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EPA United States Environmental Protection Agency

Simulating Human Variability in Toxicokinetics with R Package "httk"

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Center for Computational Toxicology and Exposure

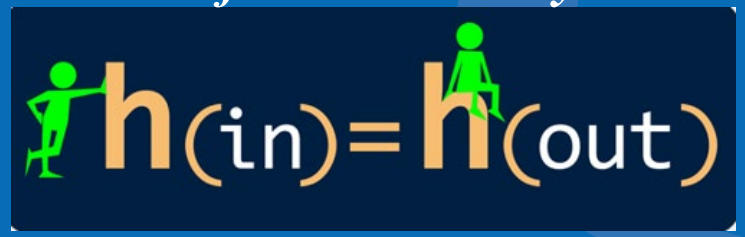
Office of Research and Development

U.S. Environmental Protection Agency

Thursday, November 10, 2022

Human In, Human Out:

Using Primary and Population Data for PBPK Analyses



US EPA Office of Research and Development

- The Office of Research and Development (ORD) is the scientific research arm of EPA
  - 543 peer-reviewed journal articles in 2019
- Research is conducted by ORD's four national centers, and three offices organized to address:
  - Public health and env. assessment; comp. tox. and exposure; env. measurement and modeling; and env. solutions and emergency response.
- 13 facilities across the United States
- Research conducted by a combination of Federal scientists (including uniformed members of the **Public Health Service**); contract researchers; and postdoctoral, graduate student, and post-baccalaureate trainees

ORD Facility in
Research Triangle Park, NC

Simulating Human Variability in Toxicokinetics with R Package "httk"

Learning Objectives

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- For what can I use HTTK?
- How does HTTK simulate human variability?
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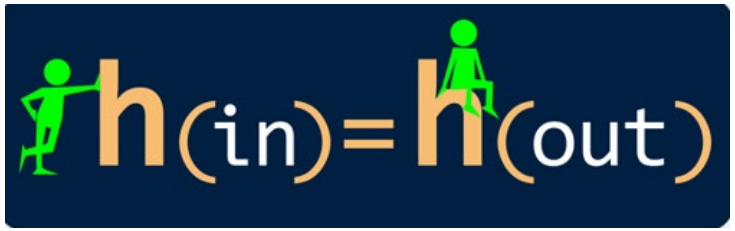

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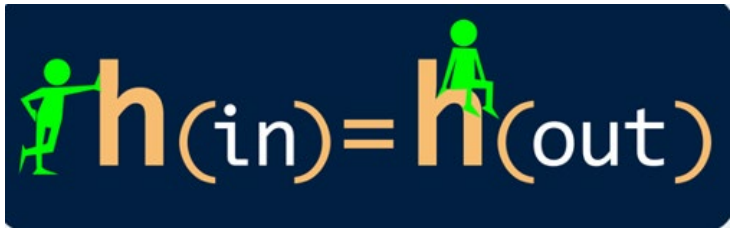
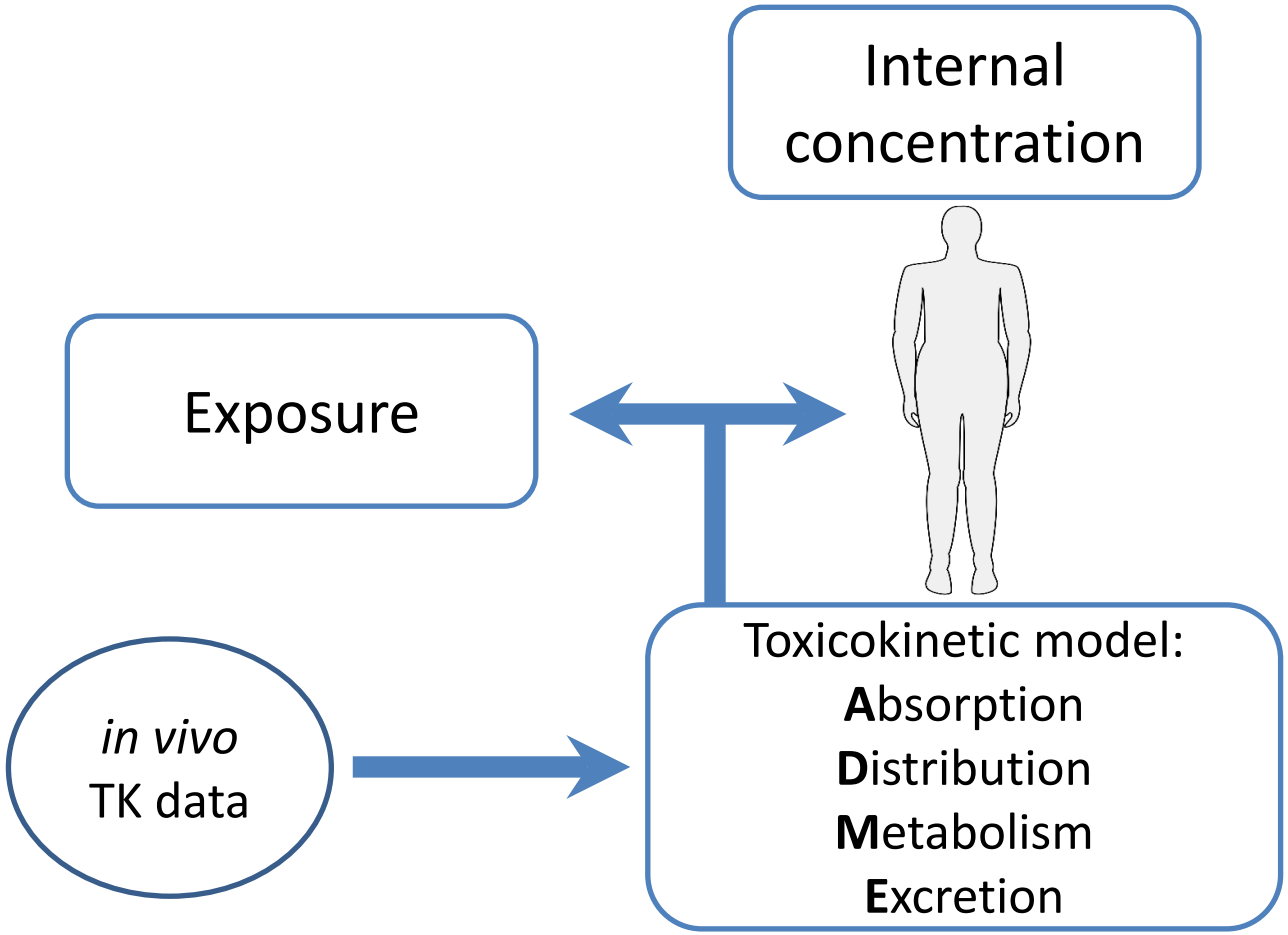
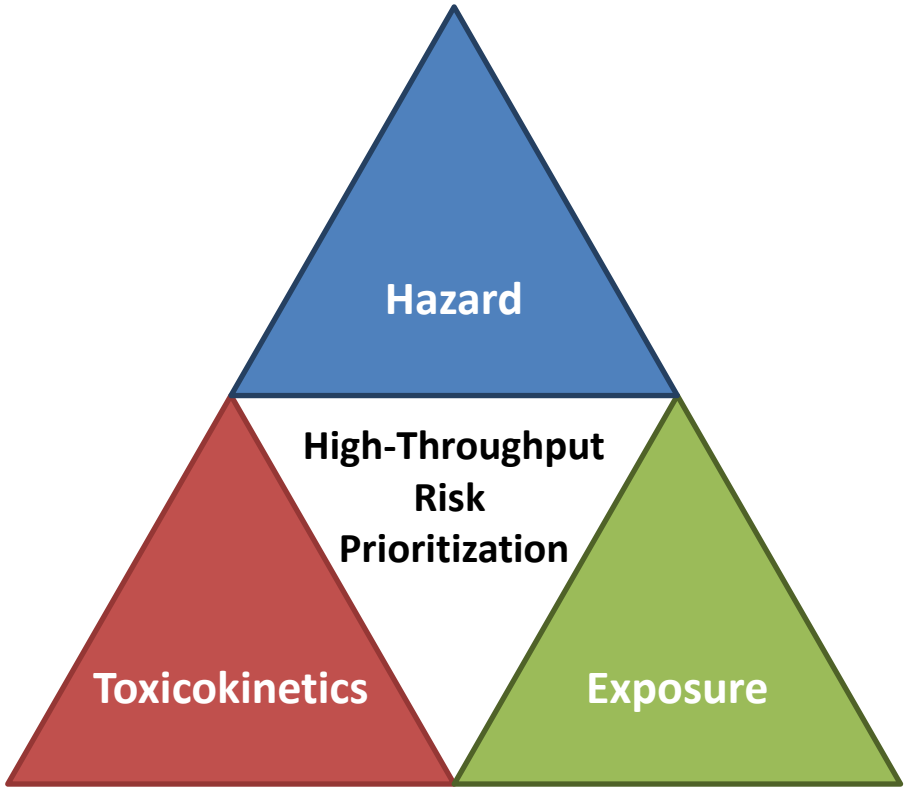


Toxicokinetics

- Toxicokinetics describes the absorption, distribution, metabolism, and excretion of a chemical by the body:
  - Chemical-specific
  - Links exposure with internal concentrations

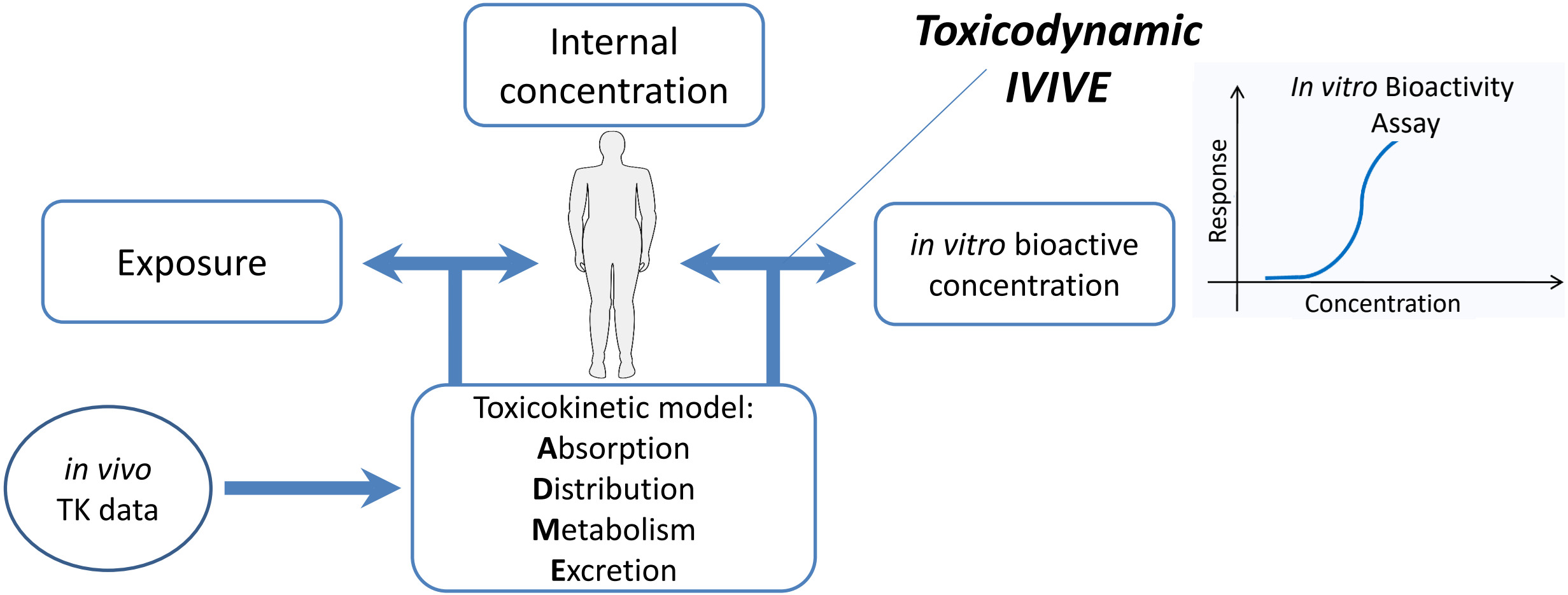




Breen *et al.* (2021)

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.* (2021)

Most Chemicals Lack Toxicokinetic Data

- Most non-pharmaceutical chemicals – for example, flame retardants, plasticizers, pesticides, solvents – do not have human *in vivo* TK data.
- Non-pesticidal chemicals are unlikely to have any *in vivo* TK data, even from animals

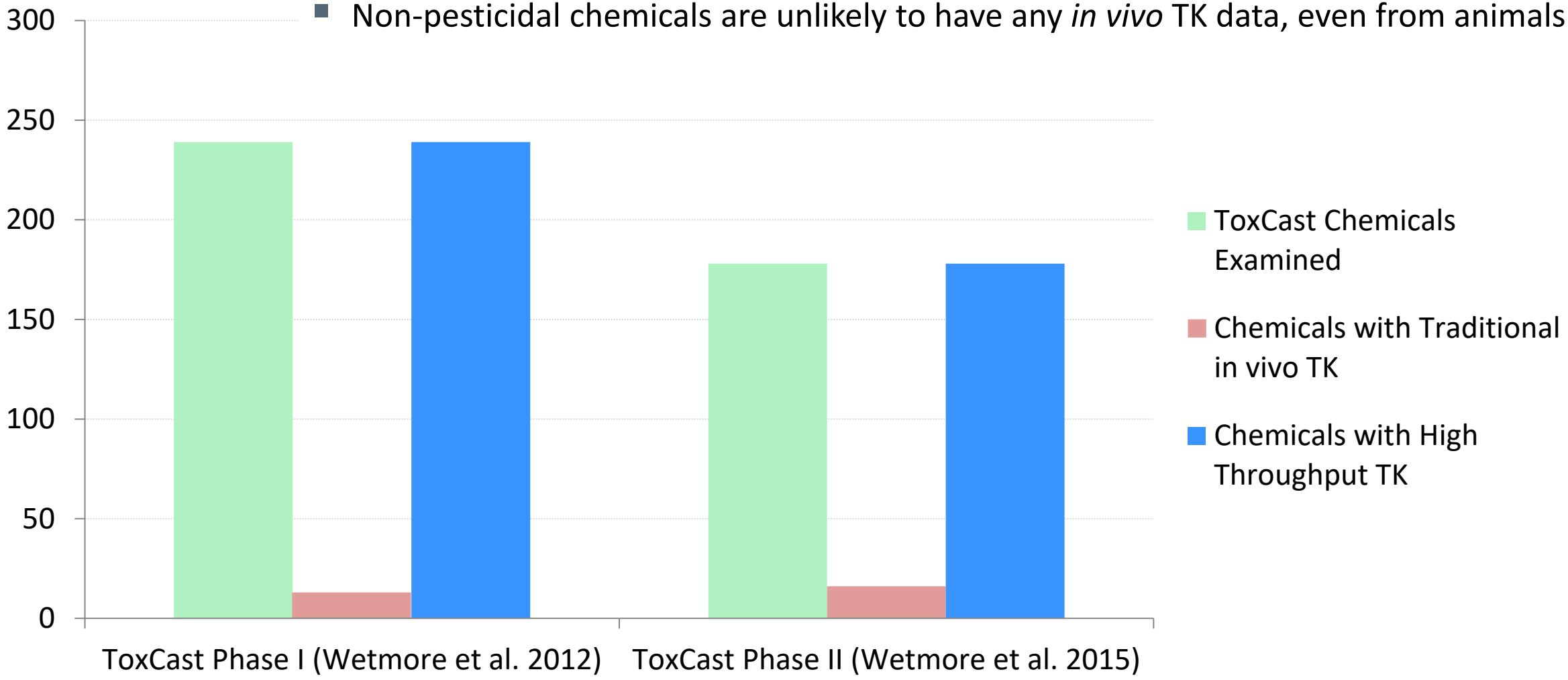


Figure from Bell *et al.* (2018)

High Throughput Toxicokinetics (HTTK)

- To provide toxicokinetic data for larger numbers of chemicals collect *in vitro*, high throughput toxicokinetic (HTTK) data
(for example, Rotroff *et al.*, 2010, Wetmore *et al.*, 2012, 2015)
- HTTK methods have been used by the pharmaceutical industry to determine range of efficacious doses and to prospectively evaluate success of planned clinical trials
(Jamei, *et al.*, 2009; Wang, 2010)
- The **primary goal** of HTTK is to provide a human dose context for bioactive *in vitro* concentrations from HTS (that is*, in vitro-in vivo* extrapolation, or **IVIVE**)
(for example, Wetmore *et al.*, 2015)
- A **secondary goal** is to provide **open-source data and models** for evaluation and use by the broader scientific community (Pearce *et al.*, 2017a)

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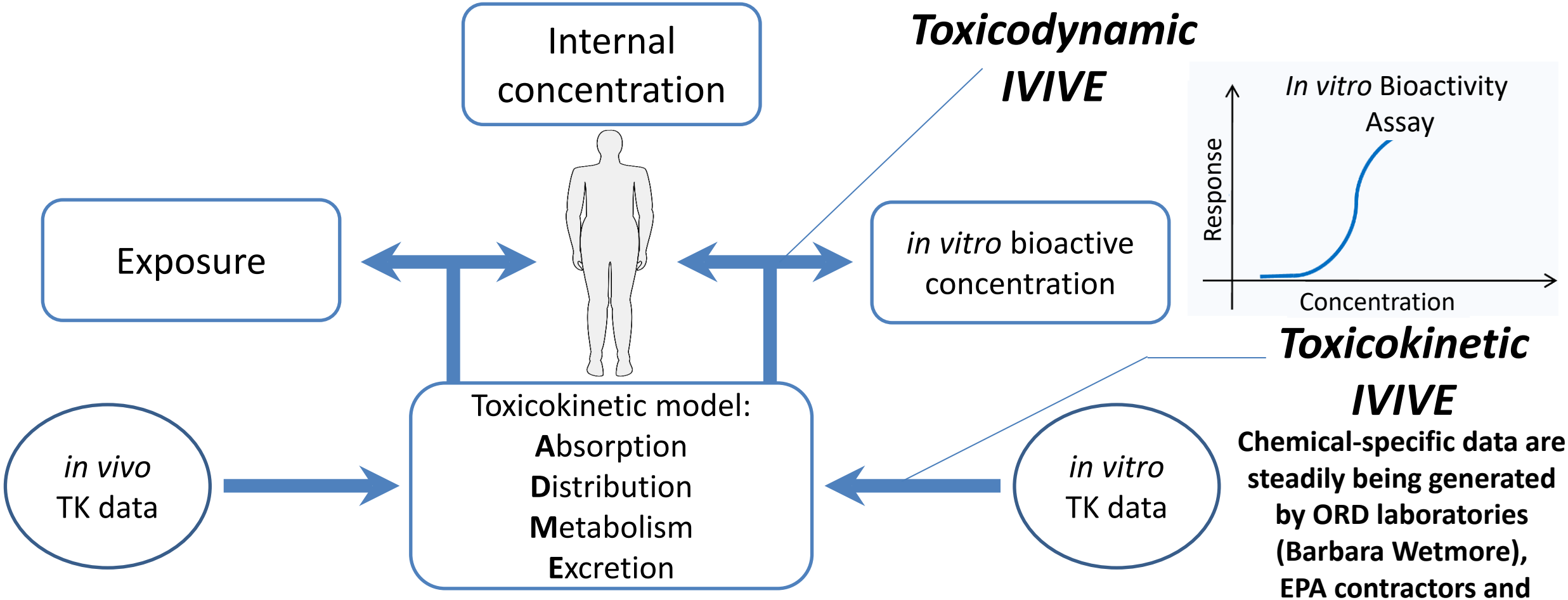

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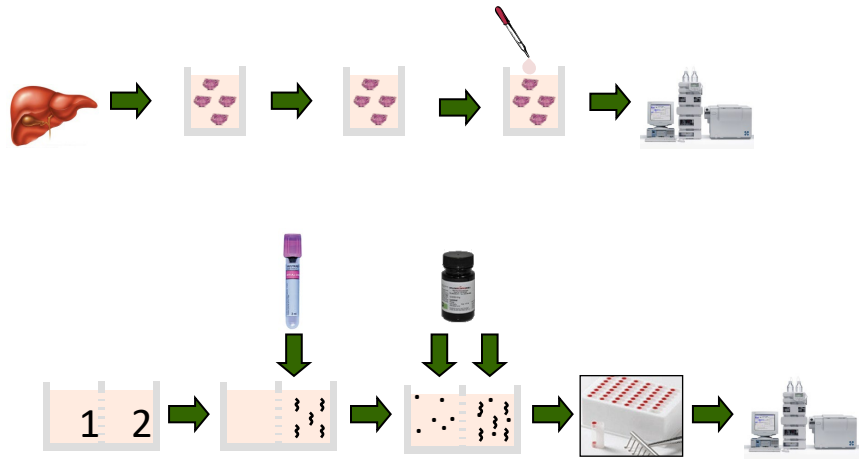
High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data



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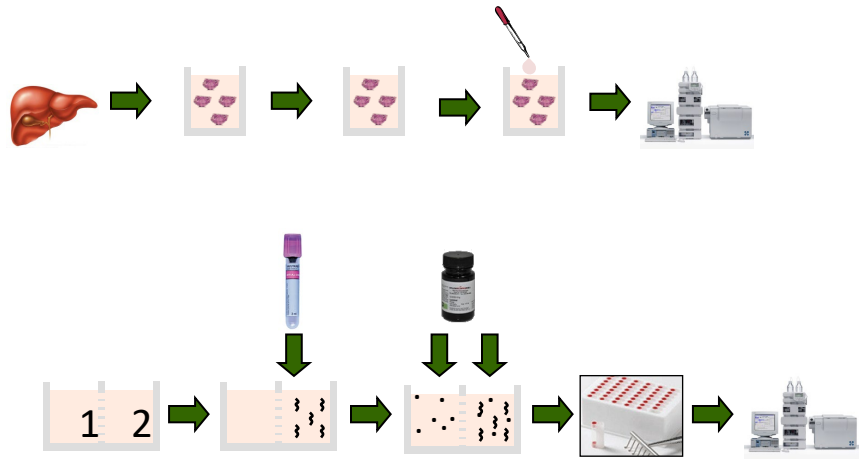
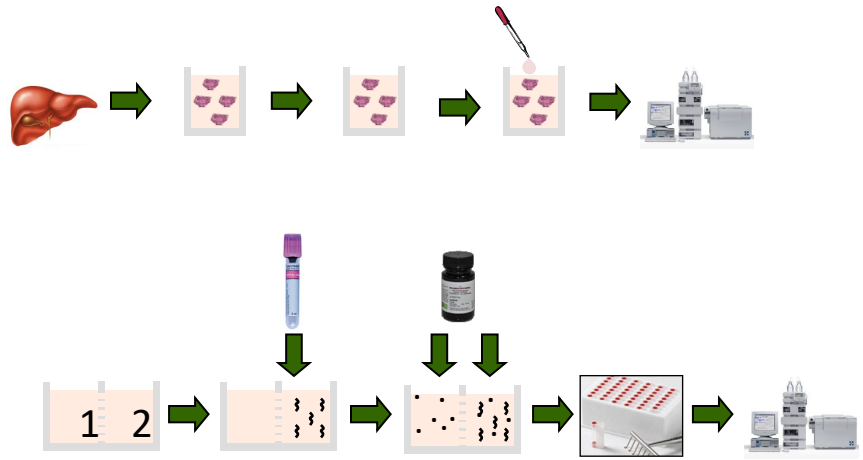
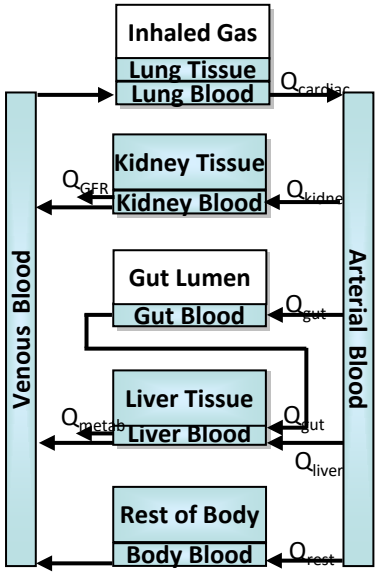


Rotroff *et al.* (2010)
Wetmore *et al.* (2012)
Wetmore *et al.* (2015)
Wambaugh *et al.* (2019)

High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data + generic toxicokinetic model





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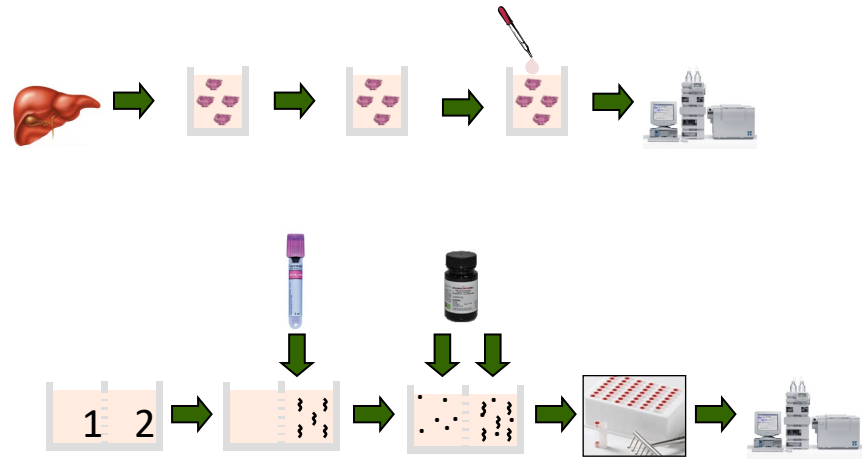

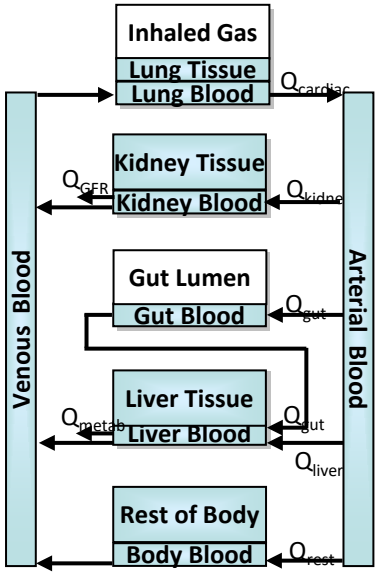

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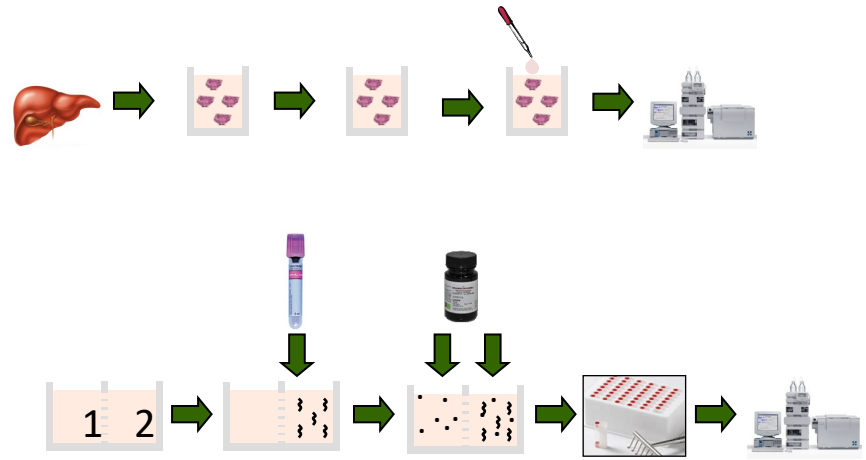
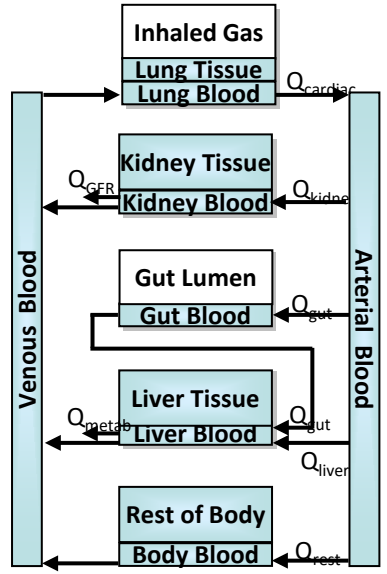
Kapraun et al. (2022)

High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data + generic toxicokinetic model = high(er) throughput toxicokinetics





= *httk*

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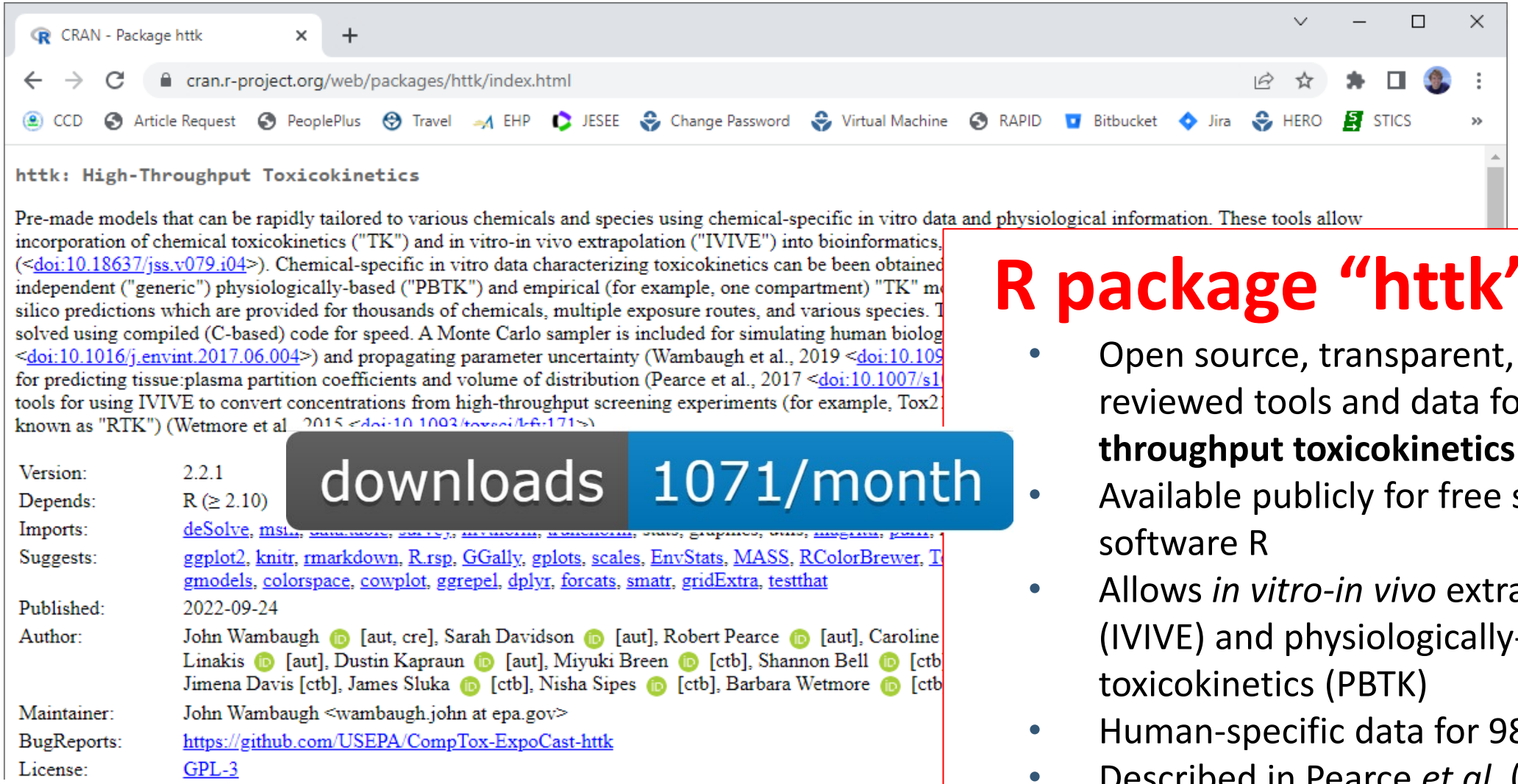
Open Source Tools and Data for HTTK

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.* (2017a)

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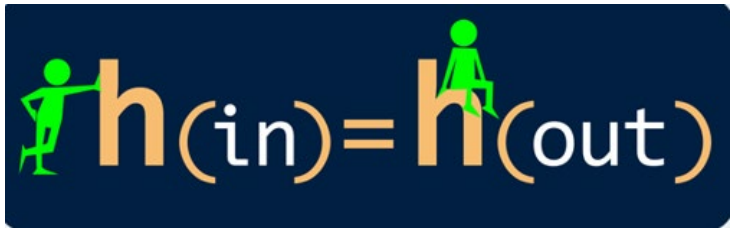


Modules within R Package "httk"

Feature	Description	Reference
Chemical Specific *In Vitro* Measurements	Metabolism and protein binding for ~1000 chemicals in human and ~200 in rat	Wetmore *et al.* (2012, 2013, 2015), plus others
Chemical-Specific *In Silico* Predictions	Metabolism and protein binding for ~8000 Tox21 chemicals	Sipes *et al.* (2017)
Generic toxicokinetic models	One compartment, three compartment, physiologically-based oral, intravenous, inhalation, and gestational exposure (PBTK)	Pearce *et al.* (2017a), Linakis *et al.* (2020)
Tissue partition coefficient predictors	Modified Schmitt (2008) method	Pearce *et al.* (2017b)
Variability Simulator	Based on NHANES biometrics	Ring *et al.* (2017)
In Vitro Disposition	Armitage et al. (2014) model	Honda *et al.* (2019)
Uncertainty Propagation	Model parameters can be described by distributions reflecting uncertainty	Wambaugh *et al.* (2019)

IVIVE by Scaling Factor

- There are many approaches to IVIVE, but we choose a relatively simple one:
- We make various assumptions that allow conversion of an *in vitro* concentration $[\boldsymbol{X}]$ (µM) into an **administered equivalent dose** (AED) with units of mg/kg body weight/day:

$$\mathbf{AED} = \boldsymbol{F_{IVIVE}} \times [\boldsymbol{X}]$$

- **AED** is the **external dose rate** that would be needed to **cause a given steady-state plasma concentration**
- F_{IVIVE} is a scaling factor that varies by chemical

IVIVE by Scaling Factor

- For a given chemical, $F_{IVIVE} = 1 / C_{ss,95}$
- $C_{ss,95}$ is the steady-state plasma concentration as the result of a 1 mg/kg/day exposure

$$\mathbf{AED_{95}} = \frac{[\boldsymbol{X}]}{\boldsymbol{C_{ss,95}}}$$

- The "95" refers to the upper 95th percentile – due to human variability and measurement uncertainty there are a range of possible C_{ss} values
- All of this assumes that the individuals have enough time to come to "steady-state" with respect to their daily exposures

Don't forget:

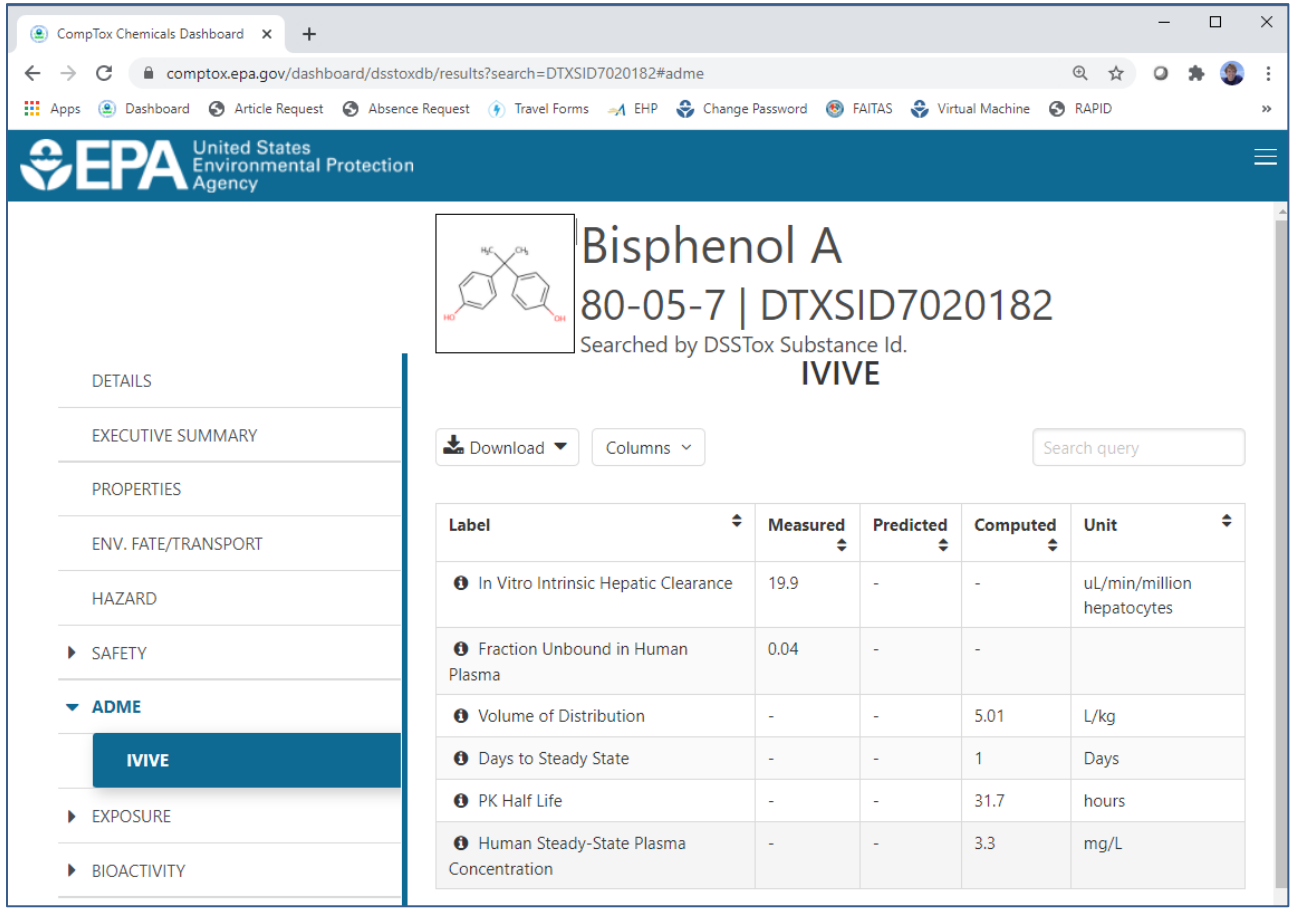
$$\mu\boldsymbol{M} = \mathbf{1000}\frac{\mathbf{1}}{\boldsymbol{MW}}\frac{\boldsymbol{mg}}{\boldsymbol{L}}$$

HTTK on the CompTox Chemicals Dashboard

- The CompTox Chemicals Dashboard provides $C_{ss,95}$ values for >1000 chemicals

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

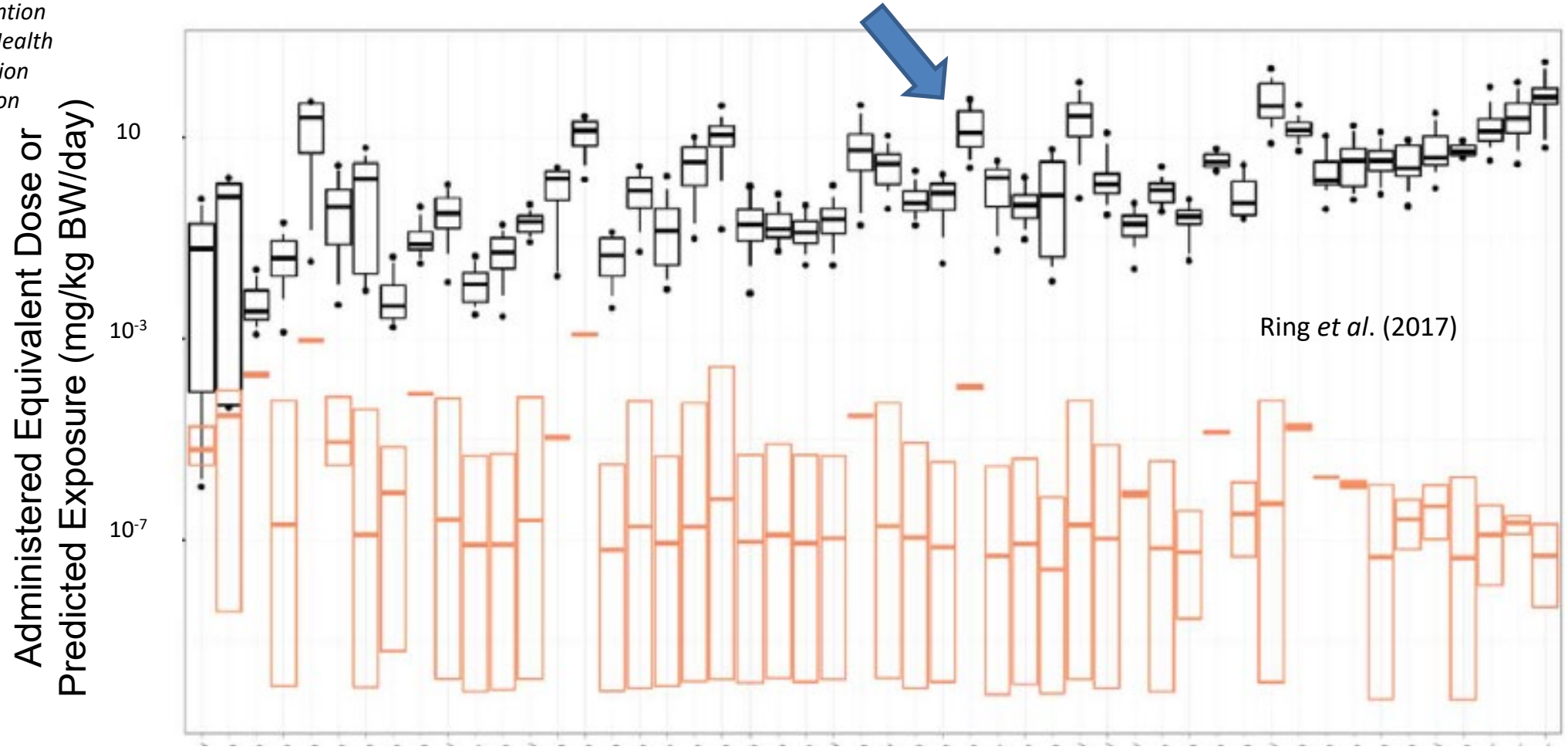
- We use EPA's R package "httk" to provide IVIVE predictions
- The value reported is calculated assuming a 1 mg/kg/day dose rate
- We give the upper 95th percentile of the calculated values based on a Monte Carlo simulation of human variability and uncertainty



IVIVE Allows Chemical Prioritization

CDC NHANES: U.S. Centers for Disease Control and Prevention National Health and Nutrition Examination Survey

In Vitro Screening + IVIVE can estimate doses needed to cause bioactivity (Wetmore *et al.*, 2015)



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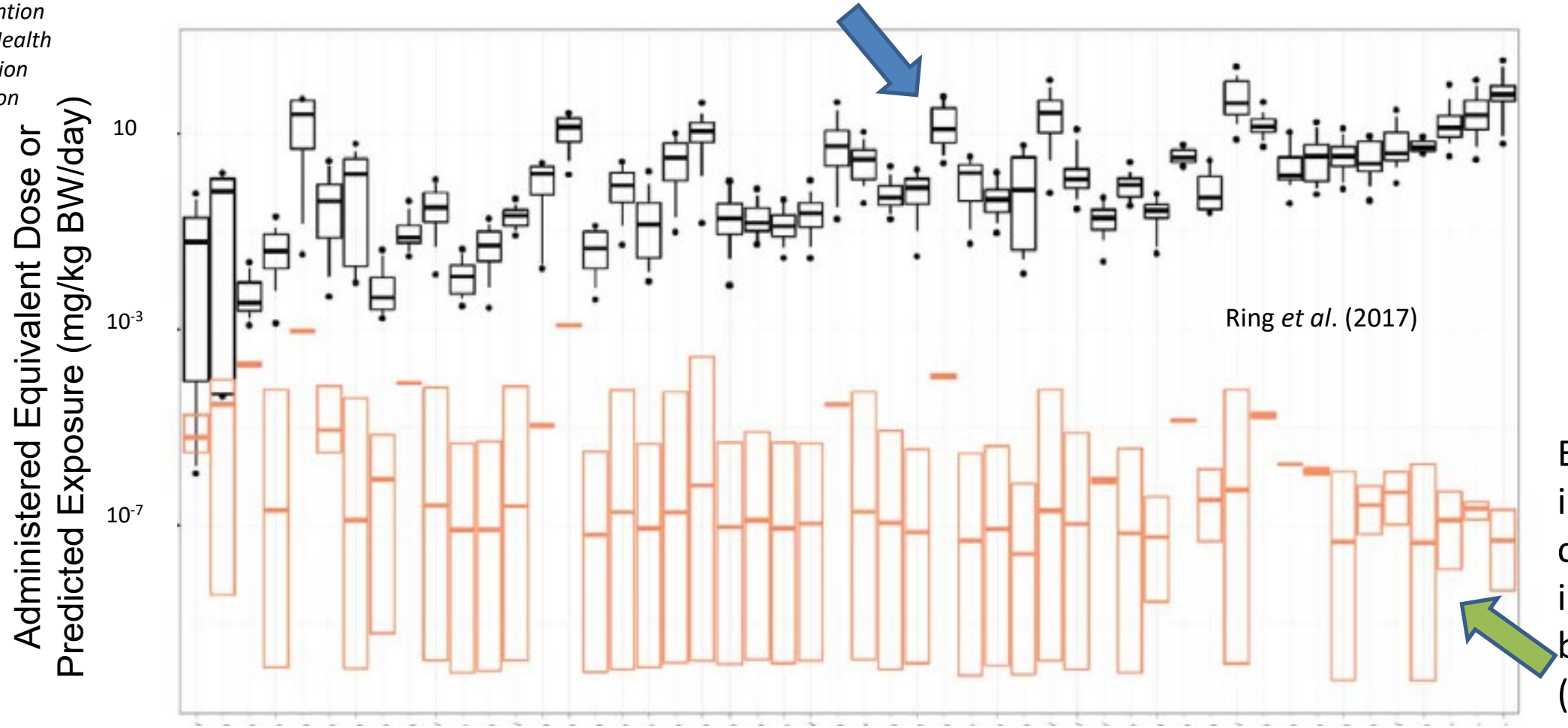

Exposure intake rates can be inferred from biomarkers (Wambaugh *et al.*, 2014)

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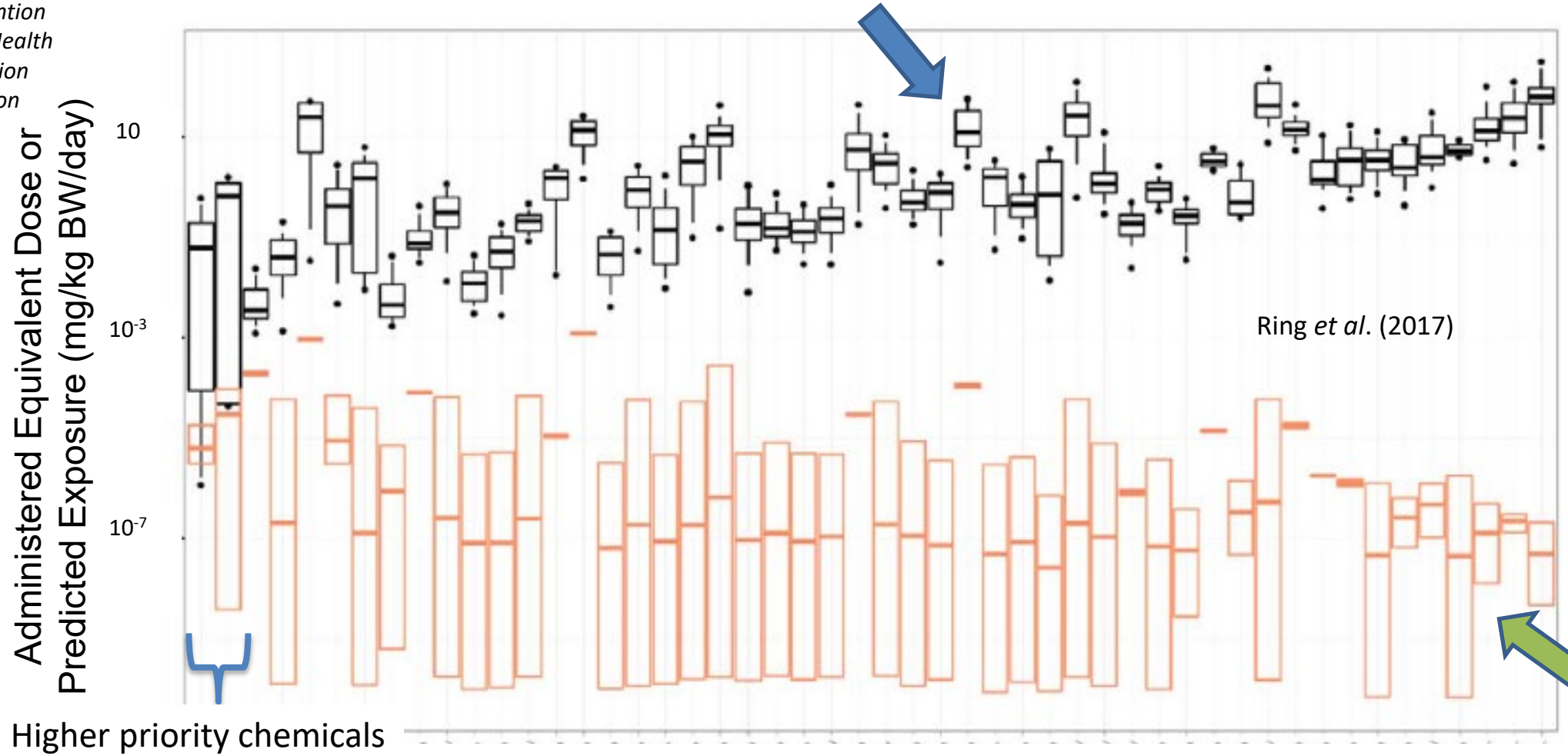

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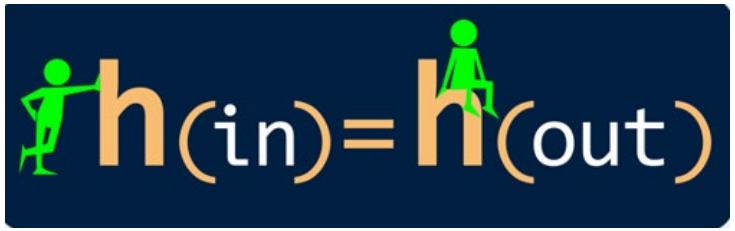


Variability

Different crayons have different colors…

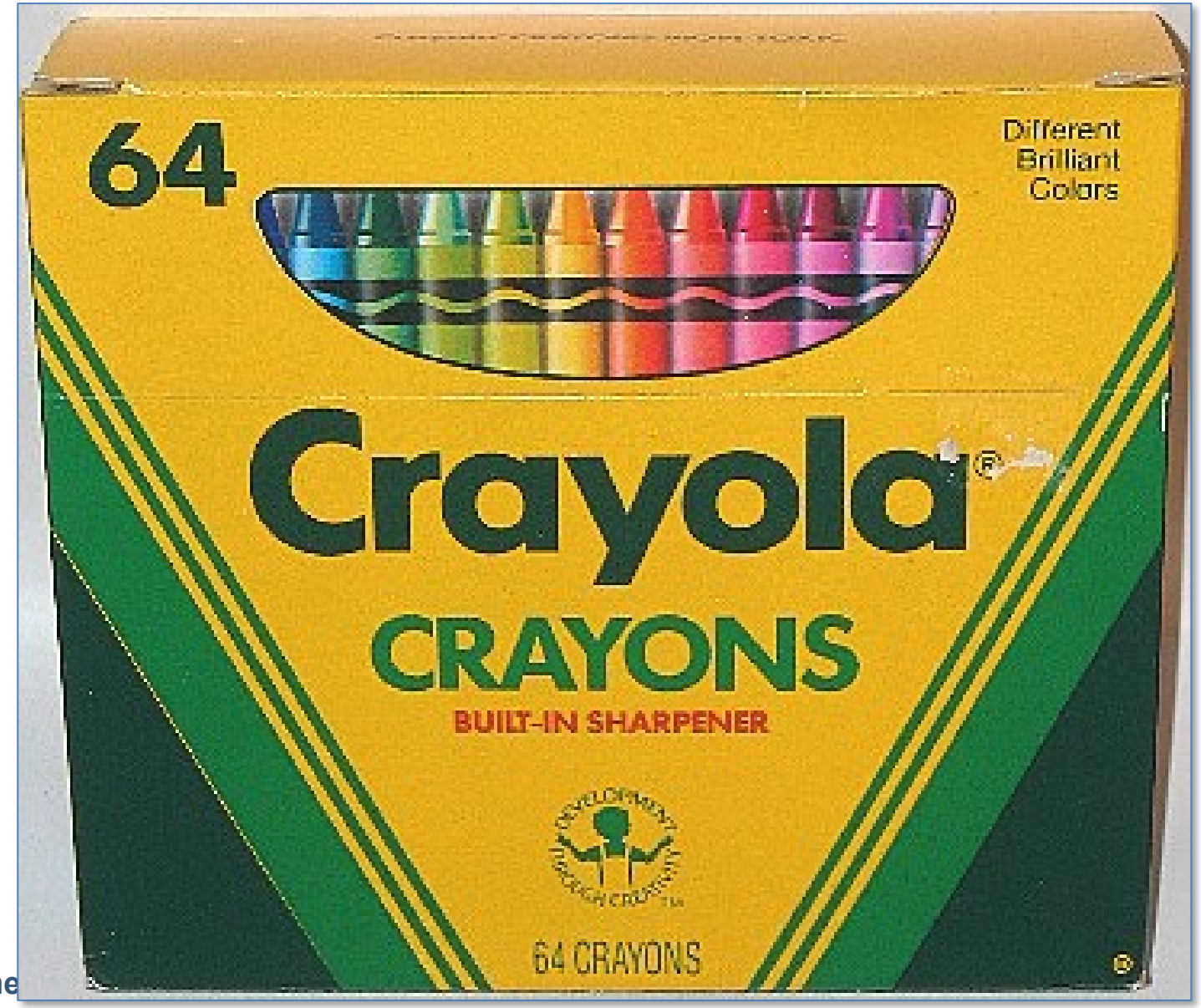
Variability

Different crayons have different colors, and none of them are the “average” color

Uncertainty

Until I open the box, I don't know what colors I have...

...especially if my nine-year-old has been around.



Population simulator for HTTK

Correlated Monte Carlo sampling of physiological model parameters built into R “httk” package (Pearce et al., 2017):

Sample CDC National Health and Nutrition Examination Survey (NHANES) biometrics for actual individuals:

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

Slide from Caroline Ring

Ring *et al*. (2017)

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

(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.)

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Regression equations from literature
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(+ residual marginal variability)

Predict physiological quantities

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.)

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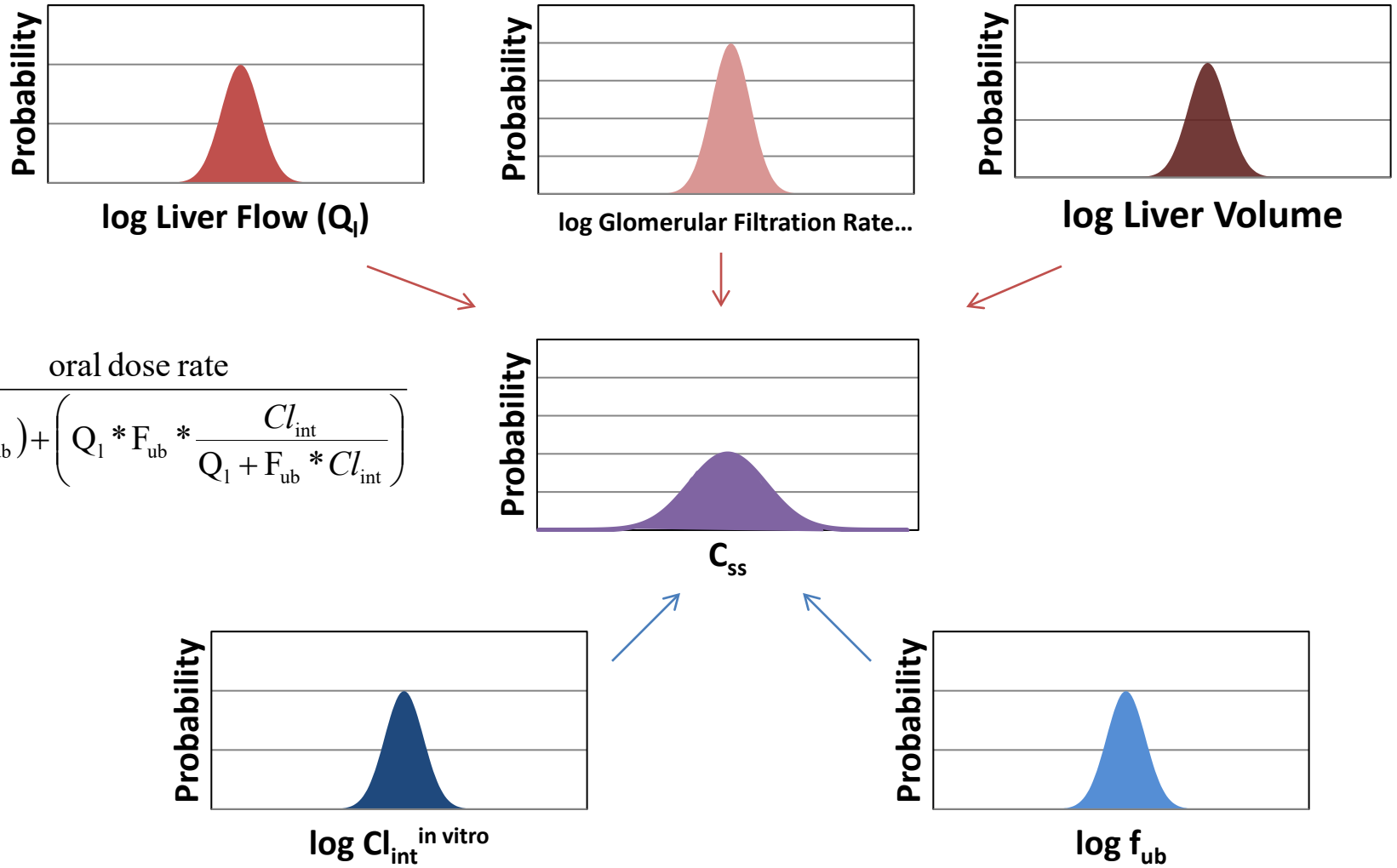
Monte Carlo Sampling

- Can be used for variability and uncertainty



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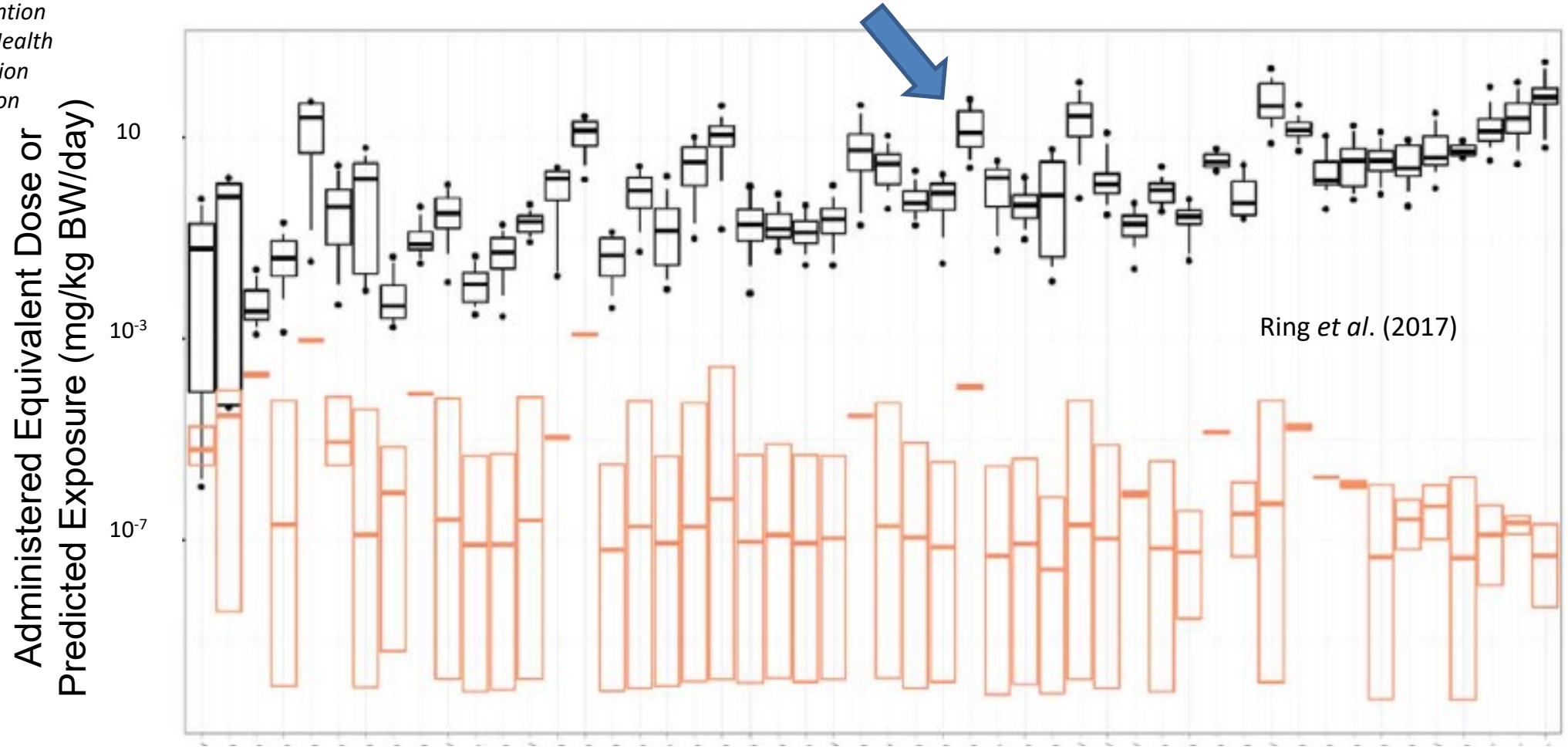
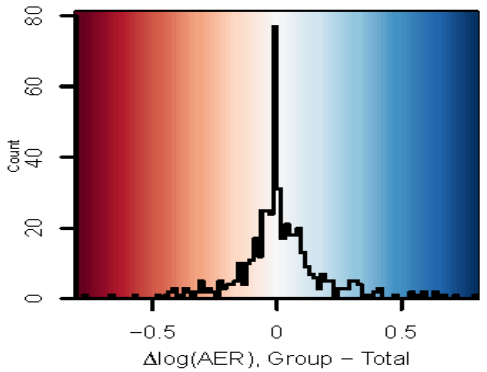
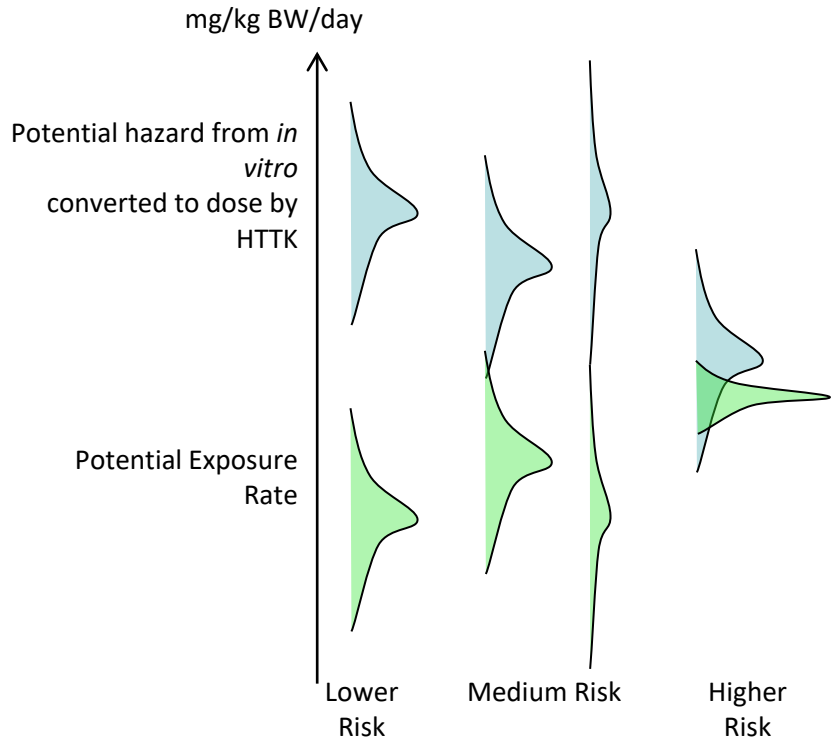
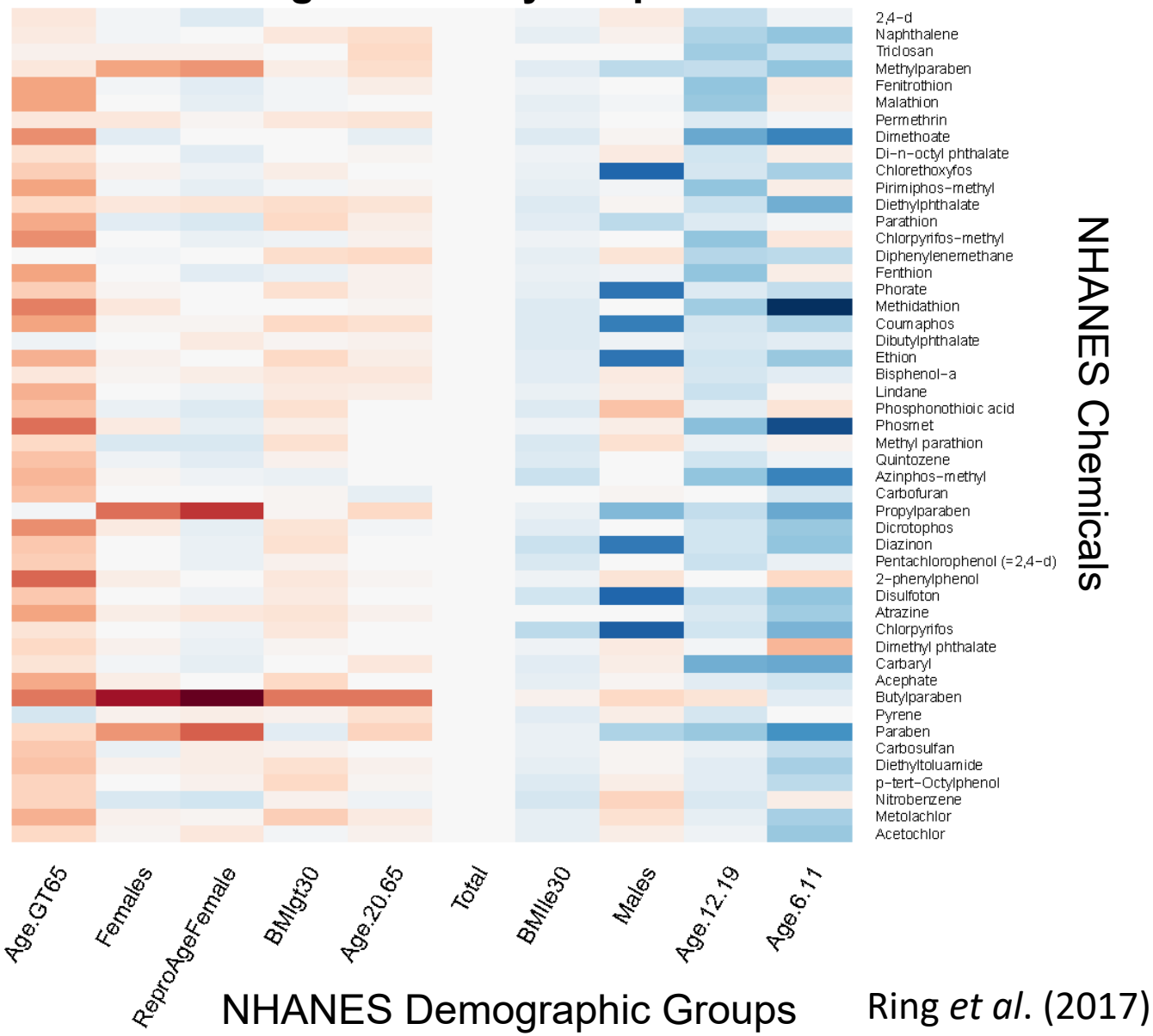


Life-stage and Demographic Specific Predictions

- We use HTTK to calculate margin between bioactivity and exposure for specific populations







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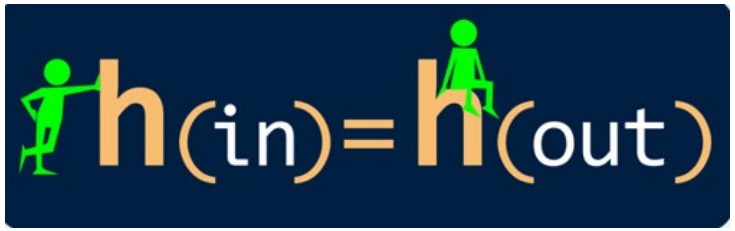
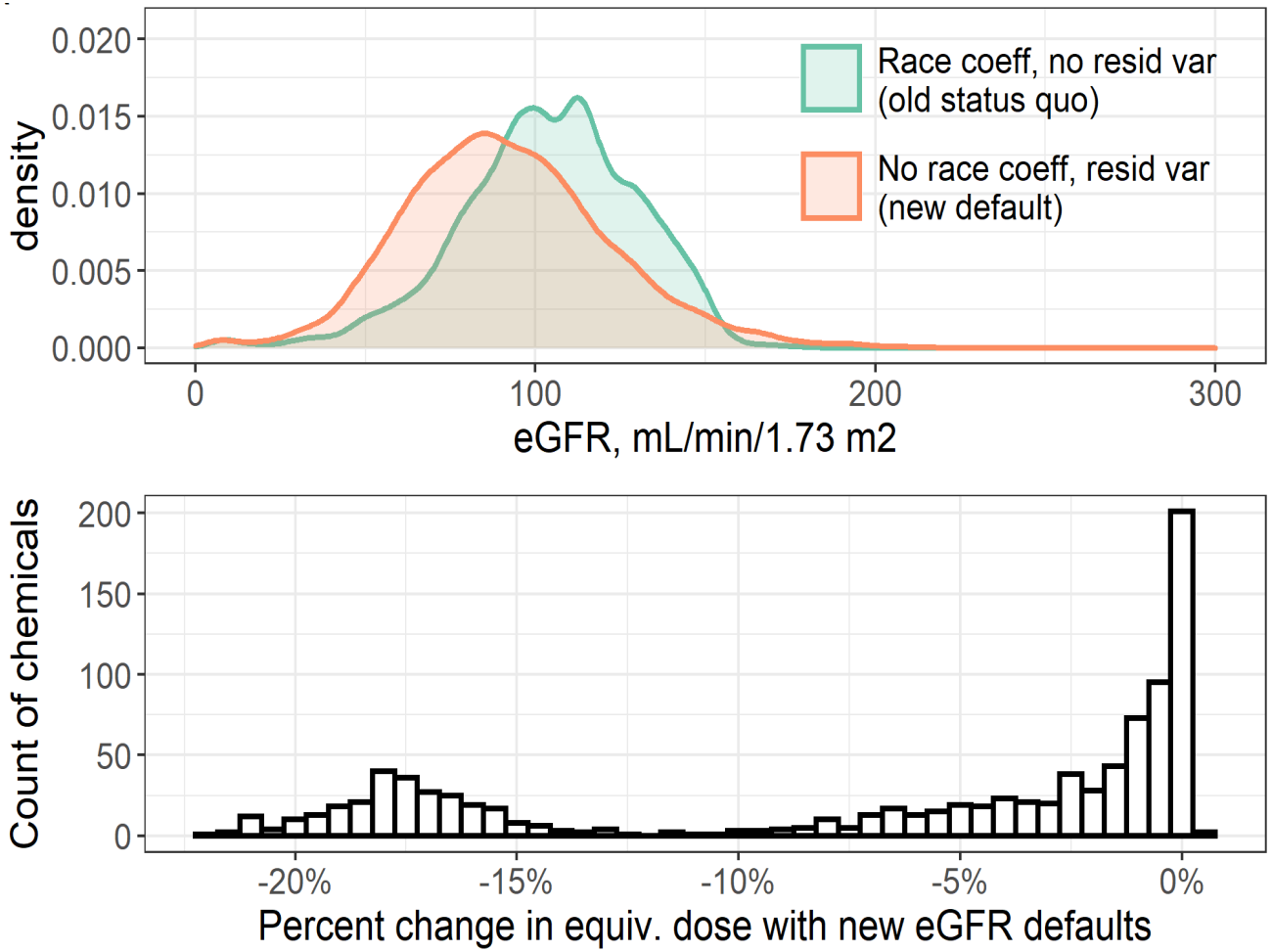


Recent Updates to "HTTK-pop"

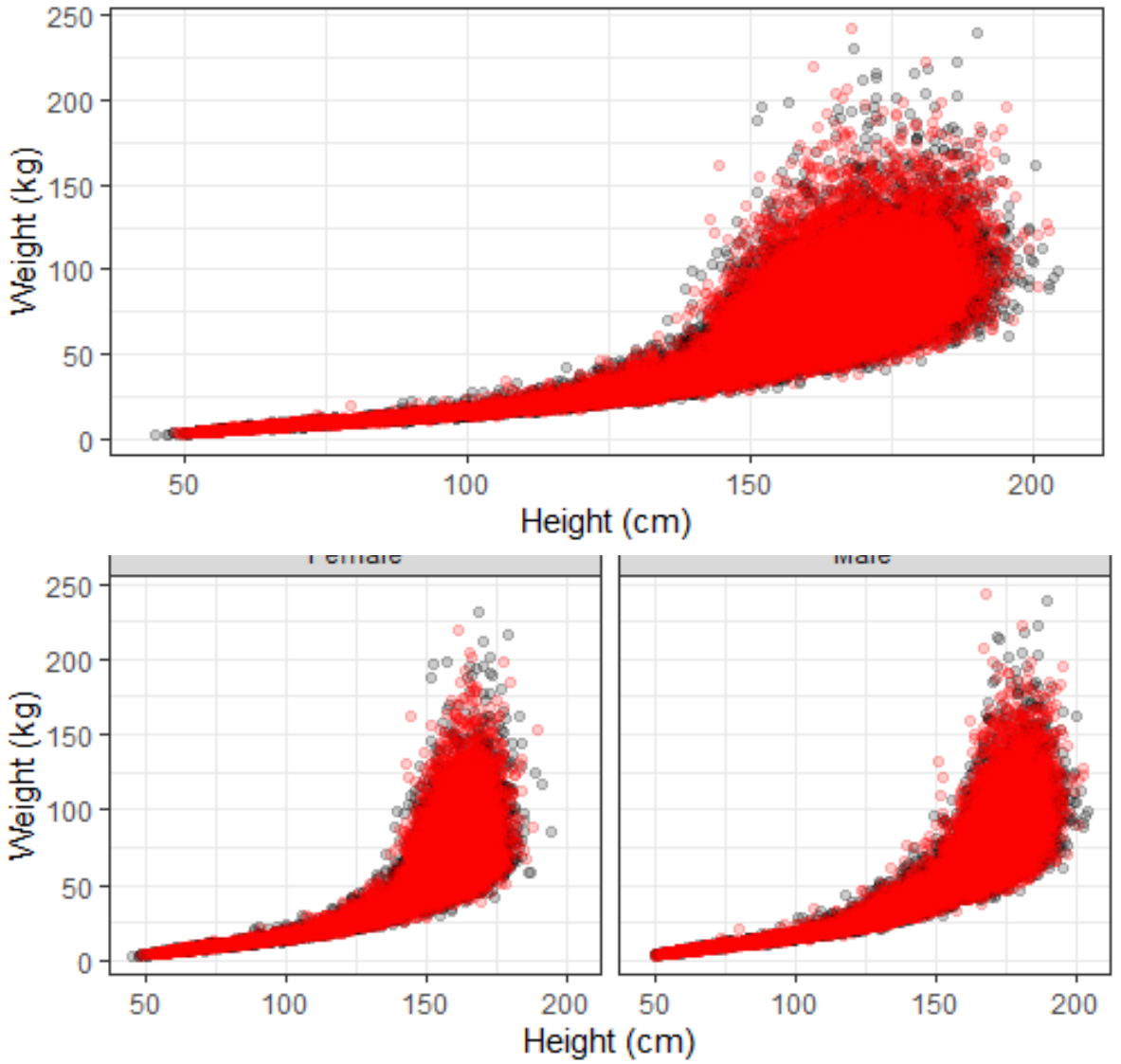
- HTTK-Pop uses the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which predicts GFR based on serum creatinine measurements, age, sex, and whether race is "black" or "non-black".
- The estimated GFR is approximately 16% higher in "black" than "non-black" persons
- Recent publications have questioned whether this "race coefficient" is appropriate (Eneanya et al., 2019)
- Breen et al. (2022) updated the HTTK-Pop algorithms and data, including removal of the race factor



Slide from Breen et al. (2022)

Recent Updates to "HTTK-pop"

- NHANES releases new cohorts covering two-year periods, with the most recent being 2017-2017
- Breen et al. (2022) recently updated the httk-pop NHANES cohort to these most recent data
- The mean body weights for the updated cohort were increased as compared with the previous cohort while no significant changes in the mean body heights for three subgroups



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	Total		Male		Female		Adults		Youth	
Weight (kg)	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean
NHANES 2007-2012	67.6	64.2	73.0	67.5	63.0	60.9	79.0	82.0	30.8	37.7
NHANES 2013-2018	67.8	65.2	72.9	68.2	63.5	62.4	79.2	82.7	32.2	38.8
Two-sample t-test (95% CI)		[0.5, 1.6]		[-0.1, 1.6]		[0.7, 2.2]		[0.2, 1.3]		[0.4, 1.9]
Height (cm)	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean
NHANES 2007-2012	161.9	151.6	169.9	156.0	157.6	147.2	167.3	167.6	132.6	127.7
NHANES 2013-2018	161.2	151.7	169.4	156.0	157.2	147.5	166.4	166.8	133.8	128.8
Two-sample t-test (95% CI)		[-0.5, 0.6]		[-0.8, 0.9]		[-0.4, 1.0]		[-1.1, -0.6]		[0.1, 2.1]

Figure from Breen et al. (2022)

Conclusions

- HTTK allows dosimetric adjustment of high-throughput screening (HTS) data
  - Thousands of chemicals
  - Open source, free, and evaluated software
- HTTK accounts for human population diversity using biometrics from the CDC NHANES to predict toxicokinetic model parameters
  - Variability is simulated using a Monte Carlo approach
- Breen et al. (2022) updated R package "httk" to the most recent three NHANES cohorts and adds children under the age of 6
- Toxicodynamic variability is not included
- HTTK *in vitro* parameters are generated from pooled adult tissues

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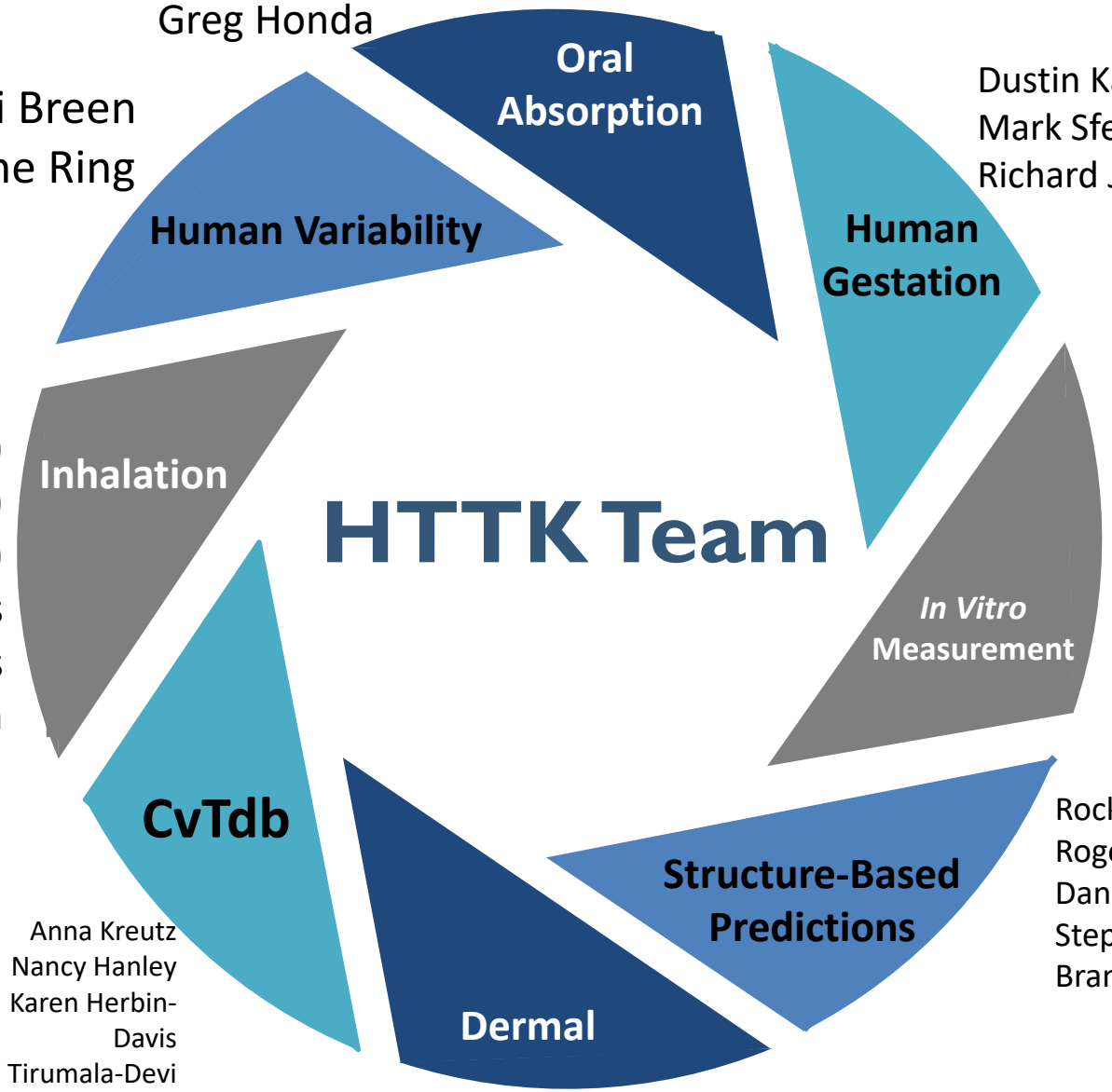

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