EPA
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Informatics Tools for Chemical Safety

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Bernard Harris Memorial Symposium:
Risk in the 21st Century
May 10, 2018

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EPA Office of Research and Development

United States Environmental Protection Agency

- The Office of Research and Development (ORD) is the scientific research arm of EPA
  - 558 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
- 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 chemical signatures 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

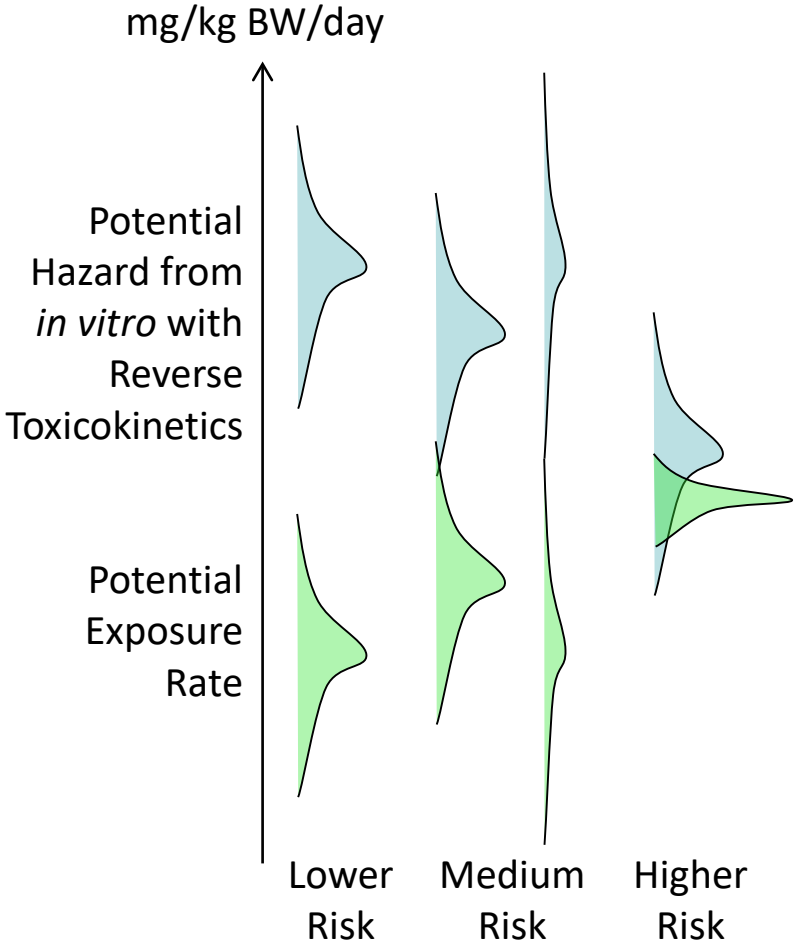
Chemical Regulation in the United States

- Most other chemicals, ranging from industrial waste to dyes to packing materials, are covered by the 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
- TSCA was updated in June, 2016 to allow evaluation of these and other chemicals
  - Methods are being developed to prioritize these existing and new chemicals for testing

November 29, 2014

Chemical Risk = Hazard + Exposure

- National Research Council (1983) identified chemical risk as a function of both inherent hazard and exposure
- To address thousands of chemicals, we need to use “high throughput methods” to prioritize chemicals for additional study
- **High throughput risk prioritization** needs:
  1. high throughput **hazard** characterization (from HTT project)
  2. high throughput **exposure** forecasts
  3. high throughput **toxicokinetics** (*i.e.*, dosimetry) linking hazard and exposure



Risk Assessment in the 21st Century

United States Environmental Protection Agency

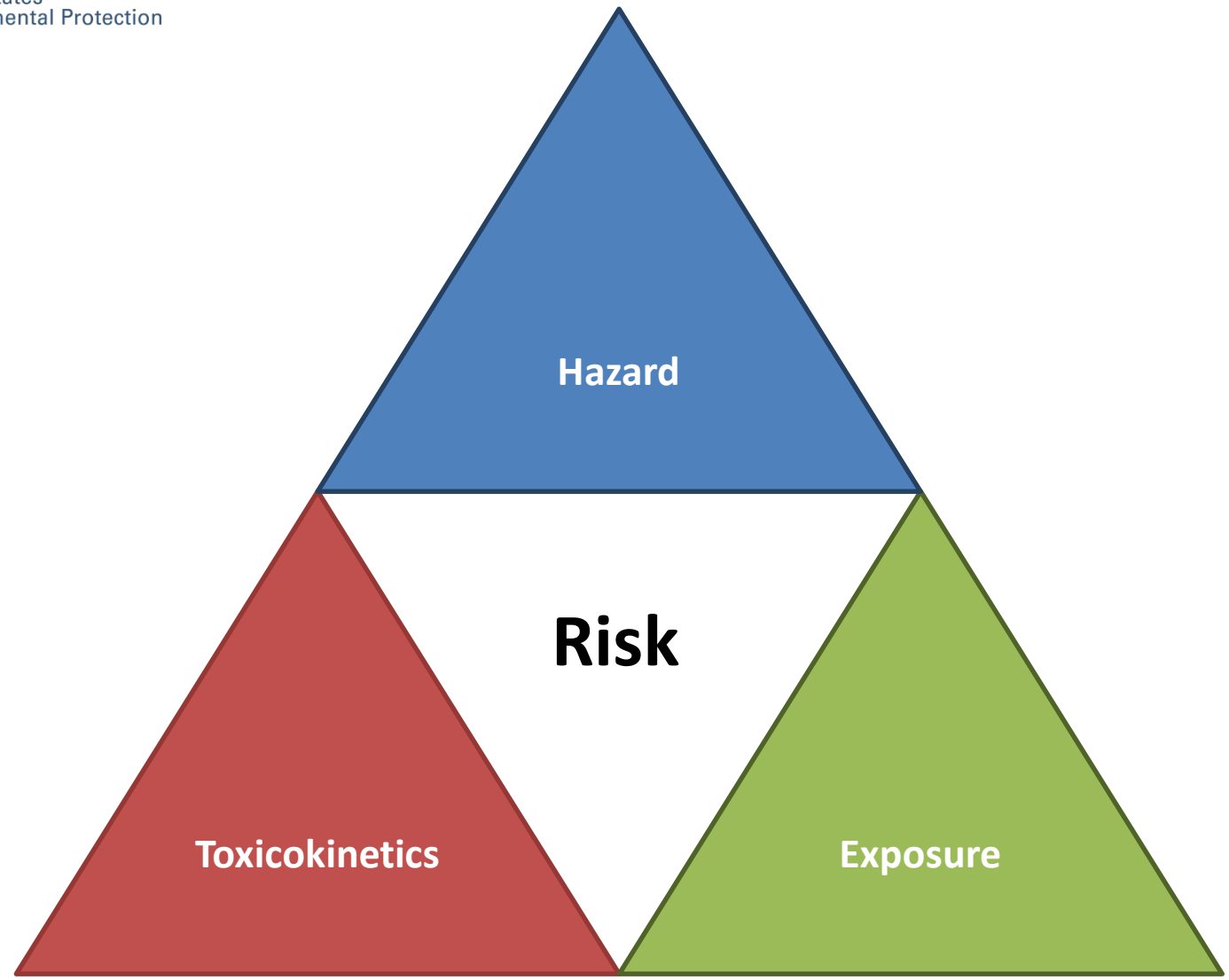
"Translation of high-throughput data into risk-based rankings is an important application of exposure data for chemical priority-setting. Recent advances in high-throughput toxicity assessment, notably the ToxCast and Tox21 programs (see Chapter 1), and in high-throughput computational exposure assessment (Wambaugh et al. 2013, 2014) have enabled first-tier risk-based rankings of chemicals on the basis of margins of exposure…"

"…The committee sees the potential for the application of **computational exposure science** to be highly valuable and credible for comparison and **priority-setting among chemicals in a risk-based context**."

January 5, 2017

Three Components for Chemical Risk

United States Environmental Protection Agency



High-Throughput Risk Prioritization

EPA United States Environmental Protection Agency

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

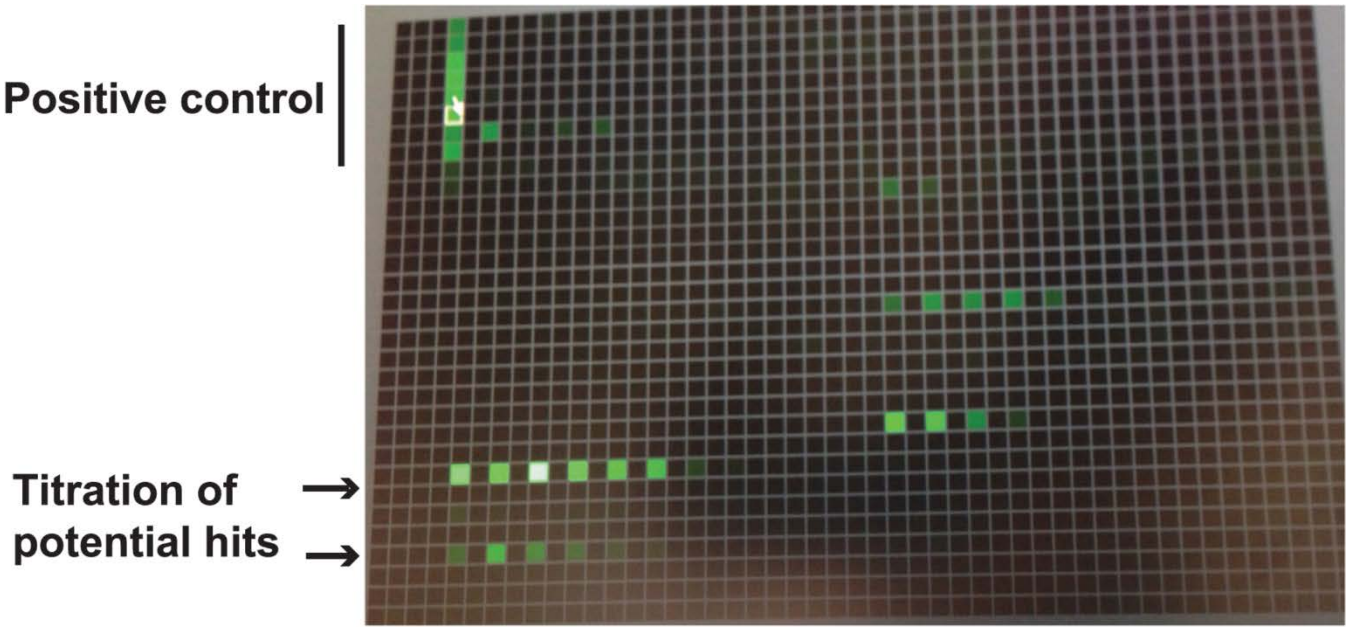
High-throughput Screening

Hertzberg and Pope (2000):

- "New technologies in high-throughput screening have significantly increased throughput and reduced assay volumes"

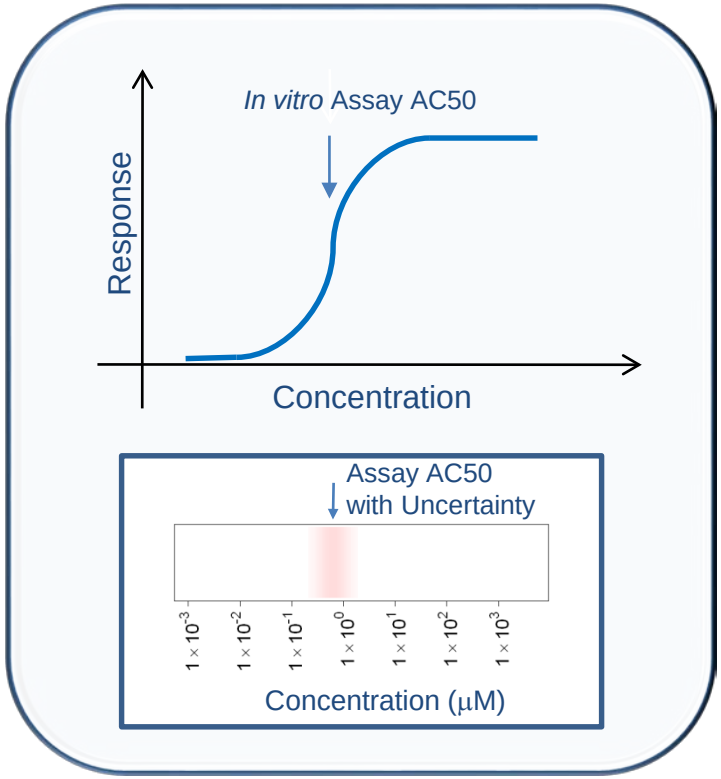
- "Key advances over the past few years include new fluorescence methods, detection platforms and liquid-handling technologies."

Kaewkhaw et al. (2016)



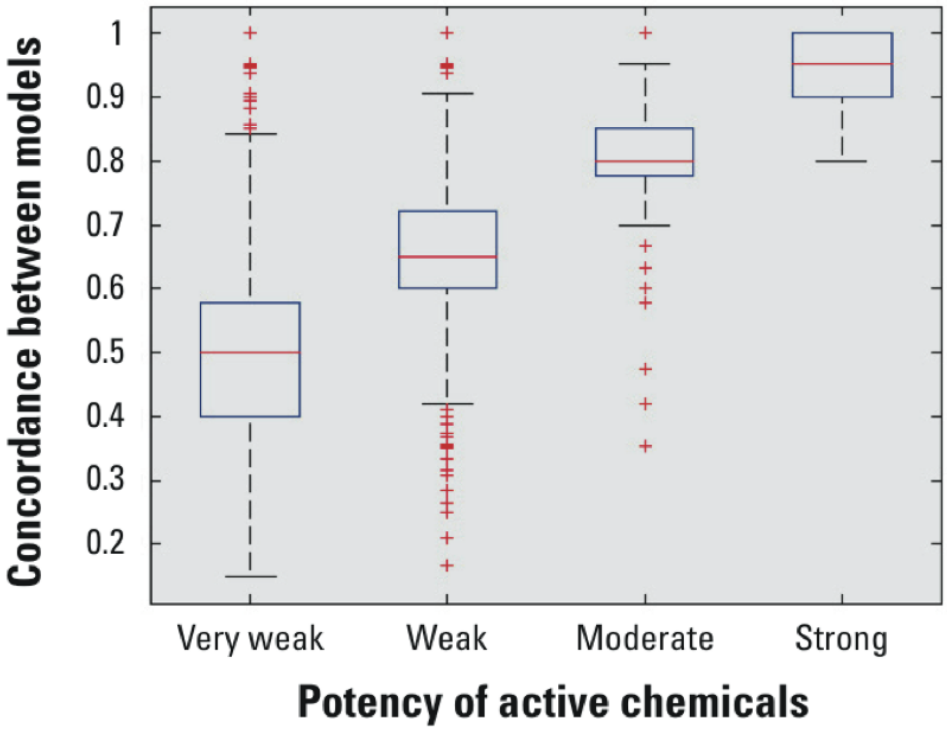
Toxicity Testing in the 21st Century

- We might estimate concentrations causing relevant bioactivity *in vitro* using high throughput screening (HTS)
- **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 assays (Kavlock *et al.*, 2012)
- Most assays conducted in dose-response format (identify 50% activity concentration – AC50 – and efficacy if data described by a Hill function, Filer *et al.*, 2016)
- All data is public: http://comptox.epa.gov/dashboard/



CERAPP: Collaborative Estrogen Receptor Activity Prediction Project

- ToxCast can only test those compounds that can be obtained, are soluble, and are not volatile: **There is a need for predictive models**
- CERAPP combined multiple models developed in collaboration with 17 groups in the United States and Europe to predict estrogen receptor (ER) activity
- Mostly used a common training set of 1,677 chemicals tested by ToxCast to make predictions for 32,464 chemical structures



- Predictions were evaluated on a set of 7,522 chemicals curated from the literature
- A consensus model was built by weighting models based on their evaluated accuracies

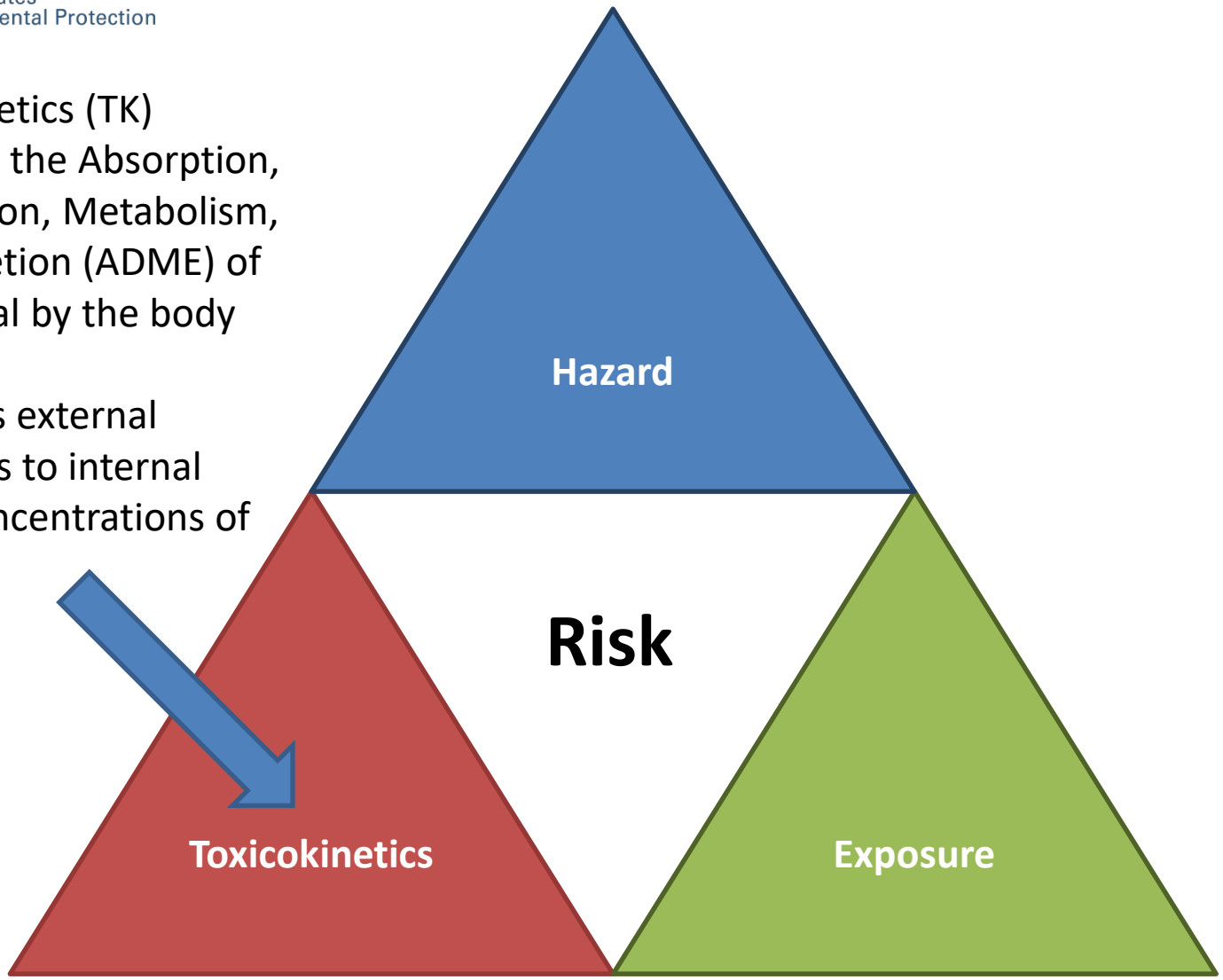
Mansouri *et al.*, (2016)

Toxicokinetics

United States Environmental Protection Agency

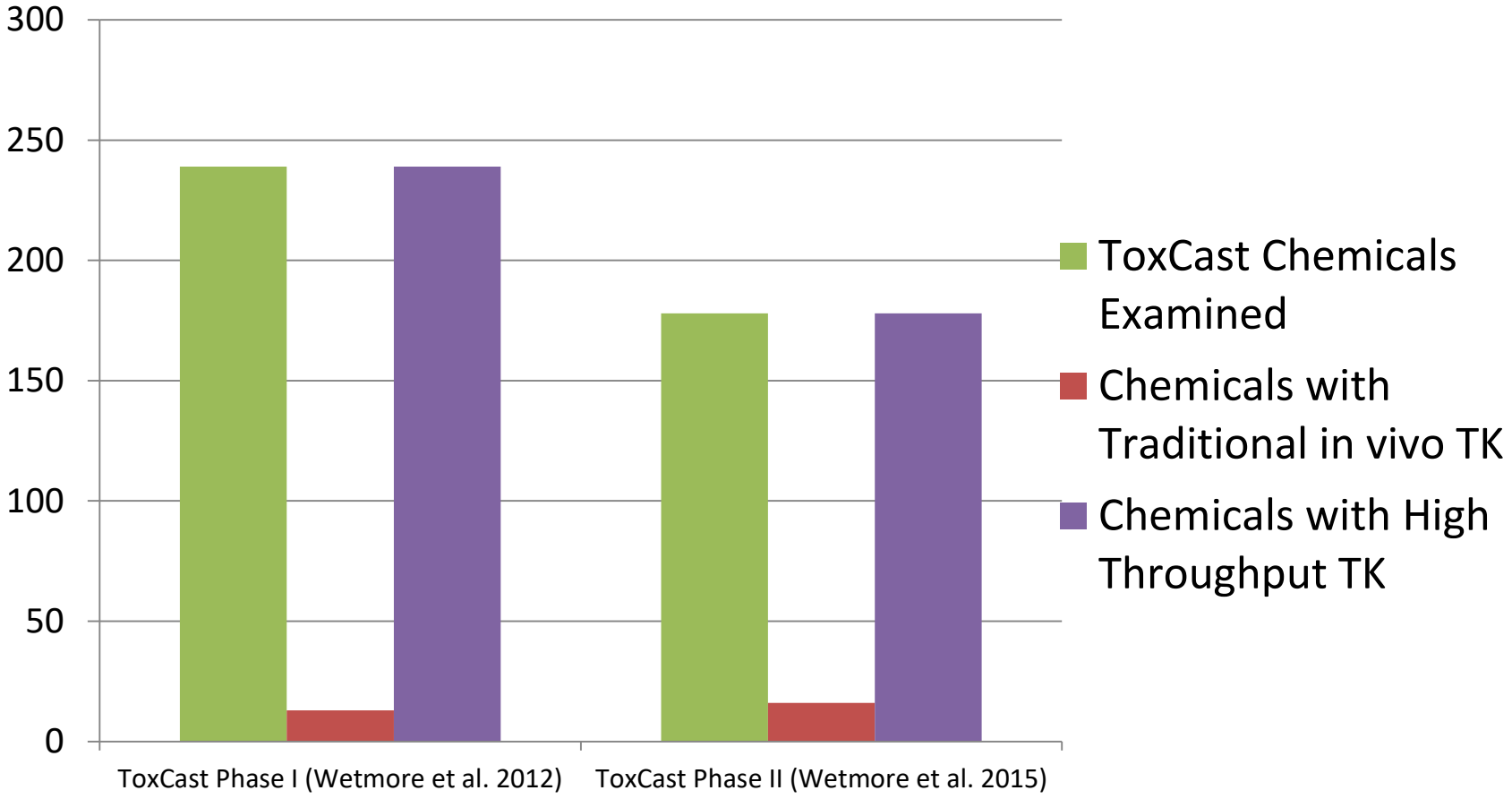
Toxicokinetics (TK) describes the Absorption, Distribution, Metabolism, and Excretion (ADME) of a chemical by the body

TK relates external exposures to internal tissue concentrations of chemical



Most Chemicals Do Not Have Toxicokinetic data

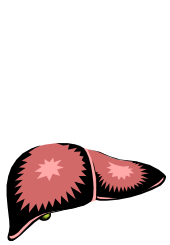
Wetmore et al. (2012) use *in vitro* methods adapted from pharma to fill gaps

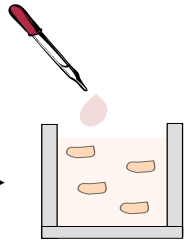


High-Throughput Toxicokinetics (HTTK)

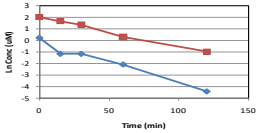
United States Environmental Protection Agency

- 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)





Human Hepatocytes (10 donor pool)



Intrinsic Hepatic Clearance (Cl_{int})

Measurements require chemical-specific methods for concentration

In Vitro - In Vivo Extrapolation

Predicted Plasma Concentrations

Human Plasma (6 donor pool)

Plasma Protein Binding (f_{up})

Rotroff et al. (2010) 35 chemicals
Wetmore et al. (2012) +204 chemicals
Wetmore et al. (2015) +163 chemicals

Figure from Barbara Wetmore

Open Source Tools and Data for HTTK

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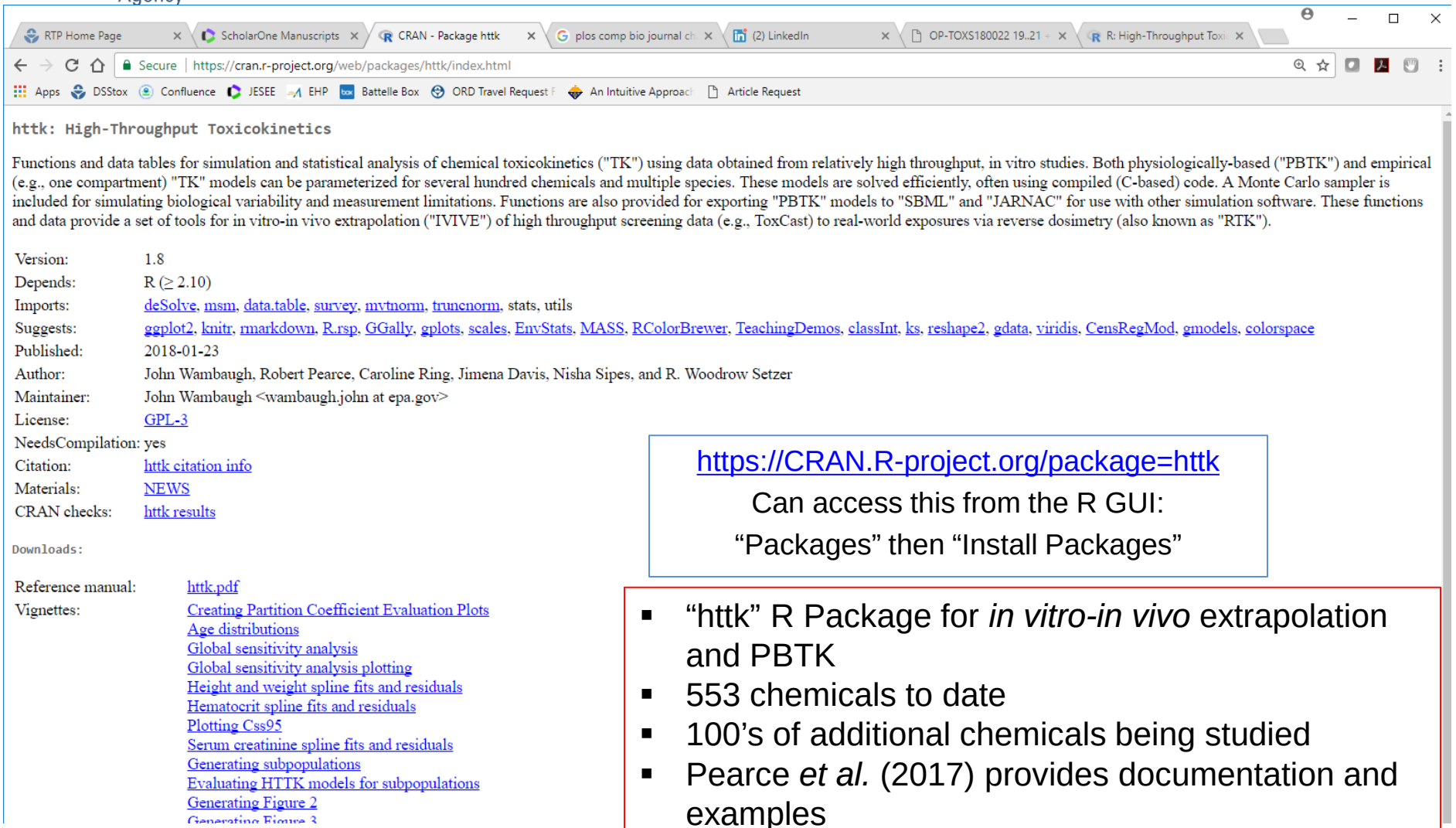


RTP Home Page | ScholarOne Manuscripts | CRAN - Package httk | plos comp bio journal | (2) LinkedIn | OP-TOXS180022 19..21 | R: High-Throughput Toxi

Secure https://cran.r-project.org/web/packages/httk/index.html

Apps DSStox Confluence JESEE EHP Battelle Box ORD Travel Request An Intuitive Approac Article Request

httk: High-Throughput Toxicokinetics

Functions and data tables for simulation and statistical analysis of chemical toxicokinetics ("TK") using data obtained from relatively high throughput, in vitro studies. Both physiologically-based ("PBTK") and empirical (e.g., one compartment) "TK" models can be parameterized for several hundred chemicals and multiple species. These models are solved efficiently, often using compiled (C-based) code. A Monte Carlo sampler is included for simulating biological variability and measurement limitations. Functions are also provided for exporting "PBTK" models to "SBML" and "JARNAC" for use with other simulation software. These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of high throughput screening data (e.g., ToxCast) to real-world exposures via reverse dosimetry (also known as "RTK").

Version:	1.8
Depends:	R (≥ 2.10)
Imports:	deSolve, msm, data.table, survey, mvtnorm, truncnorm, stats, utils
Suggests:	ggplot2, knitr, rmarkdown, R.rsp, GGally, gplots, scales, EnvStats, MASS, RColorBrewer, TeachingDemos, classInt, ks, reshape2, gdata, viridis, CensRegMod, gmodels, colorspace
Published:	2018-01-23
Author:	John Wambaugh, Robert Pearce, Caroline Ring, Jimena Davis, Nisha Sipes, and R. Woodrow Setzer
Maintainer:	John Wambaugh <wambaugh.john at epa.gov>
License:	GPL-3
NeedsCompilation:	yes
Citation:	httk citation info
Materials:	NEWS
CRAN checks:	httk results

Downloads:

Reference manual:	httk.pdf
Vignettes:	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

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

Can access this from the R GUI:

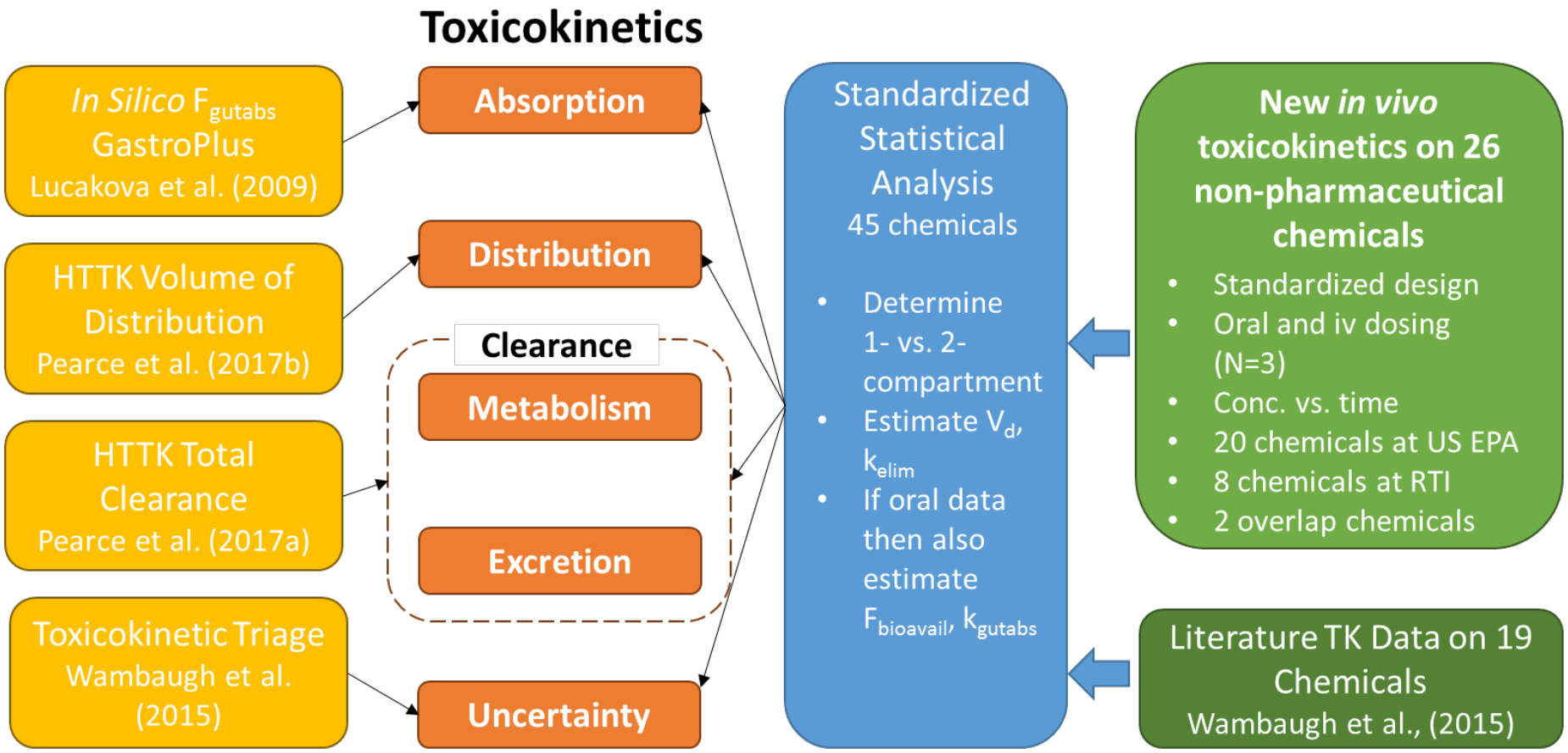
"Packages" then "Install Packages"

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

Building Confidence in HTTK

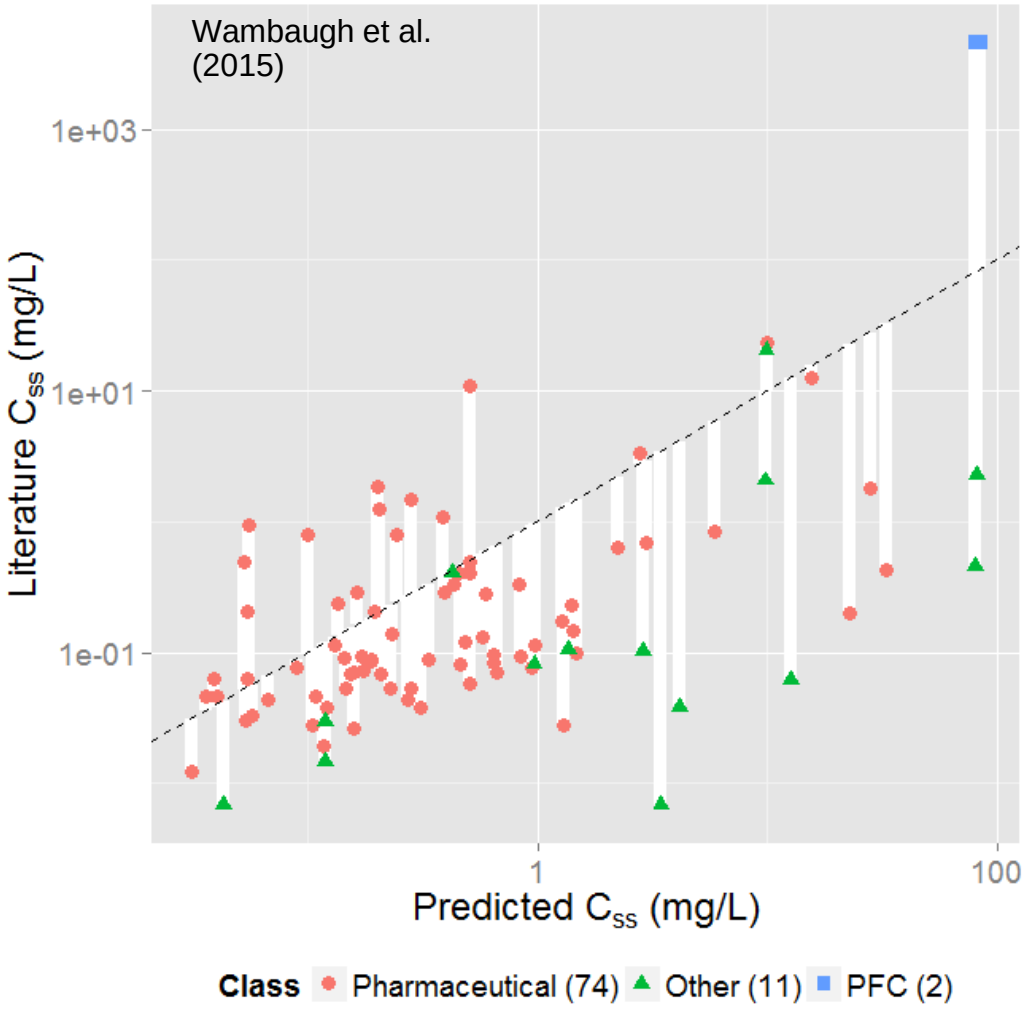
We collected new data for 26 chemicals more commonly associated with non-therapeutic and/or unintentional exposure

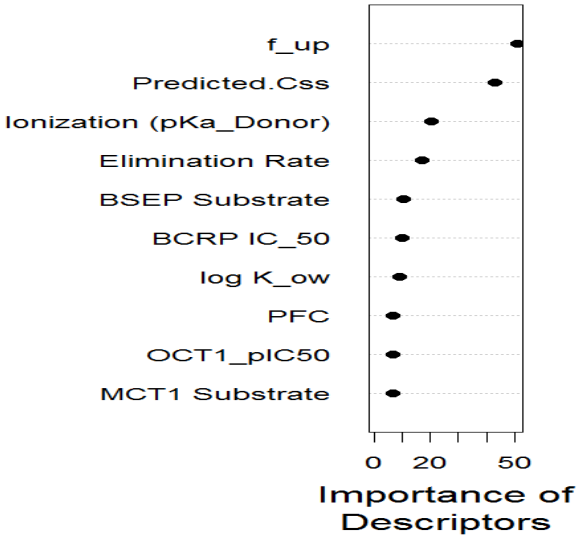
Minimal design – six animals per study (3 dosed per oral / 3 iv)



Wambaugh et al. (Tox. Sci., *just accepted*)

Evaluating Predictions of Steady-State Plasma Concentration (C_{ss})





- When we compare the C_{ss} predicted from *in vitro* HTTK with *in vivo* C_{ss} values determined from the literature we find limited correlation (R^2 ~0.34)
- The dashed line indicates the identity (perfect predictor) line:
  - Over-predict for 65
  - Under-predict for 22
- The white lines indicate the discrepancy between measured and predicted values (the residual)

Predicting Error in HTTK Predictions

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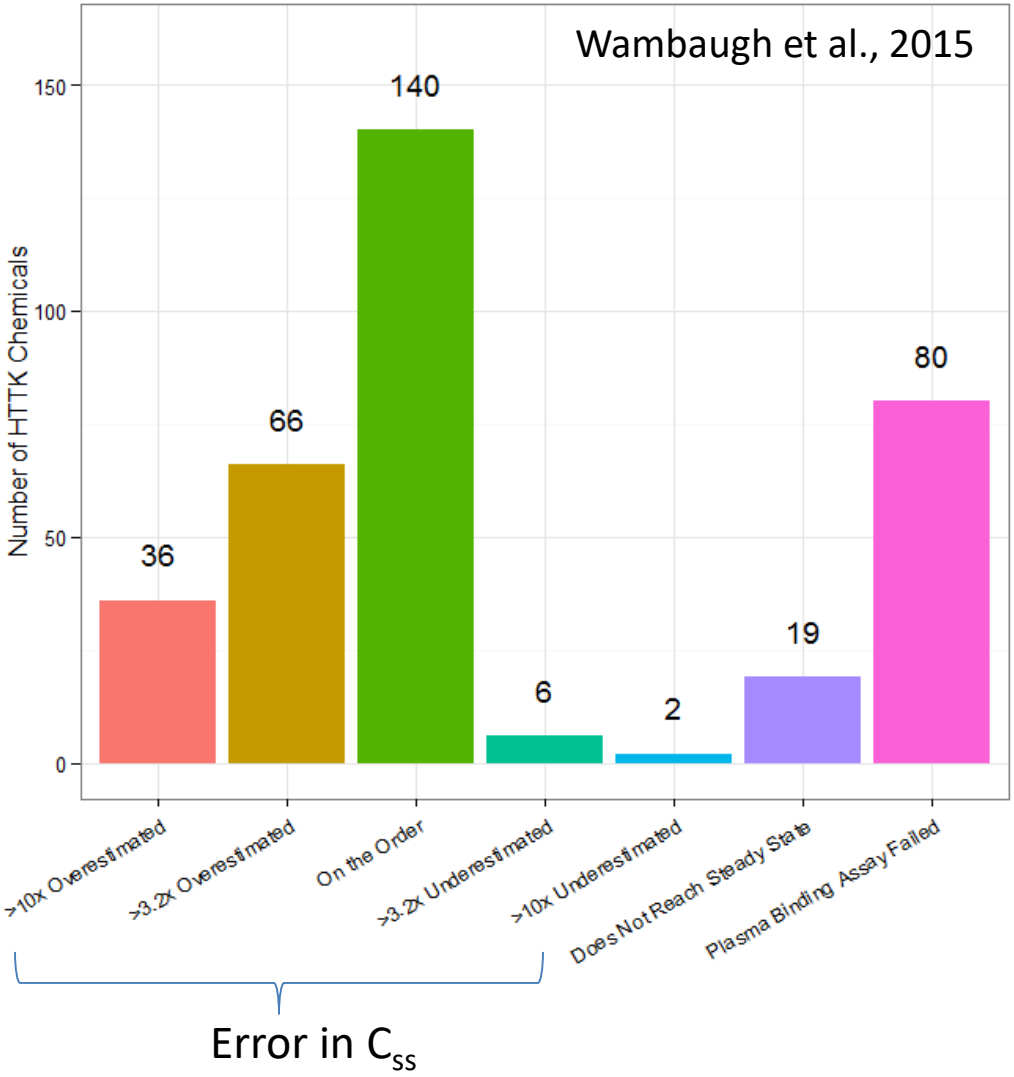
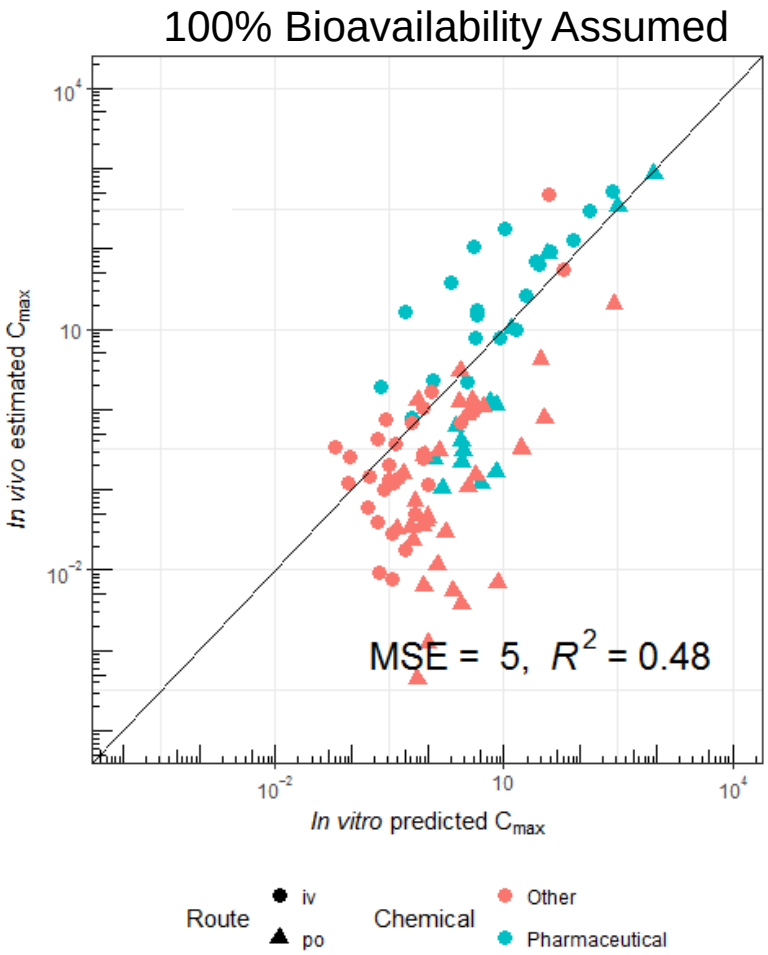
- For most compounds in the environment there will be no clinical trials
- Uncertainty must be well characterized
  - We compare to *in vivo* data to get **empirical estimates of HTTK uncertainty**
  - Any approximations, omissions, or mistakes should work to increase the estimated uncertainty when evaluated systematically across chemicals
- Through comparison to *in vivo* data, a cross-validated (Random Forest, Breiman, 2001) predictor of success or failure of HTTK has been constructed
- We also have categories for chemicals that do not reach steady-state or for which plasma binding assay fails



Statistical Evaluation of HTTK



Statistical Evaluation of HTTK

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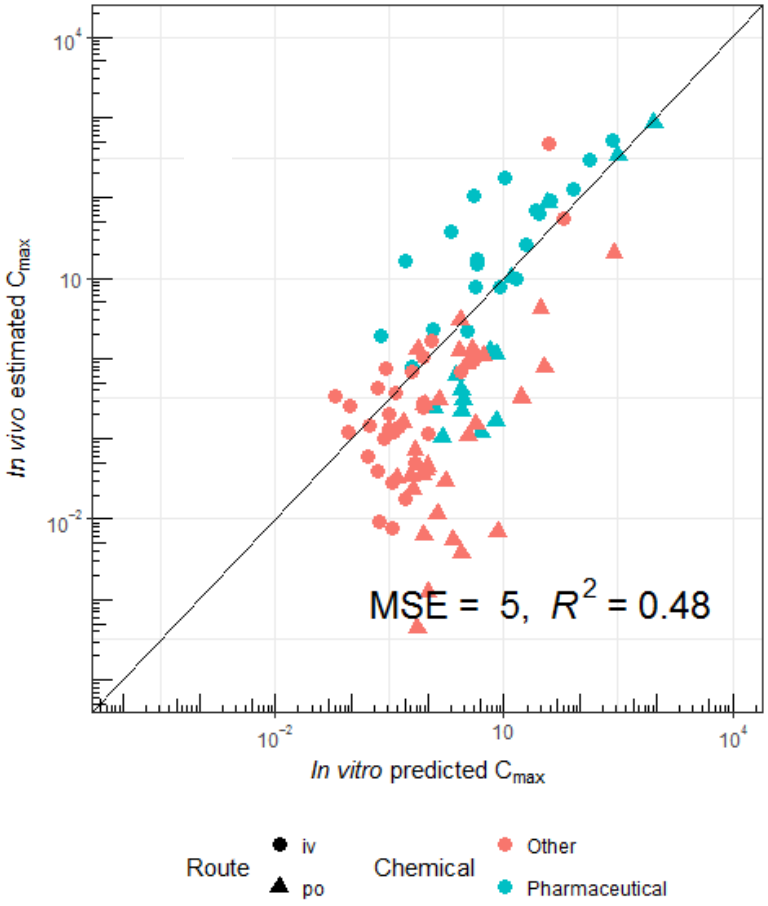
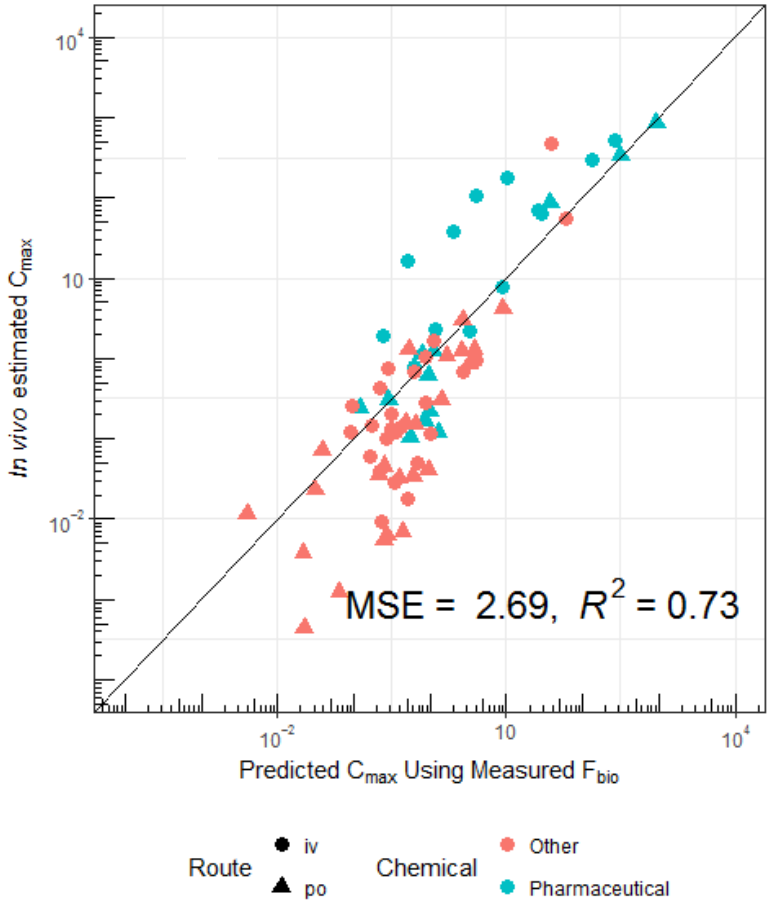
100% Bioavailability Assumed



In Vivo Measured Bioavailability Used



New Exposure Data and Models

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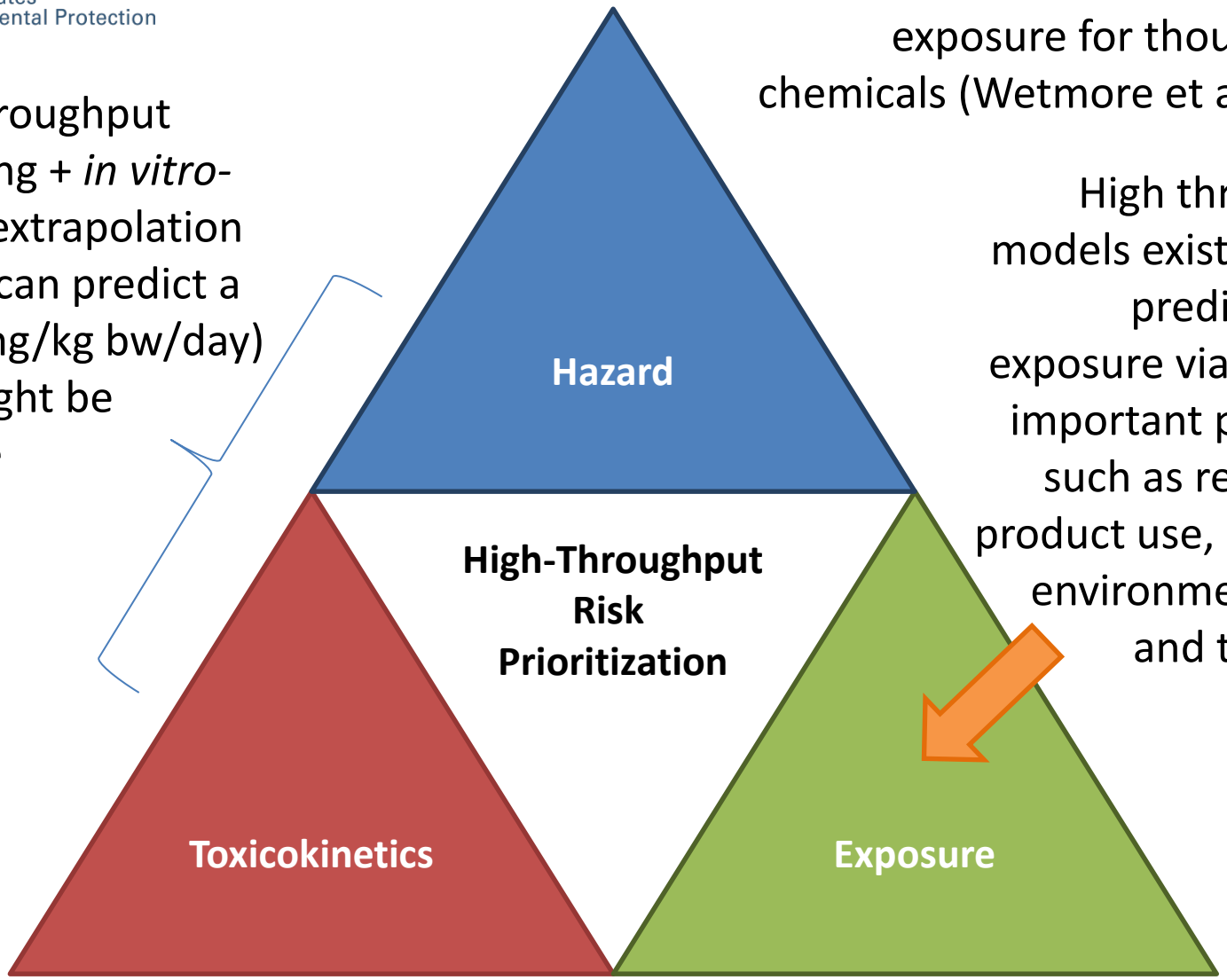
Need methods to forecast exposure for thousands of chemicals (Wetmore et al., 2015)

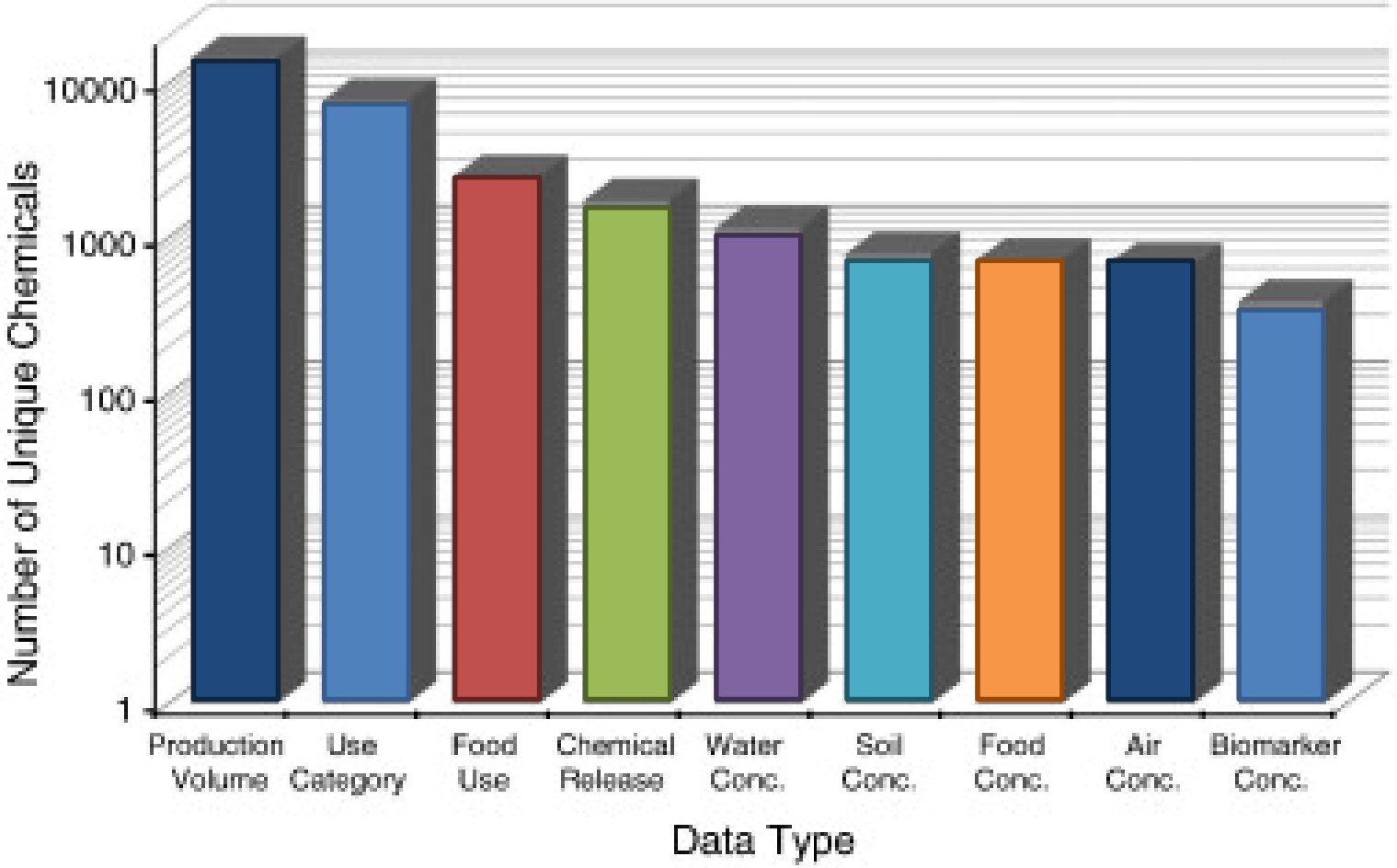
High throughput screening + *in vitro-in vivo* extrapolation (IVIVE) can predict a dose (mg/kg bw/day) that might be adverse

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



Limited Available Data for Exposure Estimation

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



Can we use models to generate the exposure information we need?

What Do We Know About Exposure?

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), …

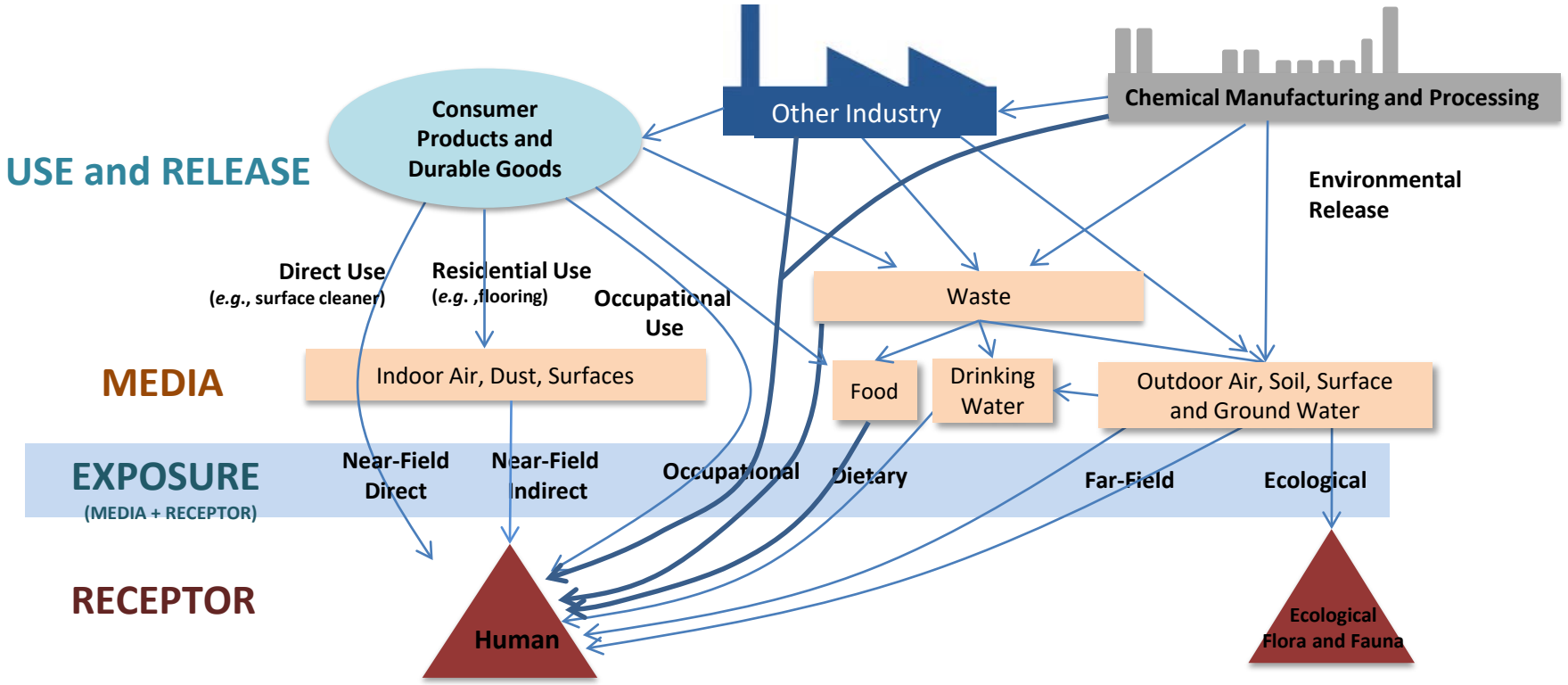
Designed to be representative of US population according to census data

Data sets publicly available (http://www.cdc.gov/nchs/nhanes.htm)

Includes measurements of:

- Body weight
- Height
- **Chemical analysis of blood and urine**

Forecasting Exposure is a Systems Problem

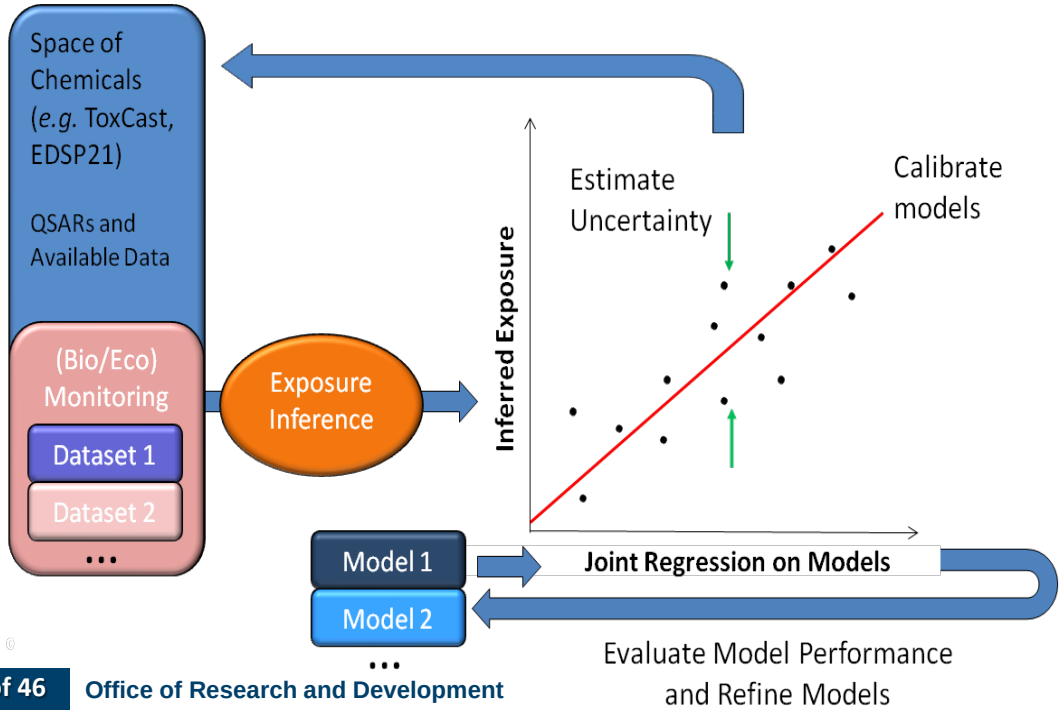


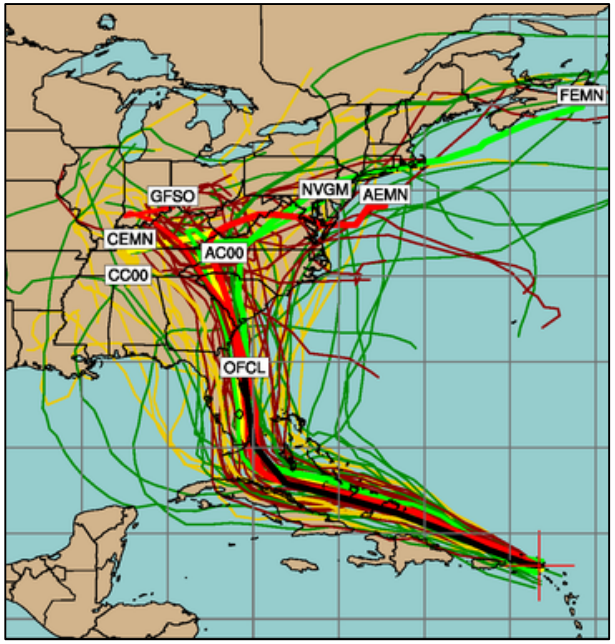
- **Exposure event unobservable:** Can try to predict exposure by characterizing pathway
- Some pathways have much higher average exposures: In home "Near field" sources significant (Wallace, *et al.,* 1987)

Figure from Kristin Isaacs

Consensus Exposure Predictions with the SEEM Framework

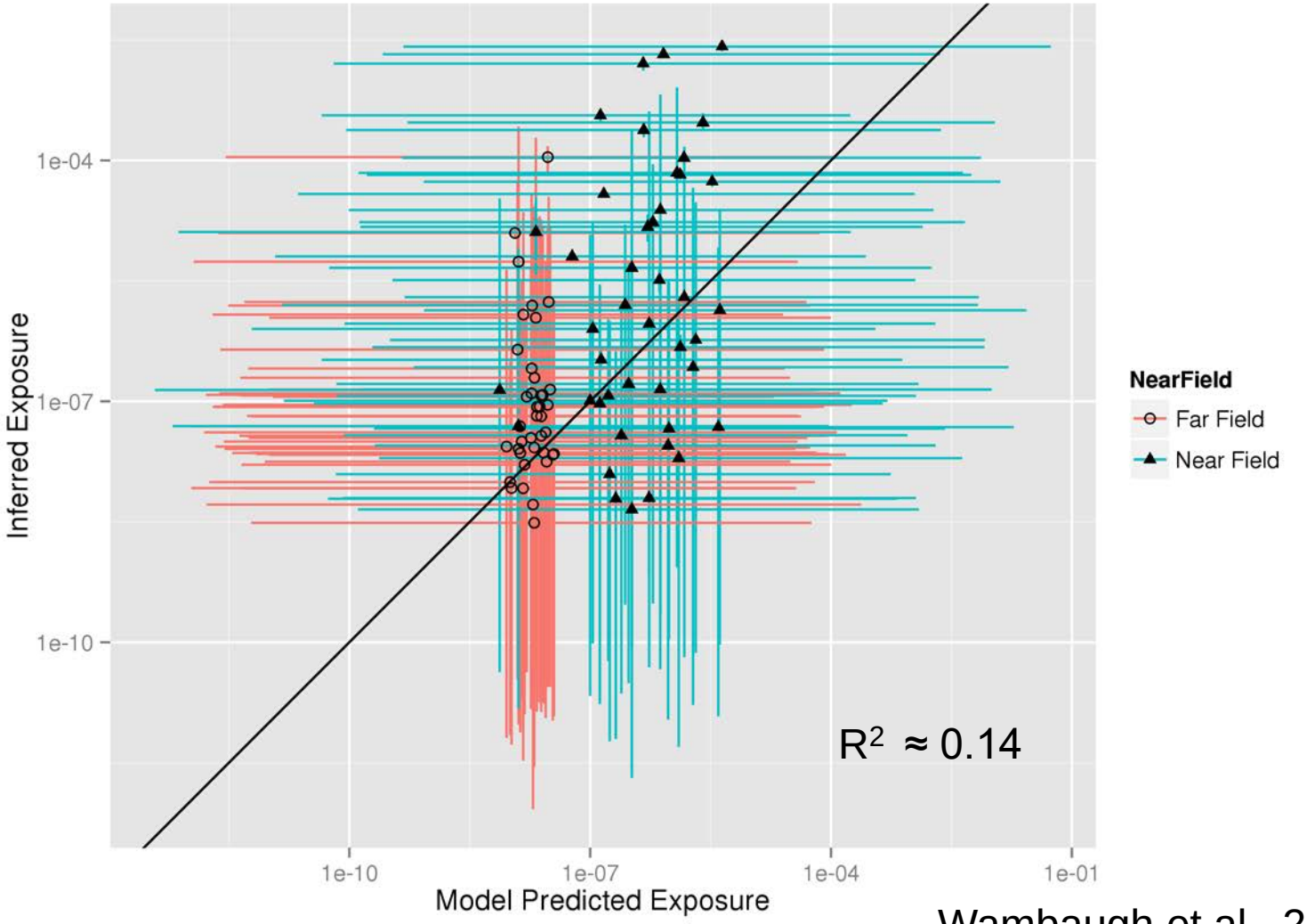
- Different exposure models incorporate **knowledge**, **assumptions**, and **data** (Macleod, et al., 2010)
- We incorporate multiple models (including SHEDS-HT, ExpoDat) into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM) framework**
- Evaluation is similar to a sensitivity analysis: What models are working? What data are most needed?





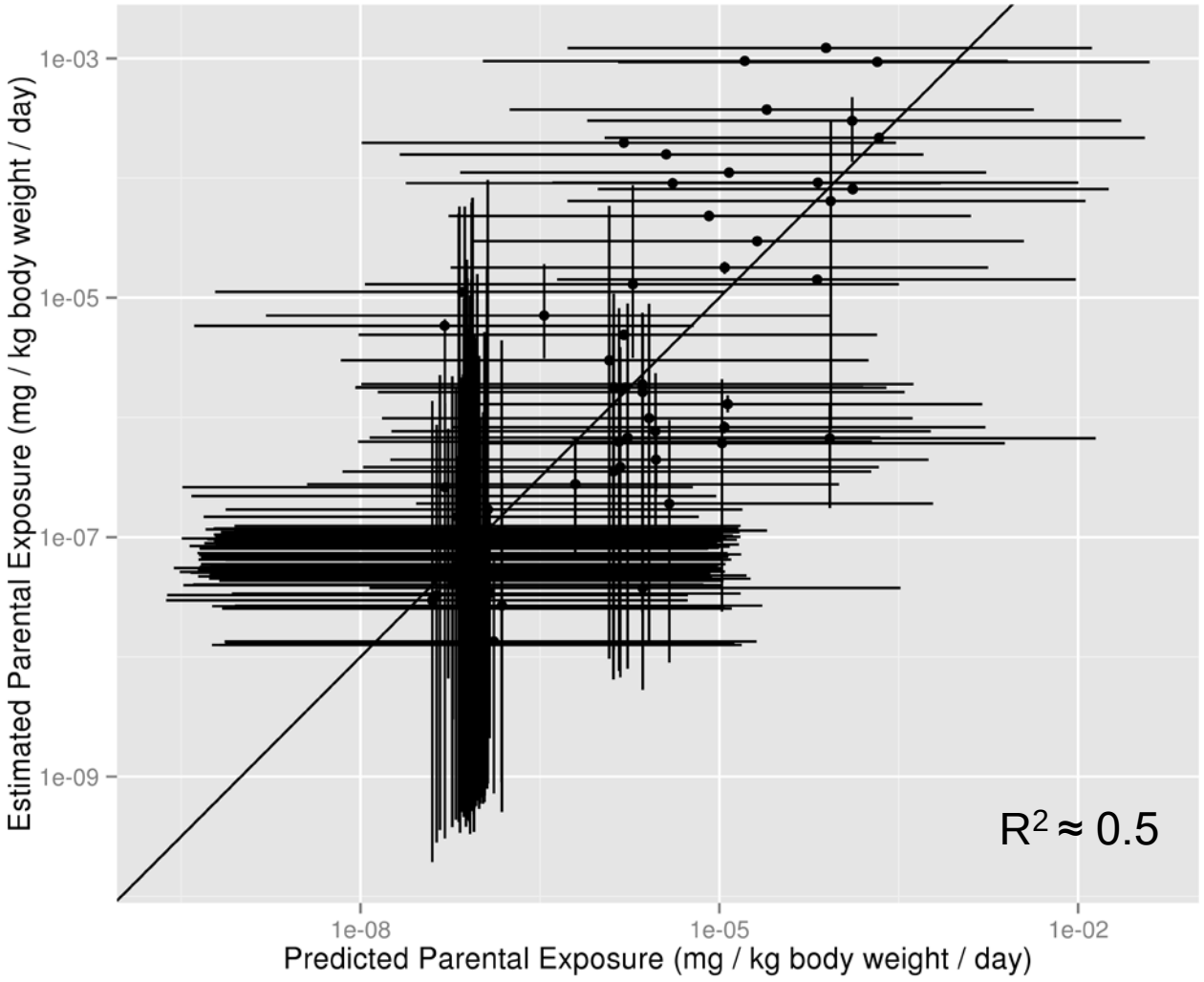
Integrating Multiple Models

First Generation SEEM



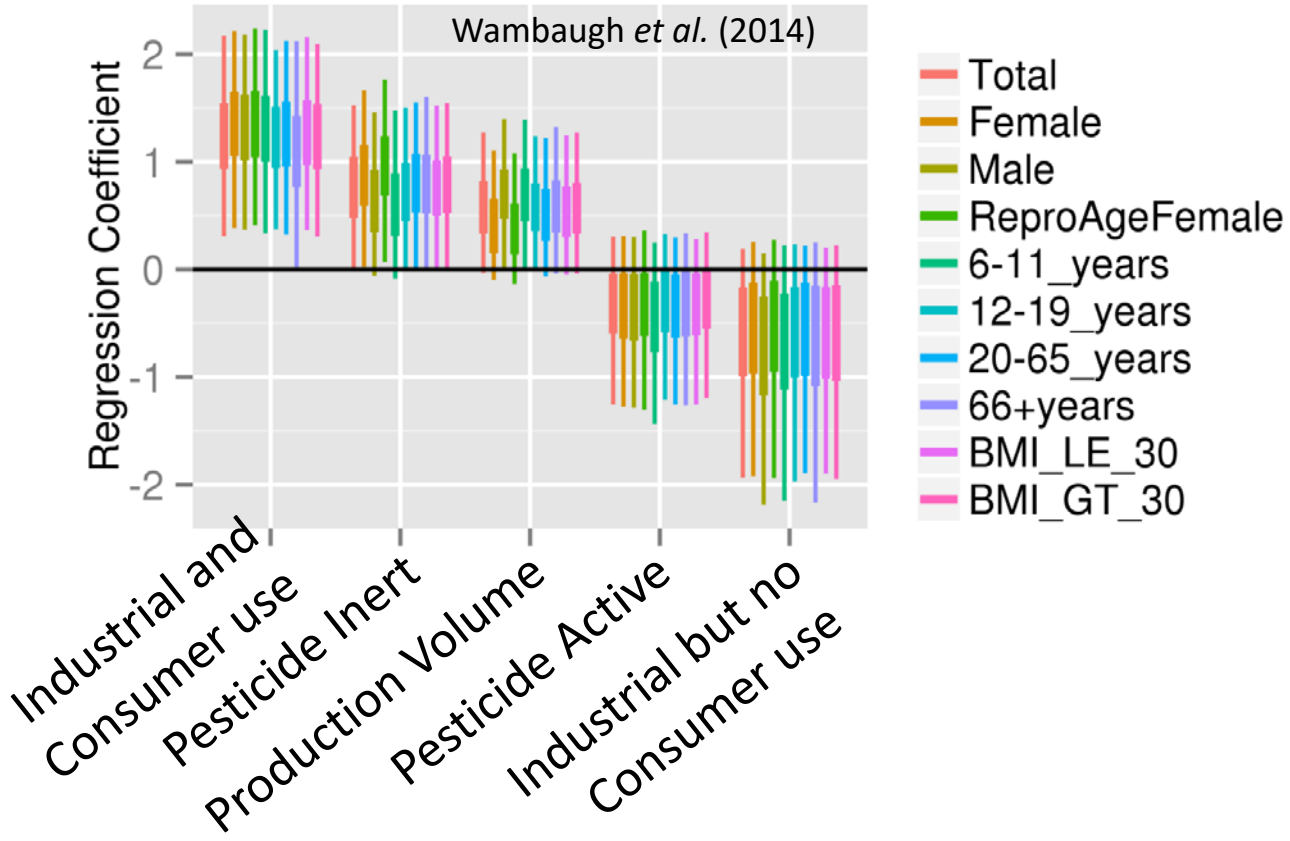
Wambaugh et al., 2013

Second Generation SEEM



Wambaugh et al, 2014

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
- Chemical use identifies relevant pathways
- Some pathways have much higher average exposures (Wallace et al., 1987)

Chemical Use: Chemicals and Products Database

United States Environmental Protection Agency


Contents lists available at ScienceDirect

Toxicology Reports

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

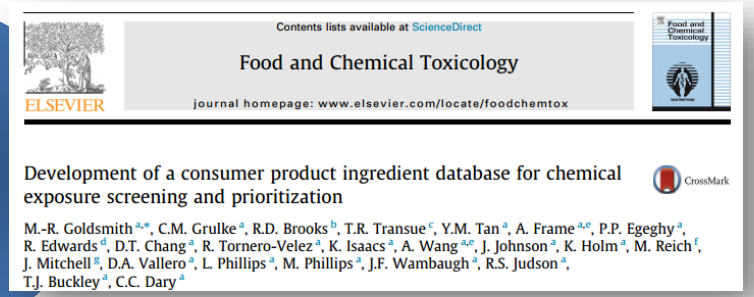
Exploring consumer exposure pathways and patterns of use for chemicals in the environment

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

CPCat

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,c], 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

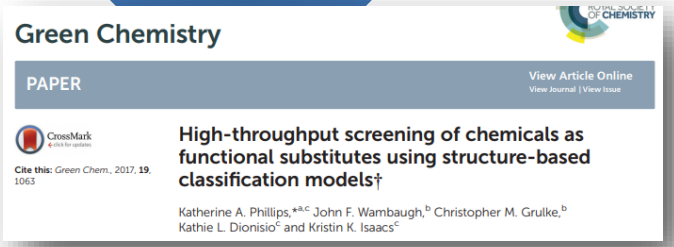
CPDat

EPA United States Environmental Protection Agency

Chemistry Dashboard

Functional Use Data

The roles chemicals play in products


Green Chemistry

PAPER

View Article Online

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]

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

Occurrence data

Ingredient Lists


Journal of Exposure Science and Environmental Epidemiology (2018) 28, 216–222

www.nature.com/jes

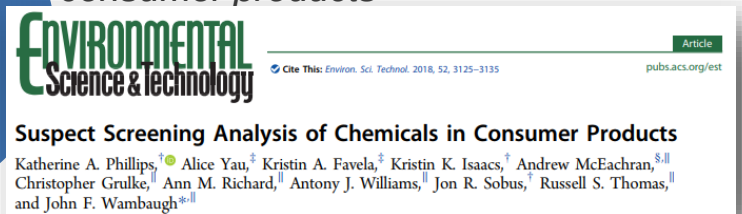
ORIGINAL ARTICLE

Consumer product chemical weight fractions from ingredient lists

Kristin K. Isaacs[1], Katherine A. Phillips[1], Derya Biryol[1,2], Kathie L. Dionisio[1] and Paul S. Price[1]

Measured Data

Measurement of chemicals in consumer products


Environmental Science & Technology

Article

Cite This: Environ. Sci. Technol. 2018, 52, 3125−3135

pubs.acs.org/est

Suspect Screening Analysis of Chemicals in Consumer Products

Katherine A. Phillips,[†] Alice Yau,[‡] Kristin A. Favela,[‡] Kristin K. Isaacs,[†] Andrew McEachran,[§,∥] Christopher Grulke,[∥] Ann M. Richard,[∥] Antony J. Williams,[∥] Jon R. Sobus,[†] Russell S. Thomas,[∥] and John F. Wambaugh*[,∥]

Slide from Kristin Isaacs

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)	Fantke et al. (2011, 2012, 2016)	940	Dietary
USETox Pesticide Scenario (2.0)	Rosenbaum et al. (2008)	8167	Far-Field Industrial
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 (Near-Field)
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	Residential

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."

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

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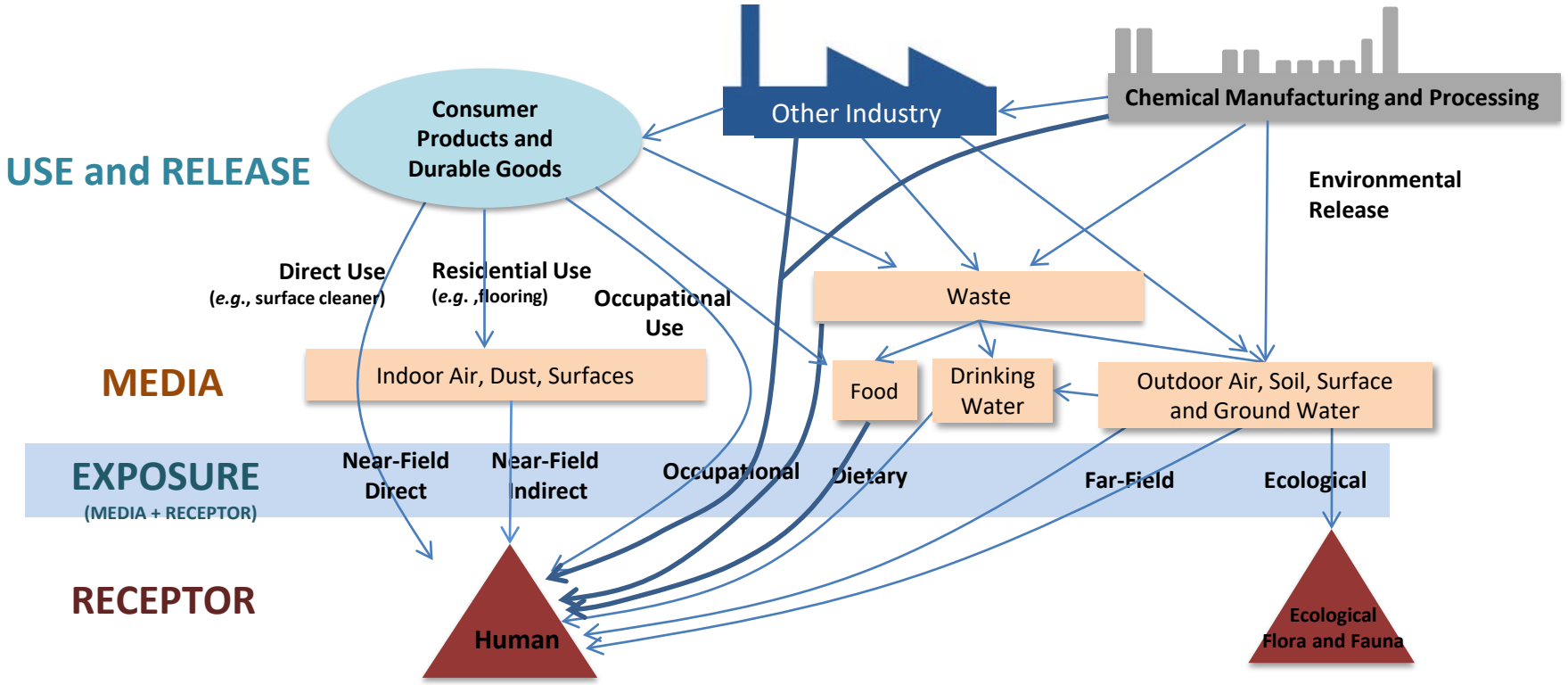
Supporting Information

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

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

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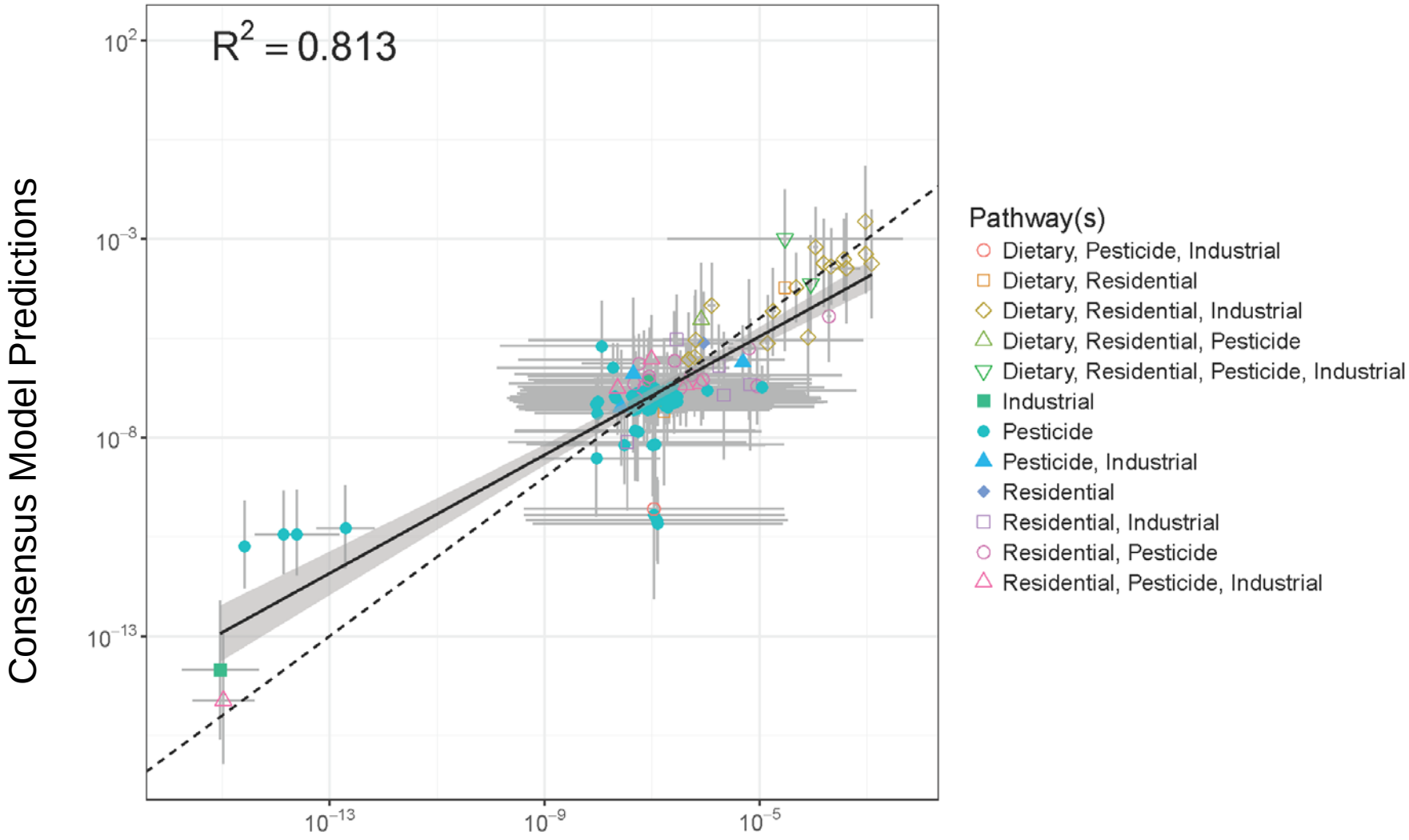
Predicting Pathways

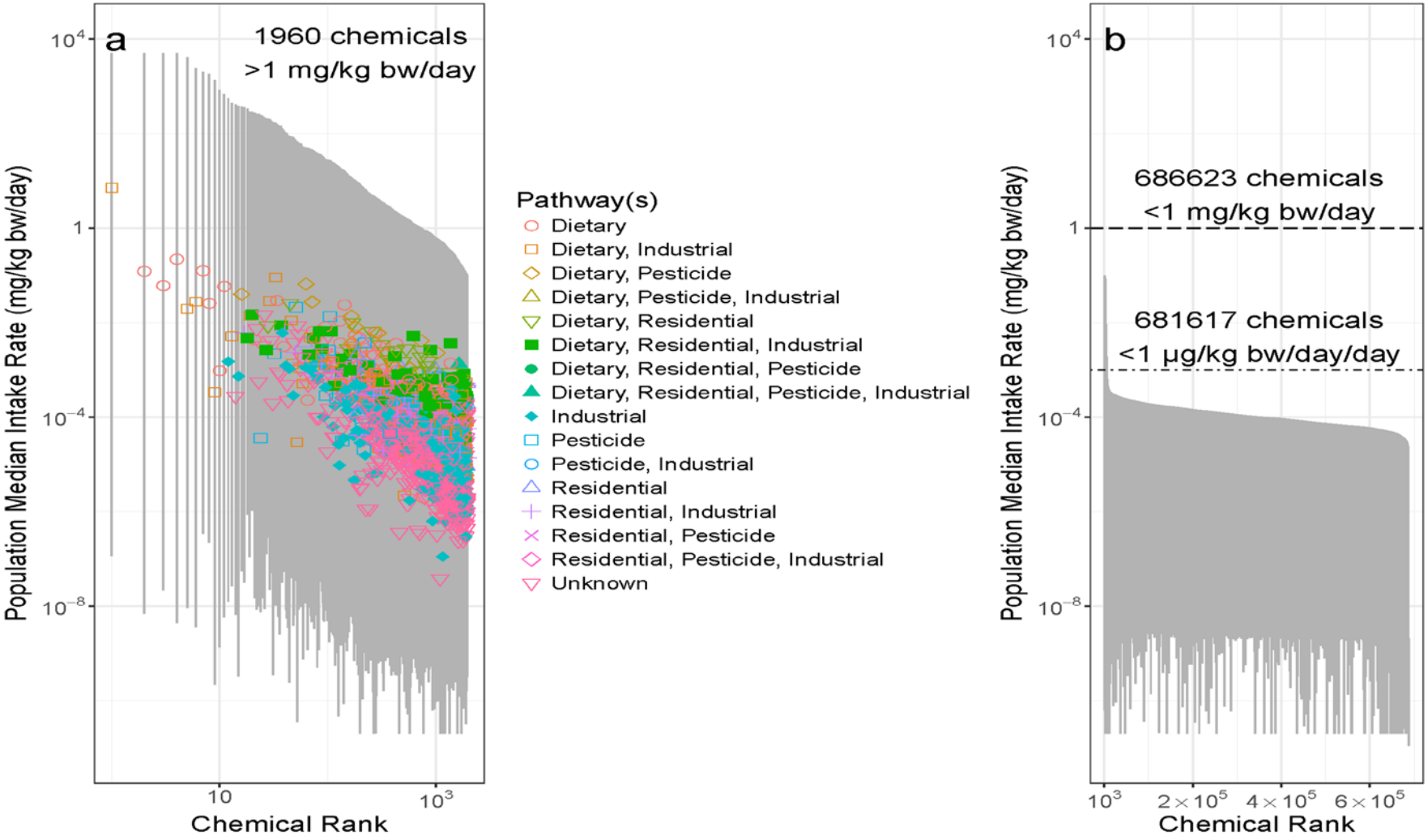
We use the method of Random Forests to relate chemical structure and properties to exposure pathway

	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	27	25	73	CPDat (consumer_use, building_material), ExpoCast, NHANES Curation	CPDat (Agricultural, Industrial), FDA CEDI, NHANES Curation
Far-Field Pesticide	94	1480	6522	20	36	80	REDs, Swiss Pesticides, Stockholm Convention, CPDat (Pesticide), NHANES Curation	Pharmapendium, Industrial Positives, NHANES Curation
Far Field Industrial	42	5089	2913	19	17	81	CDR HPV, USGS Water Occurrence, NORNAN PFAS, Stockholm Convention, CPDat (Industrial, Industrial_Fluid), NHANES Curation	Pharmapendium, Pesticide Positives, NHANES Curation

Pathway-Based Consensus Modeling



High Throughput Exposure Prediction



Exposure-Based Priority Setting

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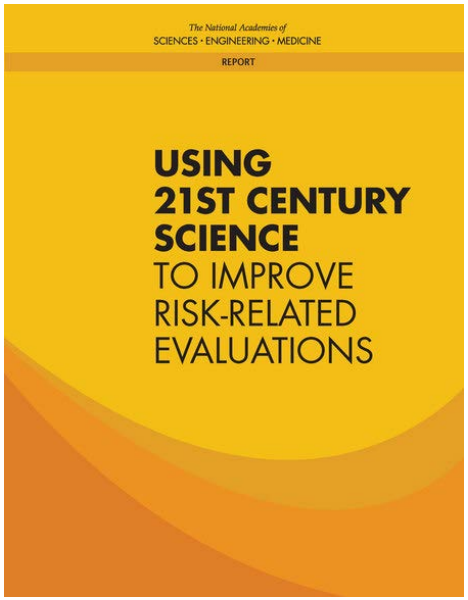

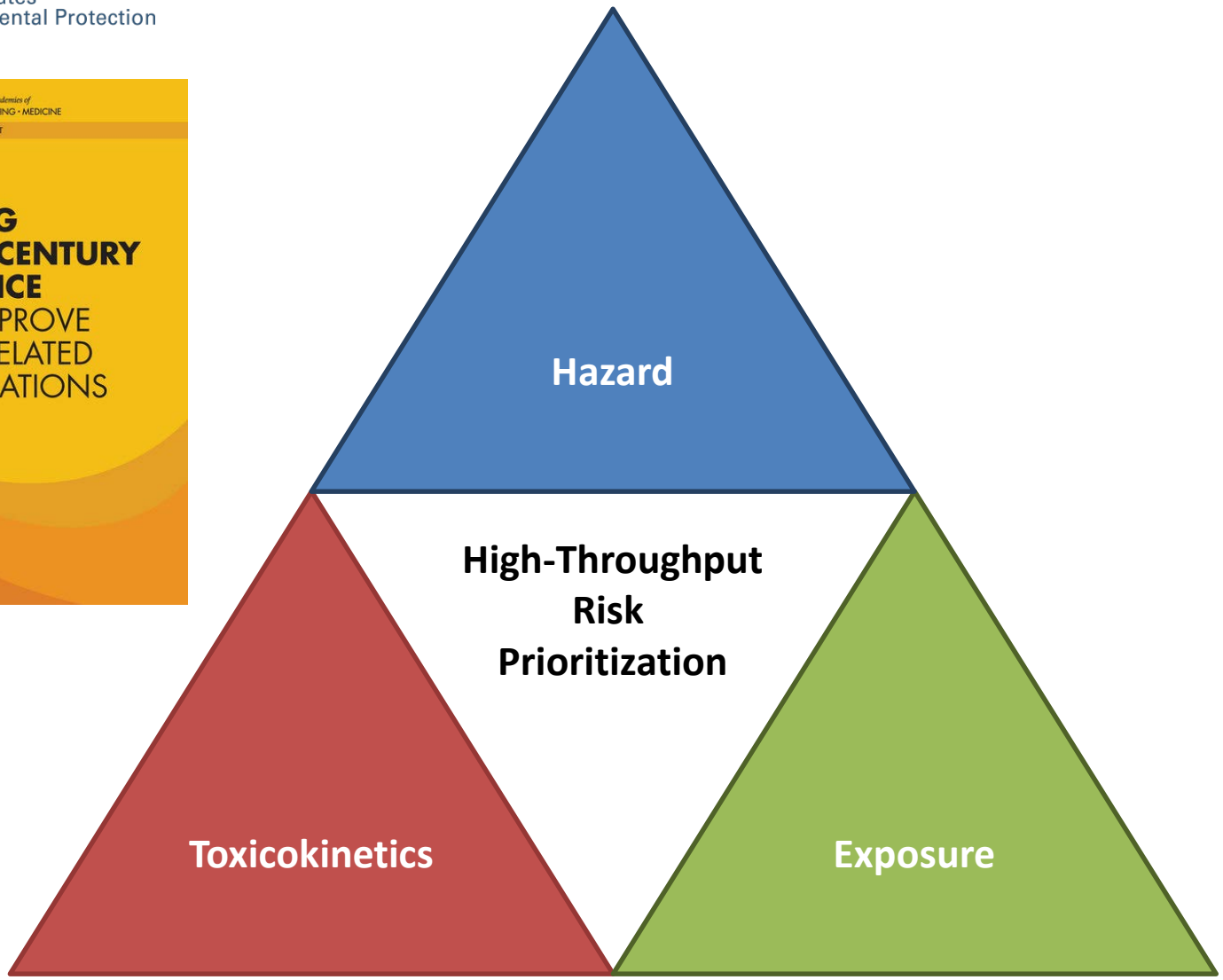

High Throughput Risk Prioritization

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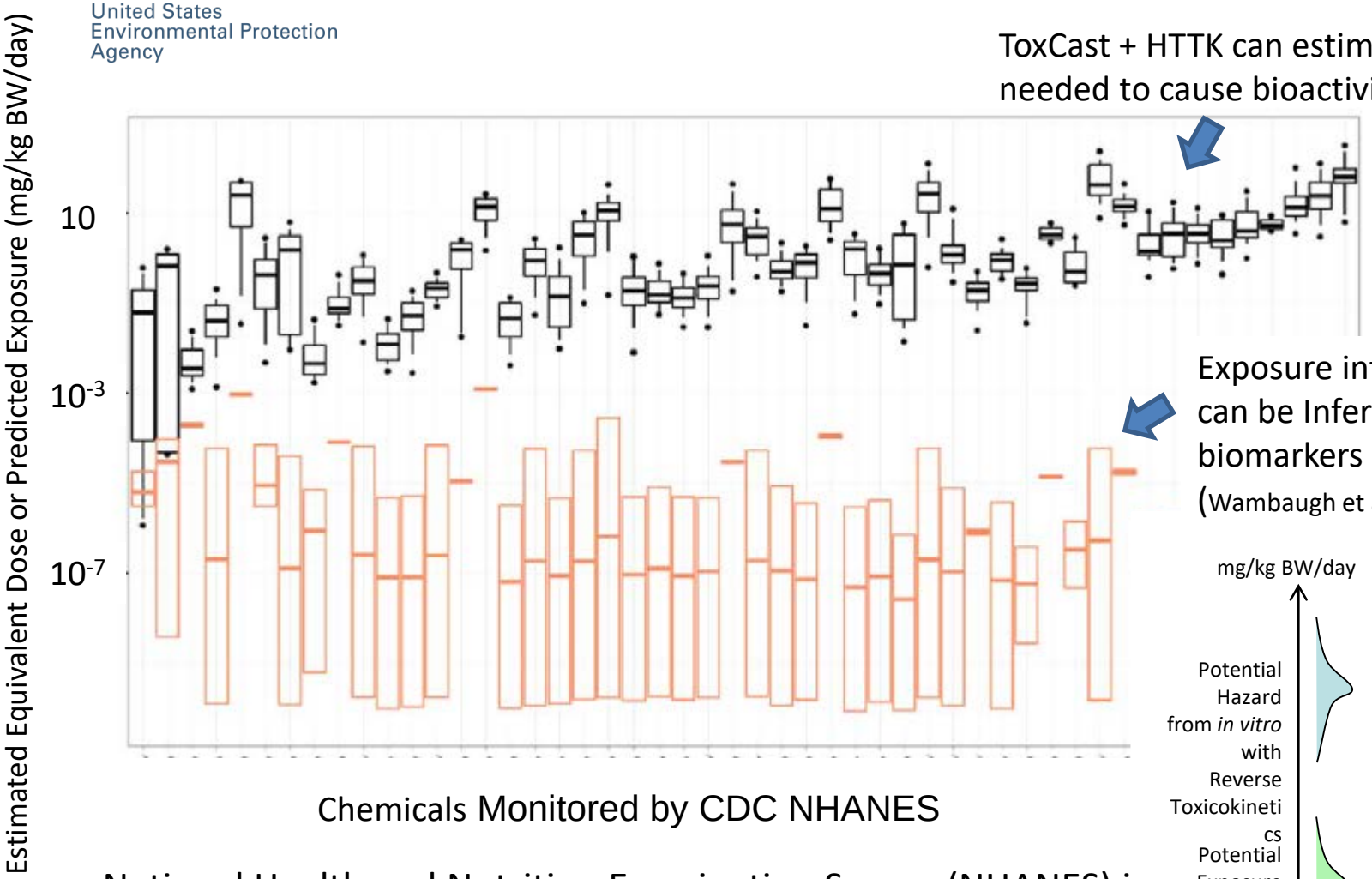
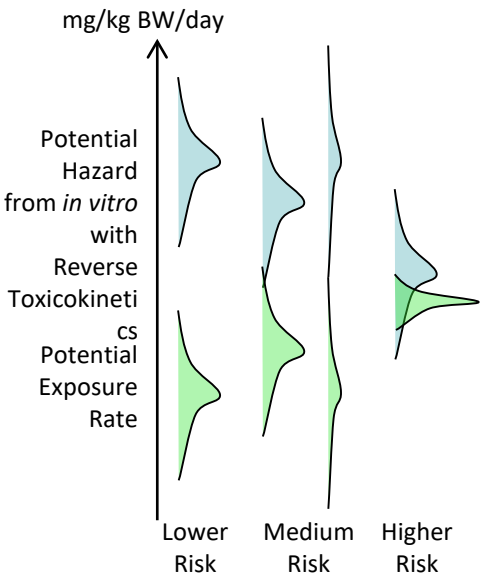
ToxCast + HTTK can estimate doses needed to cause bioactivity



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

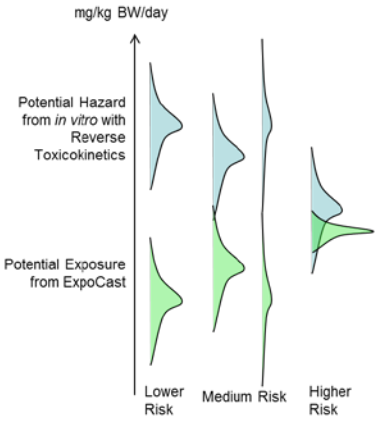


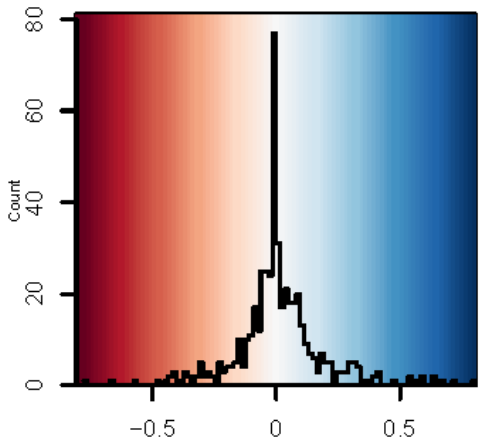
National Health and Nutrition Examination Survey (NHANES) is an ongoing survey that covers ~10,000 people every two years

Ring *et al*. (2017)

Life-stage and Demographic Specific Predictions

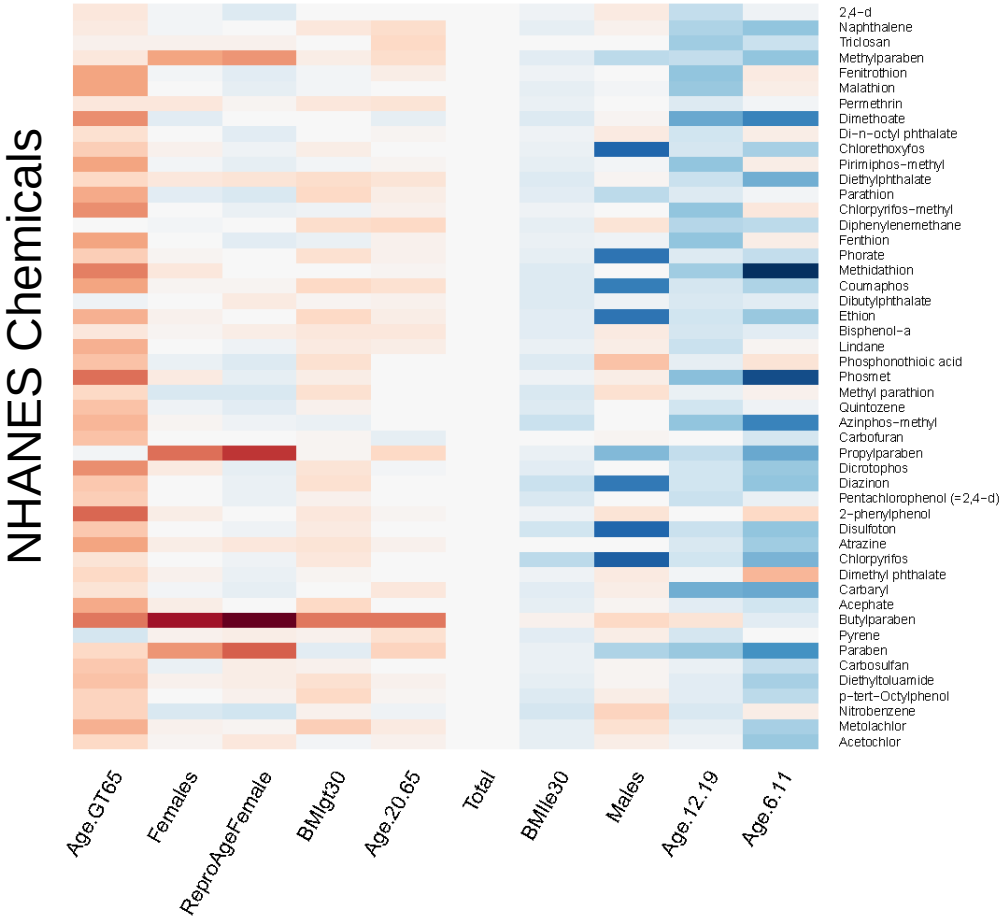
- Can calculate margin between bioactivity and exposure for specific populations





Change in Risk Relative to Total Population

Change in Activity:Exposure Ratio



Ring *et al*. (2017)

The Problem of Mixtures

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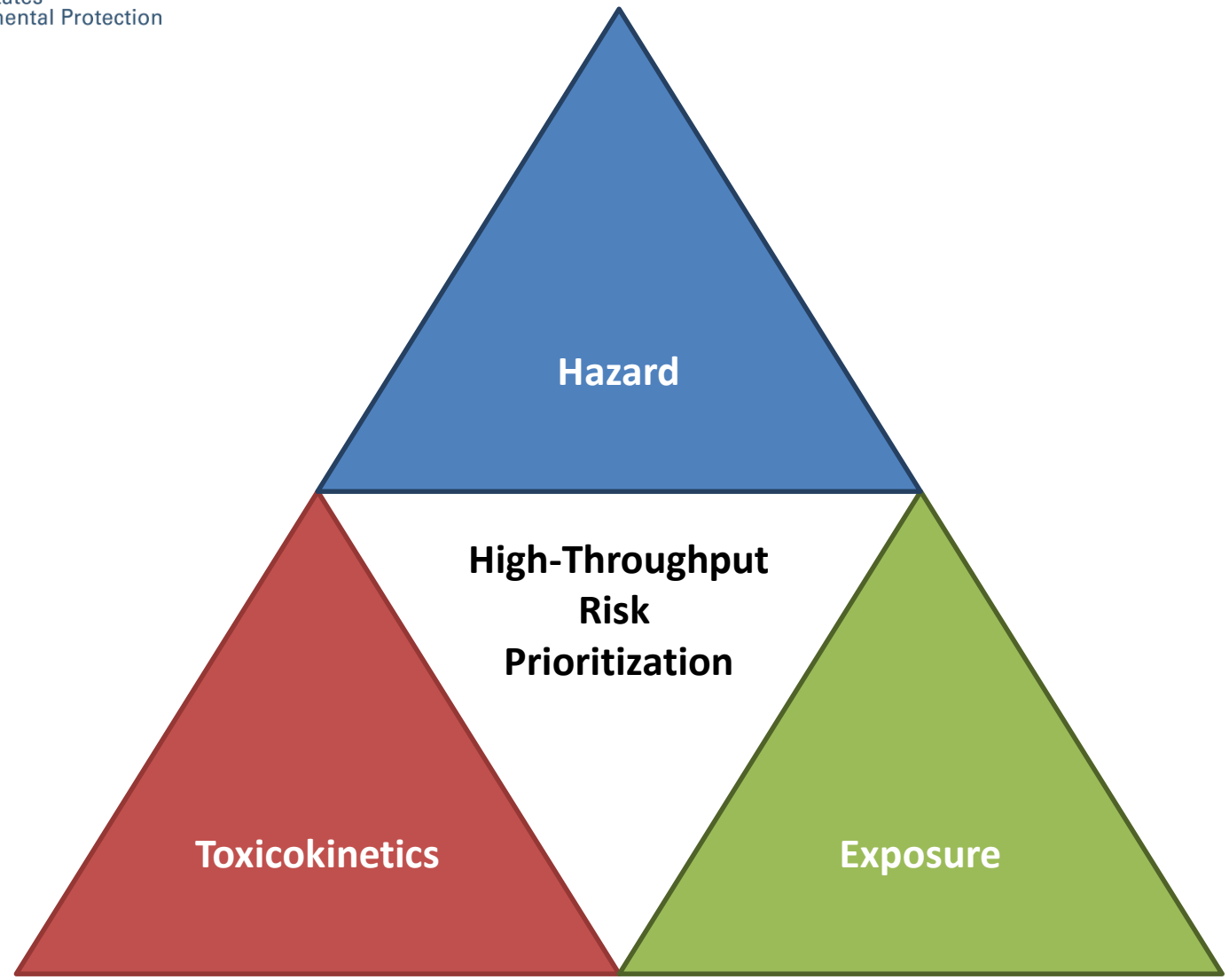

The Structure of Chemical Exposure

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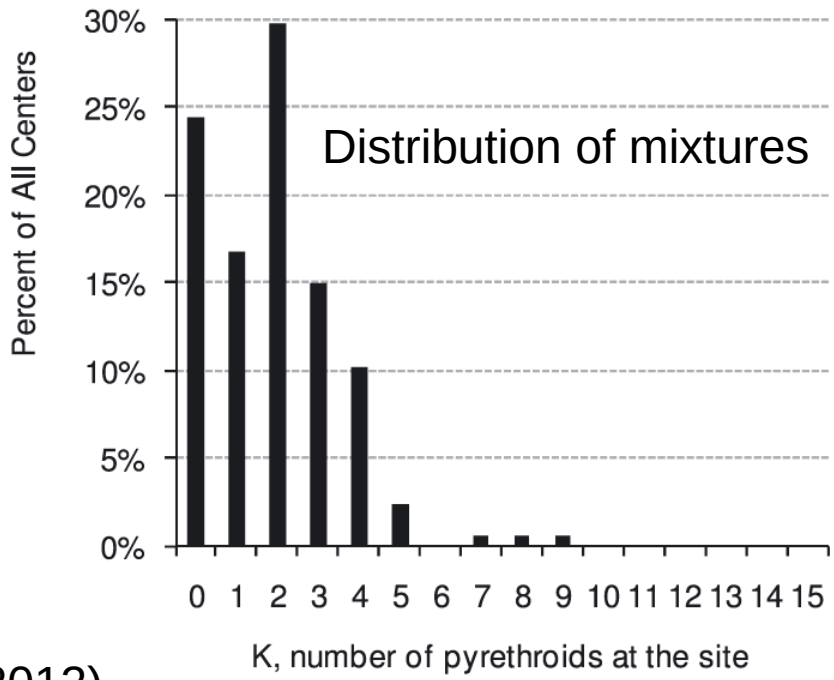
finch species

	Cuba	Hispanolia	Jamaica	Puerto Rico	Guadeloupe	
Loxigilla noxis	0	0	0	0	1	**1**
Melanospiza richardsoni	0	0	0	0	0	**0**
Tiara olivacea	1	1	1	1	0	**4**
Tiara bicolor	0	1	1	1	1	**4**
Tiara canora	1	0	0	0	0	**1**
Loxipasser anoxanthus	0	0	1	0	0	**1**
	2	**2**	**3**	**2**	**2**	**11**

chemical species

	site 1	site 2	site 3	site 4	site 5	
chemical 1	1	0	0	0	1	**2**
chemical 2	1	1	0	1	1	**4**
chemical 3	0	0	0	0	1	**1**
chemical 4	1	0	0	0	0	**1**
chemical 5	0	0	1	0	0	**1**
chemical 6	0	0	1	0	0	**1**
	3	**1**	**2**	**1**	**3**	**10**

- For **n** chemicals **2^n** combinations are possible
  - However, not all are observed
- Diamond (1975): Not all finch species present on all islands of Caribbean
- Tornero-Velez et al. (2012): Not all chemical combinations present at all sites



Tornero-Velez et al. (2012)

Kapraun et al. (2017) EHP

- Targeted analytical chemistry used to quantitate concentration of specific chemicals in urine
  - Samples must be divided up for each chemical tested
  - NHANES cohort divided up to allow enough sample for testing all chemicals

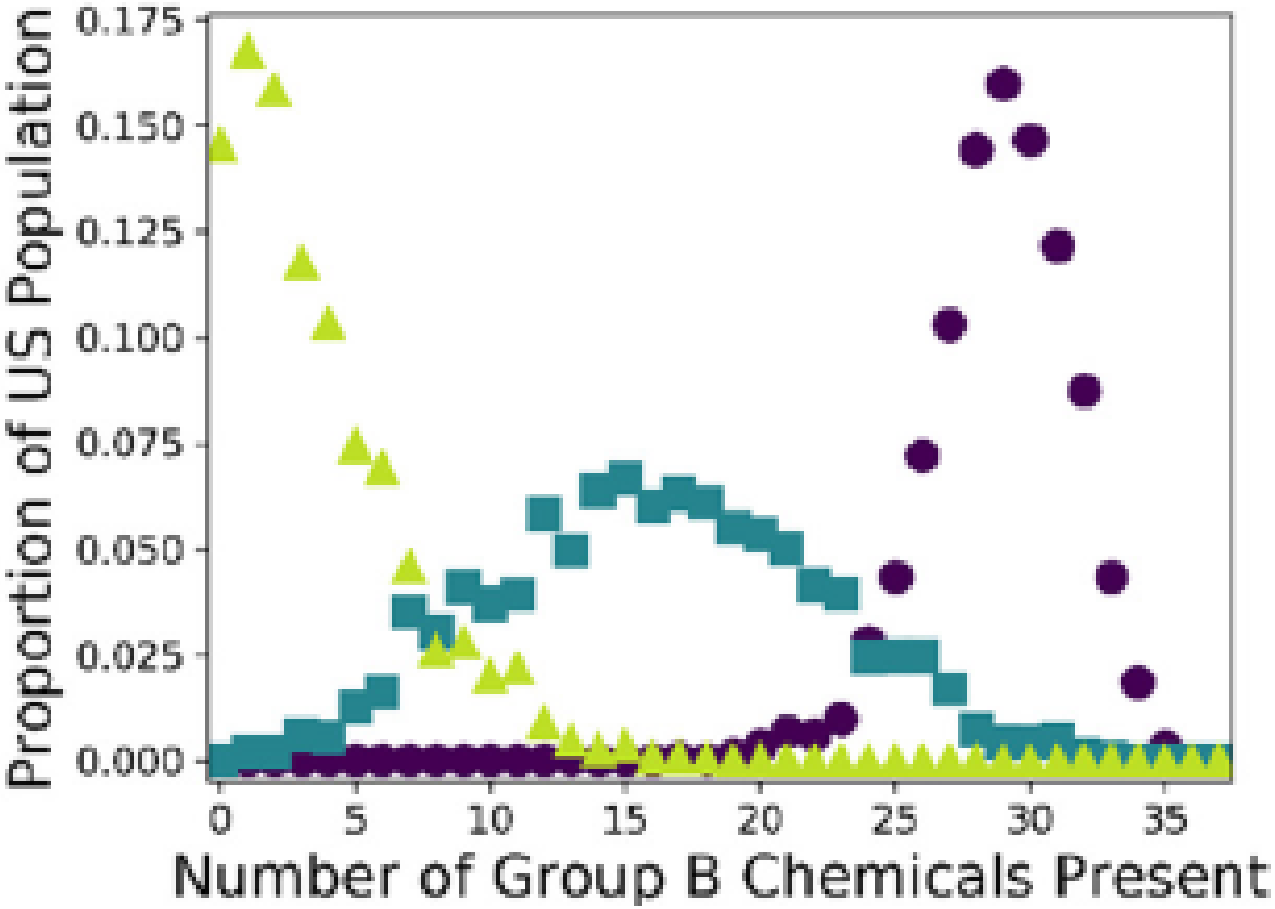
Table 4. Summary information for each of the National Health and Nutrition Examination Survey (NHANES) 2009–2010 subsamples.

Category	Subsample A	Subsample B	Subsample C
Number of subjects	2,741	2,736	2,132
Number of chemicals	29	37	40
Maximum weight	476,883.0	426,061.1	413,068.1
Minimum weight	14,002.7	13,975.1	12,659.3
Sum of weights	258,281,689.4	272,911,664.0	226,021,580.6
Records needed	18,445.1	19,528.5	17,854.1

- We will focus on “Sub-sample B” PAHs, Phenols, Pesticides, and Phthalates

Co-Occurrence of Chemicals in Individuals

The number of chemicals (out of 37) “present” in individuals depends upon where you set the limit

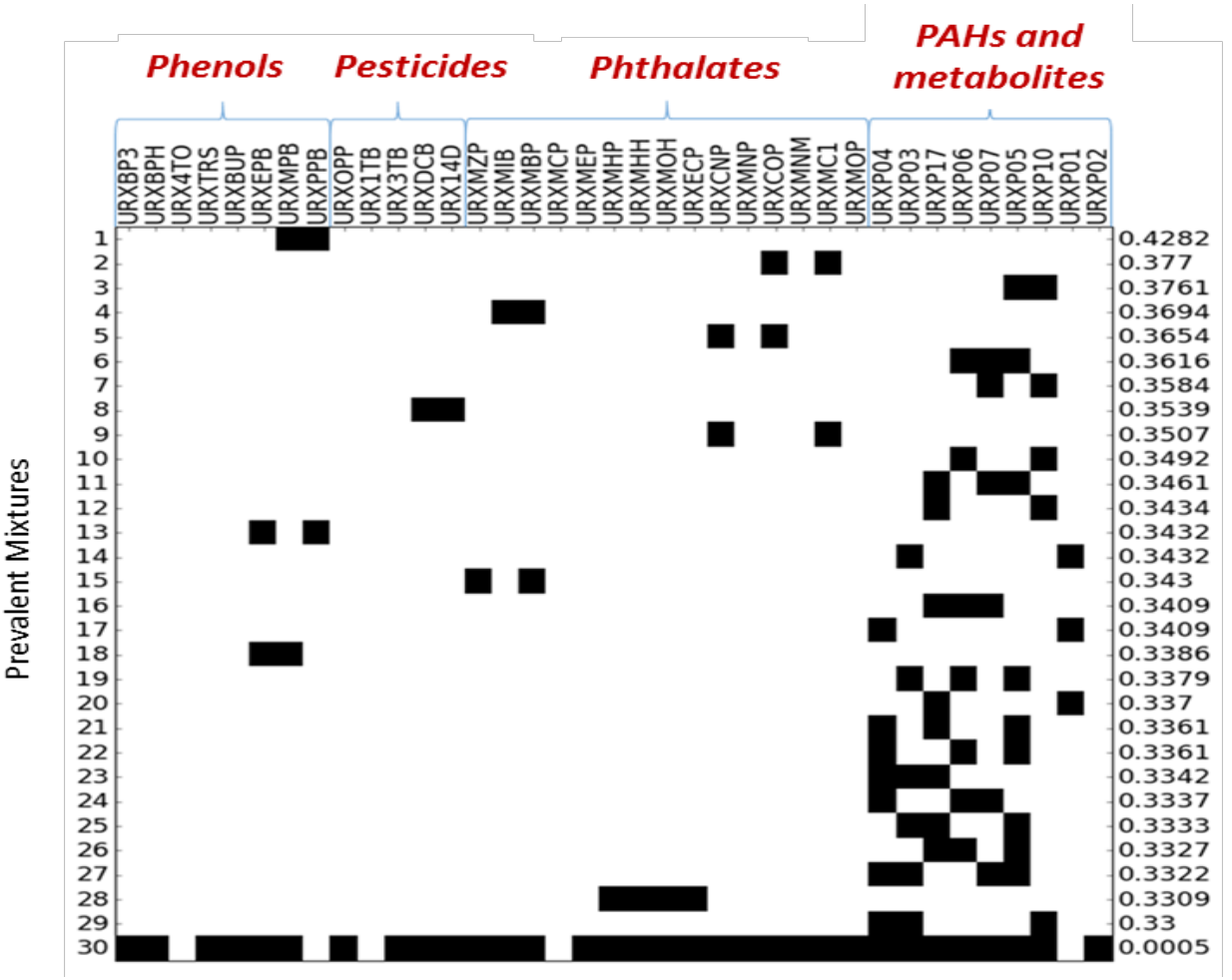


Ideally we would use some sort of chemical toxicity informed point of departure but don’t have that for all chemicals

Kapraun et al. (2017)

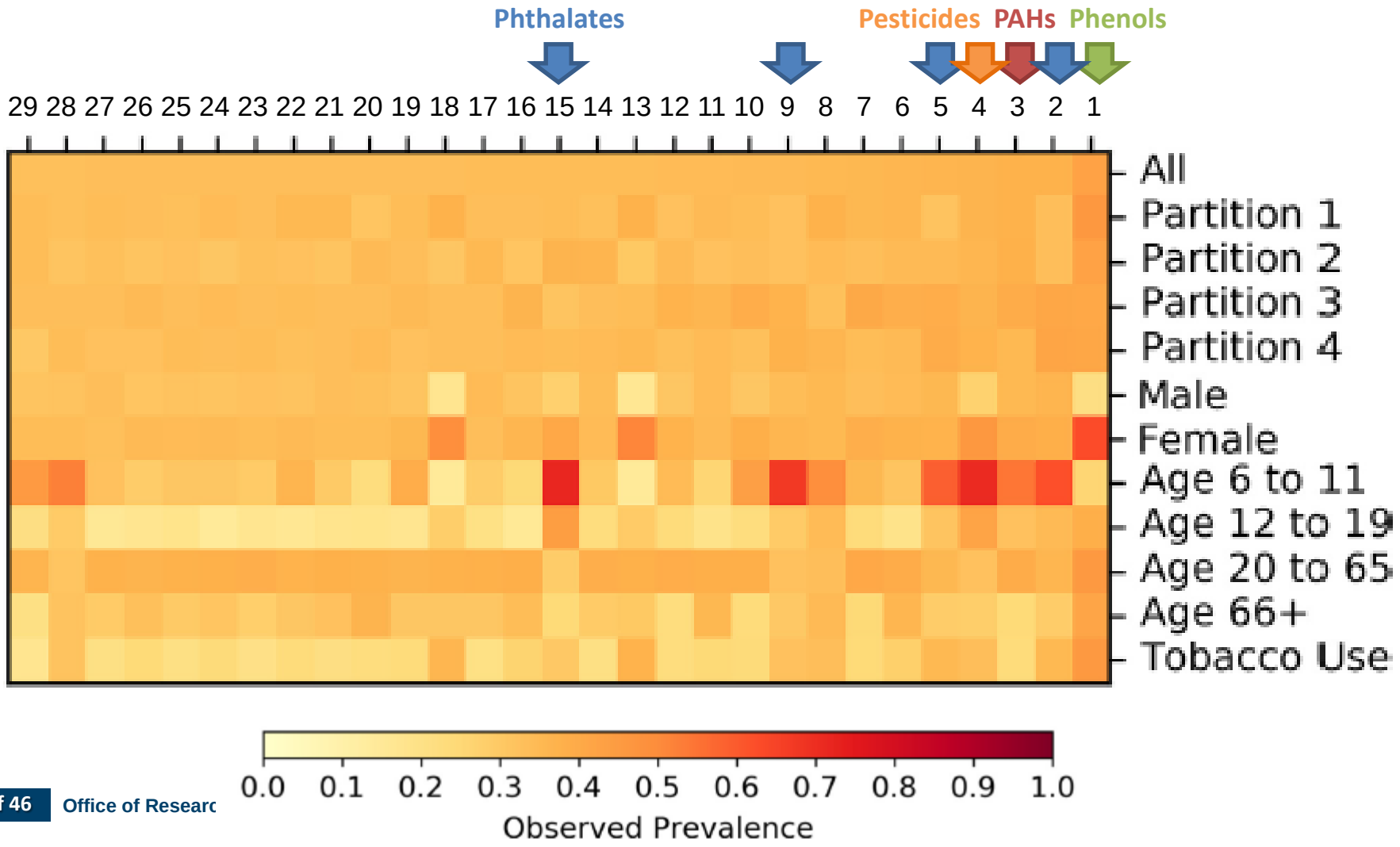
Identifying Prevalent Mixtures

- Kapraun et al. (2017) used frequent itemset mining (FIM, Borgelt, 2012) to identify combinations of items (chemicals) that co-occur together within CDC NHANES samples from same individual
- Used total population median concentration as threshold for “presence”
- Identified a few dozen mixtures present in >30% of U.S. population



Kapraun et al. (2017)

Demographic-Specific Prevalence of Combinations



Kapraun et al. (2017)

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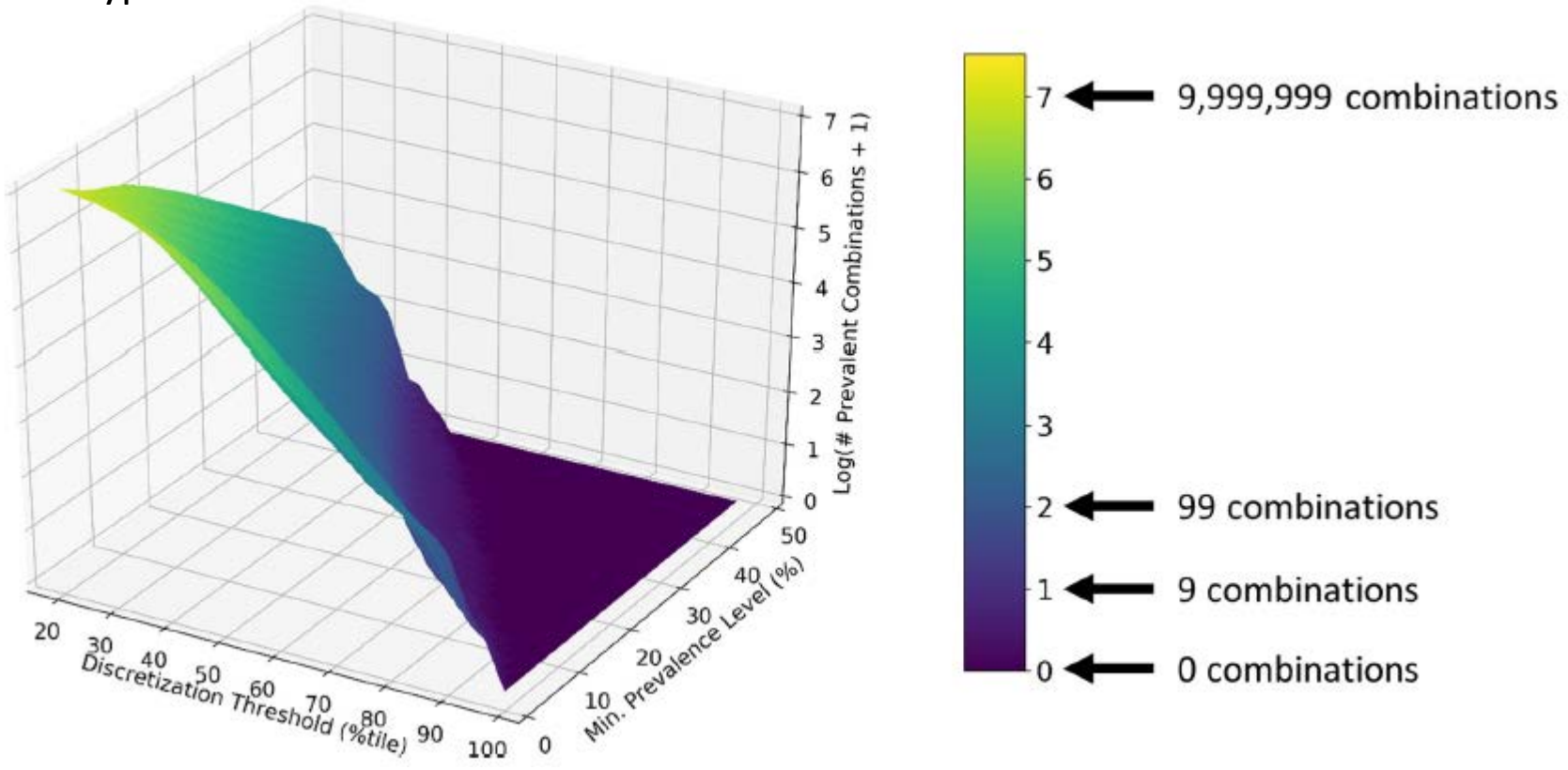
A Testable Number of Combinations

While high throughput screening (HTS) allows thousands of tests, there are millions of hypothetical combinations

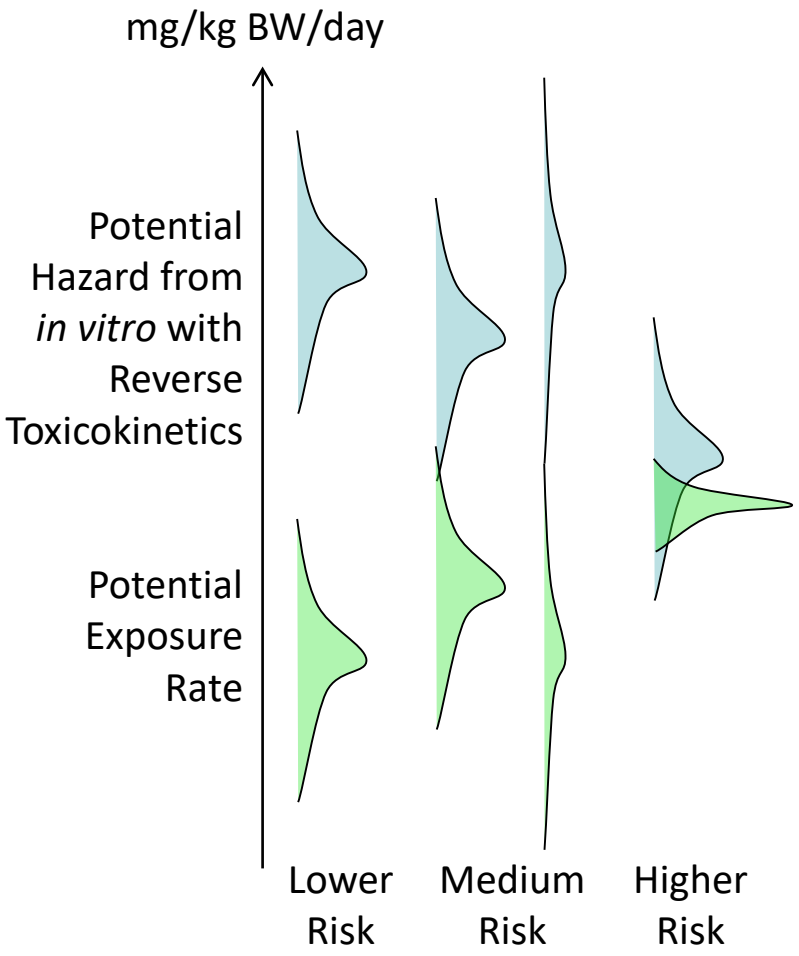


"Exposure based priority setting" (NAS, 2017) allows identification of most important mixtures to test

Kapraun et al. (2017)

Conclusions

- We would like to know more about the risk posed by thousands of chemicals in the environment – which ones should we start with?
- Using *in vitro* methods originally developed for pharmaceuticals, we can make useful predictions of hazard and TK for large numbers of chemicals
- Exposure data is also key to risk-based prioritization
  - Consensus modeling provides one path forward, but only as good as available data (at best)
- All of these methods are uncertain, but if that uncertainty can be quantified, we can make informed decisions
  - Safety factors in one form or another date back at least to the third century B.C. engineer Philo of Byzantium



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