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Incorporating Population Variability in Toxicokinetic Modeling for Risk-Based Prioritization

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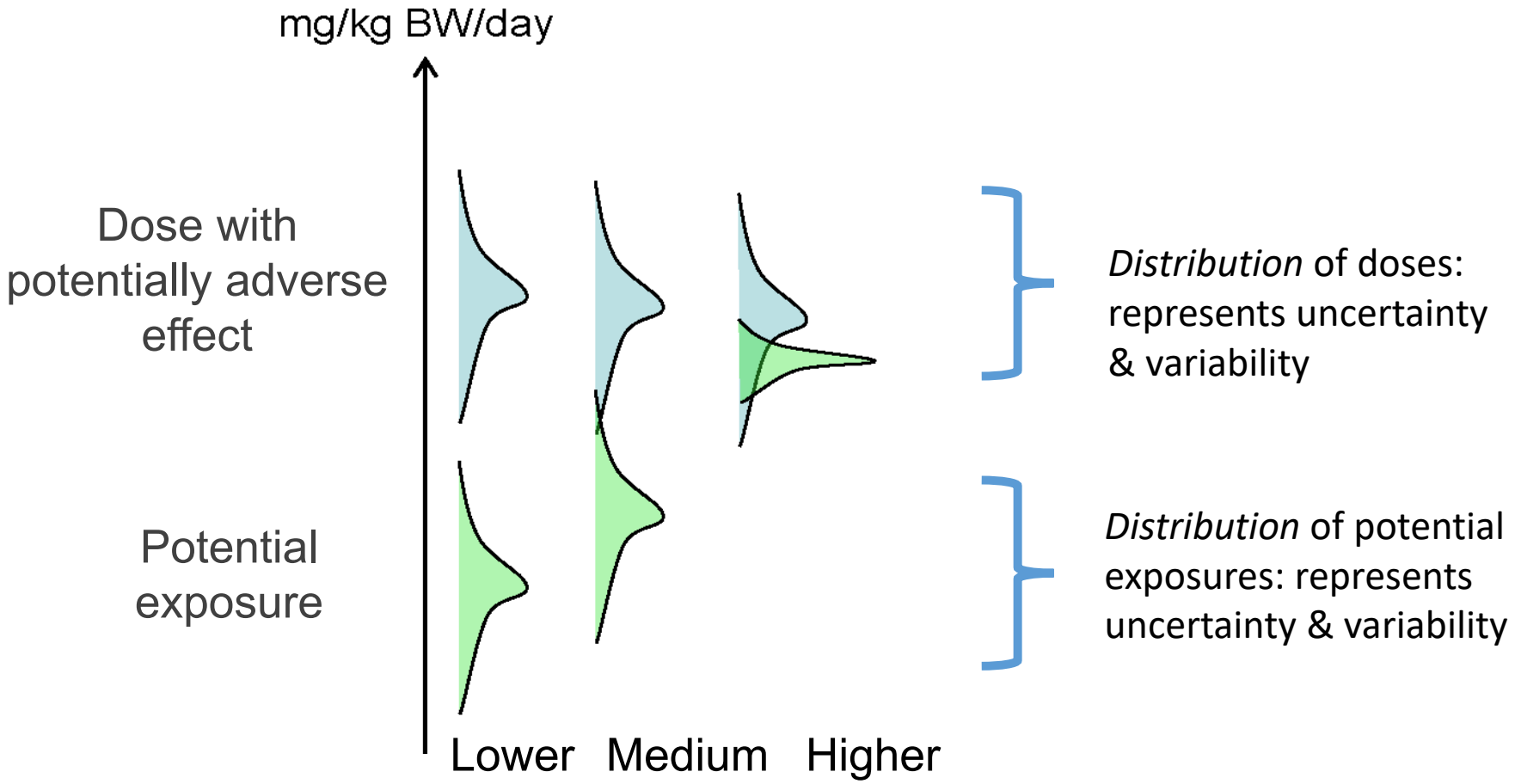
Society of Toxicology 2021 Virtual Meeting
"Closing the Data Gap: Assessing Population Variability Using Next-Generation Tools in Toxicology"
Thursday, March 18, 2021

Risk is a function of both hazard and exposure



High-throughput chemical prioritization: rapidly prioritize large numbers of chemicals that may not have much data

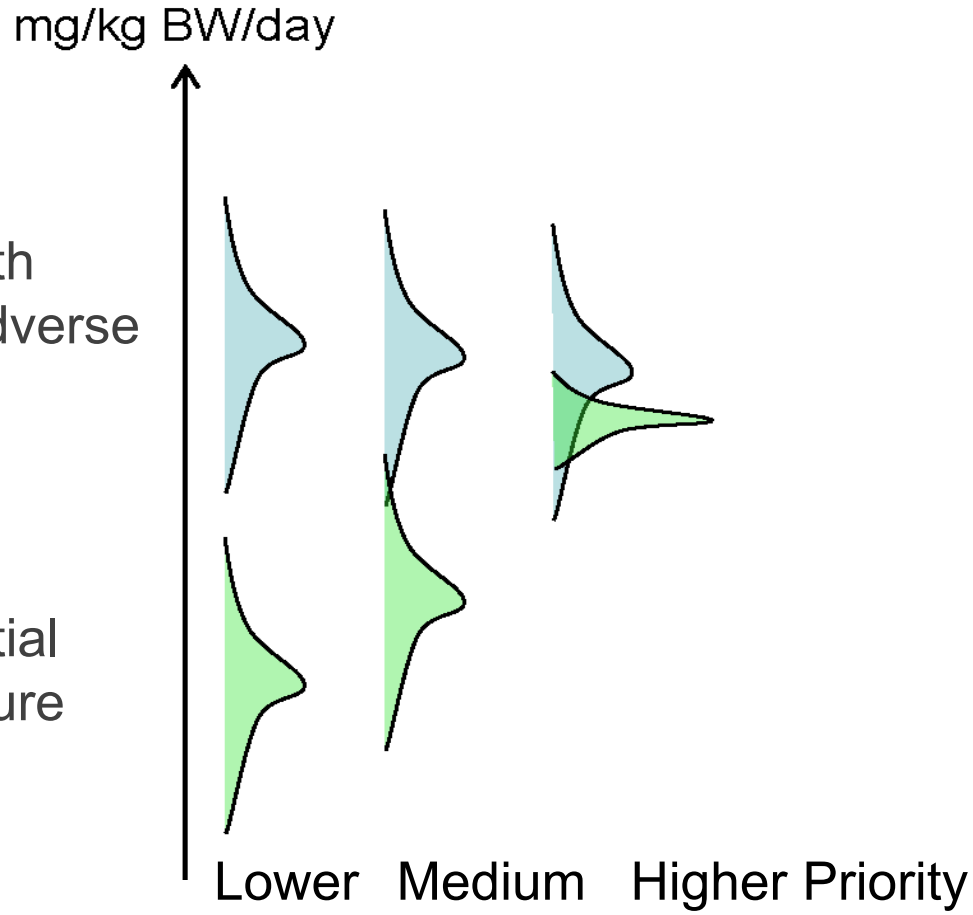
Chemicals may not have *in vivo* tox studies – estimate using *in vitro* HT screening assays (e.g. ToxCast/Tox21) [Schmidt 2009; Dix et al. 2007; Kavlock et al. 2018]

Chemicals may not have detailed exposure data – estimate using HT exposure models [Wambaugh et al. 2013; Wambaugh et al. 2014; Ring et al. 2019]

in vitro-in vivo extrapolation (IVIVE)

Dose with potentially adverse effect

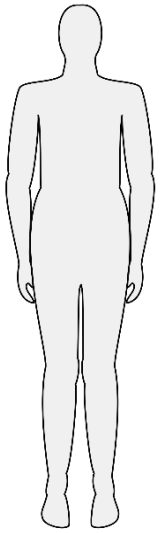
Potential exposure



[NRC 2007; Bell et al. 2018; Bessems et al. 2014]

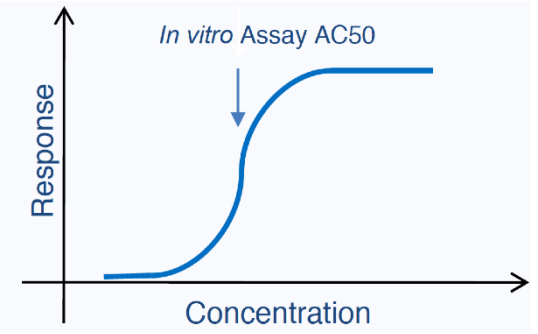
IVIVE is performed using toxicokinetic (TK) modeling: relate external dose and body concentration by describing "what the body does to the chemical"

External dose



Body concentration (assumed same as *in vitro* bioactive conc.)

Toxicokinetic model:
Absorption
Distribution
Metabolism
Excretion



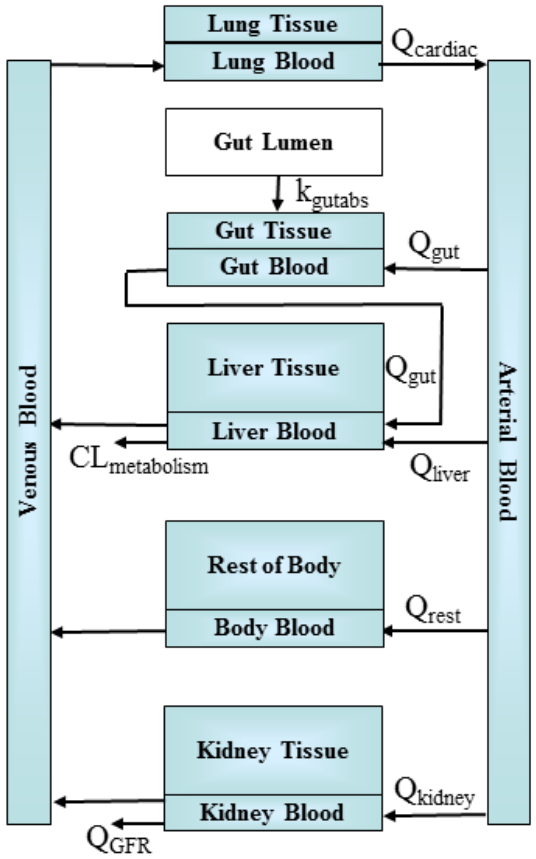
[Tan et al. 2007;
Rotroff et al. 2010;
Wetmore et al. 2015]

For high-throughput chemical prioritization: *High-throughput* TK (HTTK)

Generic physiologically-based TK (PBTK) model: can be parameterized for many chemicals with minimal chemical-specific data requirements

+

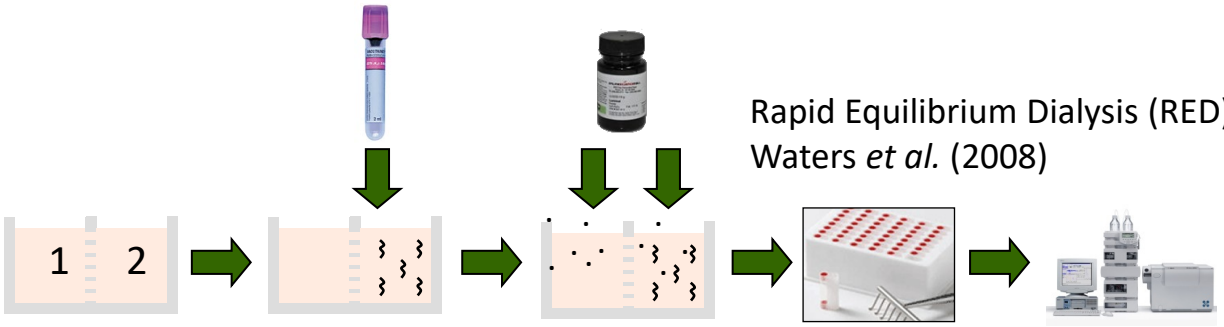
In vitro measurements of the minimal chemical-specific TK model parameters (hepatic clearance rate & plasma protein binding)



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

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

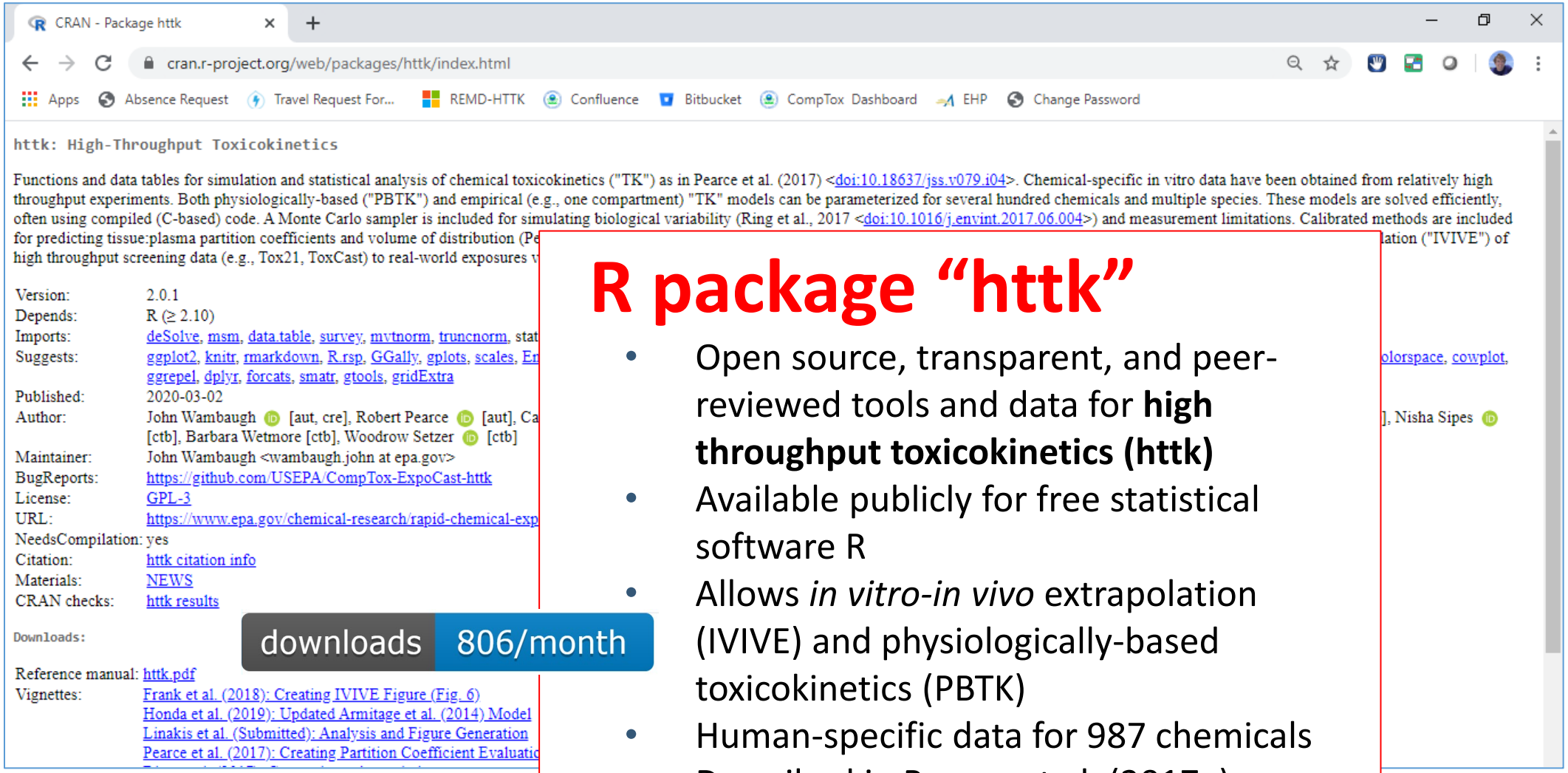
Rapid Equilibrium Dialysis (RED)
Waters *et al.* (2008)



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

HTTK models & data freely available in R package “httk”

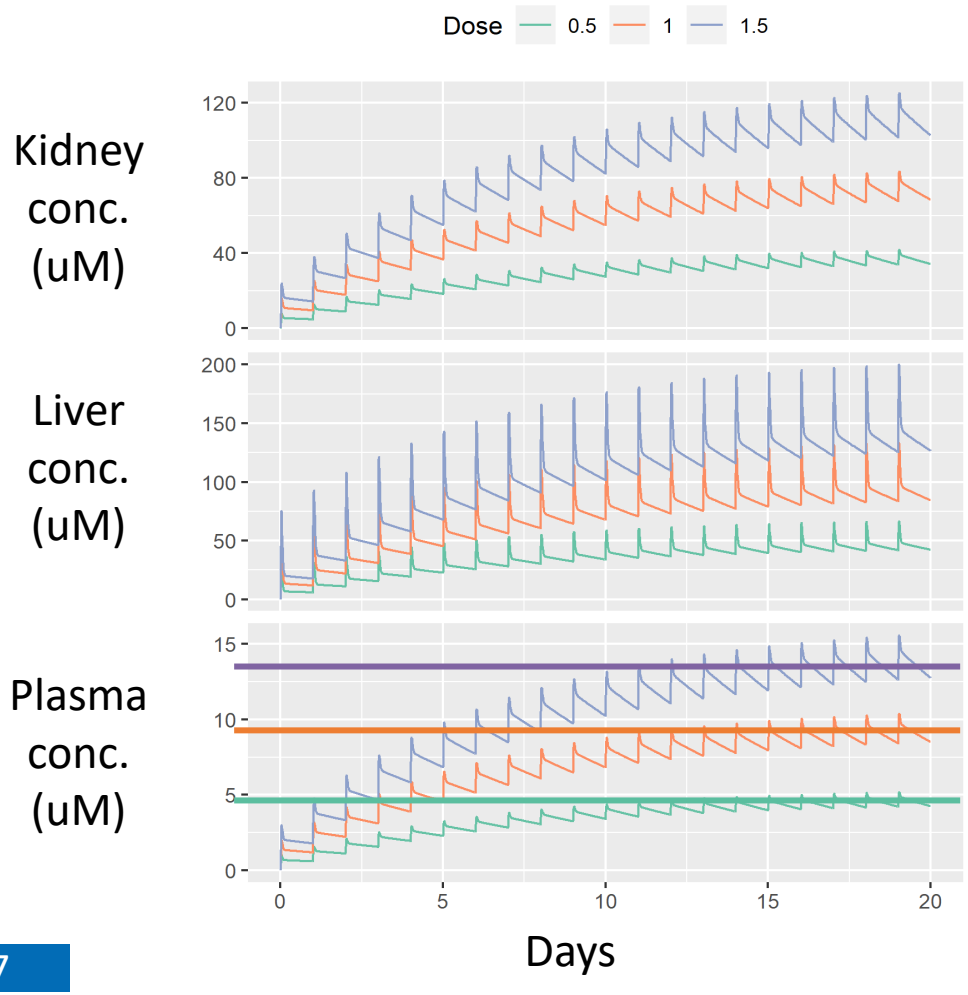
https://CRAN.R-project.org/package=httk

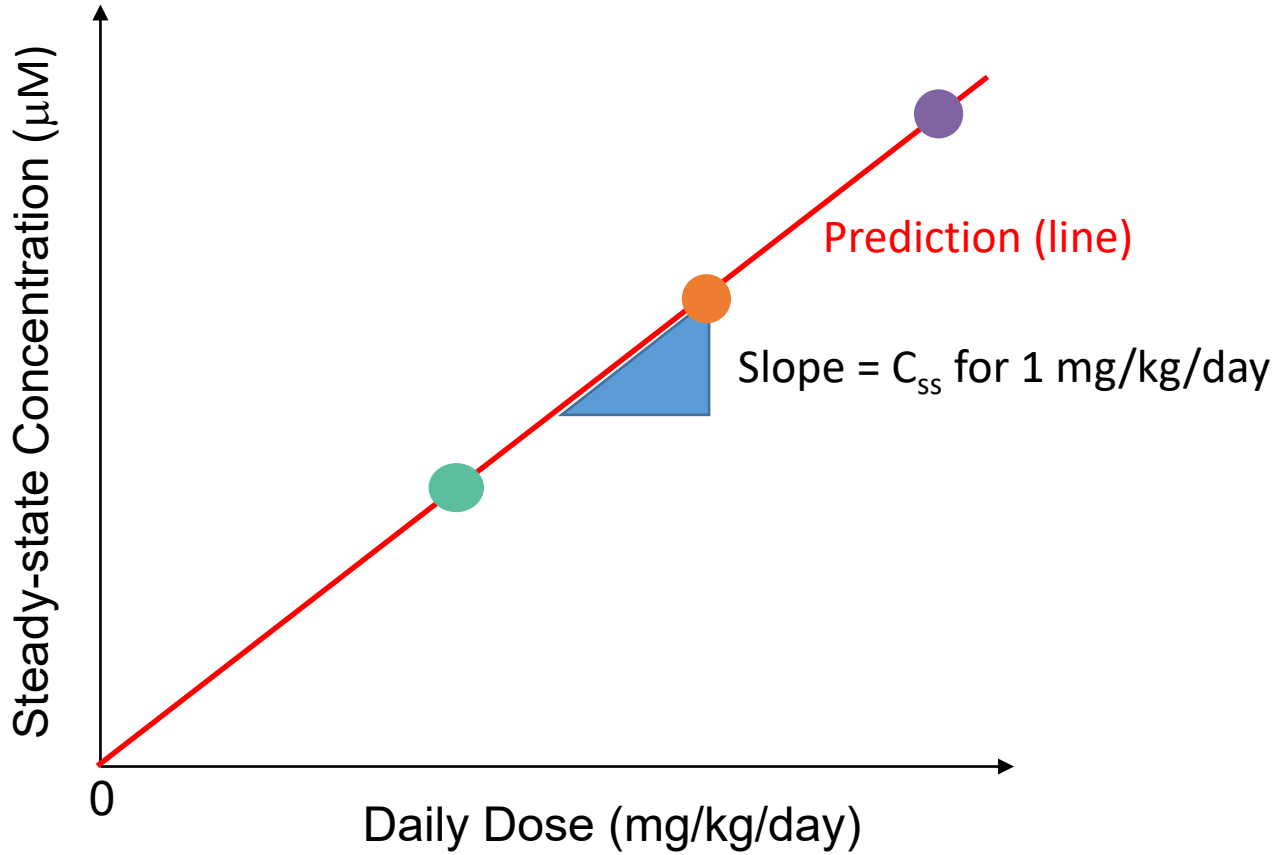


R package “httk”

- 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 data for 987 chemicals
- Described in Pearce et al. (2017a)

For prioritization: focus on steady-state plasma concentration (C_{ss}) & simple TK models where C_{ss} is linear with dose

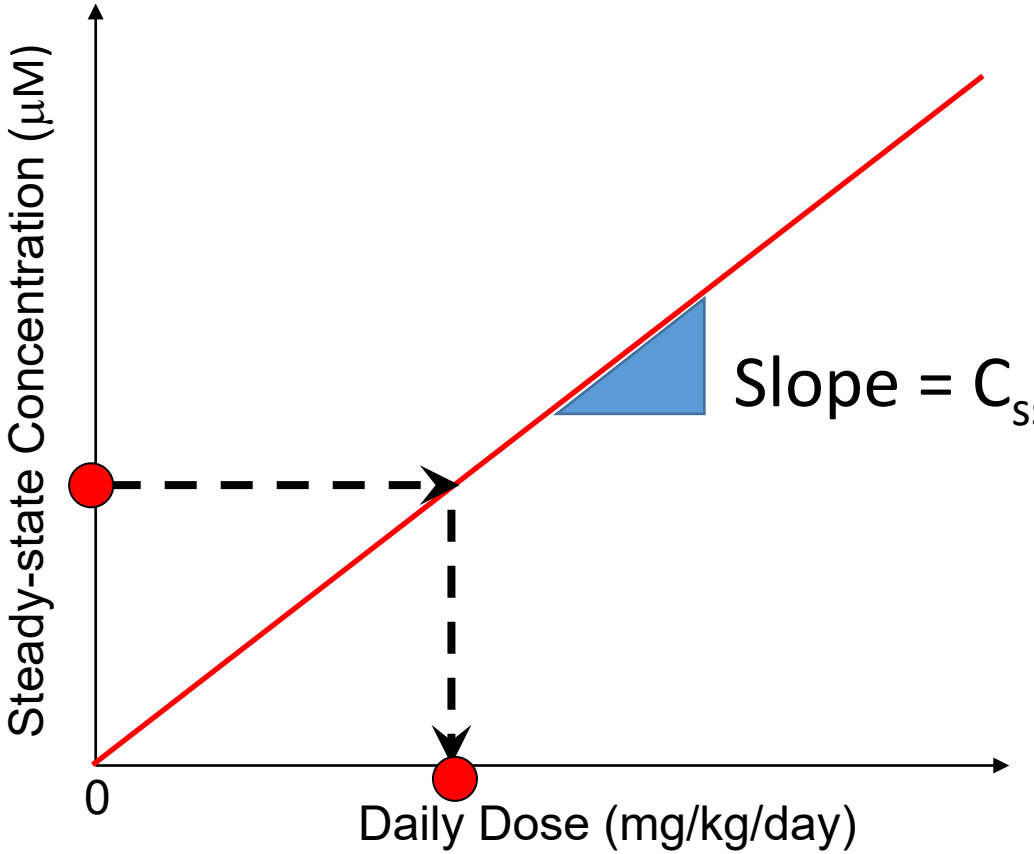




Wetmore *et al.* (2012)

Linear relation makes it easy to do IVIVE: convert concentration to equivalent dose — as long as you know the slope of the line!

Concentration of interest: e.g. *in vitro* bioactive concentration



Slope = C_{ss} for 1 mg/kg/day

in `httk` R package:
`calc_analytic_css()`

Equivalent dose

Wetmore *et al*. (2012)

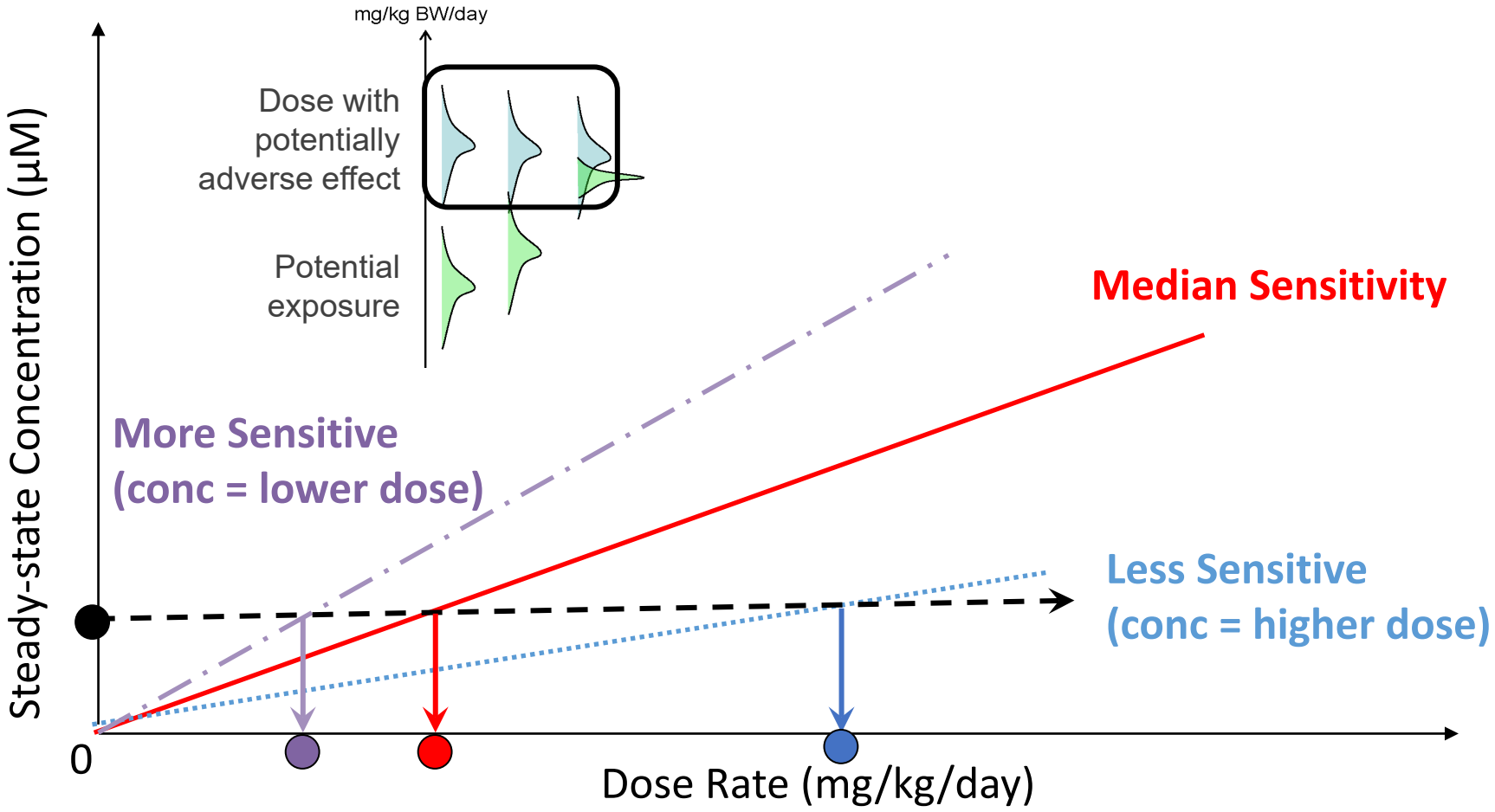
Q: What determines the slope of the line?
A: The TK model parameters.

Chemical-specific parameters	
Intrinsic hepatic clearance rate	Measured in HT *in vitro* assays (Rotroff *et al.* 2010; Wetmore *et al.* 2012, 2014, 2015; Wambaugh *et al.* 2019) or predicted *in silico* (Sipes *et al.* 2017)
Fraction unbound to plasma protein	
Tissue:blood partition coefficients (for compartmental models)	Predict from phys-chem properties and tissue properties (Pearce et al., 2017)
Physiological parameters	
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	

TK model parameters represent biology — so they have population variability

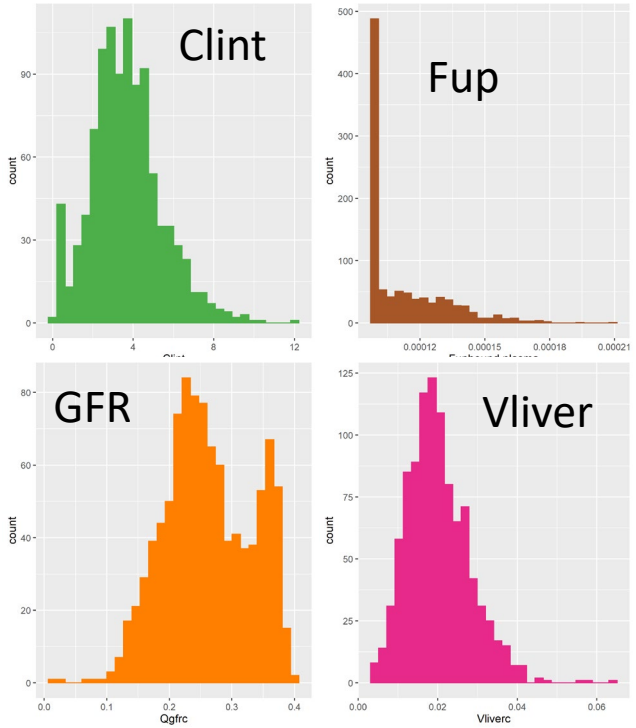
Chemical-specific parameters	
Intrinsic hepatic clearance rate	Represent chemical-body interactions — vary with individual genetics, environmental factors, age, etc.
Fraction unbound to plasma protein	
Tissue:blood partition coefficients (for compartmental models)	
Physiological parameters	
Tissue masses (including body weight)	Represent physiology — vary with individual genetics, environmental factors, age, etc.
Tissue blood flows	
Glomerular filtration rate (passive renal clearance)	
Hepatocellularity	

That means the slope of the line varies across the population — so a single *in vitro* concentration corresponds to a *distribution* of external doses.



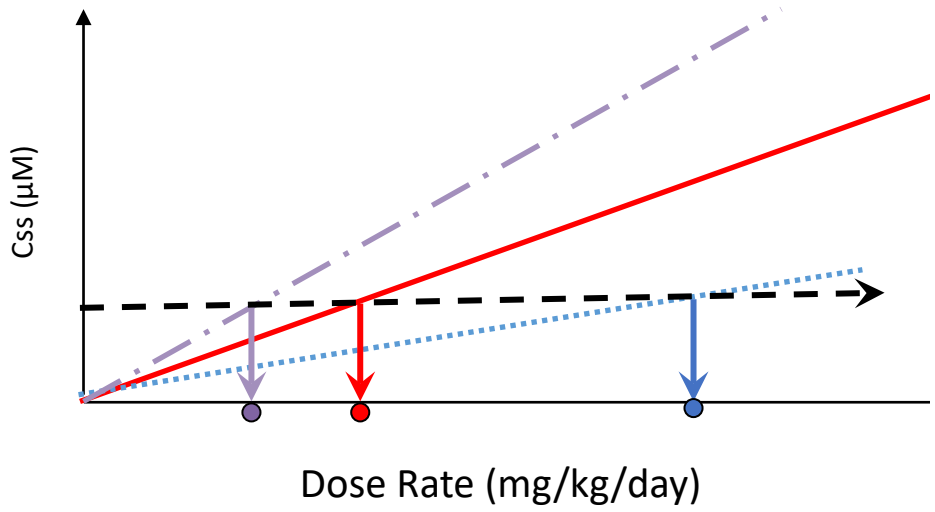
Monte Carlo approach to population TK in IVIVE

Sample from population distribution of TK parameters

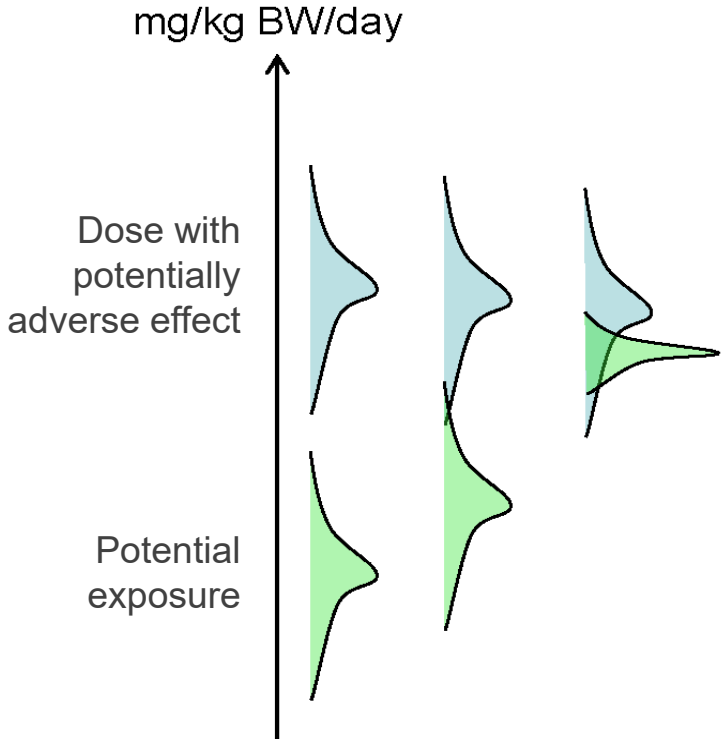


(+ other params)

Calculate corresponding distribution of slopes for dose-Css relation & equivalent doses for *in vitro* bioactive concentration of interest



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

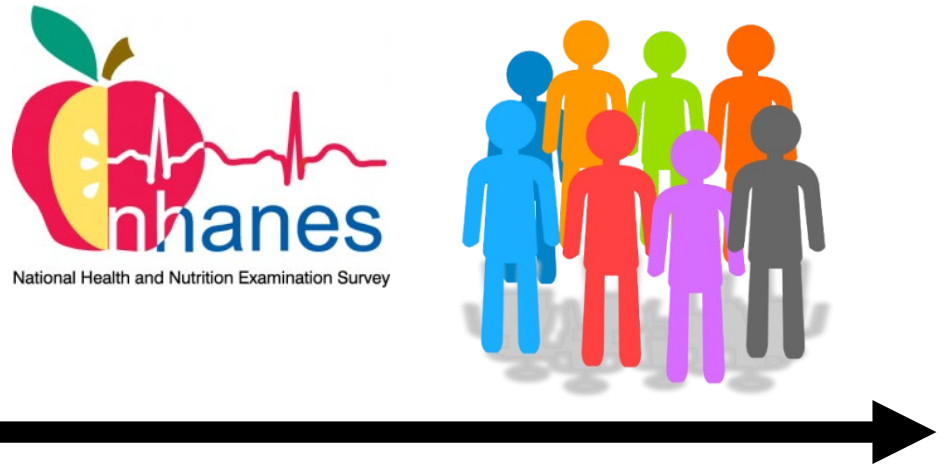


HTTK-Pop: correlated Monte Carlo approach to population TK

Based on physiology data measured as part of the US CDC National Health and Nutrition Examination Survey (NHANES) — publicly available on the web at https://www.cdc.gov/nchs/nhanes/index.htm

Sample NHANES-measured quantities for actual individuals:

- Sex
- Race/ethnicity
- Age
- Height
- Weight
- Serum creatinine
- Hematocrit



Regression equations from literature (McNally *et al.*, 2014) (+ residual marginal variability)

Predict physiological TK quantities (as used by generic TK model) for each individual:

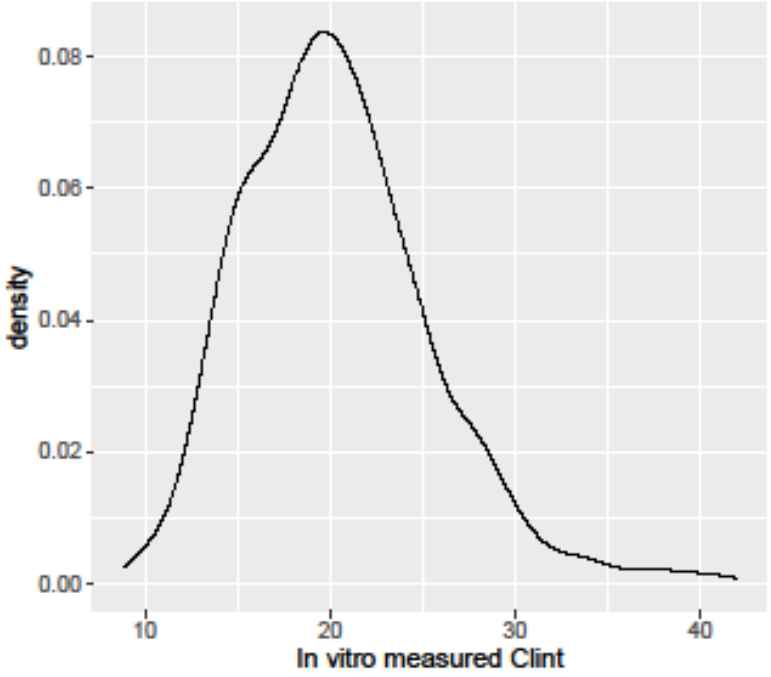
- Tissue masses
- Tissue blood flows
- GFR (kidney function)
- Hepatocellularity

(Similar approach used in SimCYP [Jamei et al. 2009], GastroPlus, PopGen [McNally et al. 2014], P3M [Price et al. 2003], physB [Bosgra et al. 2012], etc.)

Ring *et al*. (2017)

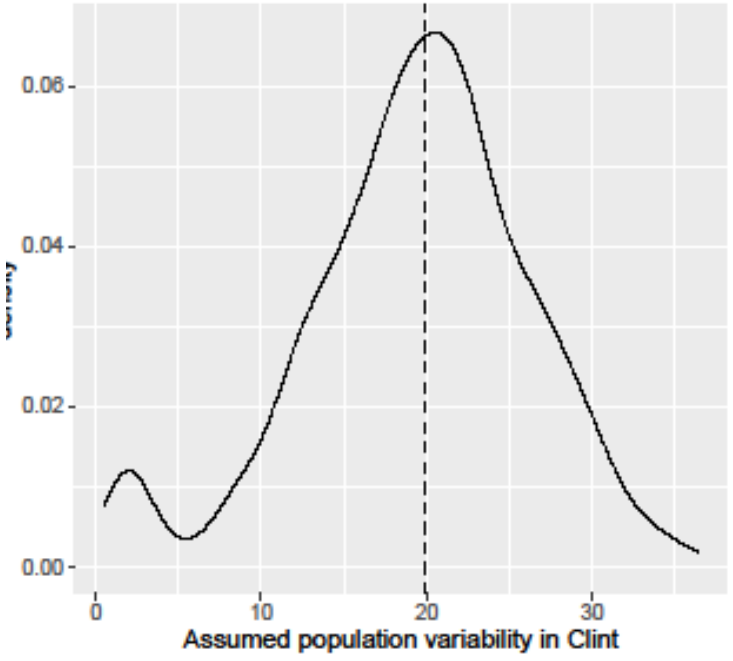
Monte Carlo approach to propagating both *uncertainty* and *variability* in chemical-specific TK parameters

Quantify uncertainty for *in vitro* measured value
Describe as distribution for each chemical



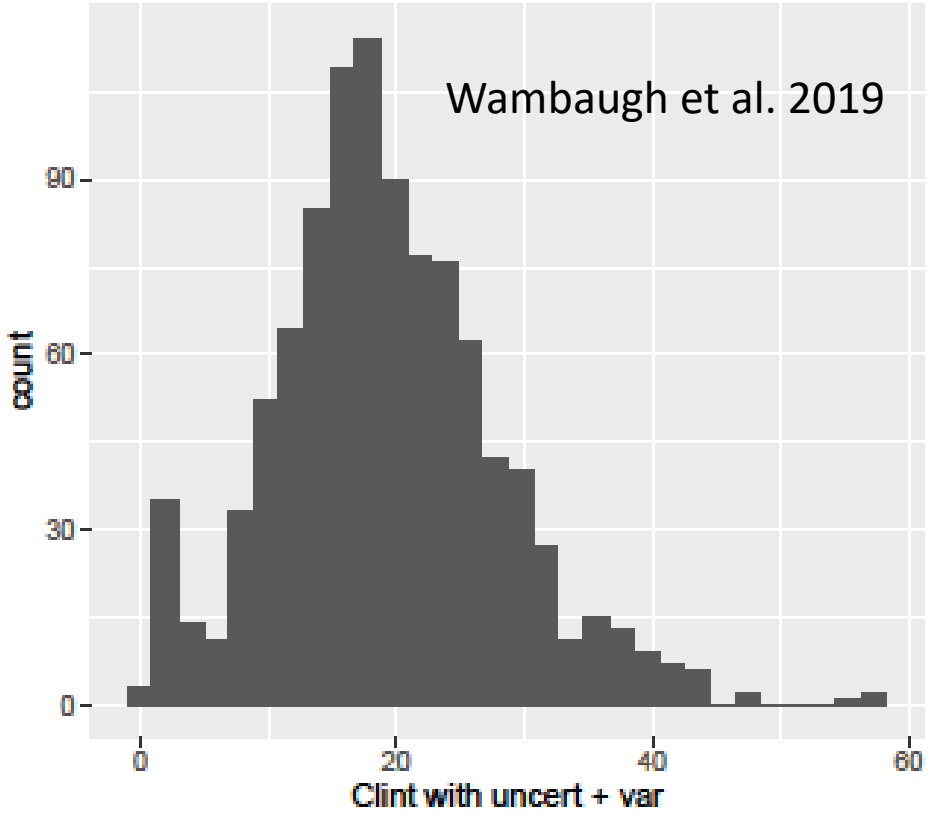
Wambaugh et al. 2019

Assume population variability around *in vitro* measured value



Ring et al. 2017

Two-stage Monte Carlo to get sampled values for each simulated individual that include both uncertainty & variability



Note: This example is just a hypothetical illustration, not real data

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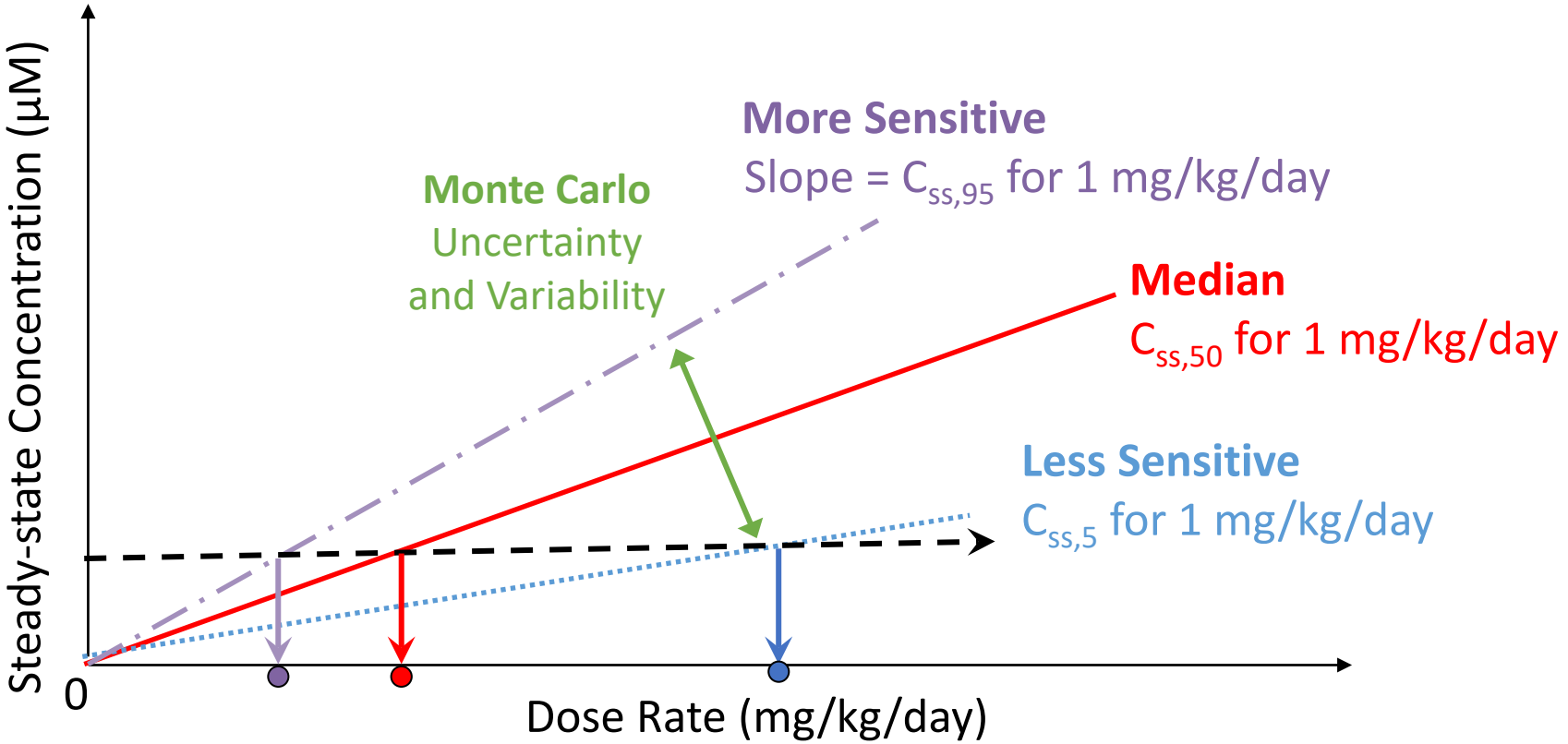
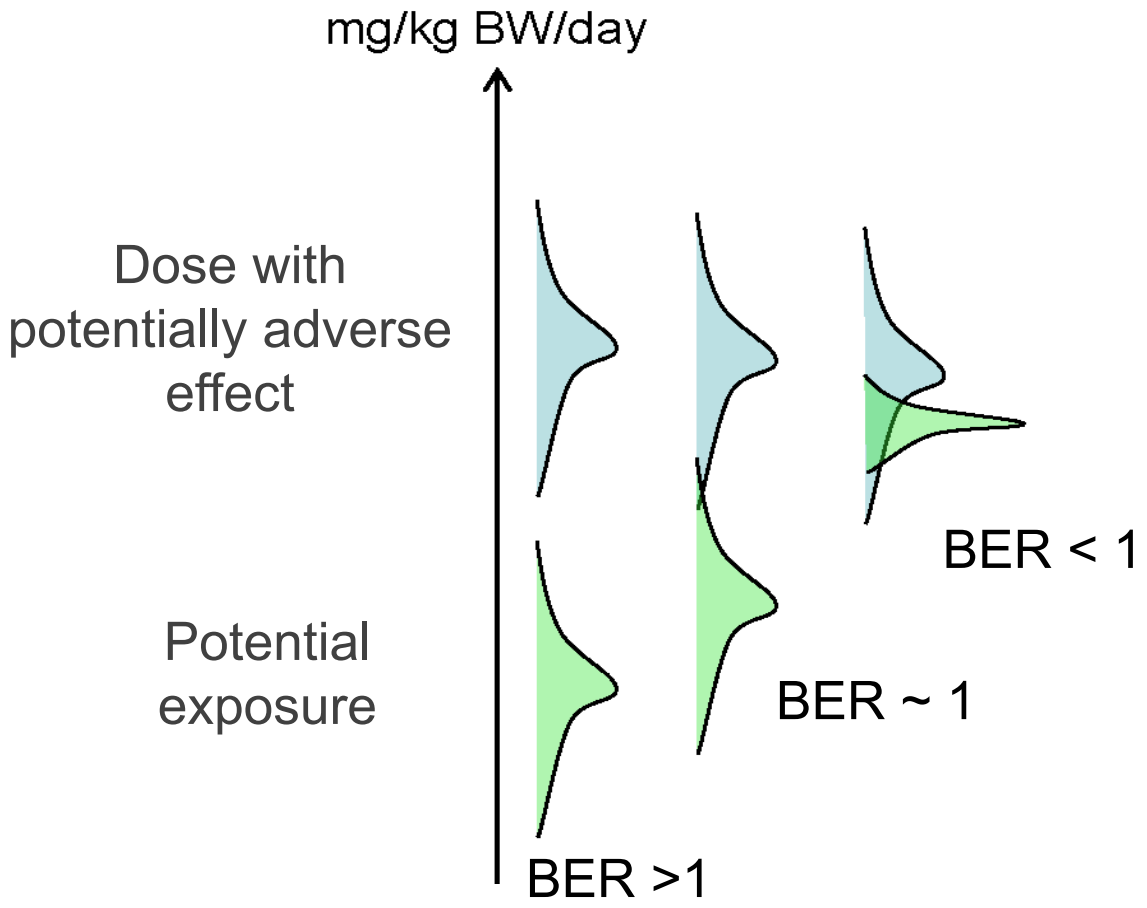
HTTK-Pop lets us estimate equivalent dose for the most-sensitive portion of the population

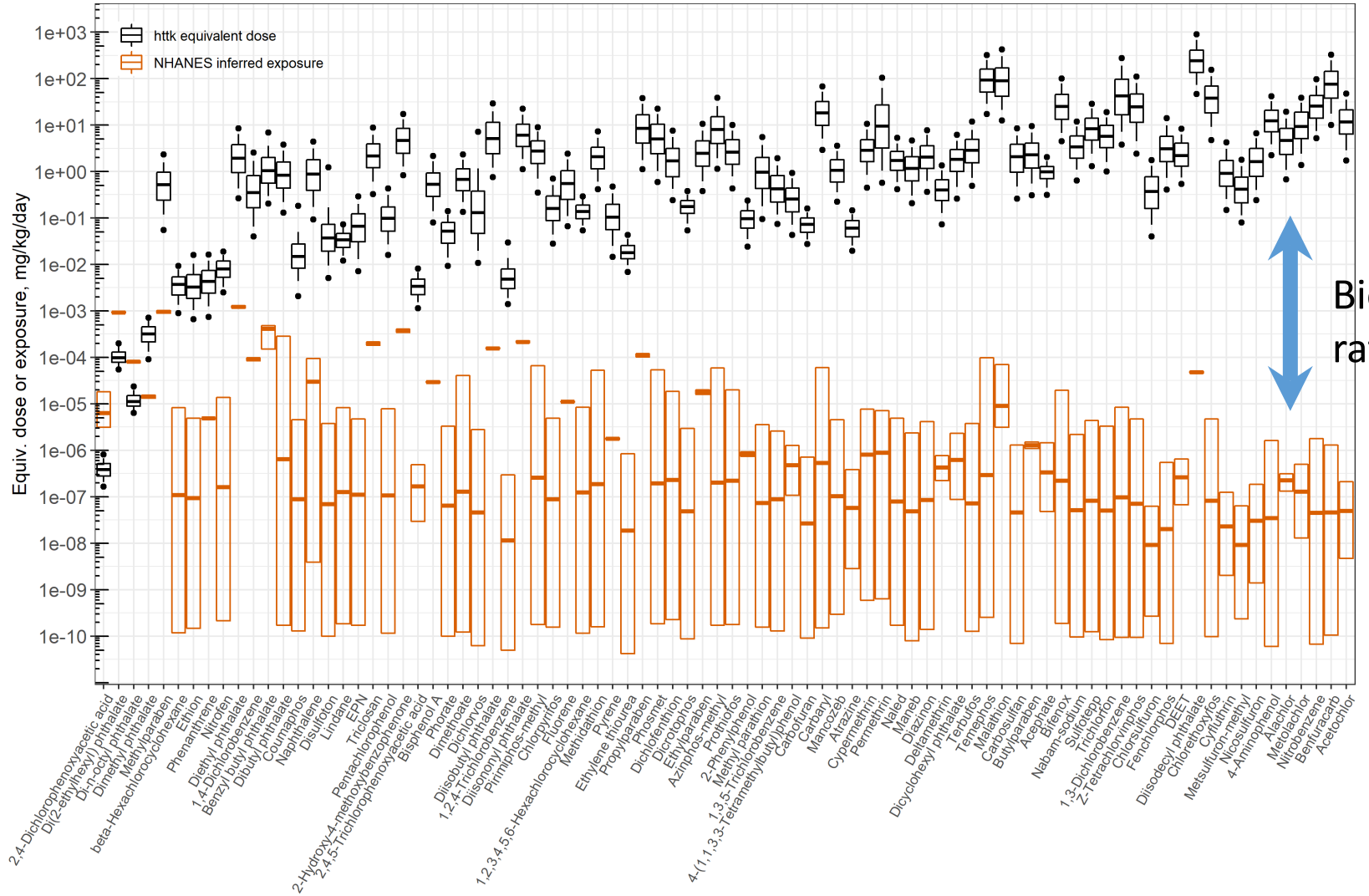
The most-sensitive 5% of the population (the steeper, 95th percentile slope) has the lowest equivalent dose (see purple lines in this graphic) —
in other words, this is the level of exposure where we predict that the most sensitive 5% of the population might potentially see some effects.



Then, we compare the low-end equivalent dose to the high-end potential exposure to calculate Bioactivity-Exposure Ratio (BER)



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



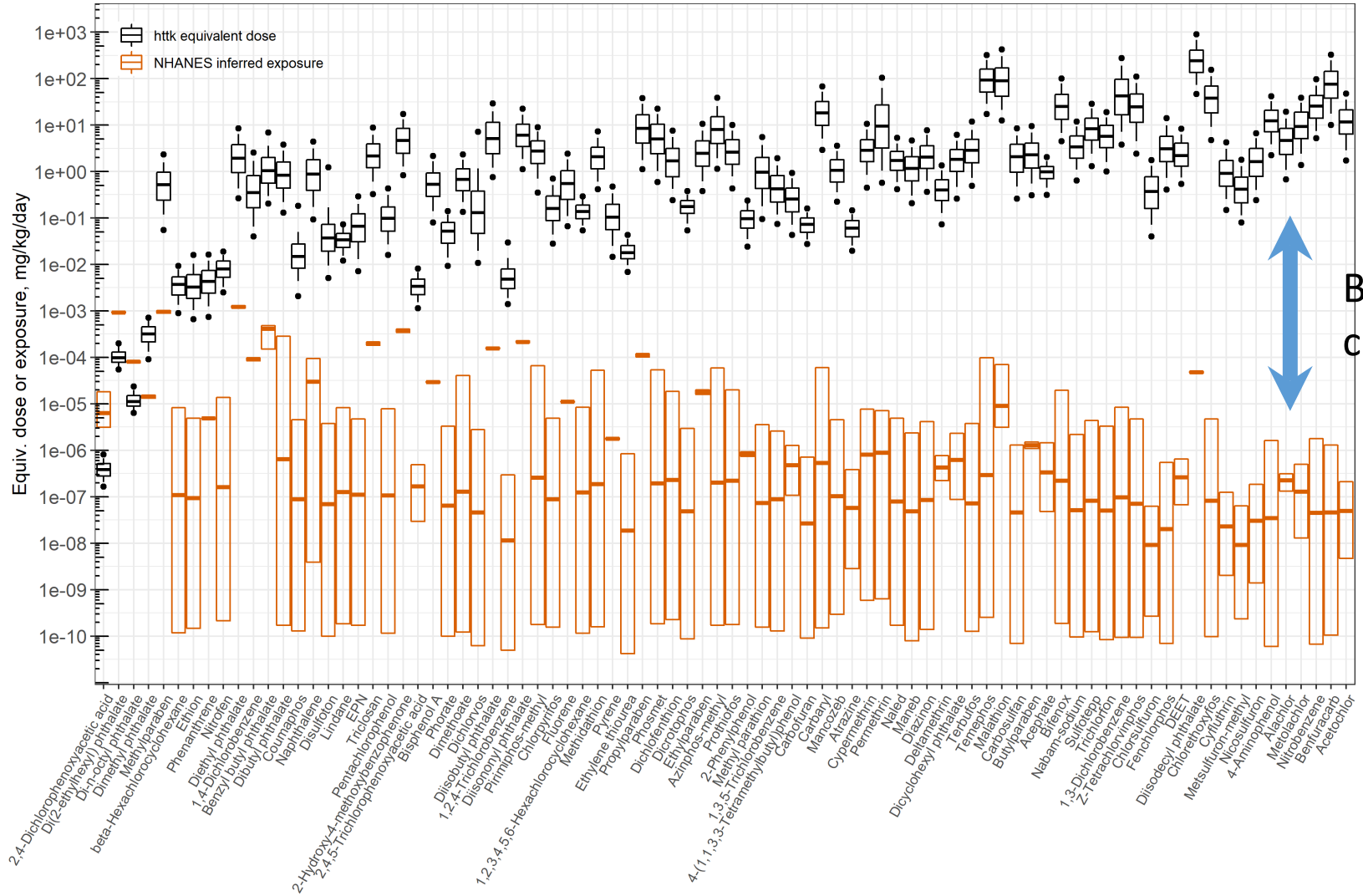
Population distributions of equivalent dose for 10th percentile ToxCast AC50 (bottom point = most-sensitive 5%)

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)

How might this prioritization change for potentially-sensitive subpopulations?



Equivalent dose might shift if subpopulation TK distribution is different from the overall US population

BER might therefore shift — changing prioritization?

Exposures might shift if subpopulation-specific NHANES-inferred exposures were different from overall US population

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

Evaluating potentially-sensitive subpopulations

- Potential population median exposures were inferred from NHANES urine biomonitoring data for 10 subpopulations of interest: ages 6-11; ages 12-19; ages 66+; men; women; reproductive-aged women (age 18-45); BMI < 30, and BMI > 30 (Wambaugh et al. 2014; Ring et al. 2017)

- Used HTTK-Pop to simulate population TK variability for the same 10 subpopulations & calculate equivalent doses for ToxCast AC50s.

- Computed BERs for each chemical and each subpopulation.

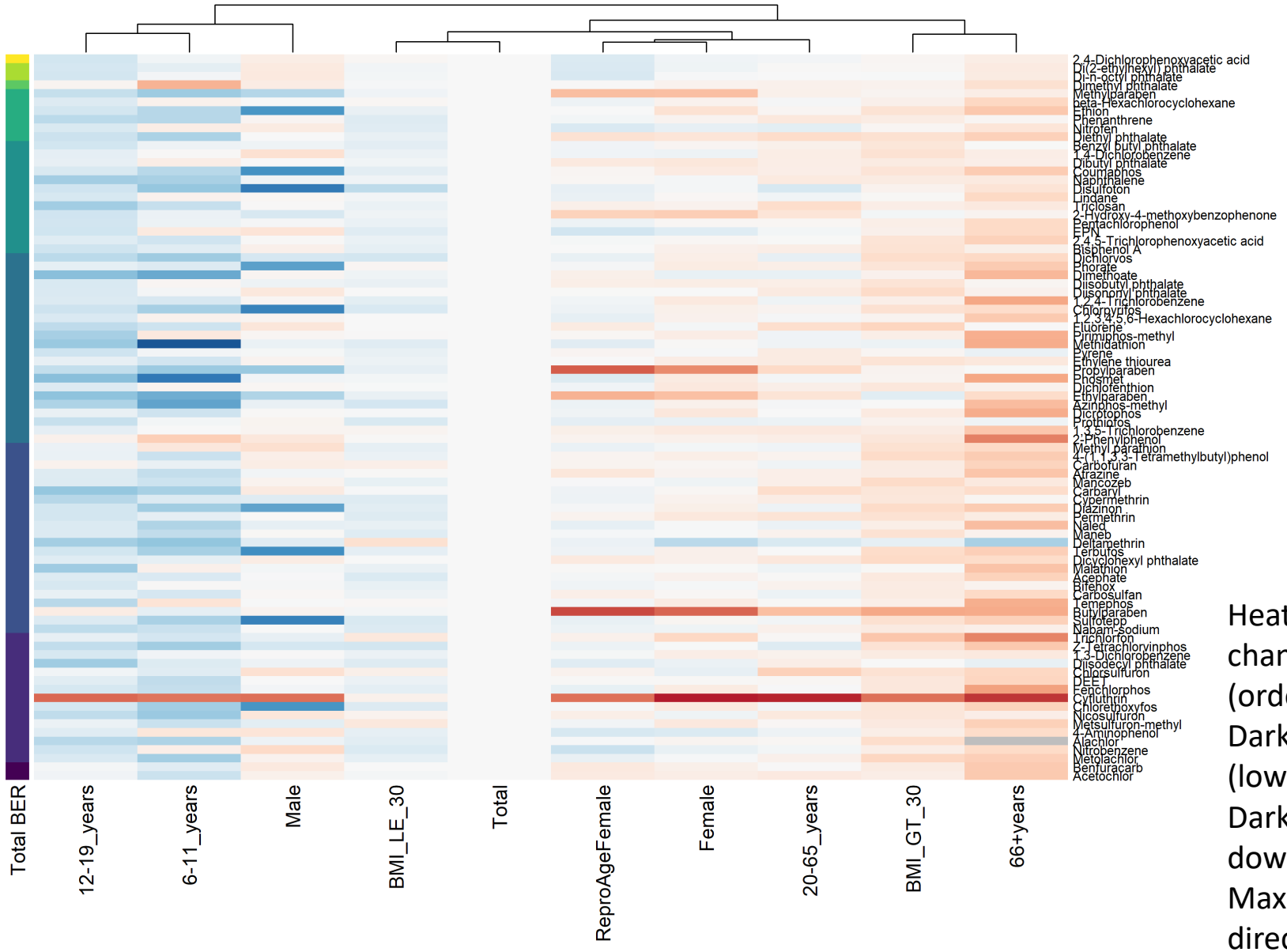
- How much did BERs change, relative to the BER for the same chemical in the Total US population?

How different are subpopulation BERs vs. Total population?

Rows: Chemicals (listed in same order as for Total population BER rankings)

Sidebar colors indicate BER order of magnitude in Total population

Columns: Potentially-sensitive subpopulations



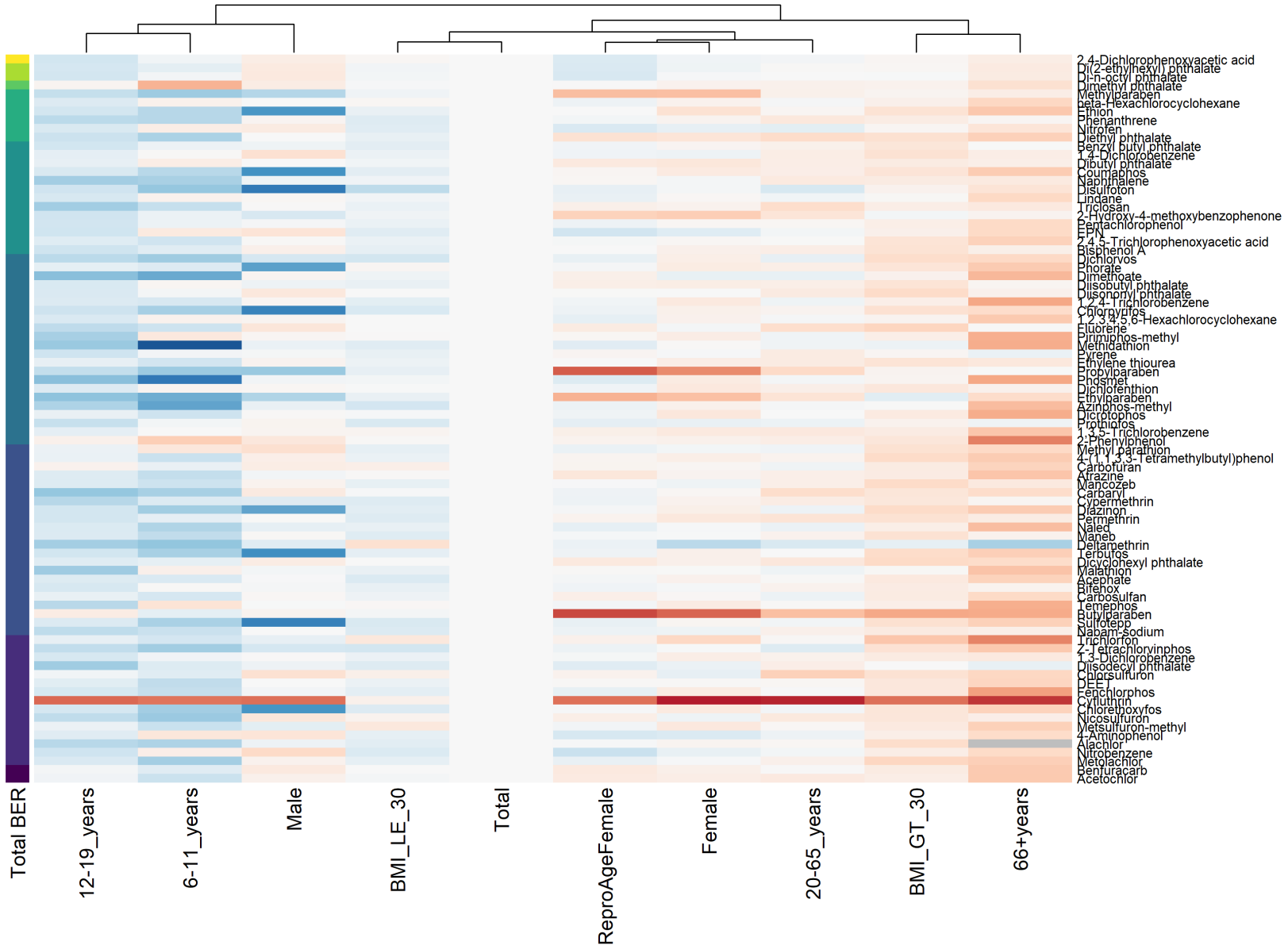
Updated version of analysis from Ring et al. (2017)

Heatmap colors: BER change vs. Total population (order of magnitude)
Darker blue = BER shifts up (lower priority)
Darker red = BER shifts down (higher priority)
Max shift = 10x either direction

How different are subpopulation BERs vs. Total population?

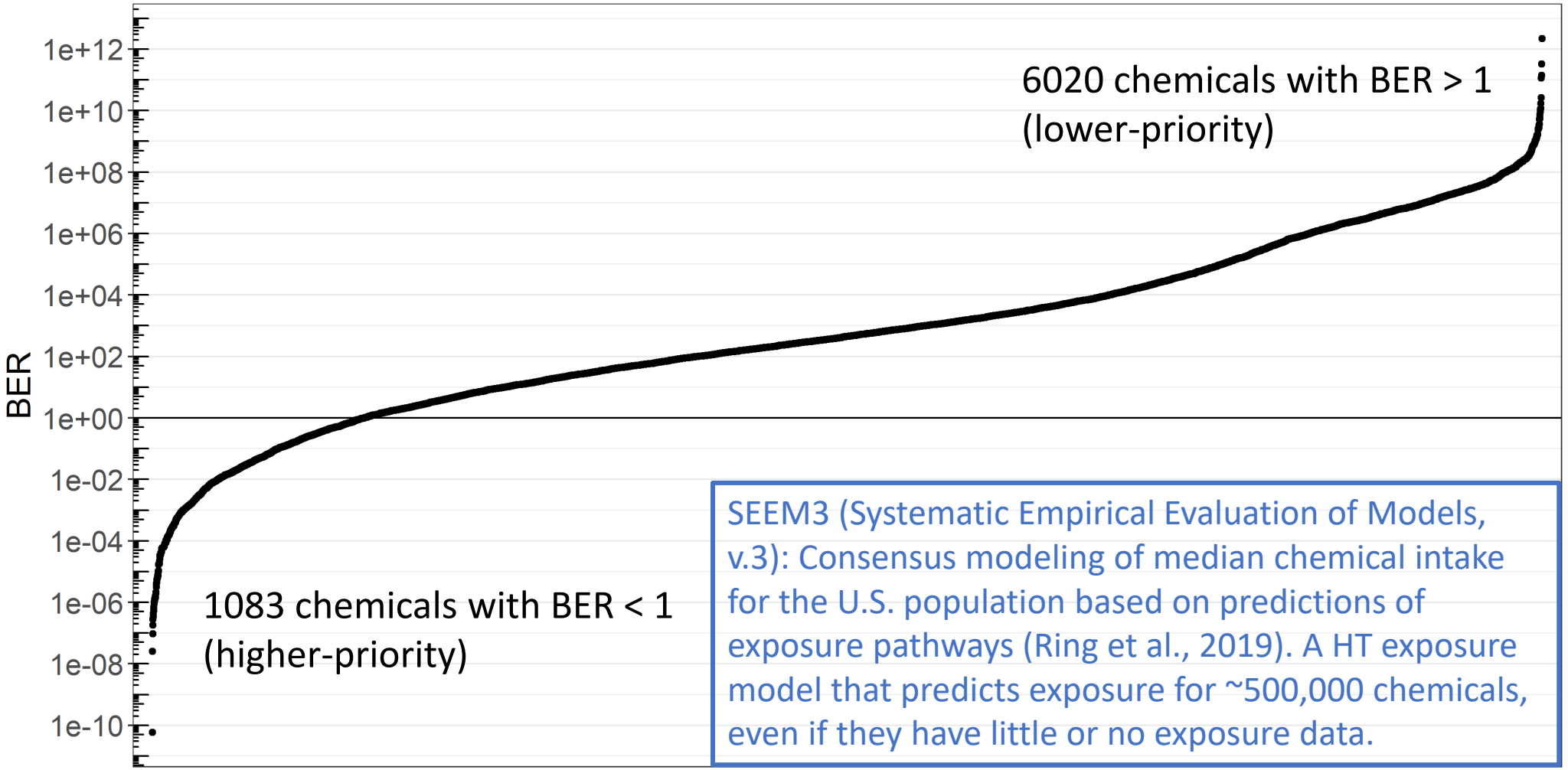
For these chemicals & subpopulations, BER shifts aren't big enough to substantially change chemical prioritization.

However, we do see some chemical-specific shifts — and some broader subpopulation-wide shifts across chemicals — illustrating the potential of subpopulation-specific prioritization.



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



SEEM3 (Systematic Empirical Evaluation of Models, v.3): Consensus modeling of median chemical intake for the U.S. population based on predictions of exposure pathways (Ring et al., 2019). A HT exposure model that predicts exposure for ~500,000 chemicals, even if they have little or no exposure data.

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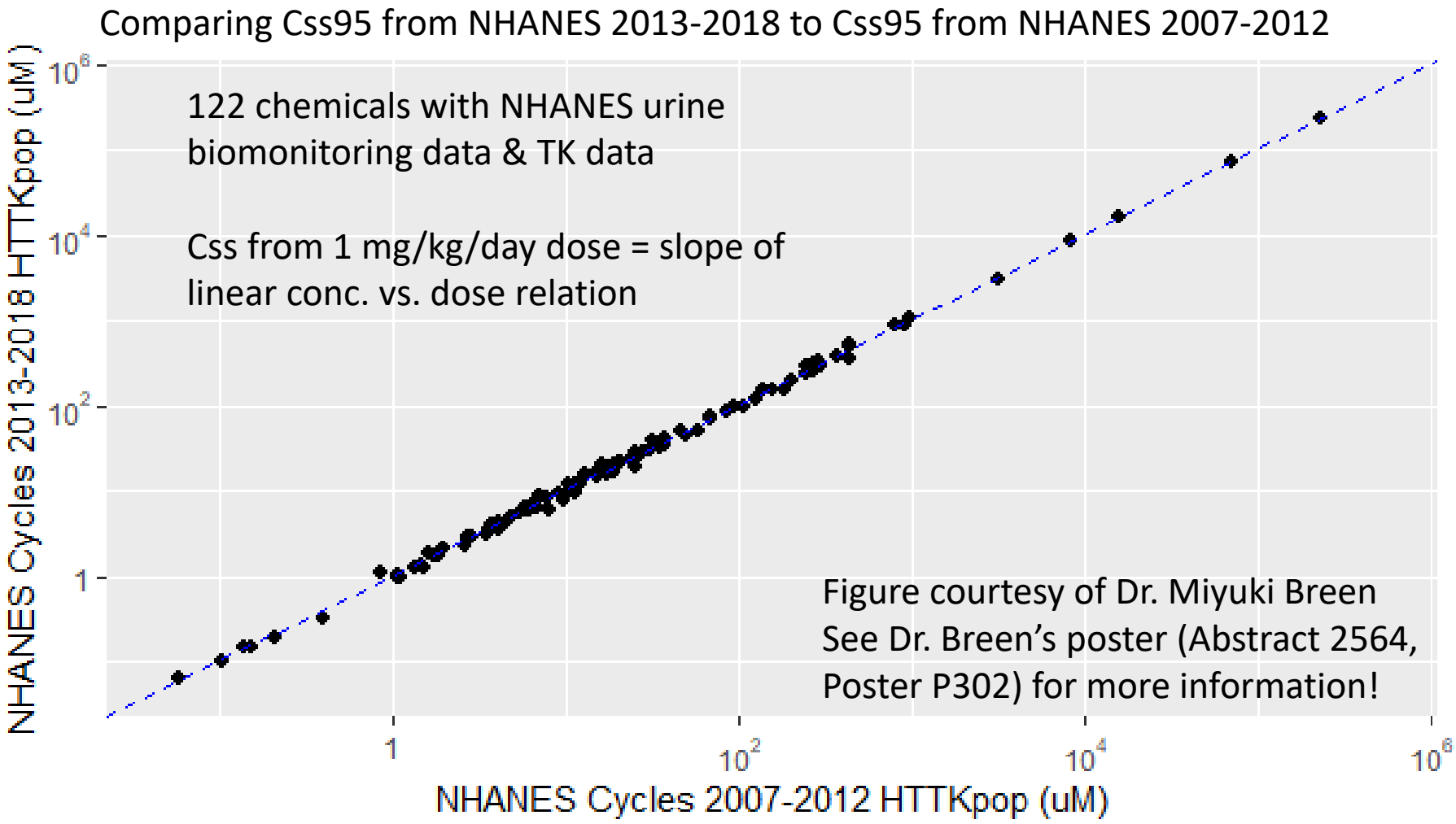
Active work is ongoing to update and expand HTTK, HTTK-Pop, and exposure models!

- HTTK-Pop is being updated to include the most recent NHANES data (2013-2018) (Breen et al., in prep)
- New HT-PBTK models are being developed
  - an inhalation TK model (Linakis et al., 2020; Breen et al., in prep) – currently available in httk package (though not yet for IVIVE/reverse TK)
  - a dermal TK model (Evans et al., in prep) — not yet available in httk package, but watch this space
  - a gestational/fetal TK model (Kapraun et al., 2018; Kapraun et al., in prep) — not yet available in httk package, but watch this space
- HT exposure models are being updated

HTTK-Pop is being updated to include more recent NHANES data (2013-2018) (Breen et al., in prep)

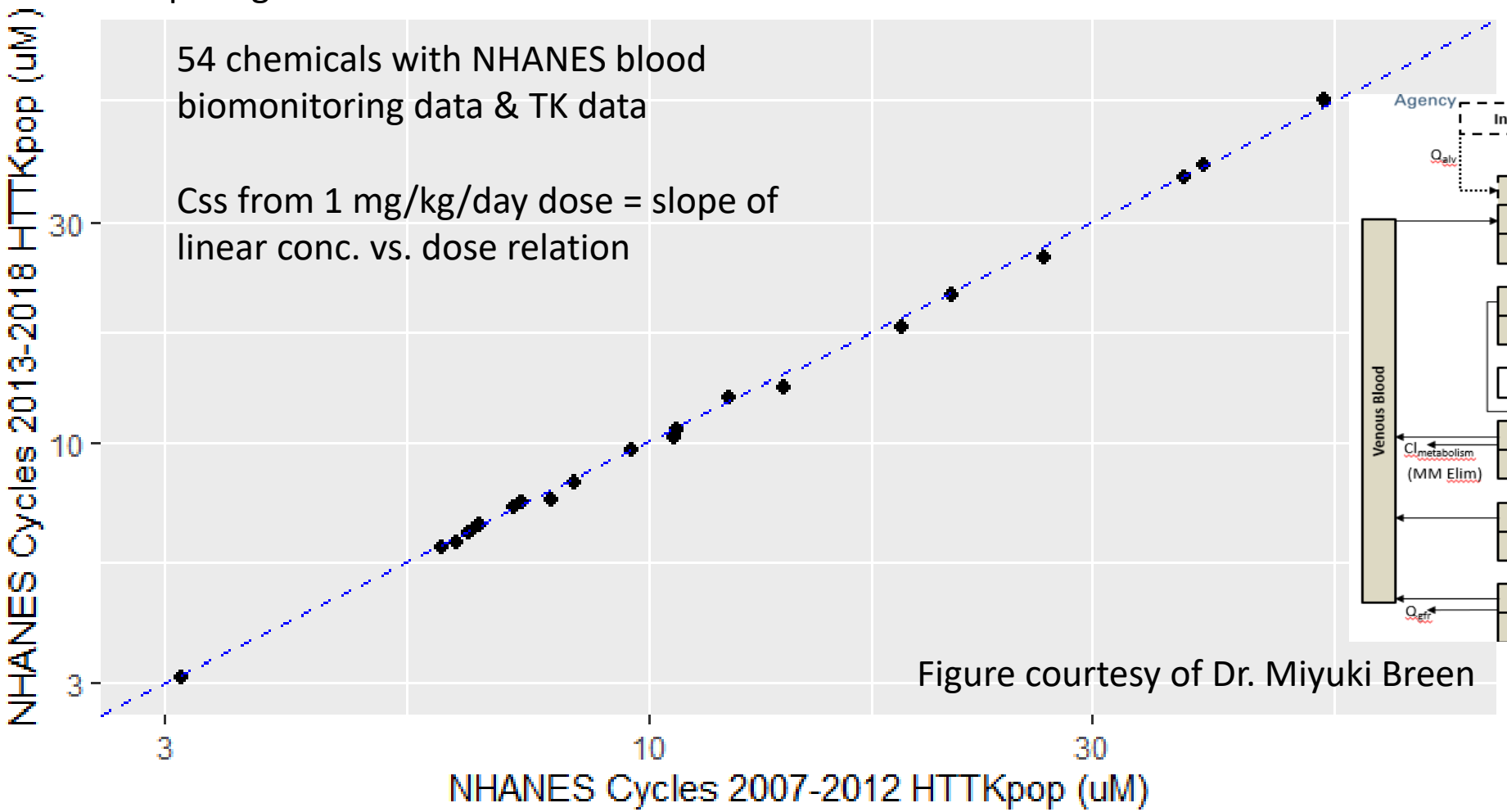


Gas inhalation PBTK model added to httk (Linakis et al., 2020) & being linked with HTTK-Pop for population TK (Breen et al., in prep)

Comparing Css95 from NHANES 2013-2018 to Css95 from NHANES 2007-2012

54 chemicals with NHANES blood biomonitoring data & TK data

Css from 1 mg/kg/day dose = slope of linear conc. vs. dose relation



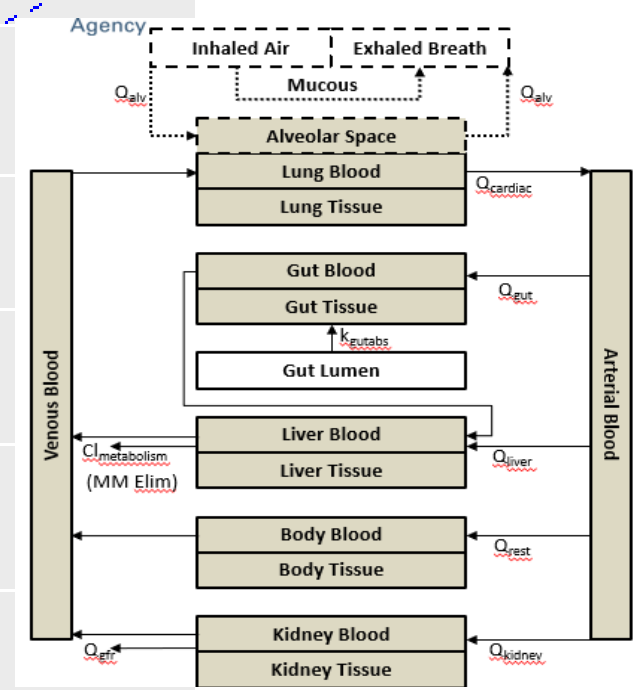


Figure courtesy of Dr. Miyuki Breen

NHANES population exposure inferences are being updated to reflect latest NHANES biomonitoring data

(Stanfield et al. in prep)

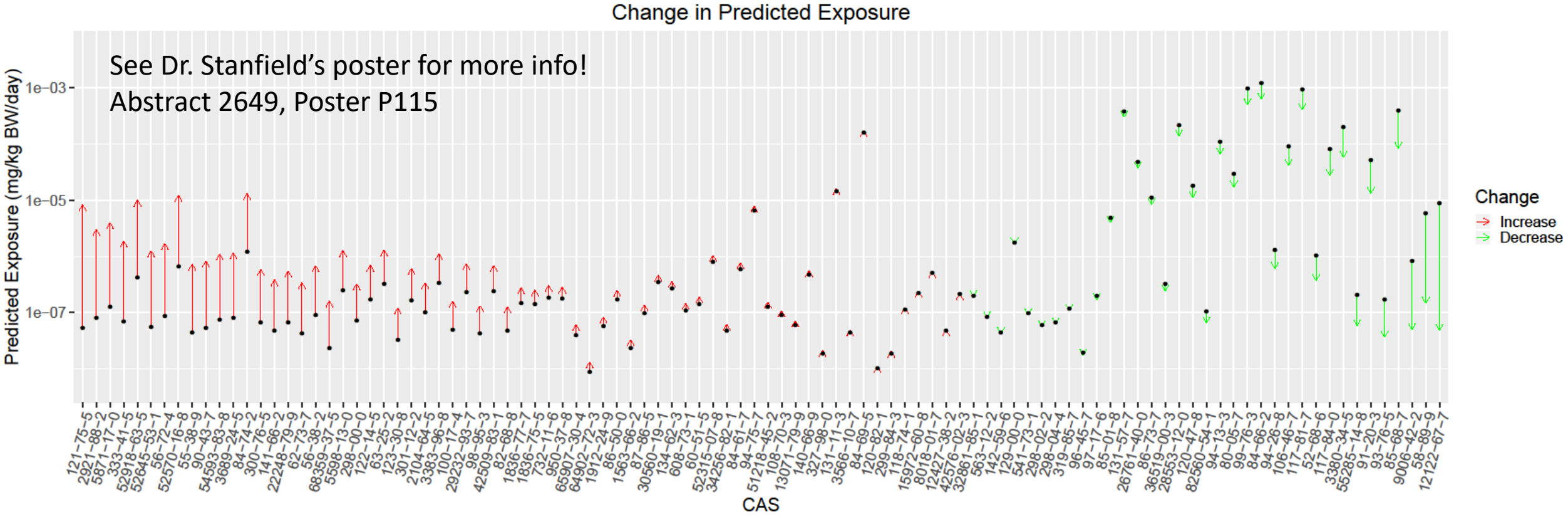


Figure courtesy of Dr. Zachary Stanfield

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Conclusions

- High-throughput toxicokinetics (HTTK) allows IVIVE — extrapolating *in vitro* HT screening bioactivity to external doses
  - implemented in free, open-source R package “httk”
- Monte Carlo approach to simulating population TK (HTTK-Pop) allows high-throughput evaluation of population TK variability in IVIVE
  - specifically, characterization of population distribution of equivalent doses for a given *in vitro* bioactive concentration
- Combining population TK with population exposure estimates (e.g. via ExpoCast or SEEM3) allows rapid chemical prioritization based on bioactivity-exposure ratio (BER), a metric of potential risk
- Including population TK variability allows estimates to be protective of most-sensitive portion of the population and potentially-sensitive subpopulations
- Many updates and additions to httk and HTTK-Pop are in progress!

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