April 13, 2021

United States Environmental Protection Agency

NAMS 101
New Approach Methodologies for Exposure

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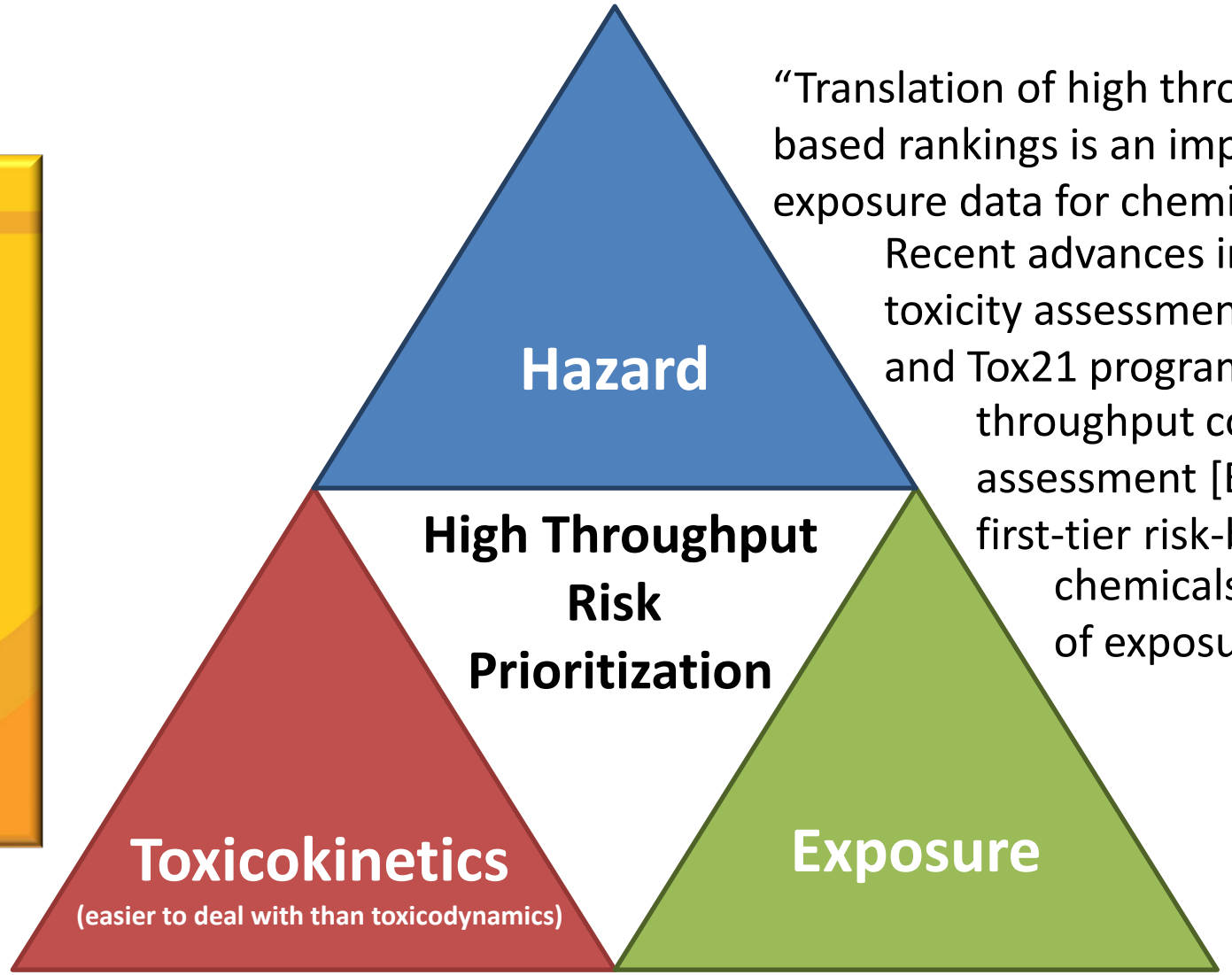
The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA

Calculating Chemical Risk

NASEM (2017)



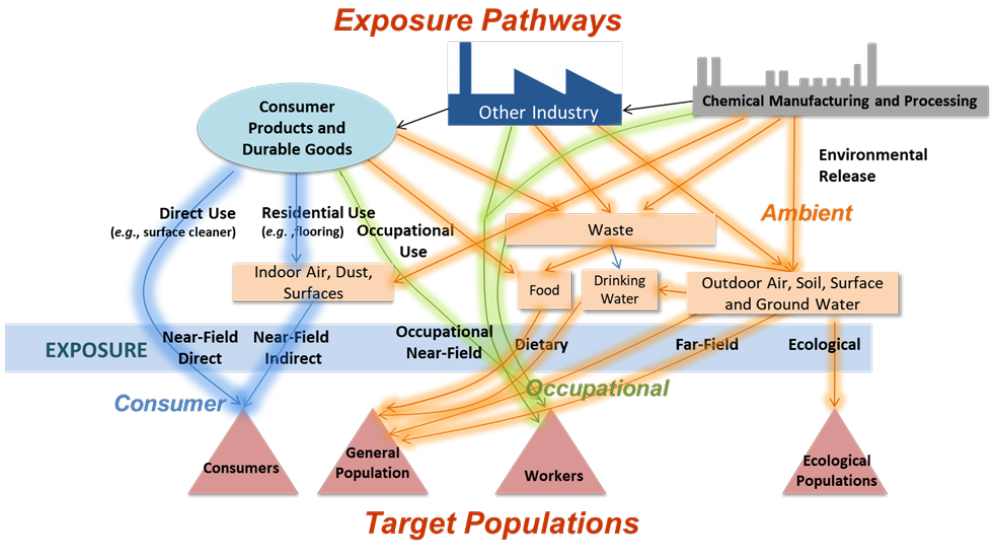
"Translation of high throughput data into risk-based rankings is an important application of exposure data for chemical priority-setting.

Recent advances in high throughput toxicity assessment, notably the ToxCast and Tox21 programs… and in high throughput computational exposure assessment [ExpoCast] have enabled first-tier risk-based rankings of chemicals on the basis of margins of exposure" - National Academies of Sciences, Engineering, and Medicine (NASEM)

In order to perform risk-based ranking we need data on hazard, toxicokinetics, and exposure…

NAMs for Exposure Science

- The tools to characterize both toxicity and exposure have evolved significantly in the past decade
- NAMs for exposure science are being developed to enable risk assessors to more rapidly address public health challenges and chemical regulation



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Current Opinion in Toxicology

New approach methodologies for exposure science

John F. Wambaugh[1], Jane C. Bare[2], Courtney C. Carignan[3], Kathie L. Dionisio[4], Robin E. Dodson[5], Olivier Jolliet[6], Xiaoyu Liu[7], David E. Meyer[2], Seth R. Newton[4], Katherine A. Phillips[4], Paul S. Price[4], Caroline L. Ring[8], Hyeong-Moo Shin[9], Jon R. Sobus[4], Tamara Tal[10], Elin M. Ulrich[4], Daniel A. Vallero[4], Barbara A. Wetmore[4] and Kristin K. Isaacs[4]

Abstract

Chemical risk assessment relies on knowledge of hazard, the dose–response relationship, and exposure to characterize potential risks to public health and the environment. A chemical with minimal toxicity might pose a risk if exposures are extensive, repeated, and/or occurring during critical windows across the human life span. Exposure assessment involves understanding human activity, and this activity is confounded by interindividual variability that is both biological and behavioral. Exposures further vary between the general population and susceptible or occupationally exposed populations. Recent computational exposure efforts have tackled these problems through the creation of new tools and predictive models. These tools include machine learning to draw inferences from existing data and computer-enhanced screening analyses to generate new data. Mathematical models provide frameworks describing

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[10] National Health and Environmental Effects Research Laboratory, Office of Research and Development, United States Environmental Protection Agency, Research Triangle Park, NC 27711, USA

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Current Opinion in Toxicology 2019, 15:76–92

This review comes from a themed issue on **Risk Assessment in Toxicology**

Edited by **Anne Marie Vinggaard** and **Richard Judson**

Available online 31 July 2019

For a complete overview see the Issue and the Editorial

https://doi.org/10.1016/j.cotox.2019.07.001

NAMs for Exposure Science

Exposure NAM Class	Description	Traditional Approach	NAM Makes Use of					
			Measurement	Toxicokinetics	Models	Descriptors	Evaluation	Machine Learning
Measurements	New techniques including screening analyses capable of detecting hundreds of chemicals present in a sample	Targeted (chemical-specific) analyses	-	●	●	●		●
Toxicokinetics	High throughput methods using *in vitro* data to generate chemical-specific models	Analyses based on *in vivo* animal studies	●	-		●		●
HTE Models	Models capable of making predictions for thousands of chemicals	Models requiring detailed, chemical- and scenario-specific information	●	●	-	●		
Chemical Descriptors	Informatic approaches for organizing chemical information in a machine-readable format	Tools targeted at single chemical analyses by humans				-		●
Evaluation	Statistical approaches that use the data from many chemicals to estimate the uncertainty in a prediction for a new chemical	Comparison of model predictions to data on a per chemical basis	●	●	●	●	-	●
Machine Learning	Computer algorithms to identify patterns	Manual Inspection of the Data	●	●		●		-
Prioritization	Integration of exposure and other NAMs to identify chemicals for follow-up study	Expert decision making	●	●	●	●	●	●

Wambaugh et al., (2019)

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Wambaugh et al., (2019)

Chemical Property NAMs

United States Environmental Protection Agency


Contents lists available at ScienceDirect

Food and Chemical Toxicology

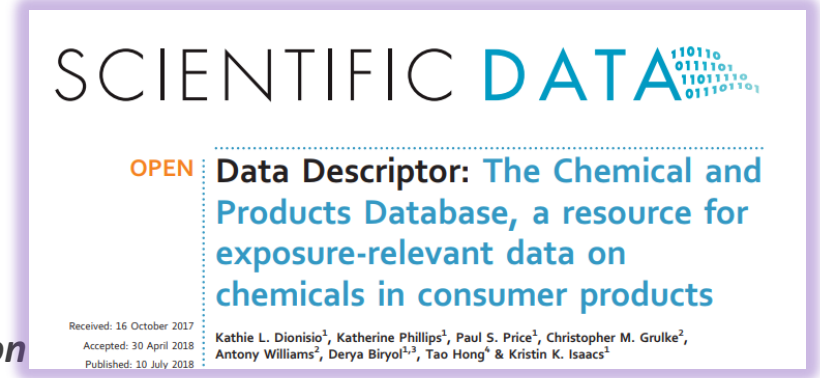
journal homepage: www.elsevier.com/locate/foodchemtox

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]

MSDS Data

Occurrence and quantitative chemical composition


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

Kathie L. Dionisio[1], Katherine Phillips[1], Paul S. Price[1], Christopher M. Grulke[2], Antony Williams[2], Derya Biryol[1,3], Tao Hong[4] & Kristin K. Isaacs[1]

Broad "index" of chemical uses


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

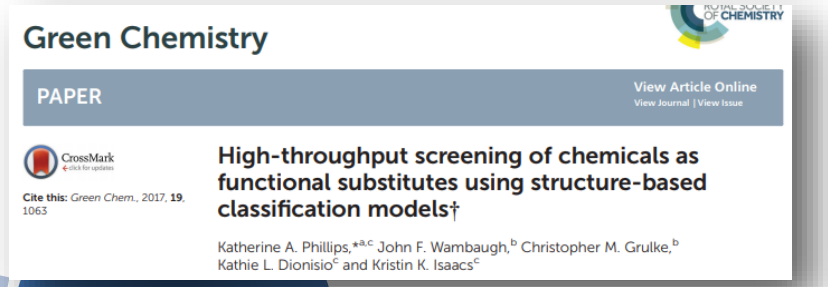
Kathie L. Dionisio[a], Alicia M. Frame[b,1], Michael-Rock Goldsmith[a,2], John F. Wambaugh[b], Alan Liddell[c,3], Tommy Cathey[d], Doris Smith[b], James Vail[b], Alexi S. Ernstoff[e], Peter Fantke[e], Olivier Jolliet[f],

CPCat

CPDat

EPA United States Environmental Protection Agency

Chemistry Dashboard


Green Chemistry

PAPER

View Article Online

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

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

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

Functional Use Data

The roles that chemicals serve in products

Ingredient Lists


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

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www.nature.com/jes

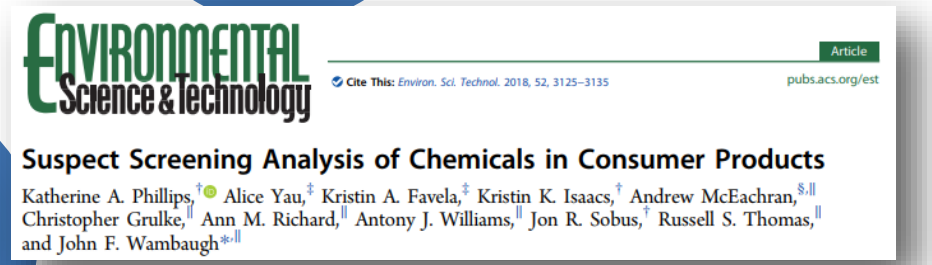
ORIGINAL ARTICLE

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]

Occurrence data

Measured Data


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*[,∥]

Measurement of chemicals in consumer products

https://comptox.epa.gov/dashboard

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Wambaugh et al., (2019)

Machine Learning NAMS

United States Environmental Protection Agency

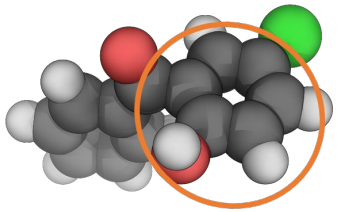
Chemical Functional Use Database (FUSE)

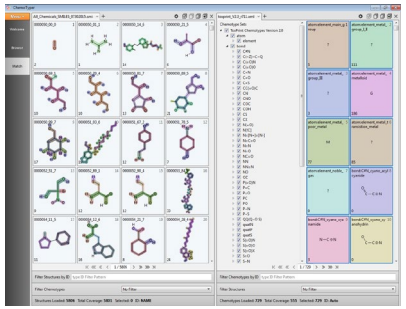
Positive Examples

Negative Examples

Random Forest Classification Models (Breiman, 2001) with five-fold cross validation

Chemical Structure and Property Descriptors





Successful Model

Failed Model

Probabilistic Predictions of Potential Chemical Uses

Phillips *et al.* (2017)

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Wambaugh et al., (2019)

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Wambaugh et al., (2019)

Published and Ongoing NTA Studies in the ExpoCast Project

United States Environmental Protection Agency

Source and Release

Pilot: 20 Consumer Product Categories

Phillips *et al.*, *Env. Sci. Tech*. 2018

Recycled Consumer Materials

Lowe *et al.*, *Submitted*

Consumer Product Emissions from Different Substrates

Fate and Transport

Residential Air

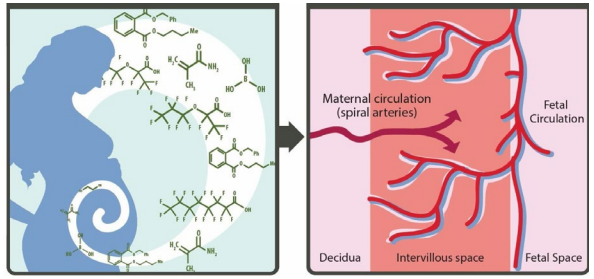
Residential Dust

Rager *et al.*, *Env. Int.*, 2016

Exposure

Pooled Human Blood

Human Placenta



Rager *et al.*, *Repro. Tox.* , 2020

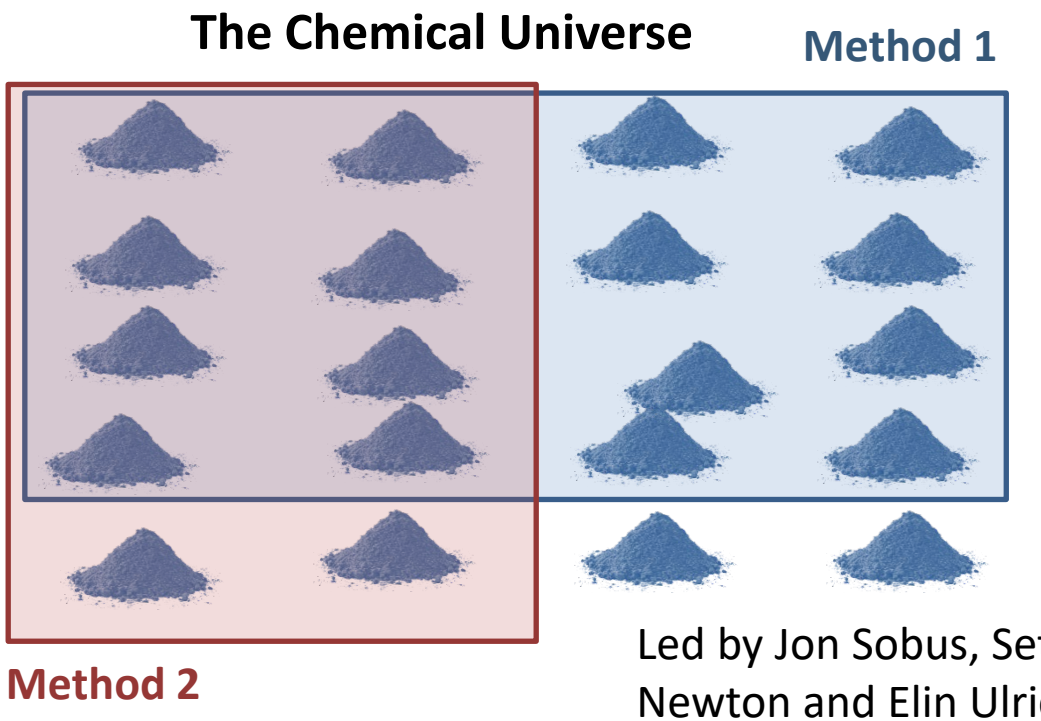
Emerging Science: How can we **quantify** concentrations of chemicals in media using NTA?

Slide from Kristin Isaacs

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

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

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



Led by Jon Sobus, Seth Newton and Elin Ulrich

- Phase 1:
  - Collaborators provided 10 mixtures of 100-400 ToxCast chemicals each
  - Mass spectrometry equipment vendors provided with individual chemical standards

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

Sobus et al. (2017)

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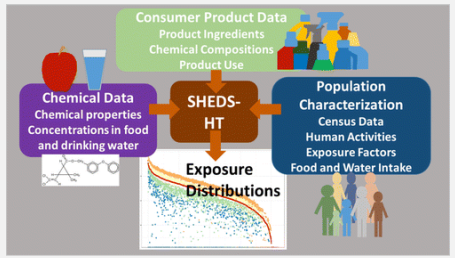
Wambaugh et al., (2019)

High Throughput Models for Key Pathways

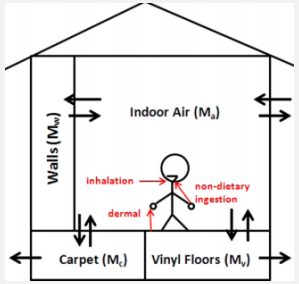
Consumer (Near-Field) Pathways

SHEDS-HT *(Isaacs et al., 2014)*



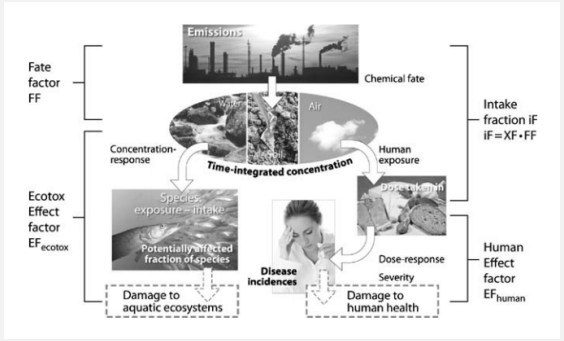
RAIDAR-ICE *(Li et al., 2018)*

FINE *(Shin et al., 2015)*

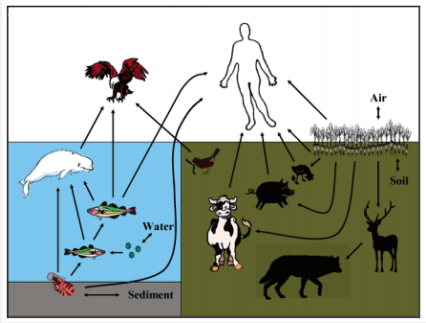


Ambient (Far-Field) Pathways

UseTox *(Rosenbaum et al., 2008)*

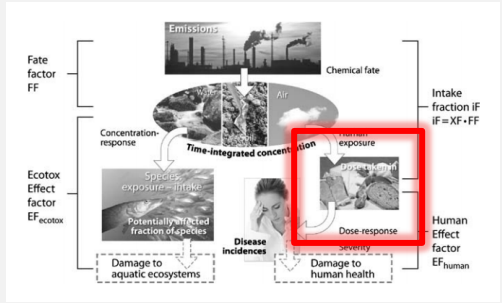


RAIDAR *(Arnot et al., 2006, 2008)*

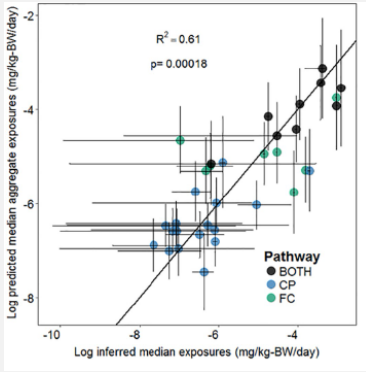


Dietary Pathways

UseTox *(Rosenbaum et al. (2008)*



SHEDS-HT *(Biryol et al., 2017)*



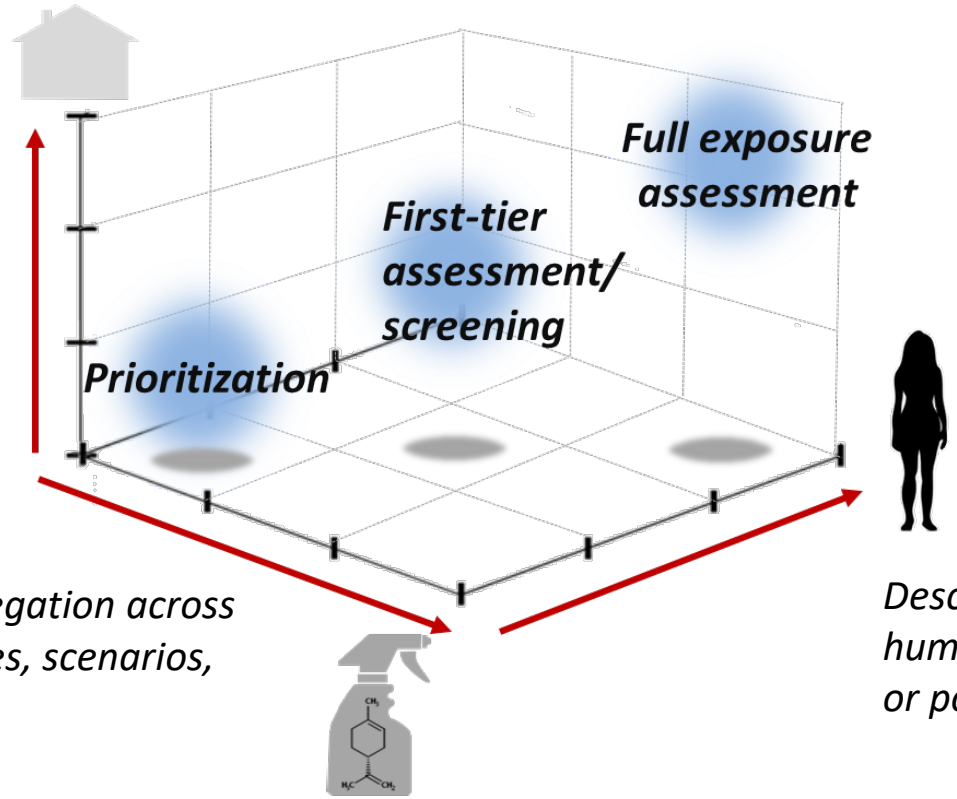
Slide from Kristin Isaacs

Fit-for-Purpose Exposure Modeling Frameworks

United States Environmental Protection Agency

Increasing Complexity

Mechanistic description of the built environment and exposure processes, including temporal variability



Level of aggregation across sources, routes, scenarios, chemicals

Description of human behavior or population

Slide from Kristin Isaacs

Fit-for-Purpose Exposure Modeling Frameworks

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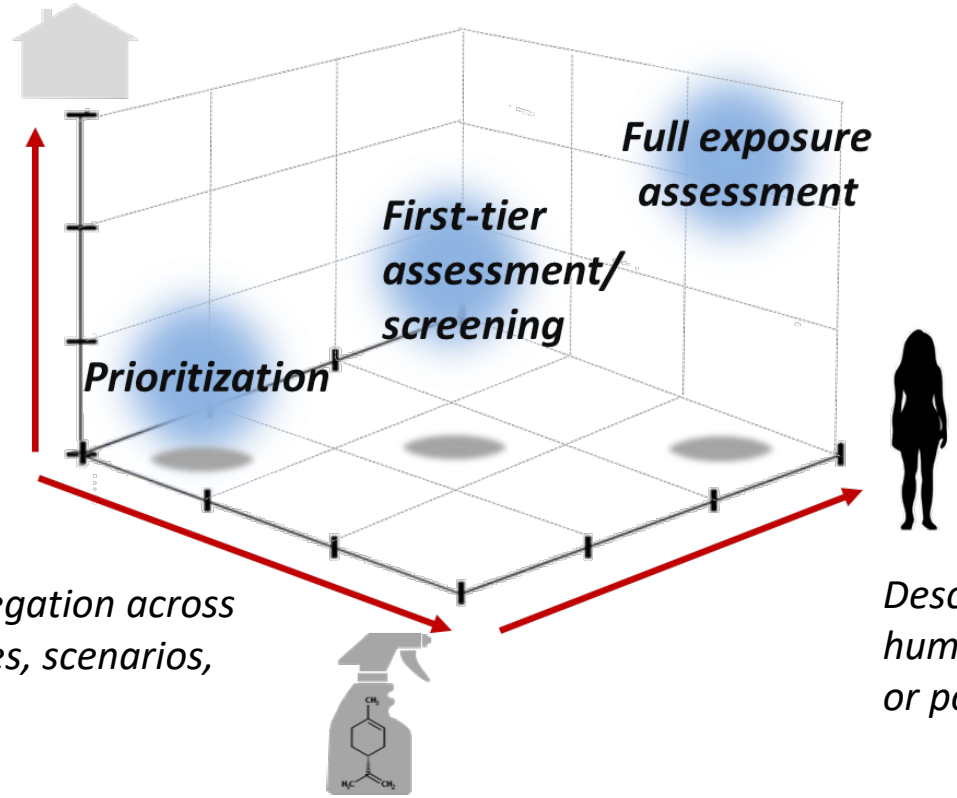
Mechanistic description of the built environment and exposure processes, including temporal variability



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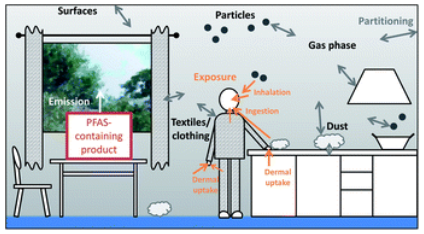
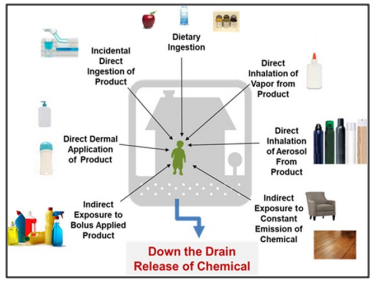
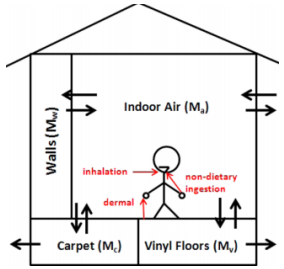


Eichler and Little, 2020



SHEDS-HT, Isaacs et al., 2014

Li et al., 2018



FINE, Shin et al., 2015

- Models of different levels of complexity have **overlapping data needs**
- They also share some **universal challenges**

Consumer Exposure Model

EPA, 2019

Slide from Kristin Isaacs

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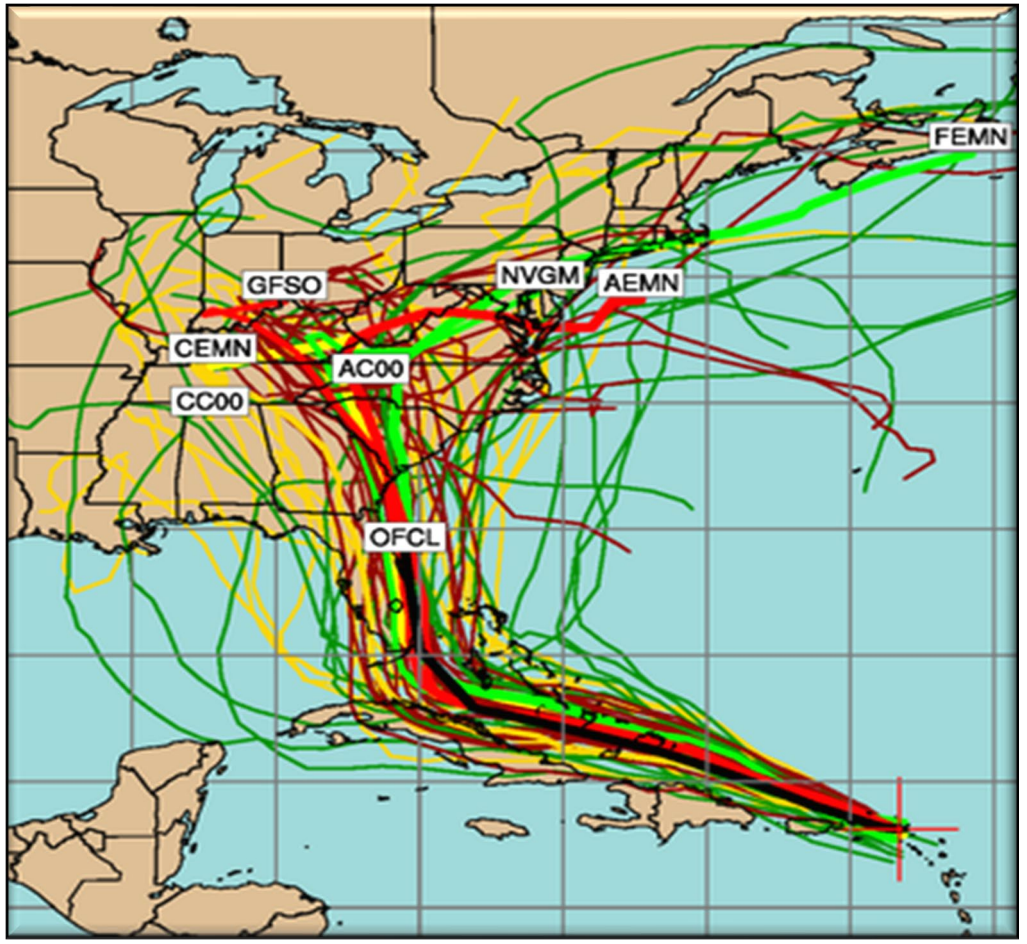
Wambaugh et al., (2019)

Ensemble Predictions

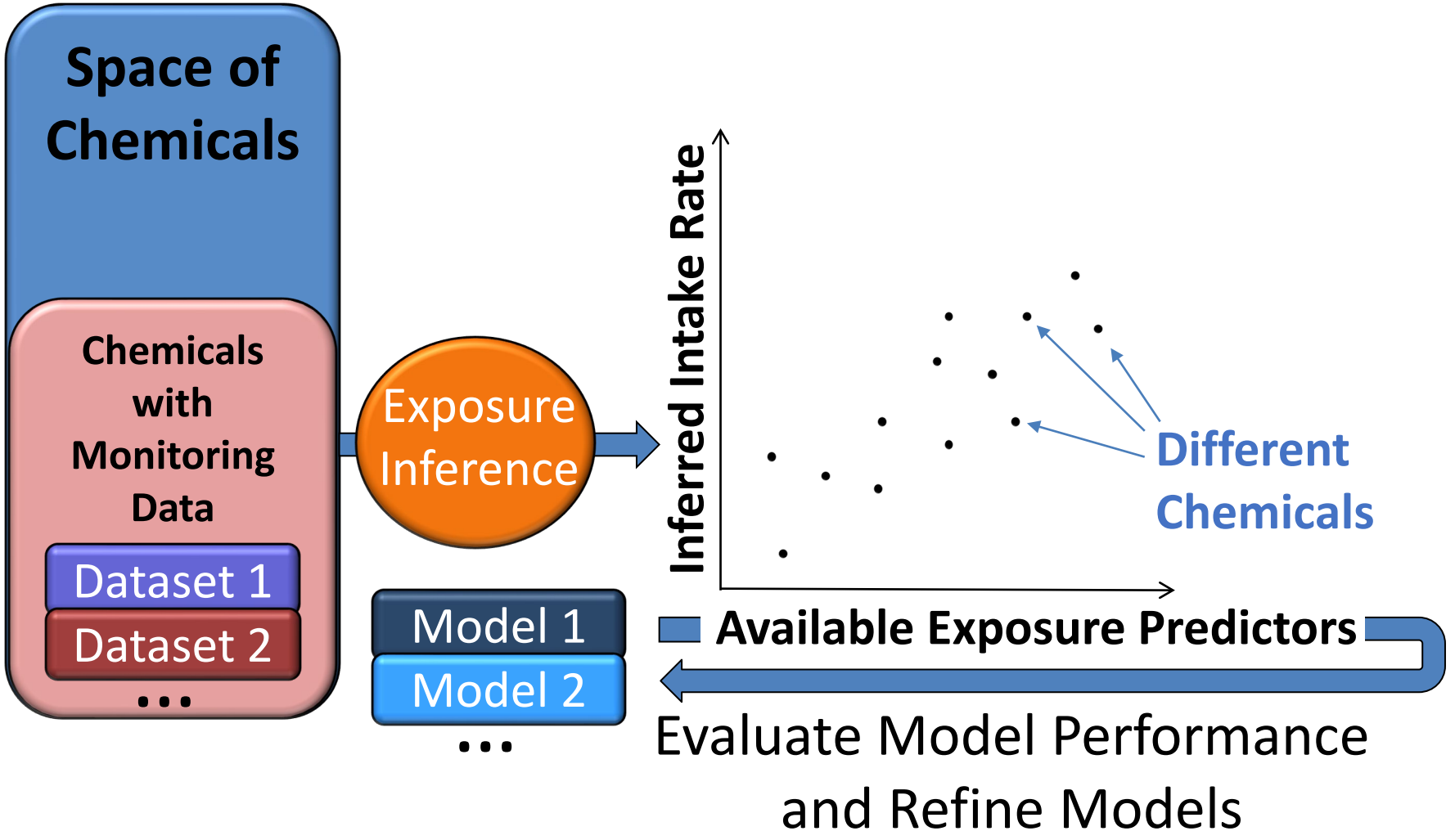
- We can use ensemble methods to make more stable models and characterize uncertainty
- "Ensemble methods are learning algorithms that construct a set of classifiers and then classify new data points by taking a (weighted) vote of their predictions." Dietterich (2000)
- Ensemble systems have proven themselves to be very effective and extremely versatile in a broad spectrum of problem domains and real-world applications (Polikar, 2012)
- Ensemble learning techniques in the machine learning paradigm can be used to integrate predictions from multiple tools. (Pradeep, 2016)



Hurricane Path Prediction is an Example of Integrating Multiple Models

Evaluating Exposure Models with the SEEM Framework

- We use Bayesian methods to incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)** (Wambaugh et al., 2013, 2014; Ring et al., 2018)



Wambaugh et al., 2018

Evaluating Exposure Models with the SEEM Framework

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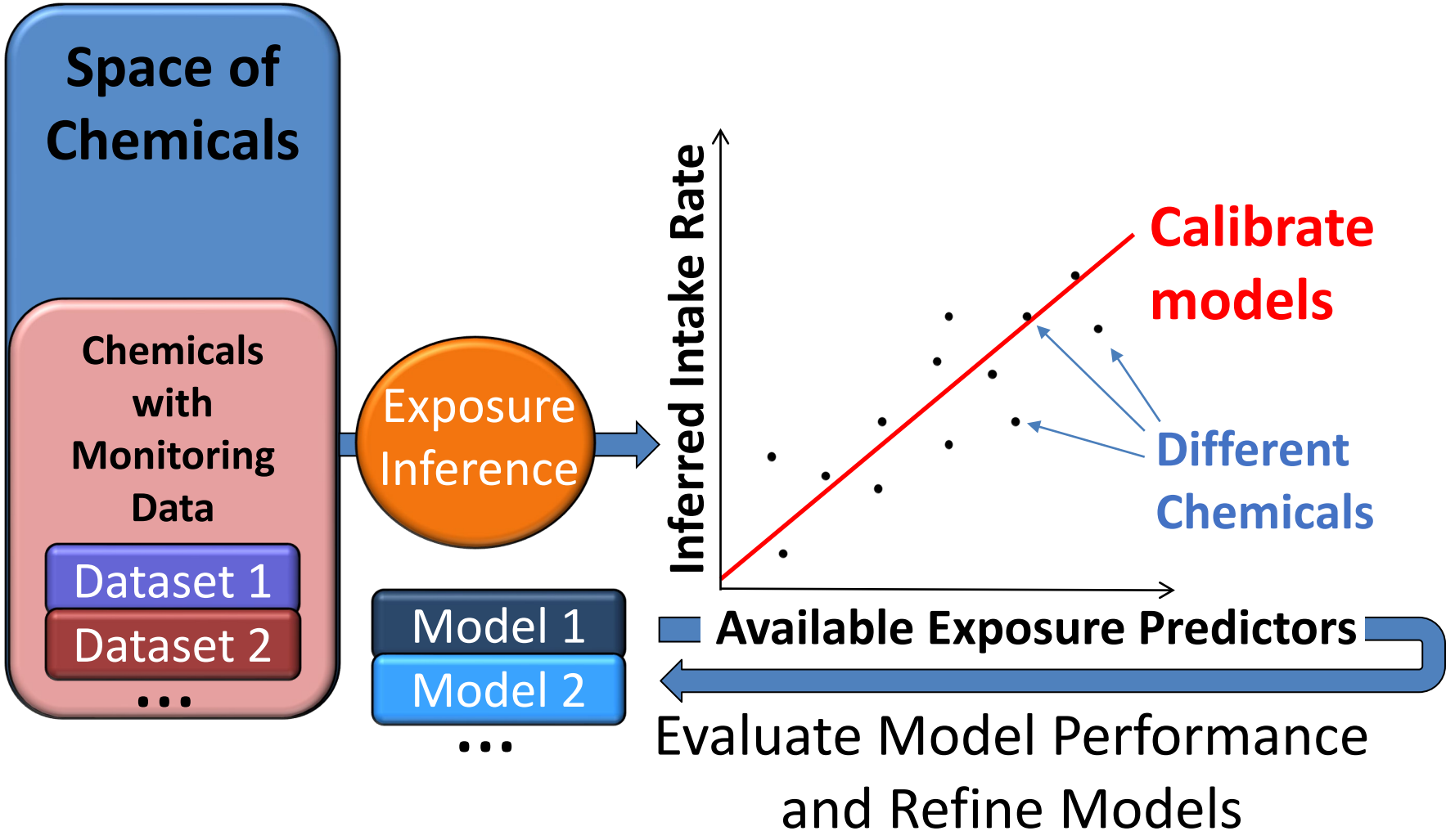

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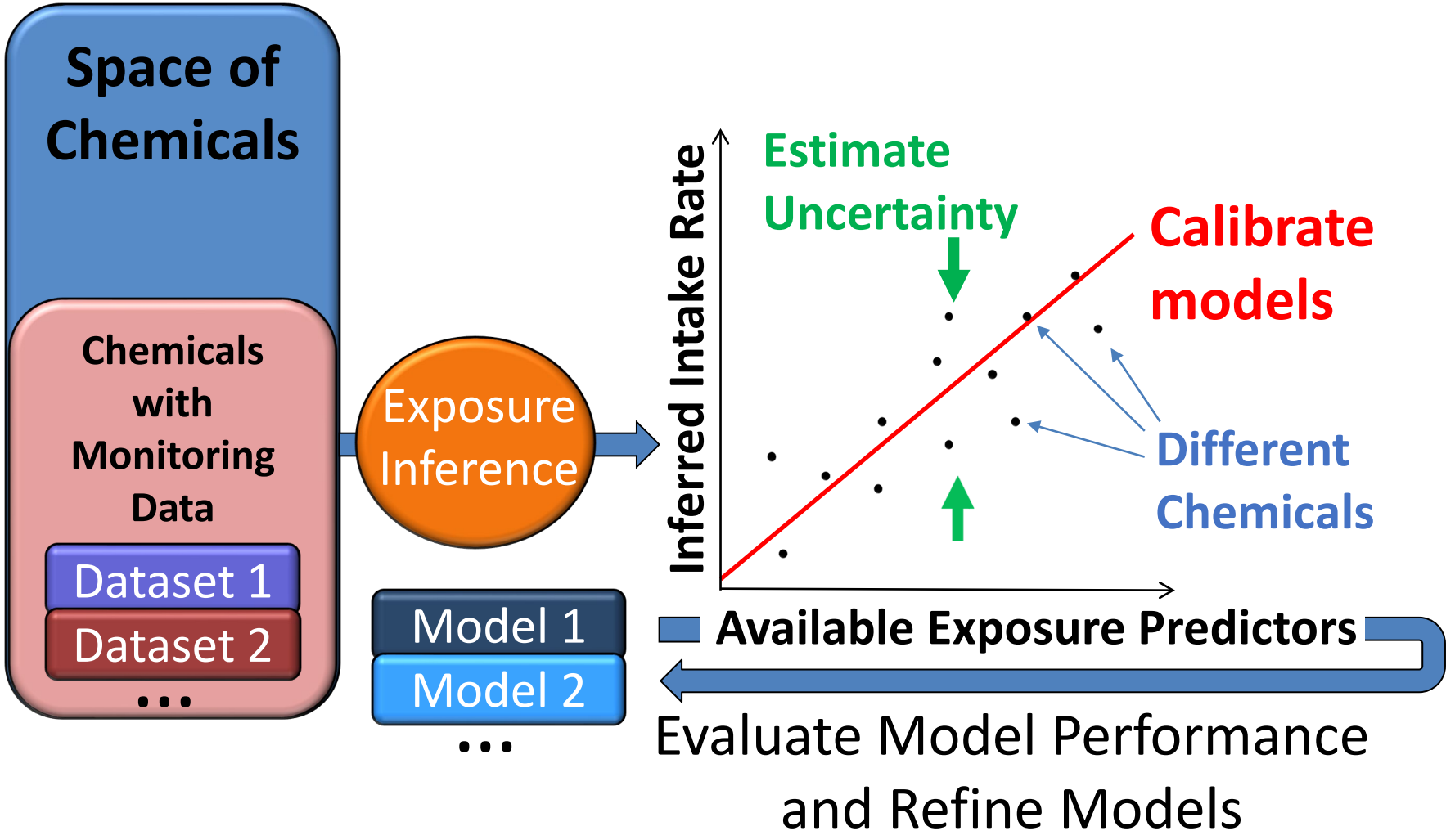

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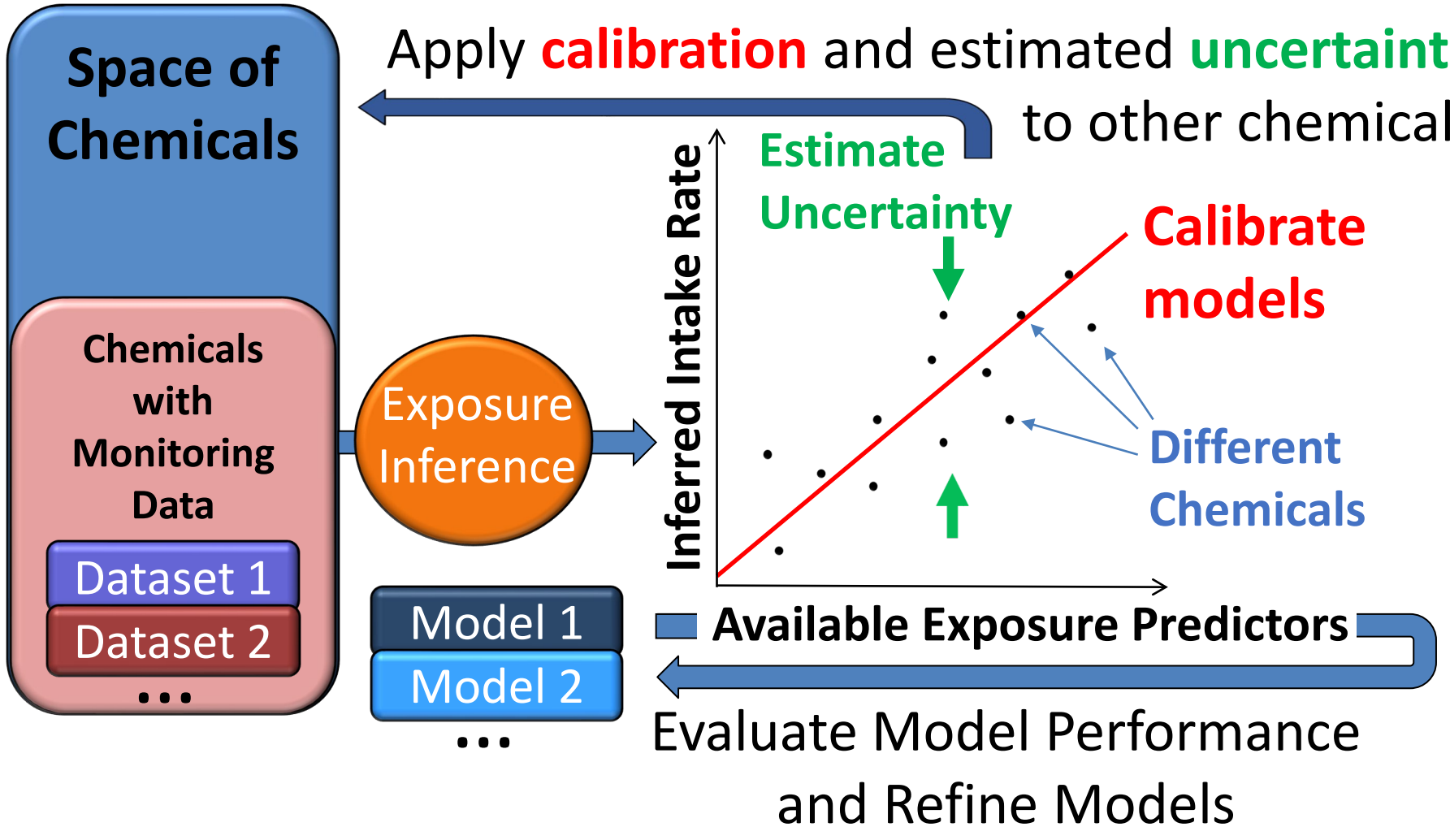


Wambaugh et al., 2018

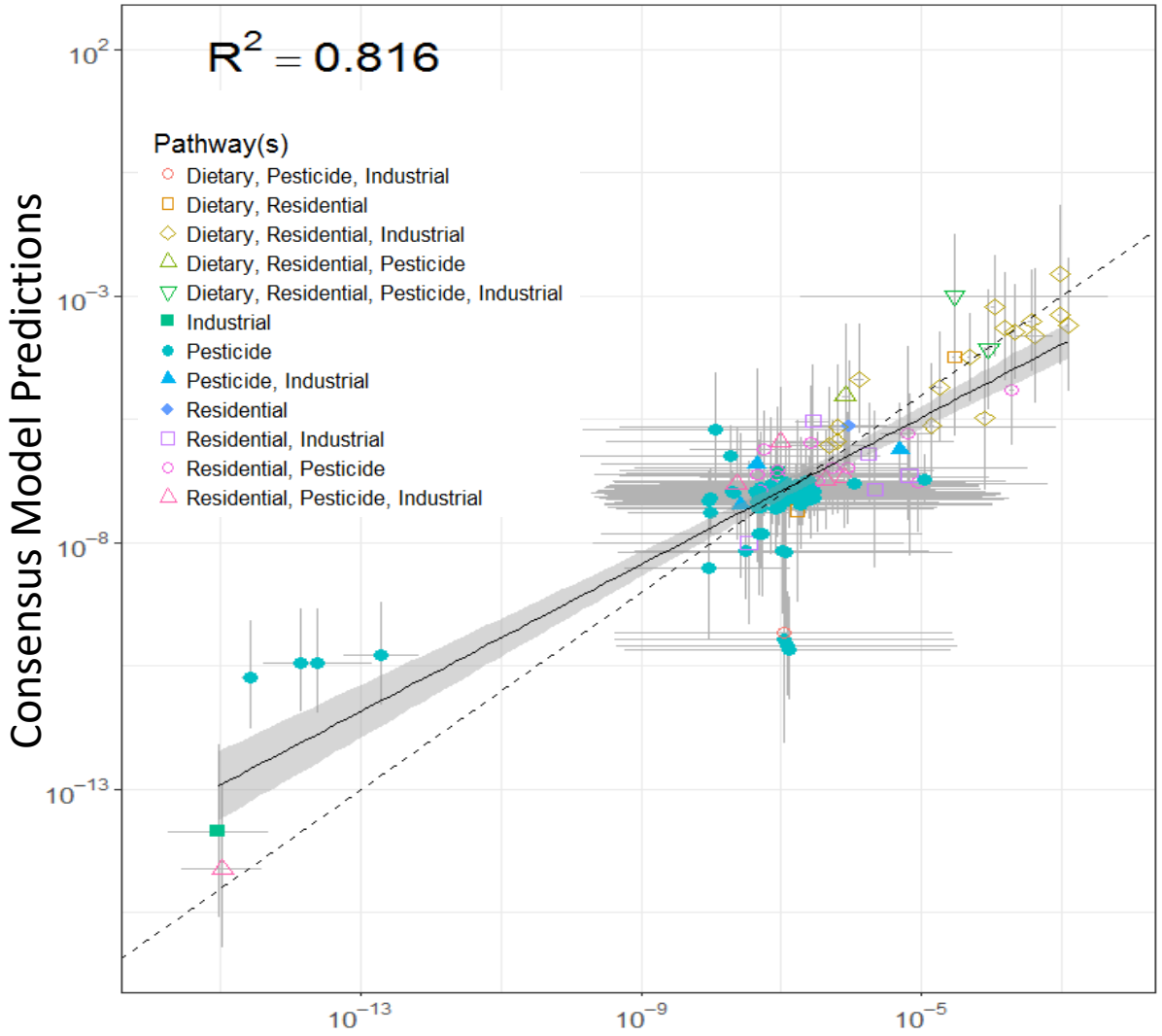
SEEM3 Collaboration

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	Pathway(s)
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

Ring et al., 2018

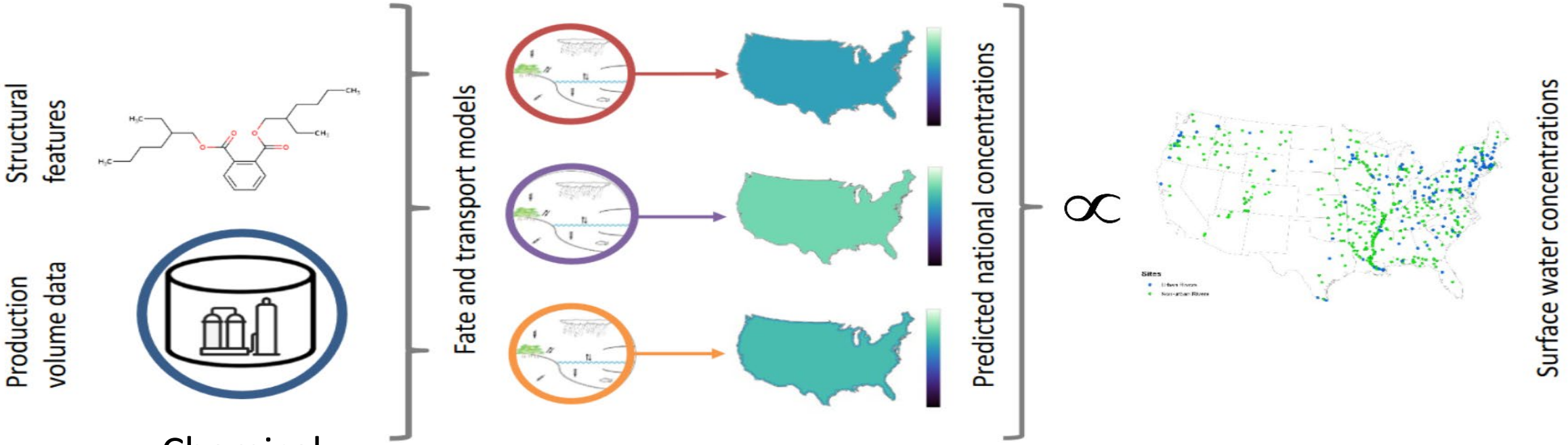
SEEM3: Pathway-Based Consensus Modeling



- SEEM3 consensus model provides estimates of human median intake rate (mg/kg/day) for nearly 500,000 chemicals via the CompTox Chemicals Dashboard (http://comptox.epa.gov/dashboard)
- SEEM3 first predicts relevant exposure pathways from chemical structure – model predictions are then weighted according to the models' abilities to explain NHANES data
- We rely on pathway determinations from CPDat
- We rely on NHANES biomonitoring data
  - 2014 FIFRA Scientific Advisory Panel identified need for broader sets of evaluation data

Ring et al., 2018

EcoSEEM Metamodel for Surface Water Chemical Concentrations



Chemical-specific information (*l*)

→

Release (loading) and fate predictors (*p*)

→

EcoSEEM metamodel (*m*)

←

USGS/EPA water monitoring data (*y*)

$$\ln y_i = m_0 + \sum_{j=1}^{n_j} \sum_{k=1}^{n_{kj}} m_{jk} \ln\left(l_{ji} p_{ki}\right)$$

Sayre et al,
in preparation

Slide from Risa Sayre

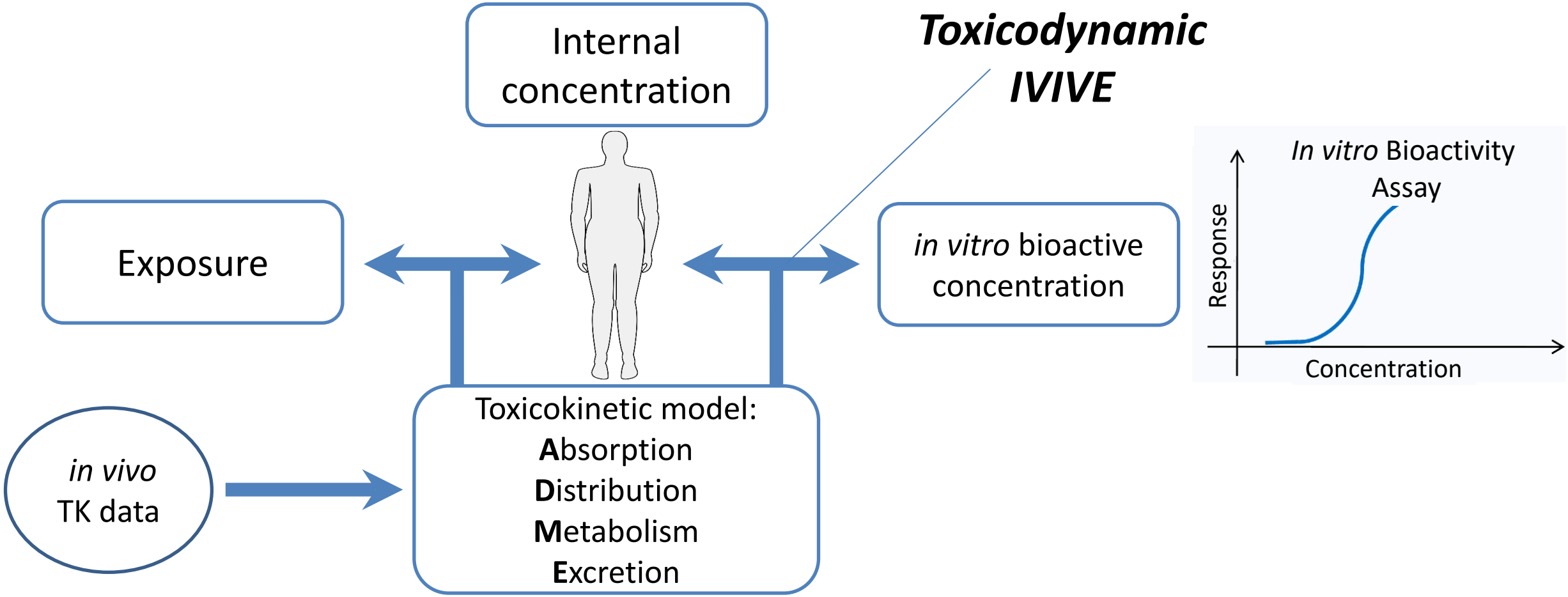
NAMs for Exposure Science

Exposure NAM Class	Description	Traditional Approach	NAM Makes Use of: Measurement	Toxicokinetics	Models	Descriptors	Evaluation	Machine Learning
Measurements	New techniques including screening analyses capable of detecting hundreds of chemicals present in a sample	Targeted (chemical-specific) analyses	-	●	●	●		●
Toxicokinetics	High throughput methods using *in vitro* data to generate chemical-specific models	Analyses based on *in vivo* animal studies	●	-		●		●
HTE Models	Models capable of making predictions for thousands of chemicals	Models requiring detailed, chemical- and scenario-specific information	●	●	-	●		
Chemical Descriptors	Informatic approaches for organizing chemical information in a machine-readable format	Tools targeted at single chemical analyses by humans				-		●
Evaluation	Statistical approaches that use the data from many chemicals to estimate the uncertainty in a prediction for a new chemical	Comparison of model predictions to data on a per chemical basis	●	●	●	●	-	●
Machine Learning	Computer algorithms to identify patterns	Manual Inspection of the Data	●	●		●		-
Prioritization	Integration of exposure and other NAMs to identify chemicals for follow-up study	Expert decision making	●	●	●	●	●	●

Wambaugh et al., (2019)

In Vitro-In Vivo Extrapolation (IVIVE)

- Translation of *in vitro* high throughput screening requires chemical-specific toxicokinetic models
  - Needed for anywhere from dozens to thousands of chemicals



Breen et al. (submitted)

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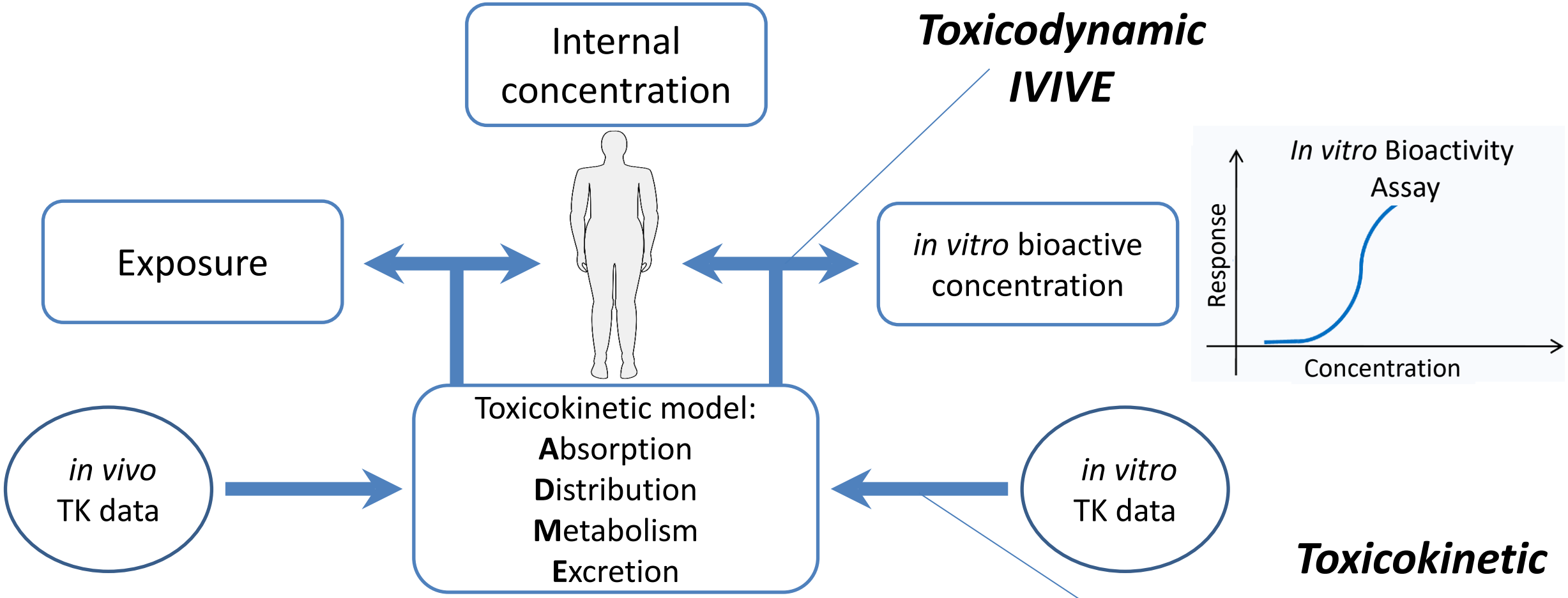
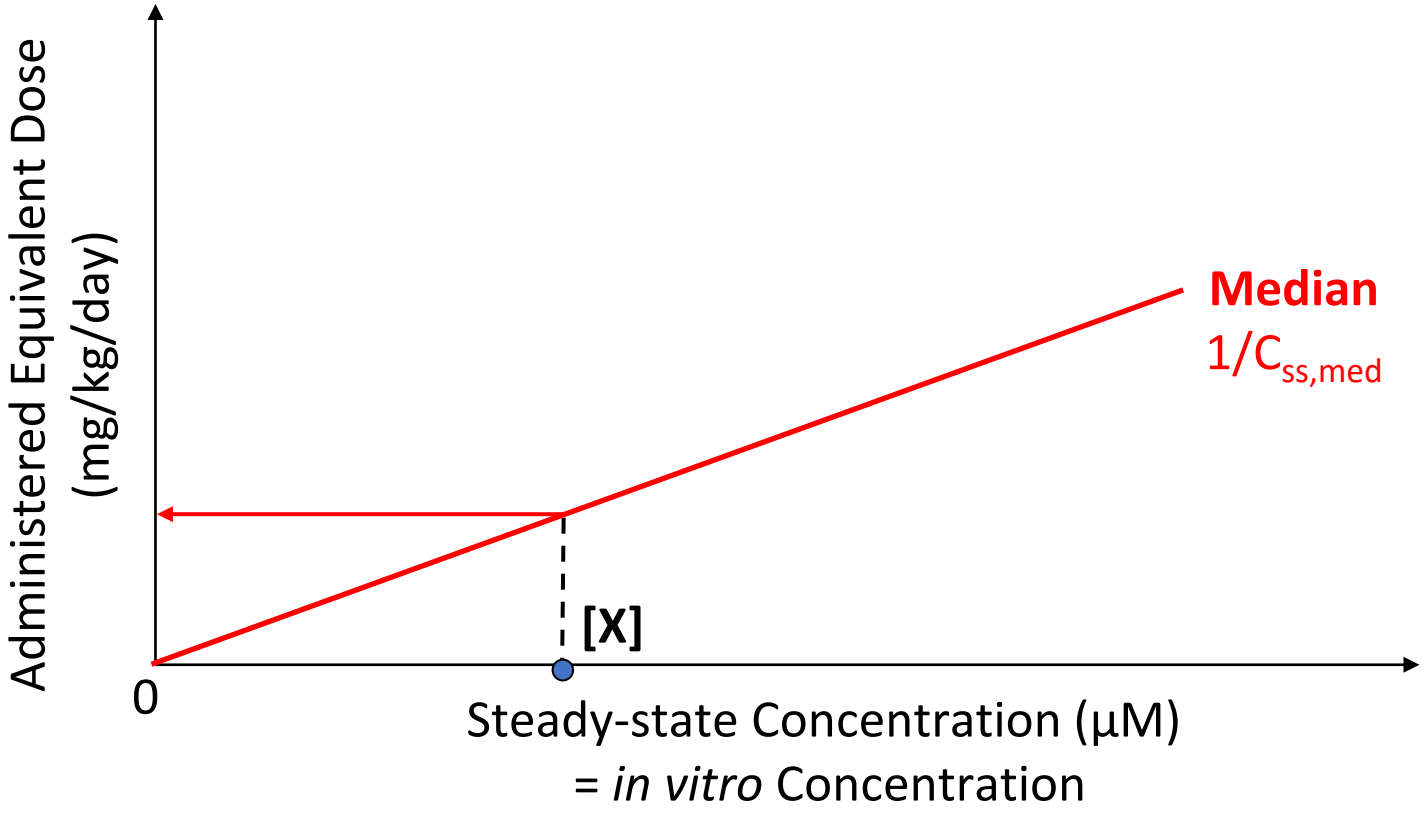


Breen et al. (submitted)

Reverse Dosimetry (IVIVE)

$$\mathbf{AED}_{C_{ss}} = \frac{[X]}{C_{ss}}$$



Breen et al. (submitted)

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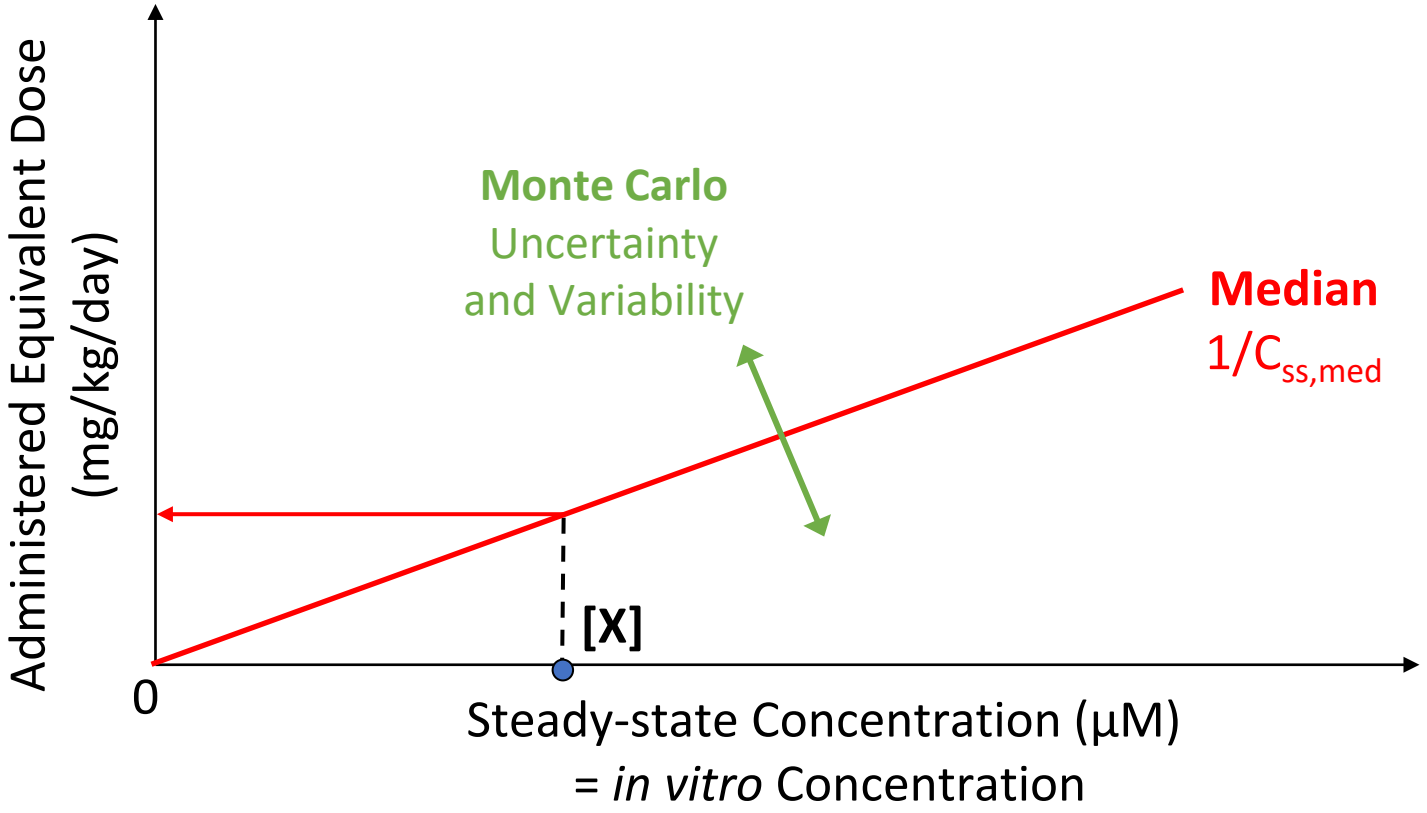

Breen et al. (submitted)

Reverse Dosimetry (IVIVE)

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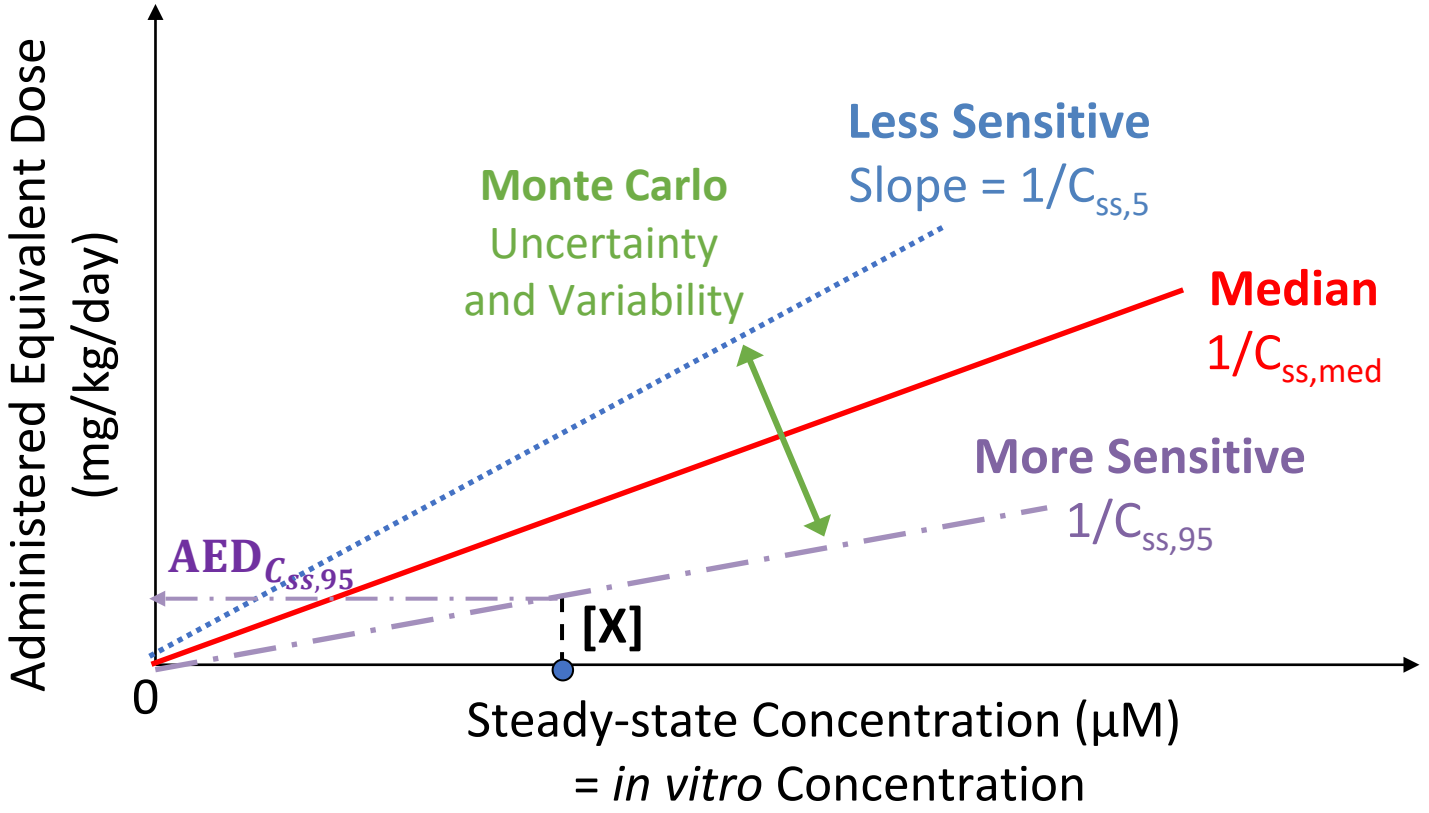
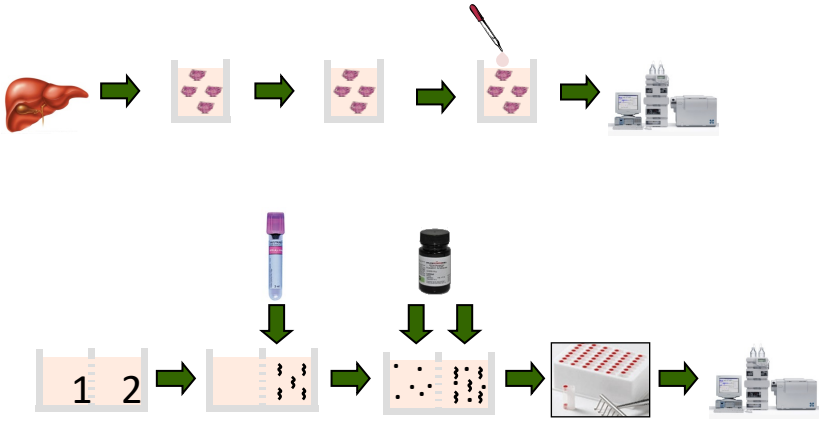


Breen et al. (submitted)

High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data



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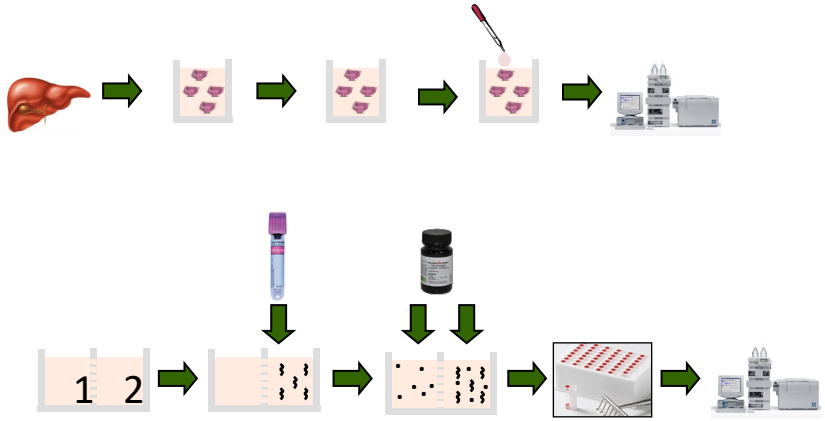
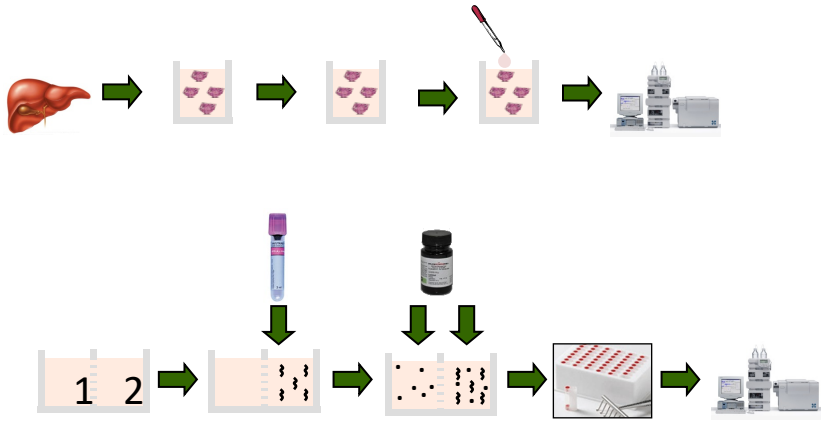
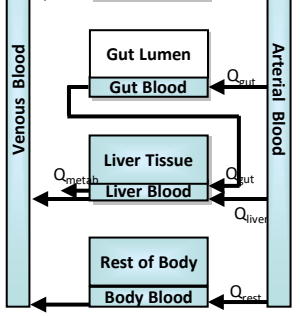


Rotroff et al. (2010)
Wetmore et al. (2012)
Wetmore et al. (2015)
Wambaugh et al. (2019)

High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data + generic toxicokinetic model





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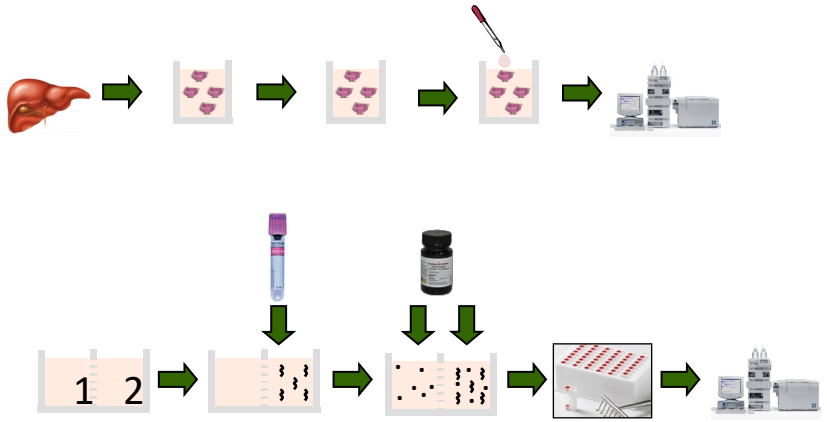

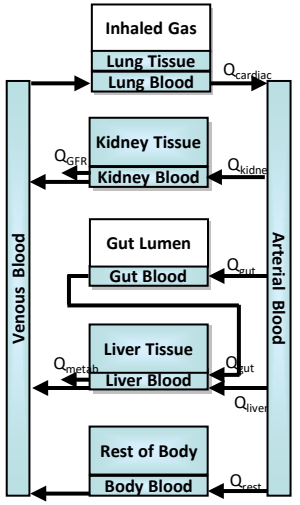

Rotroff et al. (2010)
Wetmore et al. (2012)
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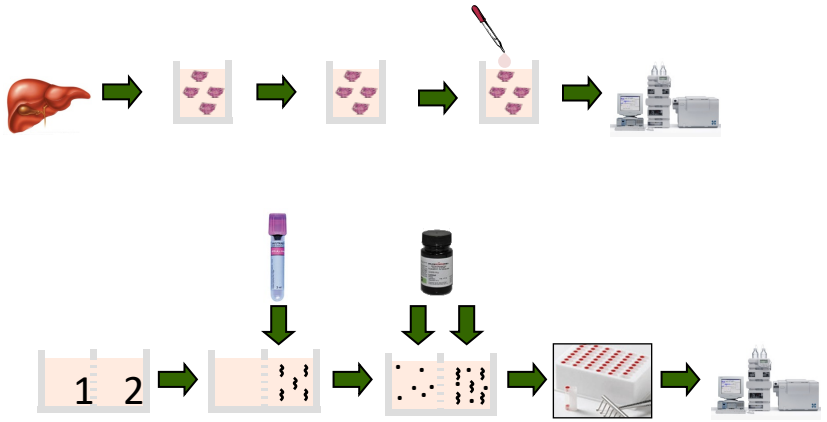
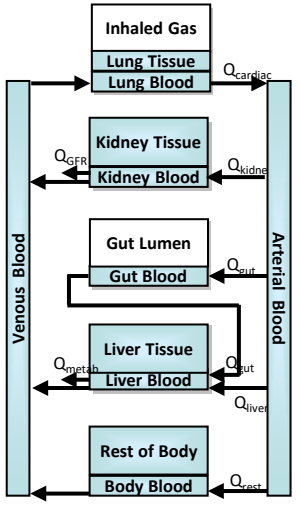
Wambaugh et al. (2015)
Pearce et al. (2017)
Ring et al. (2017)
Linakis et al. (2020)

High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data + generic toxicokinetic model

= high(er) throughput toxicokinetics





= *httk*

Rotroff et al. (2010)
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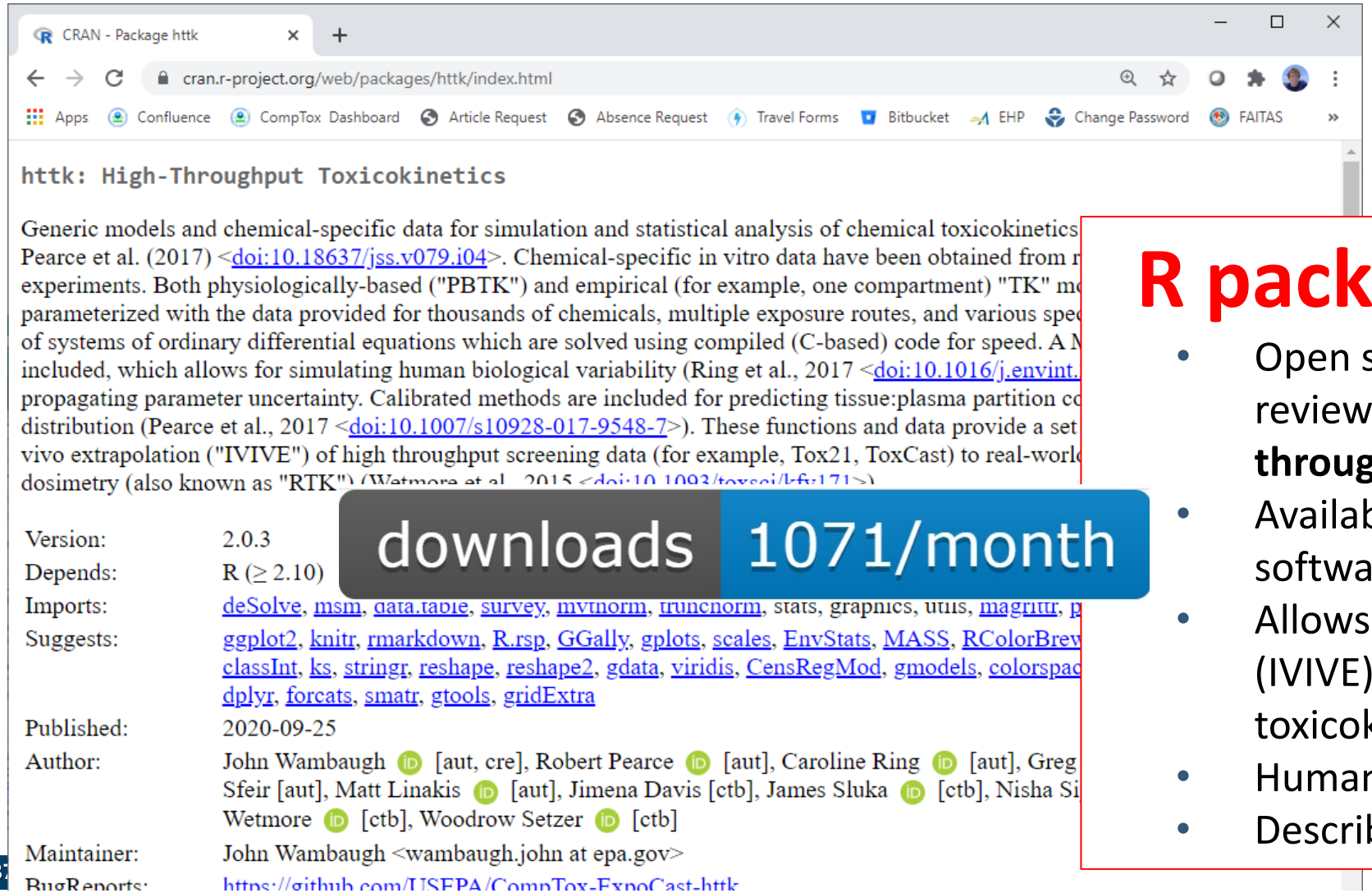
Open-Source Tools and Data for HTTK

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



R package "httk"

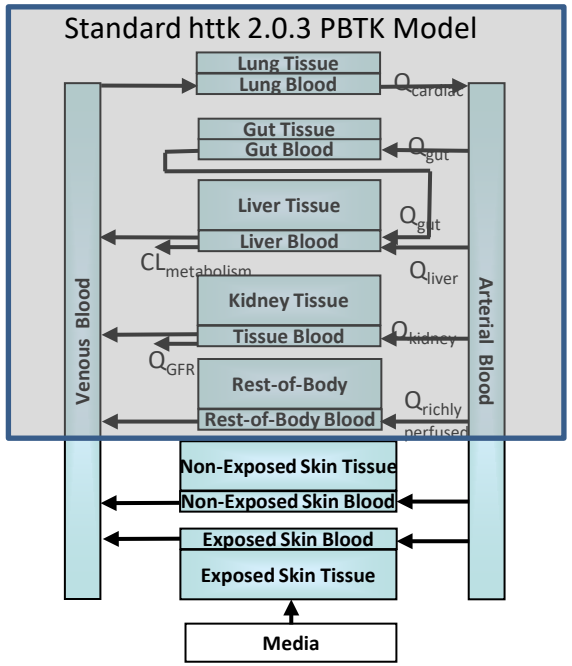
- Open source, transparent, and peer-reviewed tools and data for **high throughput toxicokinetics (httk)**
- Available publicly for free statistical software R
- Allows *in vitro-in vivo* extrapolation (IVIVE) and physiologically-based toxicokinetics (PBTK)
- Human-specific data for 987 chemicals
- Described in Pearce et al. (2017)

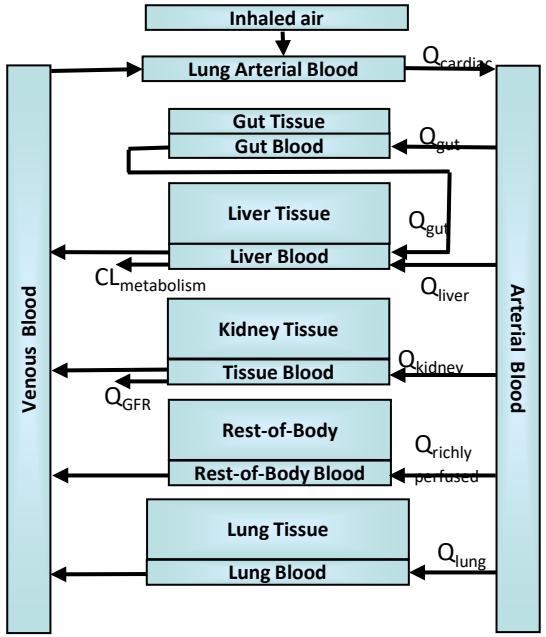
Toxicokinetics NAMs: *In Vitro* Measurements and Generic PBTK Models

United States Environmental Protection Agency

Gas and Aerosol Inhalation Exposure Route

EPA, USAF, Linakis et al. (2020)

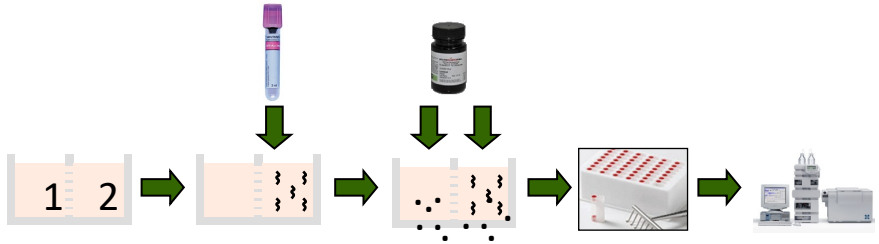




Dermal Exposure Route

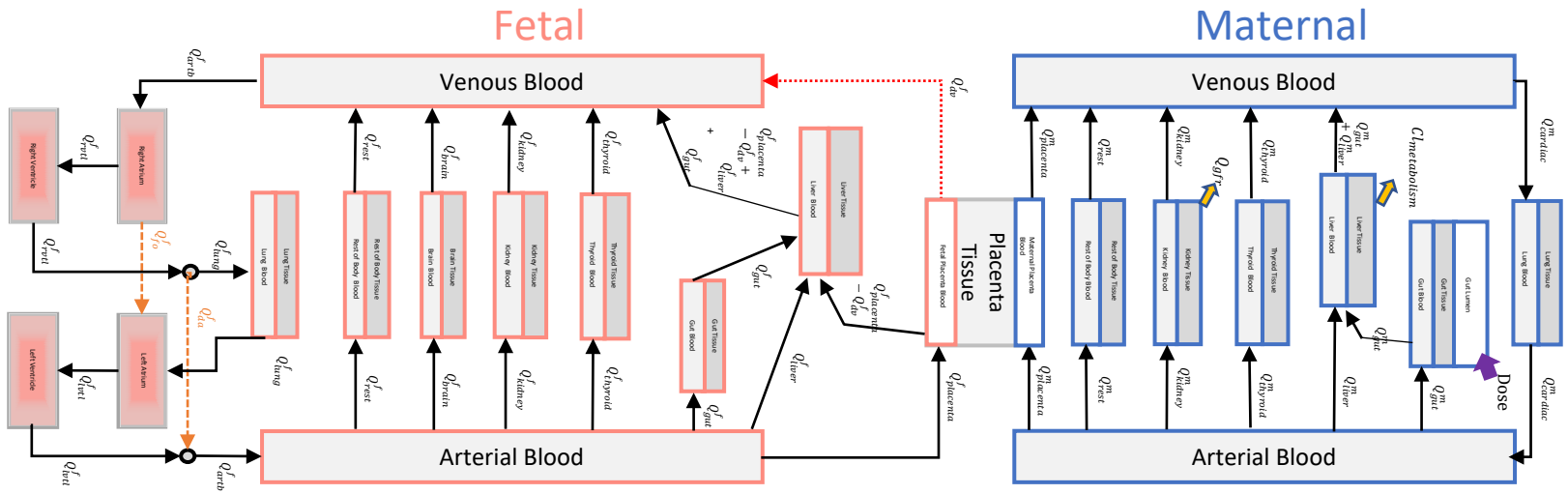
EPA, Unilever, INERIS

Wetmore et al. (2012, 2013, 2015), Wambaugh et al. (2019)



Human Gestational Model

EPA, FDA, Kapraun et al., (2020)



In Vivo TK Database

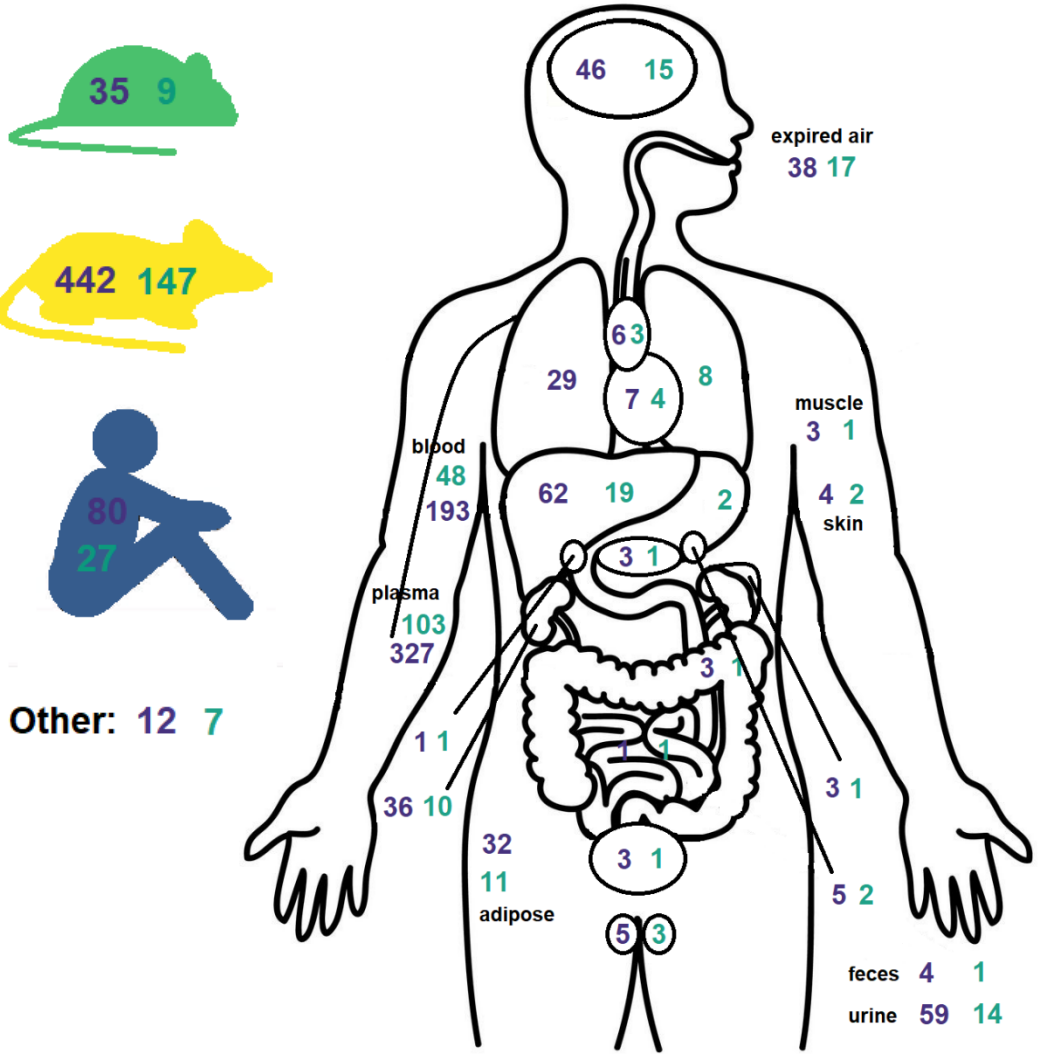
https://github.com/USEPA/CompTox-PK-CvTdb

- EPA has developed 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

- Standardized, open source curve fitting software invivoPKfit used to calibrate models to all data:

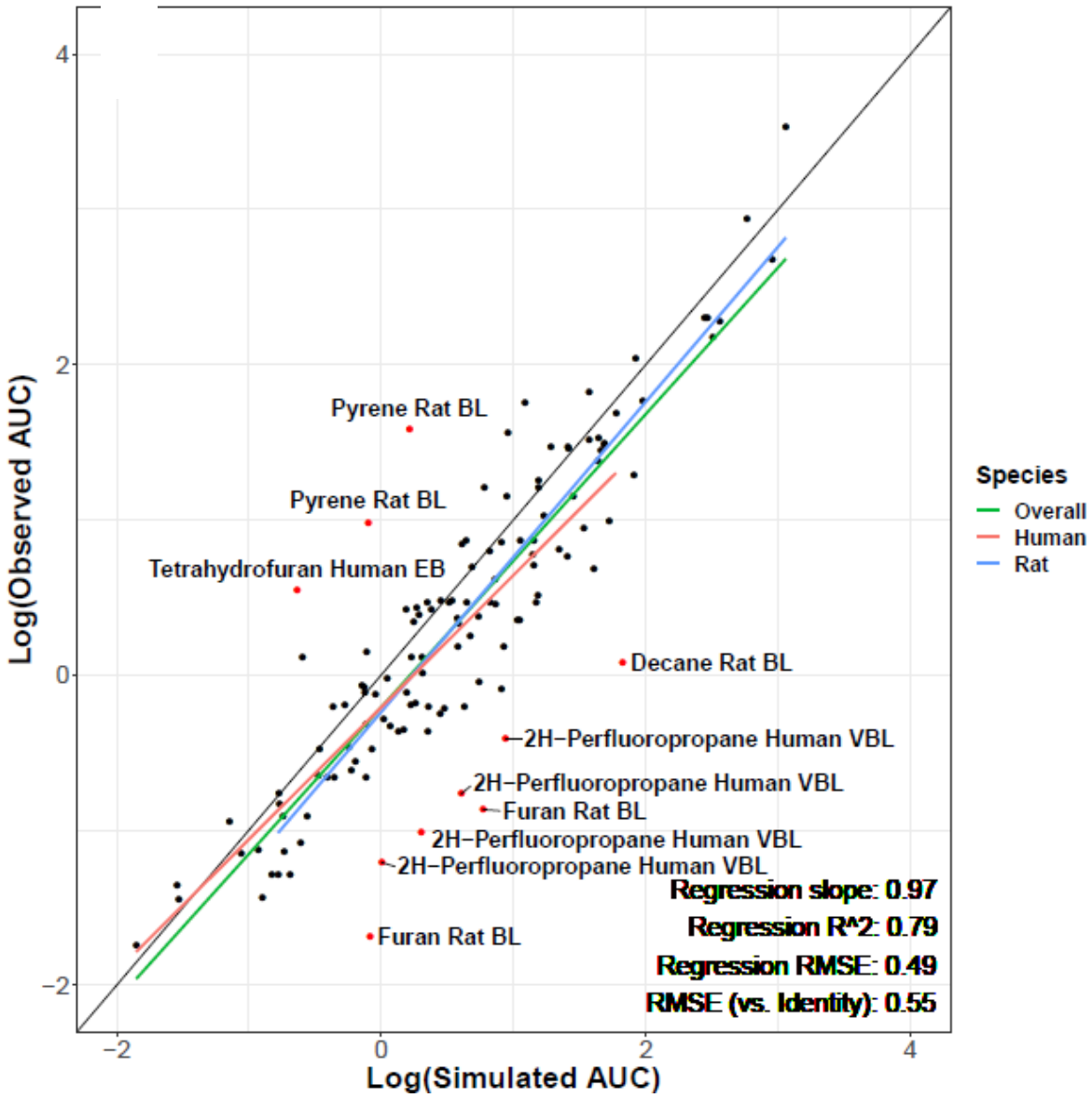
  https://github.com/USEPA/CompTox-ExpoCast-invivoPKfit



Sayre et al. (2020)

Developing Models with the CvT Database

- USAF and EPA developed generic gas inhalation physiologically-based toxicokinetic (PBTK) model
- Evaluated HTTK with CvTdb: 142 exposure scenarios across 41 volatile organic chemicals were modeled and compared to published *in vivo* data for humans and rat
- R^2 was 0.69 for predicting peak concentration
- R^2 was 0.79 for predicting time integrated plasma concentration (Area Under the Curve, AUC)



Linakis et al. (2020)

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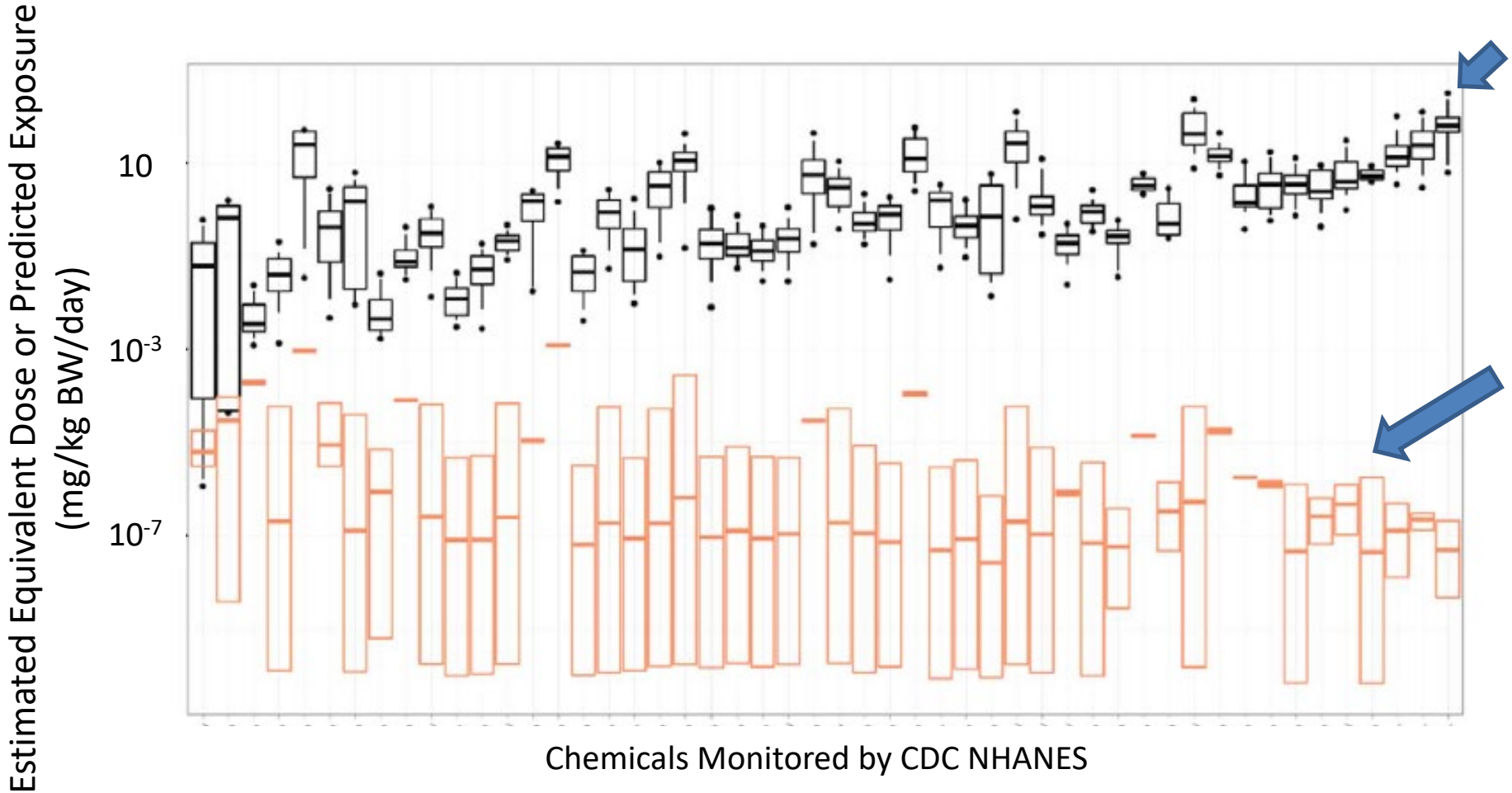
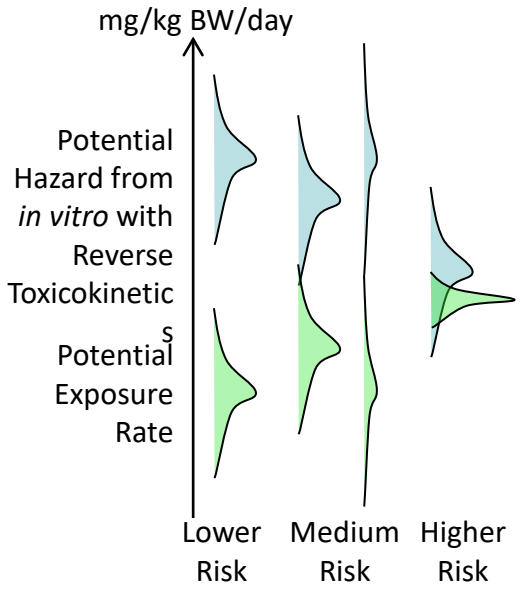
Wambaugh et al., (2019)

Chemical Prioritization NAMs



High throughput *in vitro* screening can estimate doses needed to cause bioactivity (for example, Wetmore et al., 2015)

Exposure intake rates can be inferred from biomarkers (for example, Ring et al., 2018)

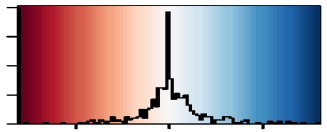


Ring *et al*. (2017)

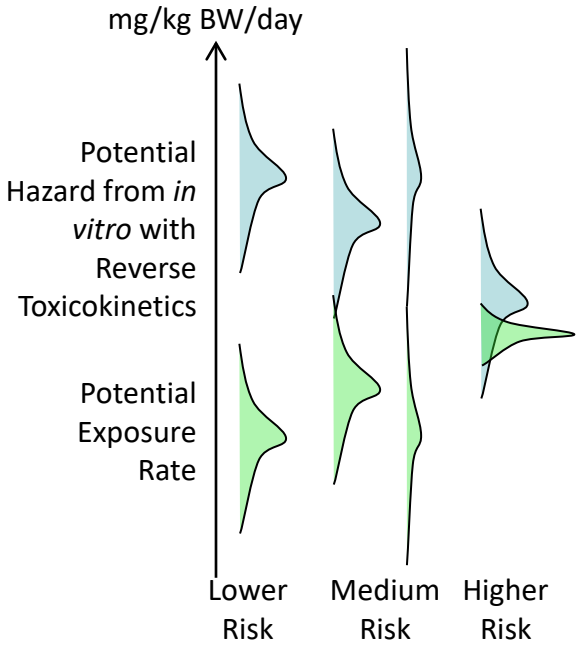
Life-stage and Demographic Specific Predictions

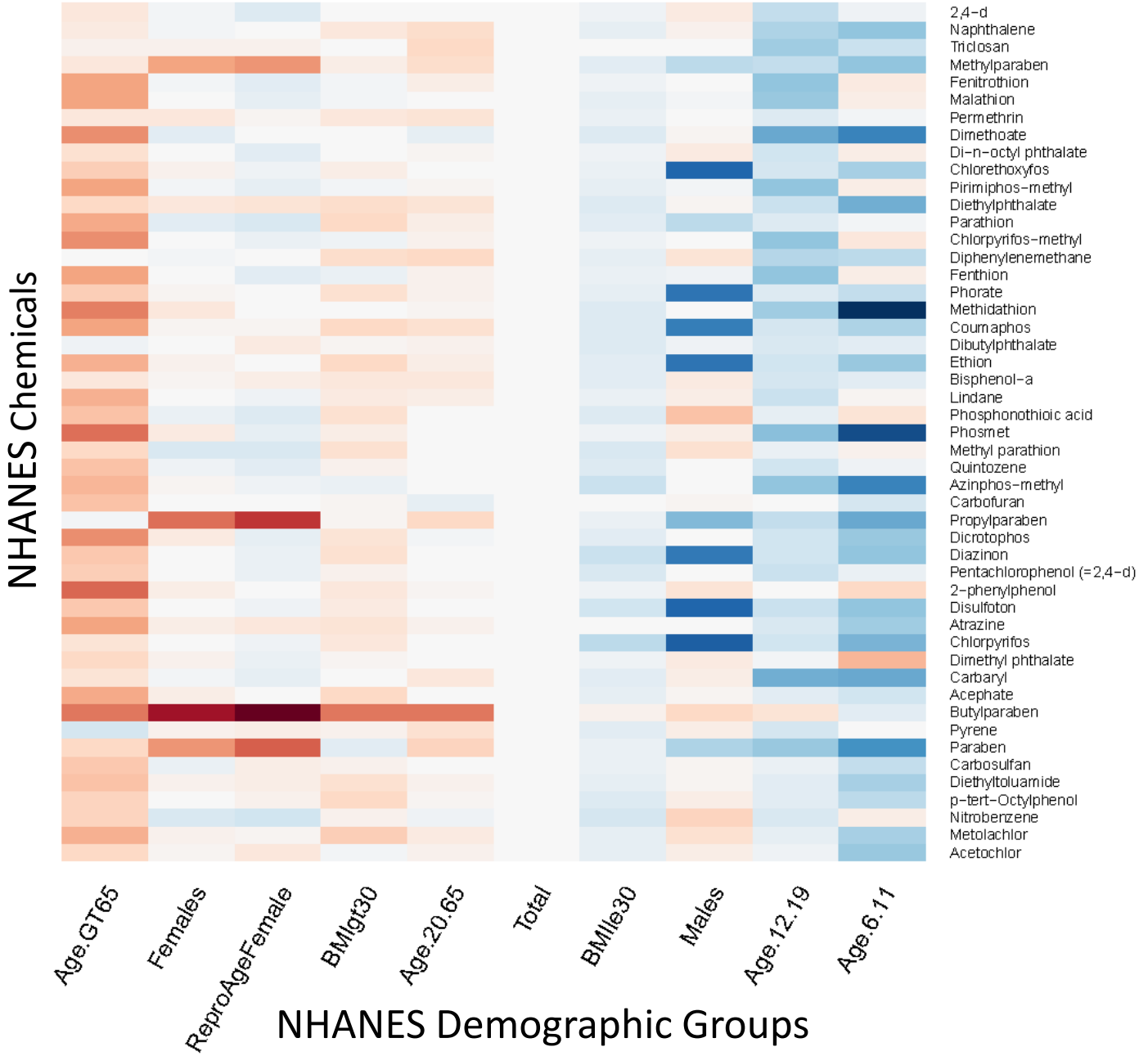
United States Environmental Protection Agency

Change in Bioactivity : Exposure Ratio (Risk)



+3x 0 -3x





- We can calculate margin between bioactivity and exposure for specific populations
- Based on variation in toxicokinetics and exposure

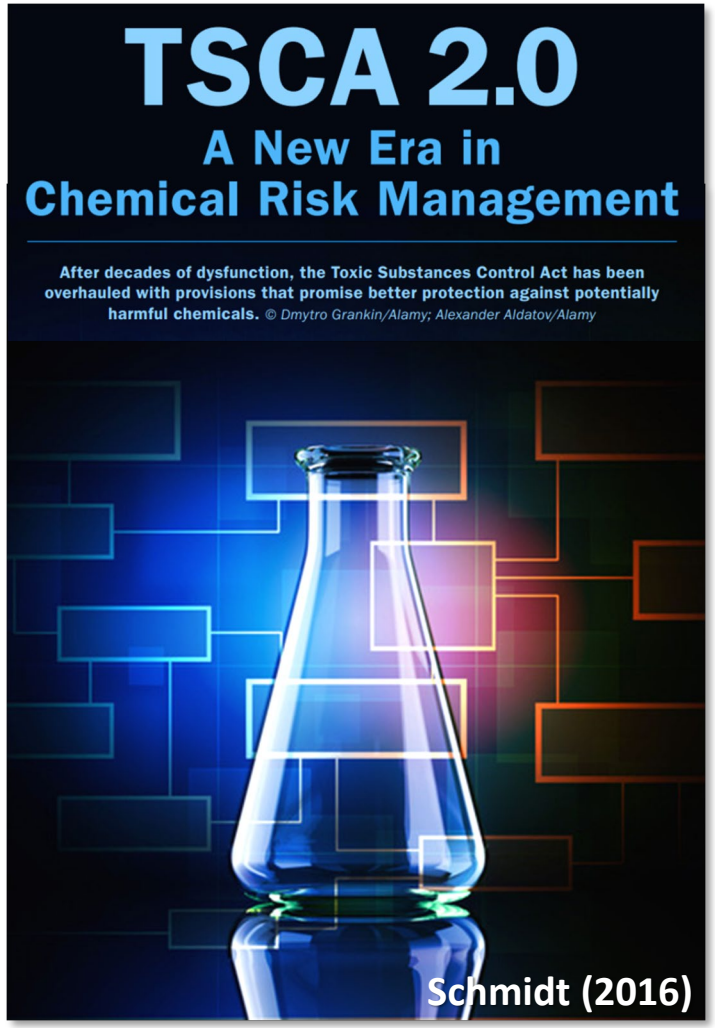
Ring *et al*. (2017)

Outlook

- In ExpoCast we develop models and perform experiments for both exposure and dosimetry (toxicokinetics)

- HTTK (high throughput toxicokinetics) includes a suite of peer-reviewed models for toxicokinetics that can be parameterized for nearly one thousand chemicals
  - Currently adding new models (aerosol, dermal, human gestational)
  - Adding new structure-based predictors for data that are currently measured *in vitro*

- SEEM (systematic empirical evaluation of models) is a consensus meta-modeling framework for exposure
  - Trained to monitoring data (developing more)
  - Trained to chemical use data (developing more)
  - Human developed, ecological and occupational in progress



ExpoCast Project (Exposure Forecasting)

Center for Computational Toxicology and Exposure

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Miyuki Breen*
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Chris Cook*
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Unilever
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Cecilie Rendal
Ian Sorrell
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Heather Pangburn
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University of Texas, Arlington
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Julia Rager
Marc Serre

United States Environmental Protection Agency

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