EPA
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Environmental Protection
Agency

Placing toxicology data in the context of exposure

Presented as part of the Texas A&M Superfund Research Center's Virtual Learning Series "Big Data in Environmental Science and Toxicology"

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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

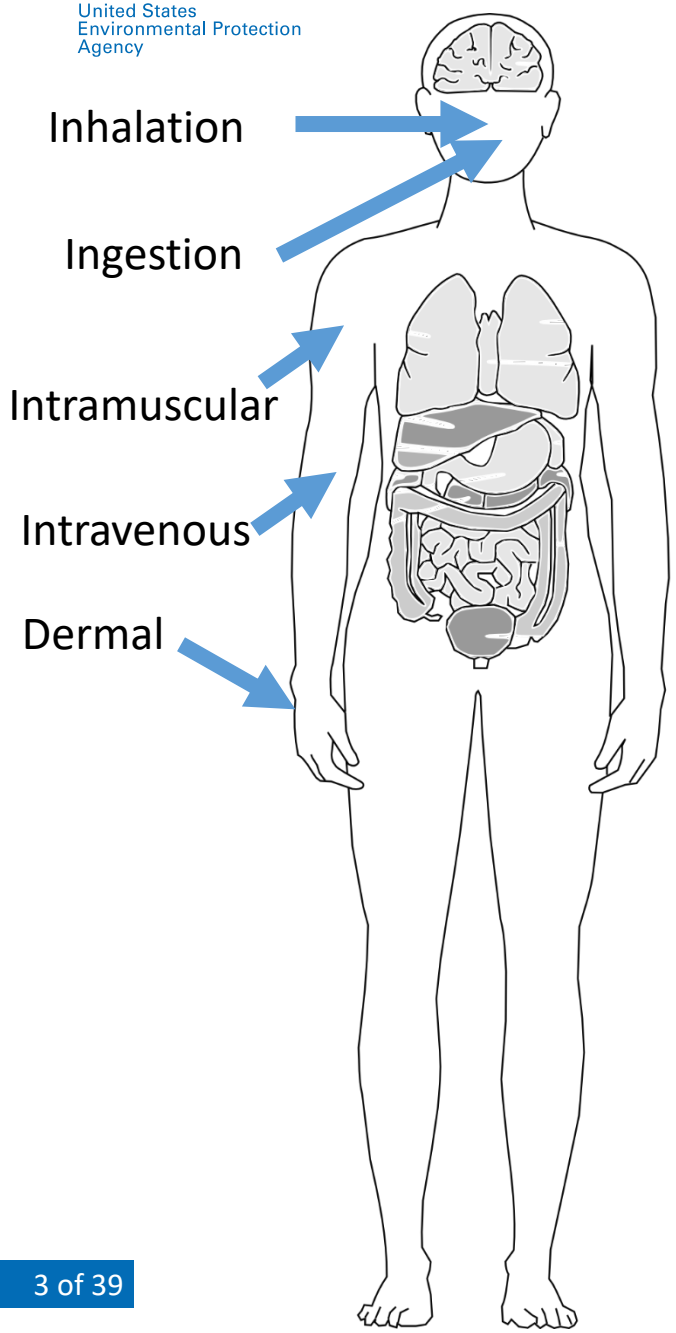
Office of Research and Development
Center for Computational Toxicology and Exposure

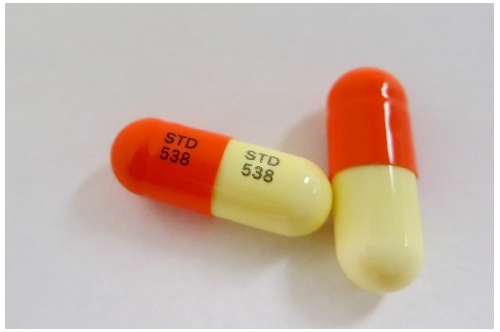
November 3, 2021

Overview

- Motivation: “The dose makes the poison”
- Risk = hazard vs. exposure
- Problem: Traditional approaches insufficient to screen thousands of chemicals
- Solution: New approach methodologies (NAMs)
  - NAMs for hazard
  - NAMs for exposure
- Problem: Hazard NAMs estimate biologically active *concentrations*. How to compare to external exposure rates?
- Solution: In vitro-in vivo extrapolation using high-throughput toxicokinetic modeling

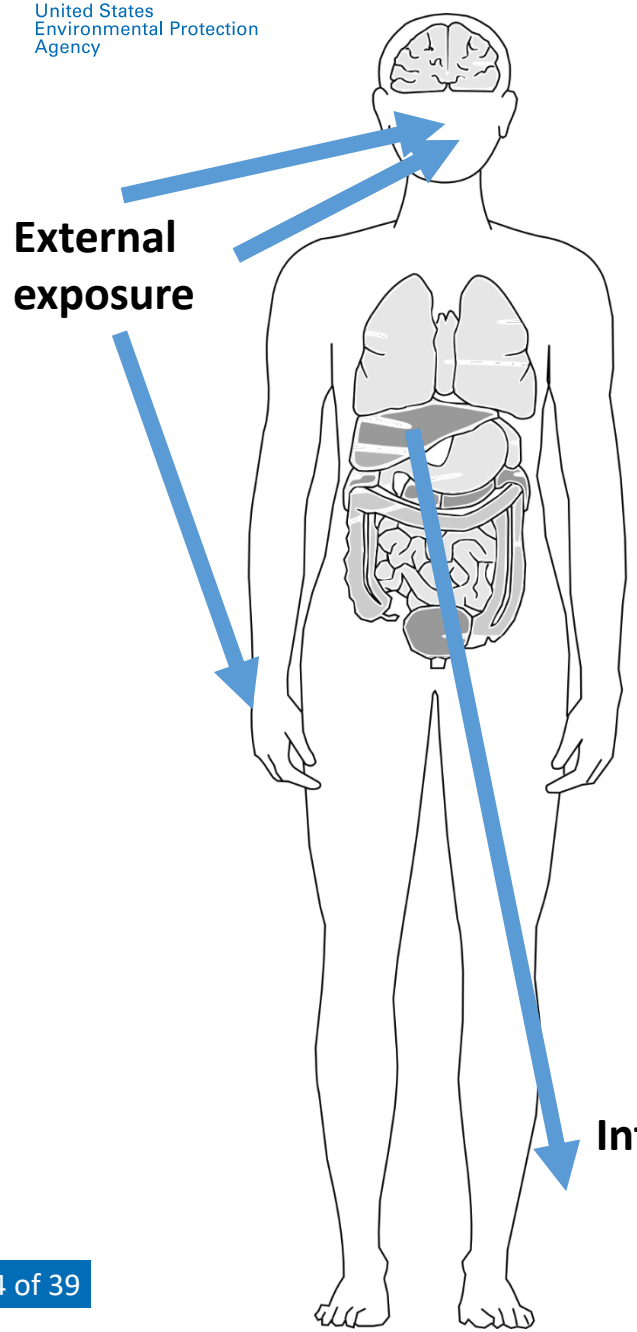
Scenario: You are exposed to chemicals





CC-BY Ali Karimian

Scenario: You are exposed to chemicals



Things you might want to know….

- What chemicals are you exposed to? How much? How often?
- Do the chemicals get inside your body?
- If so, how much gets inside?
  - For example, what is the concentration of each chemical in your blood?
- Is that enough to cause any kind of health effect?

Internal dose = Amount/concentration of chemical or drug in one or more body tissues of interest

Difficulty level: Answer these questions for thousands of environmental chemicals, and for the whole population

- Most non-food, non-drug chemicals, ranging from industrial waste to dyes to packing materials, are covered by the Toxic Substances Control Act (TSCA) and come under EPA's purview
- Currently 41,953 "active" (currently-used) chemicals on TSCA inventory, and hundreds of new ones listed every year
- Need a way to rapidly **prioritize** chemicals for more detailed evaluation

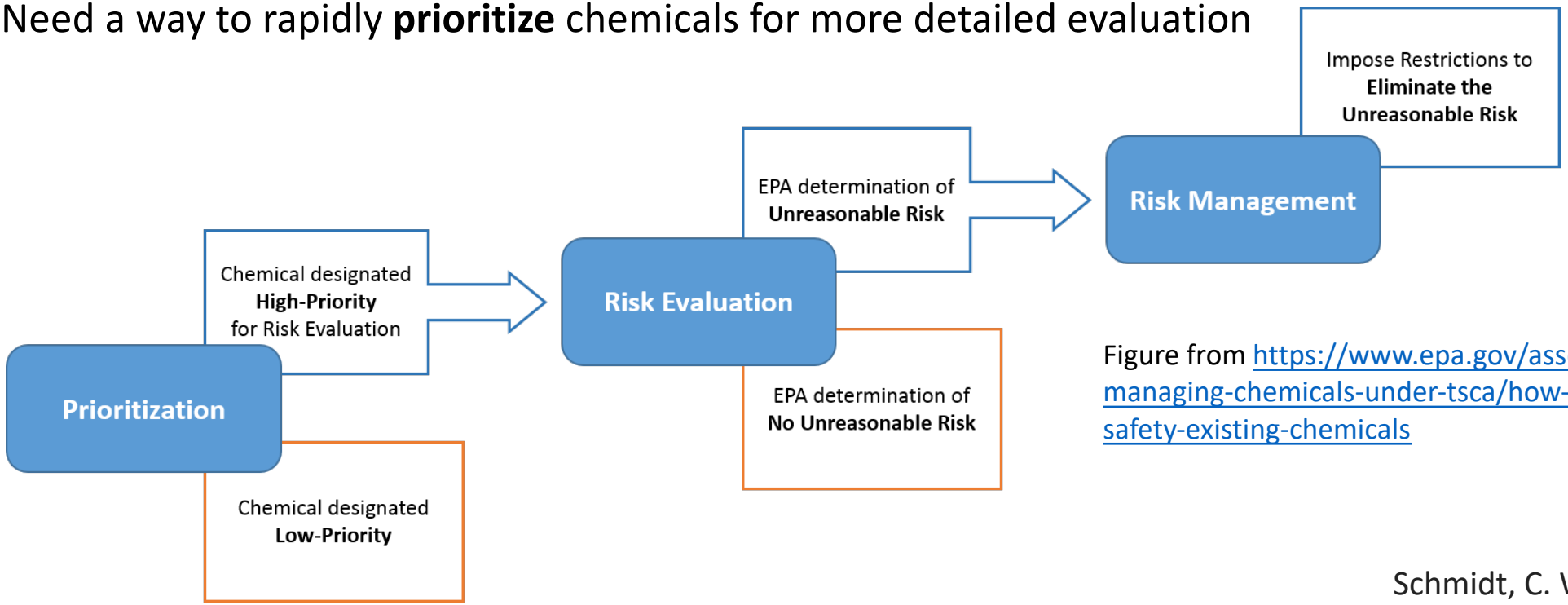
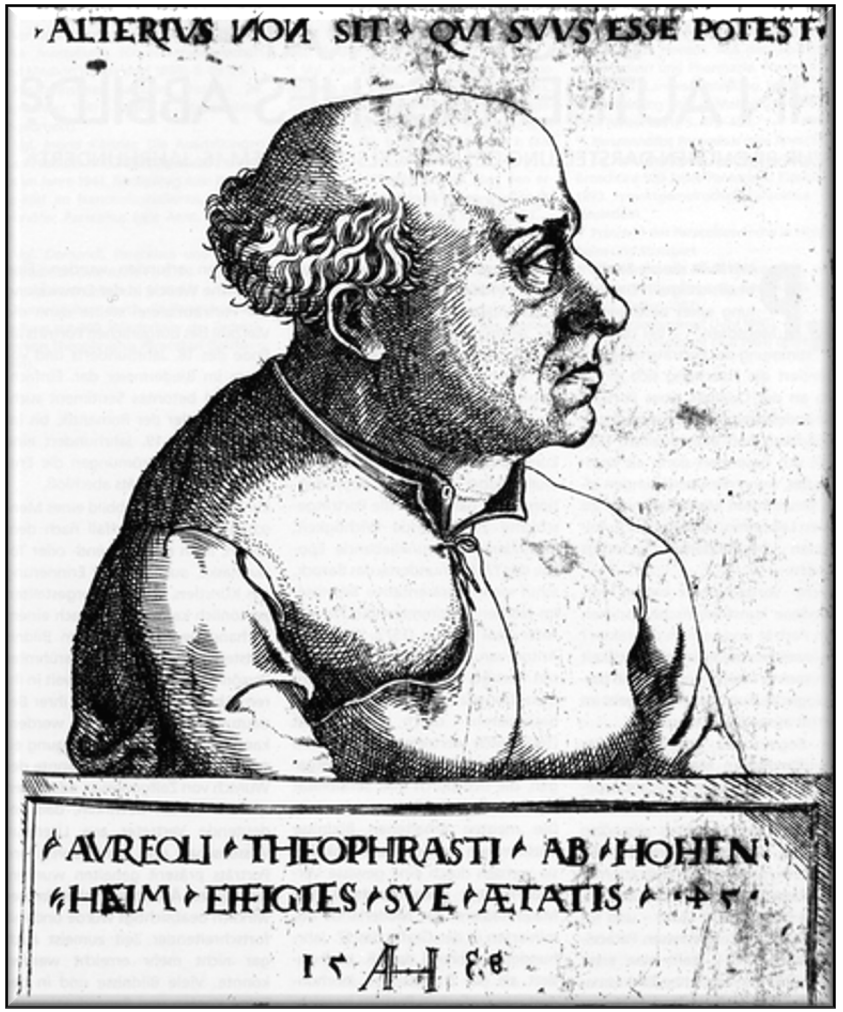


Figure from https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/how-epa-evaluates-safety-existing-chemicals

Schmidt, C. W. (2016)

Paracelsus: "The dose makes the poison"

"What is there that is not poison? All things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison" — Paracelsus (1493-1541)



Hazard: Inherent property of an agent having the potential to cause adverse effects with exposure.

***Exposure*:** Concentration or amount of an agent that reaches a target organism, system, or (sub)population in a specific frequency for a defined duration.

Dose: Total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population.

Dose-response: Relationship between dose and adverse effect occurrence or magnitude.

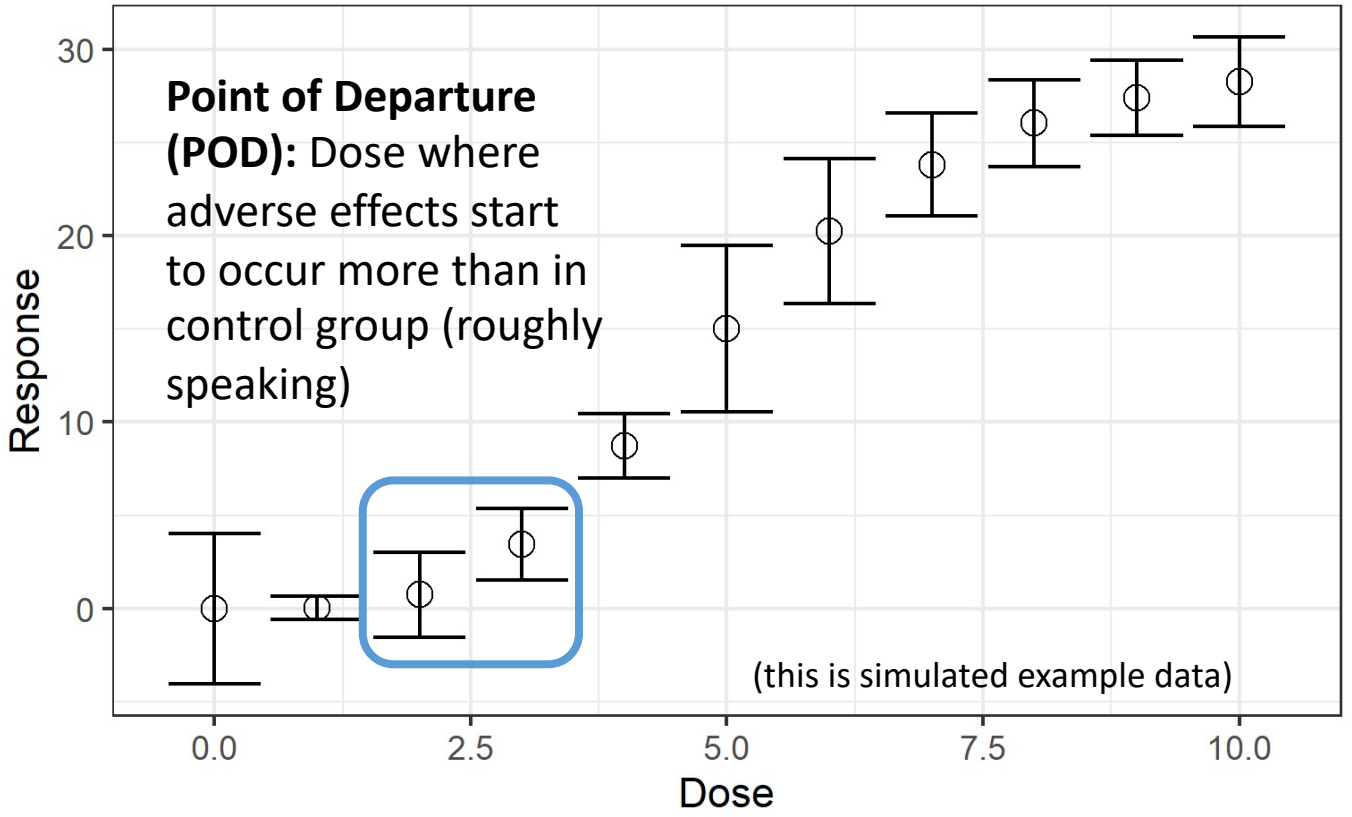
Risk: The probability of an adverse effect in an organism, system, or (sub)population caused under specified circumstances by exposure to an agent.

(Definitions adapted from IPCS Risk Assessment Terminology, 2004)

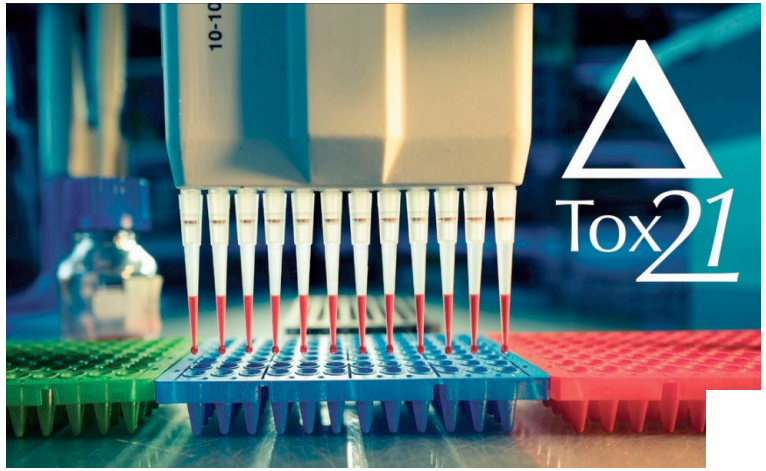
Slide adapted from John Wambaugh

Traditional hazard & dose-response data comes from studies *in vivo*, one chemical at a time

[Observe adverse effects in each dose group after days, weeks, months, or years of dosing]



New approach methodologies for hazard: *In vitro* high-throughput screening (HTS) assays, e.g. ToxCast/Tox21



Thousands of chemicals are screened in concentration-response across hundreds of *in vitro* assays for various kinds of biological activity (binding, signaling, viability…) – now with transcriptomics!

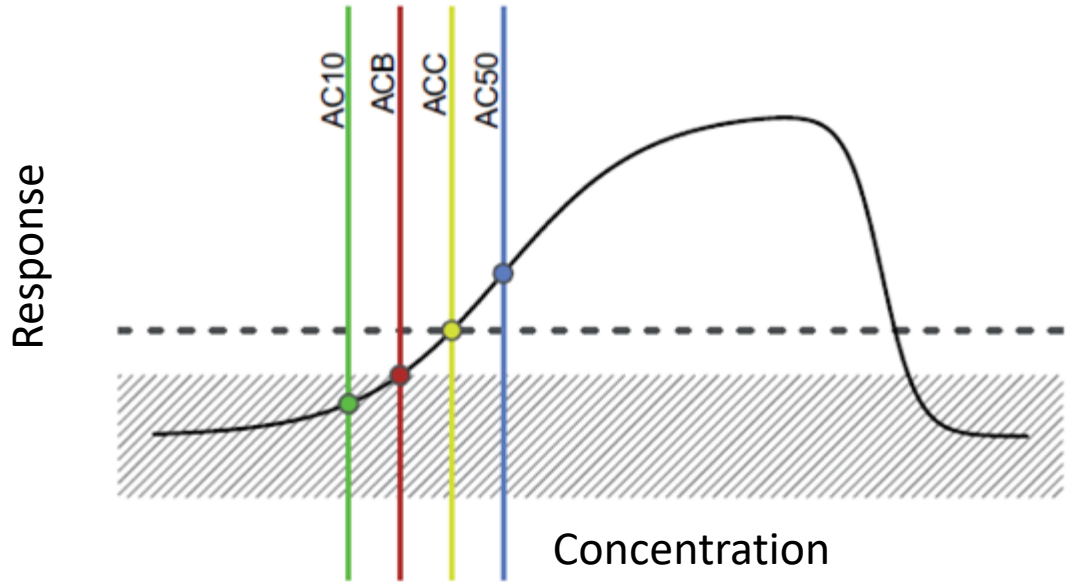
[Schmidt 2009; Dix et al. 2007; Kavlock et al. 2018; Filer *et al.*, 2016; Franzosa et al. 2021]

Data: For each chemical, ***in vitro* concentrations associated with bioactivity** in each assay, if any

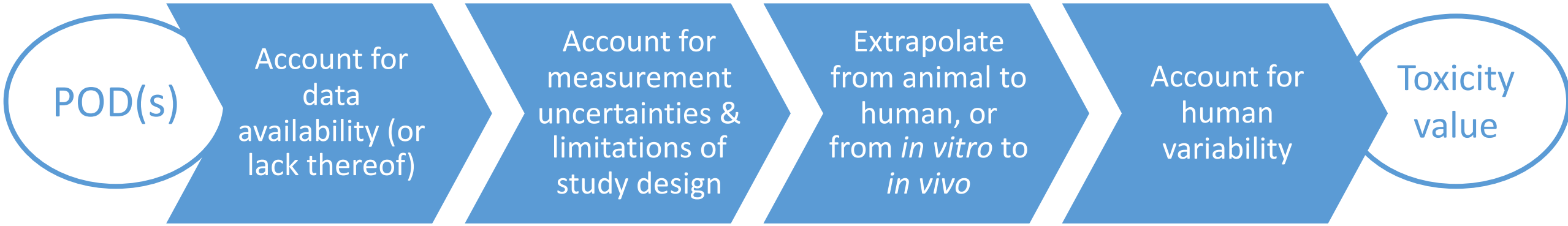
All data are public:

http://comptox.epa.gov/dashboard/

https://www.epa.gov/chemical-research/exploring-toxcast-data-downloadable-data



Hazard data is then extrapolated to develop a toxicity value: a dose below which an adverse effect is considered unlikely



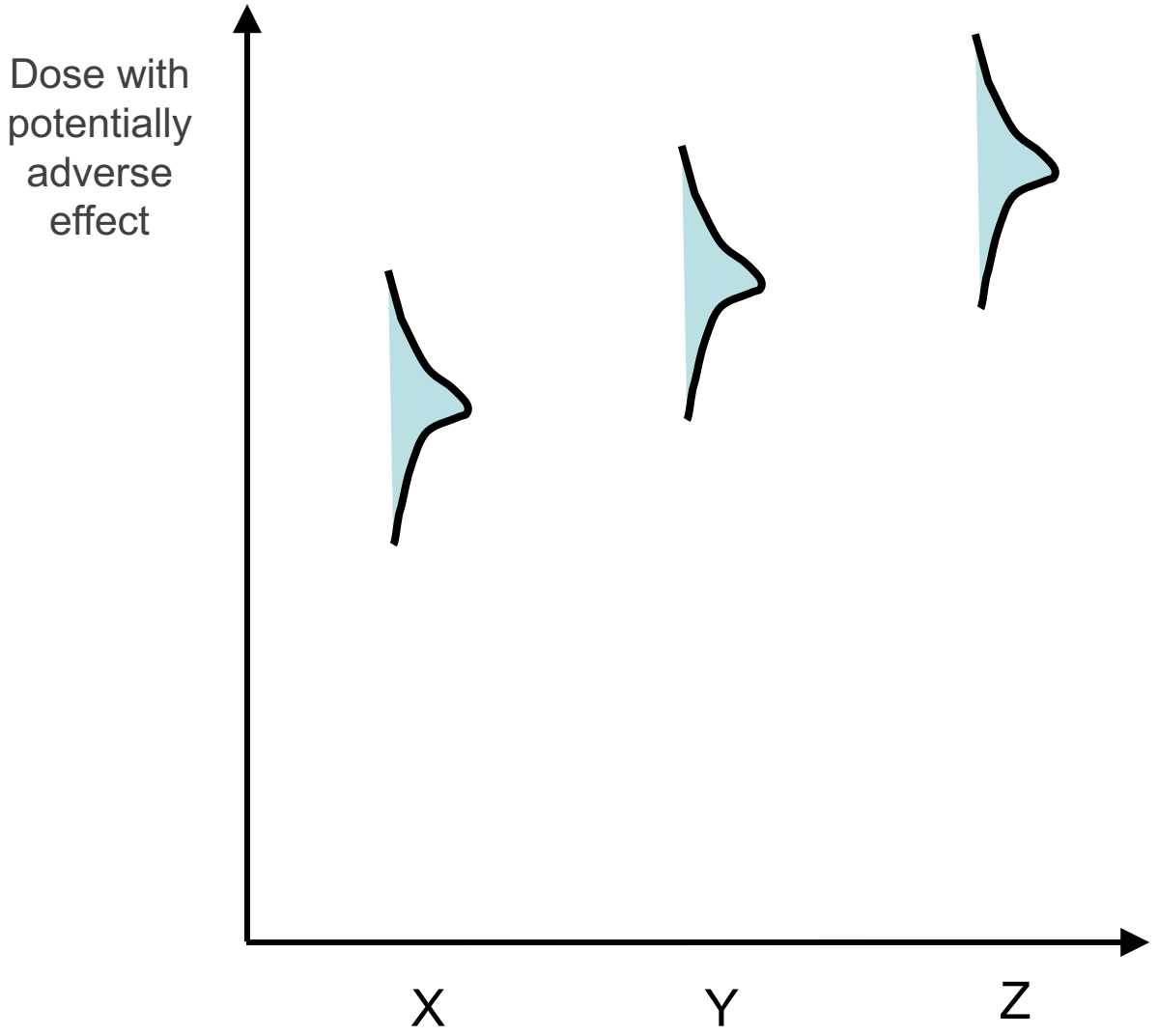
Chiu et al. (2018)
National Academies of Science (2009)
US EPA (2002)

Sometimes chemicals are ranked based on hazard/toxicity data alone

Here are some fictitious toxicity values for three chemicals, shown as distributions

Poll: Which of these three chemicals poses the greatest concern for human health?

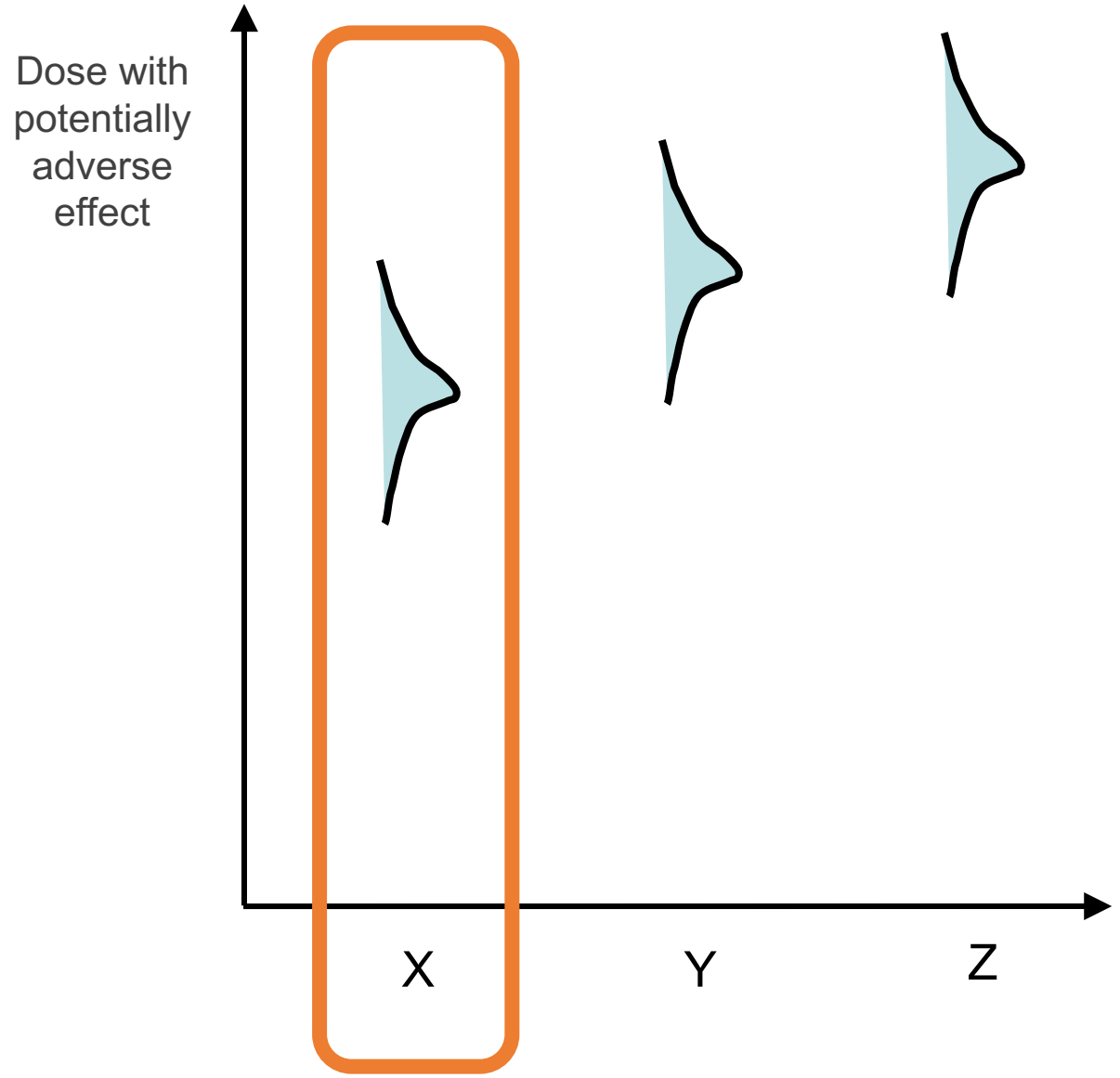
1. X
2. Y
3. Z



Sometimes chemicals are ranked based on hazard/toxicity data alone

Chemical X has the lowest toxicity value, meaning it's the most potent (produces adverse effects at the lowest dose).

But does that make it the most concerning?

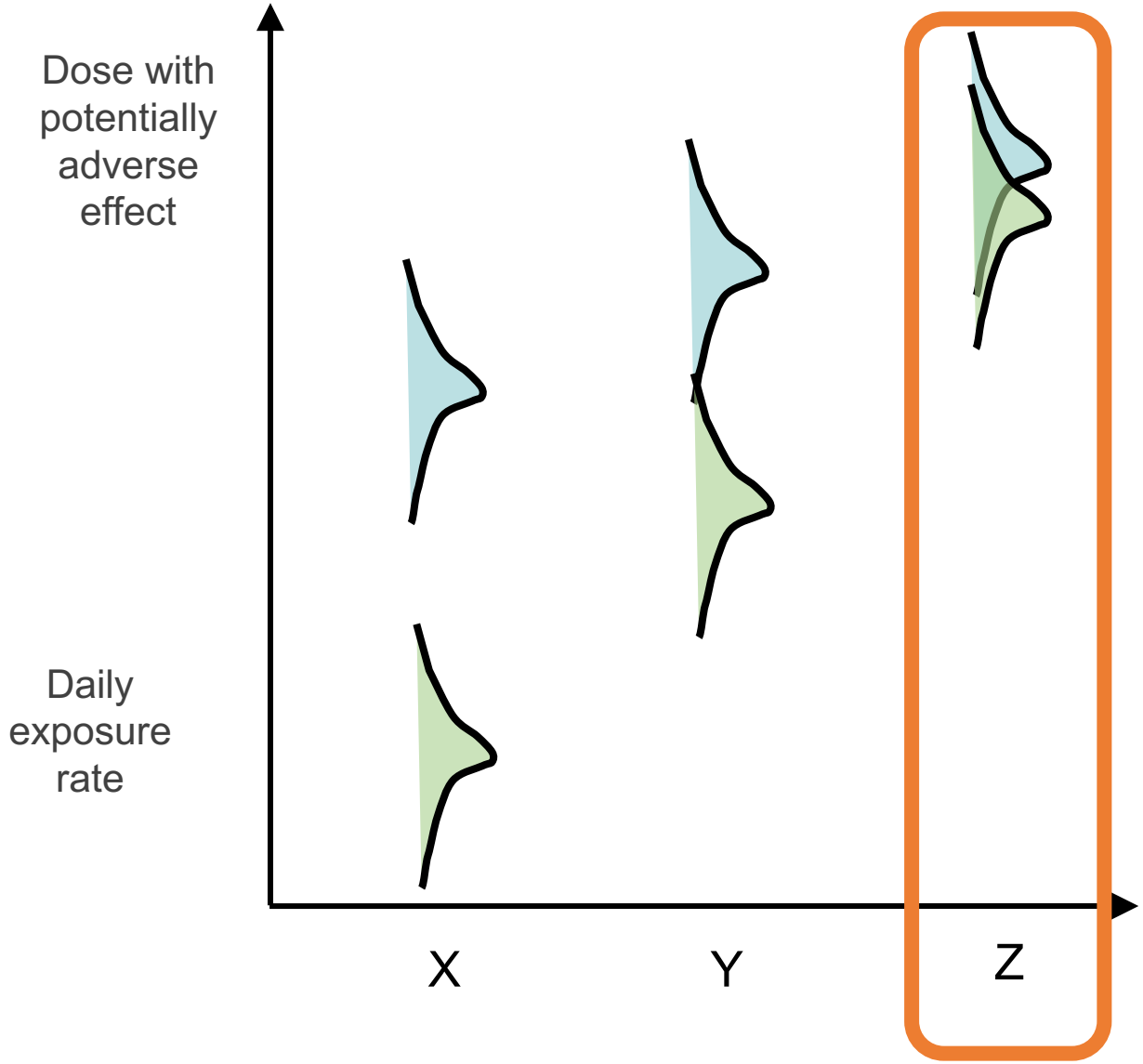


But “the dose makes the poison”: hazard/toxicity needs to be put in the context of exposure to assess risk

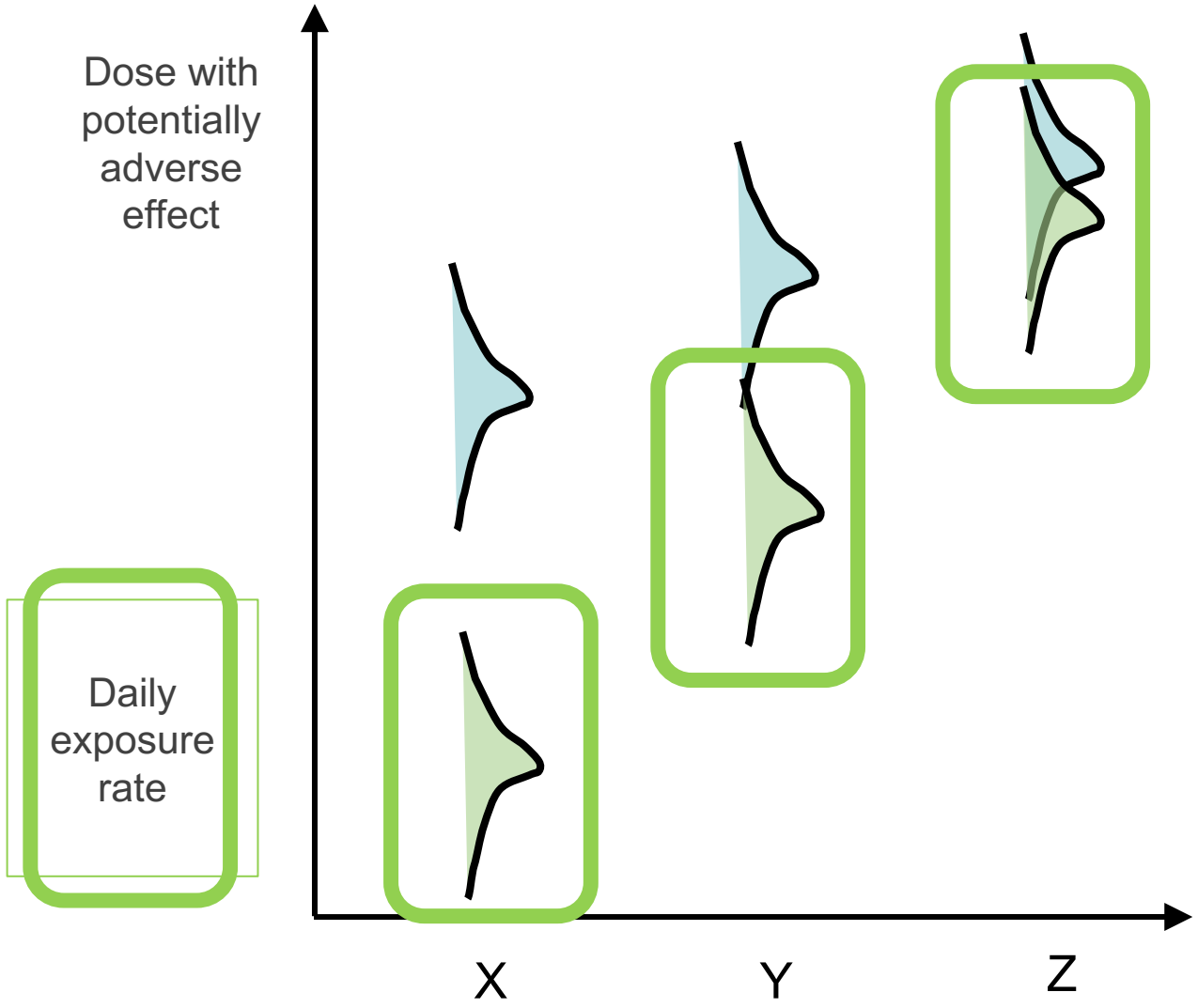
When we know exposure, **Chemical Z** is actually the most concerning!

“Margin of exposure” (MOE) approach:
MOE = Potentially hazardous dose/Estimated exposure

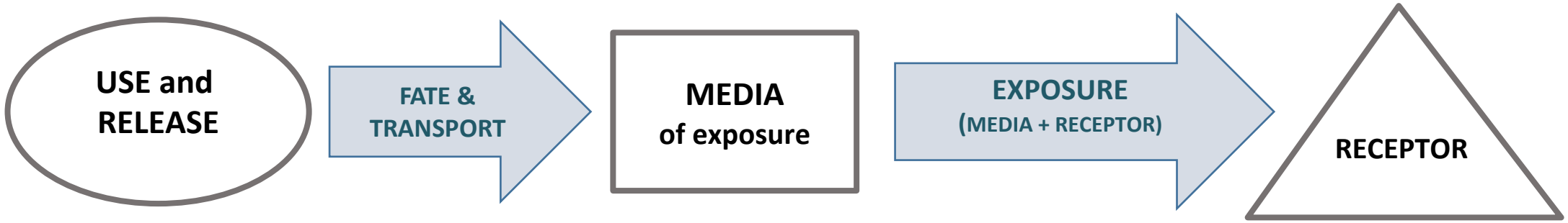
Higher MOE = less potential risk
(specific MOE thresholds exist for specific regulatory risk-assessment contexts!)



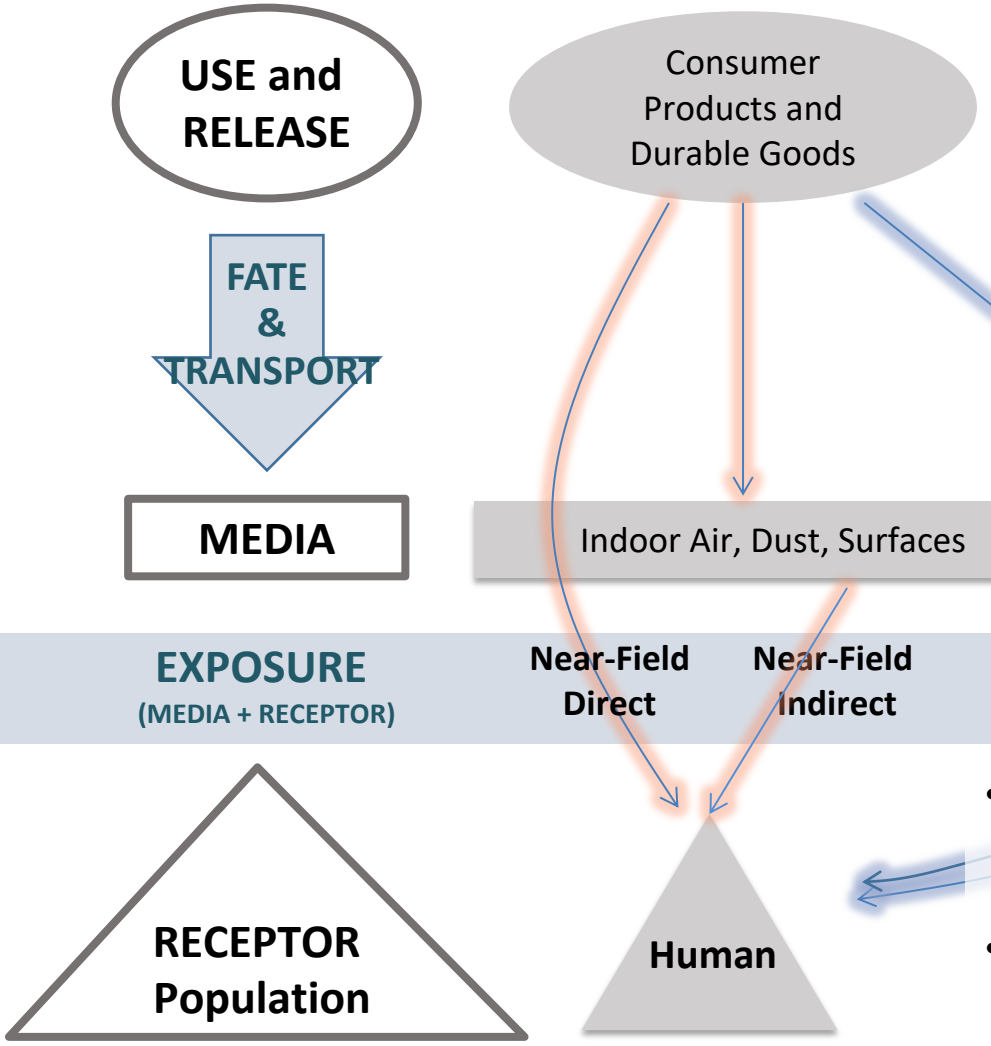
So how do we get information about exposure?



Exposure is assessed by tracing a chemical from its source (where it is released) to where a “receptor” (a person, animal, or plant) interacts with it



Example: Human exposures from consumer products

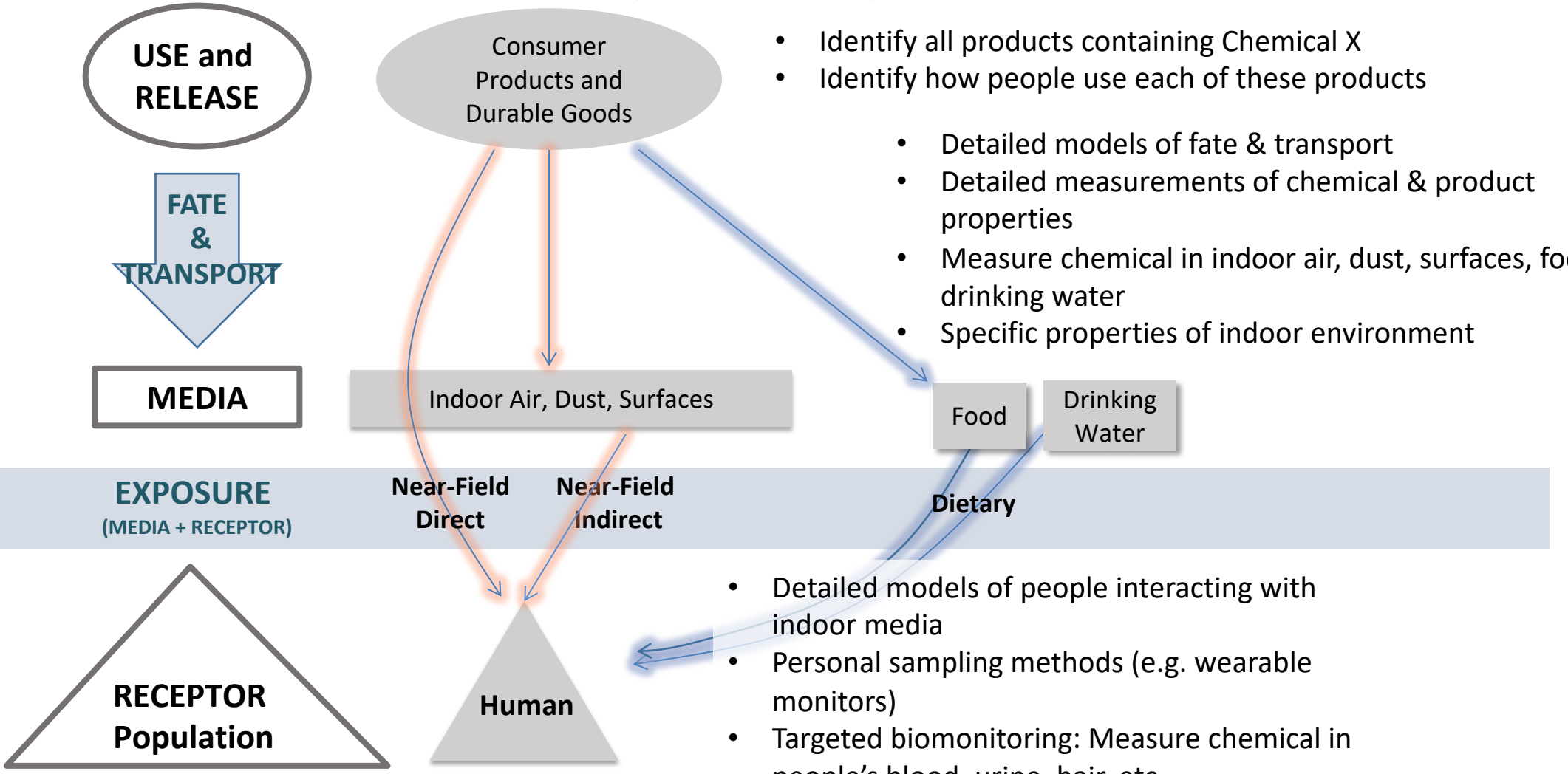


- How much of what chemicals are in which consumer products & articles?
- How do people use these products? (Frequency, duration, amount; is it sprayed, poured, rinsed off, etc.?)

- How does the chemical move through the indoor environment?
  - Indoor media monitoring
  - Indoor fate & transport modeling
  - Physical properties of product, chemical, indoor environment

- How do people interact with the indoor environment? (Inhalation rate, dust ingestion, dietary intake, etc.)
- What chemicals are found in people's bodies?

Traditional exposure assessment: Gather detailed data for one chemical at a time, in specific exposure scenarios

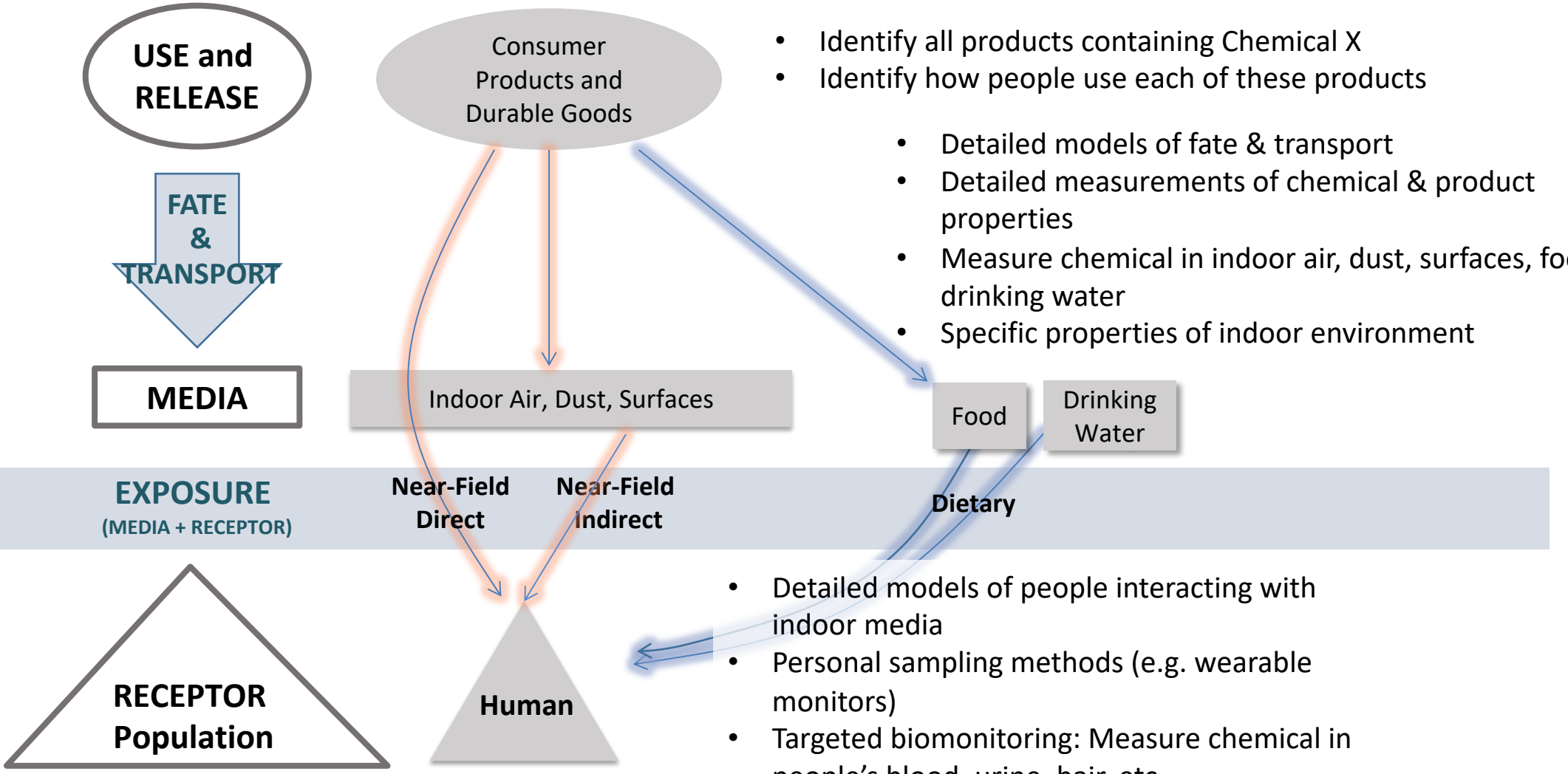


- Identify all products containing Chemical X
- Identify how people use each of these products

- Detailed models of fate & transport
- Detailed measurements of chemical & product properties
- Measure chemical in indoor air, dust, surfaces, food, drinking water
- Specific properties of indoor environment

- Detailed models of people interacting with indoor media
- Personal sampling methods (e.g. wearable monitors)
- Targeted biomonitoring: Measure chemical in people's blood, urine, hair, etc.

Difficulty level: Get exposure data for thousands of environmental chemicals, and for the whole population



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New Approach Methodologies (NAMs) for high-throughput exposure science: EPA's ExpoCast project

ExpoCast exposure NAMs aim to inform every part of the source-to-receptor exposure model, in ways that:

- identify and address key pathways of exposure
- can be applied rapidly, to large numbers of chemicals
- leverage existing information to make predictions for data-poor chemicals
- quantify error and uncertainty in predictions
- can be used to prioritize chemicals by potential risk

Exposure NAM Class	Description	Traditional Approach
Cheminformatics	Curate & organize existing exposure data for large numbers of chemicals	Tools targeted at single chemical analyses by humans
Machine Learning	Fill data gaps using computer algorithms to make inferences based on existing data	Manual inspection of the data
Non-Targeted Measurements	Screen for hundreds of unknown chemicals in environmental media using advanced analytical & computational chemistry techniques	Targeted (chemical-specific) analyses
HTE Models	Source-to-receptor exposure models that can make predictions rapidly for large numbers of chemicals	Exposure models requiring detailed, chemical- and scenario-specific information
Consensus Modeling & Evaluation	Statistical approaches that use existing exposure data and model results for many chemicals to predict exposure for a new chemical (and evaluate predictive performance of specific HTE models)	Comparison of model predictions to data on a per chemical basis

A key early ExpoCast result (2013): Consumer product exposures are an important pathway

Binary indicator for indoor/consumer use — *all by itself* — explains ~10% of variability in exposure between chemicals.

And chemicals with indoor/consumer use had *higher* exposures.

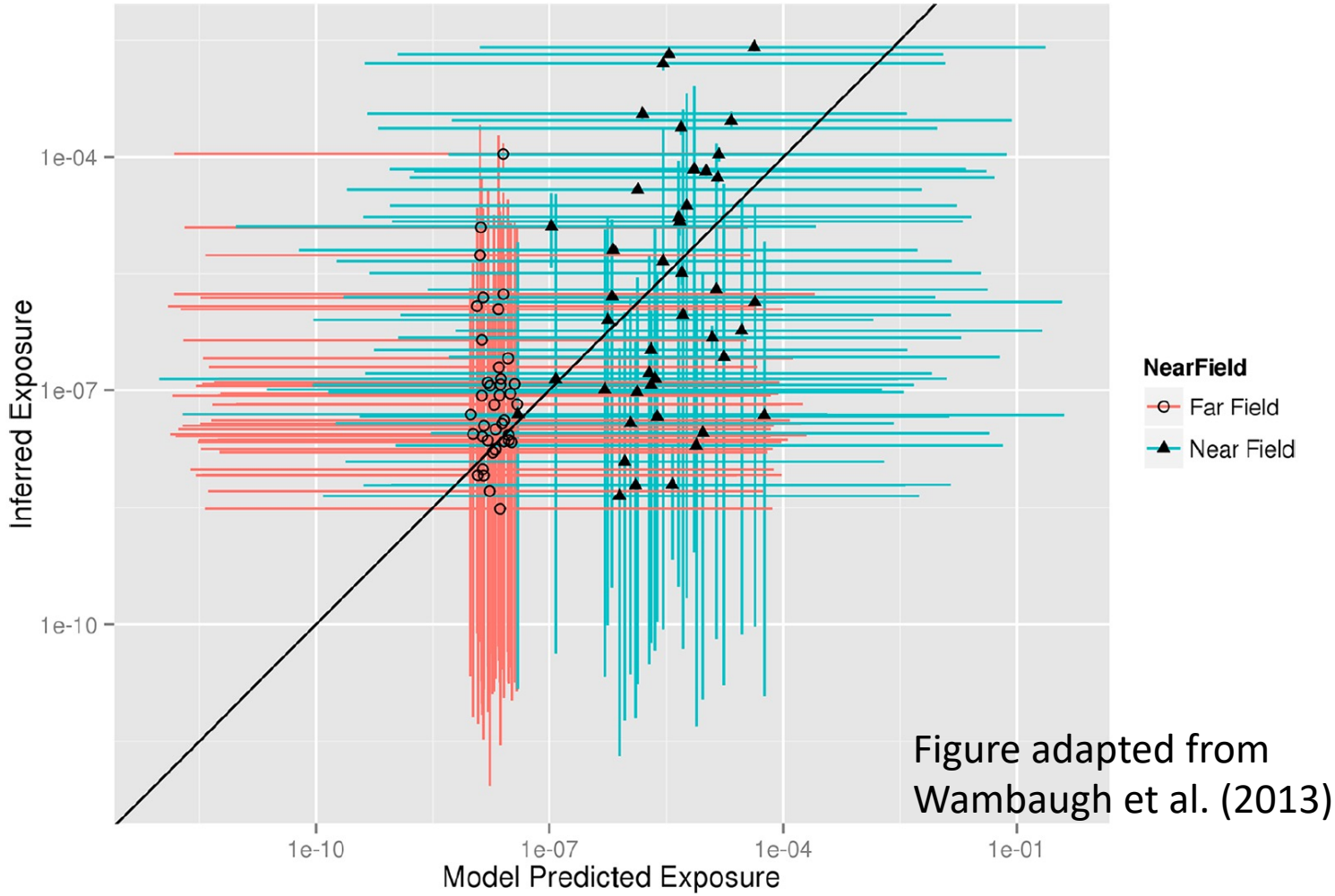
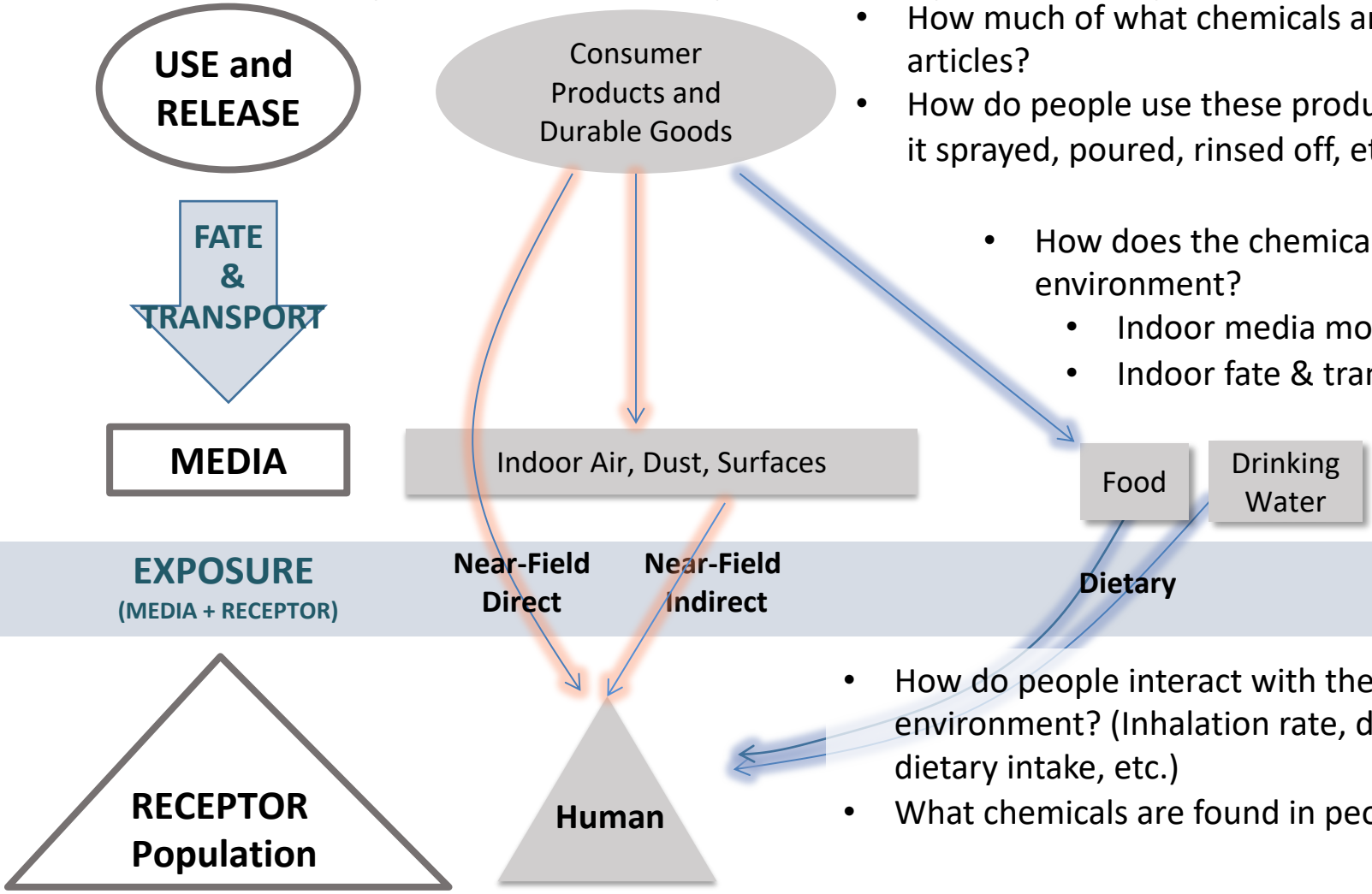


Figure adapted from Wambaugh et al. (2013)

So, many (but not all!) ExpoCast efforts have focused on consumer products exposure pathways



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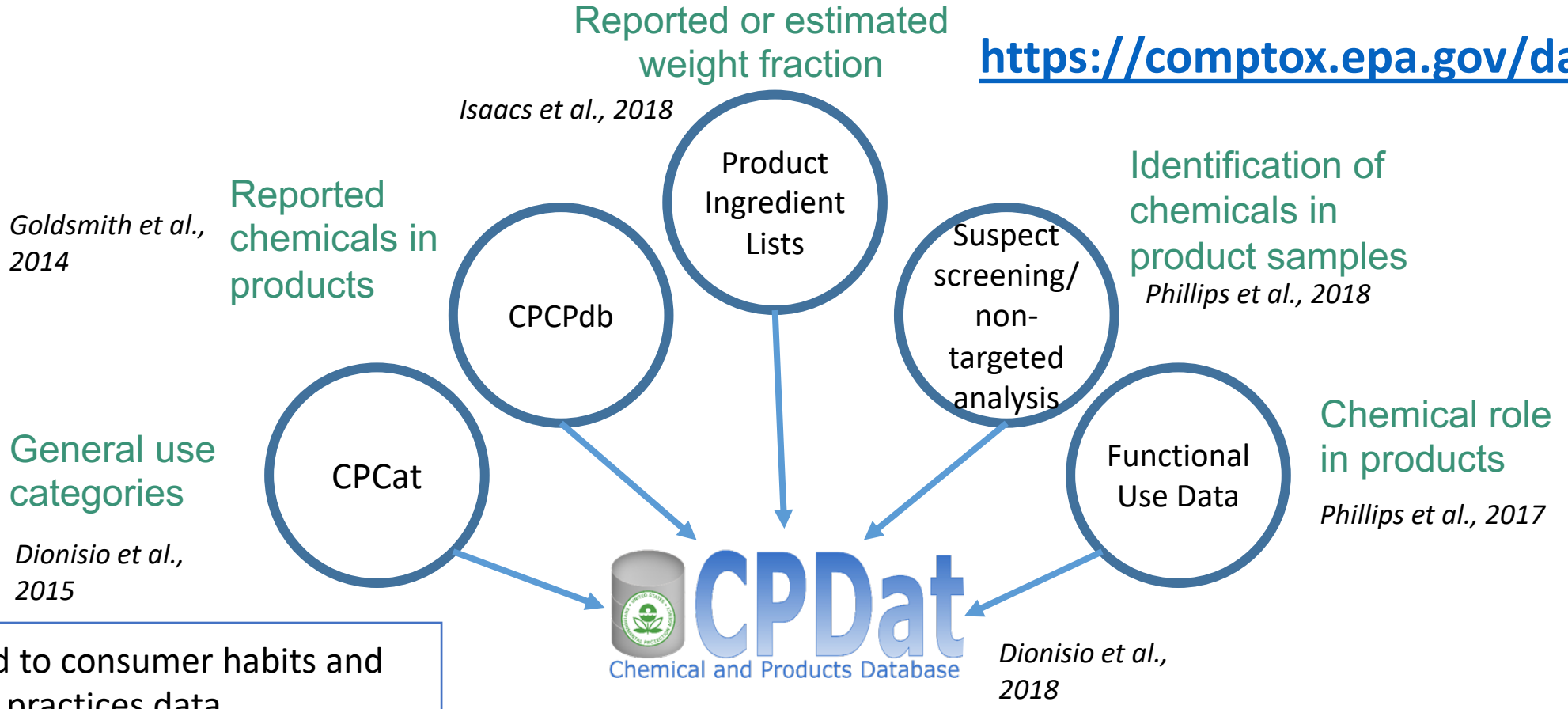
Chemical use & release for consumer products: Informatics approach to organizing existing data



https://comptox.epa.gov/dashboard

Also linked to consumer habits and practices data

Isaacs et al., 2014
Isaacs et al., 2020

- CPDat integrates heterogeneous data on many chemicals & products from many different sources
- Makes these data machine-readable, batch-searchable
- Rapidly informs chemical use for consumer exposure scenario

Chemical use: For chemicals without consumer product use data: predict unknown functional uses with machine learning

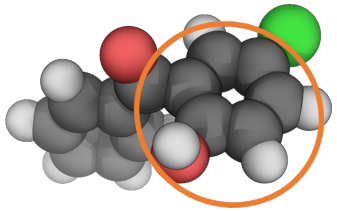
Chemical Functional Use Database (FUSE)

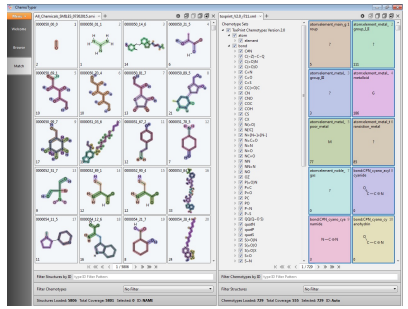
https://comptox.epa.gov/dashboard

Positive Examples

Negative Examples

Chemical Structure and Property Descriptors





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

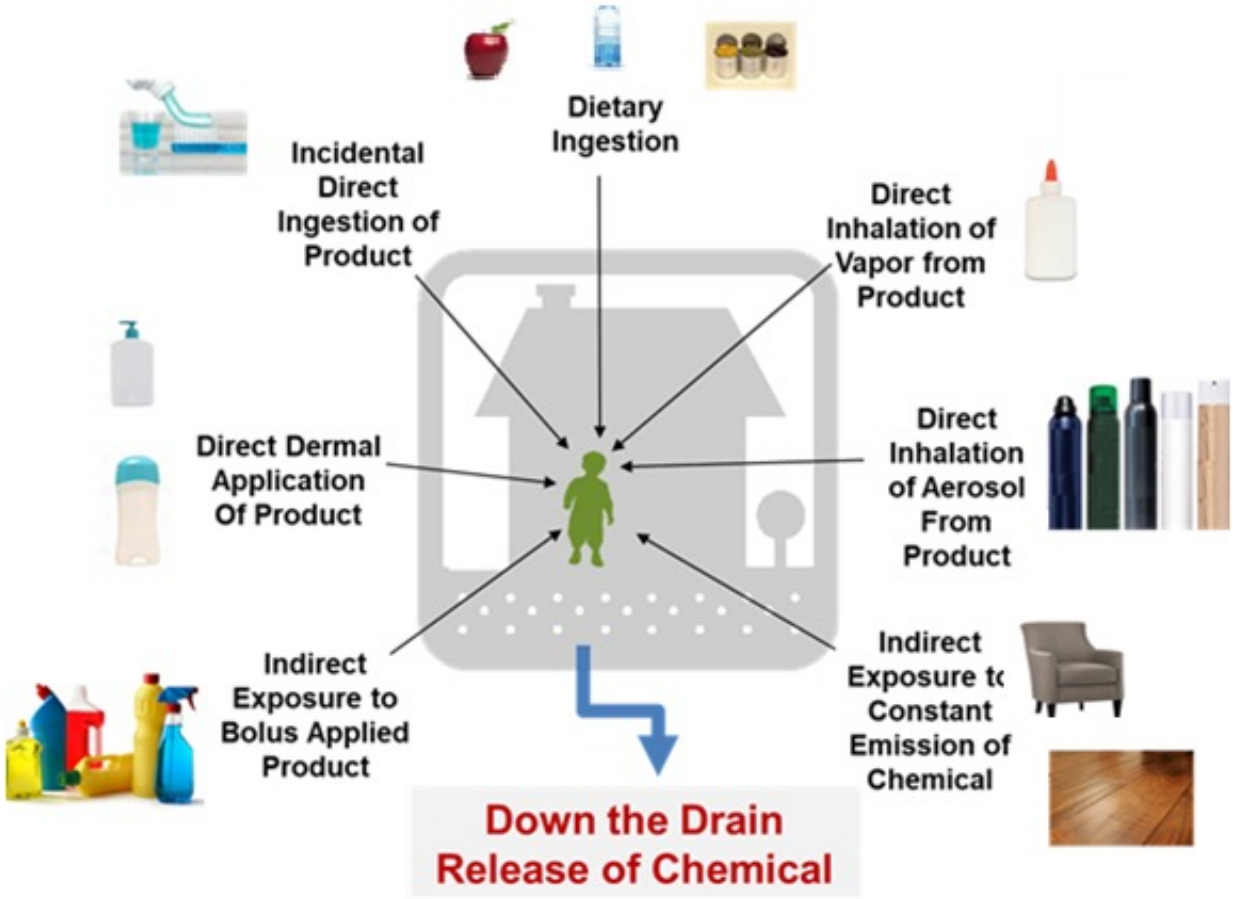
Successful Model

Failed Model

Probabilistic Predictions of Potential Chemical Uses
(including whether in consumer products)

Phillips *et al.* (2017)

Modeling exposure from source to receptor: SHEDS-HT: a high-throughput population consumer exposure model (Isaacs et al., 2014)



- Chemical use data from CPDat
- Data on population variability in consumer habits & practices from literature
- Data on population variability in diet from CDC NHANES (national dietary survey data) (https://www.cdc.gov/nchs/nhanes/index.htm)
- Data on population daily activities from EPA CHAD (https://www.epa.gov/fera/consolidated-human-activity-database-chad)
- Available as R package 'ShedsHT' **https://github.com/HumanExposure/SHEDSHTRPackage**

Non-Targeted Analysis: Which chemicals are found in consumer products? In indoor environmental media? In humans?

(Sobus et al., 2018; Ulrich et al., 2019)

Source and Release

Pilot: 20 Consumer Product Categories

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

Recycled Consumer Materials

Lowe *et al.*, *2018*

Consumer Product Emissions from Different Substrates

Fate and Transport

Residential Air

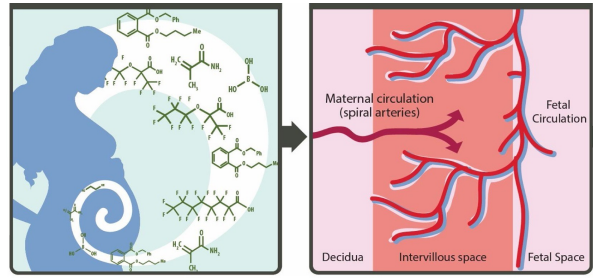
Residential Dust

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

Exposure

Pooled Human Blood

Human Placenta



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

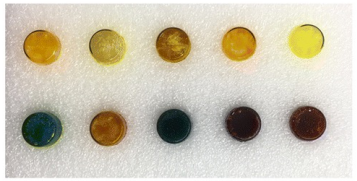
Slide adapted from Kristin Isaacs

Non-targeted Measurement NAM: EPA's Non-Targeted Analysis Collaborative Trial (ENTACT)

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

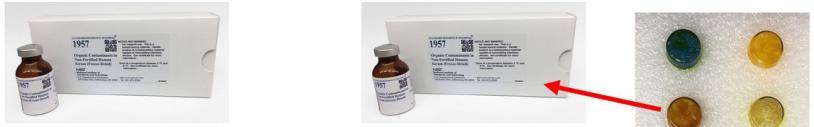
Round-robin collaborative trial: many different labs test their NTA methods

Part 1. Ten ToxCast mixtures



Part 2. Three standardized exposure relevant extracts

Unaltered Fortified

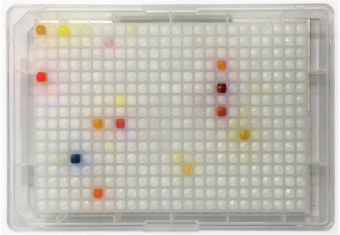


NIST SRM 1957- Organic Contaminants in Non-fortified Human Serum

Oregon State University- Outdoor air exposed silicone bands

NIST SRM 2585- Organic Contaminants in House Dust

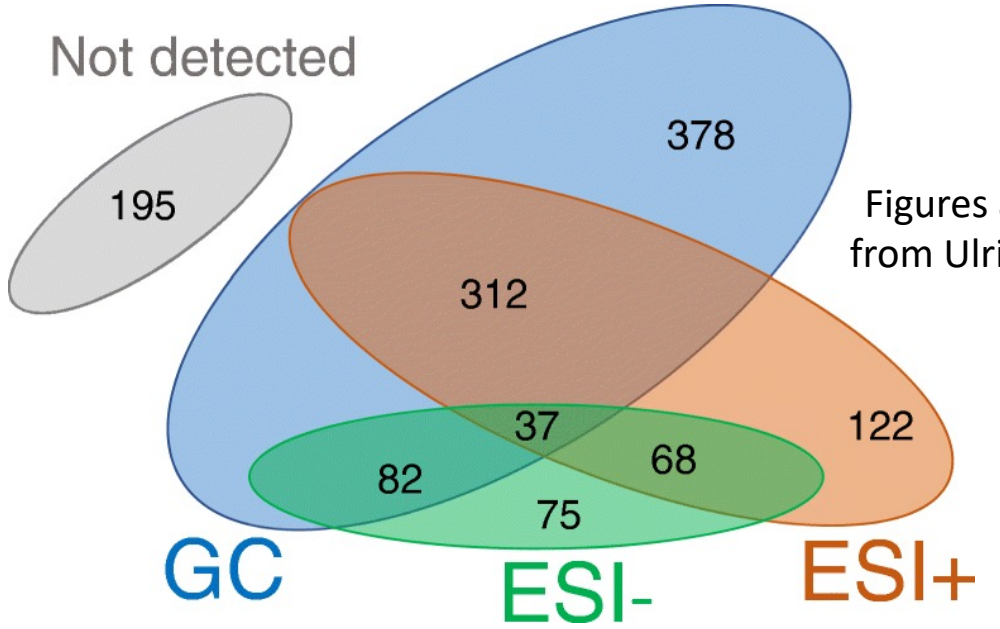
Part 3. Individual ToxCast standards



Part 1. Blinded analysis of ten mixtures of 1269 total ToxCast substances

Part 2. Blinded analysis of ToxCast mixtures spiked into environmentally relevant media (human serum, silicone wristbands, house dust)

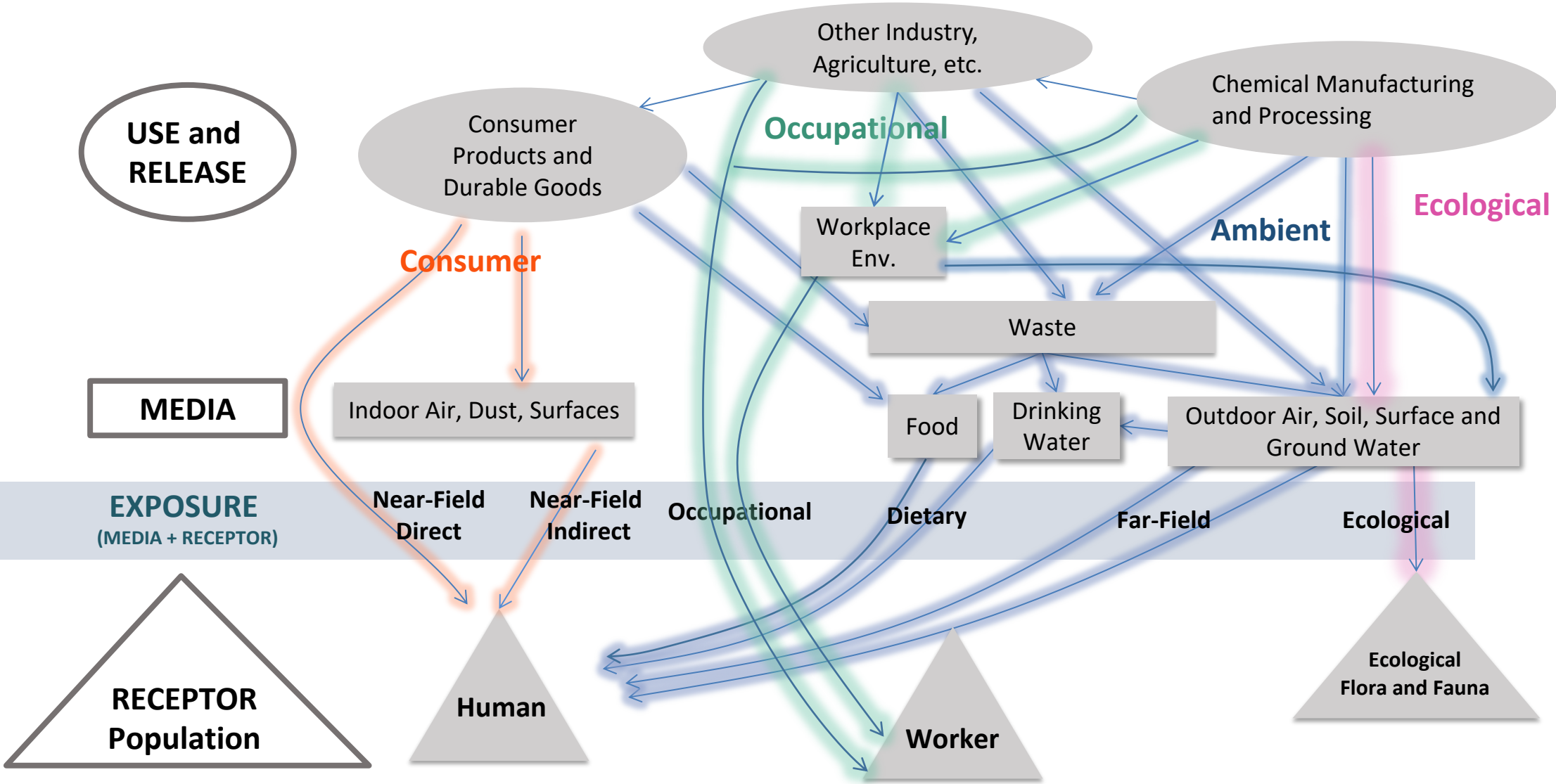
Part 3. Develop reference spectra from individual ToxCast standards



Figures adapted from Ulrich et al. (2019)

Results from Part 1: Number of ToxCast substances correctly detected by three different NTA methods

What about exposure pathways *other* than consumer/residential?



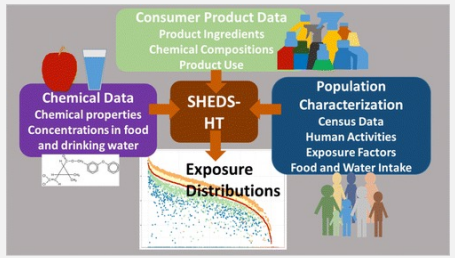
High Throughput Exposure (HTE) models can predict exposures via key pathways (for chemicals with enough data to parameterize models)

Consumer (Near-Field) Pathways

Ambient (Far-Field) Pathways

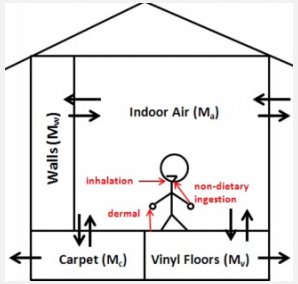
Dietary Pathways

SHEDS-HT (Isaacs et al., 2014)

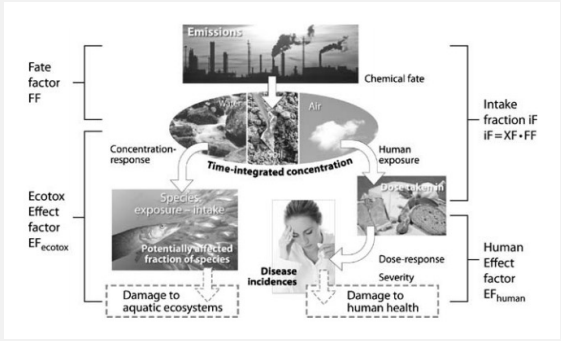


RAIDAR-ICE (Li et al., 2018)

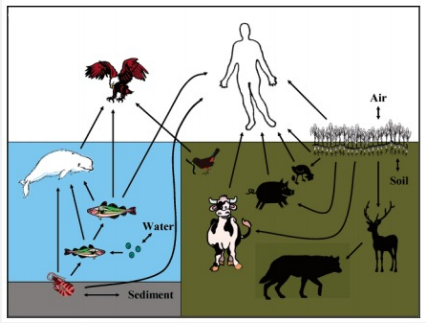
FINE (Shin et al., 2015)



UseTox (Rosenbaum et al., 2008)



RAIDAR (Arnot et al., 2006, 2008)



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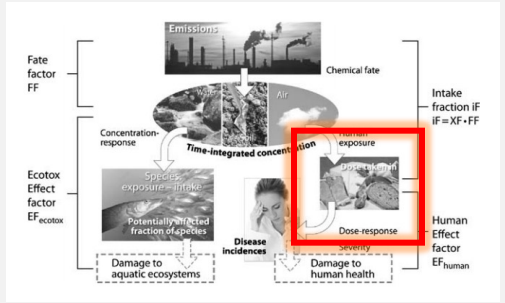
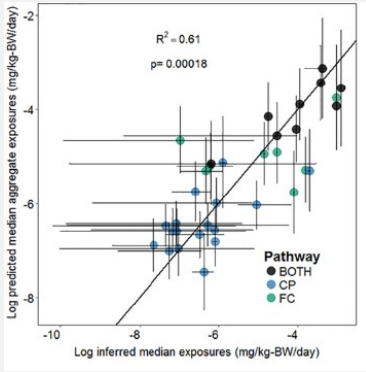


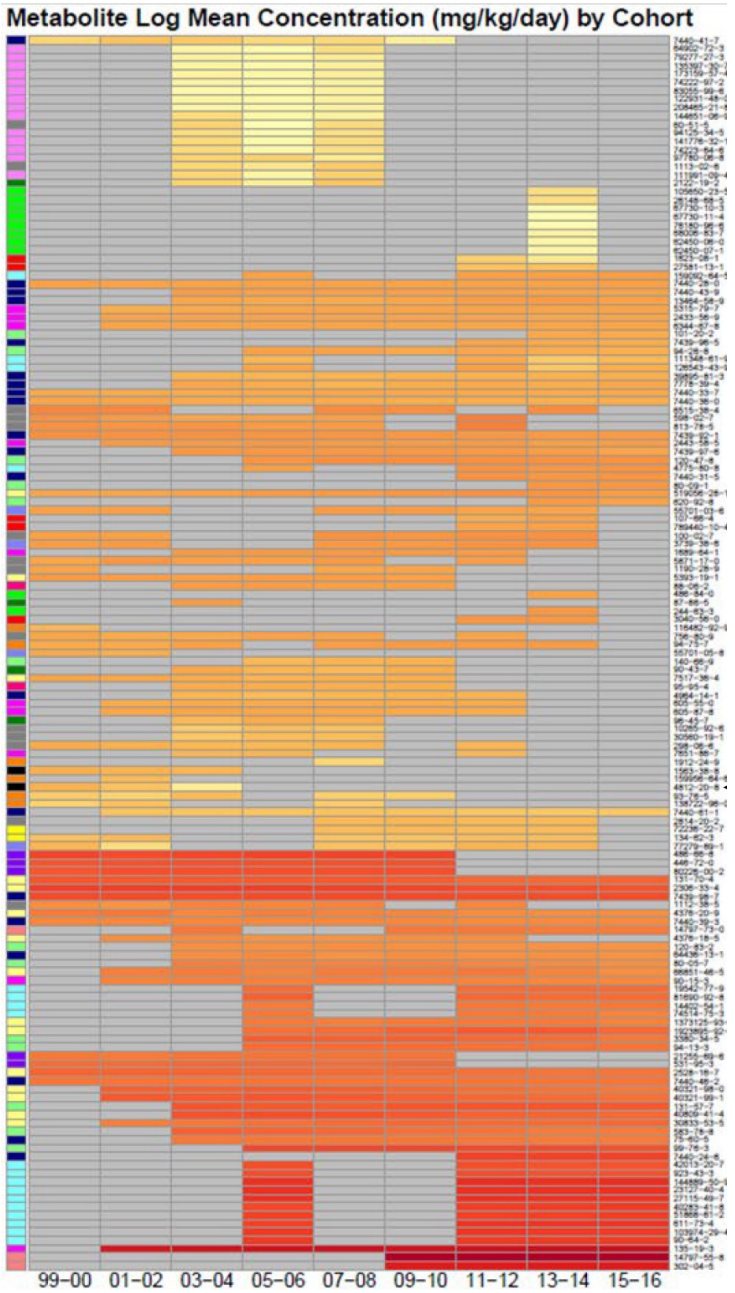
SHEDS-HT (Biryol et al., 2017)



Slide adapted from Kristin Isaacs

Aggregate exposures (over *all* pathways) can be inferred from population exposure biomonitoring

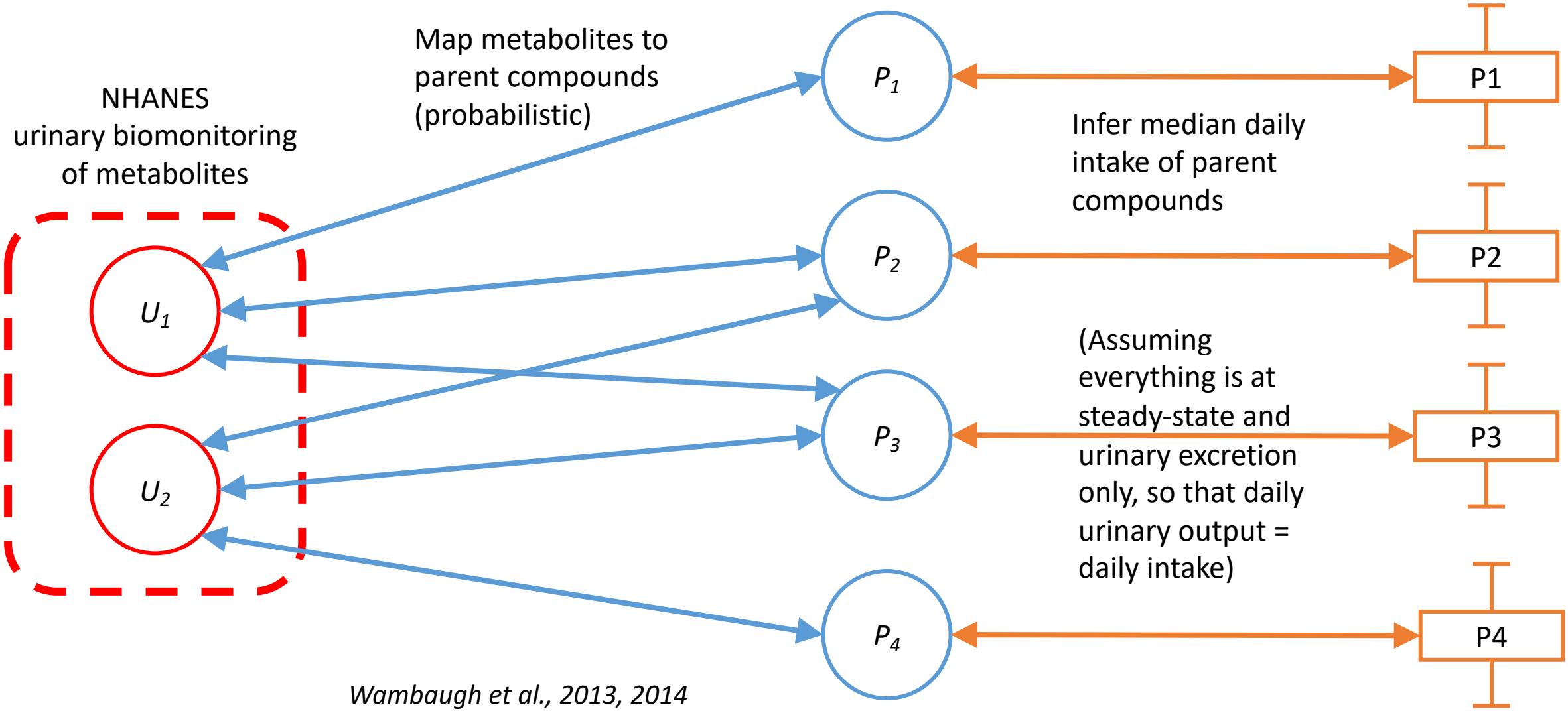
- Exposure biomonitoring measures internal body levels of various chemicals of interest, or their metabolites
  - e.g. in blood, urine, hair, breastmilk, etc.
- A key source of exposure biomonitoring data is CDC NHANES (National Health & Nutrition Examination Survey)
  - Large-scale, nationally-representative survey of US population
  - 2-year cycles: starting in 1999, most recent published data 2016
- NHANES gathers various health & nutrition data
  - Previously mentioned: dietary intake survey (used in SHEDS-HT model)
- Including urine levels of 151 metabolites (mapping to 179 possible parent chemicals) [see figure at right!]
- All data publicly available (anonymized) at https://www.cdc.gov/nchs/nhanes/index.htm



Wambaugh et al., 2013, 2014; Stanfield et al., in prep

Figure courtesy of Dr. Zachary Stanfield

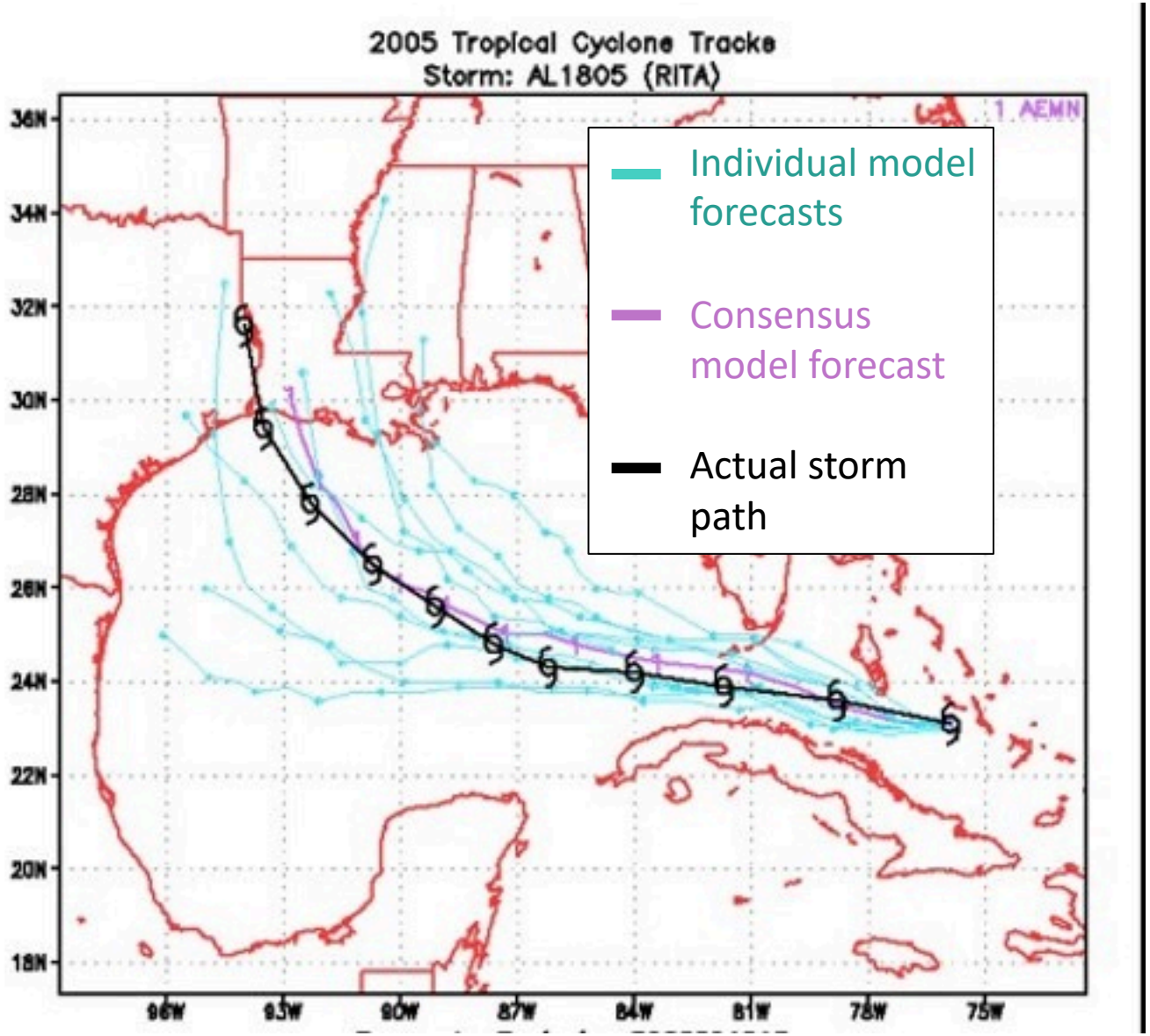
ExpoCast work: Bayesian inference of external exposures from internal biomonitoring data



Wambaugh et al., 2013, 2014
Stanfield et al., 2021

We can integrate all of these exposure models and data sources into a *consensus model* for aggregate exposure!

- Consensus models may be familiar from weather forecasting: e.g. predicting hurricane paths
- Consensus models essentially *average* the individual model predictions
- A *weighted* average can be used to correct for model biases
  - e.g. a model that usually predicts a path too far west
  - e.g. a model that usually over-predicts storm intensity
- We can make an analogous consensus model for aggregate human daily intake!

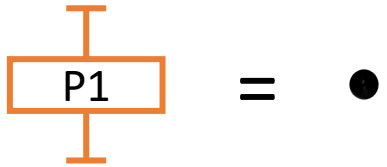


http://www.hurricanescience.org/science/forecast/models/modeltypes/ensemble/

SEEM3: A consensus model for aggregate exposure

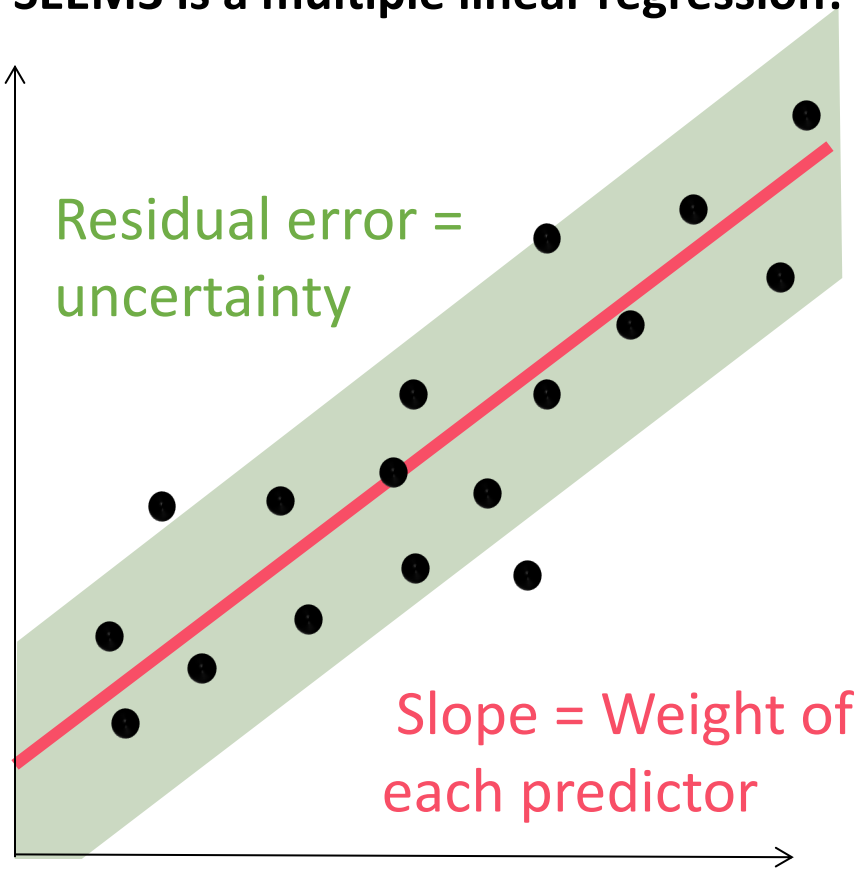
SEEM3 = Systematic Empirical Evaluation of Models, version 3
Ring et al. (2019)

Train model on inferred exposures from NHANES biomonitoring data



Bayesian inference = *Probabilistic* estimates of intercept, slopes, and uncertainty

SEEM3 is a multiple linear regression!



Intercept = Exposure when all predictors at mean value

Exposure Predictors:

- Predictions of HT exposure models (USETox, RAIDAR, FINE, SHEDS-HT…)
- Chemical production volume (U.S.)
- Existing EPA pesticide exposure assessments
- Presence on Stockholm Convention list of banned persistent organic pollutants

Missing predictor data: Impute mean

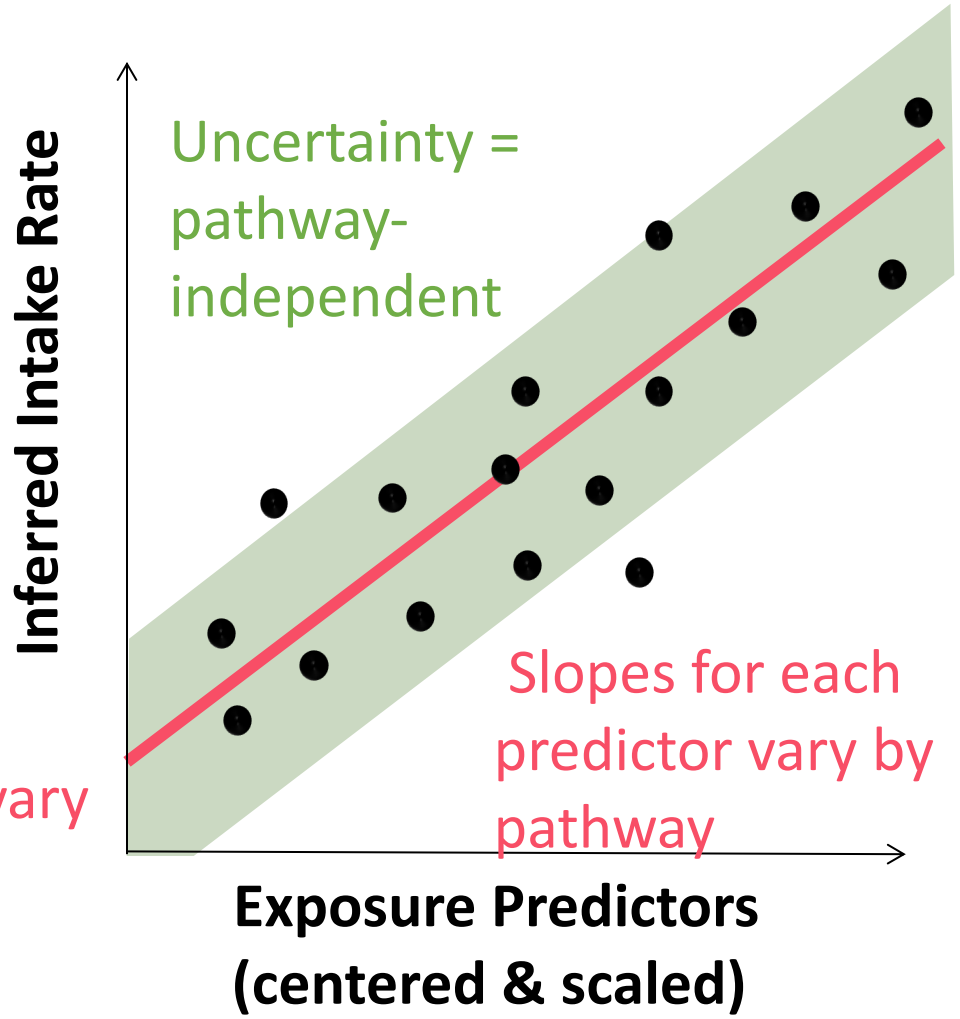
SEEM3 includes pathways of exposure

Ring et al. (2019)

Machine-learning model (random forest) predicts **exposure pathway probability** for each chemical:

- Consumer
- Dietary
- Industrial
- Pesticide

based on chemical structure & properties



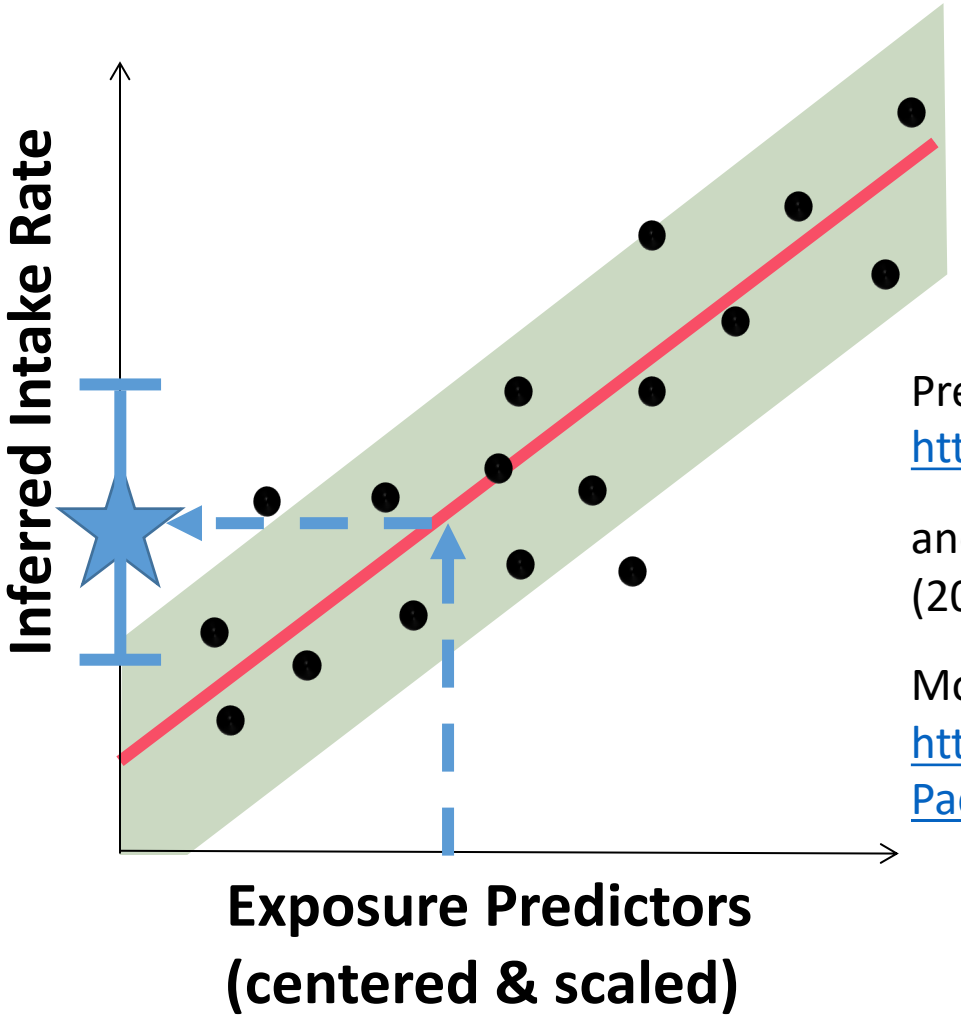
Pathway-specific weights (slopes) for each predictor = predictive strength of that predictor for that pathway

(hence the “evaluation of models” in the SEEM3 name)

SEEM3 can *predict* median exposures for data-poor chemicals – and quantify uncertainty in the predictions

There are SEEM3 predicted median exposures for 687,359 chemicals!

(Every compound with a structure in DSSTox library as of 2018)



Predictions available on https://comptox.epa.gov/dashboard

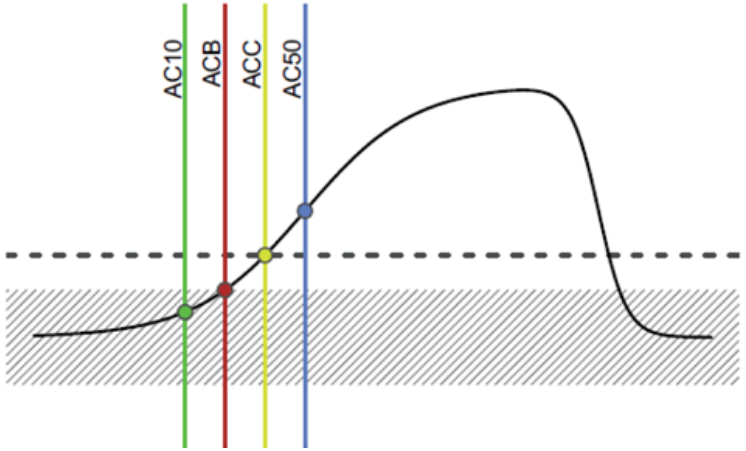
and as Supplemental Material to Ring et al. (2019)

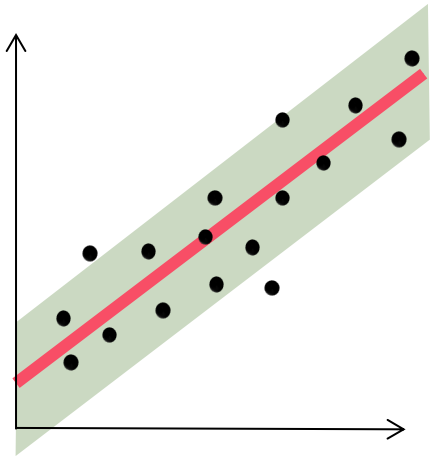
Model available as R package: https://github.com/HumanExposure/SEEM3RPackage

EPA United States Environmental Protection Agency

Web demonstration: How to find exposure data and predictions on the CompTox Chemicals Dashboard

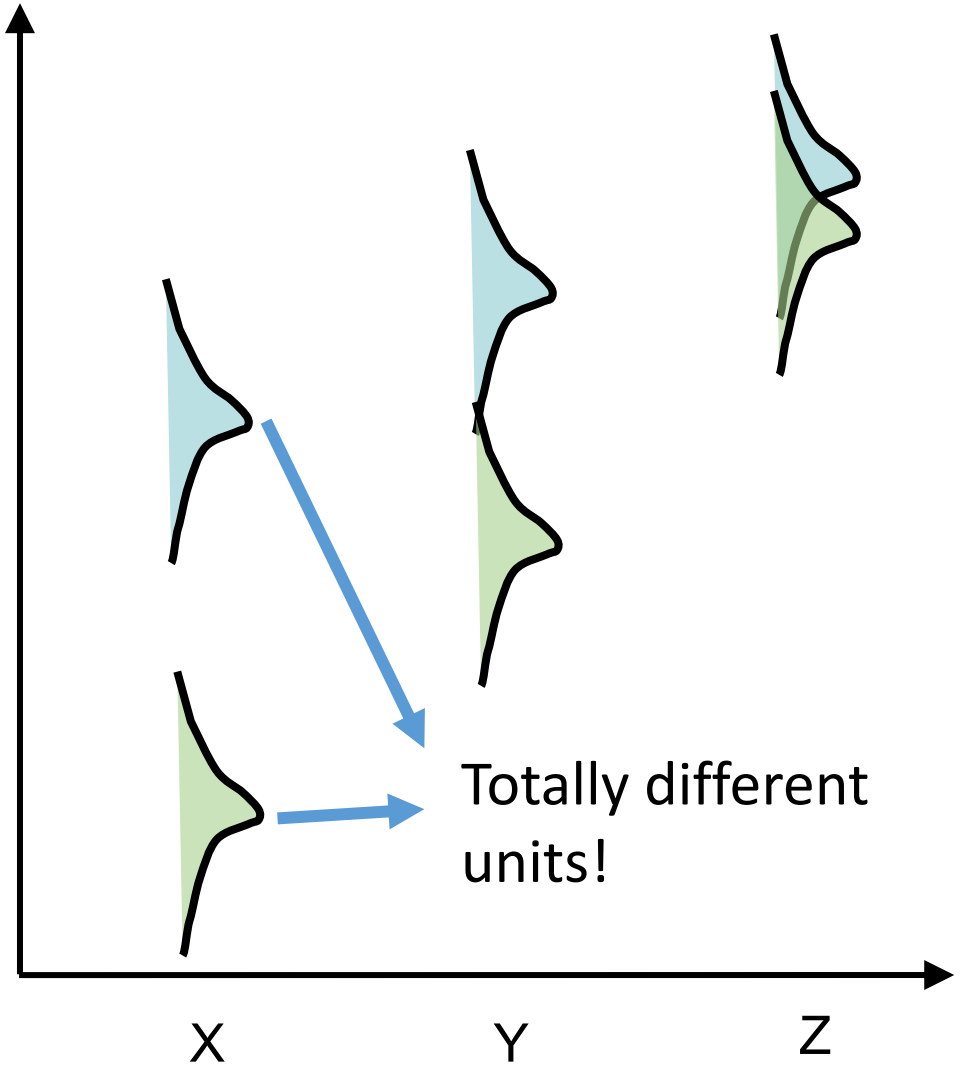
So, we can predict exposures using all of these clever computational tools. But how does that help us when we have *in vitro* hazard data only in the form of *in vitro* bioactive *concentrations?*



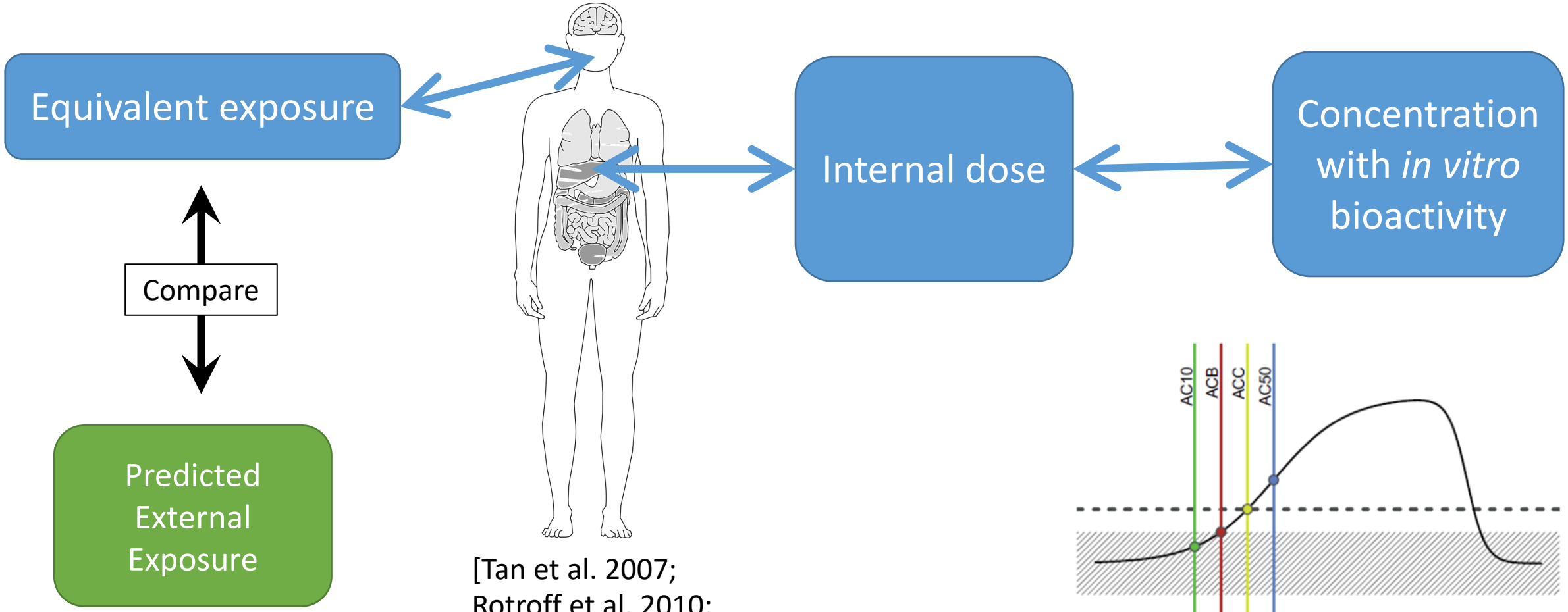


Concentration bioactive *in vitro* (uM)

Daily exposure rate (mg/kg/day)

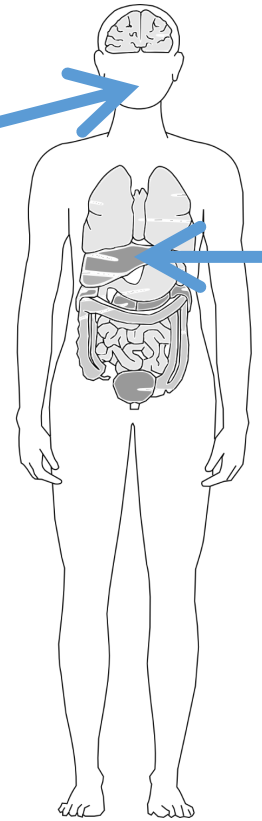


Need to link *in vitro* concentrations to *in vivo* exposures: *in vitro-in vivo* extrapolation (IVIVE) — and we need to do IVIVE for thousands of chemicals and the whole population!



[Tan et al. 2007;
Rotroff et al. 2010;
Wetmore et al. 2012, 2013, 2015]

Mapping between *in vitro* bioactive concentration and internal dose is a **toxicodynamics** problem



Equivalent exposure

Compare

Predicted External Exposure

Internal dose

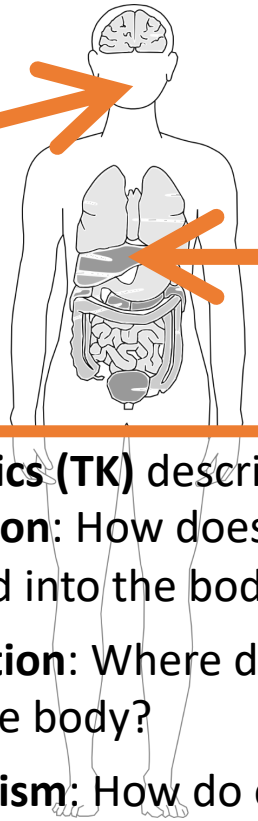
Concentration with *in vitro* bioactivity

Toxicodynamics (TD): "what the chemical does to the body"
Requires mapping *in vitro* bioactivity to *in vivo* adverse outcomes.
Lots of work is being done on this, but it's a hard problem.

For screening, we often just assume *in vitro* concentration = internal dose.

Mapping between internal dose and external exposure is a **toxicokinetics** problem

Equivalent exposure



Internal dose

Concentration with *in vitro* bioactivity

Compare

Predicted External Exposure

Toxicokinetics (TK) describes **ADME:**

- **Absorption**: How does the chemical get absorbed into the body tissues?
- **Distribution**: Where does the chemical go inside the body?
- **Metabolism**: How do enzymes in the body break apart the chemical molecules?
- **Excretion**: How does the chemical leave the body?

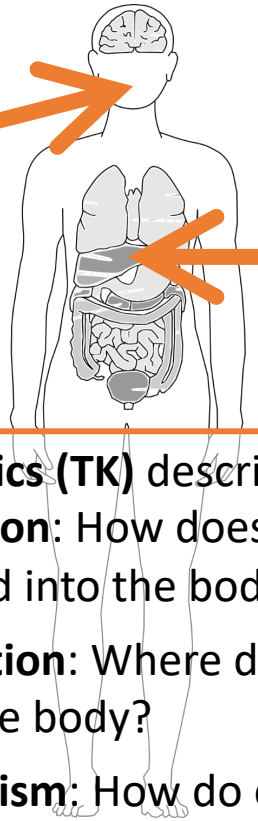
[Tan et al. 2007;
Rotroff et al. 2010;
Wetmore et al. 2012, 2013, 2015]

Mapping between internal dose and external exposure is a **toxicokinetics** problem

Equivalent exposure

Compare

Predicted External Exposure



Internal dose

Concentration with *in vitro* bioactivity

Toxicokinetics (TK) describes **ADME:**

- **Absorption**: How does the chemical get absorbed into the body tissues?
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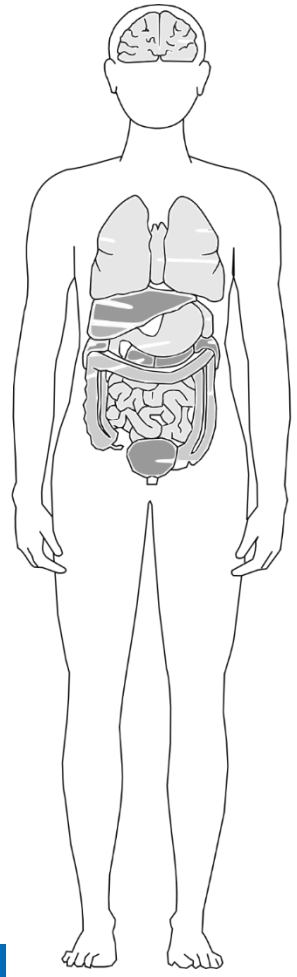
- **Excretion**: How does the chemical leave the body?

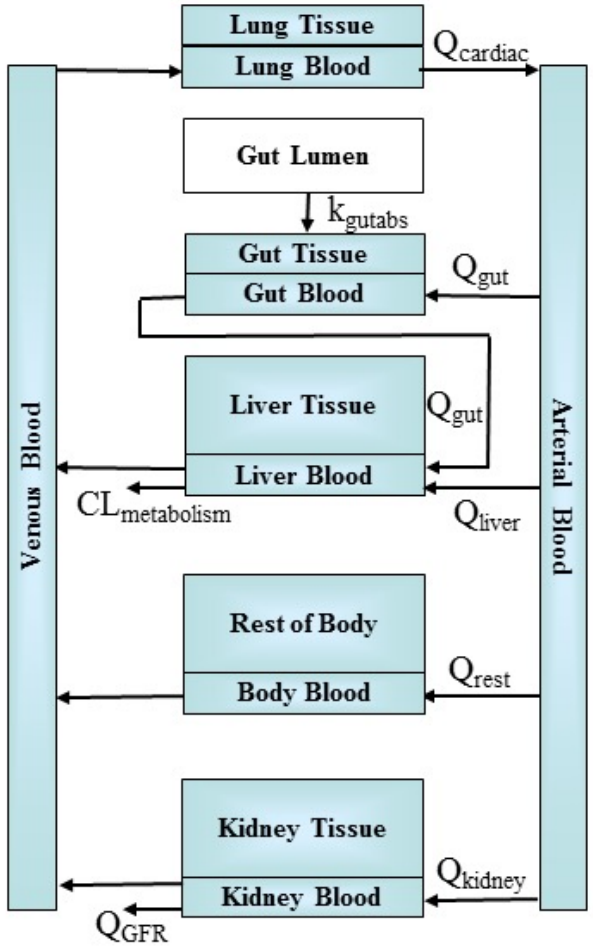
Reverse TK: Go from internal dose "backwards" to find corresponding exposure

[Tan et al. 2007;
Rotroff et al. 2010;
Wetmore et al. 2012, 2013, 2015]

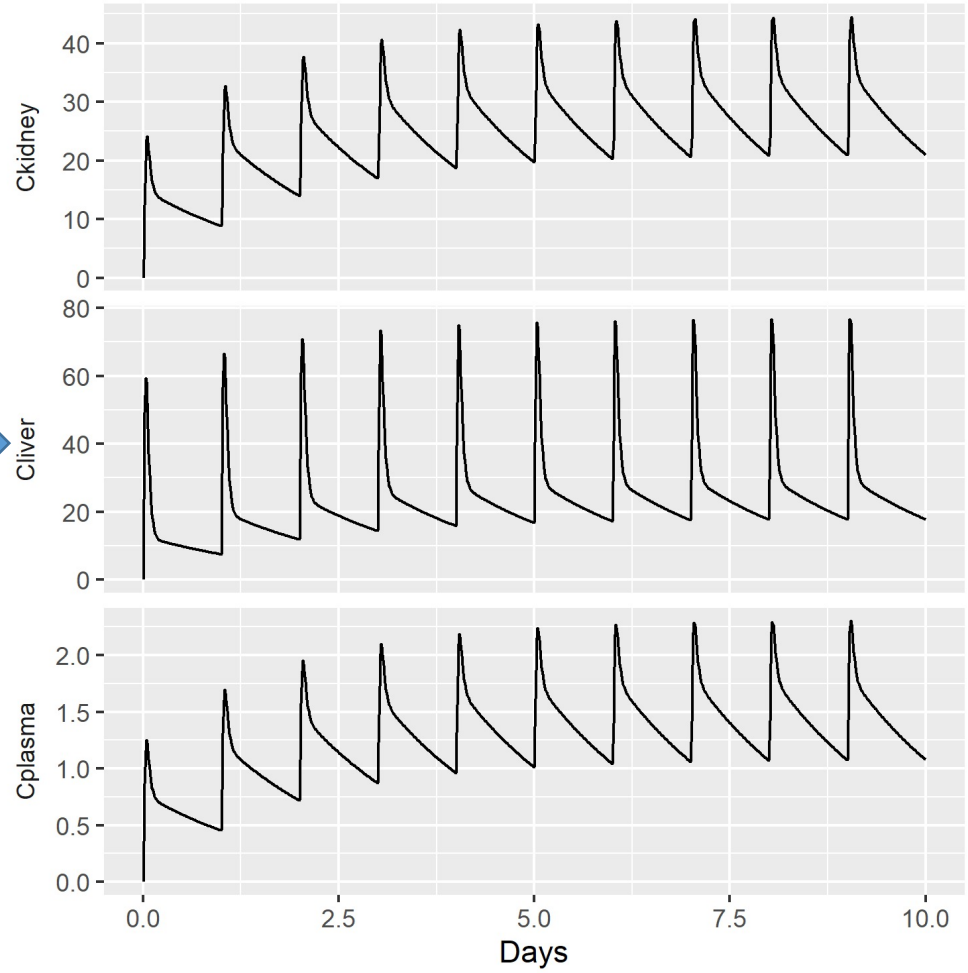
TK models describe ADME mathematically



Body as mass-balance system
Defined by parameters describing ADME



Concentration vs. time in each compartment



High-throughput IVIVE (rapid, for thousands of chemicals) requires *high-throughput* TK (HTTK)

Characteristics of HTTK model:

- **Generic:** same model structure can be applied to all chemicals
- **Minimal chemical-specific TK parameters**
  - Only describe the most important chemical-specific ADME processes
  - Can only run model for chemicals where we know these parameters — so the fewer chemical-specific parameters, the more chemicals we can run
- **Chemical-specific TK parameters that can be measured *in vitro* or predicted *in silico*,** rather than having to be measured *in vivo*
  - Use existing *in vitro* experimental methods to measure TK parameters – pharmaceutical industry has been working on this for years
- **Not too computationally intensive:** Feasible to solve rapidly for thousands of chemicals
- **Allows quantification of uncertainty & variability** in its predictions

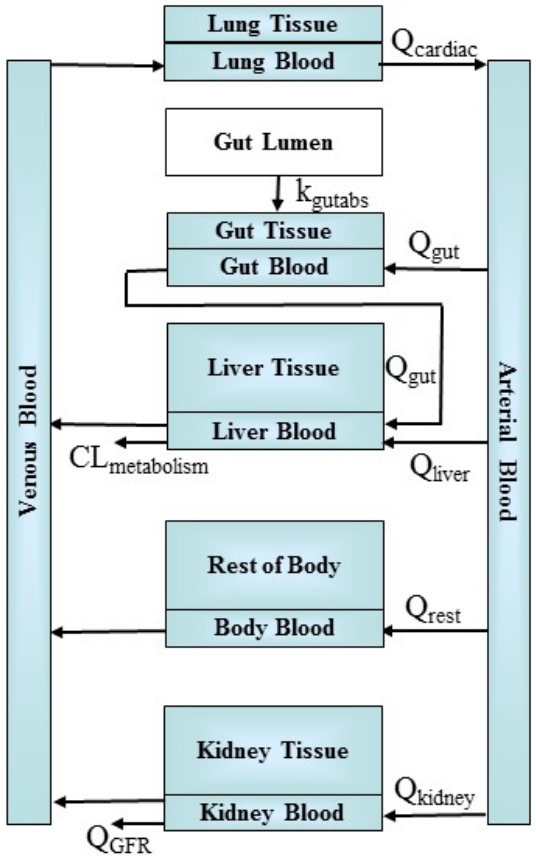
High-throughput TK (HTTK)

Generic physiologically-based TK (PBTK) model

+

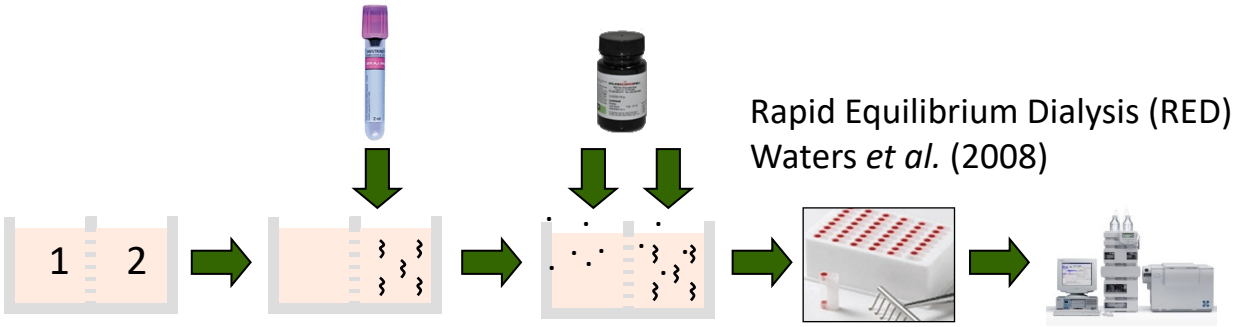
In vitro measurements of the minimal chemical-specific TK model parameters (hepatic clearance rate & plasma protein binding)

Assume clearance via first-order hepatic metabolism & passive renal filtration



Wambaugh et al. (2015)
Pearce et al. (2017a)
Ring et al. (2017)
Linakis et al. (2020)

Cryo-preserved hepatocyte suspension
Shibata *et al.* (2002)



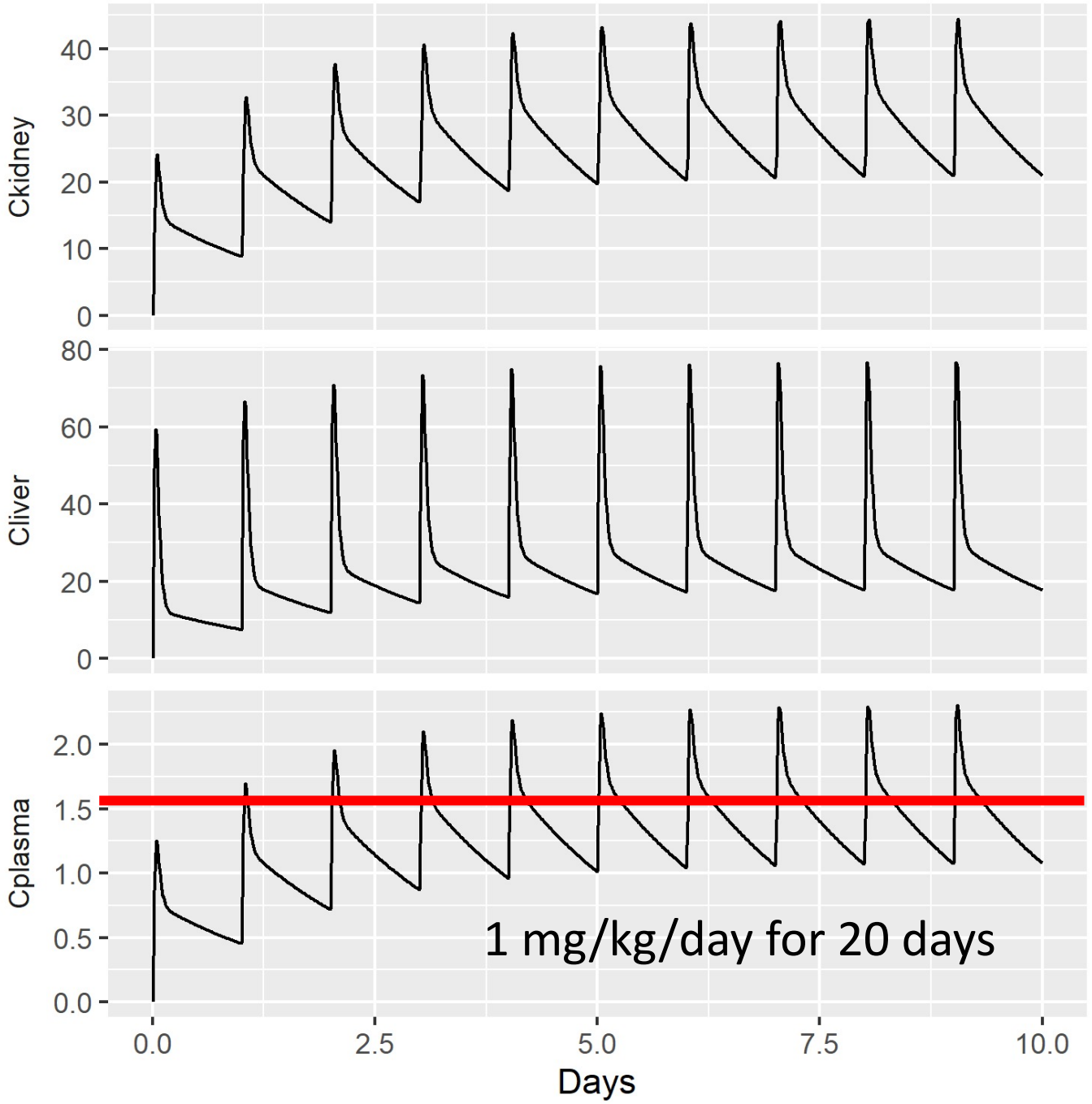
Rapid Equilibrium Dialysis (RED)
Waters *et al.* (2008)

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

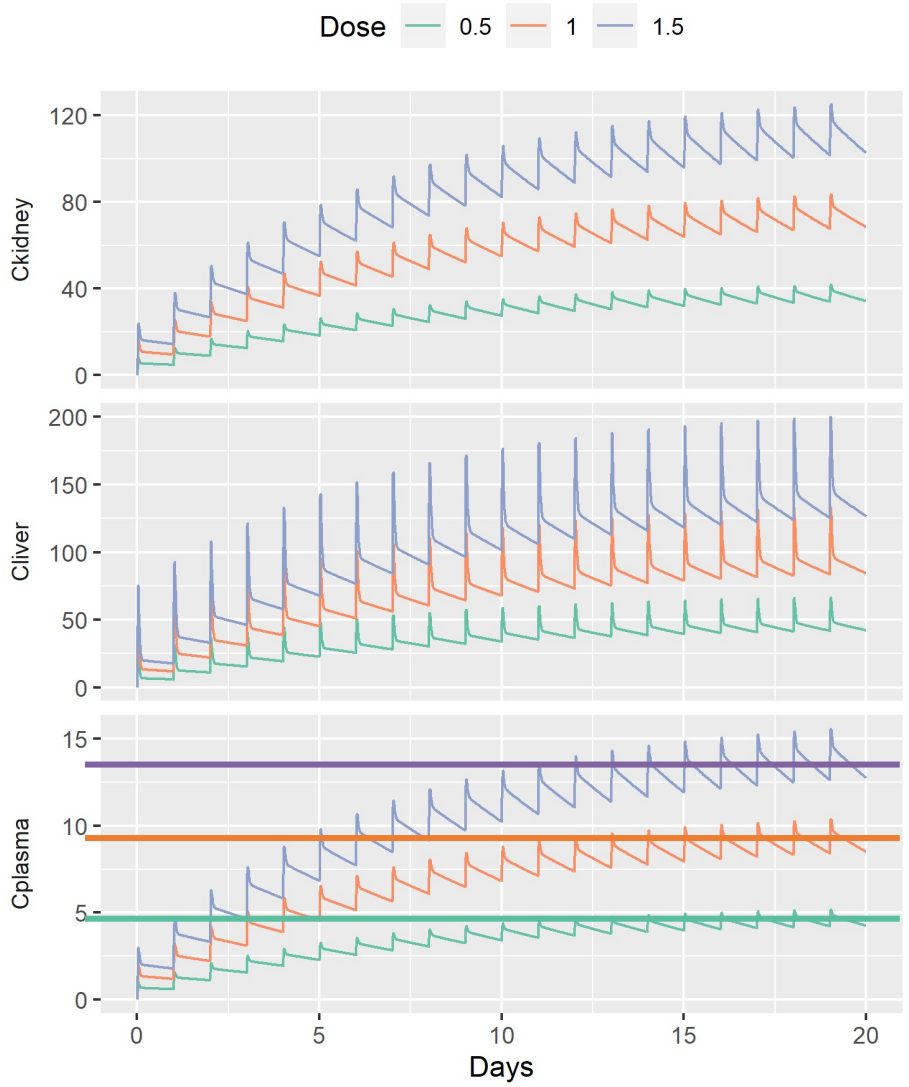
Full concentration vs. time simulations in all compartment are still too computationally intensive — need to simplify further

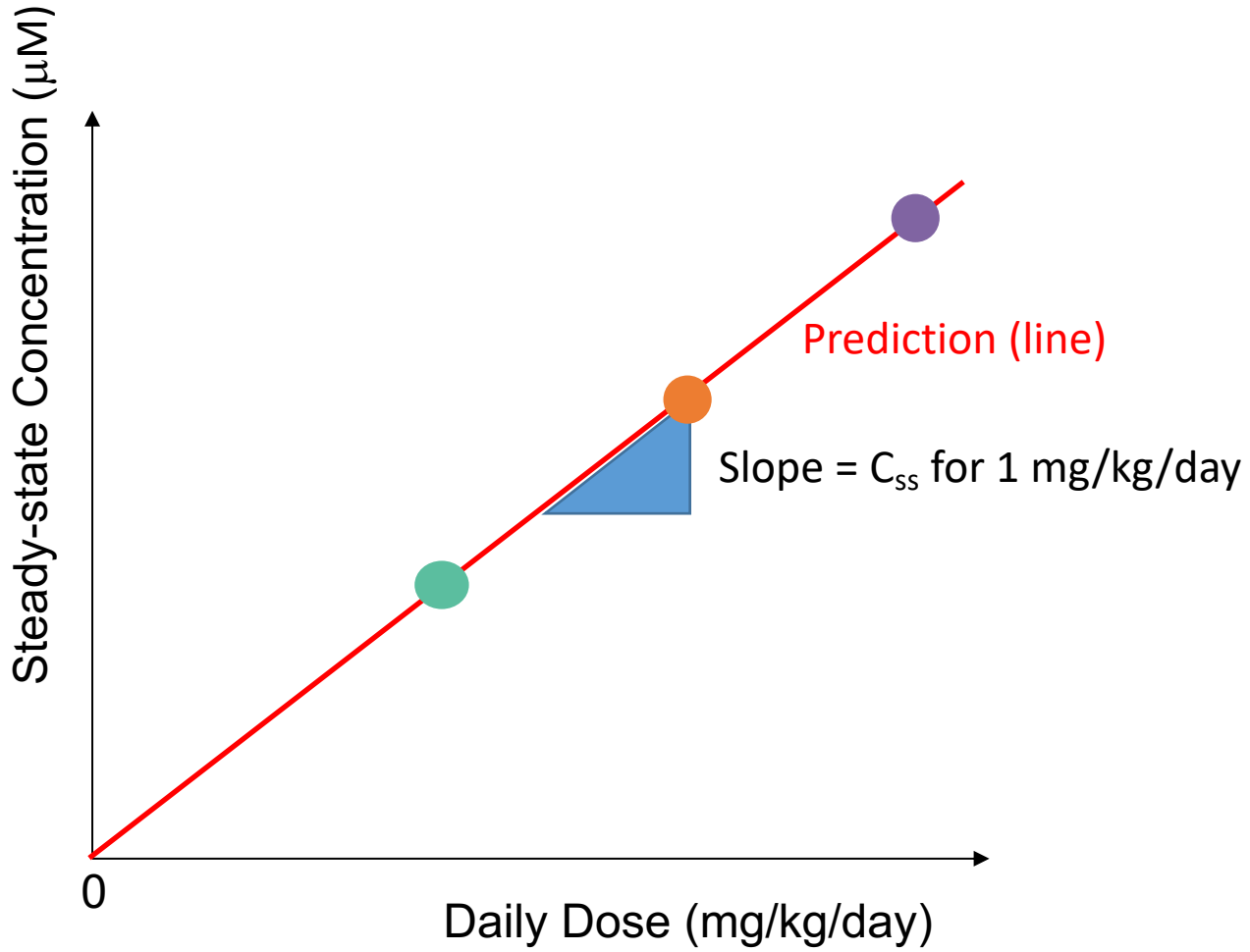
For chemical screening purposes, we are usually interested in what happens with long-term, low-level exposures

So we focus on the steady-state plasma concentration (Css)



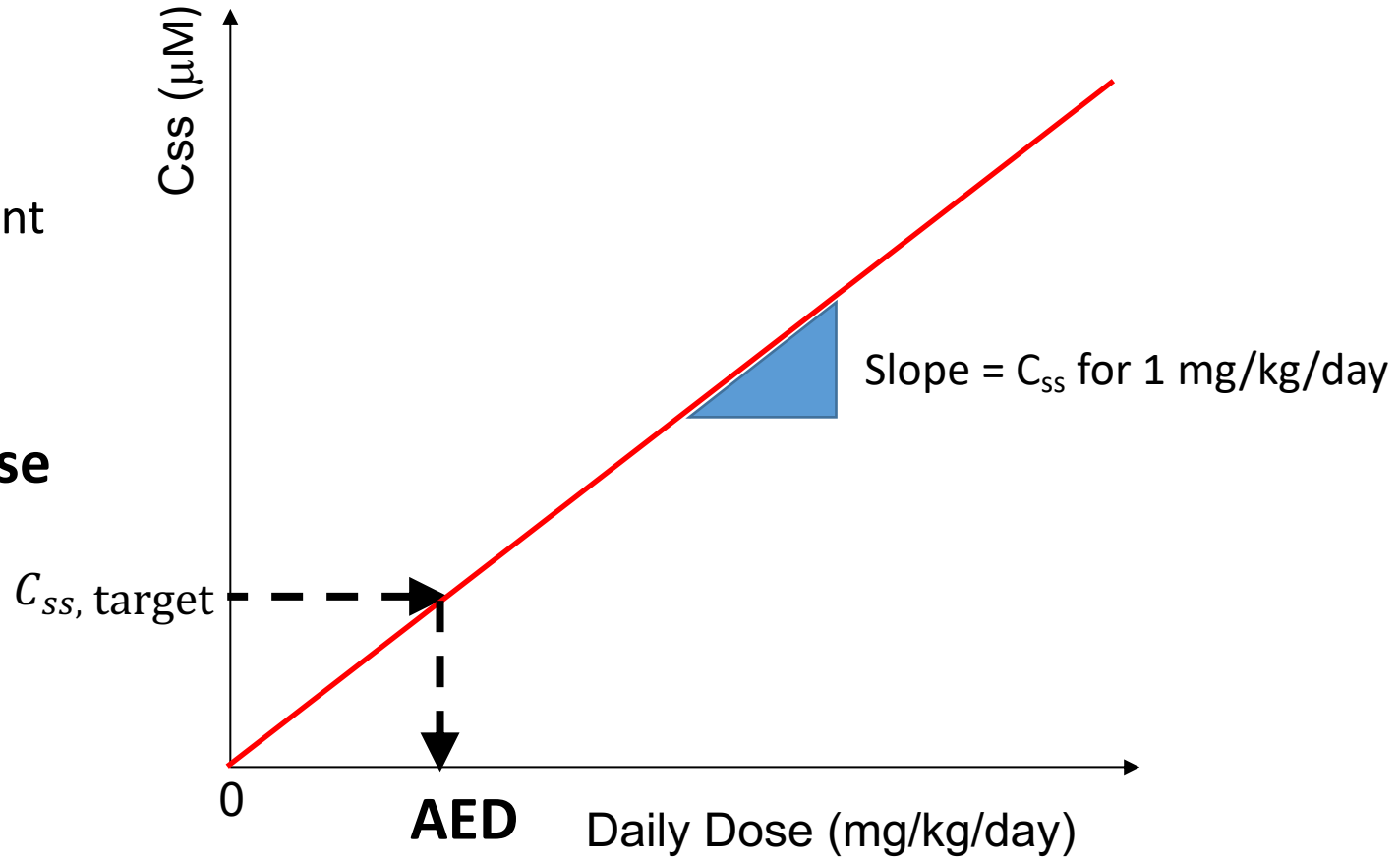
In generic PBTK model, Css has a *linear* relationship with dose





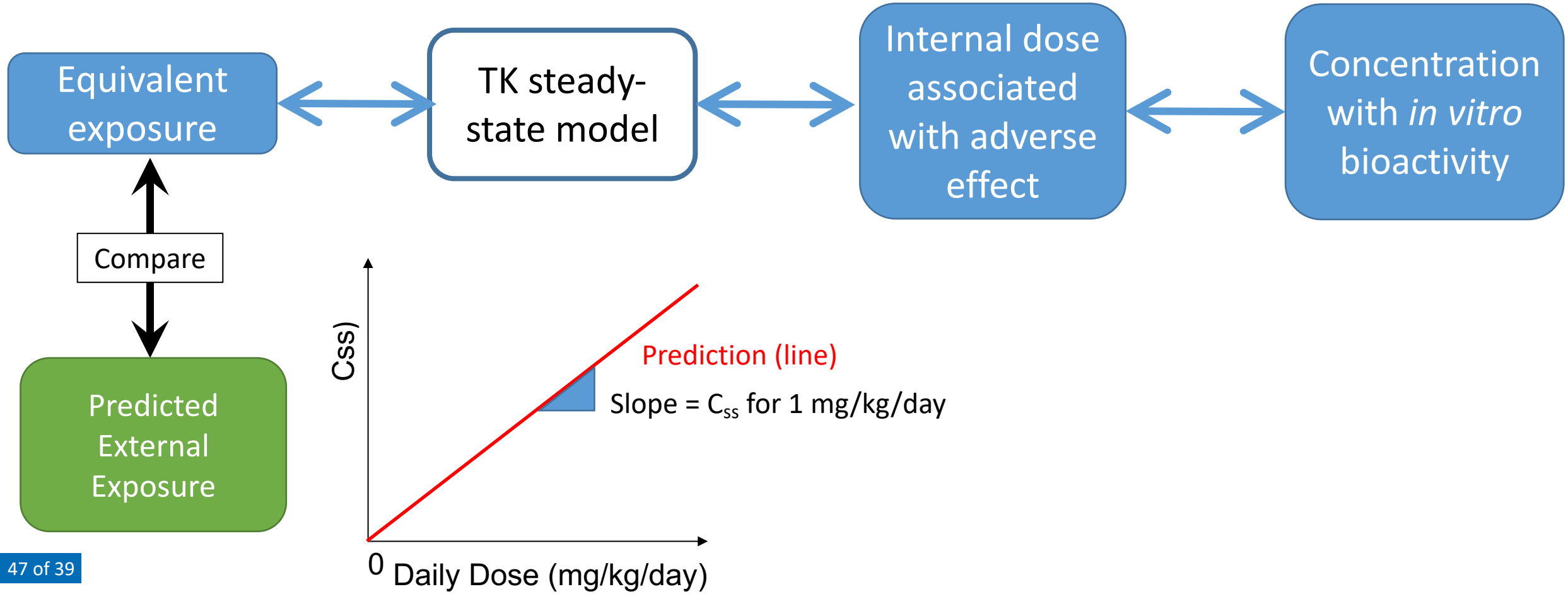
Linear Css-dose relationship makes reverse TK quick & easy

- Graphically:
  - start with the "target" concentration on the y-axis *(in vitro* bioactive concentration $C_{ss,\,\mathrm{target}}$)
  - go over to the Css-dose line
  - drop down to the x-axis
  - then read off the "administered equivalent dose" (AED) on the x-axis.
- Mathematically: $\mathrm{AED} = \frac{\mathrm{C_{ss,\,target}}}{\mathrm{slope}}$
- Interpretation: **AED = the *external* dose that would produce an *internal* body concentration equal to the *in vitro* bioactive concentration**



Wetmore *et al*. (2012)

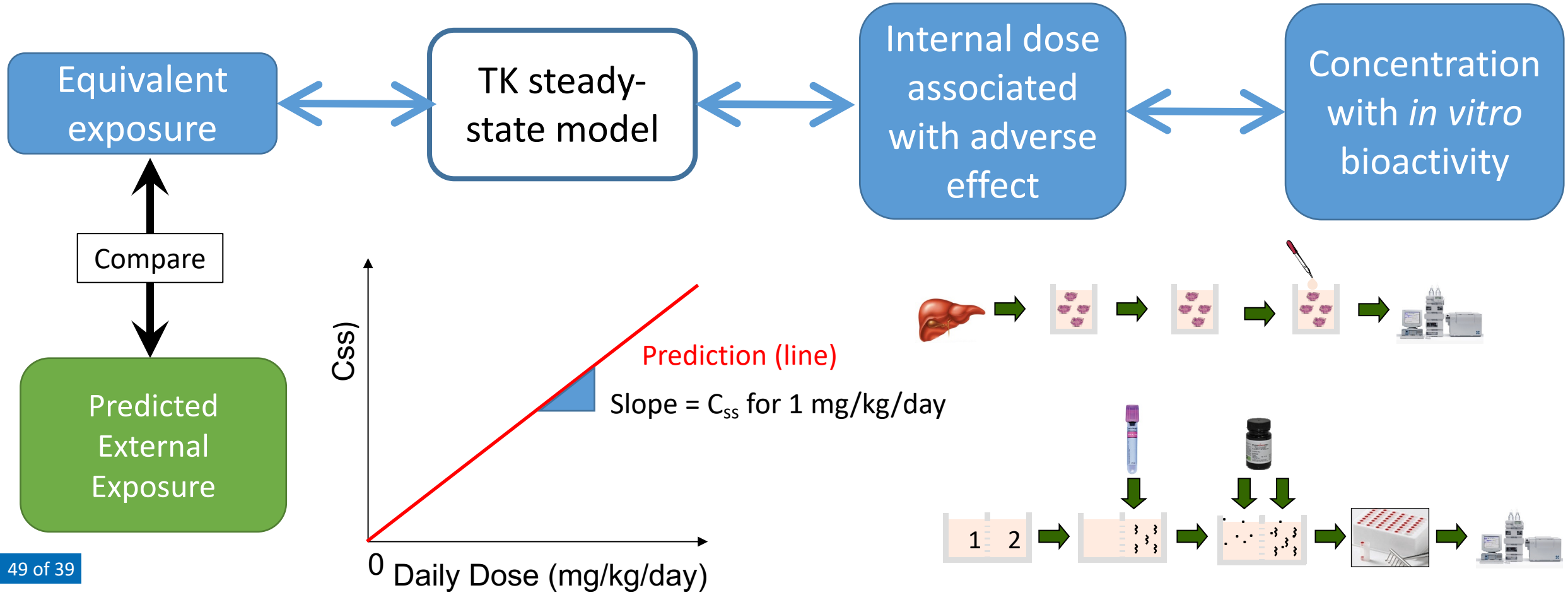
So, we can do IVIVE rapidly for large numbers of chemicals — *if we can get the slope of the Css-dose line for each chemical*



Q: What determines the slope of the line?
A: The TK model parameters that describe ADME.

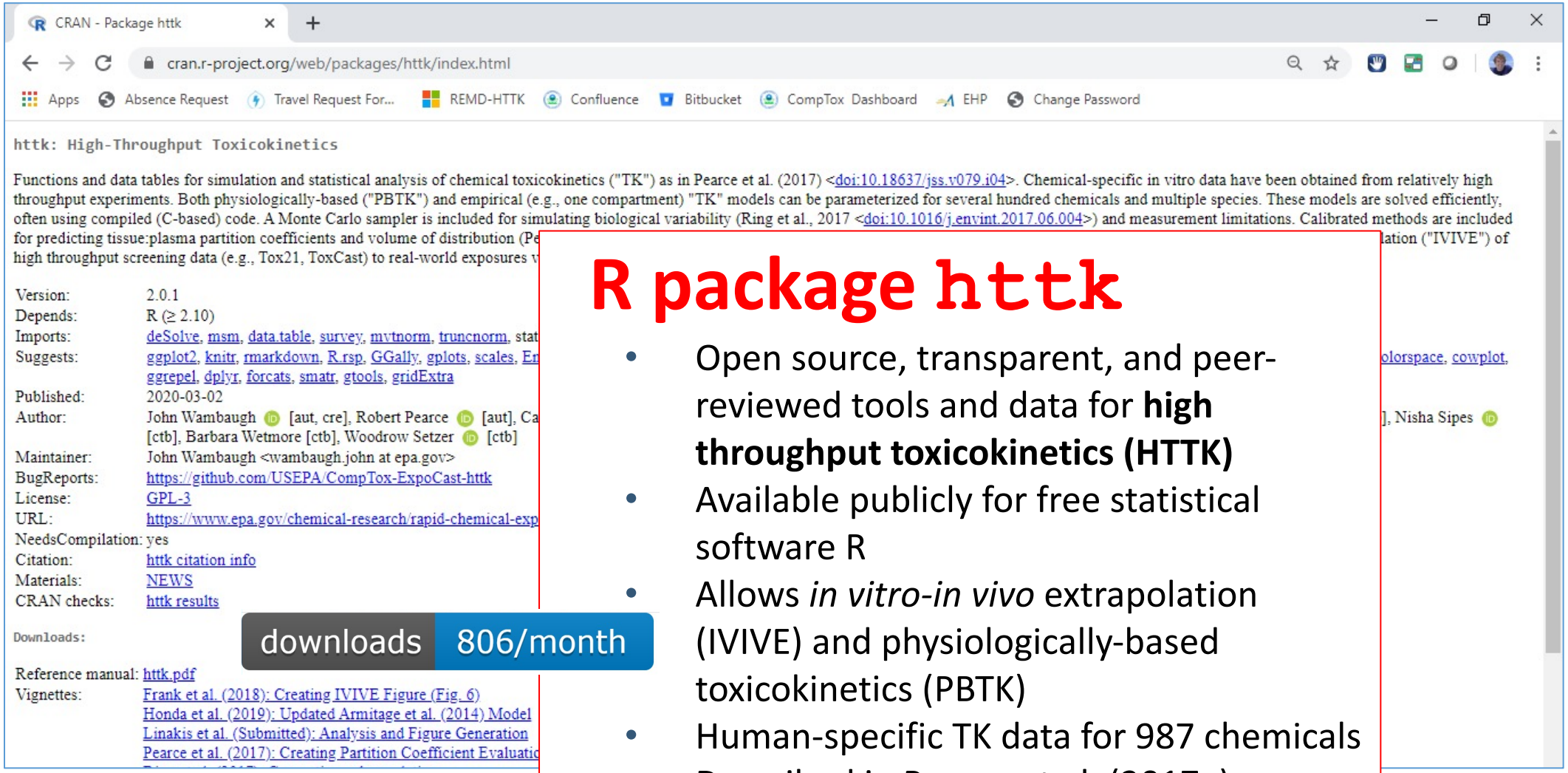
Chemical-specific parameters	How do we get the parameter values?
Intrinsic hepatic clearance rate (metabolism)	Measured in HT *in vitro* assays (Rotroff *et al.* 2010; Wetmore *et al.* 2012, 2014, 2015; Wambaugh *et al.* 2019)
Fraction unbound to plasma protein	
Tissue partition coefficients (ratio of conc. in tissue to conc. in plasma)	Predict *in silico* from phys-chem properties and tissue properties (Pearce et al., 2017b)
Physiological parameters (chemical-independent)	
Tissue masses (including body weight)	Gathered from data available in the published literature [Wambaugh et al. 2015; Pearce et al. 2017a]
Tissue blood flows	
Glomerular filtration rate (passive renal clearance)	
Hepatocellularity	

So to do high-throughput IVIVE for thousands of chemicals, all we need is the *in vitro* measured chemical-specific TK parameters!



HTTK models, data, & algorithms are freely available in R package `httk`

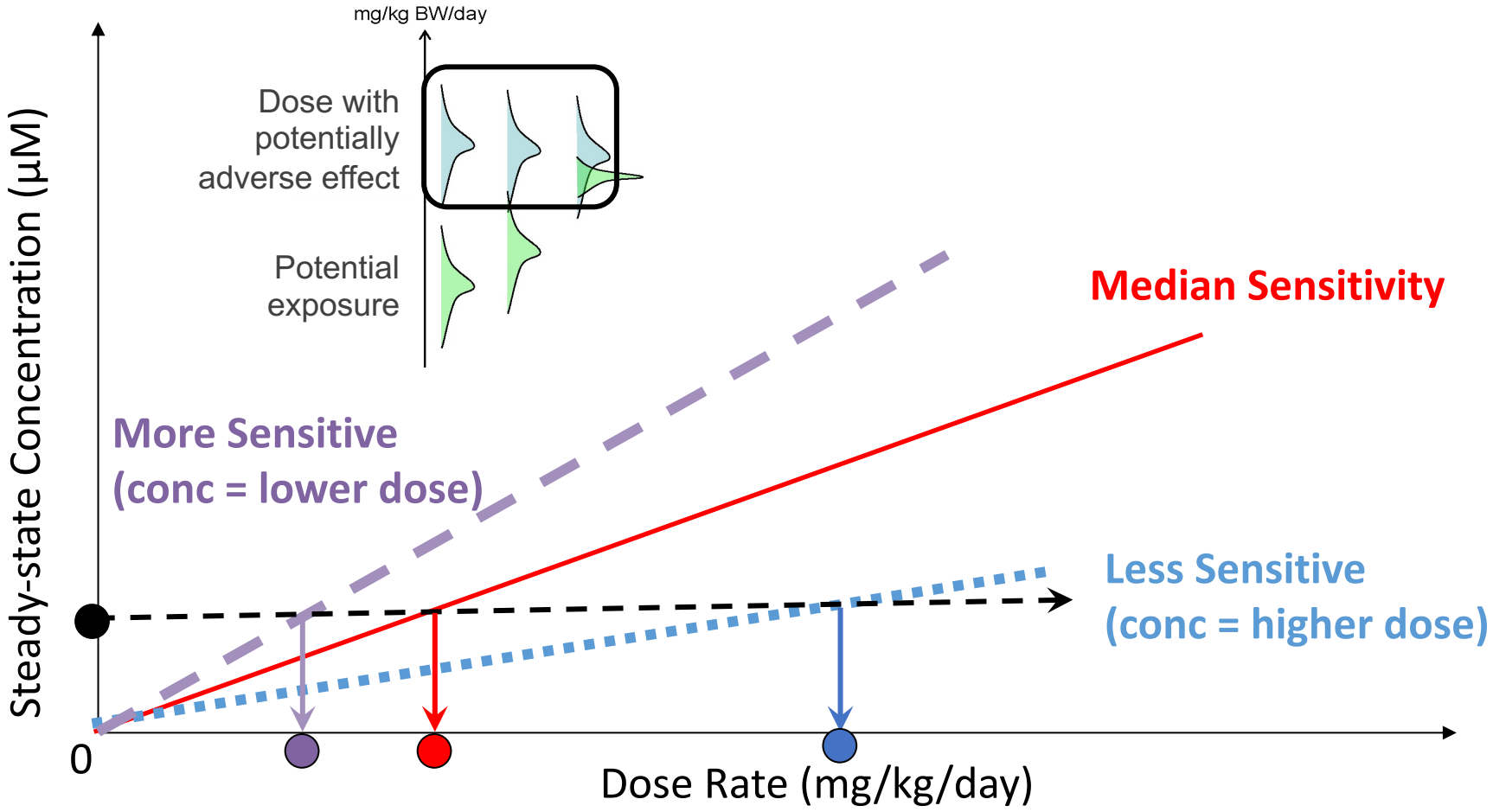
https://CRAN.R-project.org/package=httk



R package `httk`

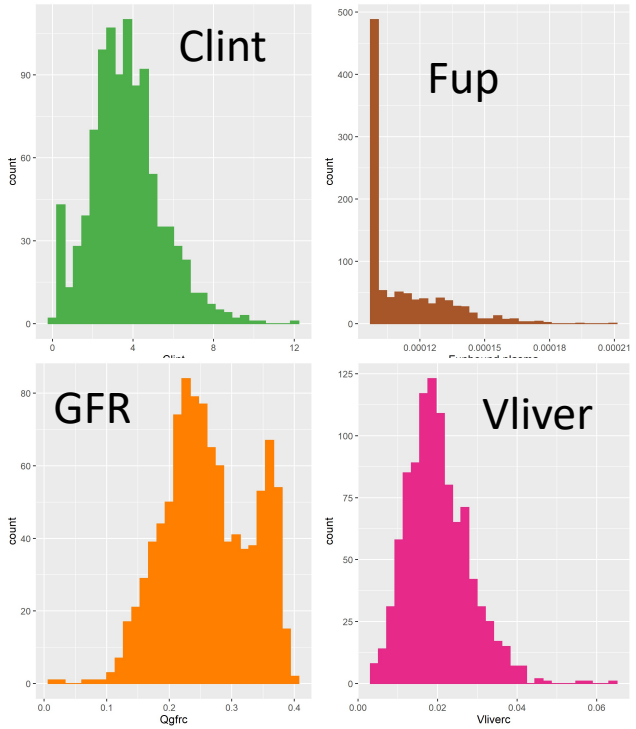
- Open source, transparent, and peer-reviewed tools and data for **high throughput toxicokinetics (HTTK)**
- Available publicly for free statistical software R
- Allows *in vitro-in vivo* extrapolation (IVIVE) and physiologically-based toxicokinetics (PBTK)
- Human-specific TK data for 987 chemicals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

Complication: Population biological variability in TK means that there is a *distribution* of Css-dose slopes — and thus a *distribution* of equivalent doses for any given *in vitro* bioactive concentration



Population variability in IVIVE can be quantified using a Monte Carlo approach: "HTTK-Pop" (Ring et al., 2017)

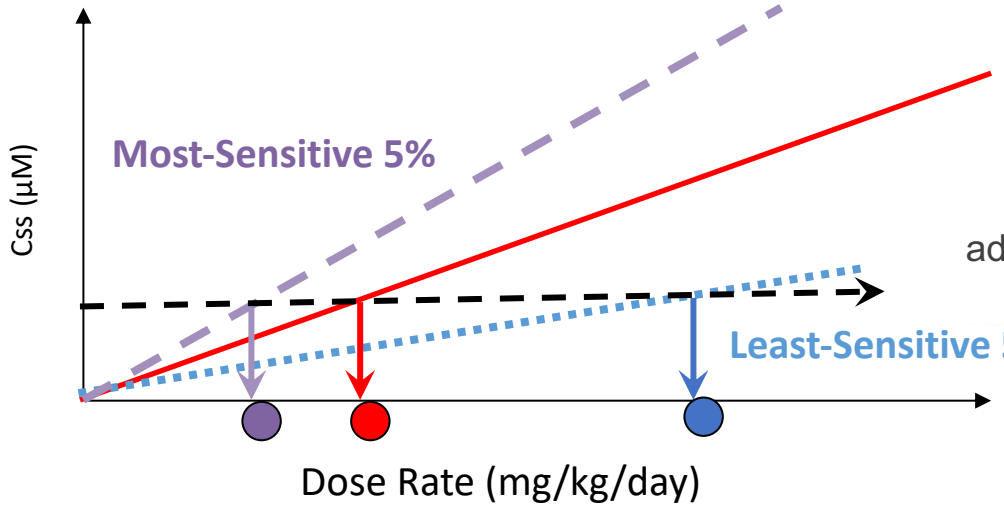
Sample from population distribution of TK parameters based on CDC NHANES data



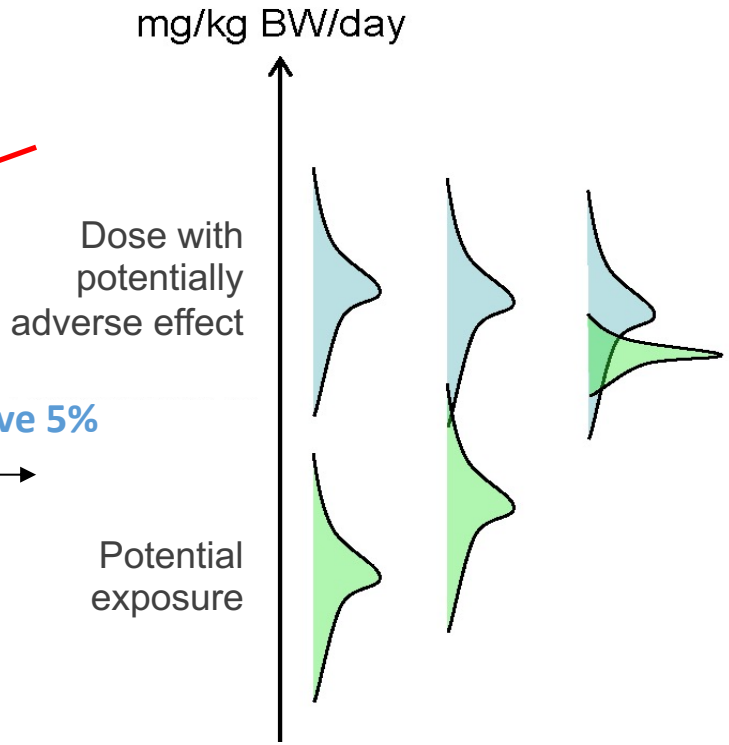
(+ other params)

Calculate Css-dose slope for each sampled set of TK model parameters

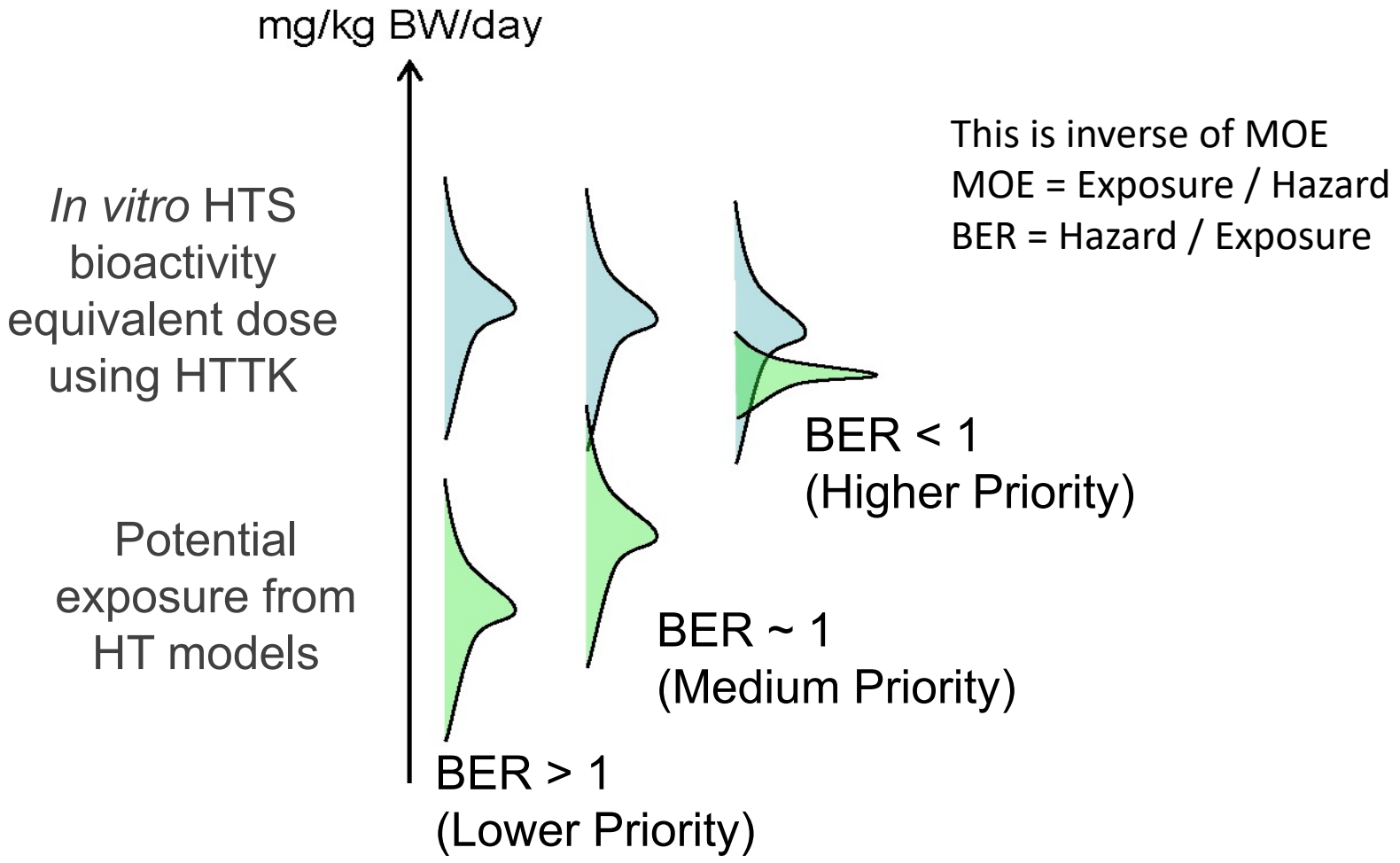
Get resulting distribution of equivalent doses



Compare equivalent dose distribution to potential exposure distribution to calculate potential risk



Compare the low-end equivalent dose to the high-end potential exposure to calculate "Bioactivity-Exposure Ratio" (BER).



Example: Using httk to find an equivalent dose & BER for a low-end ToxCast AC50 for benzo(a)pyrene

CompTox Chemicals Dashboard

comptox.epa.gov/dashboard/d

EPA United States Environmental Protection Agency | Home | Advanced Search | Batch Search | Lists | Predictions | Downloads | Copy | Share | Submit Comment | Search all data

Benzo(a)pyrene

50-32-8 | DTXSID2020139

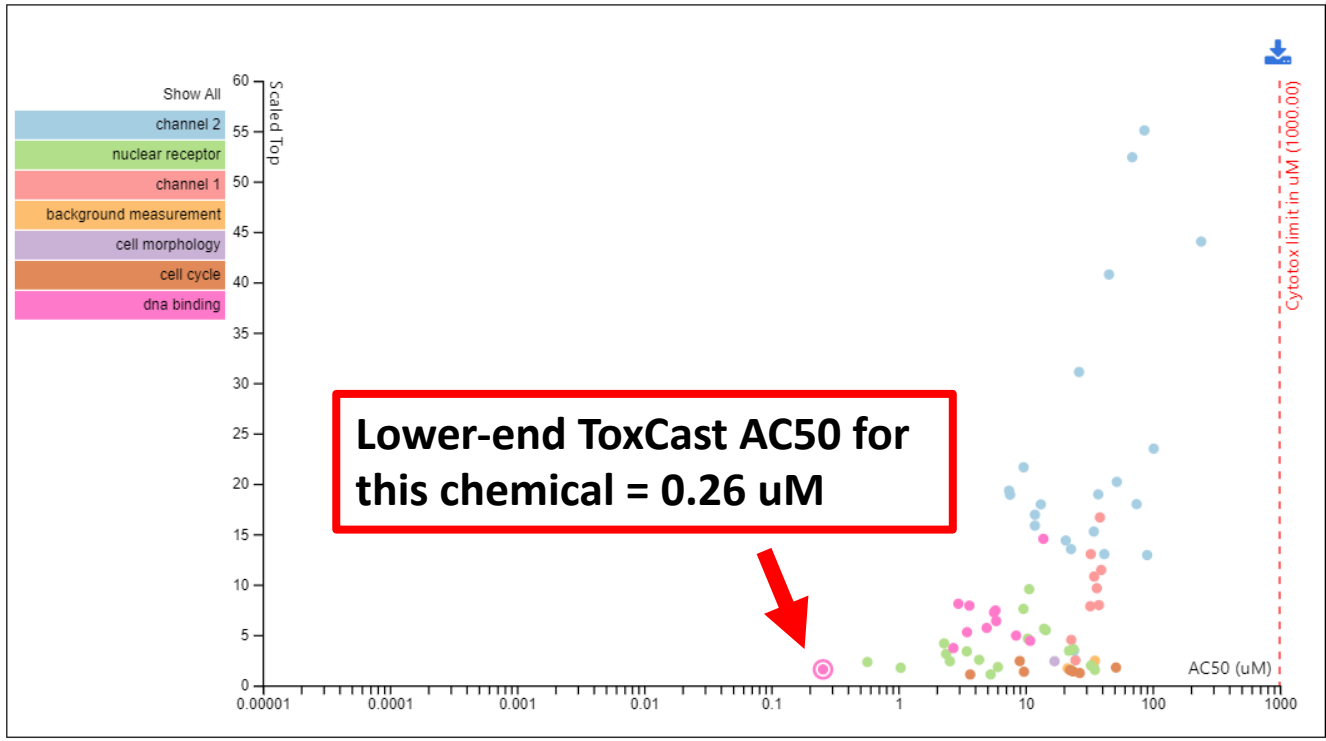
Searched by DSSTox Substance Id.

First: Get AC50 value. ToxCast AC50s can be found on the CompTox Chemicals Dashboard.

- DETAILS
- EXECUTIVE SUMMARY
- PROPERTIES
- ENV. FATE/TRANSPORT
- HAZARD
- SAFETY
- ADME
- EXPOSURE
- **BIOACTIVITY**
  - **TOXCAST: SUMMARY**
  - EDSP21
  - TOXCAST/TOX21
  - PUBCHEM
  - TOXCAST: MODELS
- SIMILAR COMPOUNDS

Chemical Activity Summary

TOXCAST DATA



Lower-end ToxCast AC50 for this chemical = 0.26 uM

ASSAY DETAILS

AC50 (uM): 0.26
Scaled top: 1.58
Assay Endpoint Name: TOX21_SSH_3T3_GLI3_Antagonist
Gene Symbol:
Organism: mouse
Tissue: embryo
Assay Format Type: cell-based
Biological Process Target: regulation of transcription factor activity
Detection Technology: Luciferase-coupled ATP quantitation
Analysis Direction: positive
Intended Target Family: dna binding
Description: Data from the assay component TOX21_SSH_3T3_GLI3_Antagonist was analyzed into 1 assay endpoint. This assay endpoint, TOX21_SSH_3T3_GLI3_Antagonist, was analyzed in the positive fitting direction relative to DMSO as the negative control and baseline of activity. Using a type of inducible reporter, loss-of-signal activity can be used to understand changes in the reporter gene as they relate to the gene GLI3. Furthermore, this assay endpoint can be referred to as a primary readout, because this assay has produced multiple assay endpoints where this one serves a reporter gene function.

To calculate population equivalent dose, use httk function `calc_mc_oral_equiv()`

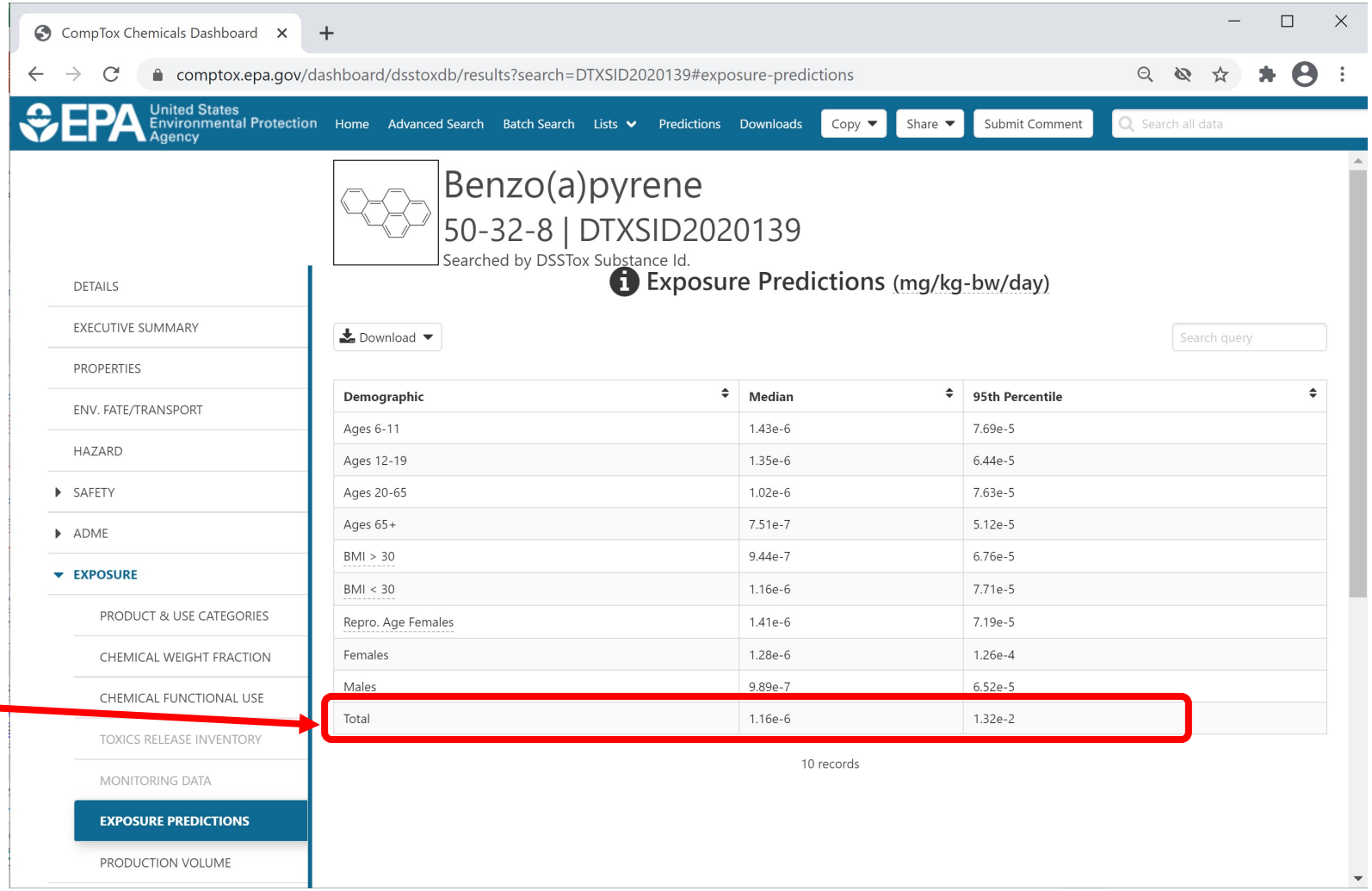
```
> library(httk)
> set.seed(42)
> #Steady-state equivalent dose (mg/kg BW/day) to produce 0.26 uM in plasma:
 calc_mc_oral_equiv(conc=0.26,
                    chem.name="benzo(a)pyrene",
                    which.quantile = c(0.95, 0.5, 0.05),
                    input.units = "uM",
                    output.units = "mgpkgpday")
uM concentration converted to mgpkgpday dose for 0.95 0.5 0.05 quantile.
     95%      50%       5%
0.003821 0.019090 0.067080
```

Compare equivalent dose to HT exposure predictions available on EPA CompTox Chemicals Dashboard

Monte Carlo equivalent dose from `httk::calc_mc_oral_equiv()`:

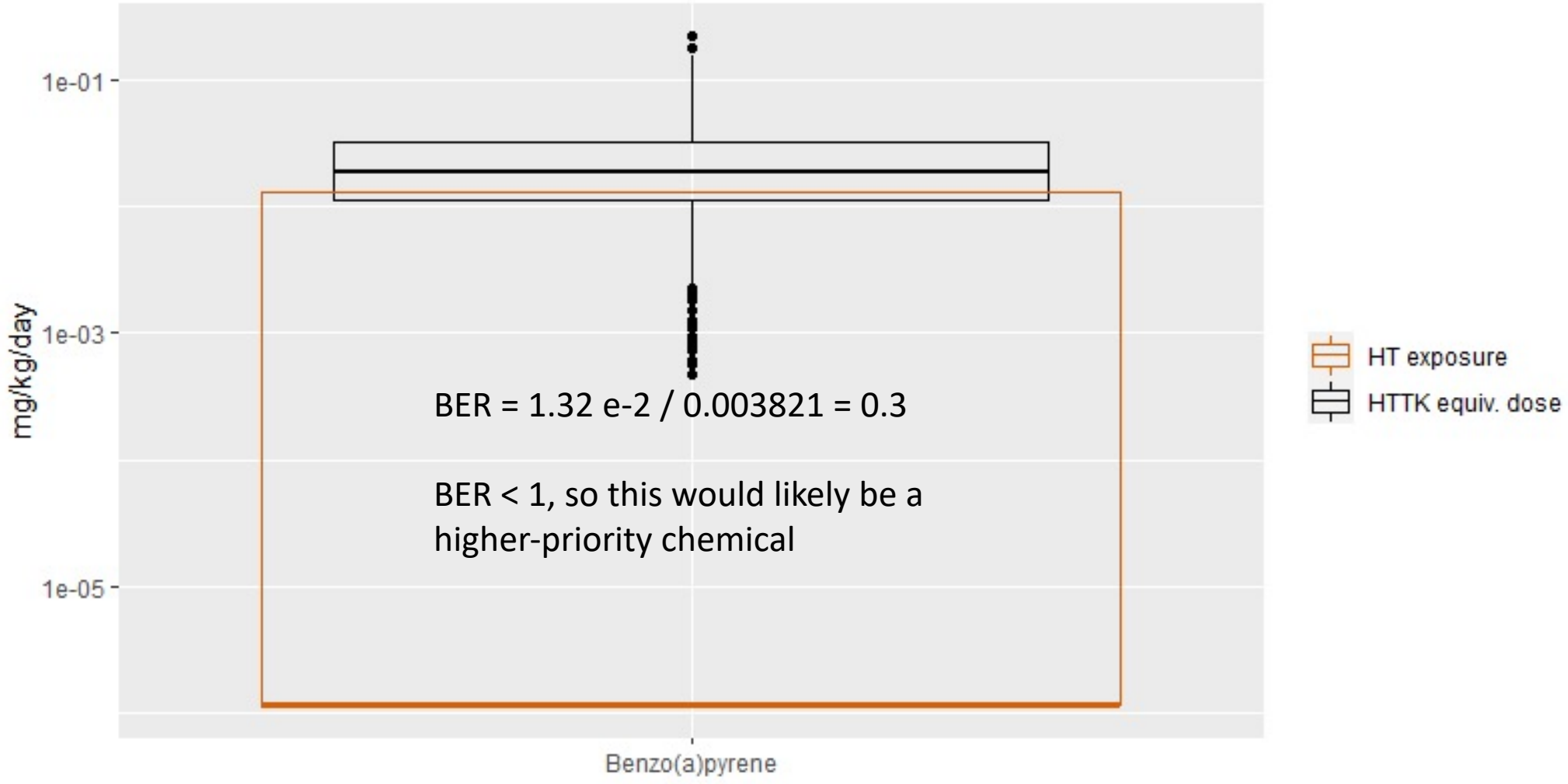
```
uM concentration converted to
mgpkgpday dose for 0.95 0.5
0.05 quantile.
     95%      50%       5%
0.003821 0.019090 0.067080
```

HT exposure predictions from Dashboard:
median = 1.16e-6;
upper bound on median = 1.32e-2
mg/kg/day

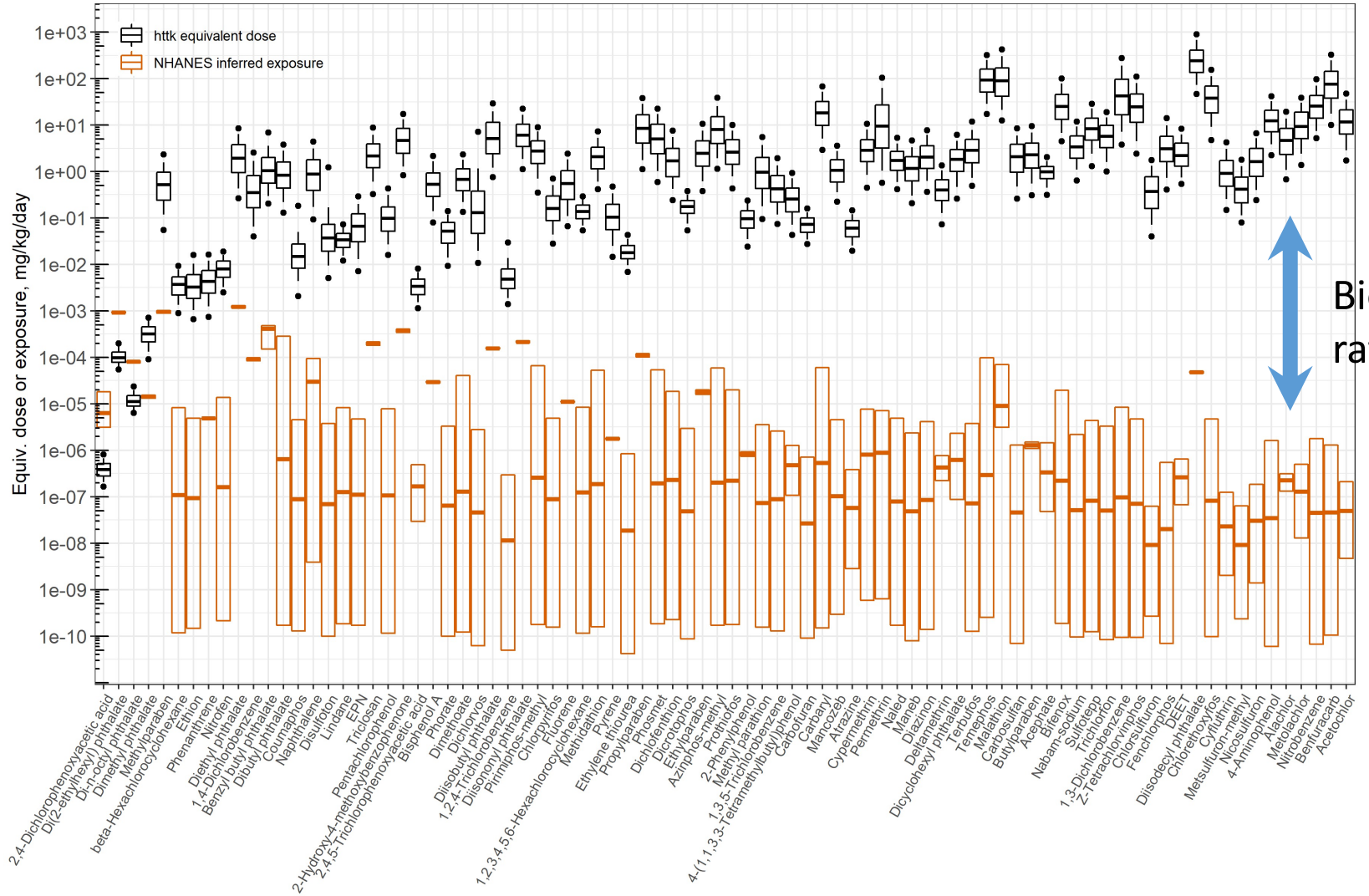


Ring et al. 2019, Wambaugh et al. 2014

BER: Graphical comparison of HTTK-predicted equivalent dose for ToxCast AC50, vs. HT exposure prediction



Example: BER-based prioritization of 84 chemicals, using IVIVE of ToxCast AC50s.



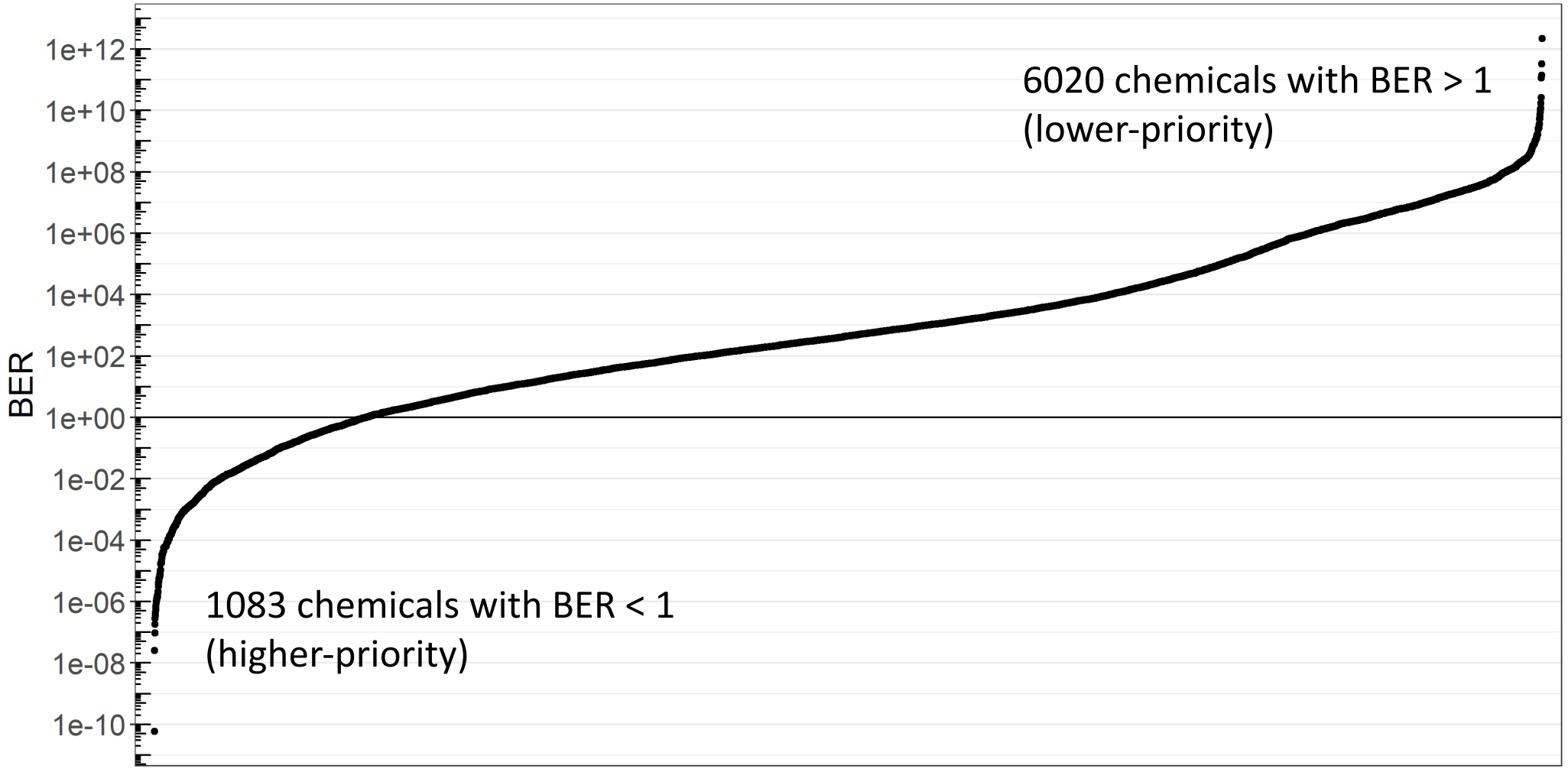
Population distributions of equivalent dose for 10th percentile ToxCast AC50 (bottom point = most-sensitive 5%)

Bioactivity-exposure ratio (BER)

Population median aggregate exposures with 95% credible interval, inferred from NHANES urinary biomonitoring data

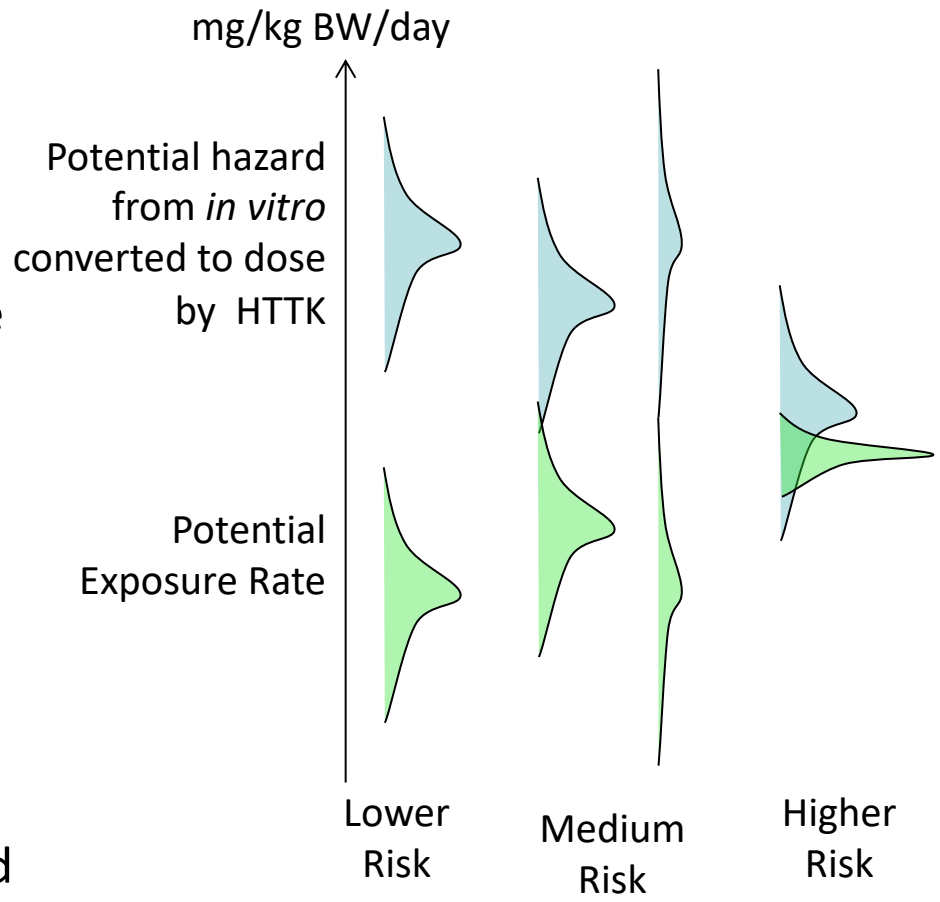
Updated version of analysis from Ring et al. (2017)

An even-more high-throughput application: BER prioritization of 7104 chemicals based on HTTK-Pop IVIVE of ToxCast AC50s and HT exposure predictions from SEEM3 model



Summary

- "The dose makes the poison": risk is a function of both hazard and exposure
- Hazard: When *in vivo* hazard data are not available, we can use *in vitro* high-throughput screening (HTS) assays
- Exposure: estimation requires tracing chemical from source to receptor
- When detailed chemical-specific exposure data are not available, we can use exposure NAMs to fill data gaps and make exposure predictions
- To compare *in vitro* HTS data to *in vivo* exposure estimates, we use high-throughput toxicokinetics (HTTK) -- generic model that can be parameterized with *in vitro* data
- The bioactivity-exposure ratio (BER) framework allows rapid risk-based chemical prioritization
- Hazard, exposure, and TK data and models are publicly available through the CompTox Chemicals Dashboard and as R packages



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

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