United States Environmental Protection Agency

EPA's Rapid Exposure and Dosimetry (RED) Project

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

EPA's Rapid Exposure and Dosimetry Project

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Elin Ulrich
Dan Vallero
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We develop exposure and toxicokinetic models, statistical methods, and chemical analyses of environmental samples including water, dust, blood, and household products

We do exposure forecasting or "ExpoCast"

Chemical Safety for Sustainability (CSS)
Jeff Frithsen, Acting National Program Director
Lead CSS
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Collaborators

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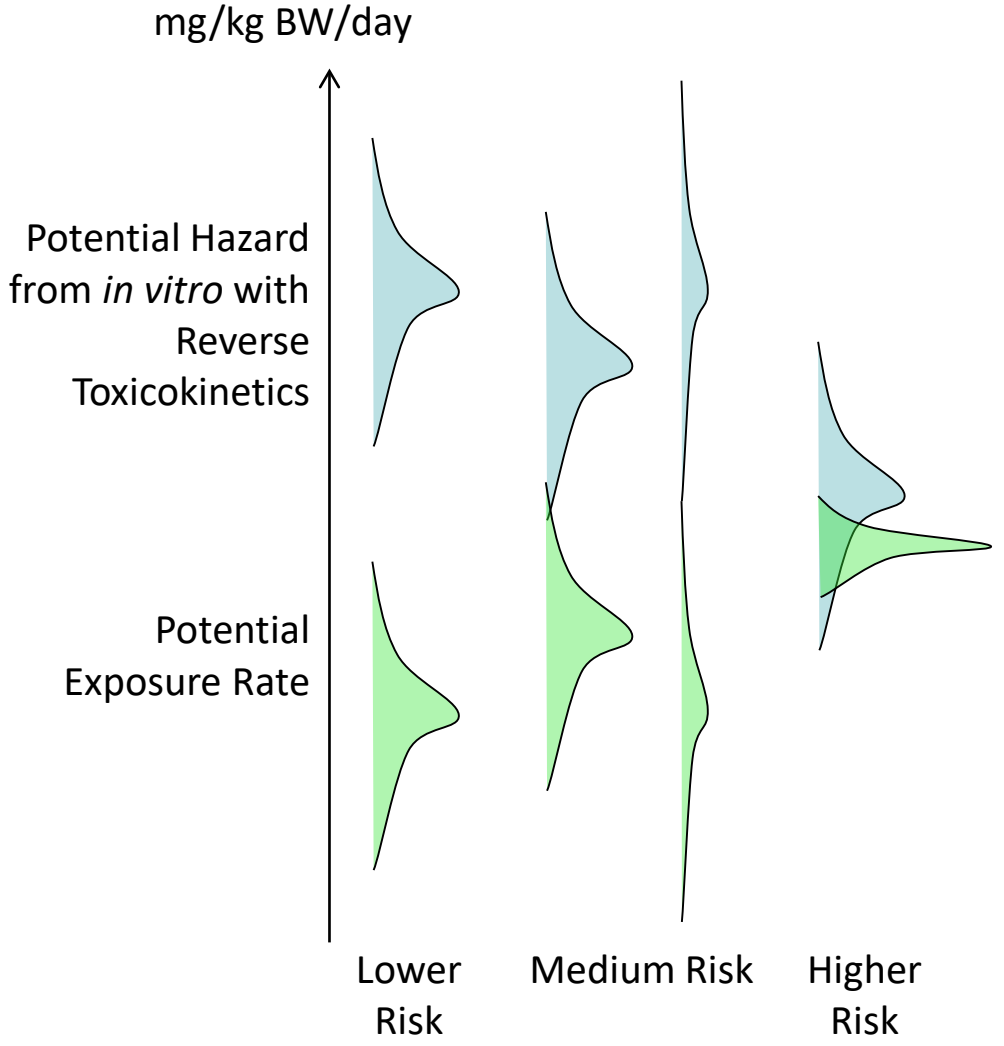
Chemical Risk = Hazard x Exposure

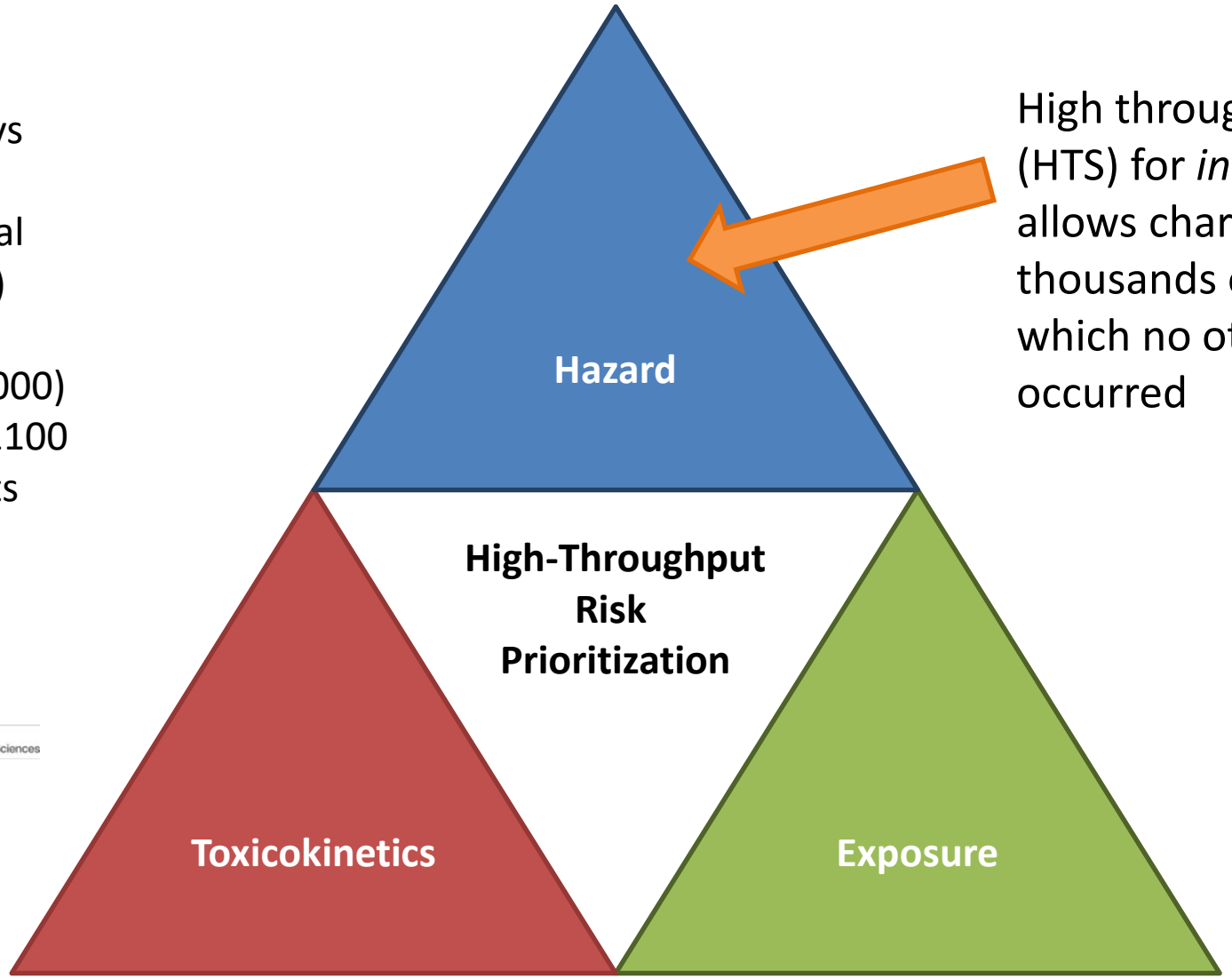
- National Research Council (1983) identified chemical risk as a function of both inherent hazard and exposure
- To address thousands of chemicals, we need new approach methodologies (NAMs) that can inform prioritization of chemicals most worthy of additional study
- High throughput risk prioritization needs:
  1. High throughput hazard characterization (Dix et al., 2007, Collins et al., 2008)
  2. High throughput exposure forecasts (Wambaugh et al., 2013, 2014)
  3. High throughput toxicokinetics (i.e., dose-response relationship) linking hazard and exposure (Wetmore et al., 2012, 2015)



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

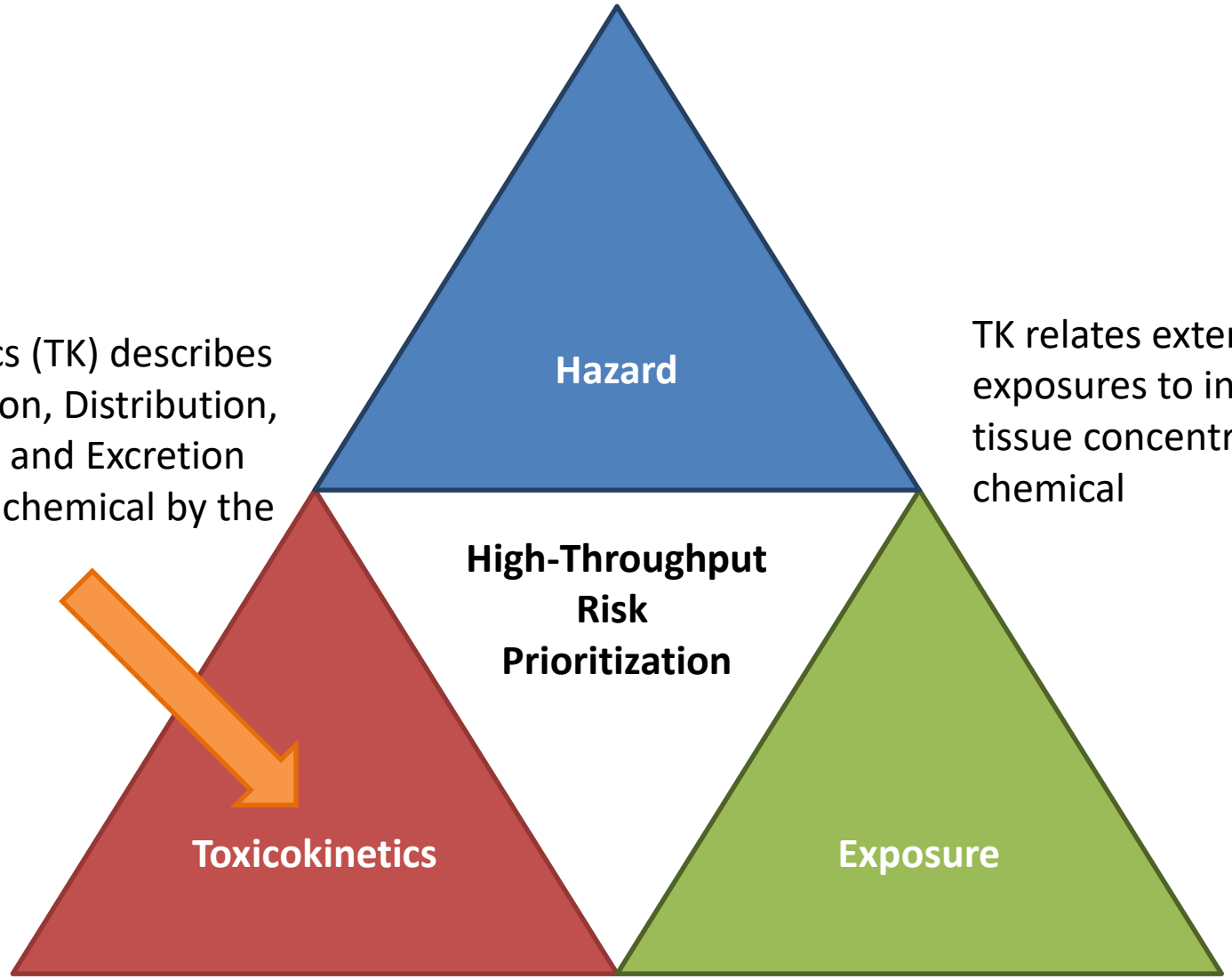
Rapid Exposure and Dosimetry "ExpoCast" Research

We are systematically addressing the areas contributing the greatest uncertainty to high throughput exposure methods:

- **Procurement and Mining of Exposure-Related Data for Support of Rapid Exposure Tools**
  - New Databases (such as CPdat)
  - Suspect screening and non-targeted analysis (SS/NTA)
- **High Throughput Toxicokinetics (HTTK) for Rapid Dosimetry**
- **Development and Evaluation of High-Throughput Human and Ecological Exposure Models**
  - SHEDS-HT: High Throughput Stochastic Human Exposure Dose Simulator
- **Statistical Methods for Model Evaluation and Calibration**
  - High throughput exposure models calibrated to exposure biomarker data (SEEM)

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

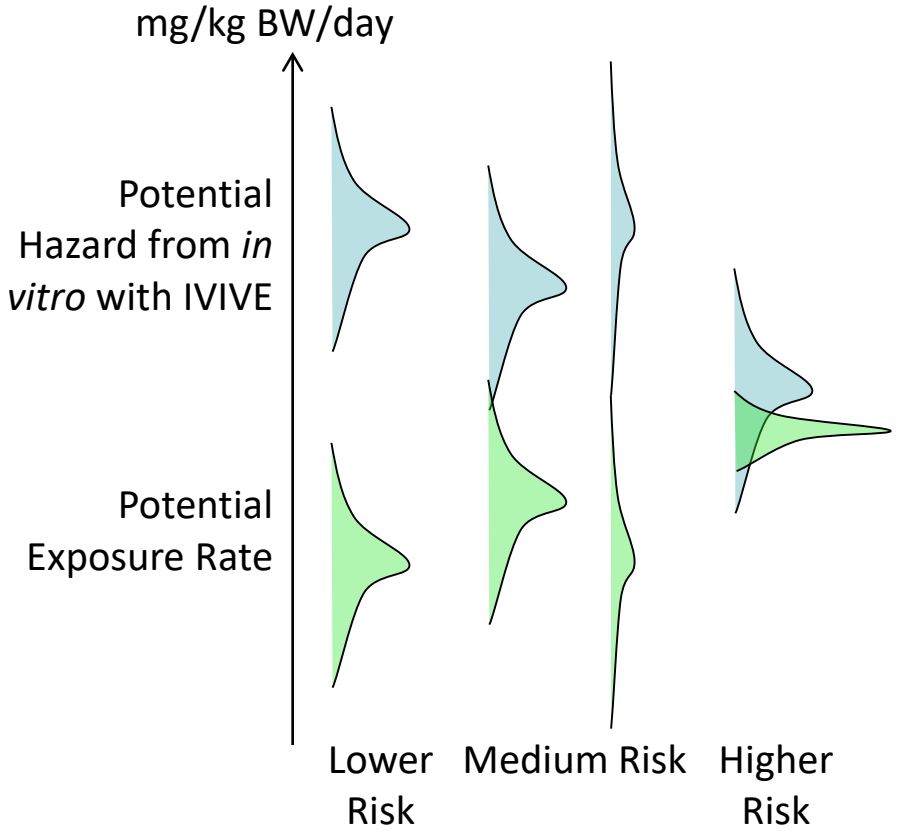
In Vitro - In Vivo Extrapolation (IVIVE)

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)

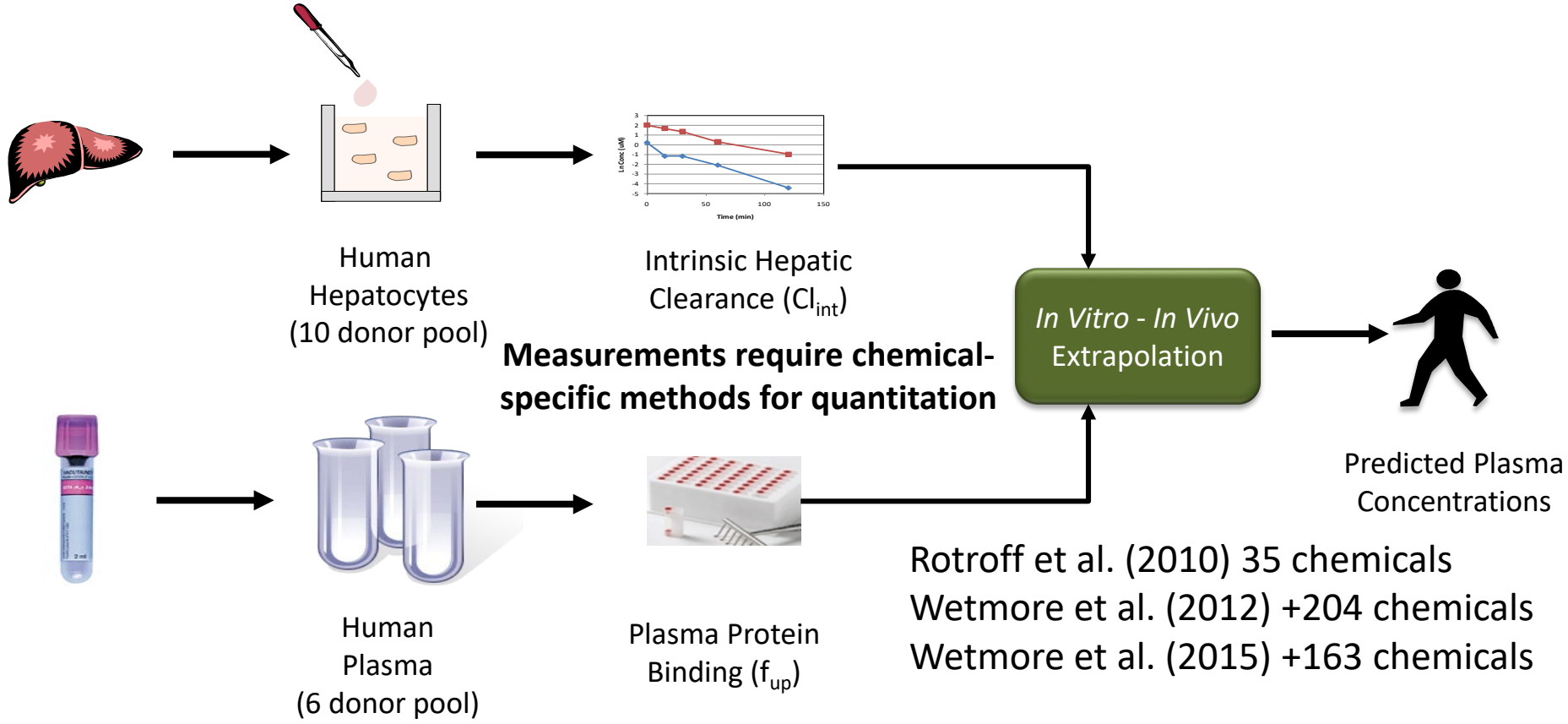
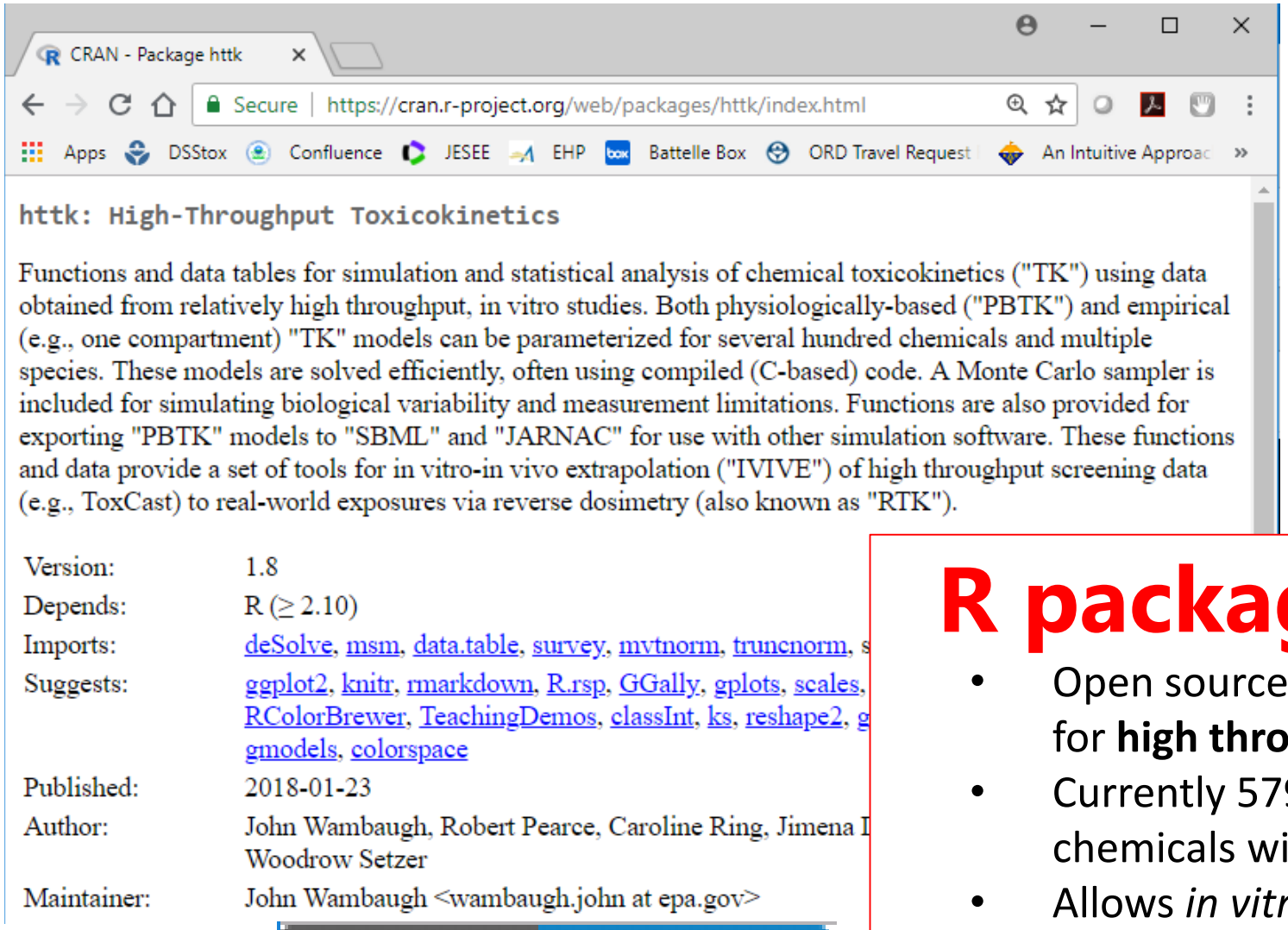


Figure from Barbara Wetmore

Open Source Tools and Data for HTTK

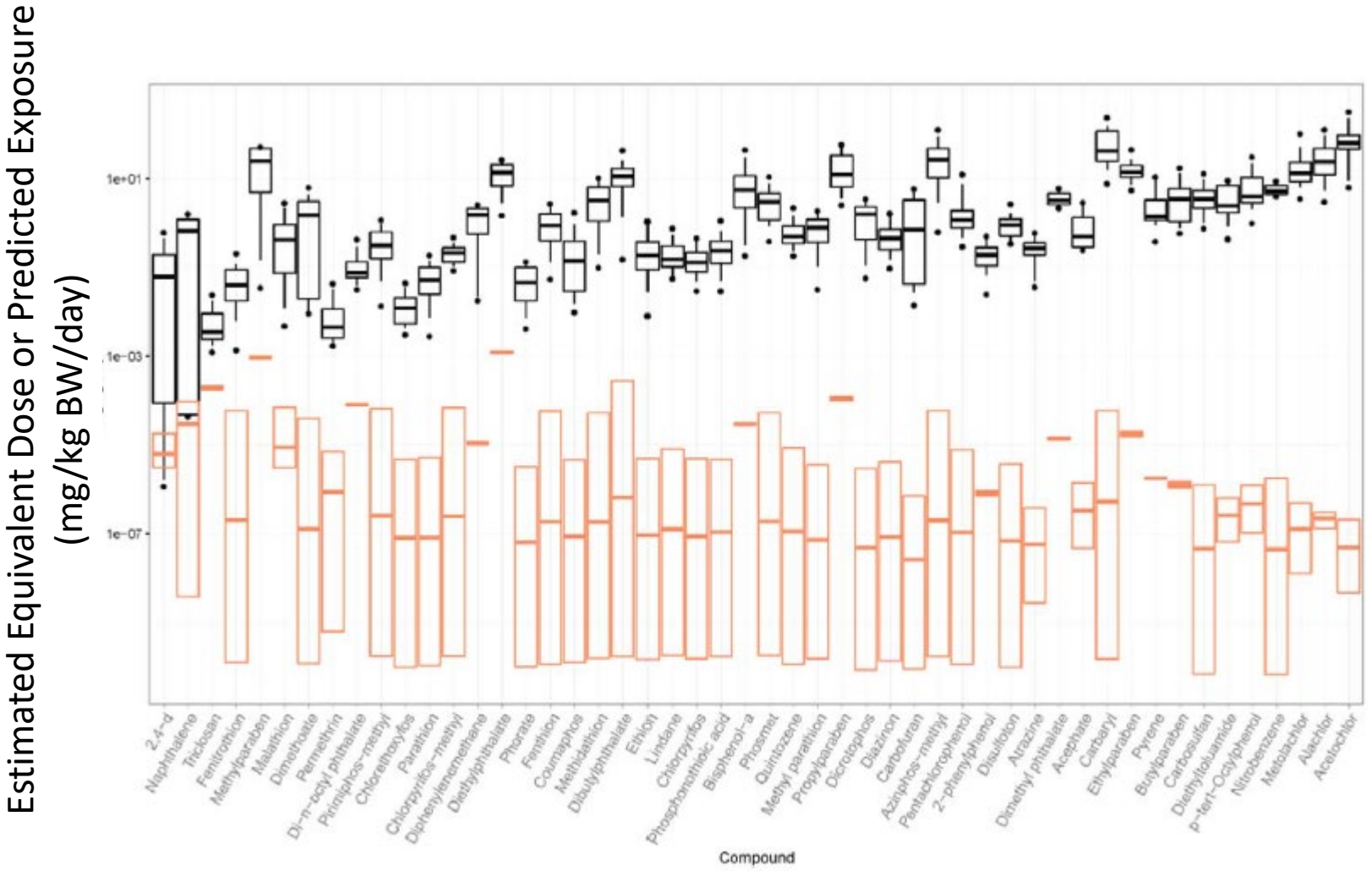
https://CRAN.R-project.org/package=httk

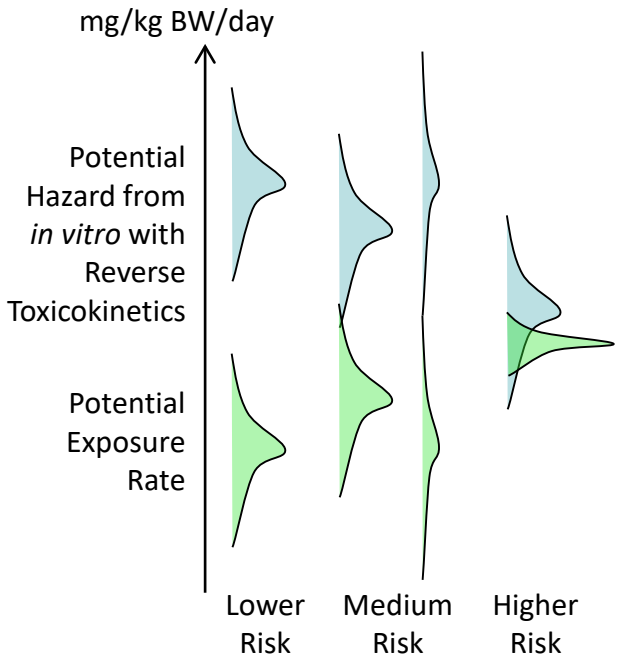


R package "httk"

- Open source, transparent, and peer-reviewed tools and data for **high throughput toxicokinetics (httk)**
- Currently 579 chemicals with human *in vitro* TK data, and 97 chemicals with rat data
- Allows *in vitro-in vivo* extrapolation (IVIVE), reverse dosimetry, and physiologically-based toxicokinetics (PBTK)

Risk-Based Ranking for Total NHANES Population

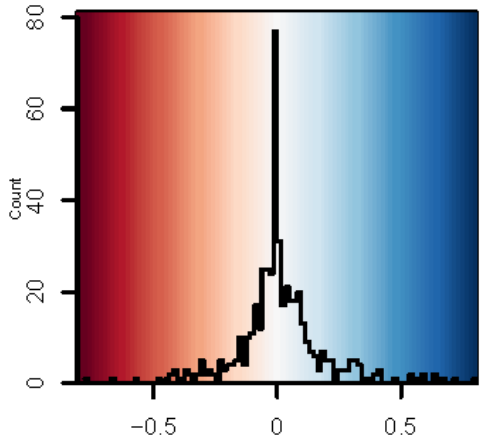




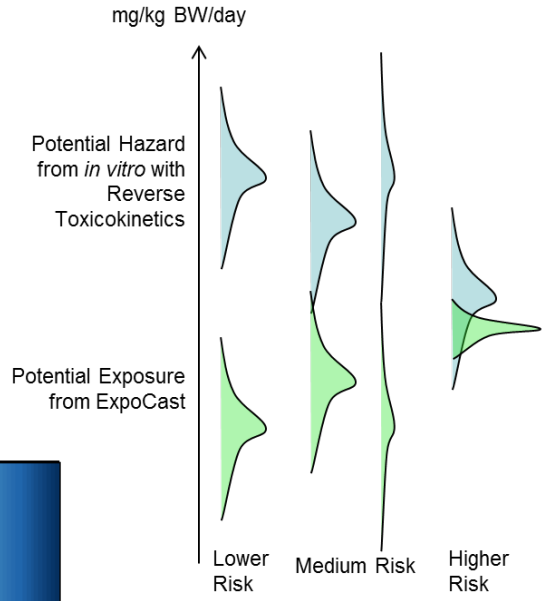
Ring *et al*. (2017)

Life-stage and Demographic Specific Predictions

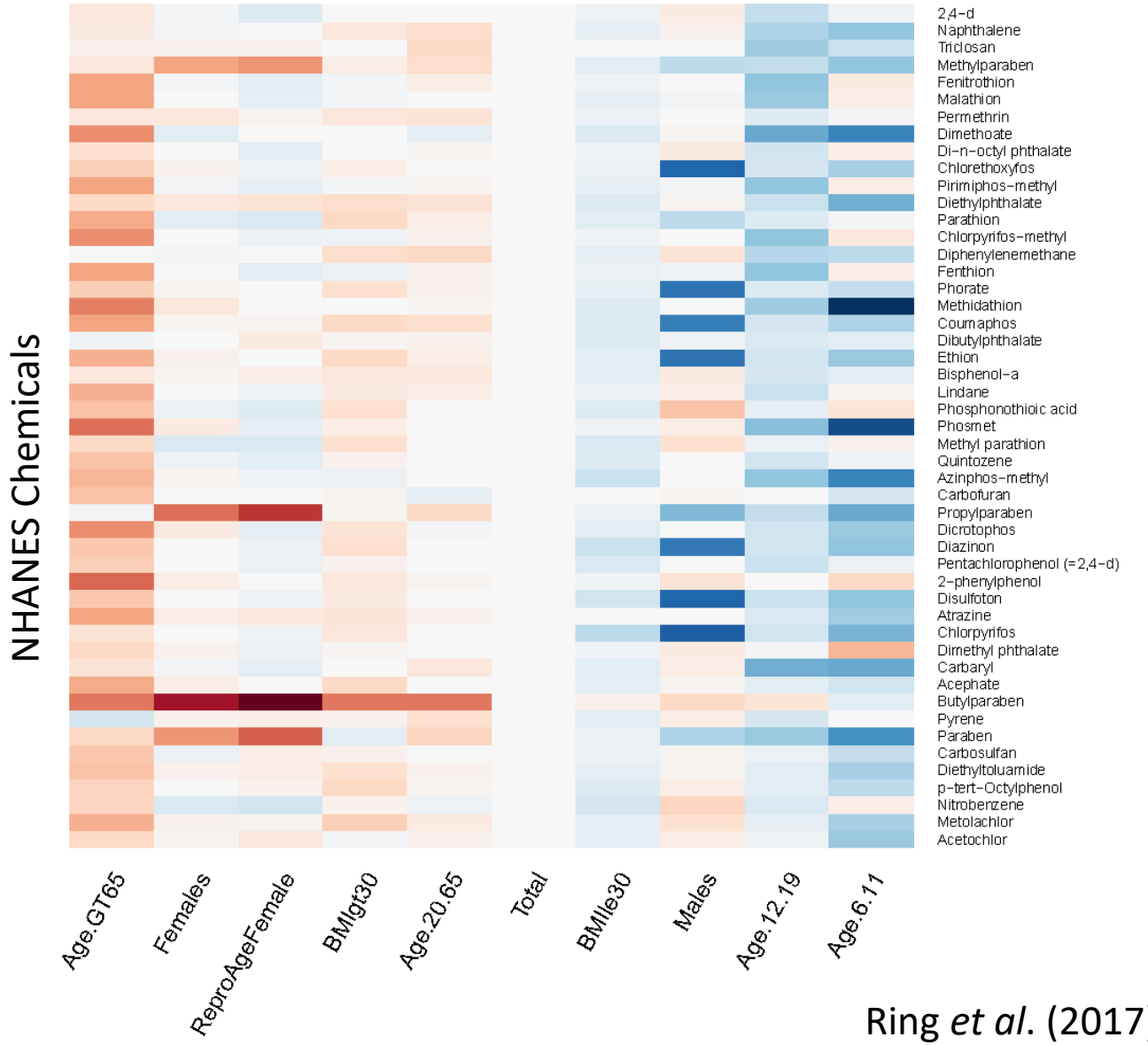
- We can calculate margin between bioactivity and exposure for specific populations
- Use biometrics from NHANES to simulate TK variability



Change in Risk Relative to Total Population



Change in Activity:Exposure Ratio



Ring *et al*. (2017)

Building Confidence in HTTK

"…the steady-state, peak, and time-integrated plasma concentrations of non-pharmaceuticals were predicted with reasonable accuracy… HTTK and IVIVE methods are adequately robust to be applied to high throughput *in vitro* toxicity screening data of environmentally-relevant chemicals for prioritizing based on human health risks."

New *in vivo* TK data was collected by EPA/NHEERL (Mike Hughes) and RTI (Tim Fennell)

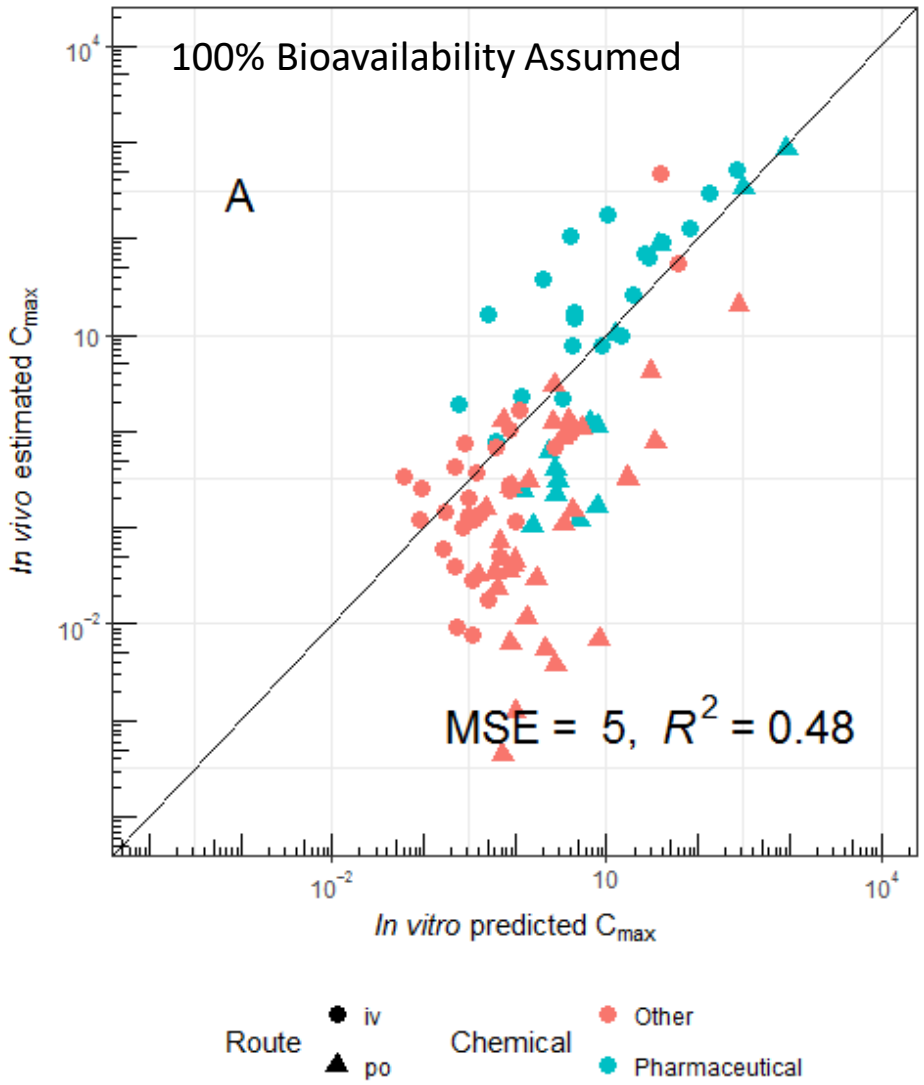
OXFORD
SOT | Society of Toxicology
www.toxsci.oxfordjournals.org
ToxSci 20 Years
TOXICOLOGICAL SCIENCES, 163(1), 2018, 152–169
doi: 10.1093/toxsci/kfy020
Advance Access Publication Date: January 27, 2018
Research Article

Evaluating *In Vitro-In Vivo* Extrapolation of Toxicokinetics

John F. Wambaugh,[*,1] Michael F. Hughes,[†] Caroline L. Ring,[*,‡,2] Denise K. MacMillan,[†] Jermaine Ford,[†] Timothy R. Fennell,[§] Sherry R. Black,[§] Rodney W. Snyder,[§] Nisha S. Sipes,[¶] Barbara A. Wetmore,[‖] Joost Westerhout,[‖] R. Woodrow Setzer,[*] Robert G. Pearce,[*,‡] Jane Ellen Simmons,[†] and Russell S. Thomas[*]

We are working to identify and areas of greatest (most impactful) uncertainty and reduce these uncertainties with new data and methods

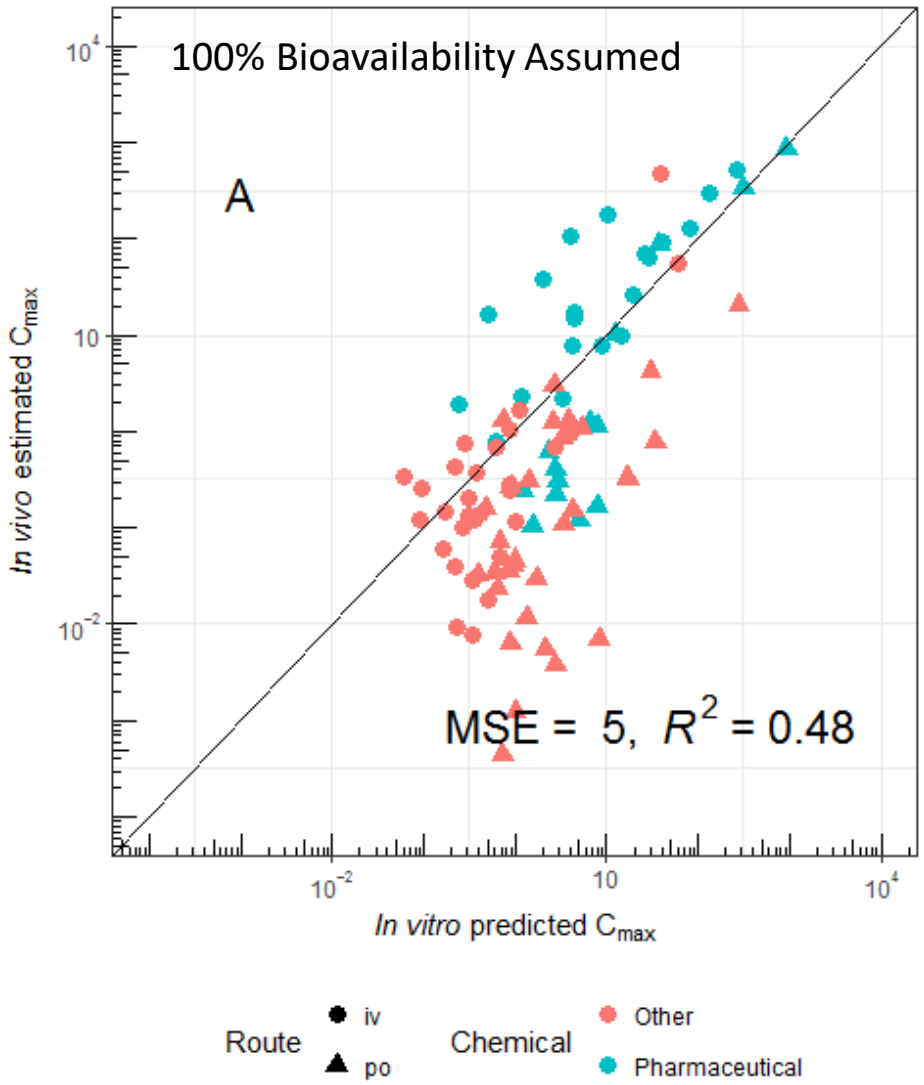
Evaluating HTTK

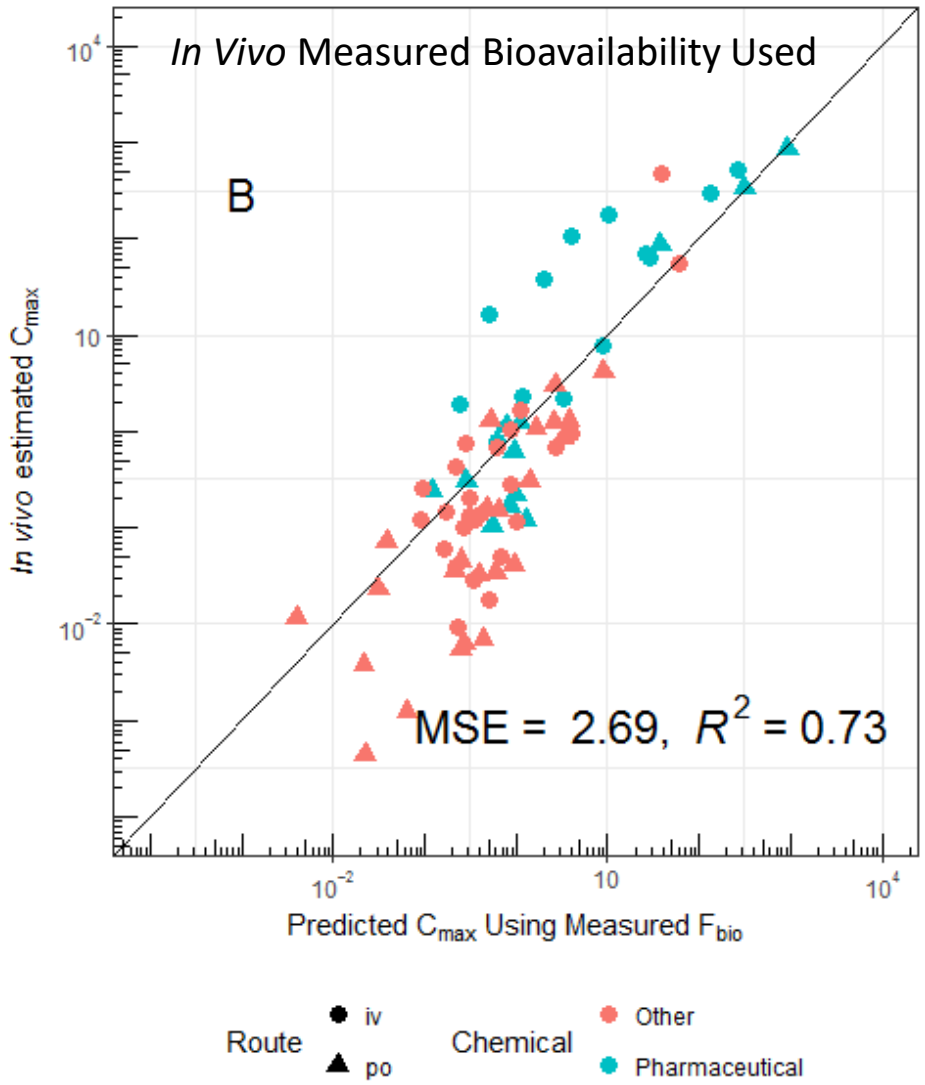


Wambaugh et al. (2018)

Evaluating HTTK

Impact of Oral Bioavailability Data





Wambaugh et al. (2018)

Evaluating HTTK

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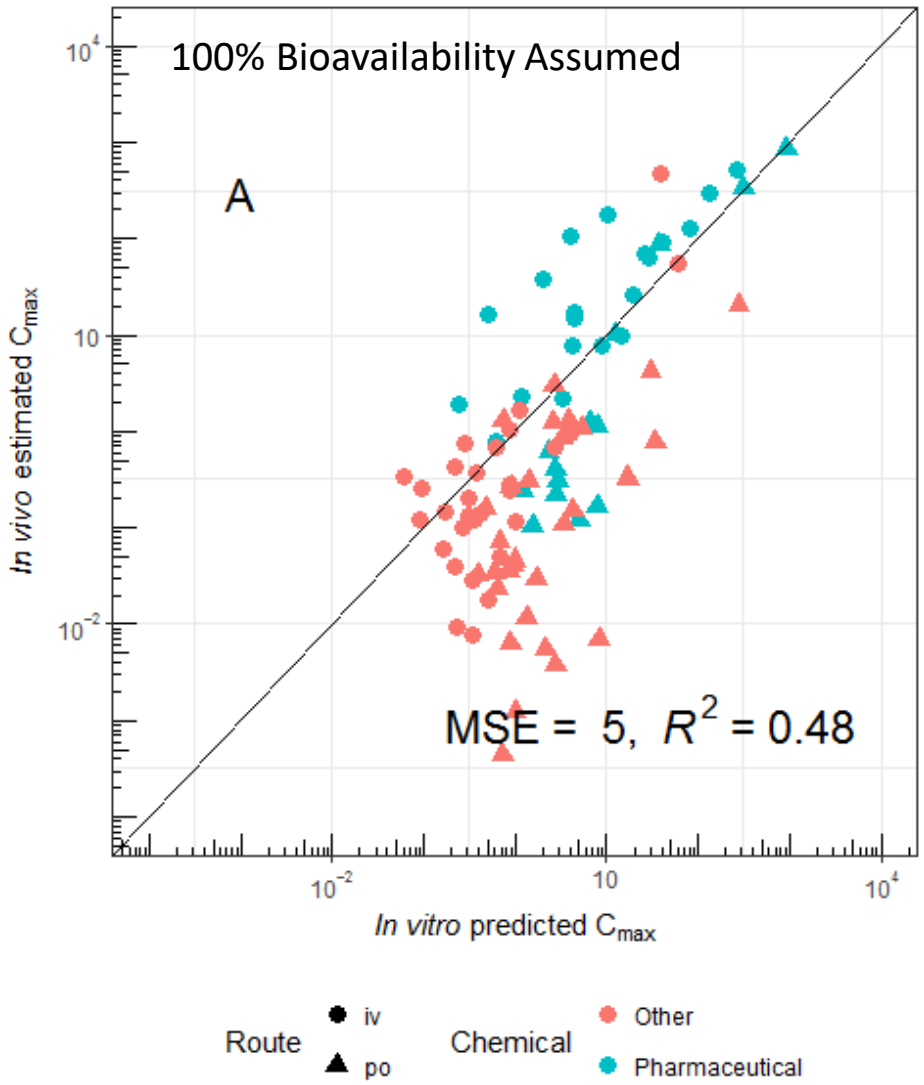
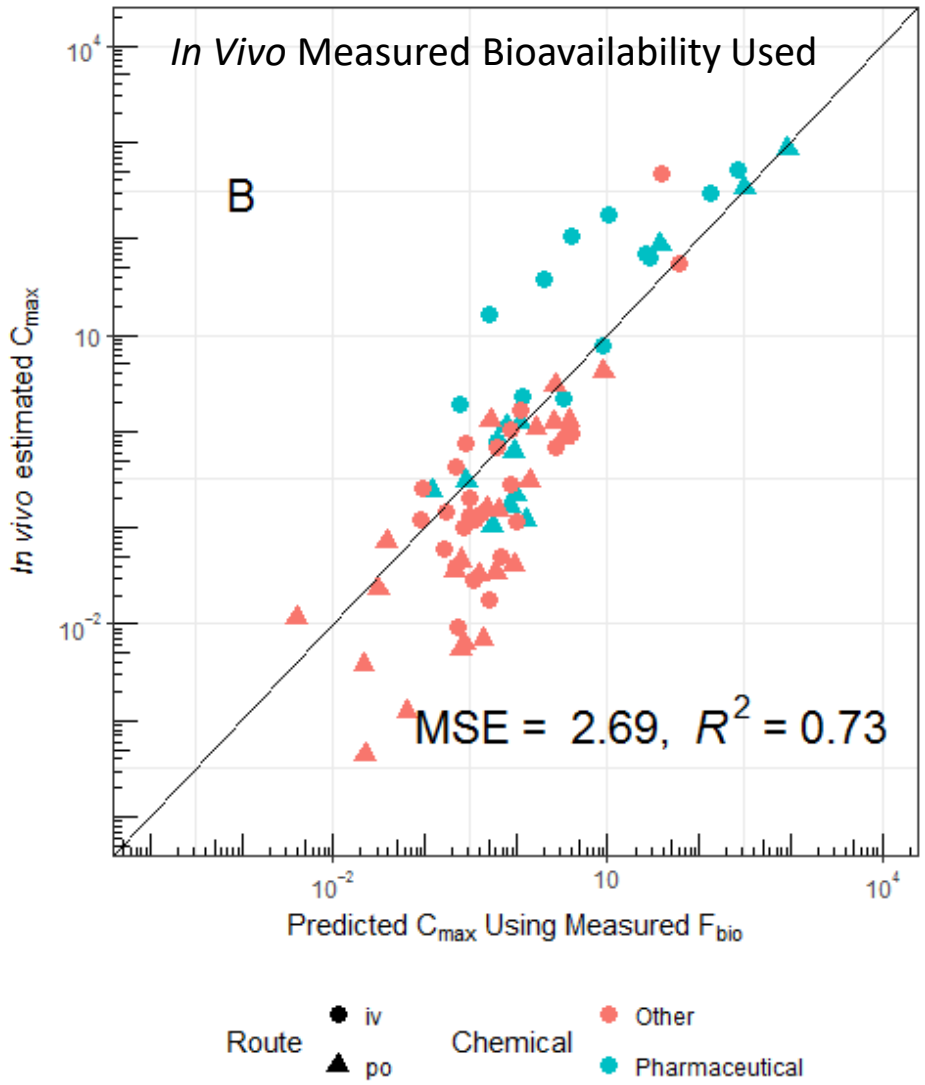




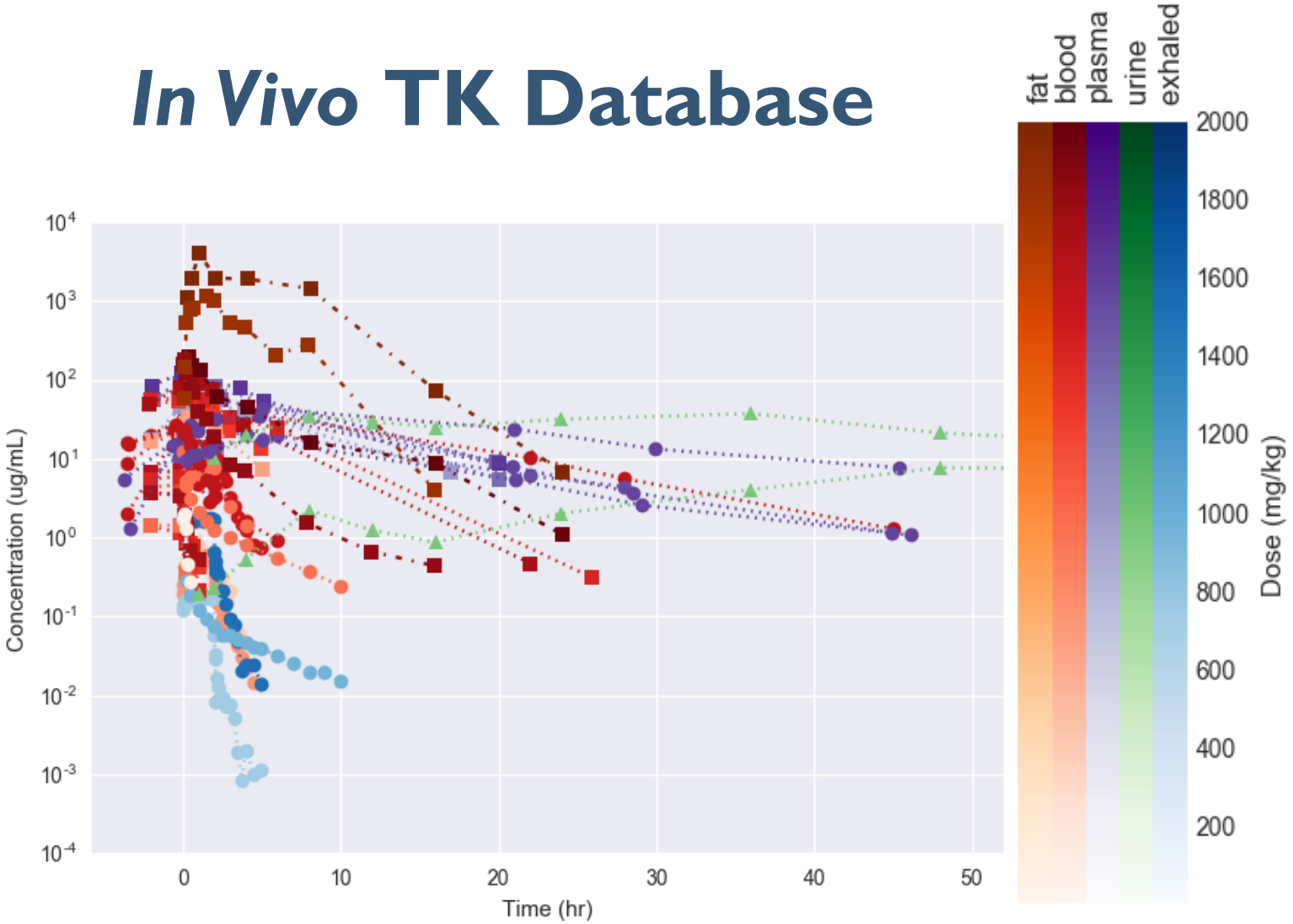
Greg Honda (NCCT) made a SOT2018 presentation on using Caco2 *in vitro* data to predict absorption for ~300 ToxCast chemicals

Wambaugh et al. (2018)

In Vivo TK Database

- EPA is developing a public database of concentration vs. time data for building, calibrating, and evaluating TK models

- Curation and development ongoing, but to date includes:
  - 198 analytes (EPA, National Toxicology Program, literature)
  - Routes: Intravenous, dermal, oral, sub-cutaneous, and inhalation exposure
- Database will be made available through web interface and through the “httk” R package

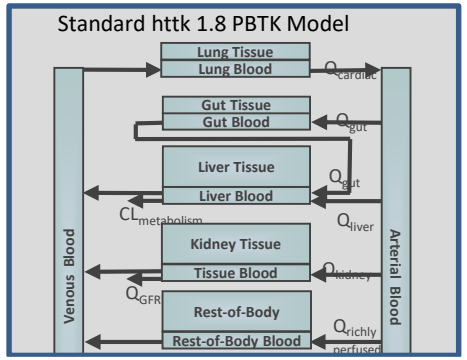


- Standardized, open source curve fitting software invivoPKfit used to calibrate models to all data:
  https://github.com/USEPA/CompTox-ExpoCast-invivoPKfit

Measured data allows evaluation of new models

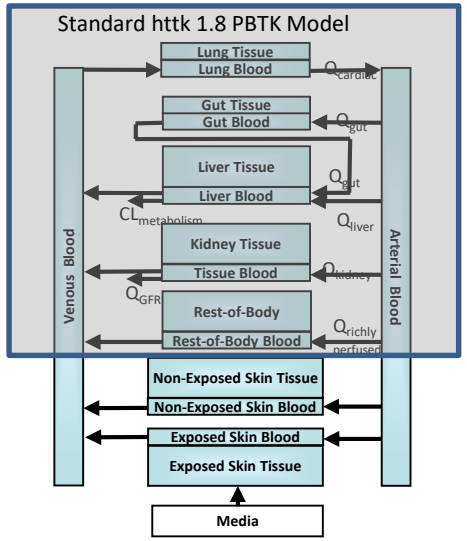
Sayre et al., in preparation

New HT-PBTK Models



- We are working to augment the basic HT-PBPTK model with new PBTK models
- Each model will be released publicly upon peer-reviewed publication
- Pre-publication models can be shared under a MTA
- We assume there will be coding errors and over-simplifications, so each publication involves curation of evaluation data from the scientific literature and through statistical analysis
- In Vivo TK (Concentration vs. Time) database (Sayre et al.) is critical to these efforts

New HT-PBTK Models



Dermal Exposure Route

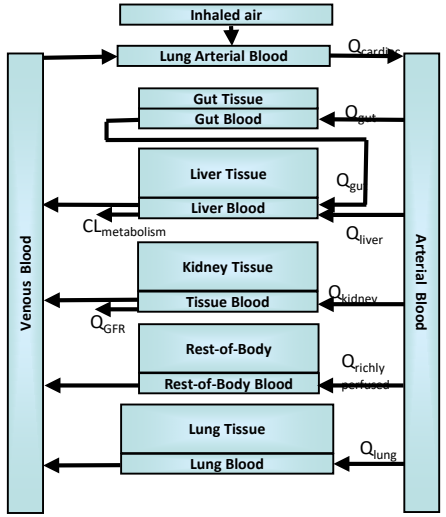
EPA, Unilever, INERIS

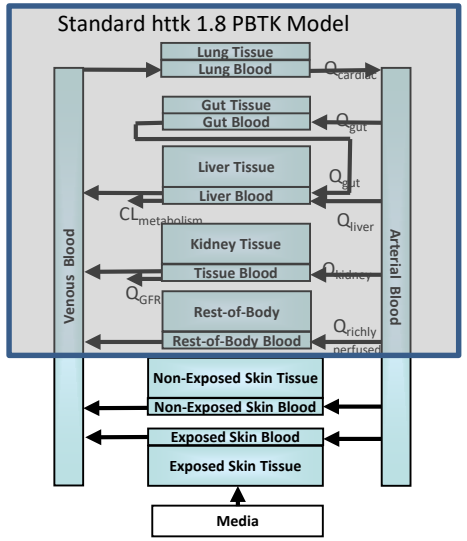
New HT-PBTK Models

Gas Inhalation Exposure Route

EPA, USAFSAM

Linakis et al., in. prep





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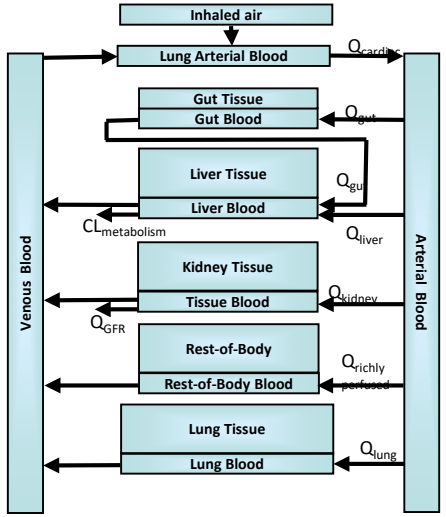
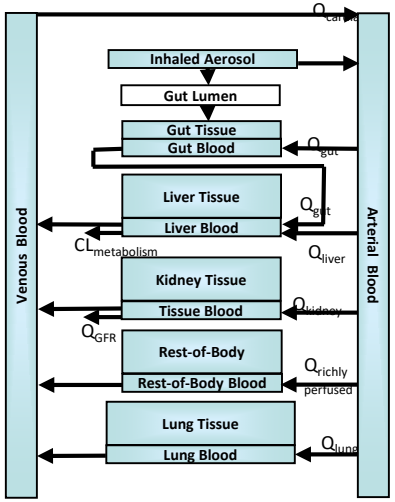
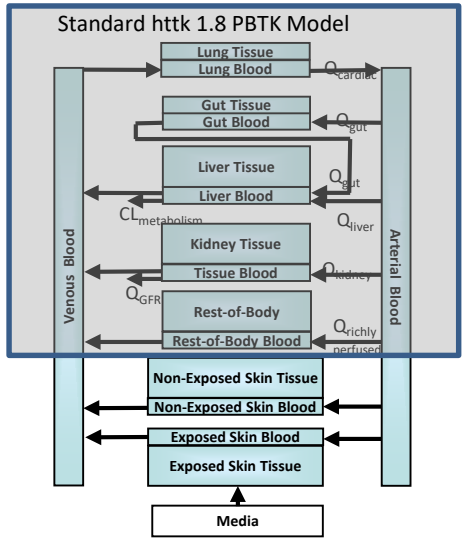


Aerosol Inhalation Exposure Route (with APEX model)

EPA, USAFSAM

Linakis et al., in. prep





Dermal Exposure Route

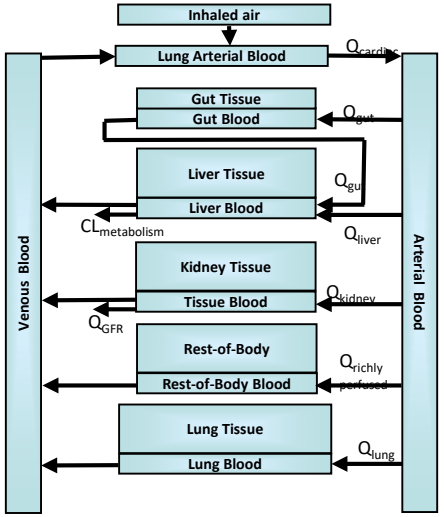
EPA, Unilever, INERIS

New HT-PBTK Models

Gas Inhalation Exposure Route

EPA, USAFSAM

Linakis et al., in. prep



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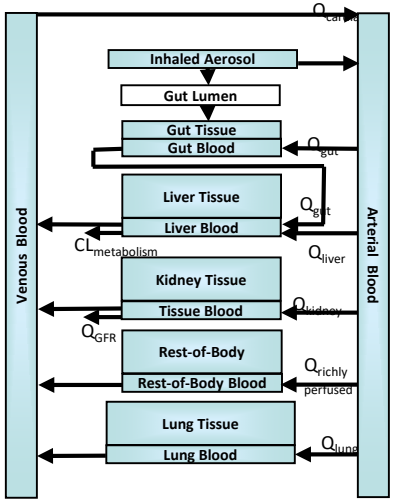
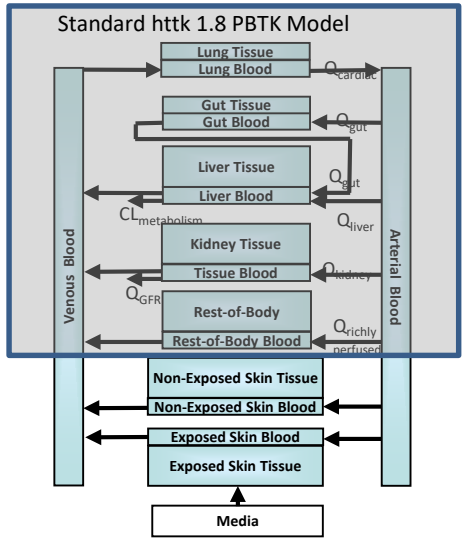
EPA, USAFSAM

Linakis et al., in. prep



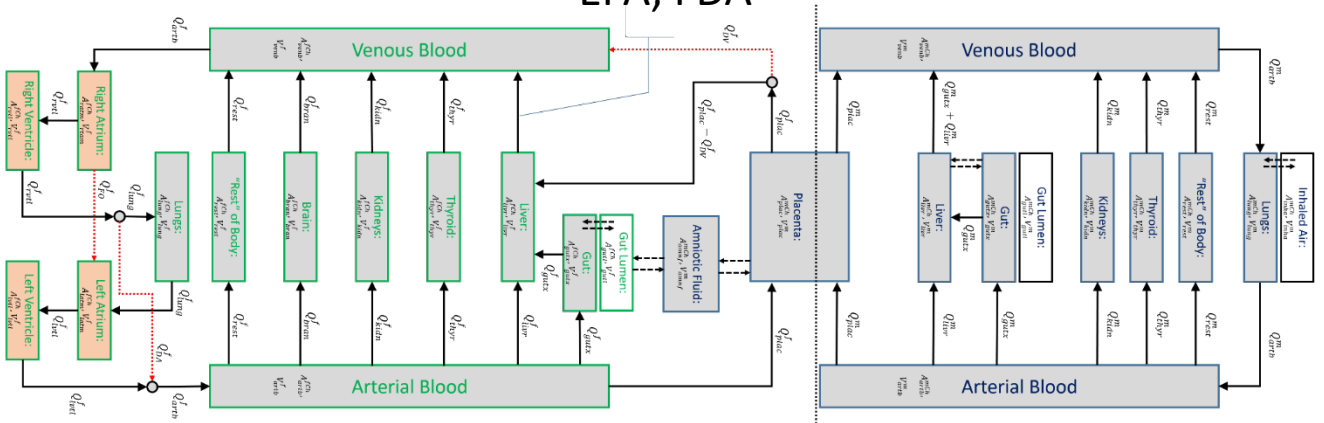


Dermal Exposure Route

EPA, Unilever, INERIS

Human Gestational Model

EPA, FDA



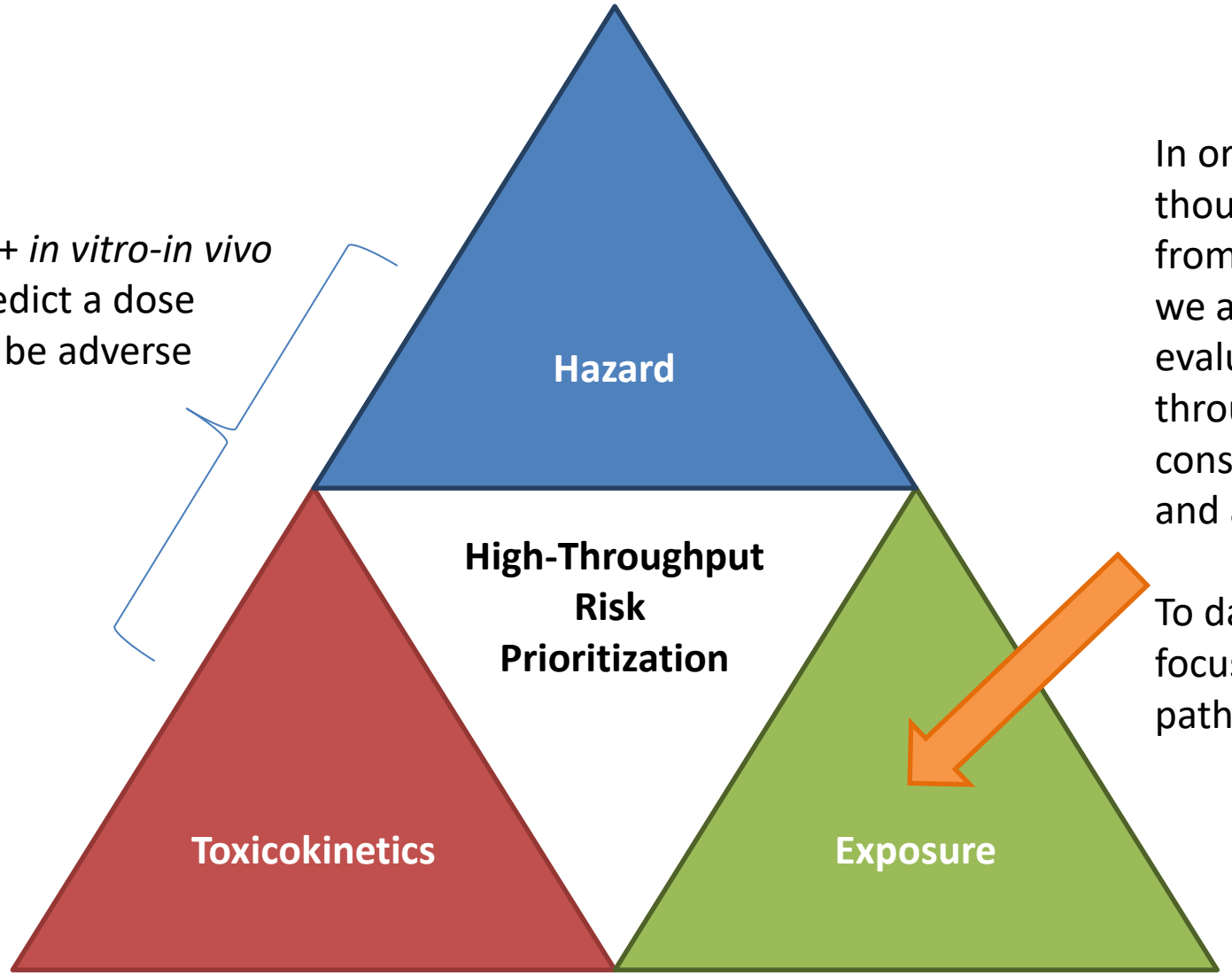
Fetus

Mother

Kapraun et al., in. prep

New Exposure Data and Models

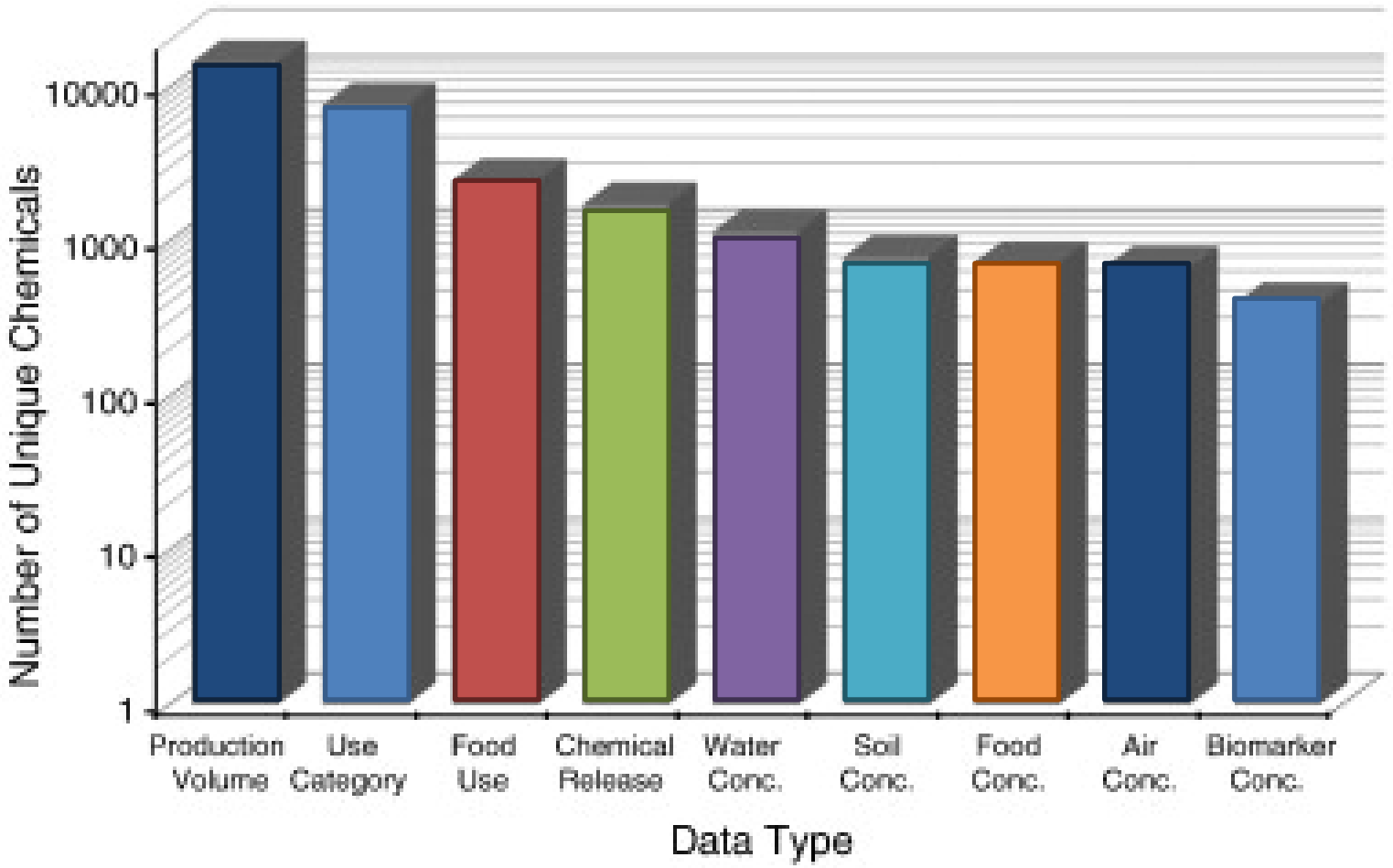
High throughput screening + *in vitro-in vivo* extrapolation (IVIVE can predict a dose (mg/kg bw/day) that might be adverse



In order to address thousands of chemicals from limited information, we are working to evaluate and develop high throughput models for consumer, occupational, and ambient pathways

To date, most efforts have focused on consumer pathways

Limited Available Data for Exposure Estimations



- Most chemicals lack exposure data (Egeghy et al., 2012)

Forecasting Exposure is a Systems Problem

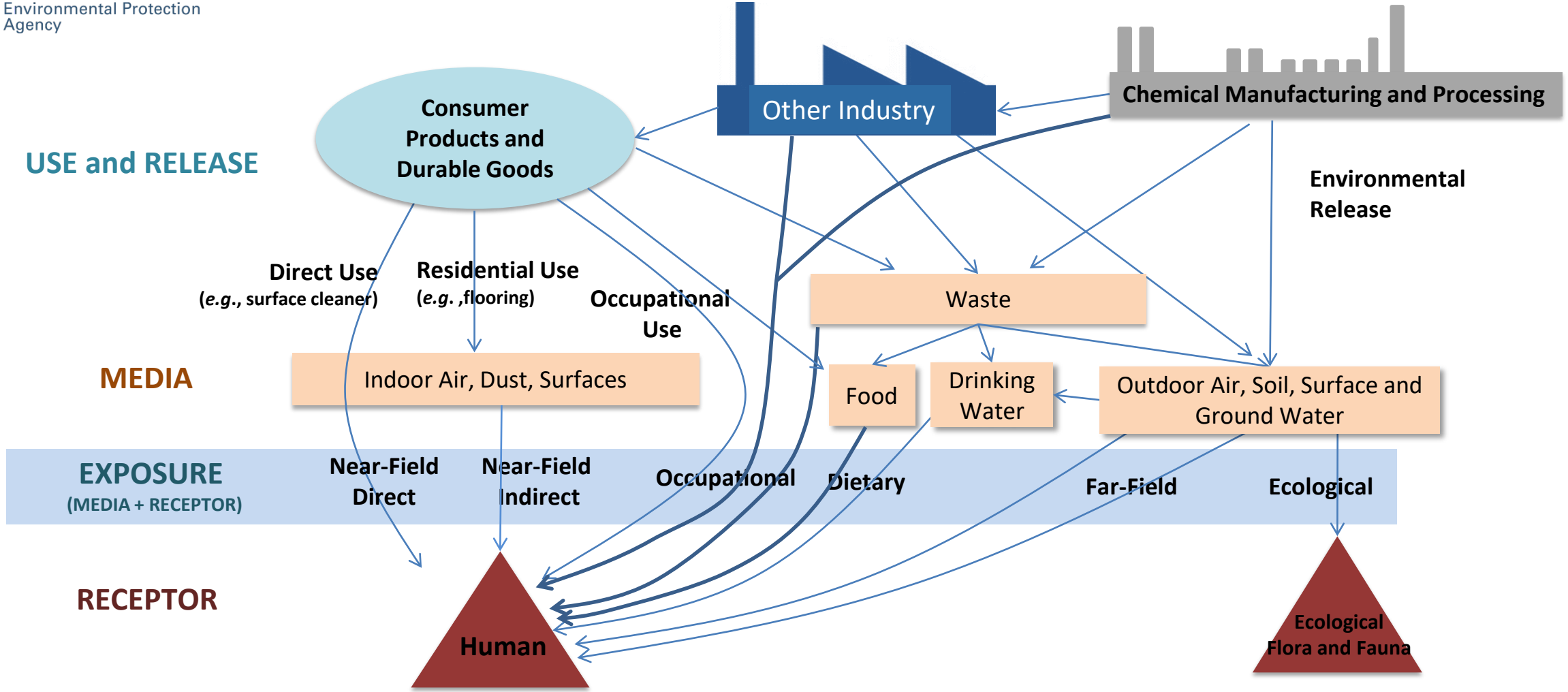


Figure from Kristin Isaacs

Forecasting Exposure is a Systems Problem

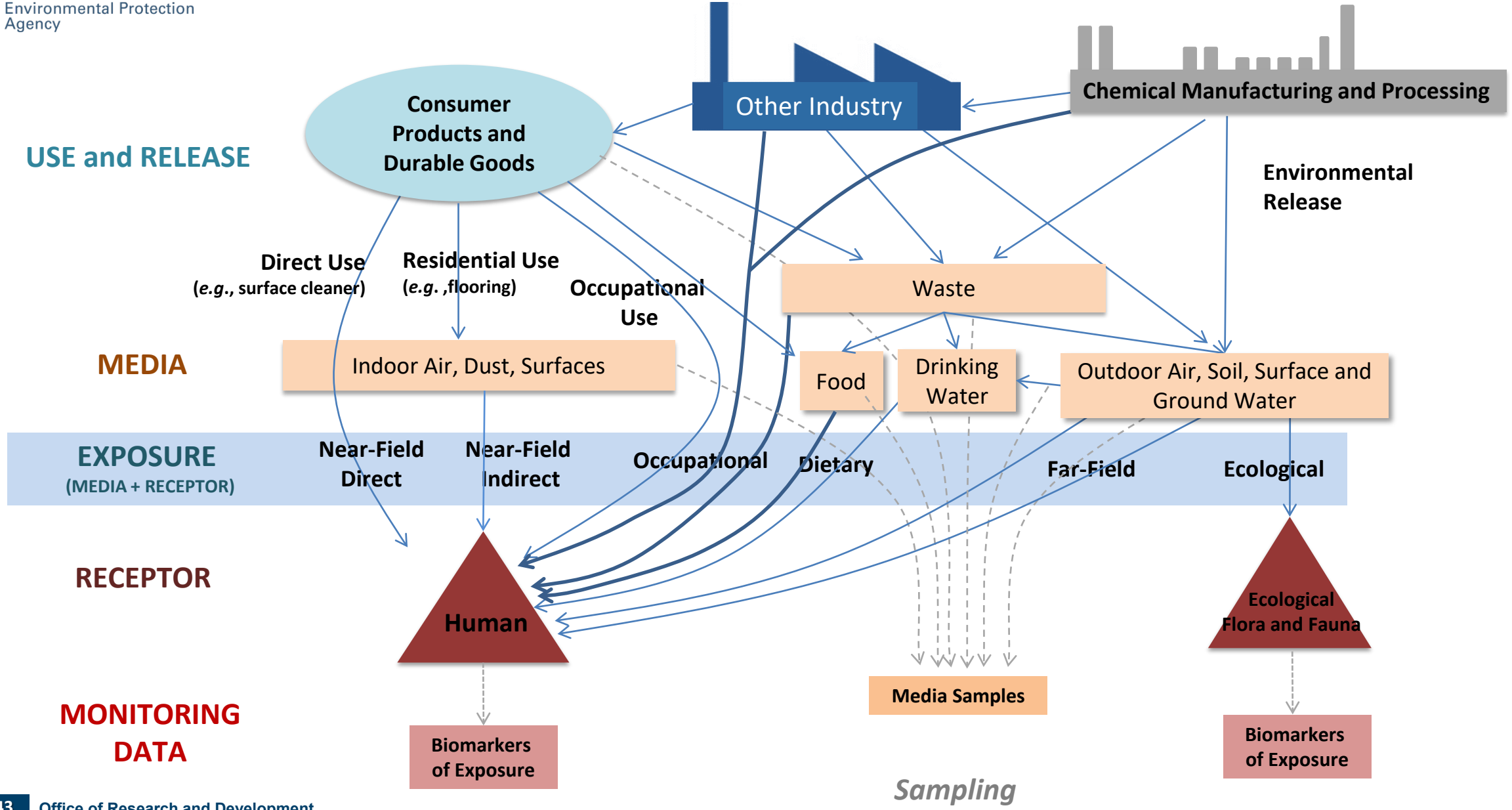


Figure from Kristin Isaacs

Consumer Pathways

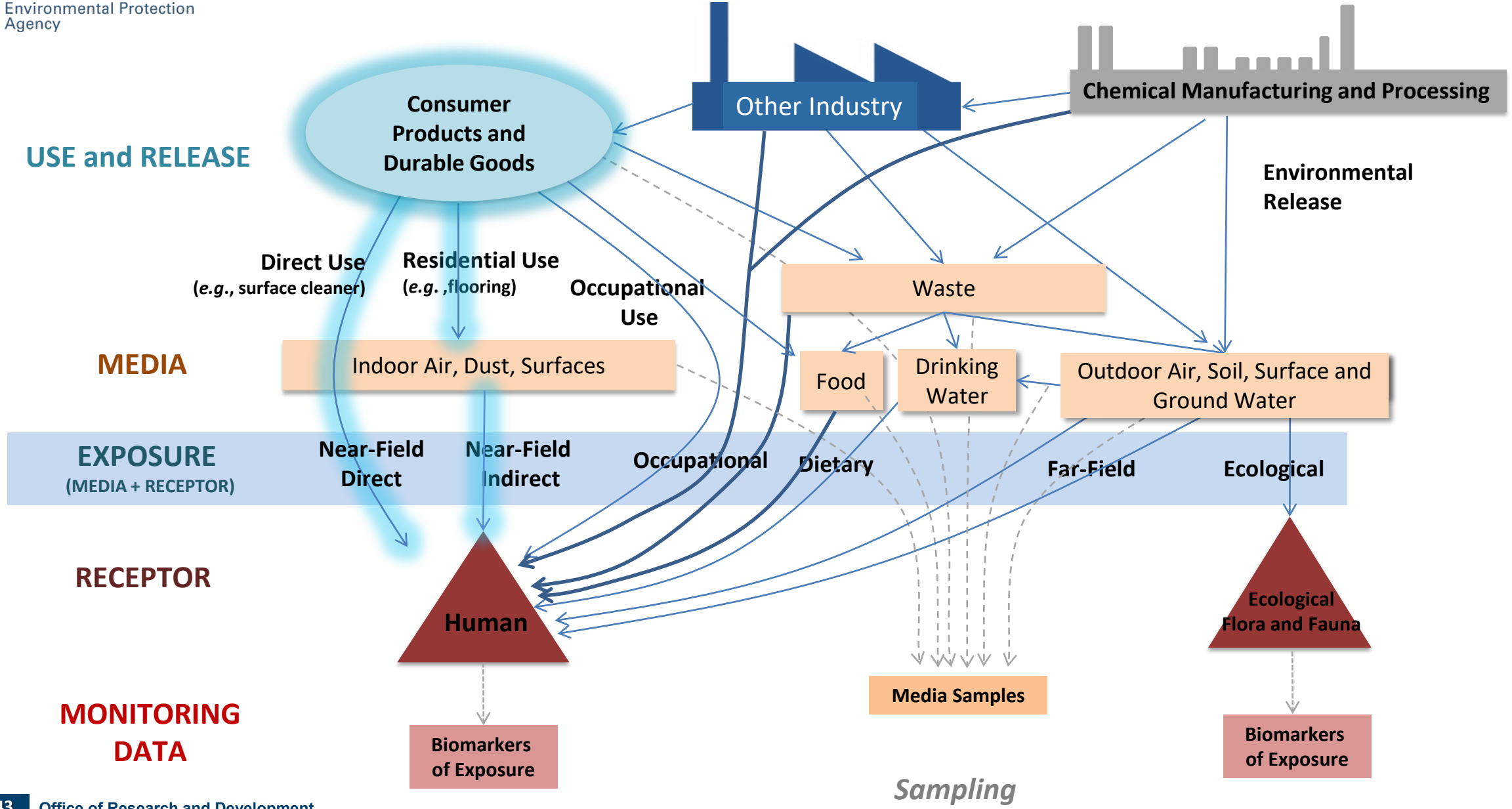
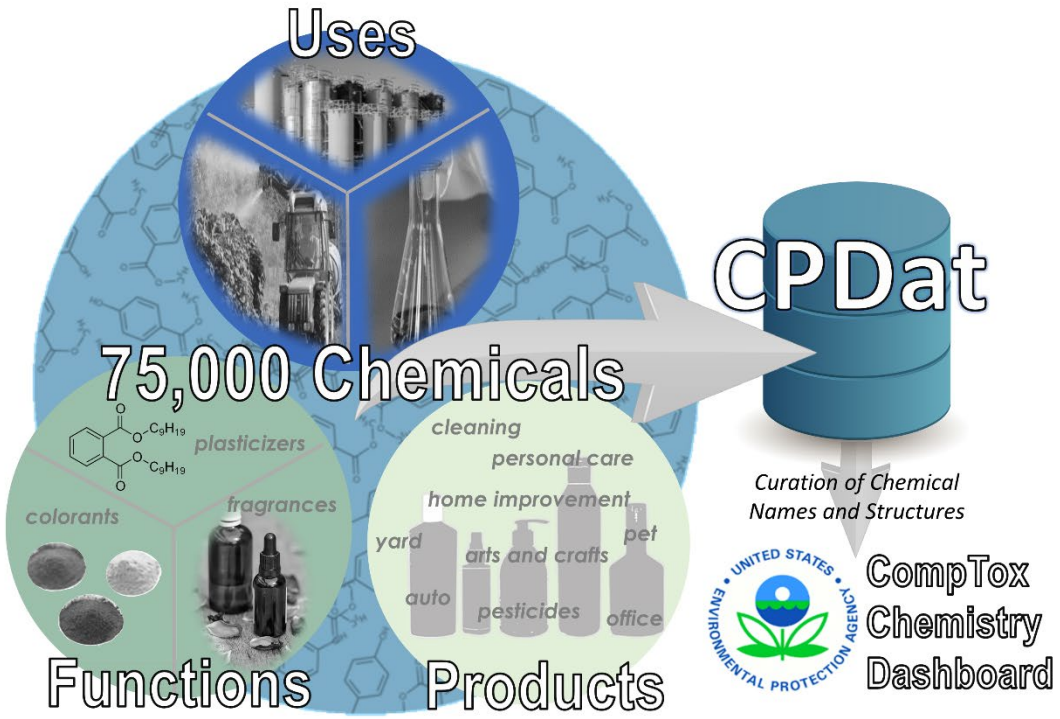


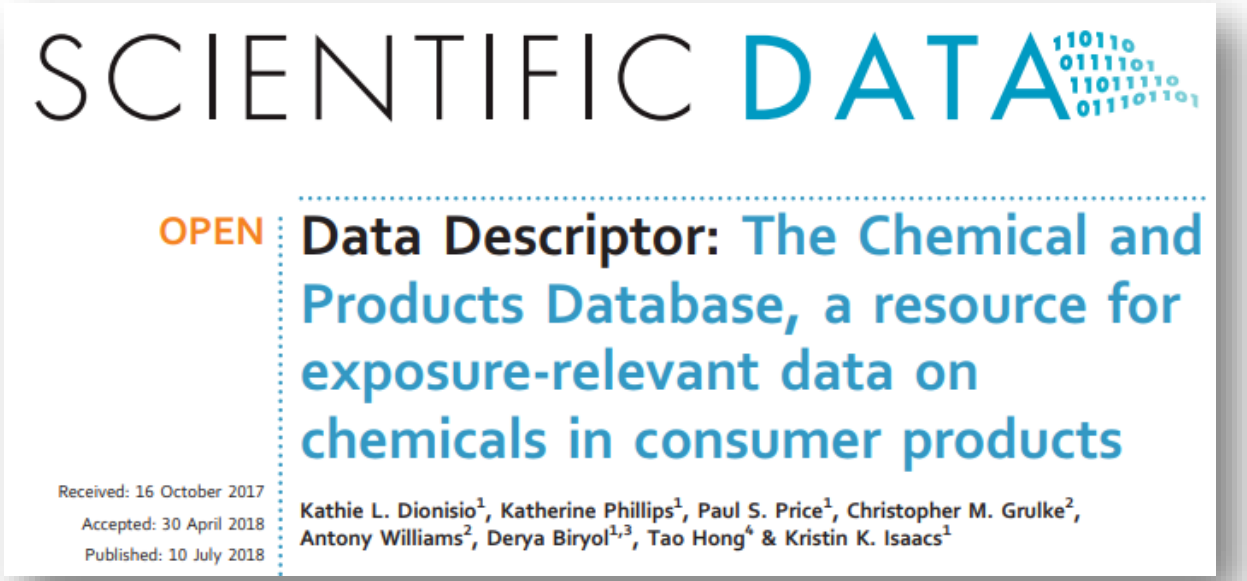
Figure from Kristin Isaacs

Chemical and Products Database (CPDat)

https://comptox.epa.gov/dashboard/

- New database of chemical and product information
- General uses, functional uses, product ingredients and compositions
- Data on 75,000 chemicals and 15,000 consumer products
- Data available via individual chemical search or via bulk download the CompTox Chemistry Dashboard




SCIENTIFIC DATA

OPEN

Data Descriptor: The Chemical and Products Database, a resource for exposure-relevant data on chemicals in consumer products

Received: 16 October 2017
Accepted: 30 April 2018
Published: 10 July 2018

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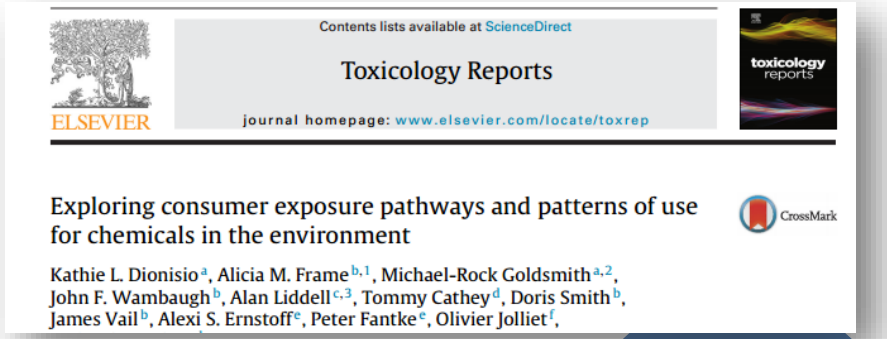
Package 'CPDat'

Chemical Use: Chemicals and Products Database (CPDat)

United States Environmental Protection Agency

Broad "index" of chemical uses

Occurrence and quantitative chemical composition


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],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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]

MSDS Data

CPCat (Chemical and Product Categories)

CPDat

Dionisio et al., (2018)

Functional Use Data and Predictions


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

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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]

Ingredient Lists

Occurrence data


Green Chemistry

PAPER

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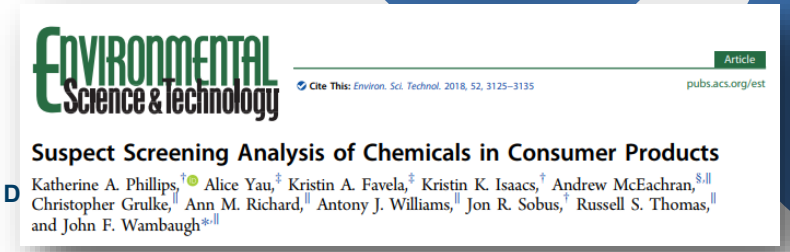
Cite this: *Green Chem.*, 2017, **19**, 1063

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]


Environmental Science & Technology

Article

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

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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*[,∥]

Household Product Analysis

Slide from Kristin Isaacs

High-Throughput Stochastic Human Exposure and Dose Simulation Model (SHEDS-HT)

- High-throughput model for simulating population exposures to chemical in consumer products via multiple product types, scenarios, and routes
- Provided publicly as an R package
- R package, code, and default input files for consumer products (derived from CPDat) available at:

https://github.com/HumanExposure/SHEDSHTRPackage

Package 'ShedsHT'

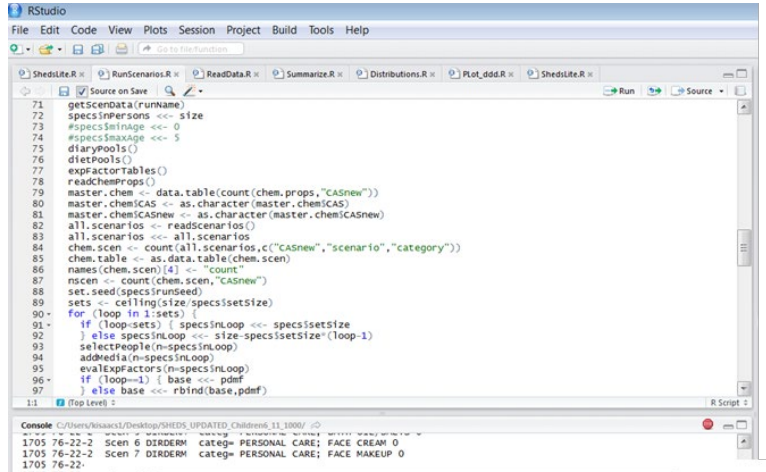
September 9, 2016

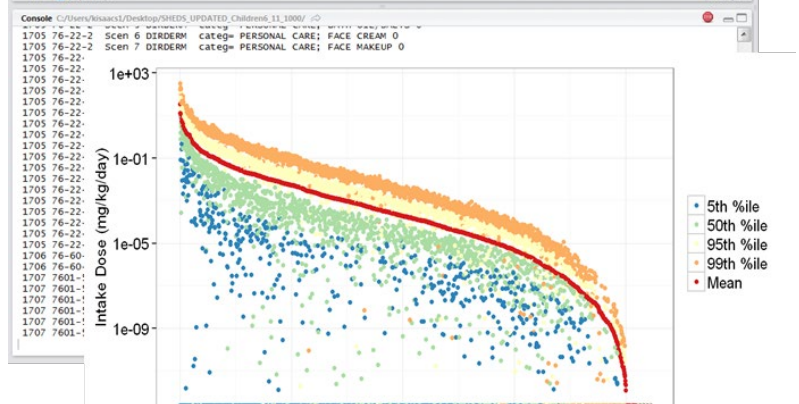
Title To run the SHEDS-HT screening model for estimating human exposure to chemicals.

Version 0.1.1

Author Kristin Isaacs [aut, cre]

Maintainer Kristin Isaacs <isaacs.kristin@epa.gov>





ENVIRONMENTAL Science & Technology

SHEDS-HT: An Integrated Probabilistic Exposure Model for Prioritizing Exposures to Chemicals with Near-Field and Dietary Sources

Kristin K. Isaacs,*[,†] W. Graham Glen,[‡] Peter Egeghy,[†] Michael-Rock Goldsmith,[§,○] Luther Smith,[‡] Daniel Vallero,[†] Raina Brooks,[∥] Christopher M. Grulke,[⊥,○] and Halûk Özkaynak[†]

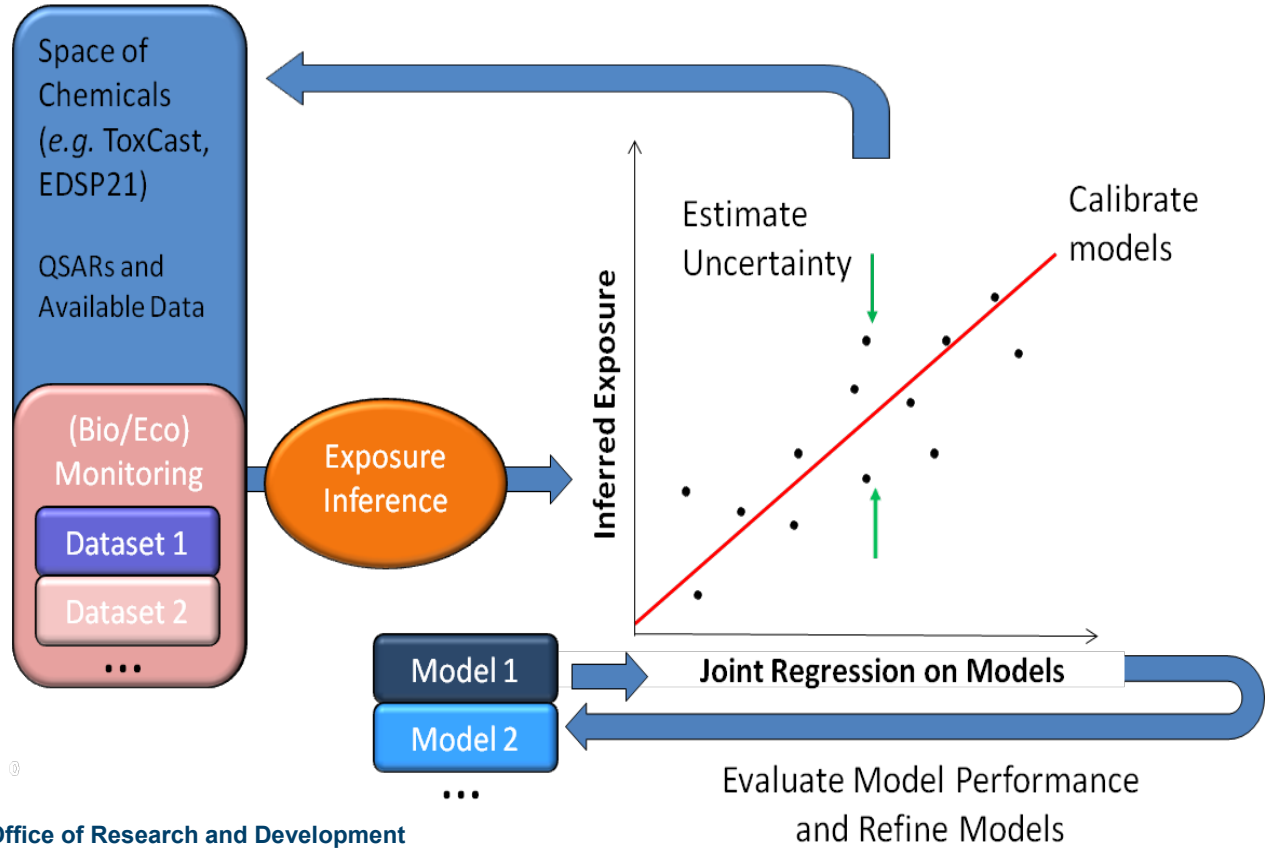
[†]U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory, 109 T.W. Alexander Drive, Research Triangle Park, North Carolina 27709, United States

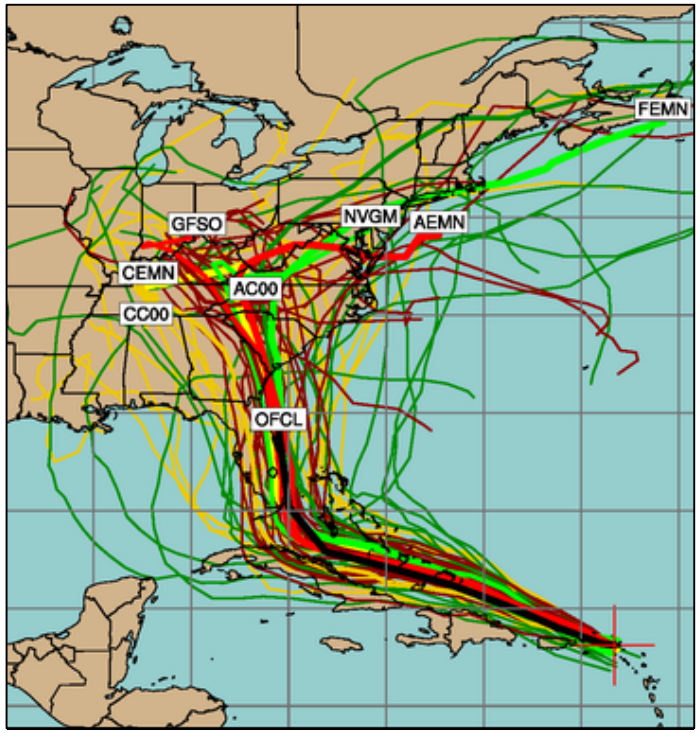
[‡]Alion Science and Technology, 1000 Park Forty Plaza Suite 200, Durham, North Carolina 27713, United States

[§]Chemical Computing Group, Suite 910, 1010 Sherbrooke Street West, Montreal, QC H3A 2R7, Canada

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)** (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

Ring et al., under revision

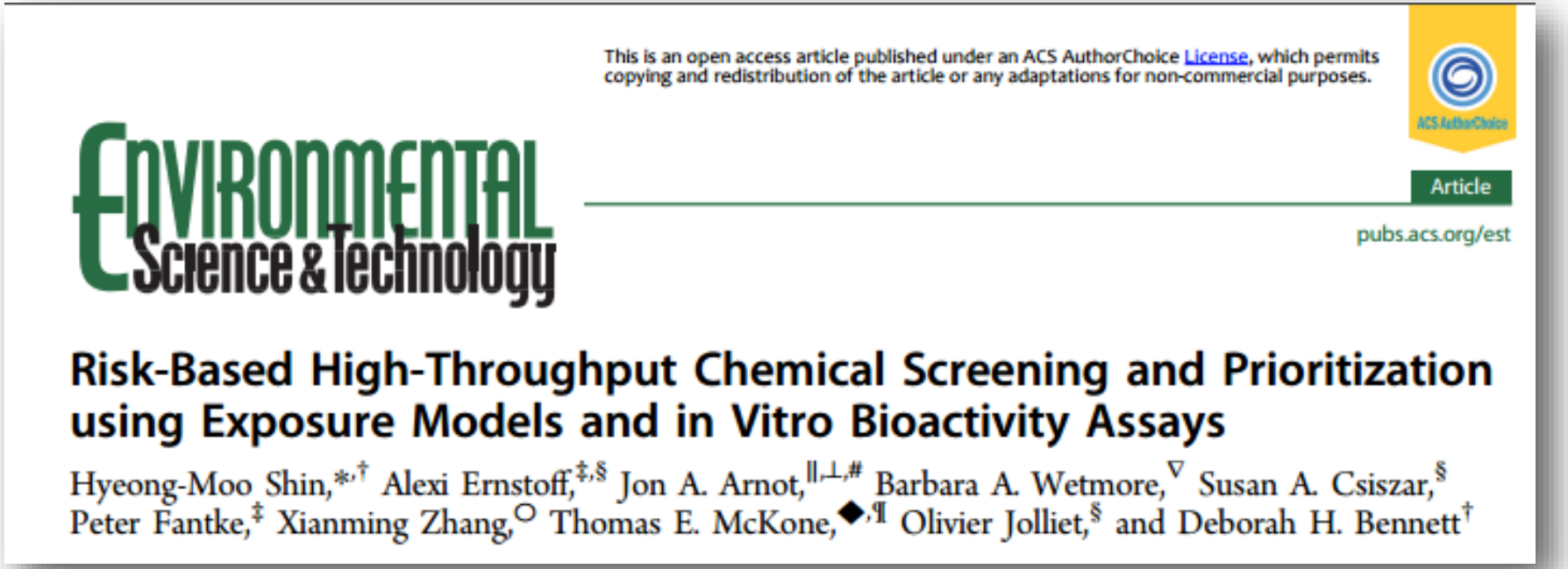
Collaboration on High Throughput Exposure Predictions

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

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

Hyeong-Moo Shin,*,† Alexi Ernstoff,‡,§ Jon A. Arnot,∥,⊥,# Barbara A. Wetmore,∇ Susan A. Csiszar,§ Peter Fantke,‡ Xianming Zhang,○ Thomas E. McKone,◆,¶ Olivier Jolliet,§ and Deborah H. Bennett†

Reducing Uncertainty by Predicting Pathways

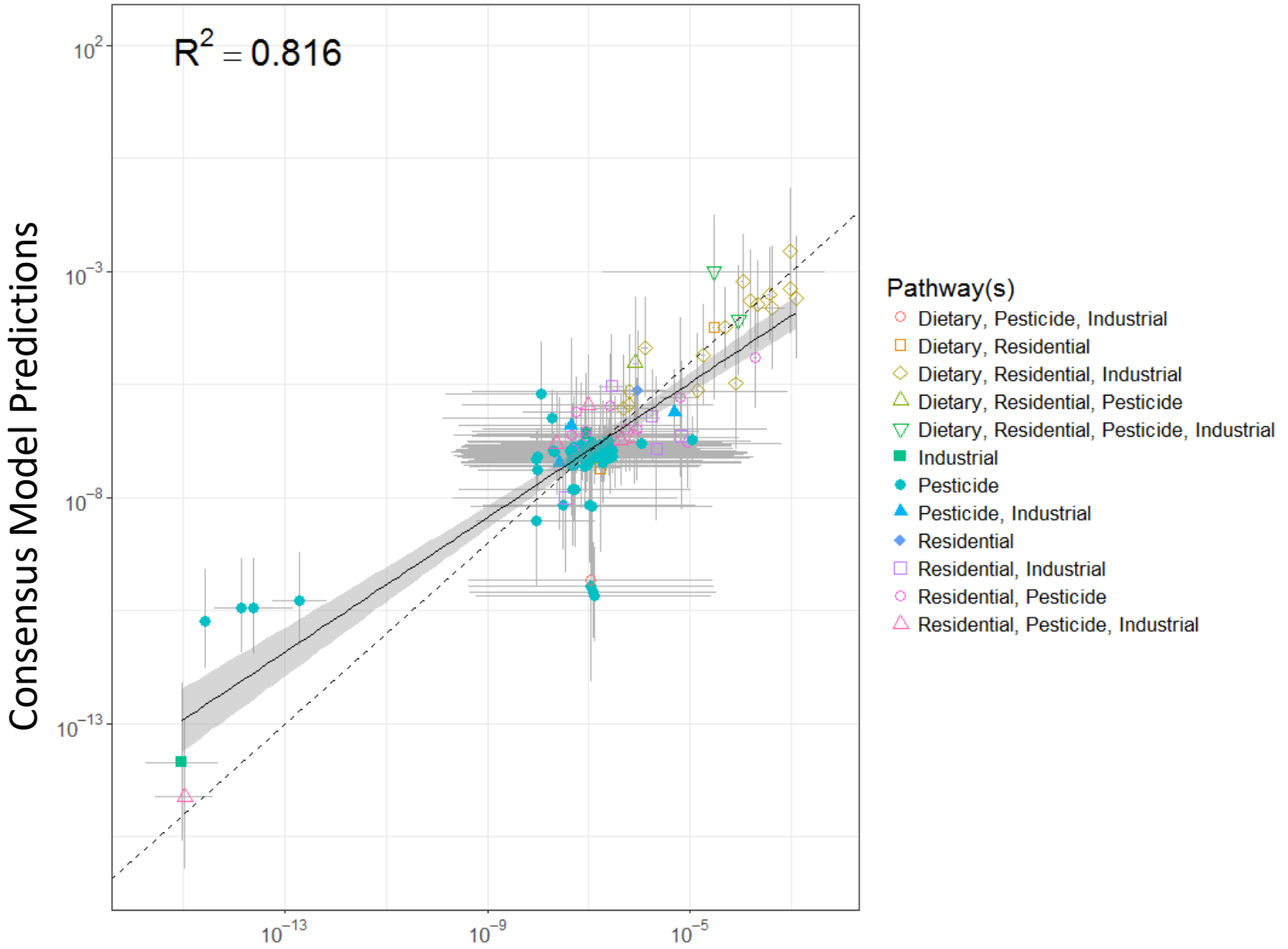
We use the method of Random Forests to relate chemical structure and properties to exposure pathway

	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	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., under revision

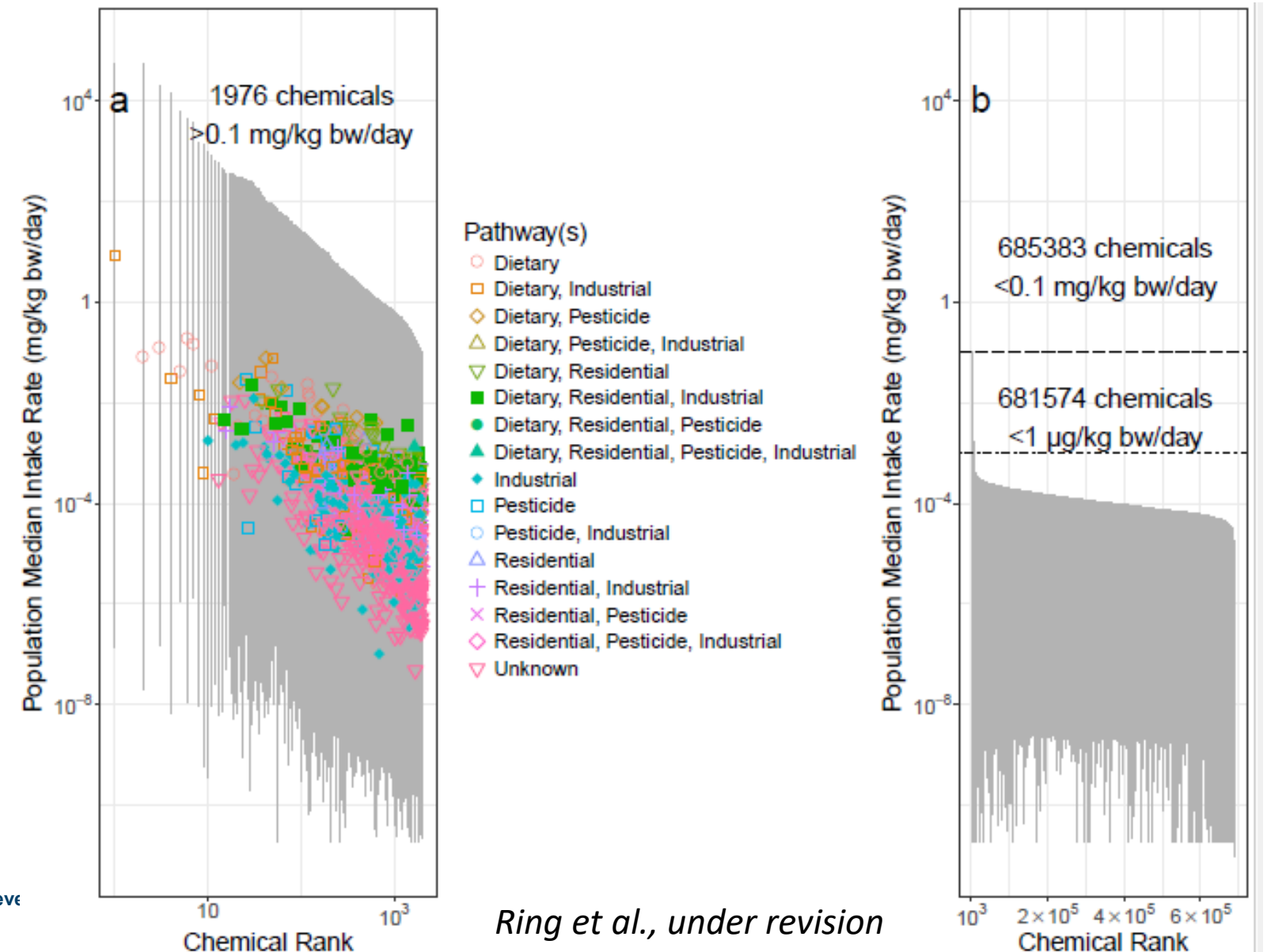
Pathway-Based Consensus Modeling

- 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., under revision

Consensus Modeling of Median Chemical Intake



Ring et al., under revision

Suspect Screening and Non-Targeted Analysis (SSA/NTA)

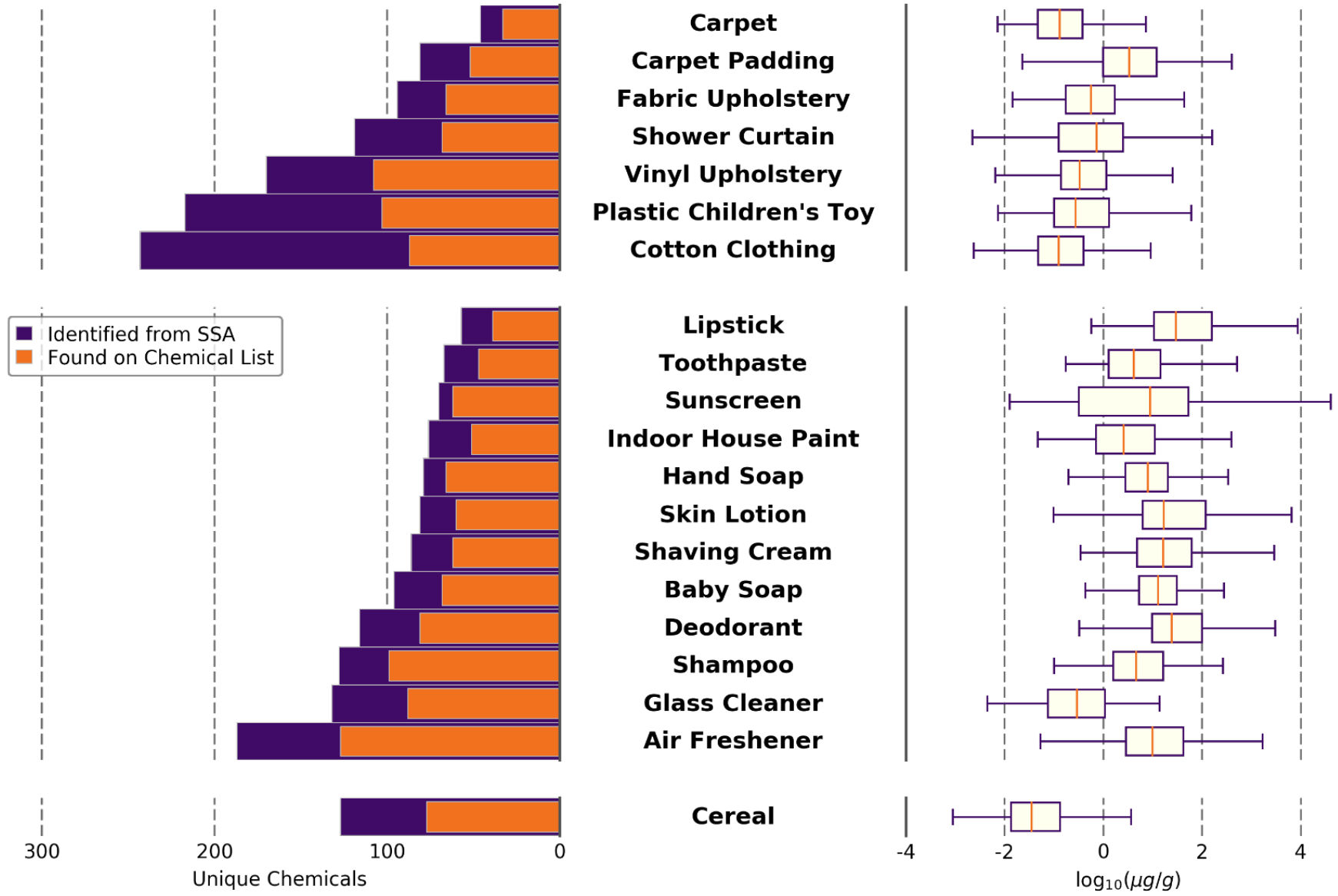
- We are working to reduce the uncertainties in high throughput exposure models. To do this we would like to to:
  - Increasing the chemical diversity of the biomonitoring data that the models are calibrated against
  - Better characterize what we are exposed to
- New SSA/NTA analytical chemistry methods allow simultaneous identification of many chemicals in a single sample (Sobus, et al., 2017)
- EPA has applied SSA/NTA methods to house dust (Rager et al., 2016), drinking water filters (Newton et al., 2017) and household products (Phillips et al., 2018)

Developing Pathway-Specific Chemical Data

In order to use models like SHEDs-HT we must approximately know the composition of household items

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



Phillips *et al.* (*2018*)

Suspect Screening and Non-Targeted Analysis (SSA/NTA)

- In order to characterize the reliability of SSA/NTA techniques, the EPA is leading a collaborative trial across more than two dozen academic and industry laboratories
- EPA's Non-Targeted Analysis Collaborative Trial is starting with synthetic mixtures formulated from the ToxCast library – will eventually look at wristbands, standard reference material (SRM) house dust, and SRM human plasma

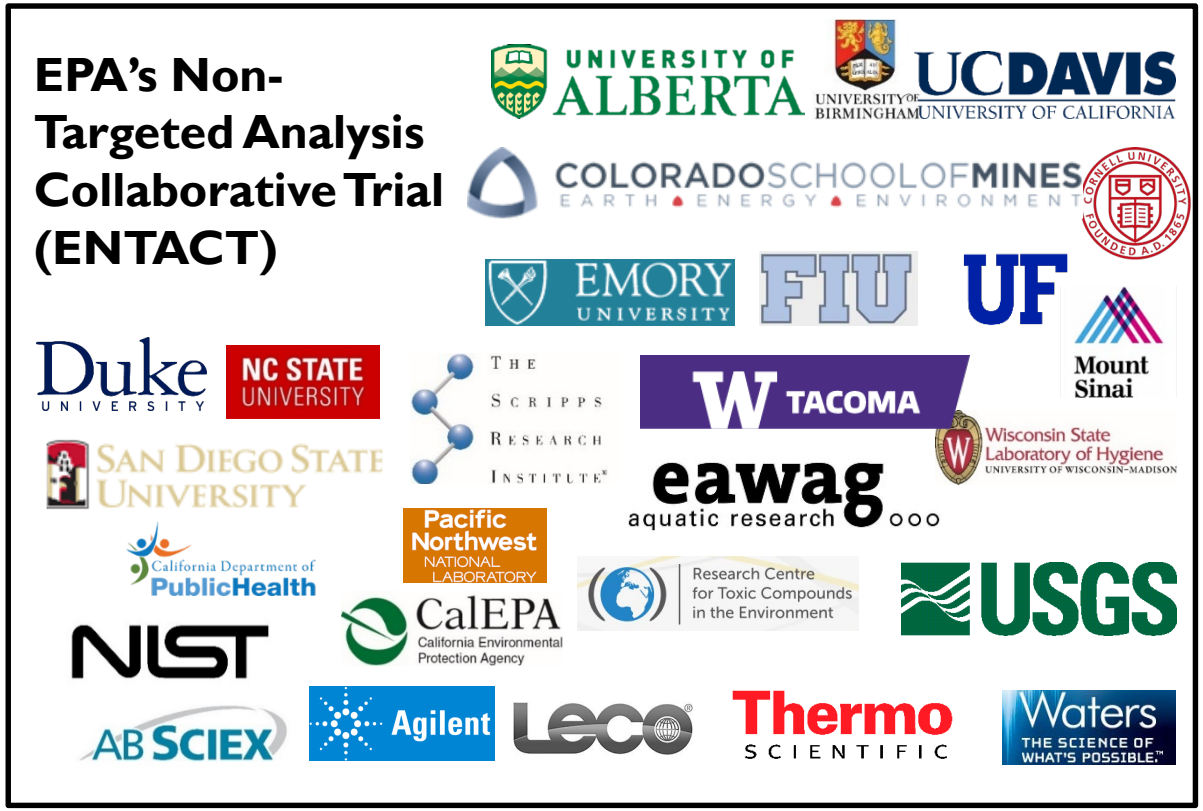
EPA collaborative trial workshop was held August 13-15 in Research Triangle Park, NC, USA

ToxCast Chemicals →

Reference House Dust →

Reference Human Serum →

Reference Silicone Wristbands →

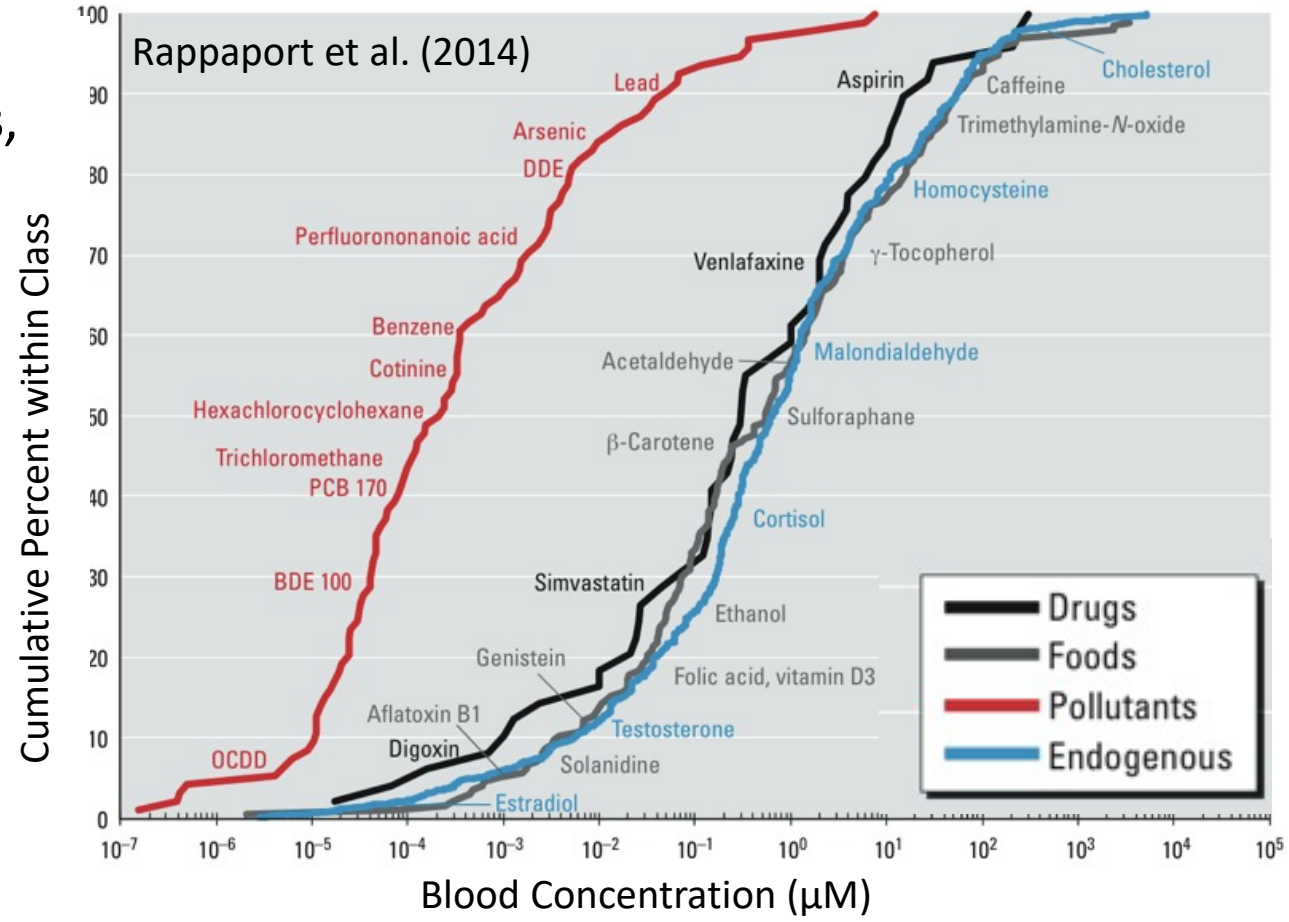


Suspect Screening of Human Tissues

We propose databases for five categories of substances found in human biomonitoring samples:

1) **endogenous metabolome**,
2a) **exogenous nutrients**,
2b) **markers of exposure to exogenous nutrients**,
3a) **xenobiotics**, and
3b) **markers of exposure to xenobiotics**

Substances are defined by their biological function, and are expected to be structurally heterogeneous. Some compounds can appear in more than one category. For example, cholesterol: it is present in cellular membranes (1), from consumption of animal fat (2a), or as an effect of glucocorticoid medication (3b).



Sayre, Wambaugh, Williams, Sobus, and Grulke

Ambient Pathways (Human and Ecological)

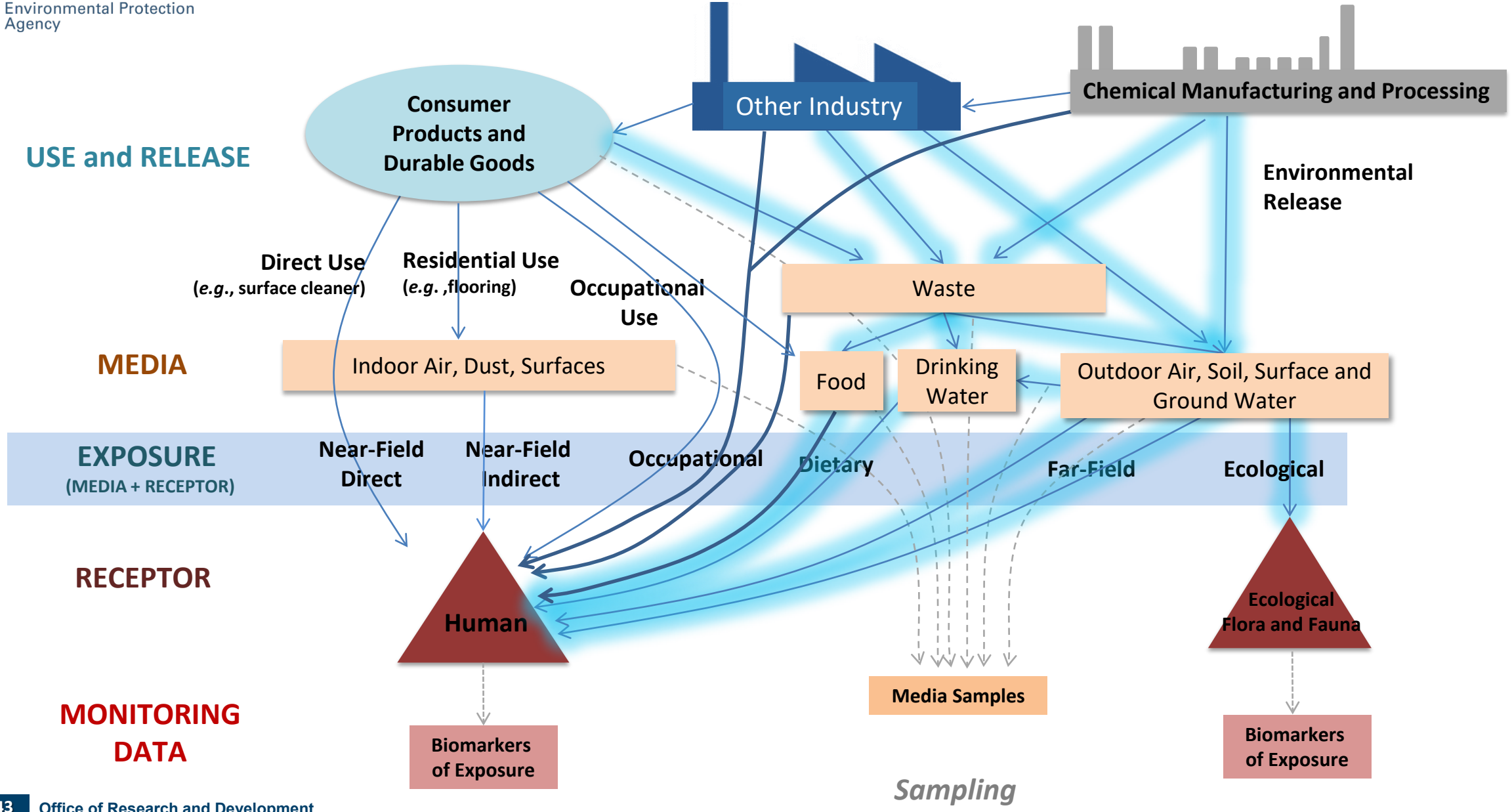
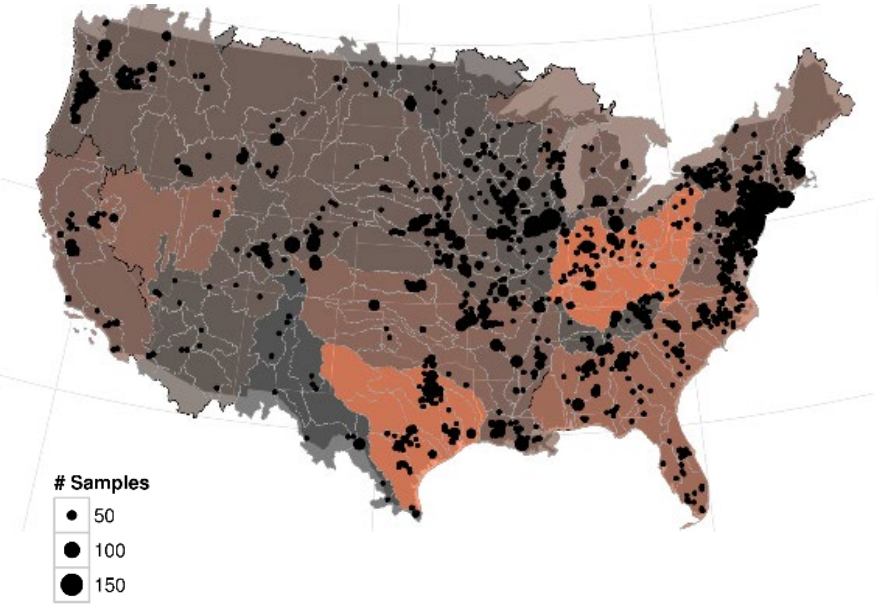


Figure from Kristin Isaacs

Ecological SEEM



Chemicals n = 91

Dataset
Setzer et al., (in prep)

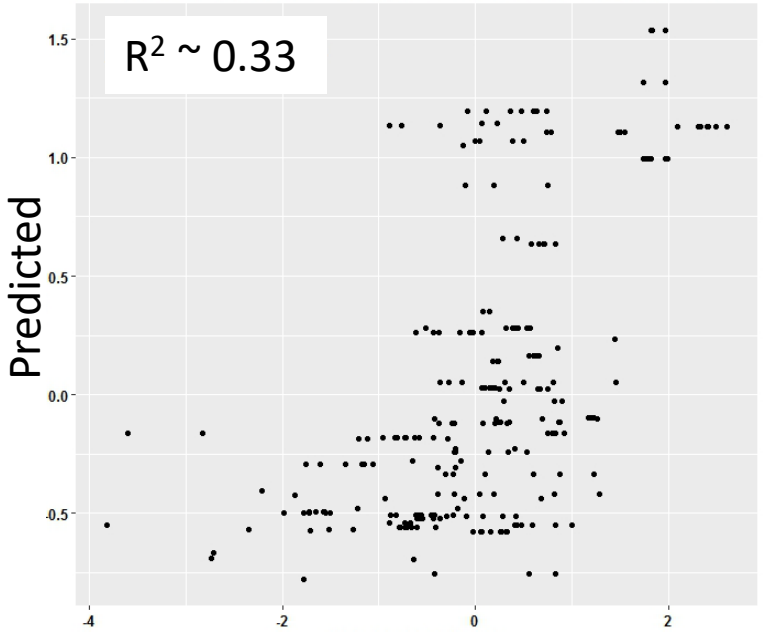
Watersheds

- **Pesticides**
- **PAHs**
- **Solvents,…**
- **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



Setzer et al., (in prep.)
Sayre et al., (in prep).

Occupational Pathways

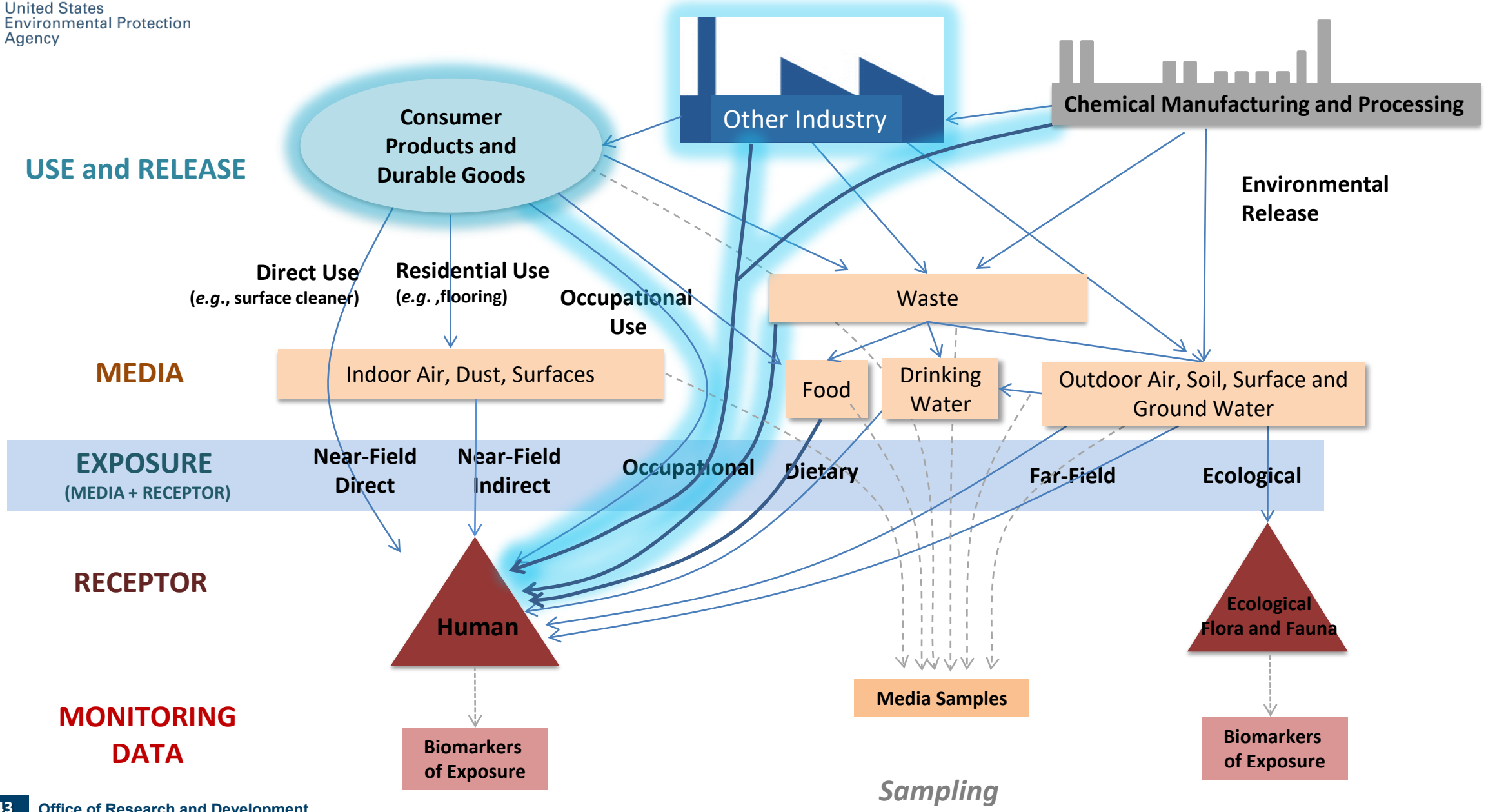


Figure from Kristin Isaacs

Summary

- High throughput screening (HTS) provides bioactivity data for thousands of chemicals as a surrogate for hazard, but you also need exposure and toxicokinetics to assess risk

- Toxicokinetics for IVIVE provides real world context to hazards indicated by HTS
  - Using *in vitro* methods developed for pharmaceuticals, we can predict TK for large numbers of chemicals, but we are currently limited by analytical chemistry

- High throughput exposure approaches can make coarse predictions of exposure
  - We are actively refining these predictions with new models and data
  - In some cases, upper confidence limit on current predictions is already many times lower than predicted hazard

- We are working to systematically identify and address those areas contributing the greatest uncertainty

- All data being made public:
  - R packages “httk”, “CPDat”. “SHEDS-HT”
  - The Comptox Chemicals Dashboard: **http://comptox.epa.gov/**

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

United States Environmental Protection Agency

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