United States Environmental Protection Agency

Estimation of Oral Bioavailability for Environmental Chemicals

Trust Your Gut: Establishing Confidence in Gastrointestinal Models

National Institutes of Health
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Conflict of Interest Statement

The authors declare no conflict of interest

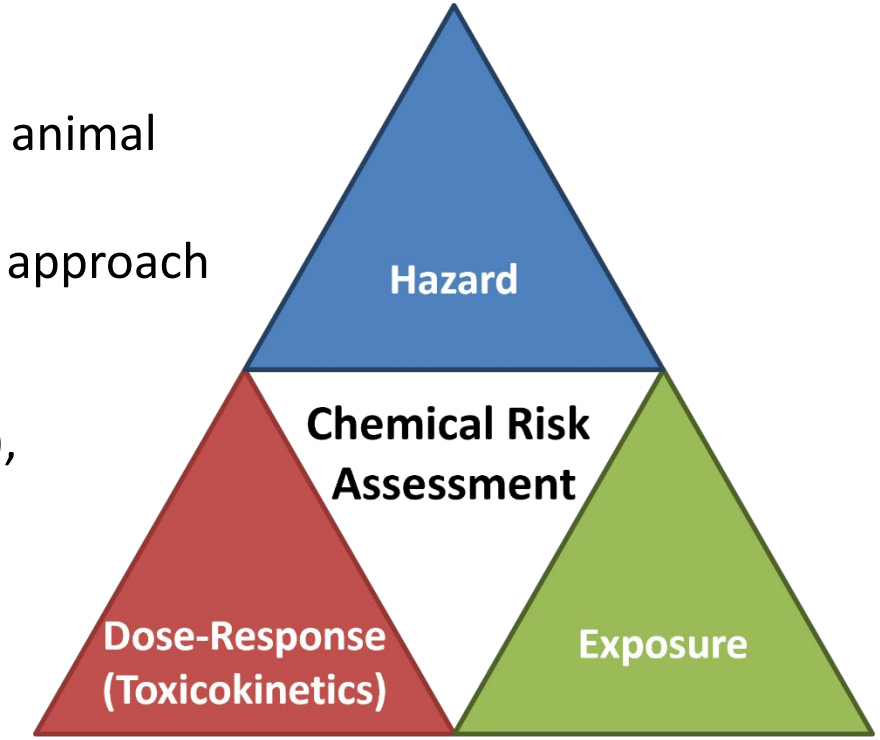
Chemical Risk Assessment Requires Understanding Dose-Response

- NRC (1983): Risk is a function of inherent chemical hazard, extent of exposure, and the dose-response relationship (including toxicokinetics)

- **Hazard:** To estimate the impact of potentially harmful chemicals we use animal and *in vitro* studies and extrapolate to humans
  - Next generation risk assessment (NGRA) is working to develop new approach methods (NAMs) that cover key biological pathways

- **Exposure:** Must consider the context (consumer/ambient/occupational), route, frequency, and extent of contact with the chemical
  - Concurrent development of NAMs for exposure includes high throughput toxicokinetics and exposure models and measurements

- **Dose-response:** Must understand quantitative relationship between magnitude of exposure and amount of effect
  - NGRA requires tools for *in vitro-in vivo* extrapolation (IVIVE)



NRC, 1983

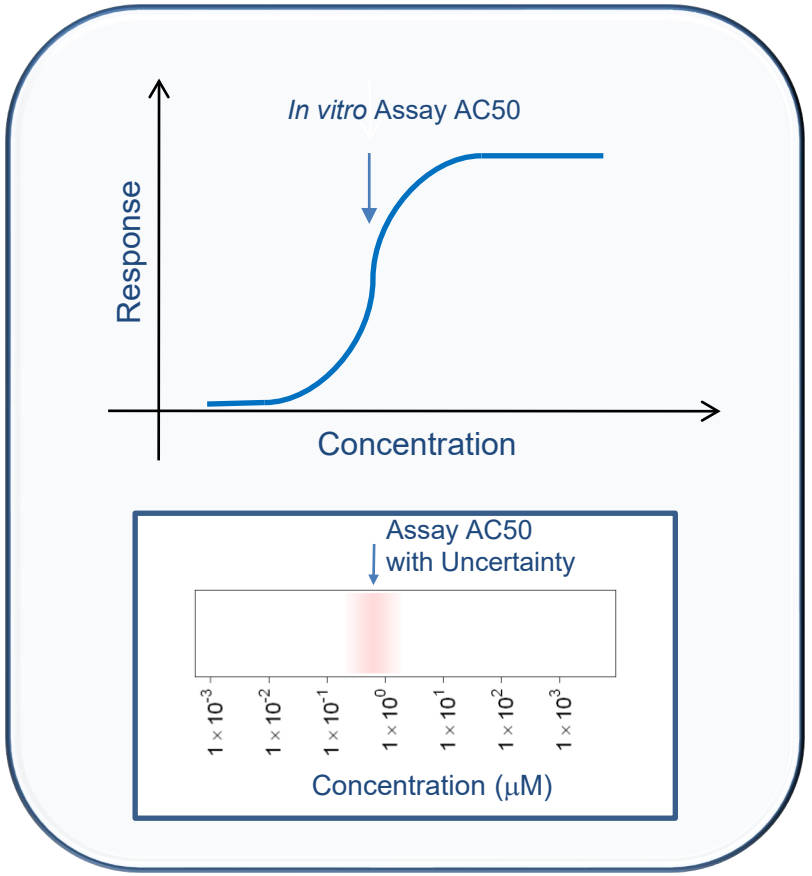
Next Generation Risk Assessment (NGRA) is Built Upon New Approach Methods (NAMs)

- We attempt to estimate points of departure *in vitro* using high throughput screening (HTS) for bioactivity as a surrogate for hazard

- **Tox21**: Examining >8,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)

- **ToxCast** (Toxicity Forecaster): >4000 chemicals (including a subset of Tox21) for >2000 additional assay endpoints (invitrodb version 3.5) (Kavlock *et al.*, 2012)

- To use HTS assays as an alternative to traditional animal studies we must link *in vitro* bioactivity concentrations and potentially toxic doses via *in vitro-in vivo* extrapolation (IVIVE).

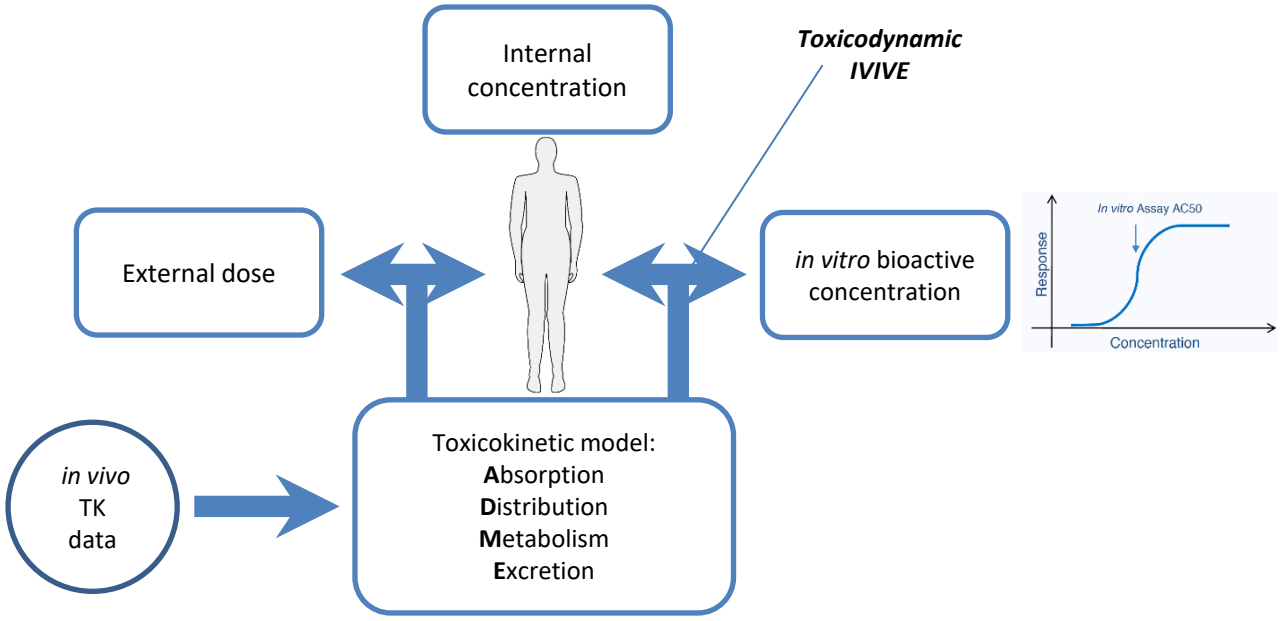


In Vitro - *In Vivo* Extrapolation (IVIVE)

IVIVE is the use of *in vitro* experimental data to predict phenomena *in vivo* (Coecke et al., 2013, Wetmore, 2015a)

- *In Vitro* Disposition:
  - Difference between nominal and effective concentration of chemical
  - Partitioning to plate wall, nutrients, volatilization

In vitro to *in vivo* extrapolation (IVIVE)



Breen et al., 2021

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  - Considers absorption, distribution, metabolism, excretion (ADME)

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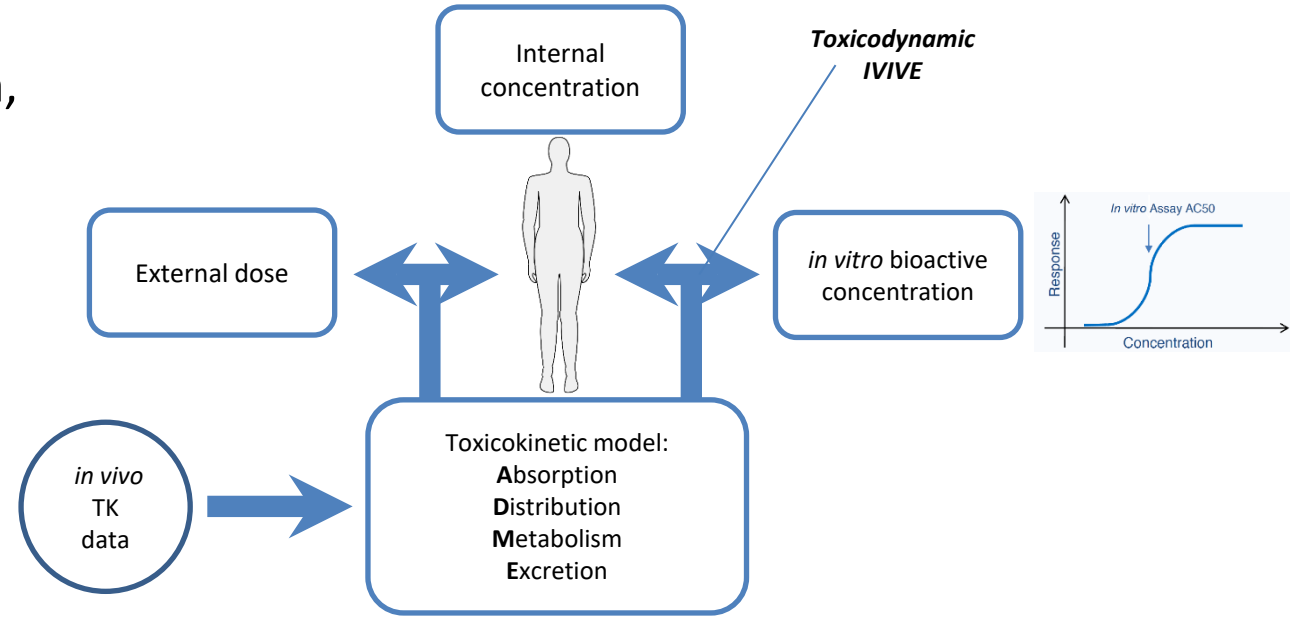

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- IVIVE-PD/TD (**Pharmacodynamics/Toxicodynamics**):
  - Effect of molecules/chemicals at biological target *in vivo*
  - Assay design/selection important
  - Perturbation as adverse/therapeutic effect, reversible/irreversible effects

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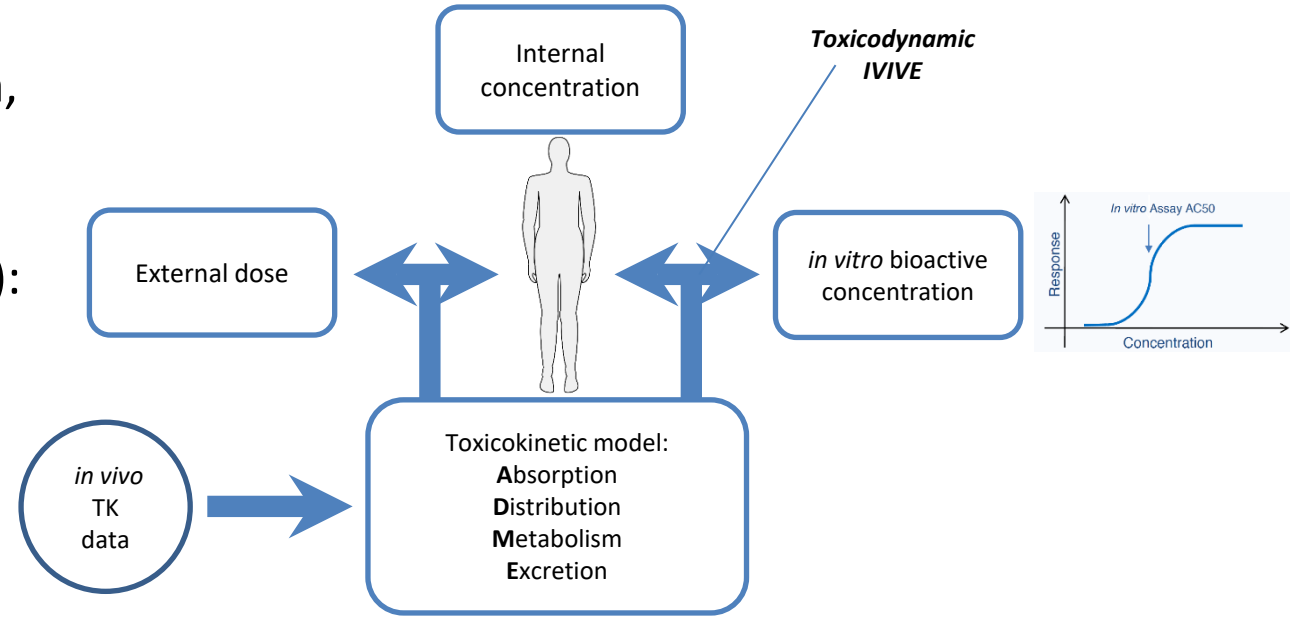


Breen et al., 2021

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

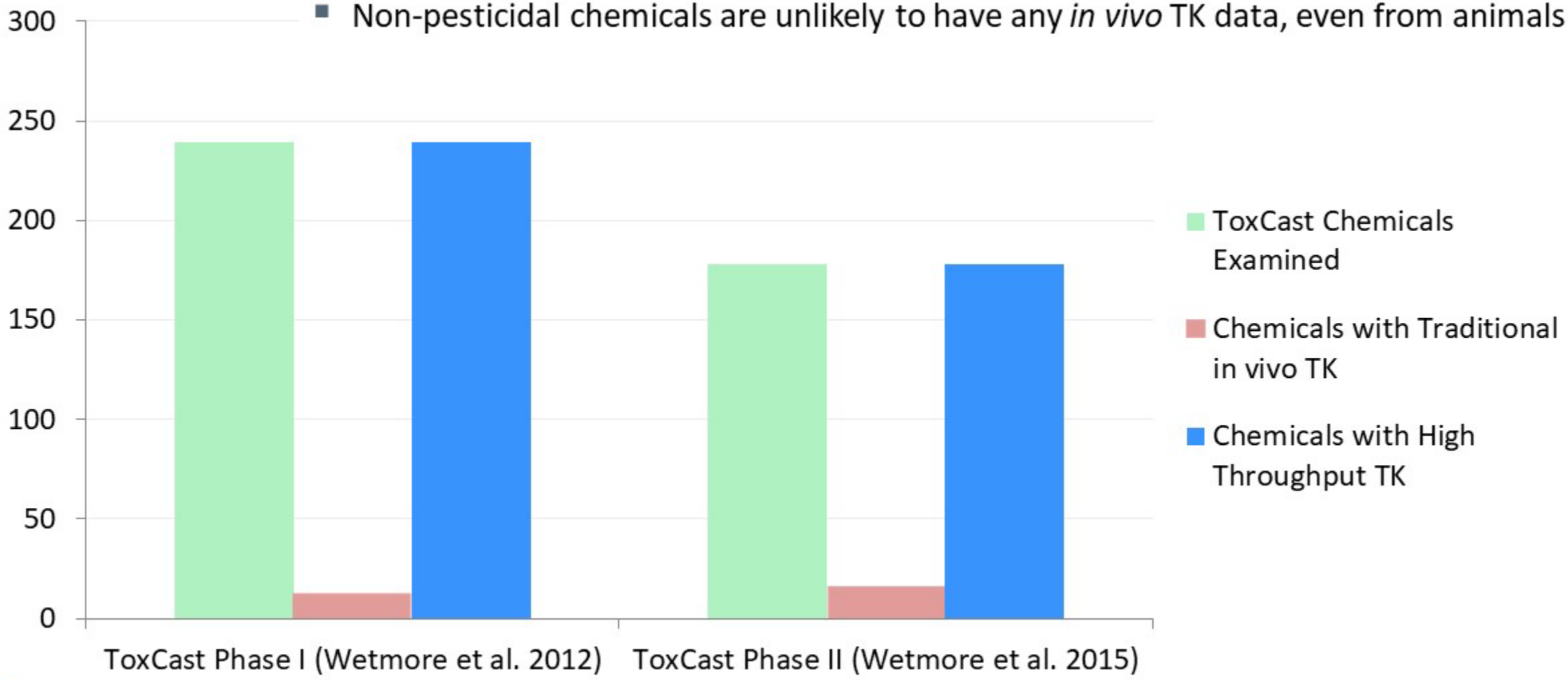


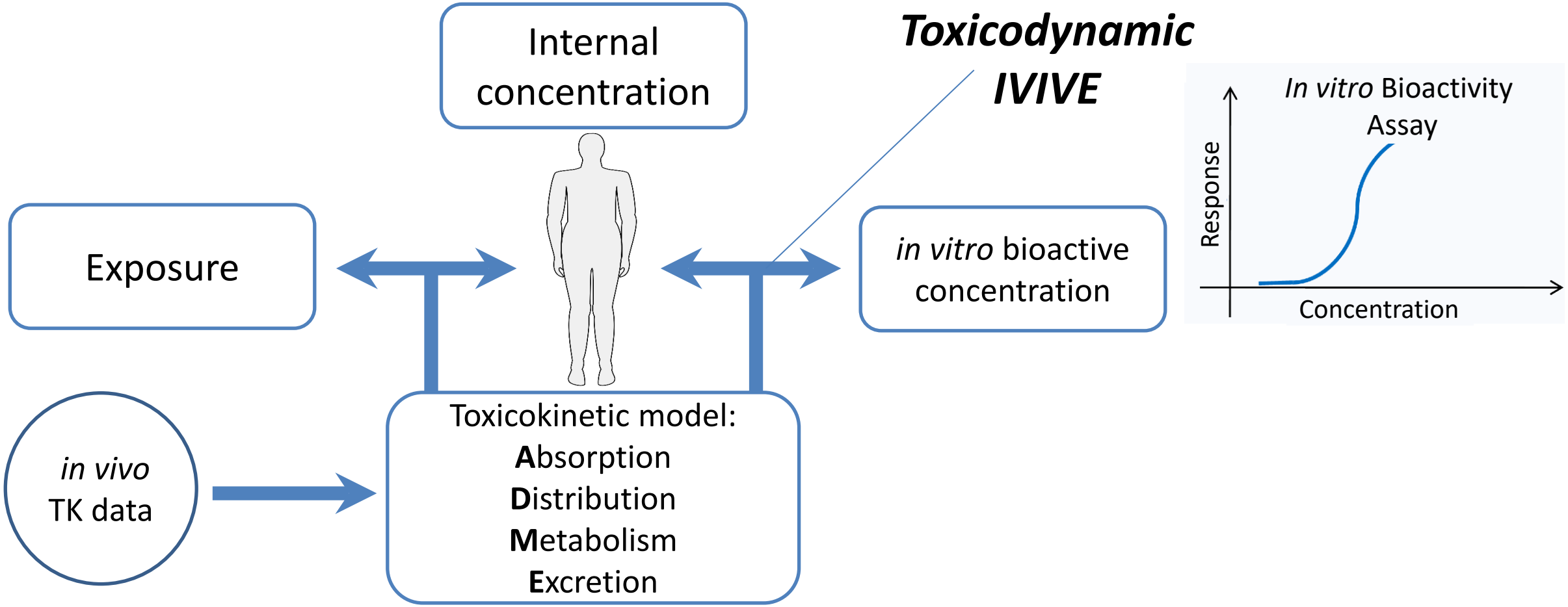
Figure from Bell *et al.* (2018)

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.*, 2017)

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



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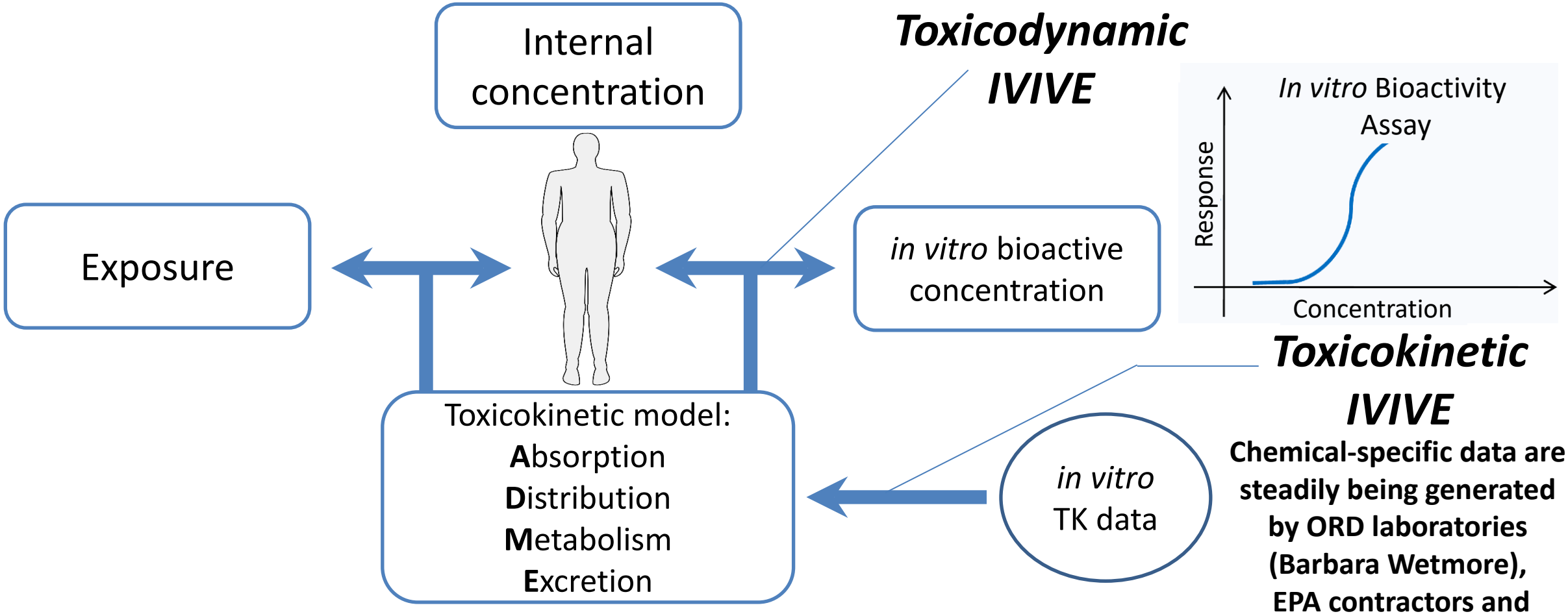

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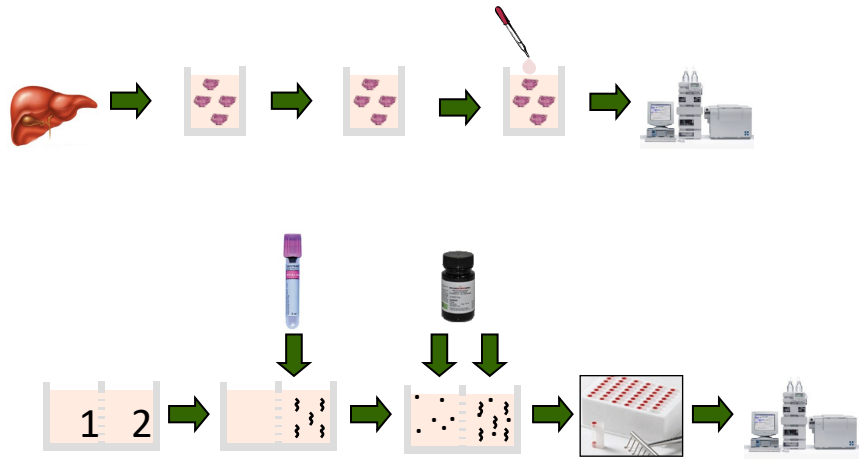
High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data



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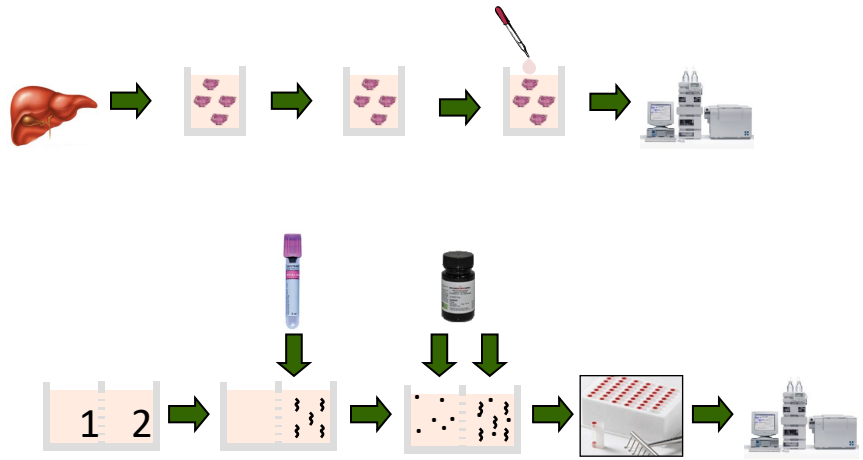

Rotroff *et al.* (2010)
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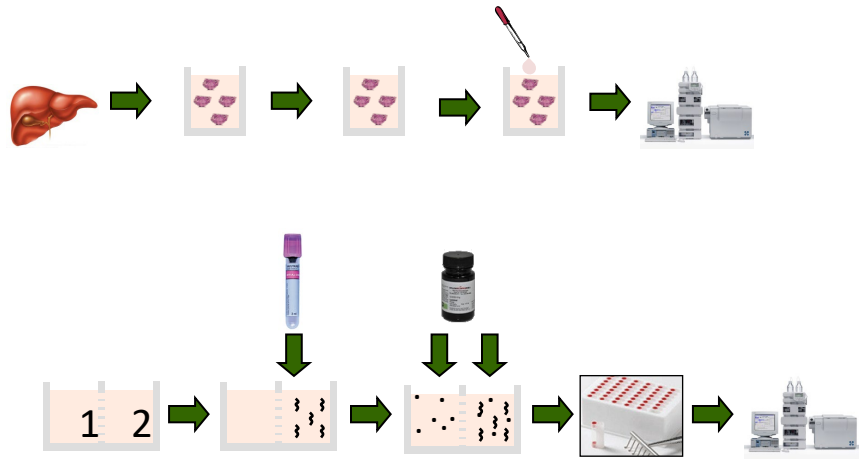
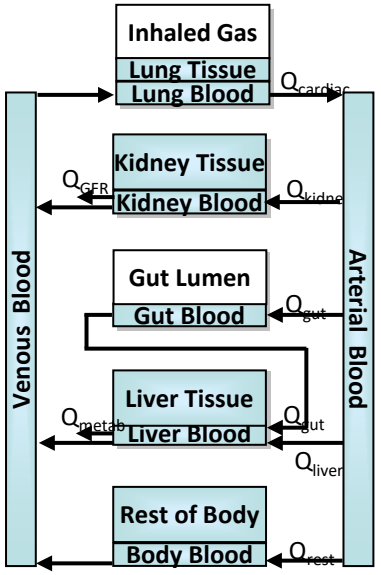
High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data + generic toxicokinetic model





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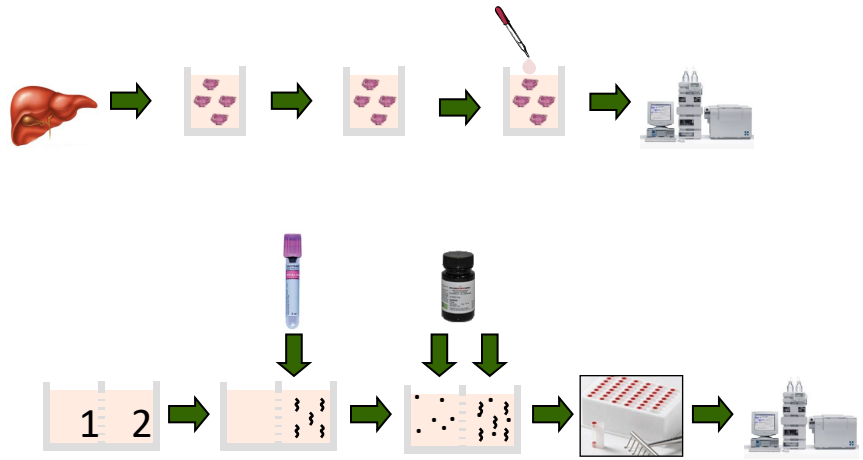

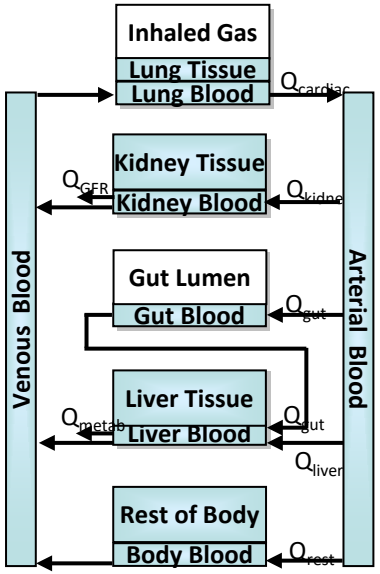

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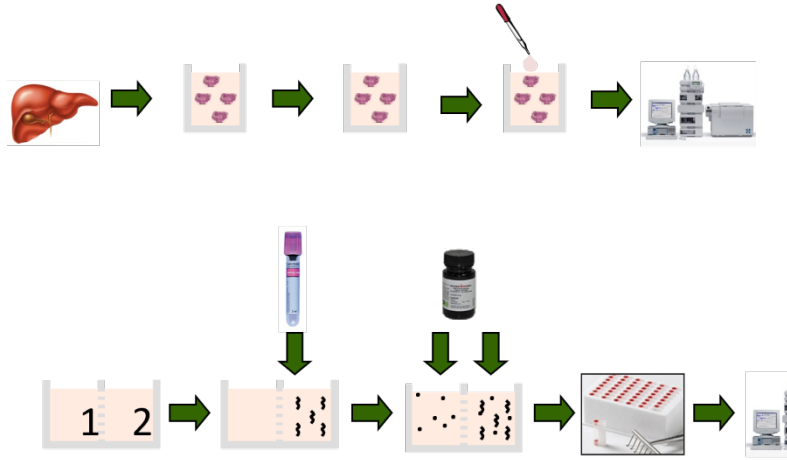
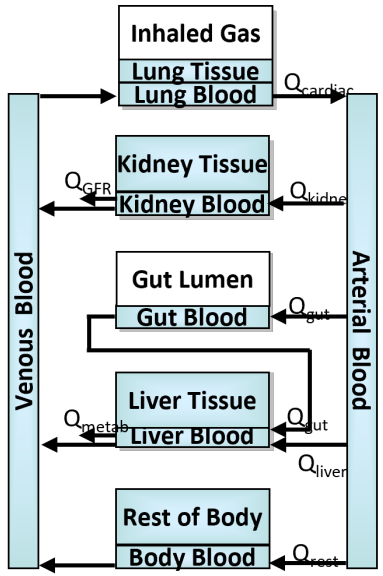
High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data + generic toxicokinetic model

= high(er) throughput toxicokinetics





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= *httk*

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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, $\mathbf{F_{IVIVE} = 1 / C_{ss,95}}$
- $C_{ss,95}$ is the steady-state plasma concentration as the result of a 1 mg/kg/day exposure
- HTTK can predict $C_{ss,95}$ using "reverse dosimetry" IVIVE (Tan et al., 2007)

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

- 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

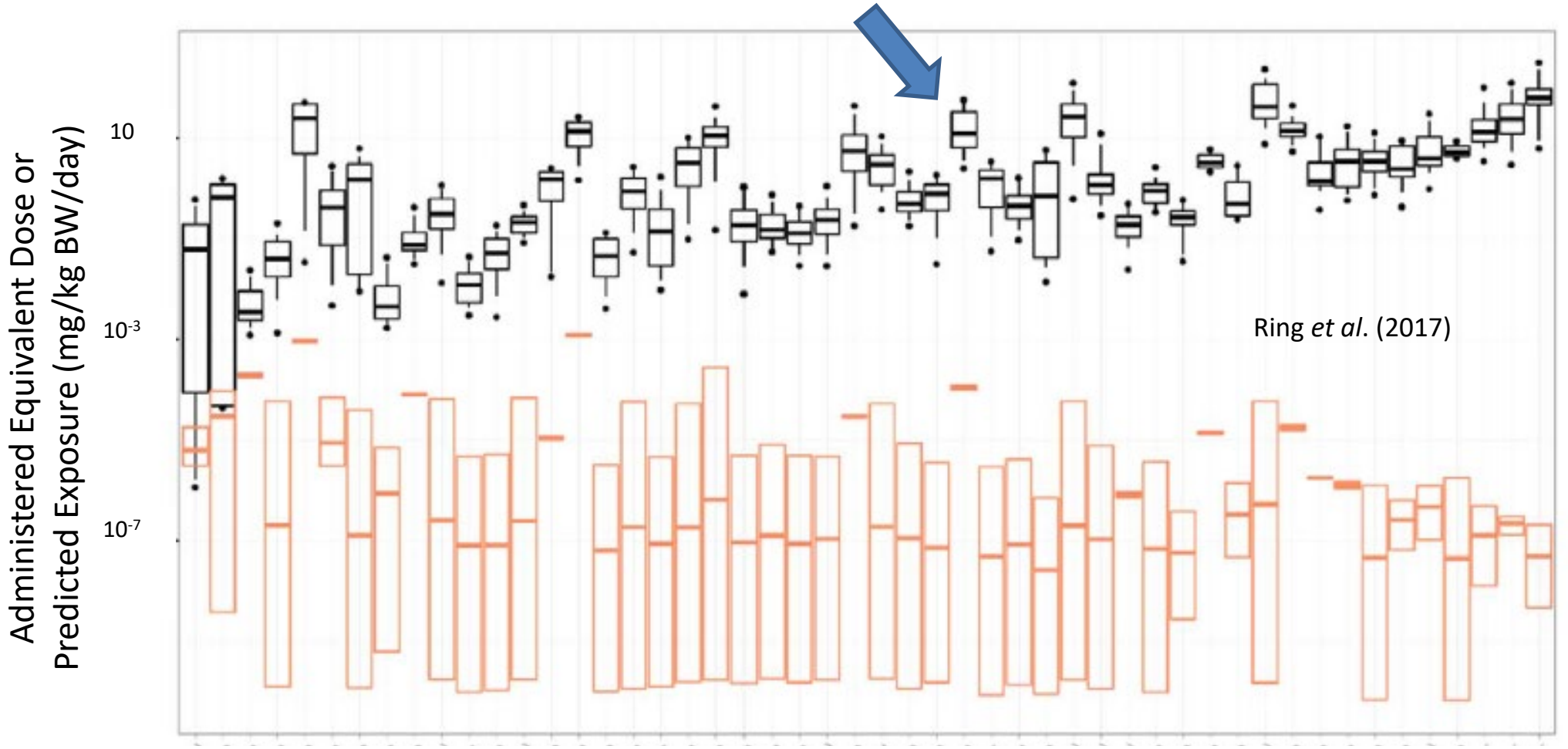
Don't forget:

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

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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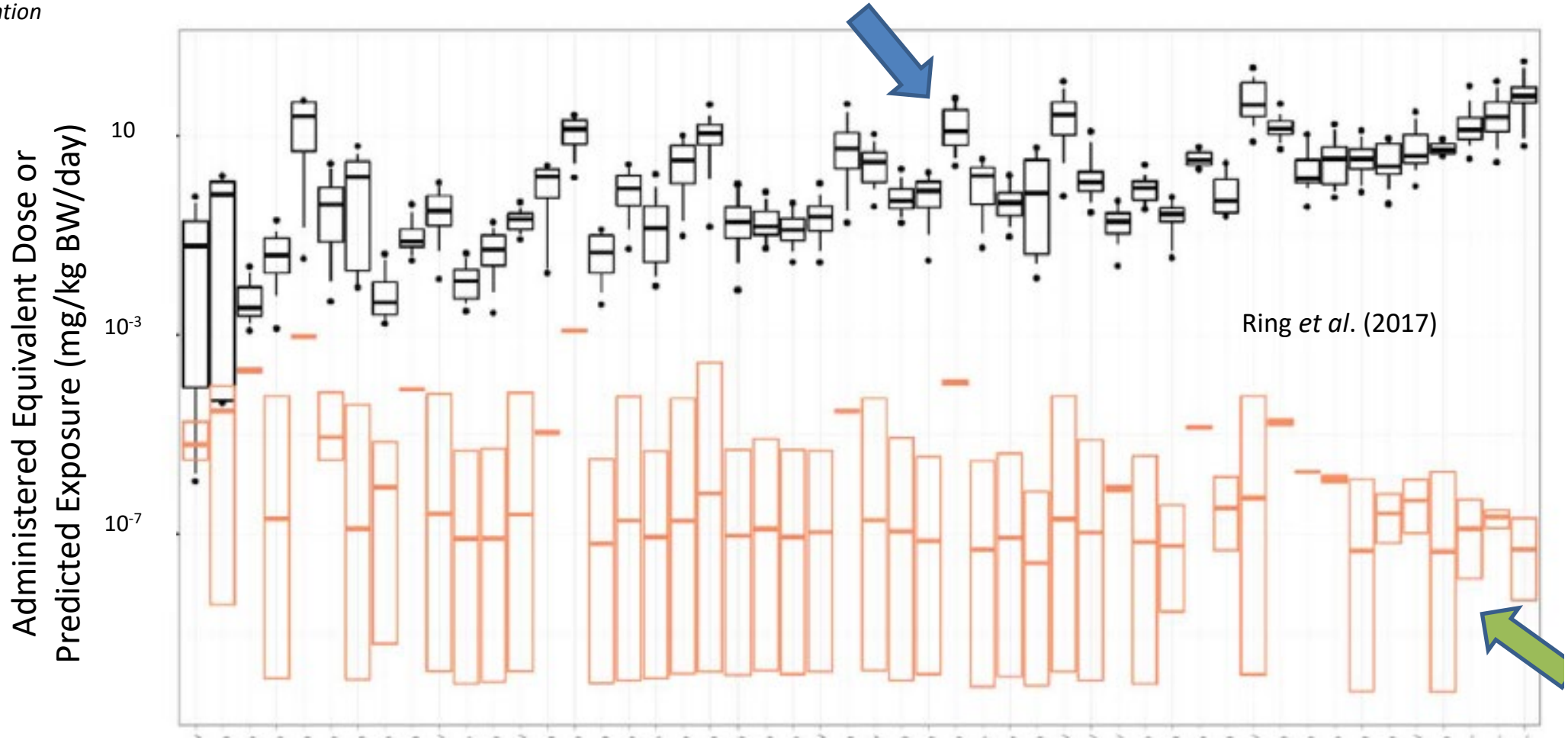

Exposure intake rates can be inferred from biomarkers
(Stanfield *et al.*, 2022)

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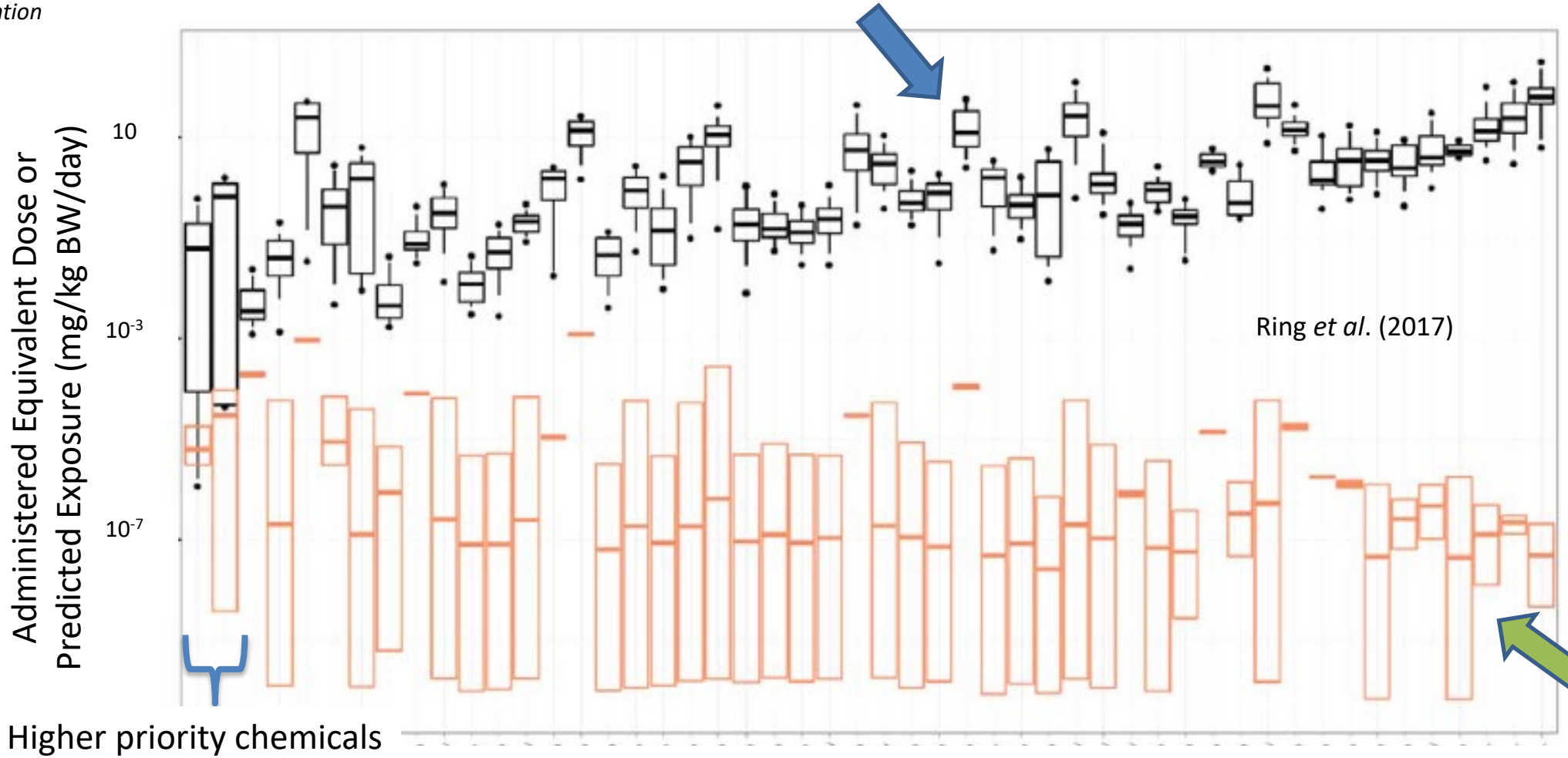

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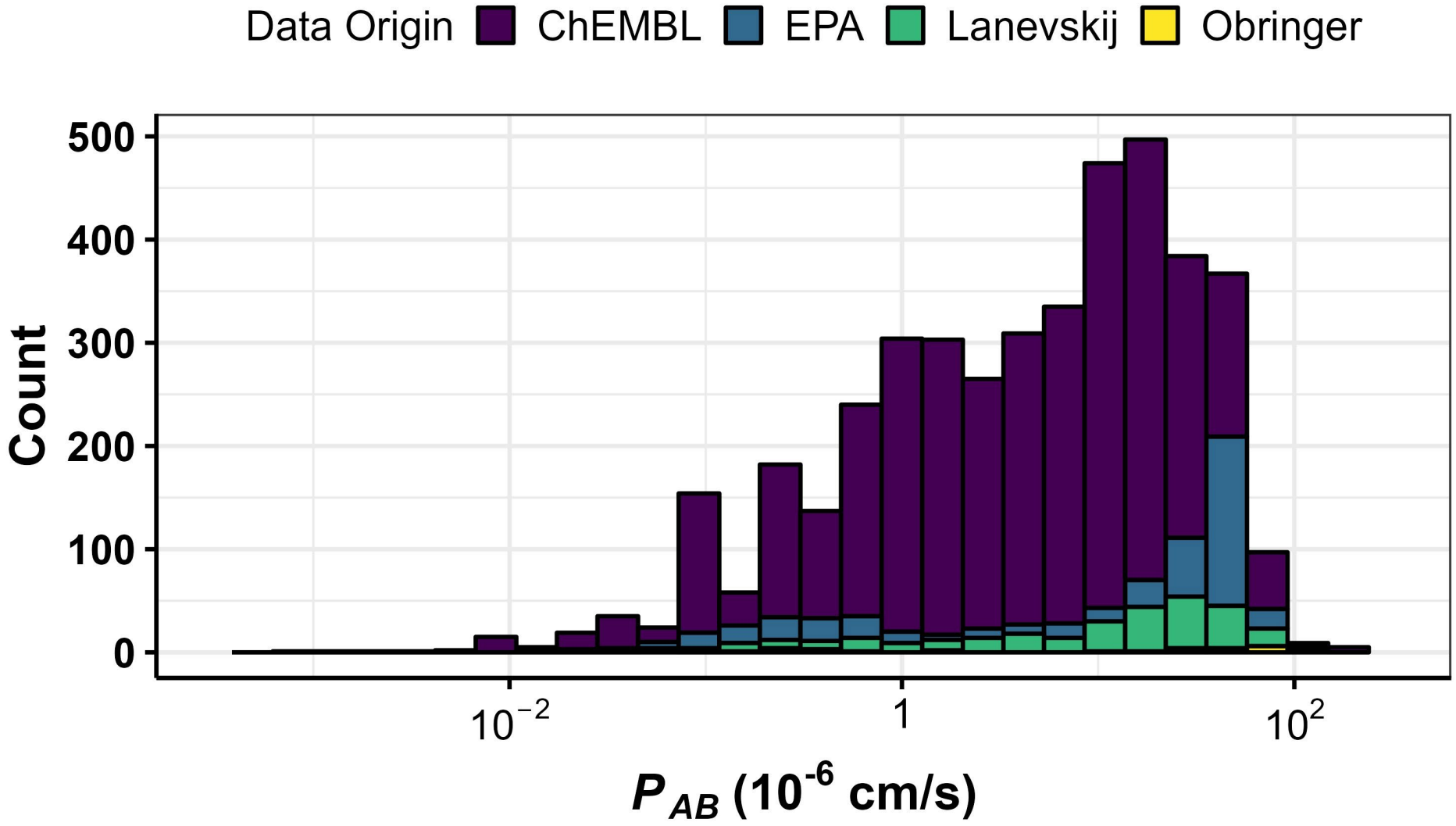
Adding Caco-2 Data to HTTK

- HTTK is limited by what TK processes can be rapidly characterized *in vitro*
- Caco-2 membrane permeability data are now available for thousands of chemicals



Honda et al. (in prep.)

Quantitative Structure-Property Relationship (QSPR) Model

- Machine learning by the method of random forests (Breiman, 2001) was used to build a model for predicting Caco-2 apical:basal membrane permeability
- Predictions are made using chemical structure descriptors (PaDEL) and predicted physcio-chemical properties (OPERA)
- We explored different ways of clustering the measurements to make the most useful predictions

	Two Equal Bins	Two Clustered Bins	Three Equal Bins	Three Clustered Bins	Four Equal Bins	Four Clustered Bins	Five Equal Bins	Five Clustered Bins
Accuracy	0.802	0.825	0.688	0.68	0.581	0.614	0.533	0.566
Kappa	0.604	0.622	0.532	0.475	0.442	0.457	0.416	0.417
Bin1	1 (0.03 - 5.38)	0.678 (0.0254 - 2.5)	0.516 (0.021 - 1.8)	0.23 (0.0101 - 0.6)	0.398 (0.0191 - 1)	0.1 (0.01 - 0.274)	0.27 (0.0113 - 0.7)	0.0342 (0.00446 - 0.0835)
Bin2	19.9 (6.5 - 77.7)	14.8 (3 - 71.1)	6 (2 - 12.8)	2.08 (0.7 - 6.3)	2.6 (1.1 - 5.6)	1 (0.3 - 2.2)	1.5 (0.77 - 3)	0.3 (0.1 - 0.609)
Bin3	–	–	28 (13.7 - 85.1)	20 (7.2 - 77.9)	11 (6.2 - 19)	7.09 (2.5 - 13.8)	6.3 (3.13 - 10)	1.6 (0.7 - 3.51)
Bin4	–	–	–	–	34.6 (20 - 103)	29.6 (14.8 - 86.6)	16 (10.4 - 22.9)	9 (3.98 - 16.3)
Bin5	–	–	–	–	–	–	39 (24 - 142)	32 (17.2 - 90.1)

Reported values are median and 95% interval

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Quantitative Structure-Property Relationship (QSPR) Model

- Machine learning by the method of random forests (Breiman, 2001) was used to build a model for predicting Caco-2 apical:basal membrane permeability (10^{-6} cm/s)
- Predictions are made using chemical structure descriptors (PaDEL) and predicted physcio-chemical properties (OPERA)
- We explored different ways of clustering the measurements to make the most useful predictions

	Three Clustered Bins
Accuracy	0.68
Kappa	0.475
Bin1	0.23 (0.0101 - 0.6)
Bin2	2.08 (0.7 - 6.3)
Bin3	20 (7.2 - 77.9)
Bin4	
Bin5	

- The model for three bins had reasonable accuracy and predicted distinct permeabilities: 0.2, 2, and 20 10^{-6} cm/s

Reported values are median and 95% interval

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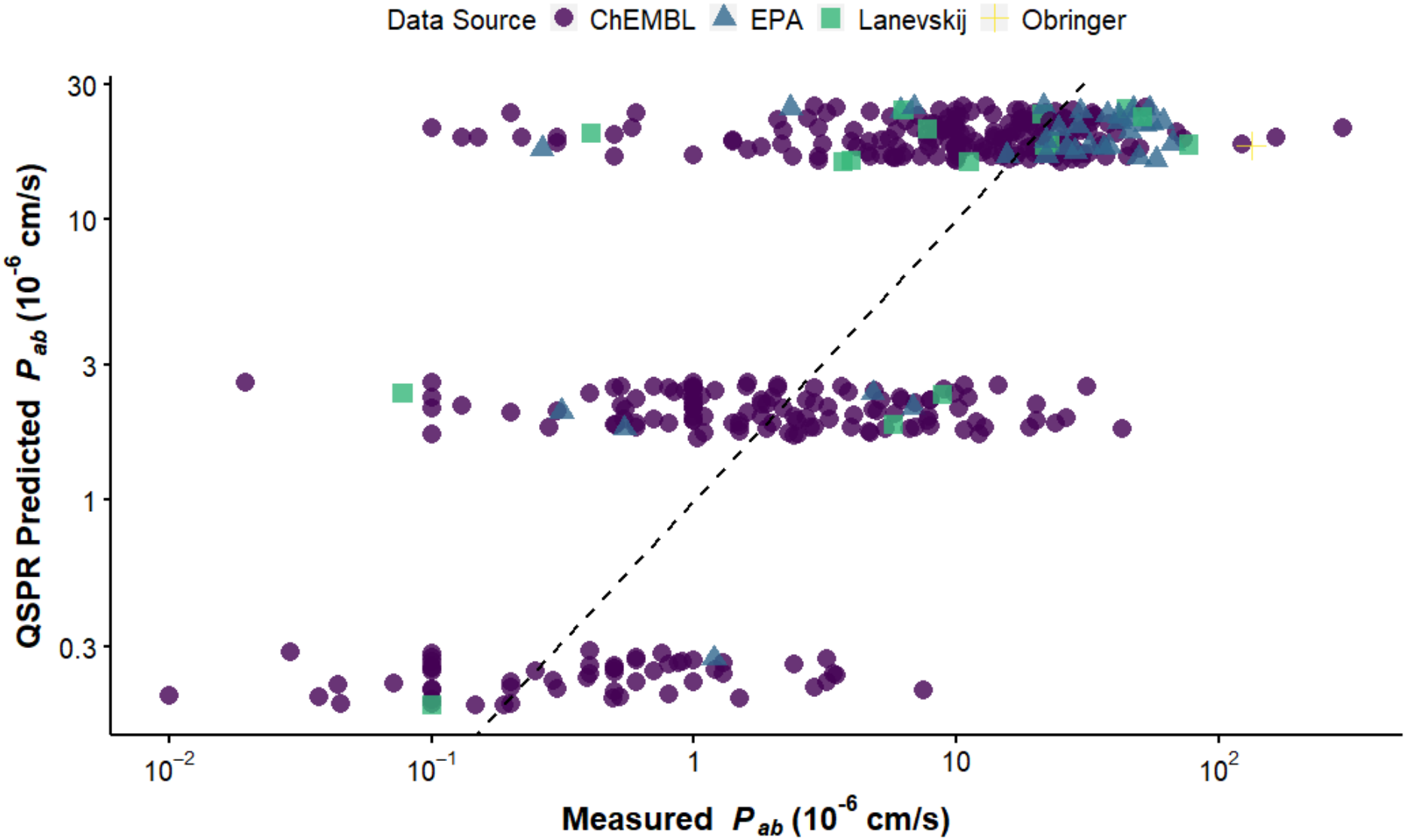
QSPR Model Evaluation

- QSPR model was evaluated using 10% of Caco-2 dataset that was withheld from model training
- 68% Balanced Accuracy



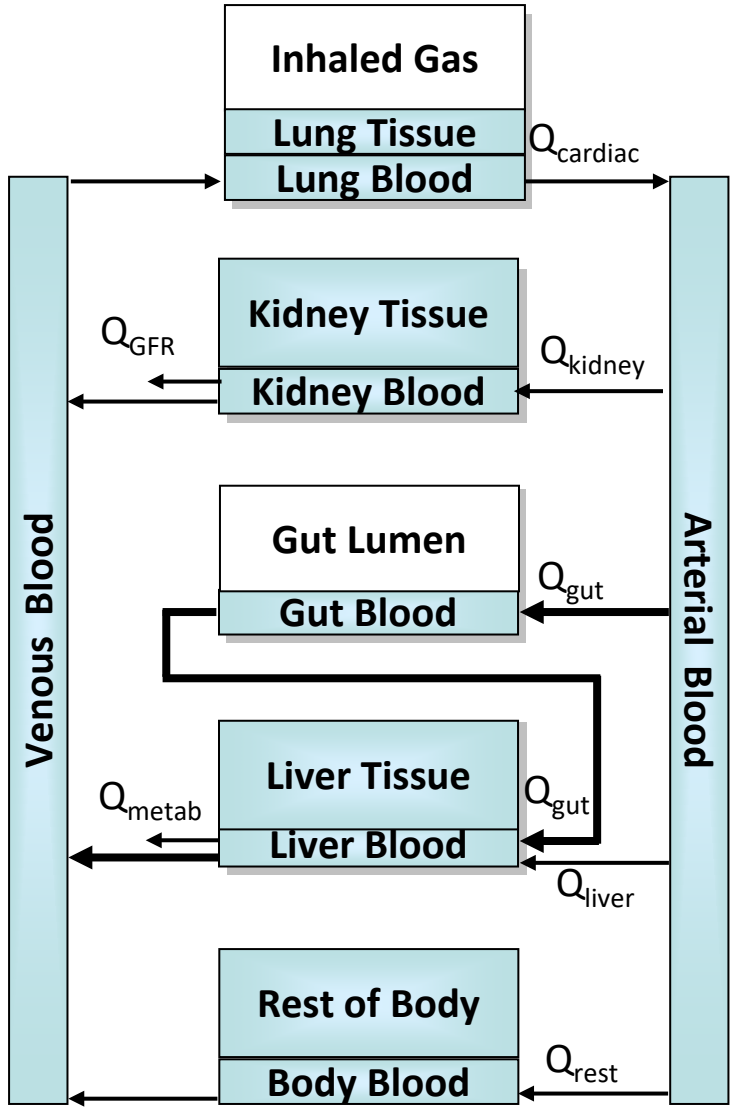
Honda et al. (in prep.)

Modifying HTTK

- We modified EPA's HTTK software (Pearce et al., 2017) to consider that systemic bioavailability (F_{bio}) can be predicted rapidly for many thousands of chemicals using:

$$F_{bio} = F_{abs} \times F_{gut} \times F_{hep}$$

- HTTK already included first-pass hepatic metabolism (F_{hep} – Rowland, et al. 1973) using *in vitro* measurement of intrinsic hepatic clearance
- We now using Caco-2 data to predict fraction absorbed from gut (F_{abs} – Darwich et al., 2010) and fraction surviving gut metabolism/transit (F_{gut} – Yang et al., 2007)
- We had previously assumed $F_{abs} = F_{gut} = 1$

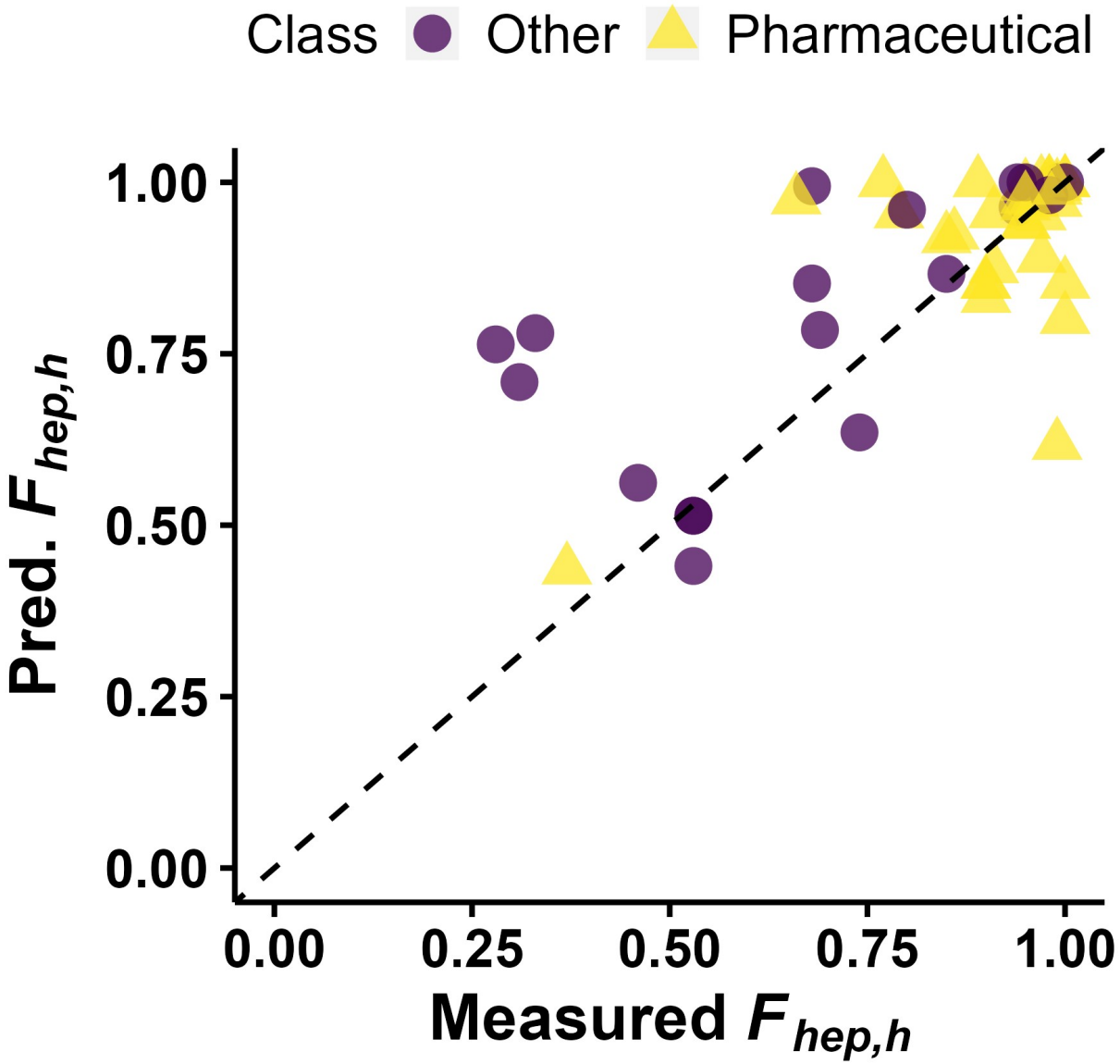


Evaluating Impact of *In Vitro* Permeability Data on HTTK

- Over the next few slides, we compare the R package "httk" model predictions for differing aspects of oral bioavailability
- We use a library of chemicals that have in vitro, chemical-specific measures of metabolism (intrinsic hepatic clearance – Cl_{int}), plasma protein binding (fraction unbound in plasma f_{up}) **and now Caco-2 membrane permeability**
- The httk chemicals include pharmaceuticals but are more representative of the broader chemical classes found occuring in commerce and the environment
- No new *in vivo* data was collected, rather we use data collected by other, cited publications

F_{hep} Model Evaluation

- We evaluated the HTTK predictions for each component of systemic bioavailability using *in vivo* data (Varma et al., 201) for various chemicals



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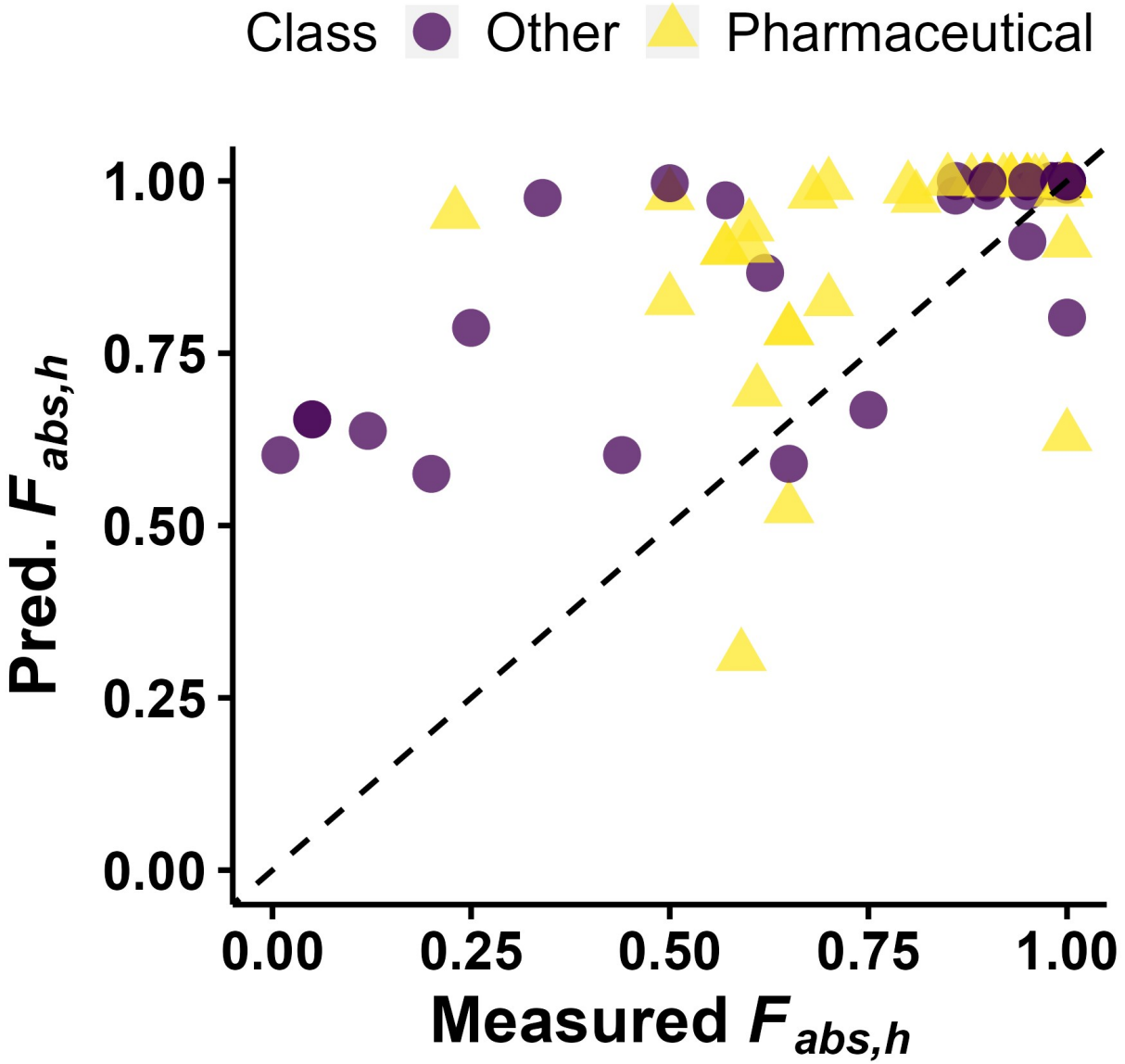
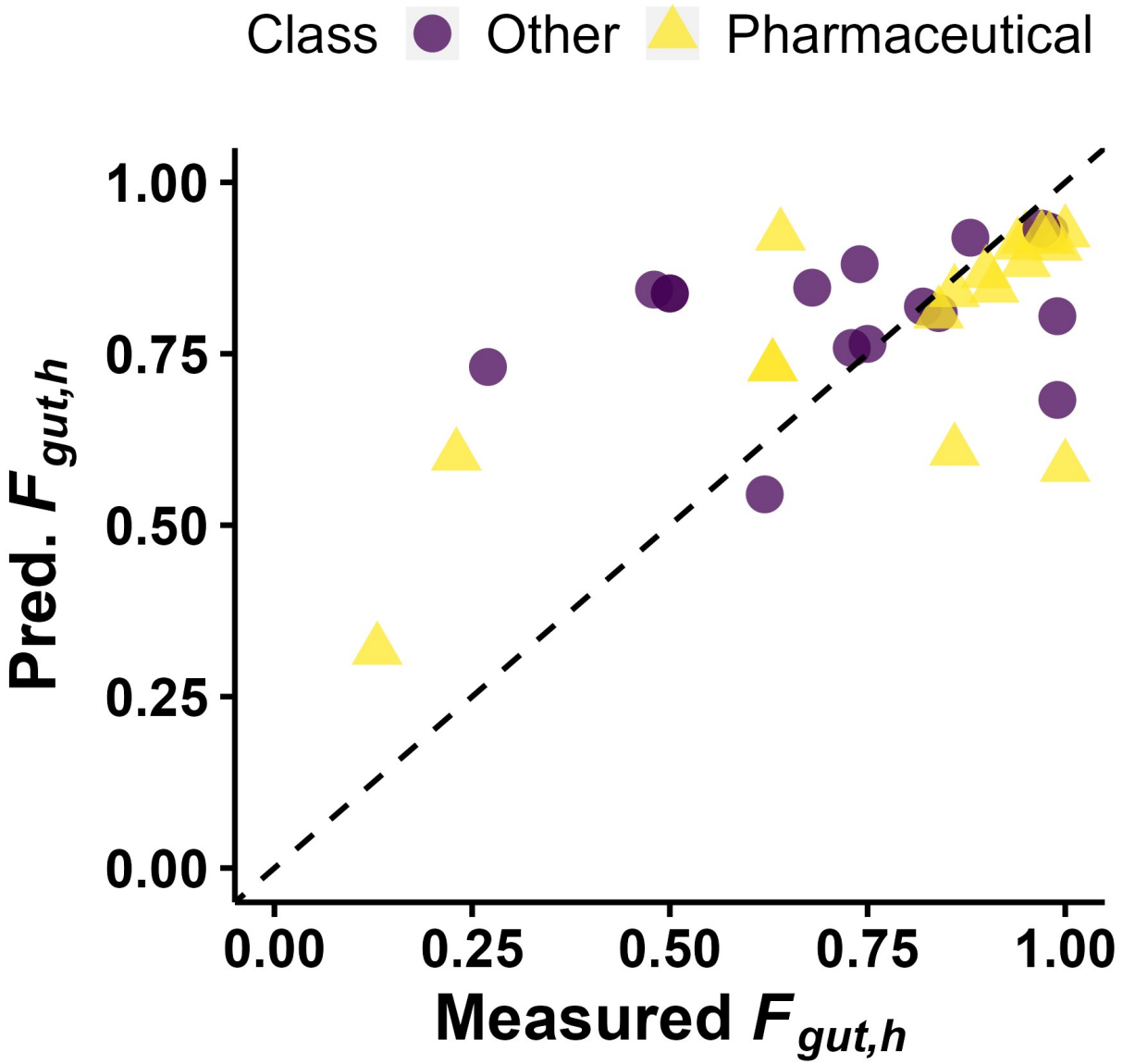


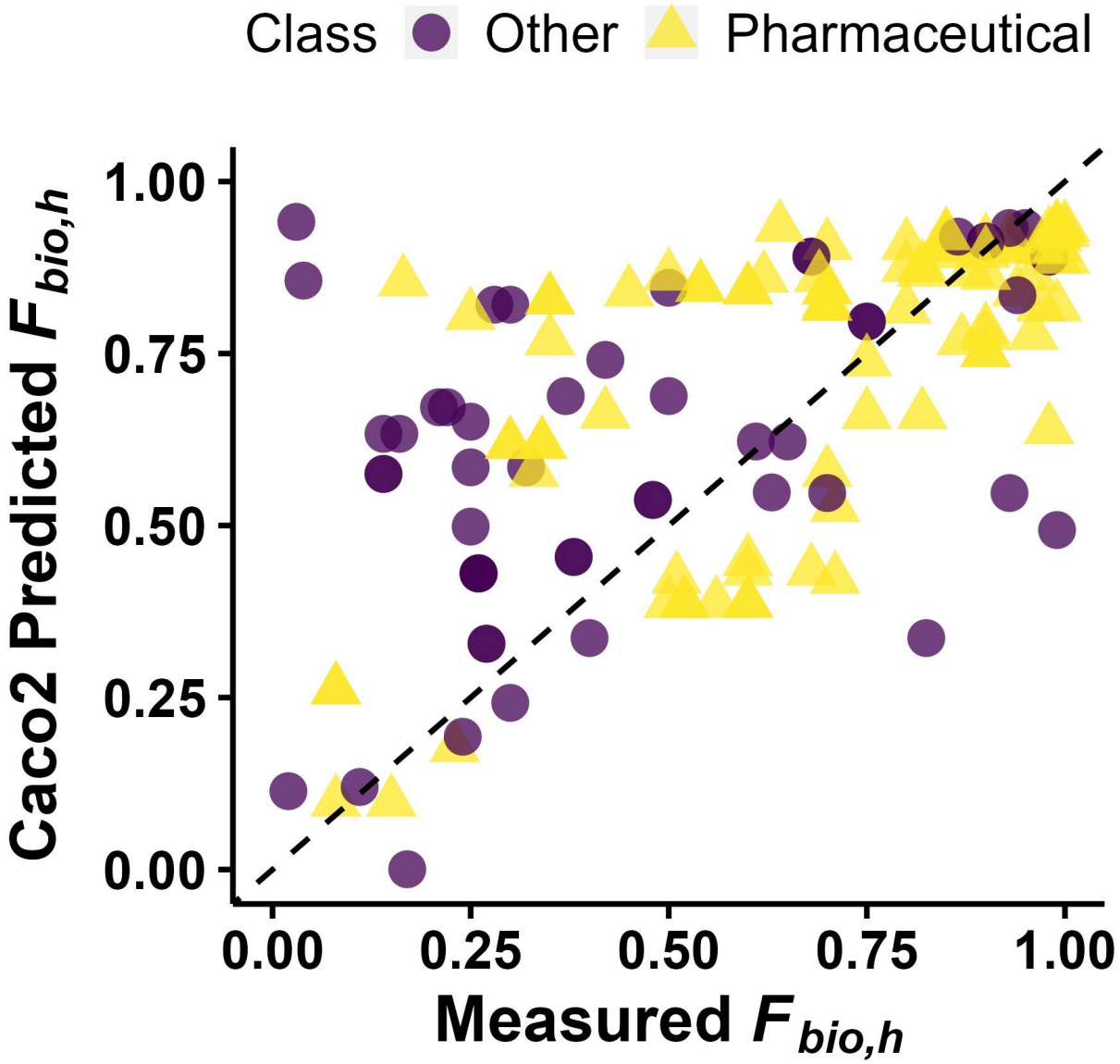
F_{gut} Model Evaluation

- We evaluated the HTTK predictions for each component of systemic bioavailability using *in vivo* data (Varma et al., 201) for various chemicals



F_{bio} Model Evaluation

- We also evaluated HTTK predictions for overall systemic bioavailaibility using *in vivo* data (Kim et al., 2014) for various chemicals

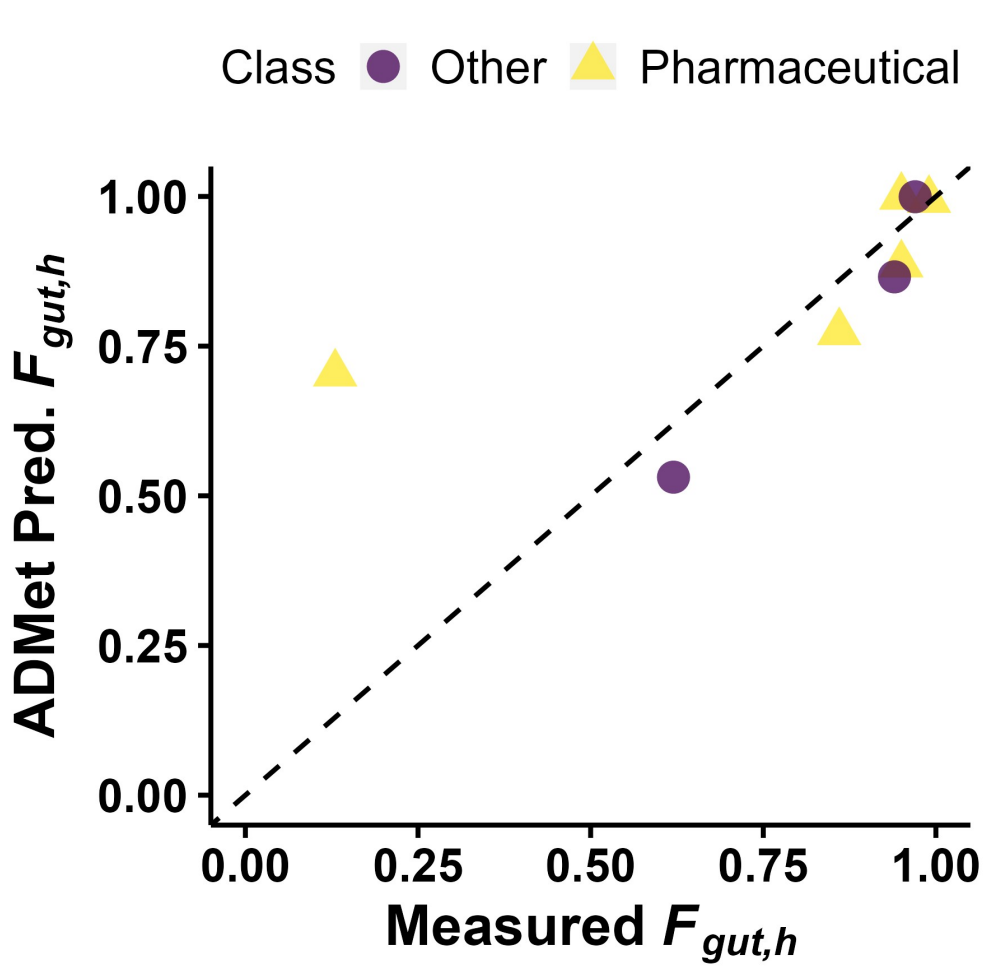


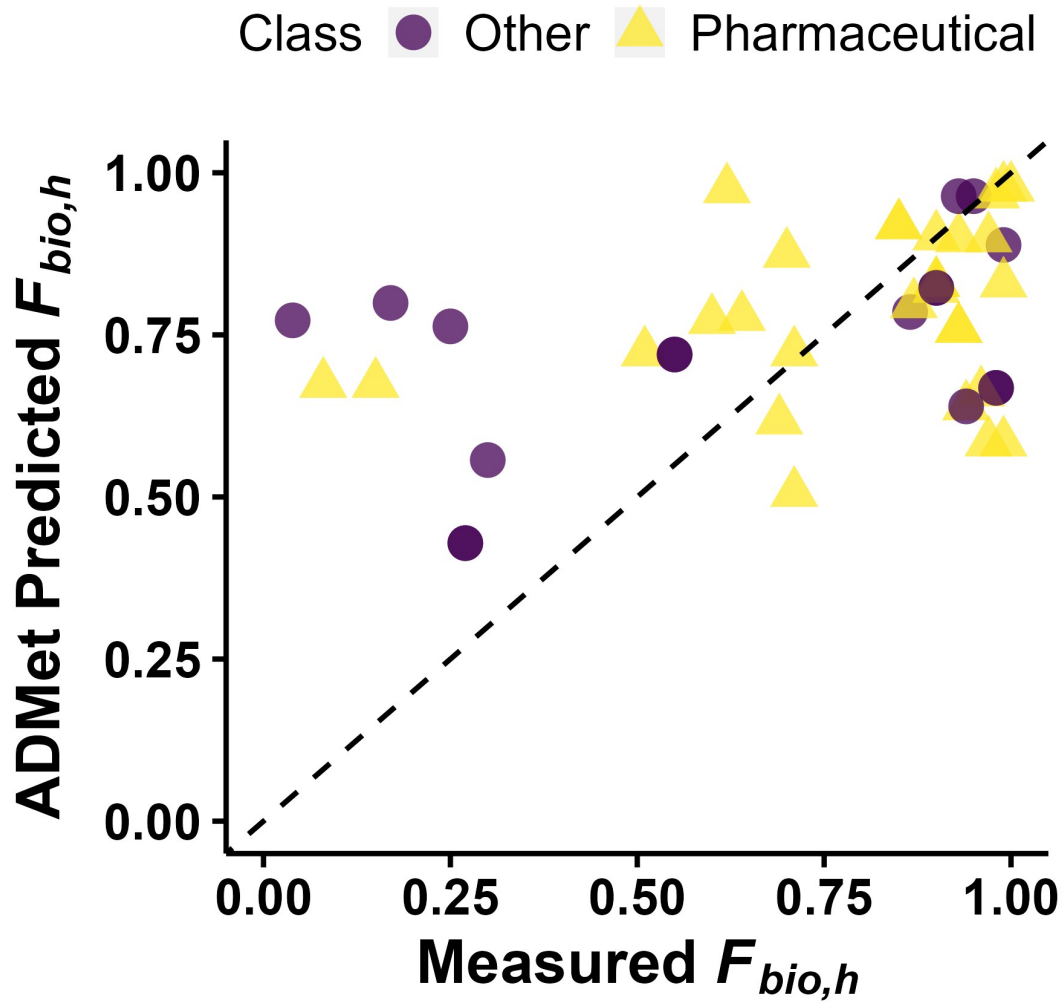
Summarizing Model Evaluations

	Number of Chemicals	Reference	R2	p.Value	RMSE
Fabs	84	Varma et al. (2010)	0.4	8.90E-11	0.237
Fgut-QGutModel	51	Varma et al. (2010)	0.23	0.00024	0.202
Fhep	51	Varma et al. (2010)	0.47	1.80E-08	0.155
Fbio	140	Kim et al. (2014)	0.37	5.60E-16	0.251
Fbio-QSPR	140	Kim et al. (2014)	0.3	1.90E-12	0.267
Fbio-PreviousHTTK	140	Kim et al. (2014)	0.2	1.70E-08	0.374

- Adding Caco-2 data improved Fbio predictions for HTTK from R^2 0.2 to 0.37
- Using QSPR gives R^2 of 0.3

Comparing with ADMet / Gastro-Plus





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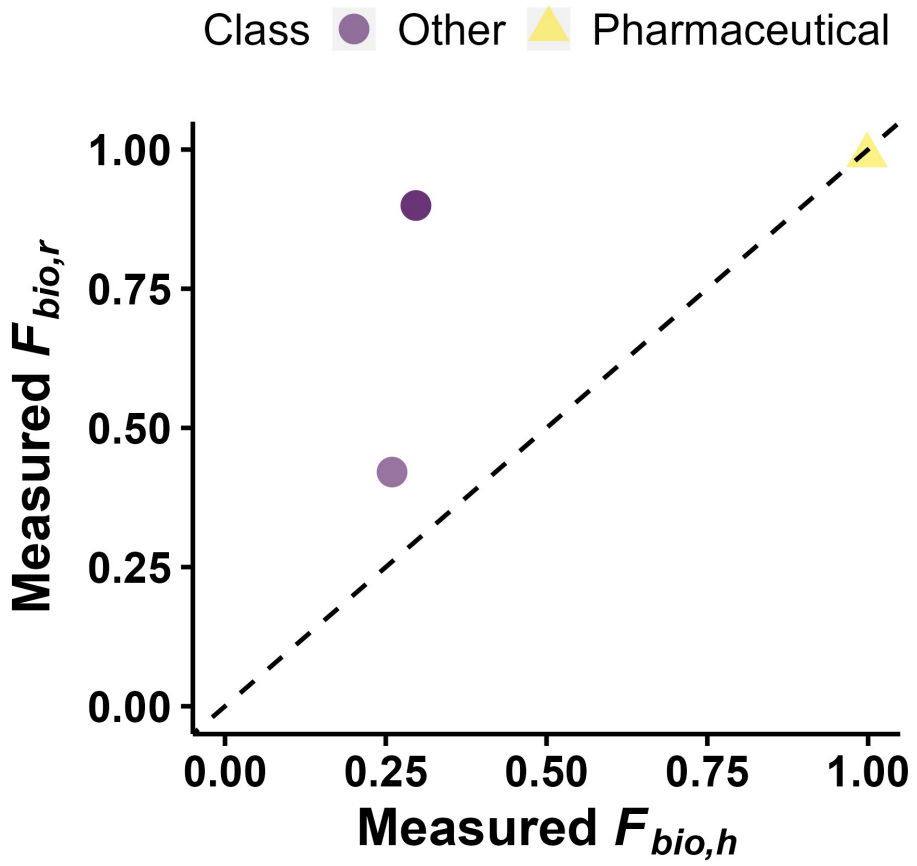
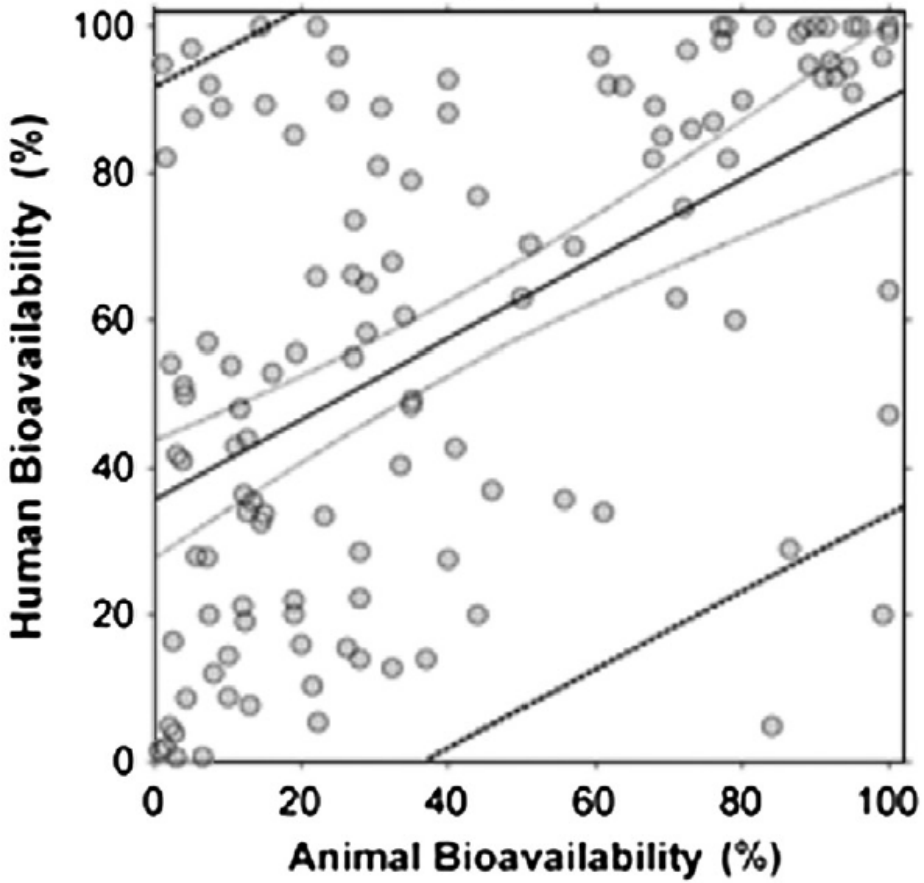
Fbio	140	Kim et al. (2014)	0.37	5.60E-16	0.251
Fbio-QSPR	140	Kim et al. (2014)	0.3	1.90E-12	0.267
Fbio-ADMet	46	Kim et al. (2014)	0.14	0.0055	0.265
Fbio-PreviousHTTK	140	Kim et al. (2014)	0.2	1.70E-08	0.374

- ADMet Predictor is largely trained to pharmaceuticals
- Includes a much more sophisticated gut model (multiple compartments)

Comparing with F_{bio} Estimated in Rat



Musther et al., 2014



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Fbio-Rat	10	Wambaugh et al. (2018)	0.2	0.11	0.352
Fbio-QSPR	140	Kim et al. (2014)	0.3	1.90E-12	0.267
Fbio-ADMet	46	Kim et al. (2014)	0.14	0.0055	0.265
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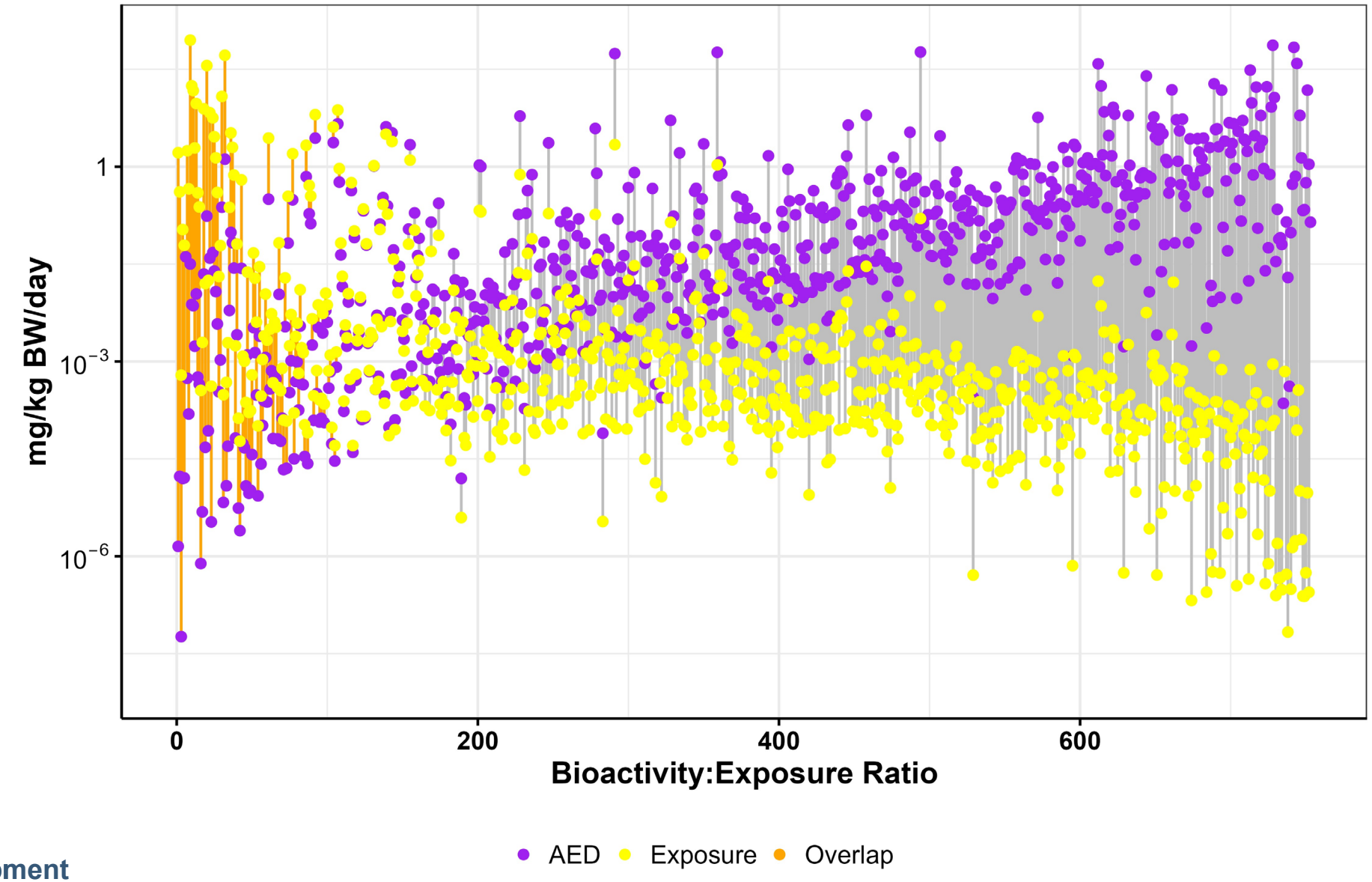
- Rat *in vivo* bioavailability is less correlated with human *in vivo* than Caco-2 predictions
- Musther et al. (2014) found R^2 of 0.28 (using 122 chemicals)

Impact on Risk Prioritizations

- The impact on risk prioritizations has been minimal so far
- Reduced F_{bio} works to increase predicted Administered Equivalent dose, therefore increasing margin of exposure
- However, most chemicals examined so far have been predicted to be well absorbed from gut
- The QSPR allows prioritization of chemicals without *in vitro* Caco-2 data



Means of Obtaining HTTK

- SimCYP SimRFlow Tool (in use by EU-ToxRisk) (Khalidi et al., 2022)
  https://www.certara.com/software/simcyp-pbpk/
- NICEATM Web-ICE (in use by US NTP) (Bell et al., 2020)
  https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox/ct-ivive/ivive
- CompTox Chemicals Dashboard (in use by US EPA) (Williams et al., 2017)
  https://comptox.epa.gov/dashboard/
- TKPlate (in use by EFSA) (Dorne et al., 2018)
  https://zenodo.org/record/2548850
- R package “httk” (general informatics community, including EPA) (Pearce et al., 2017)
  https://CRAN.R-project.org/package=httk

All these tools make use of some or all data/models from R package “httk”

Summary

- HTTK is an approach that provides toxicokinetic predictions for high throughput *in vivo-in vitro* extrapolation to inform chemical risk assessment when in vivo toxicokinetic data are unavailable
  - HTTK relies on rapid in vitro measurements of chemical properties
  - EPA's HTTK approach has now been modified to use membrane permeability to predict F_{abs} and F_{gut}
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  - First-pass hepatic metabolism was already included
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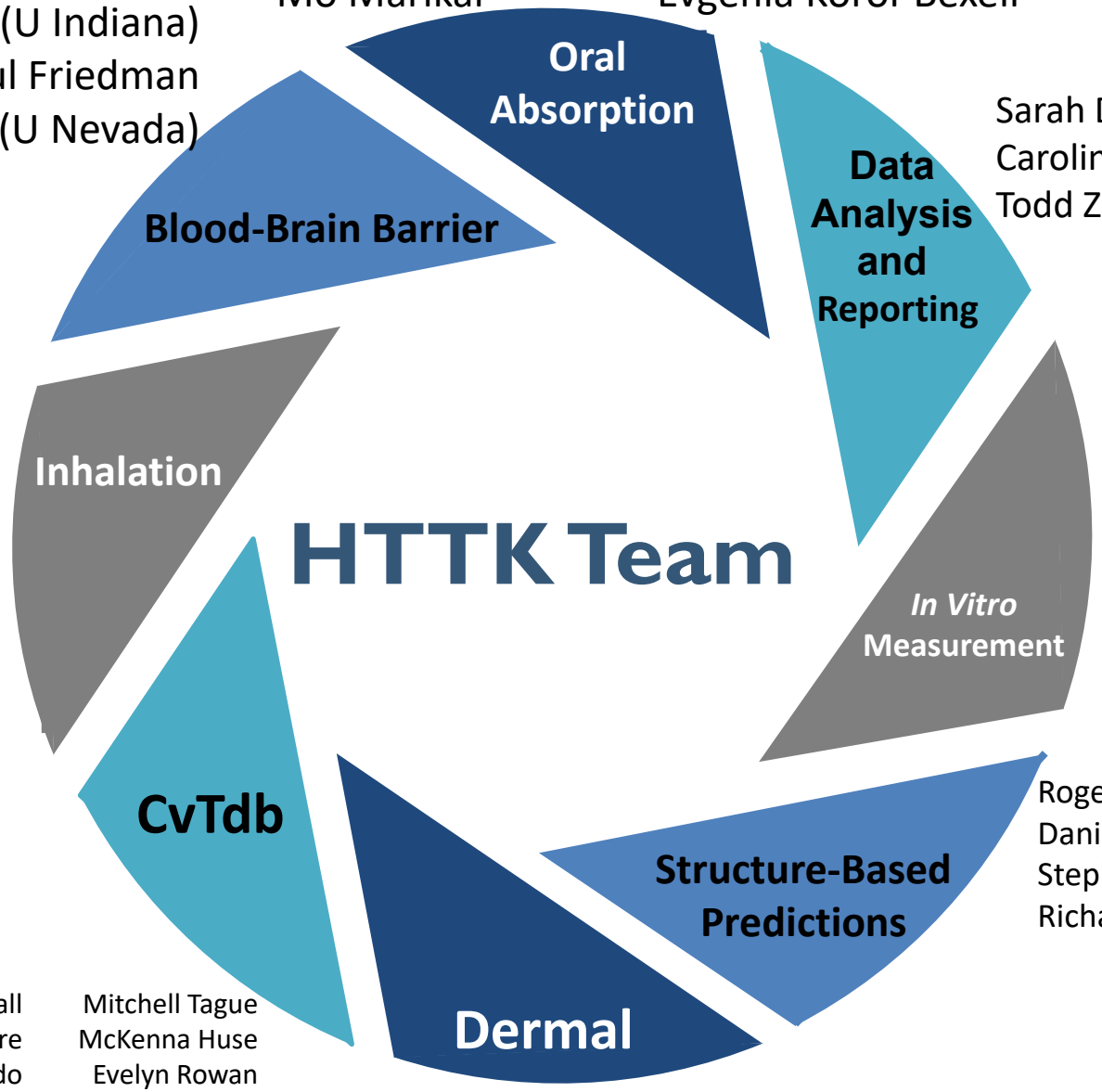
- These data were used to develop a machine learning-based quantitative structure-property relationship (QSPR) model
- Both *in vitro* Caco-2 measurements and QSPR-derived values predict human oral absorption of chemicals better than animal experiments

HTTK Team



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