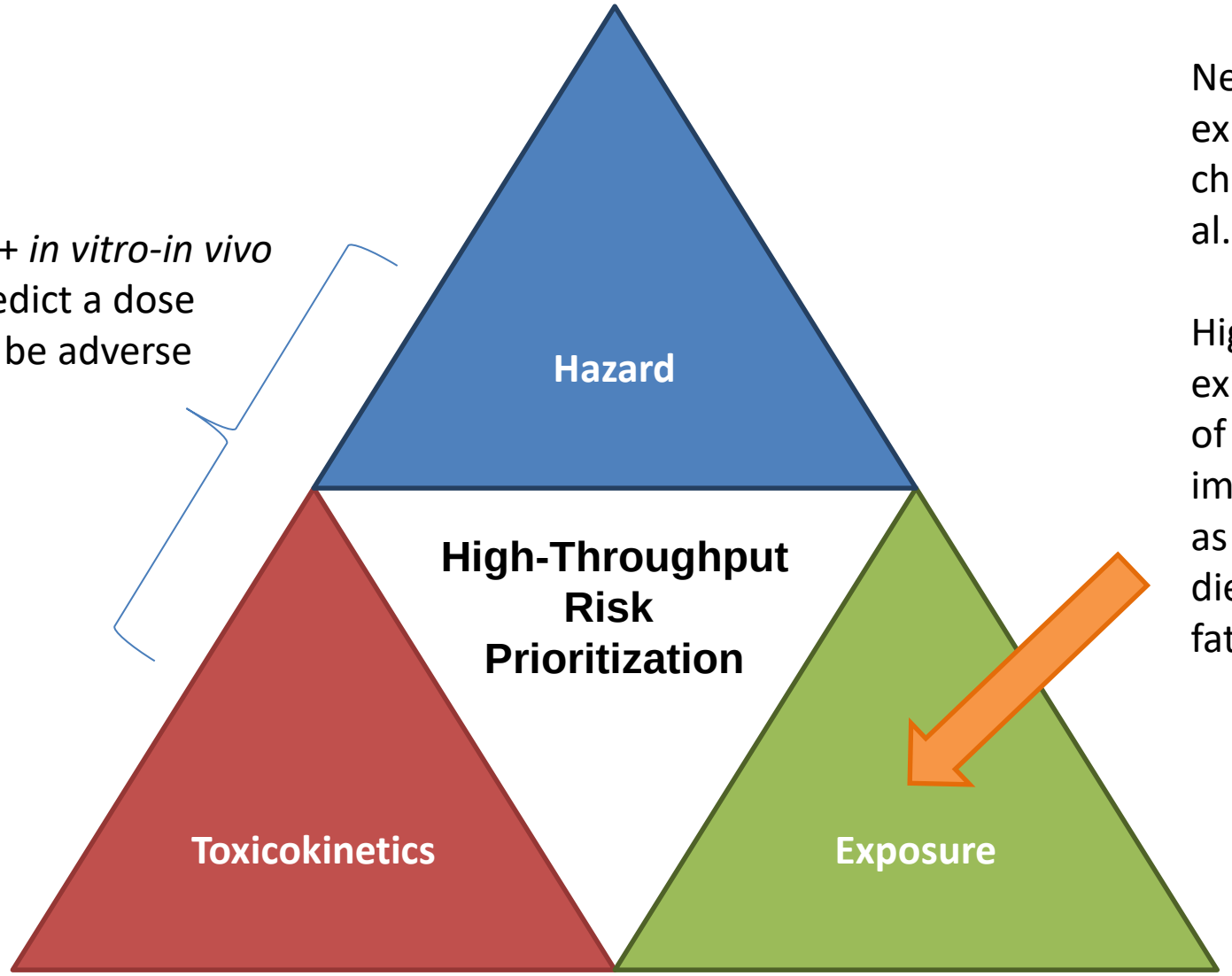


- U.S. EPA's "httk" R Package for IVIVE and **PBTK**
- *in vitro* data on 553 chemicals to date (Wetmore et al., 2012, 2015)
- 100's of additional chemicals being tested
- *In silico* predictions for ~8000 chemicals (Sipes et al., 2017)
- Pearce et al. (2017) provides documentation and examples
- Built-in 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

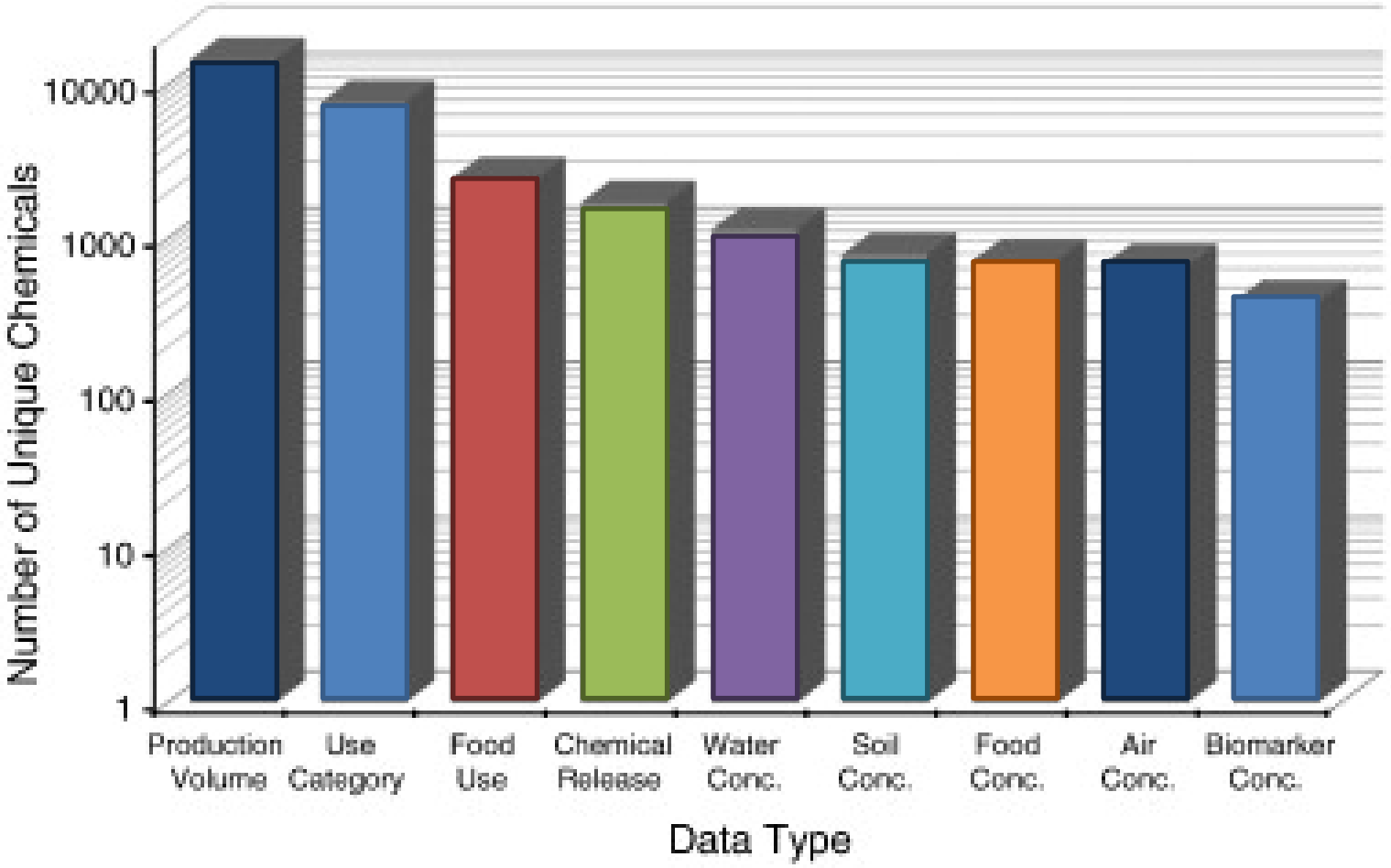


Need methods to forecast exposure for thousands of chemicals (Wetmore et al., 2015)

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

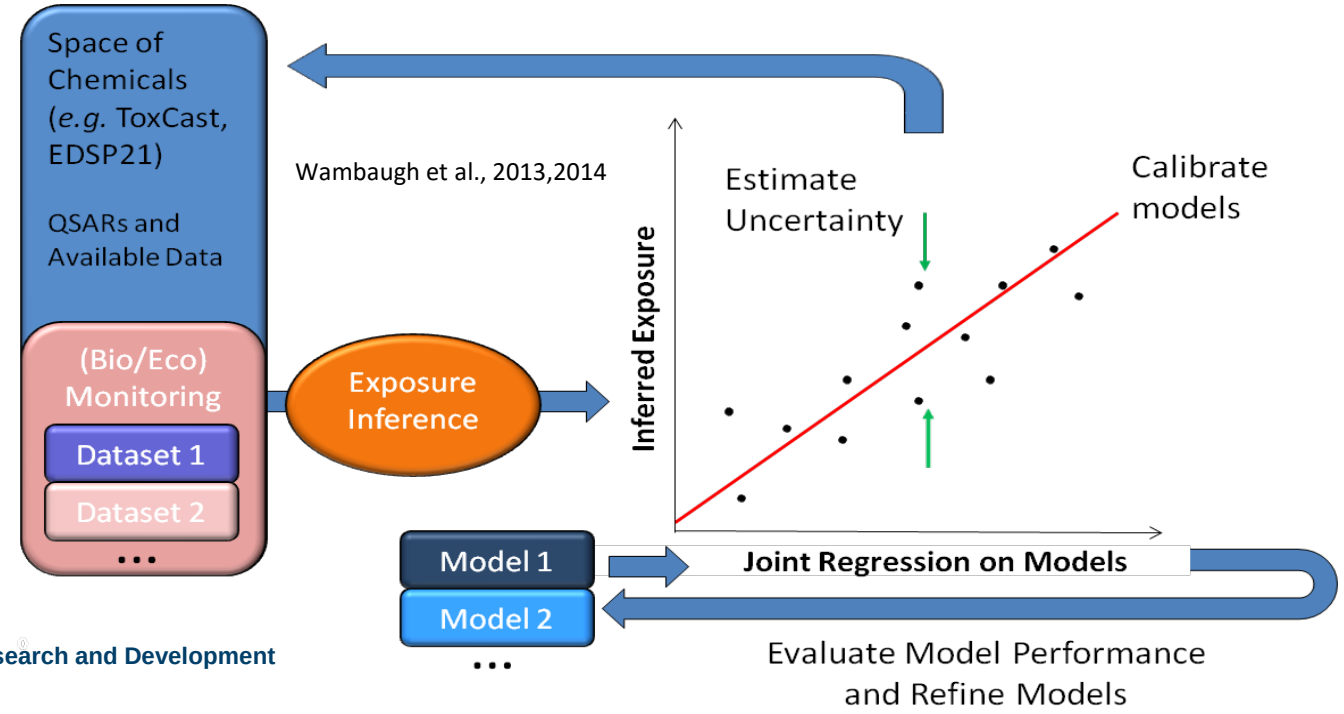
Limited Exposure Data

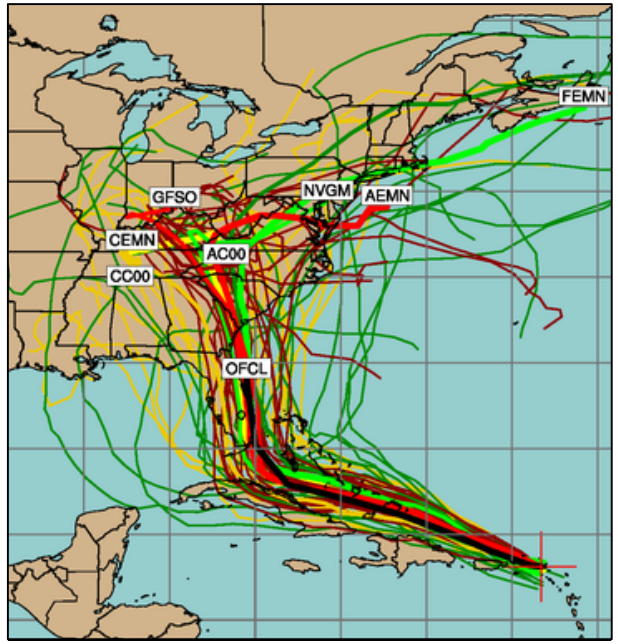
Most chemicals lack public exposure data beyond production volume (Egeghy et al., 2012)



Consensus Exposure Predictions with the SEEM Framework

- Different exposure models incorporate **knowledge**, **assumptions**, and **data** (Macleod, et al., 2010)
- 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
- Separate evaluations can be done for various demographics
- ~2000 individuals per chemical, with statistical weights allowing inference for larger U.S. populations
- To date, we have used this to draw inference about median exposure rates

National Health and Nutrition Examination Survey

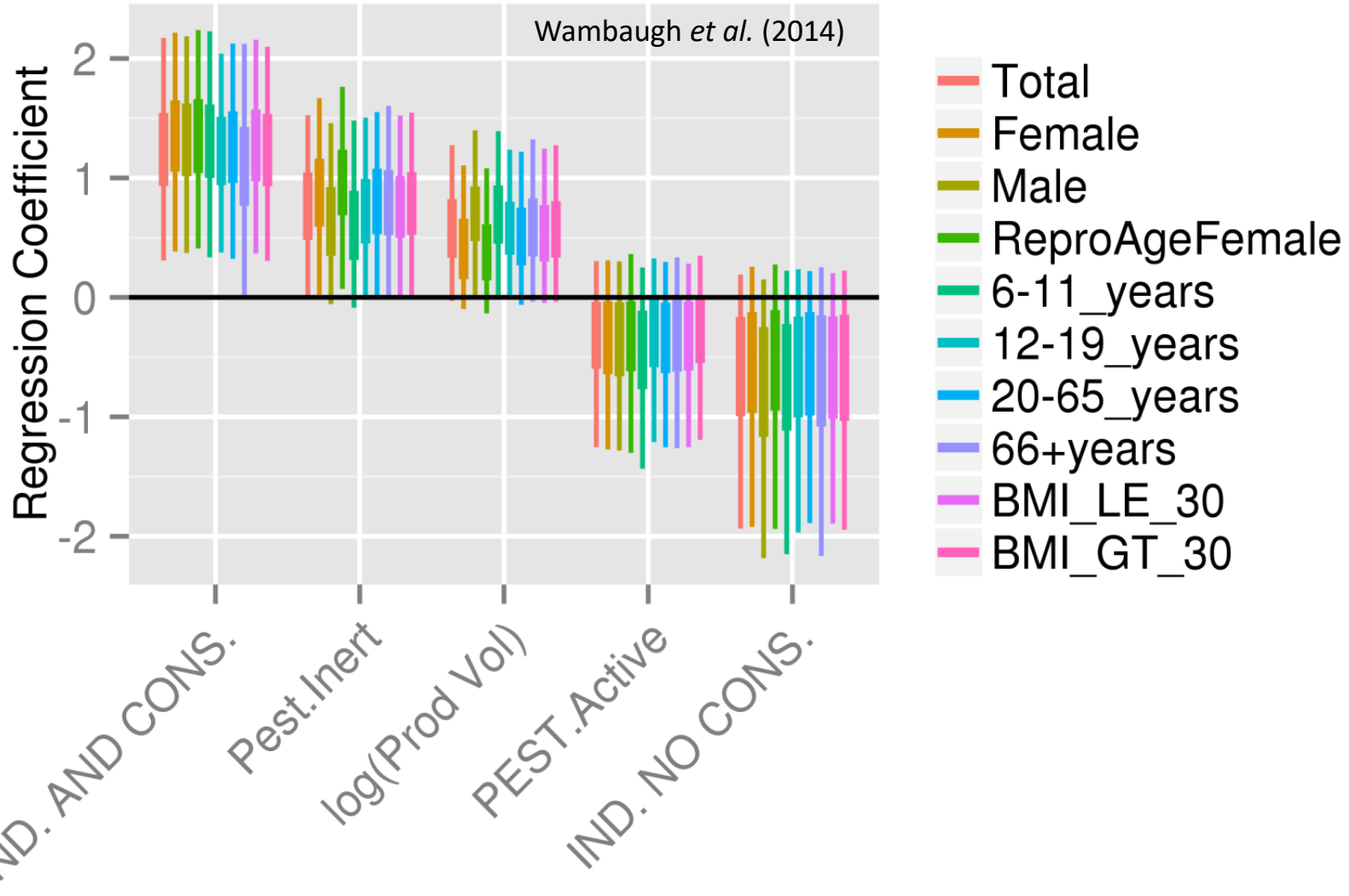
Urinary Bisphenol A (2,2-*bis*[4-Hydroxyphenyl] propane)

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)

Heuristics of Exposure



Five descriptors explain roughly 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

What we are really doing is identifying chemical exposure pathway

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

Model	Version	Reference	Dietary	Near-Field	Far-Field Pesticide	Far Field Industrial
EPA Stochastic Human Exposure Dose Simulator High Throughput (SHEDS-HT) Near-Field Direct	2017	Isaacs, et al. (2017)		1119		
SHEDS-HT Near-field Indirect	2017	Isaacs, et al. (2017)		645		
Shin-Bennett	2017	Shin et al. (2017)		1221		
Food Contact Substance Migration Model	2017	Biryol et al. (2017)	940			
EPA Pesticide Reregistration Eligibility Documents (REDs) Exposure Assessments	2015	Wetmore et al. (2012, 2015)			239	
Risk Assessment IDentification And Ranking (RAIDAR) Far-Field	2.941	Arnot et al. (2006)			7511	7511
RAIDAR-ICE Near-Field	0.803	Arnot et al. (2017)		615		
United Nations Environment Program and Society for Environmental Toxicology and Chemistry toxicity model (USETox) Pesticide Scenario	1.01	Rosenbaum (2008)			790	
USEtox Industrial Scenario	1.01	Rosenbaum (2008)				7184
EPA Inventory Update Reporting and Chemical Data Reporting (CDR)	2015	US EPA (2018)	7856	7856	7856	7856
FDA Cumulative Estimated Daily Intake (CDI)	2017	US FDA (2017)	748			
Stockholm Convention of Banned Persistent Organic Pollutants	2017	Stockholm Convention (2017)			22	225

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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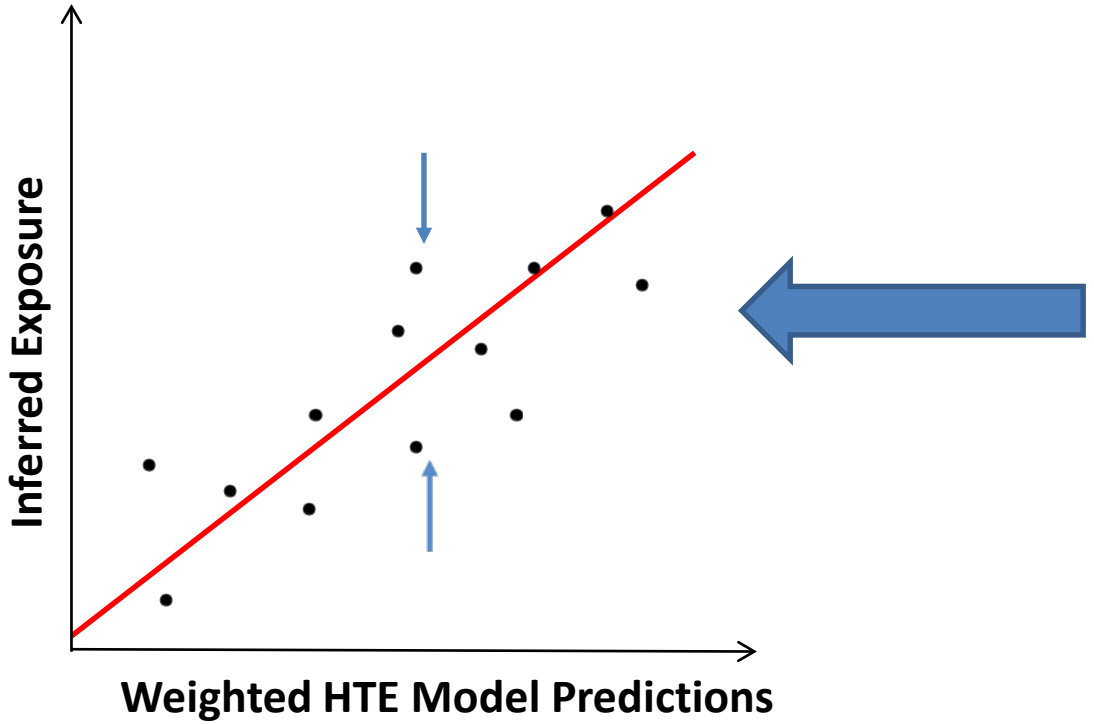
Supporting Information

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

SEEM is a Linear Regression

Multiple regression models:

$$\text{Log(Parent Exposure)} = a + m * \log(\text{Model Prediction}) + b * \text{Near Field} + \varepsilon$$

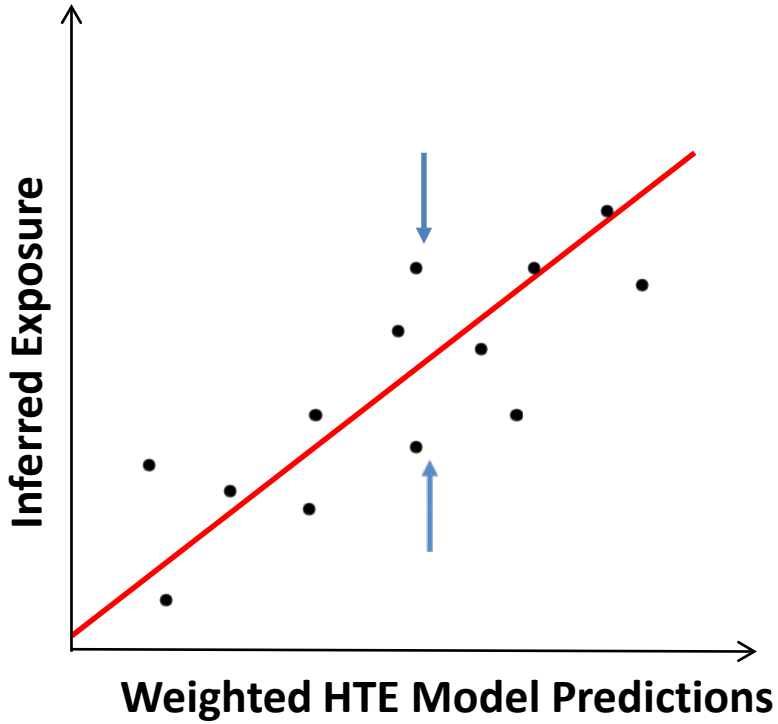


$\varepsilon \sim N(0, \sigma^2)$
Residual error, unexplained by the regression model

SEEM is a Linear Regression

Multiple regression models:

$$\text{Log(Parent Exposure)} = a + m * \log(\text{Model Prediction}) + b * \text{Near Field} + \varepsilon$$



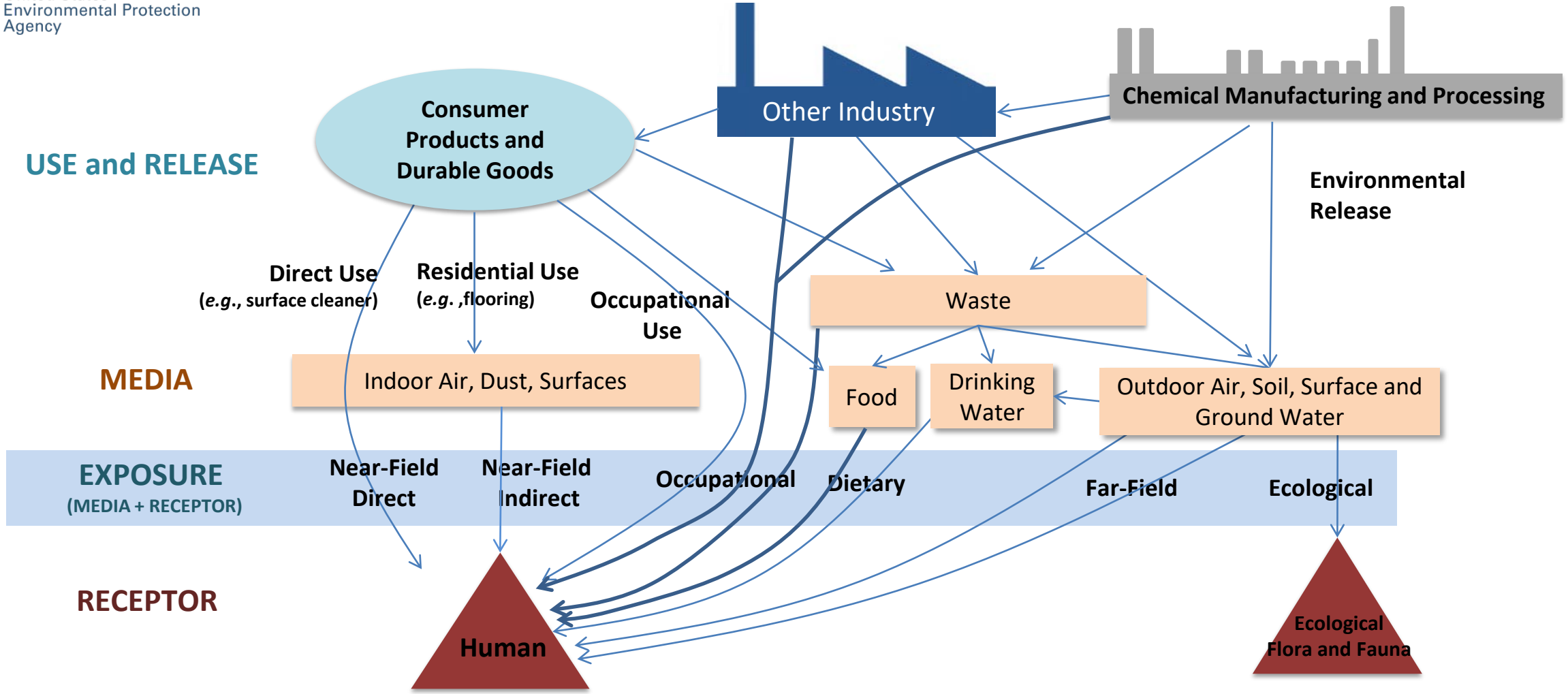
Not all models have predictions for all chemicals

- We can run SHEDS-HT (Isaacs et al., 2014) for ~2500 chemicals

What do we do for the rest?

- Assign the average value?
- Zero?

Forecasting Exposure is a Systems Problem



- **Exposure event unobservable:** 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)

Figure from Kristin Isaacs

Pathway Predictors:

Chemical Use Identifies Relevant Pathways

When averaging over many exposure models, the trick is to know which one to use…

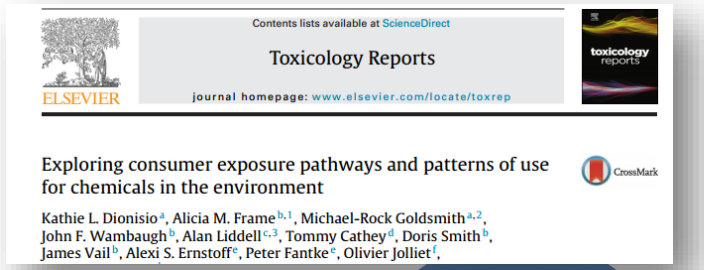
Machine learning models were built for each four exposure pathways:

1. Far-field pesticide use
2. Non-pesticide dietary exposure
3. Far-field industrial exposure (e.g. drinking water)
4. Near-field exposure (e.g., consumer products).

Pathway	Positive Pathway Training Chemicals	Negative Pathway Training Chemicals	Out of Box Error Rate	Positives Error Rate	Balanced Accuracy	Sources of Positives	Sources of Negatives
Dietary	2520	3347	25	28	75	FDA CEDI, ExpoCast*, CPDat (Food, Food Additive, Food Contact), NHANES Curation	Pharmapendium, CPDat (non-food), NHANES Curation
Near-Field	1621	552	22	7.1	78	CPDat (consumer_use, building_material), ExpoCast, NHANES Curation	CPDat (Agricultural, Industrial), FDA CEDI, NHANES Curation
Far-Field Pesticide	1404	5754	16	72	84	REDs, Stockholm Convention, CPDat(Pesticide), NHANES Curation	Pharmapendium, Industrial Positives, NHANES Curation
Far Field Industrial	4325	2833	20	13	80	CDR HPV, USGS Water Occurence, Stockholm Convention, CPDat (Indutrial, Industrial_Fluid), NHANES Curation	Pharmapendium, Pesticide Positives, NHANES Curation

*Phillips et al., accepted

Chemical Use: Chemicals and Products Database (CPDat)


Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Exploring consumer exposure pathways and patterns of use for chemicals in the environment

Kathie L. Dionisio[a], Alicia M. Frame[b,1], Michael-Rock Goldsmith[a,2], John F. Wambaugh[b], Alan Liddell[c,3], Tommy Cathey[d], Doris Smith[b], James Vail[b], Alexi S. Ernstoff[e], Peter Fantke[e], Olivier Jolliet[f],

Broad "index" of chemical uses

MSDS Data


Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Development of a consumer product ingredient database for chemical exposure screening and prioritization

M.-R. Goldsmith[a,*], C.M. Grulke[a], R.D. Brooks[b], T.R. Transue[c], Y.M. Tan[a], A. Frame[a,e], P.P. Egeghy[a], R. Edwards[d], D.T. Chang[a], R. Tornero-Velez[a], K. Isaacs[a], A. Wang[a,e], J. Johnson[a], K. Holm[a], M. Reich[f], J. Mitchell[g], D.A. Vallero[a], L. Phillips[a], M. Phillips[a], J.F. Wambaugh[a], R.S. Judson[a], T.J. Buckley[a], C.C. Dary[a]

Occurrence and quantitative chemical composition

CPCat

(Chemical and Product Categories)

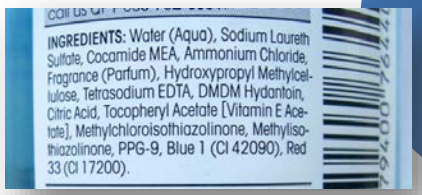
CPDat

Dionisio et al., submitted

Functional Use Data and Predictions

Package 'CPDat'

Occurrence data



Ingredient Lists


Green Chemistry

PAPER

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Cite this: *Green Chem.*, 2017, **19**, 1063

High-throughput screening of chemicals as functional substitutes using structure-based classification models†

Katherine A. Phillips,*[a,c] John F. Wambaugh,[b] Christopher M. Grulke,[b] Kathie L. Dionisio[c] and Kristin K. Isaacs[c]

EPA United States Environmental Protection Agency | Home

Chemistry Dashboard

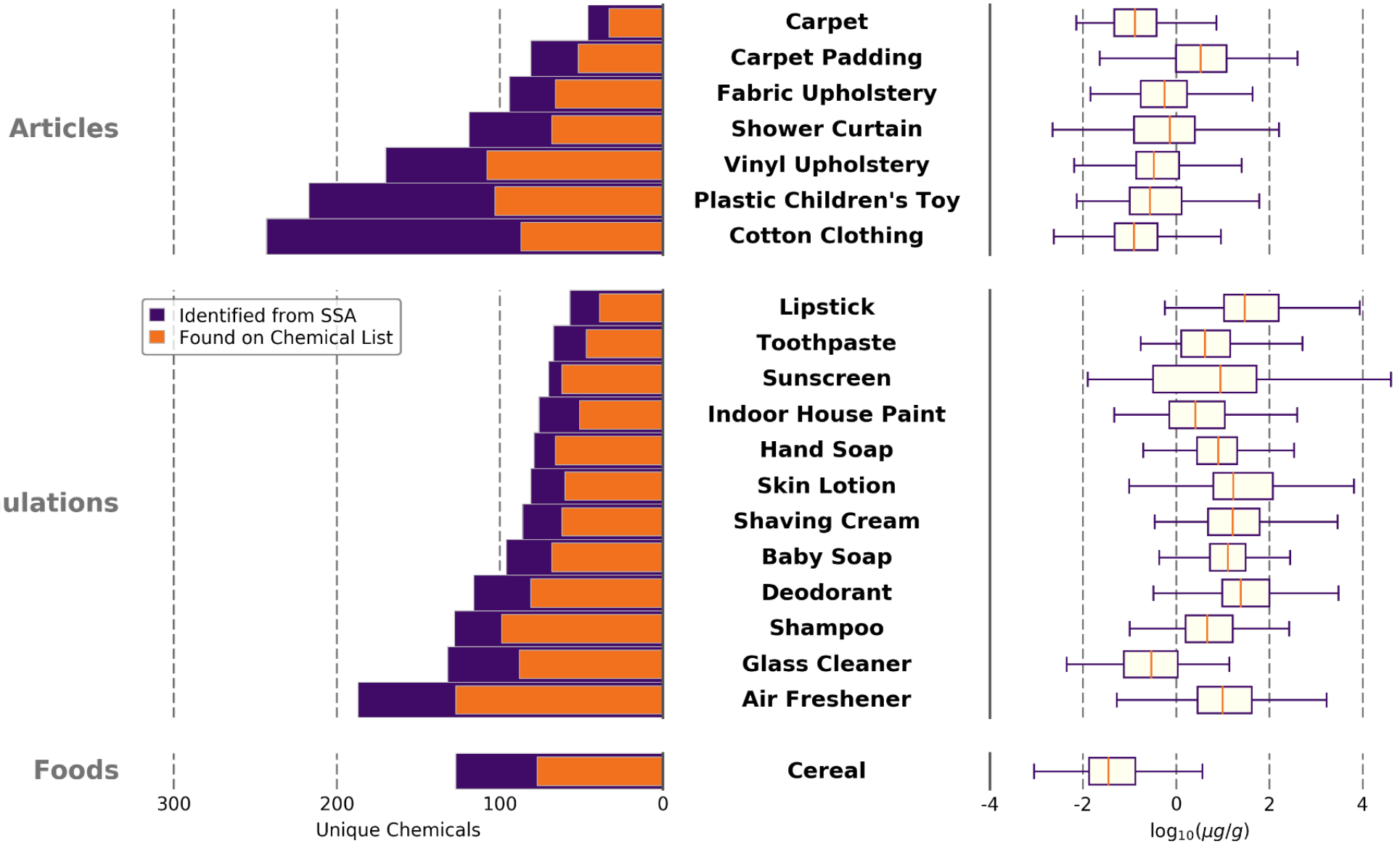
Slide from Kristin Isaacs

Developing Pathway-Specific Chemical Data

ExpoCast household item pilot study analyzed 5 examples each of 20 diverse household items.

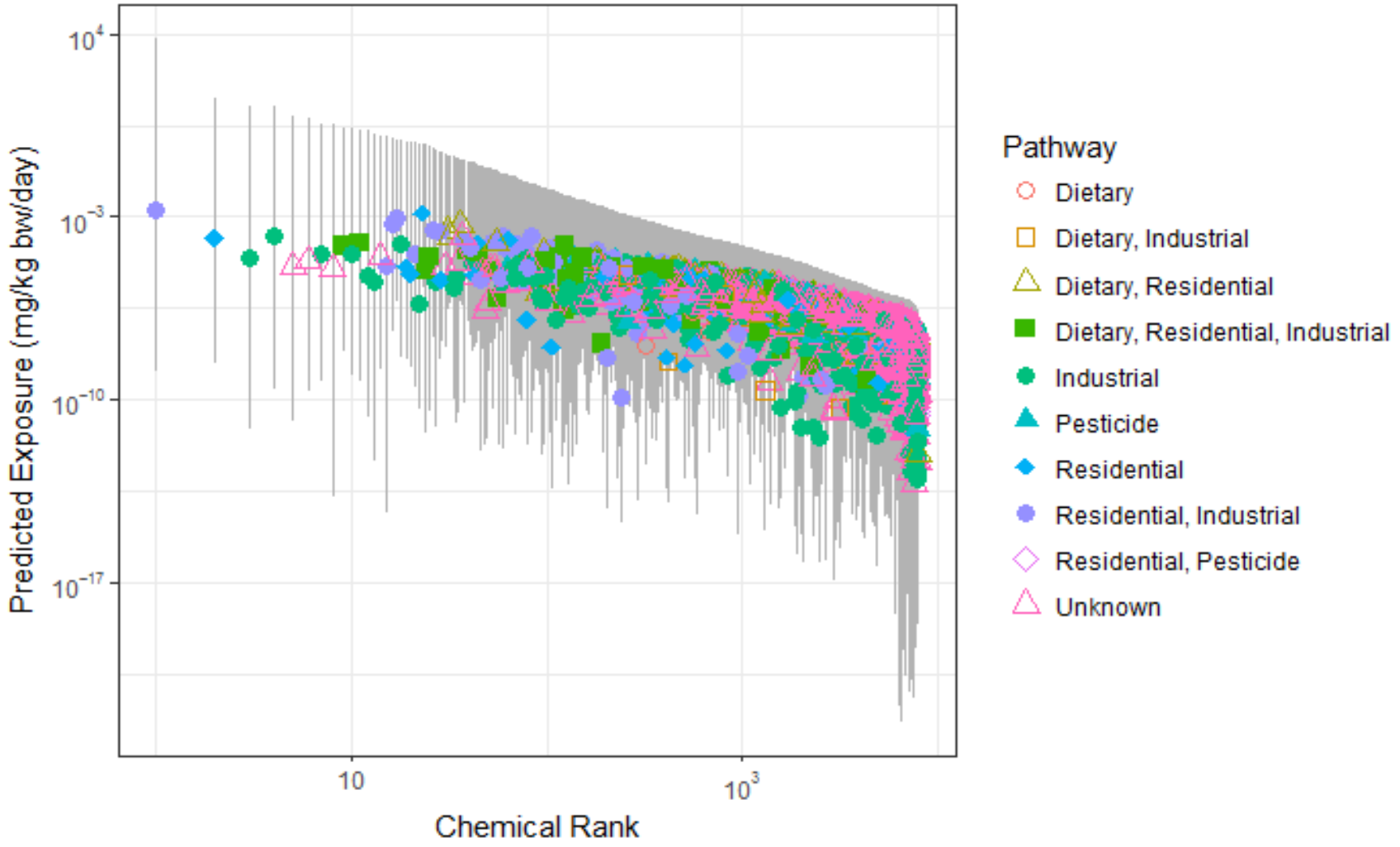
Of 1,632 chemicals confirmed or tentatively identified, 1,445 were not present in CPCPdb

This gives us positive reference chemicals – negatives even harder



Phillips *et al.* (*submitted*)

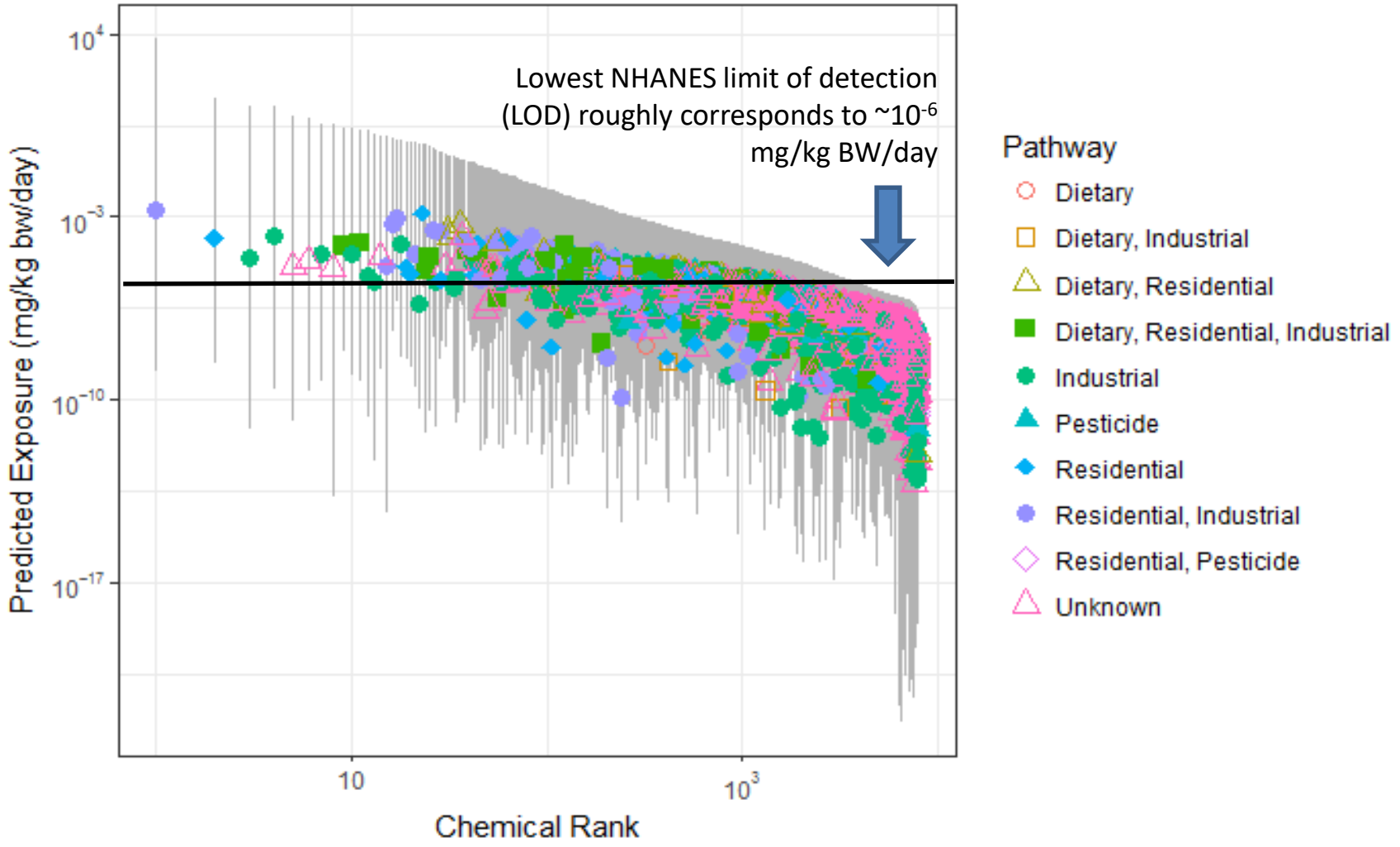
Human Exposure Predictions for 134,521 Chemicals



- 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.*)

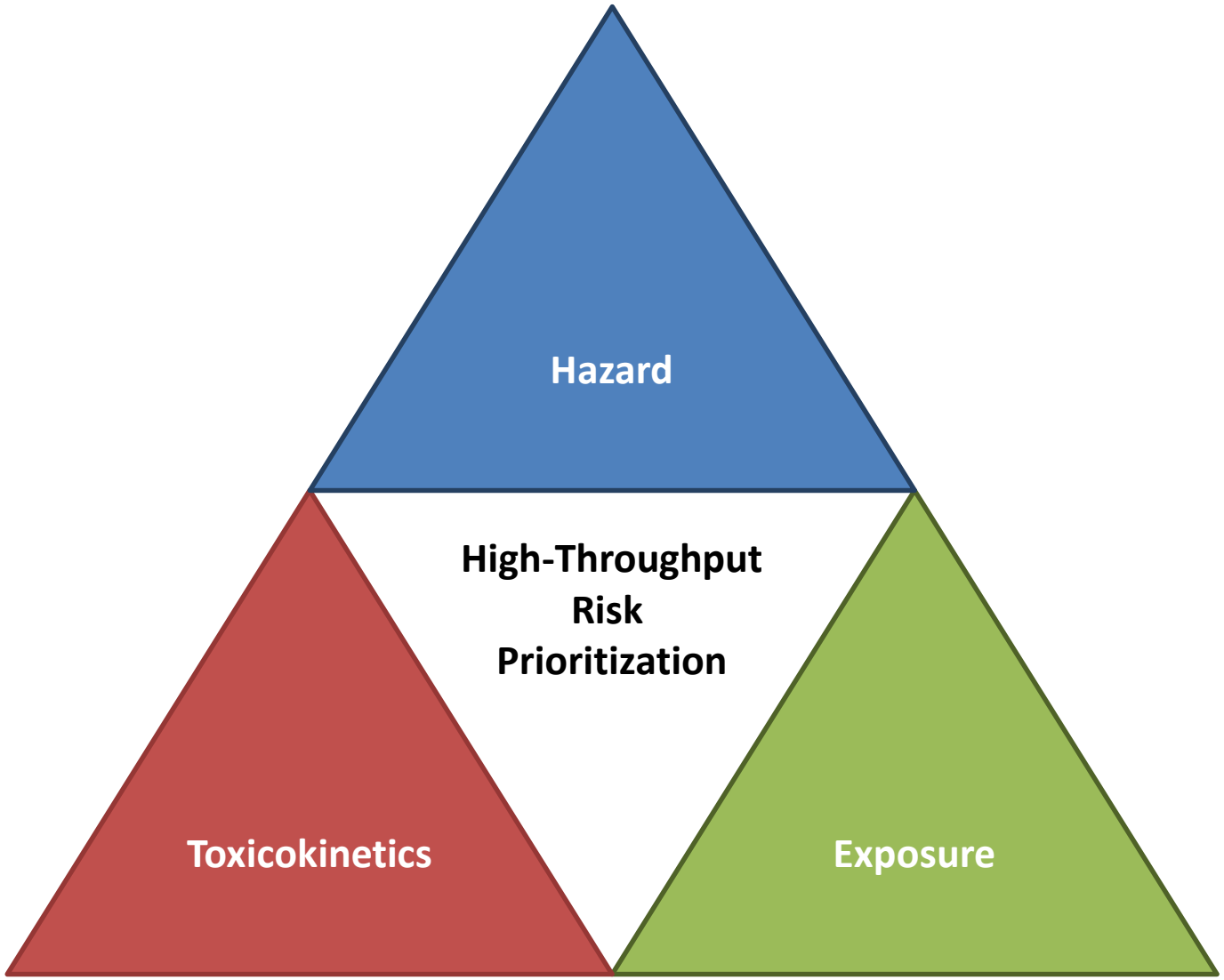
Human Exposure Predictions for 134,521 Chemicals



- Pathway predictions can be used for large chemical libraries
- Many chemicals don't have model-specific predictions, so using average prediction times weight for each relevant pathway

Ring et al. (*in prep.*)

High-Throughput Risk Prioritization

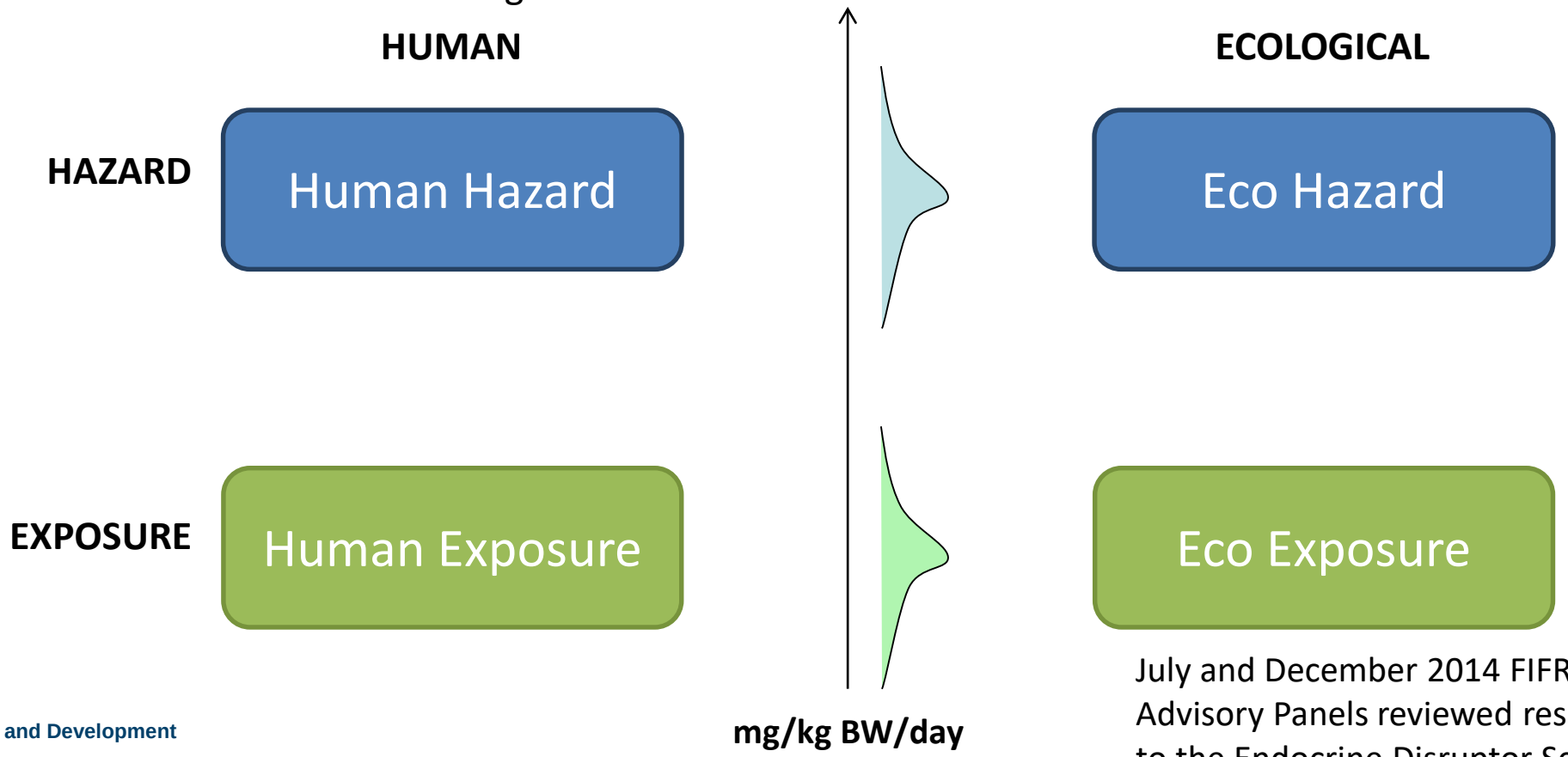


Informing EDSP Prioritization

Prioritization as in Wetmore *et al*. (2015)

The Endocrine Disruptor Screening Program (EDSP) uses a two tiered approach to screen pesticides, chemicals, and environmental contaminants for their potential effect on estrogen, androgen and thyroid hormone systems. The EDSP is outlined in two Federal Register Notices published in 1998.

All pesticide actives and chemicals in drinking water



July and December 2014 FIFRA Scientific Advisory Panels reviewed research as it applies to the Endocrine Disruptor Screening Program

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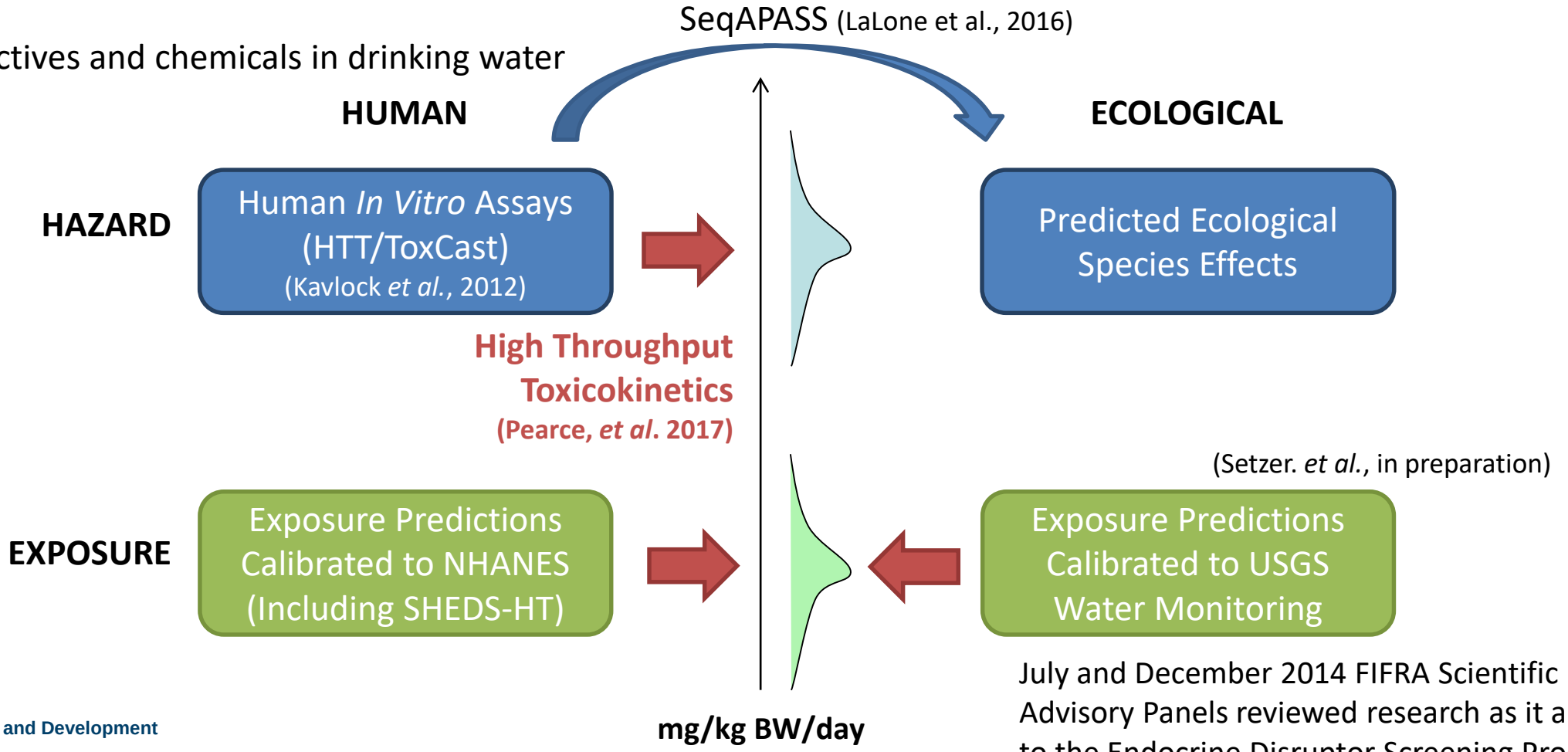
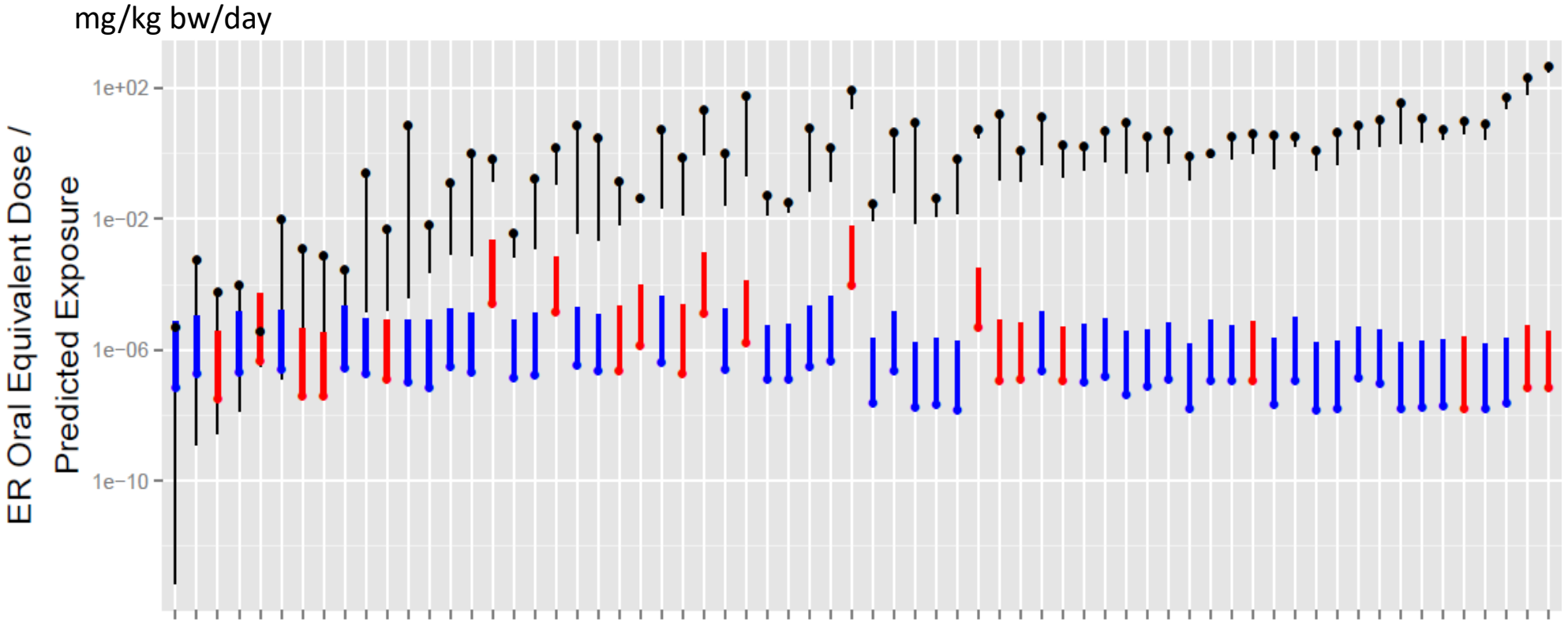
The Endocrine Disruptor Screening Program (EDSP) uses a two tiered approach to screen pesticides, chemicals, and environmental contaminants for their potential effect on estrogen, androgen and thyroid hormone systems. The EDSP is outlined in two Federal Register Notices published in 1998.

All pesticide actives and chemicals in drinking water



July and December 2014 FIFRA Scientific Advisory Panels reviewed research as it applies to the Endocrine Disruptor Screening Program

High Throughput Risk Prioritization in Practice



ToxCast Chemicals

Rapid exposure and dosimetry project helps establish exposure context for ToxCast high throughput screening

December, 2014 Panel:
"Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening"

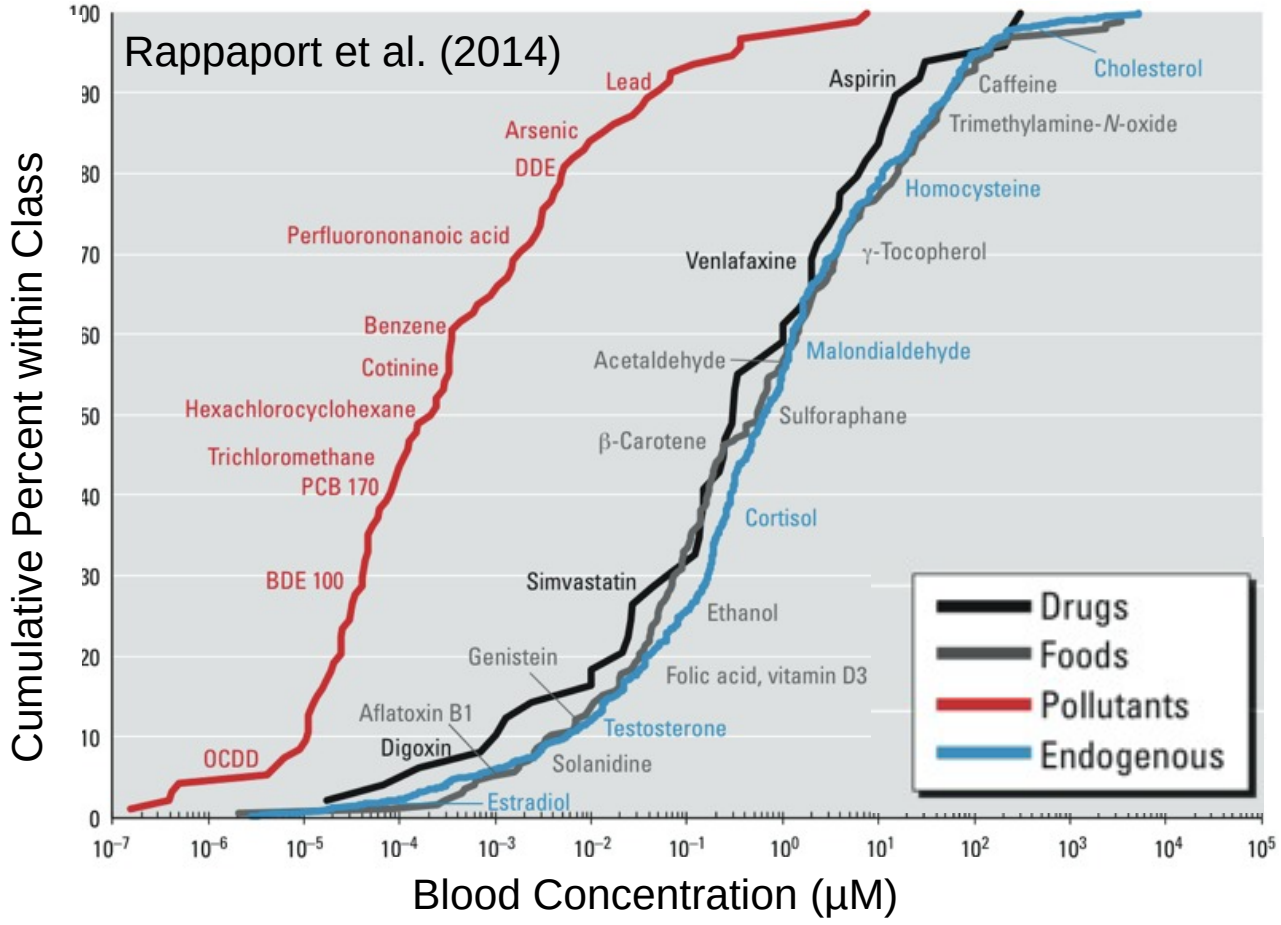
Conclusions

- Rough exposure assessments may be potentially useful if the uncertainty can be quantified and is acceptable (i.e., “fit for purpose”)

- Each exposure model incorporates different knowledge, assumptions, and data (Macleod, et al., 2010)
  - The trick is to know which model to use and when

- We use existing chemical data to predict pathways from chemical structure and properties.
  - We need additional (better?) example chemicals.
  - Initial four pathways only an example, other important pathways or groupings of pathways can be considered.

- Eventually we have got to go beyond NHANES (~130 chemicals)
  - Non-targeted analysis of blood may eventually fill this need.



EPA United States Environmental Protection Agency

Chemical Safety for Sustainability (CSS) Research Program

Rapid Exposure and Dosimetry (RED) Project

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