High-Throughput Toxicokinetics (HTTK) R package

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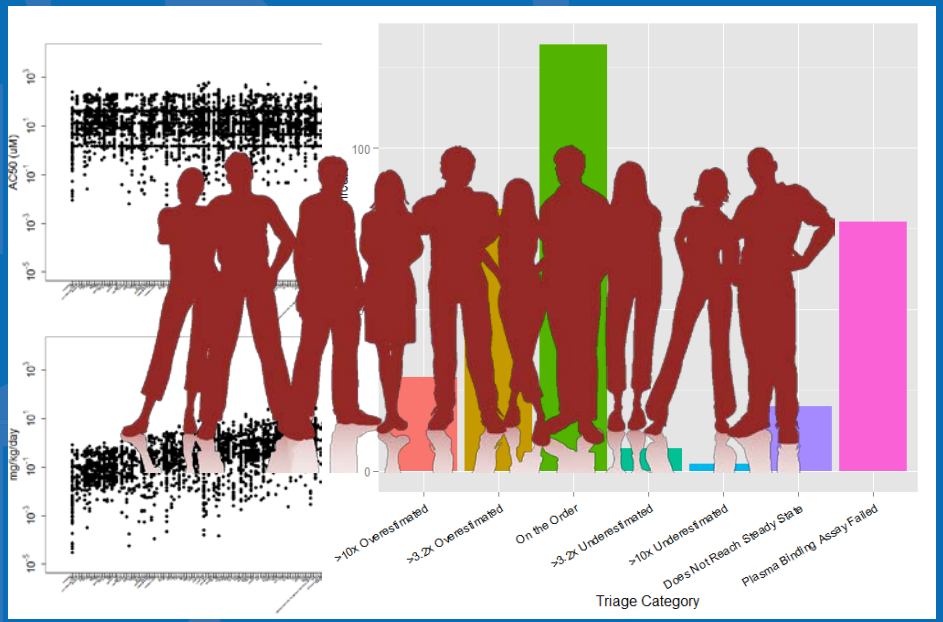

Figure includes image from Thinkstock

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Introduction

- Toxicokinetics (TK) provides a bridge between HTS and HTE by predicting tissue concentrations due to exposure
  - Traditional TK methods are resource intensive

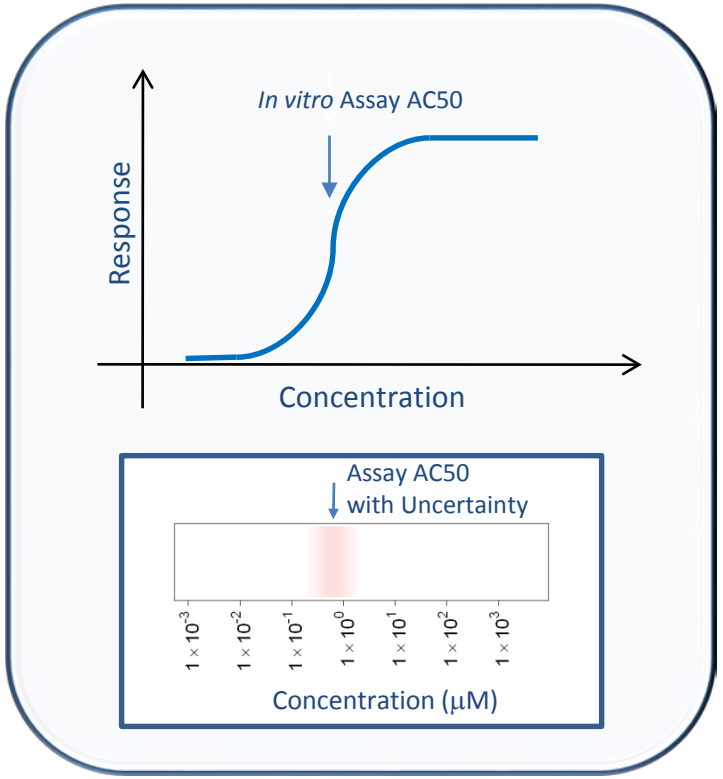
- Relatively high throughput TK (HTTK) methods have been used by the pharmaceutical industry to determine range of efficacious doses and to prospectively evaluate success of planned clinical trials (Jamei, *et al.*, 2009; Wang, 2010)

  - A key application of HTTK has been “reverse dosimetry” (also called Reverse TK or RTK)

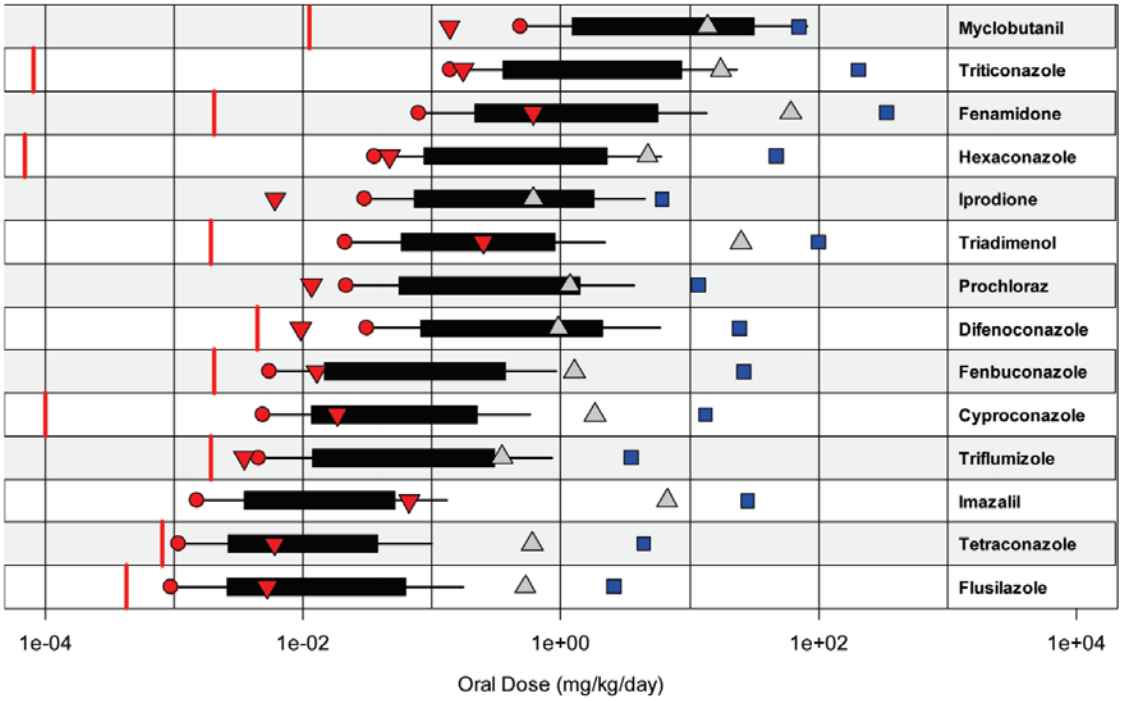
  - RTK can approximately convert *in vitro* HTS results to daily doses needed to produce similar levels in a human for comparison to exposure data (Wetmore, *et al.,* 2012)

High-Throughput Bioactivity

- **Tox21**: Examining >10,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)
- **ToxCast**: For a subset (>1000) of Tox21 chemicals ran >500 additional assays (Judson et al., 2010)
- Most assays conducted in dose-response format (identify 50% activity concentration – AC50 – and efficacy if data described by a Hill function)
- All data is public: http://actor.epa.gov/



In vitro Bioactivity, HTTK, and *in Vivo* Toxic Doses



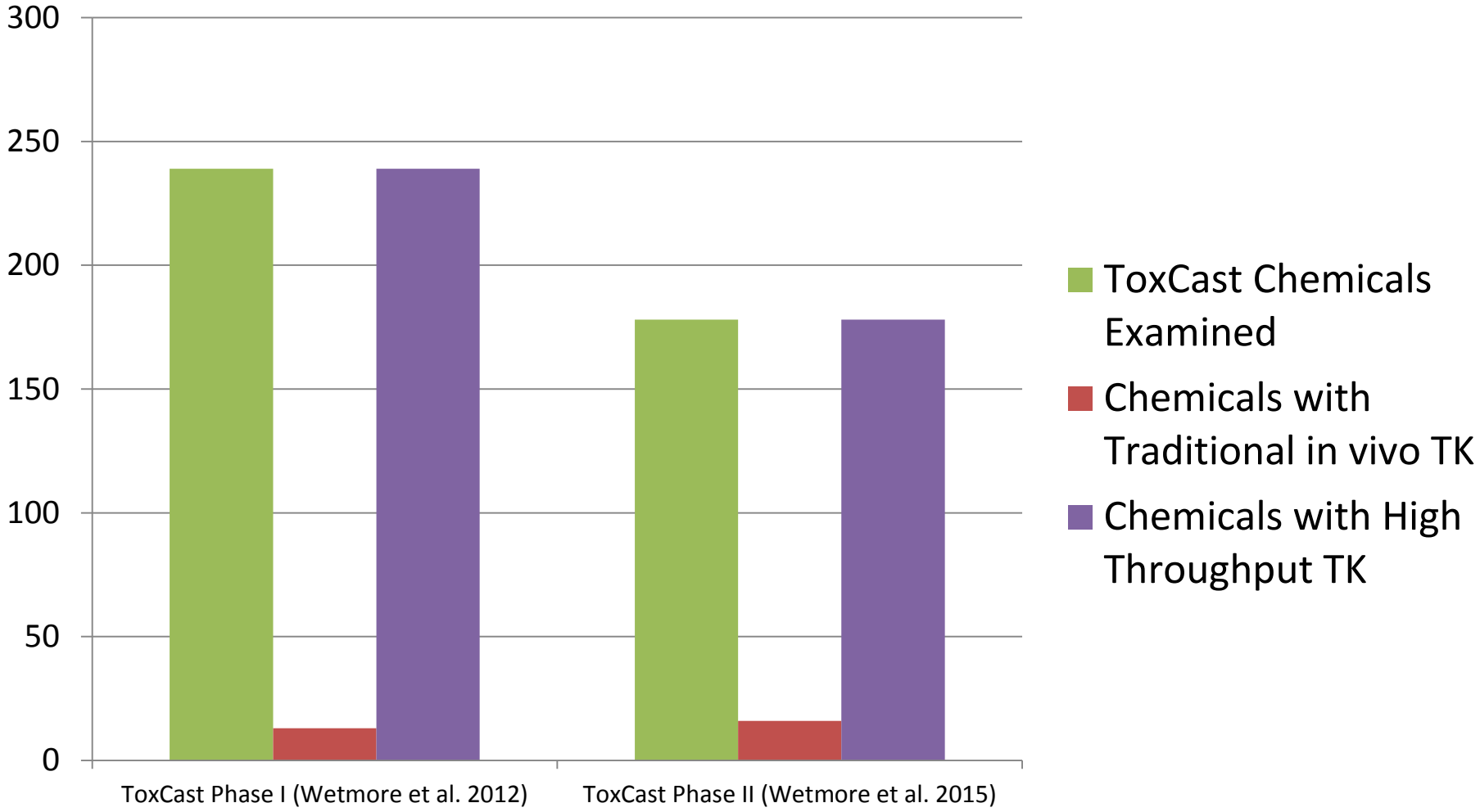
Judson *et al*. (2011)

Comparison of HTTK predicted oral equivalent doses (box and whisker plots in mg/kg/day) with doses for no effect and low effect groups in animal studies

- **Lowest Observed Effect Level**
- **No Observed Effect Level (NEL)**
- **NEL/100**

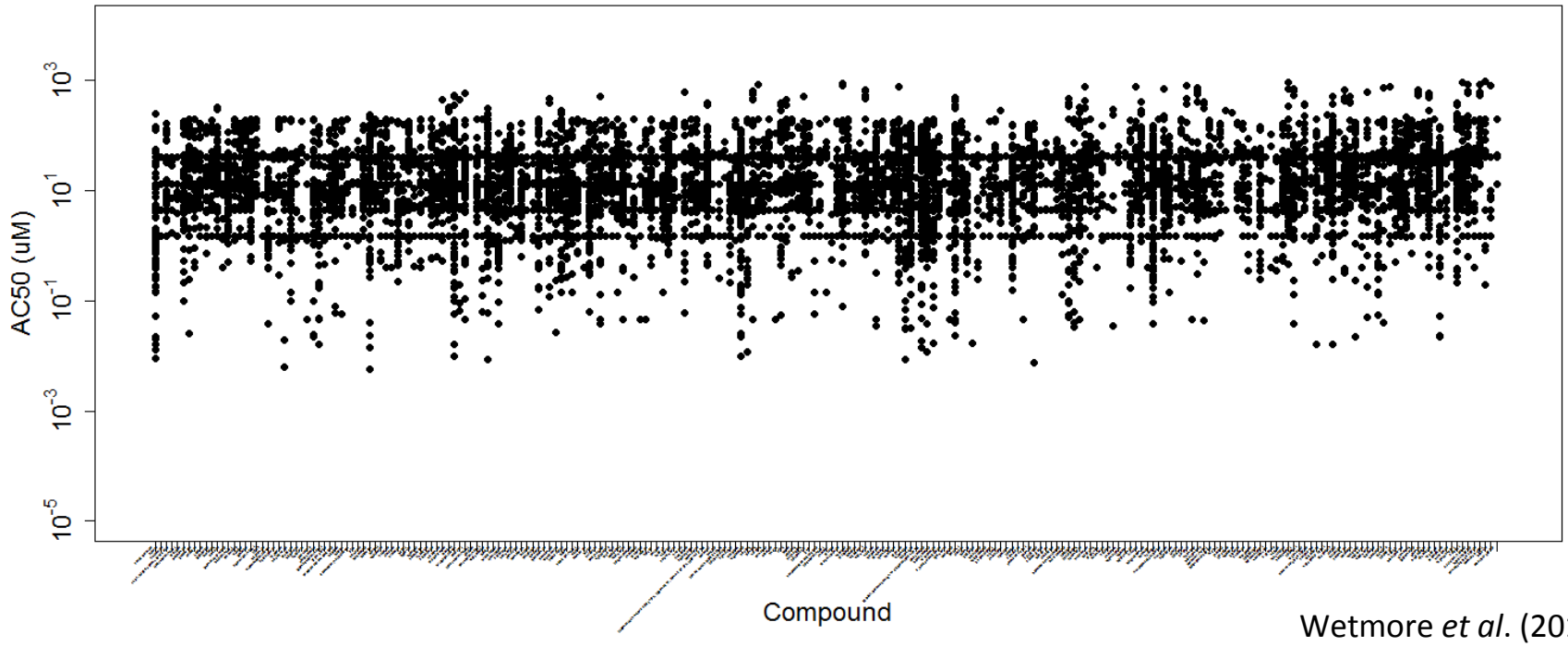
Estimated chronic exposure levels from food residues are indicated by vertical red lines. All values are in mg/kg/day.

The Need for *In Vitro* Toxicokinetics



- Studies like Wetmore et al. (2012),addressed the need for TK data using *in vitro* methods

ToxCast *in vitro* Bioactive Concentrations



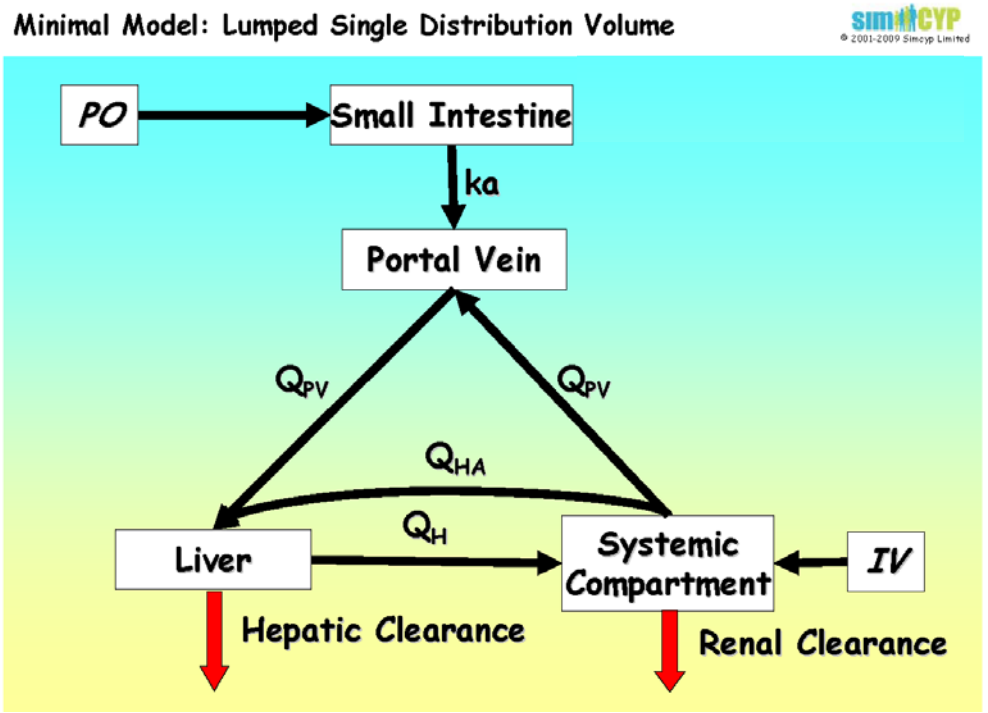
Wetmore *et al*. (2012)

- One point for each chemical-*in vitro* assay combination with a systematic (Hill function) concentration response curve
- How can we use toxicokinetics to convert these to human doses?

High Throughput Toxicokinetics (HTTK)

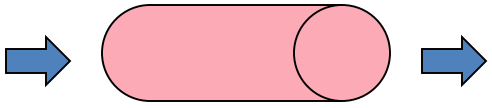
Jamei *et al*. (2009)

- *In vitro* plasma protein binding and metabolic clearance assays allow approximate hepatic and renal clearances to be calculated
- At steady state this allows conversion from concentration to administered dose
- 100% bioavailability assumed



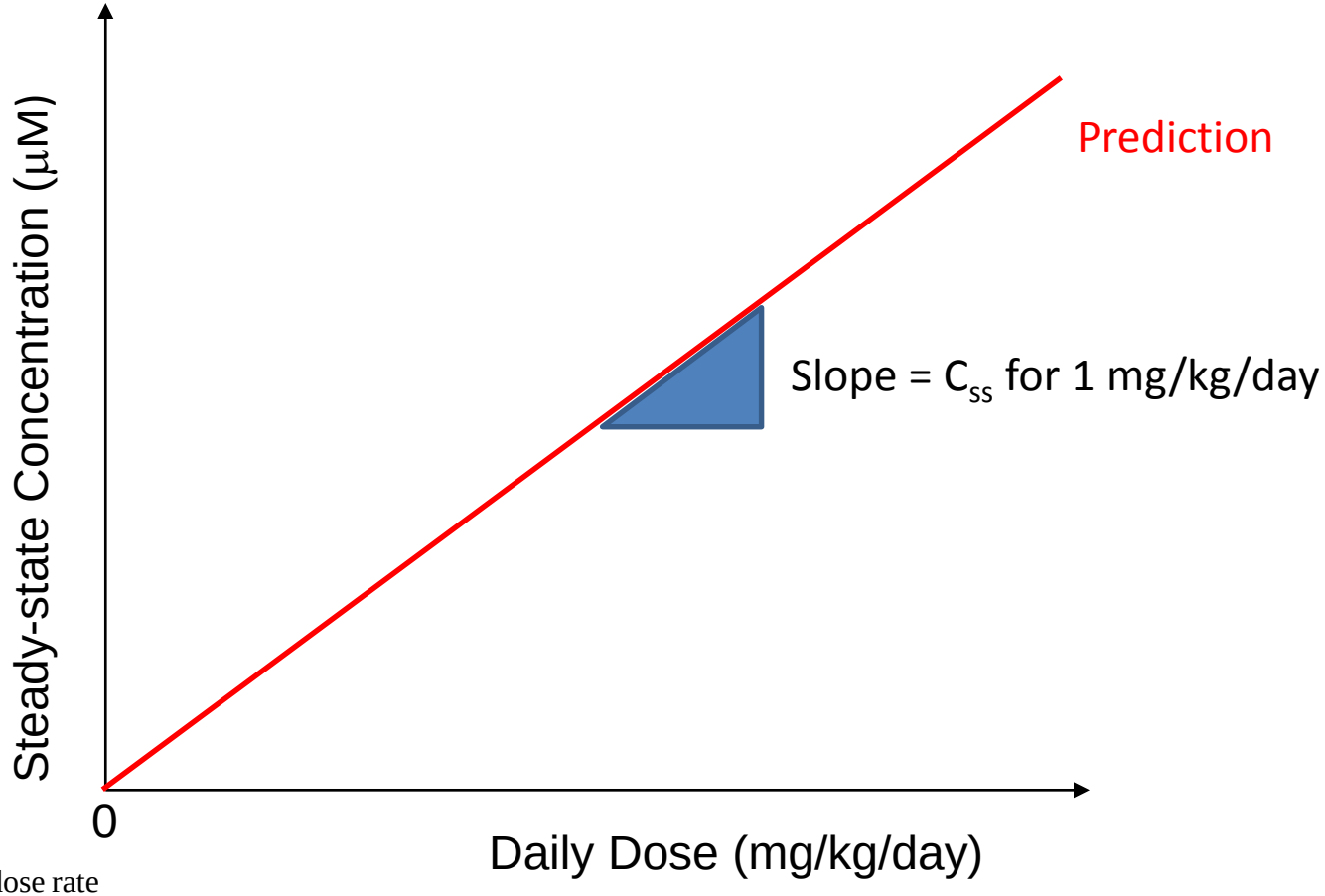
$$C_{ss} = \frac{\text{oral dose rate}}{(\text{GFR} * \text{F}_{ub}) + \left(\text{Q}_l * \text{F}_{ub} * \frac{Cl_{int}}{\text{Q}_l + \text{F}_{ub} * Cl_{int}}\right)}$$

Oral dose in (mg/kg/day)



Sum of hepatic and renal clearance (mg/kg/day)

Steady-State is Linear with Dose

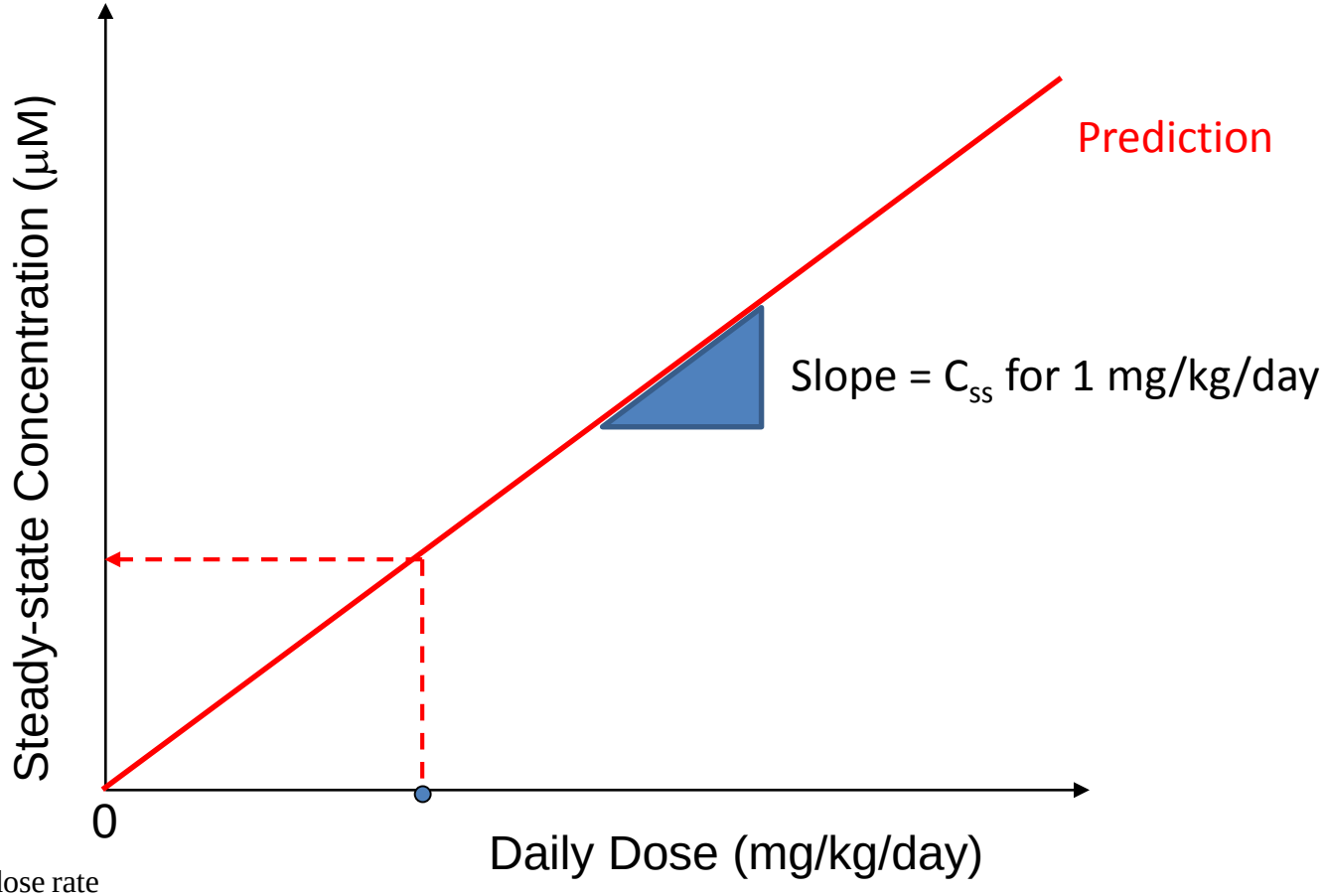


$$C_{ss} = \frac{\text{oral dose rate}}{(\text{GFR} * \text{F}_{ub}) + \left(\text{Q}_l * \text{F}_{ub} * \frac{Cl_{int}}{\text{Q}_l + \text{F}_{ub} * Cl_{int}}\right)}$$

- Can calculate predicted steady-state concentration (C_{ss}) for a 1 mg/kg/day dose and multiply to get concentrations for other doses

Wetmore *et al*. (2012)

Steady-State is Linear with Dose

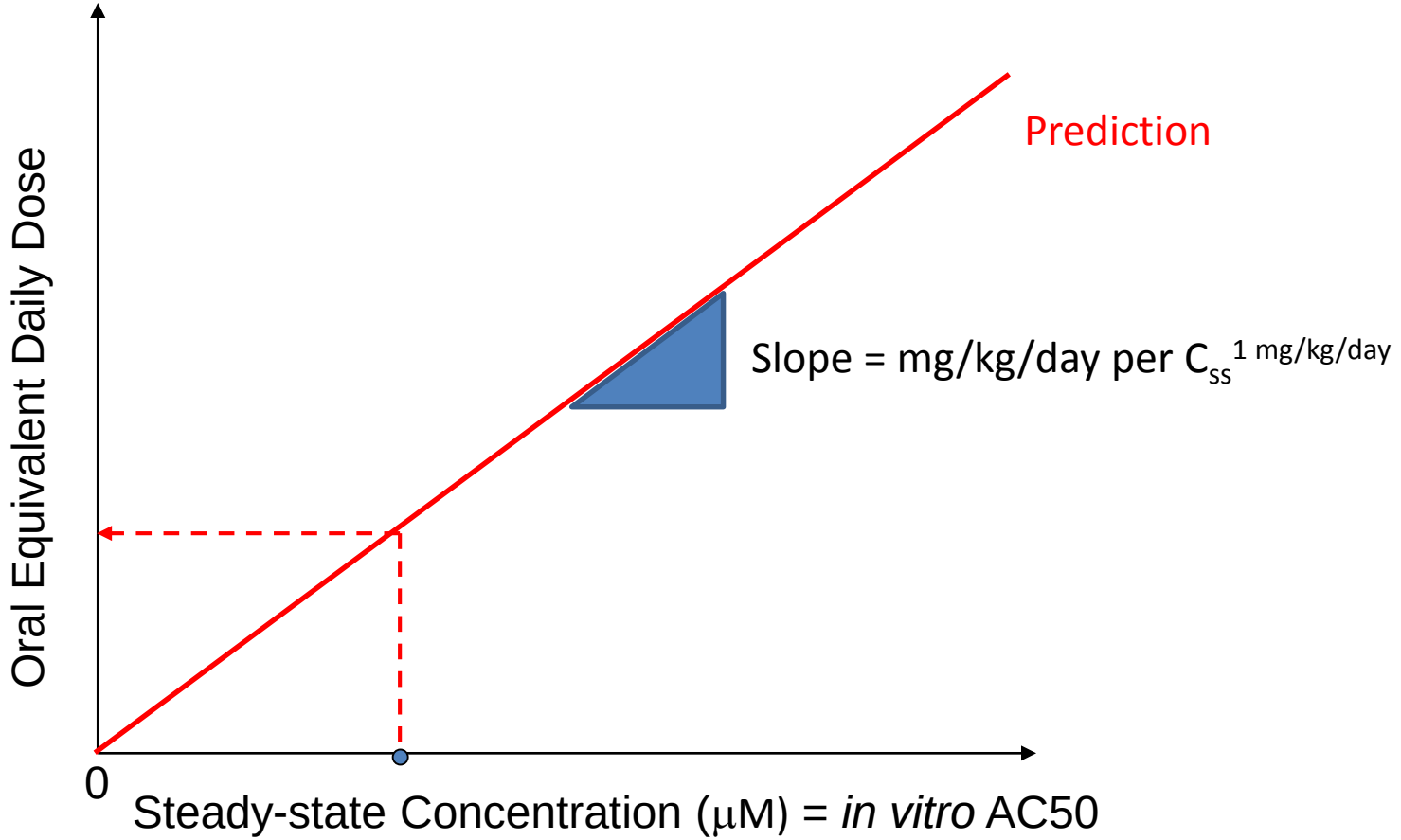


$$C_{ss} = \frac{\text{oral dose rate}}{(\text{GFR} * \text{F}_{ub}) + \left(\text{Q}_l * \text{F}_{ub} * \frac{Cl_{int}}{\text{Q}_l + \text{F}_{ub} * Cl_{int}}\right)}$$

- Can calculate predicted steady-state concentration (C_{ss}) for a 1 mg/kg/day dose and multiply to get concentrations for other doses

Wetmore *et al*. (2012)

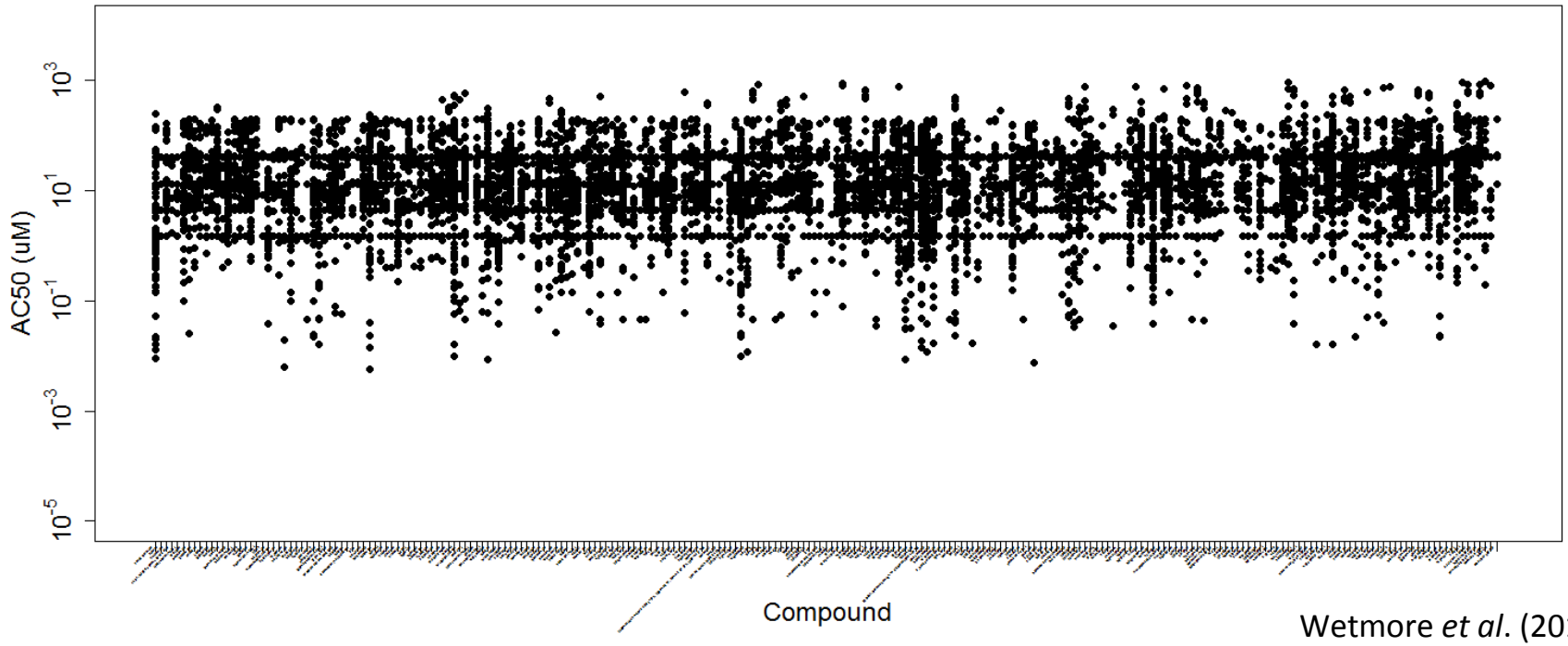
HTTK Allows Steady-State *In Vitro*-*In Vivo* Extrapolation (IVIVE)



- Swap the axes (this is the "reverse" part of reverse dosimetry)
- Can divide bioactive concentration by C_{ss} for for a 1 mg/kg/day dose to get oral equivalent dose

Wetmore *et al*. (2012)

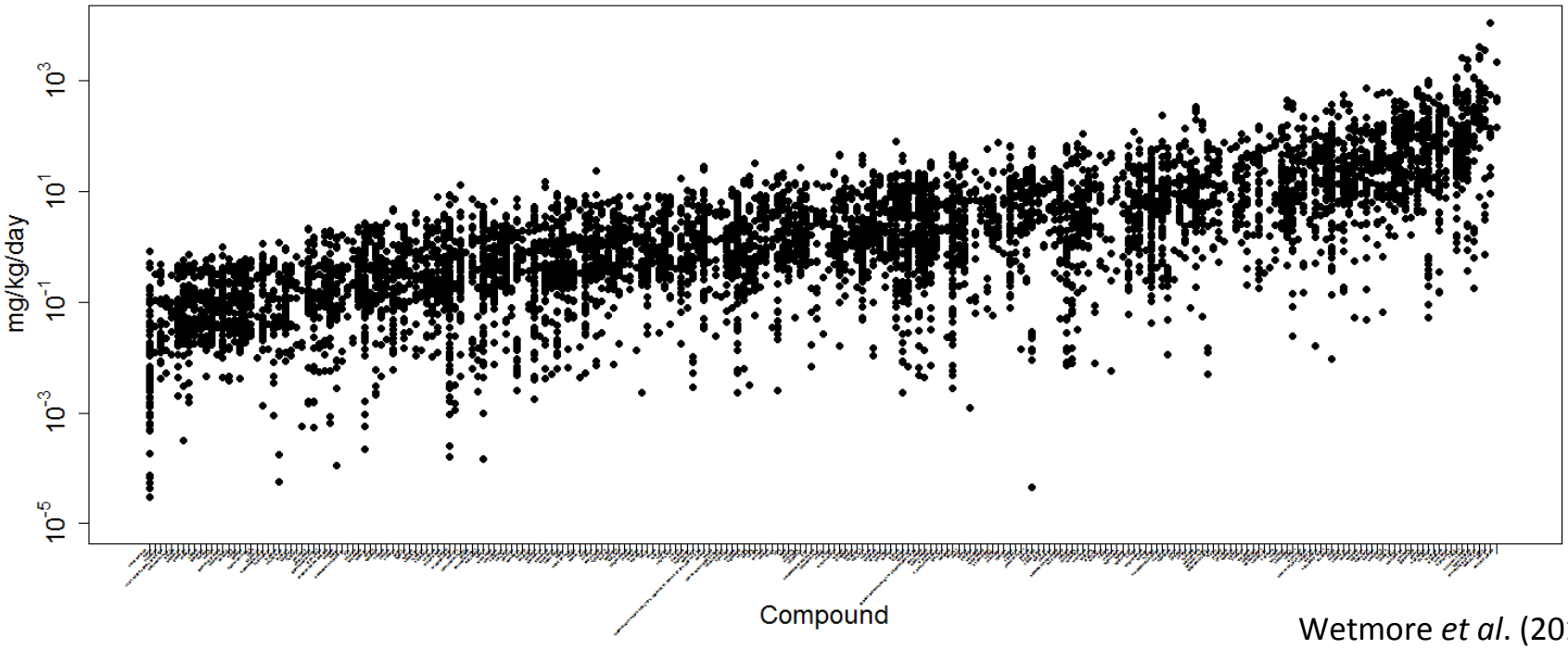
ToxCast *in vitro* Bioactive Concentrations



Wetmore *et al*. (2012)

- It appears harder to prioritize on bioactive *in vitro* concentration without *in vivo* context

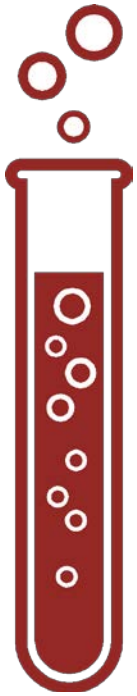
HTTK Oral Equivalents



Wetmore *et al*. (2012)

- Translation from *in vitro* to steady-state oral equivalent doses allow greater discrimination between effective chemical potencies

Reverse Dosimetry with HTTK



High Throughput *In Vitro* Bioactive Concentration

HTTK *in vitro* data

Simulated Human *In Vivo* Doses

Monte Carlo Simulation of Biological Variability

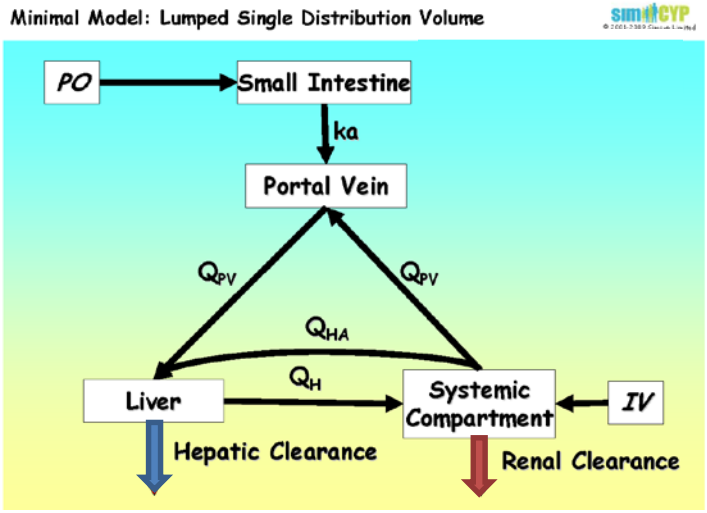
Combination of higher exposure and sensitivities

Populations that are More Sensitive

Images from Thinkstock

Variability in this Steady-State TK Model

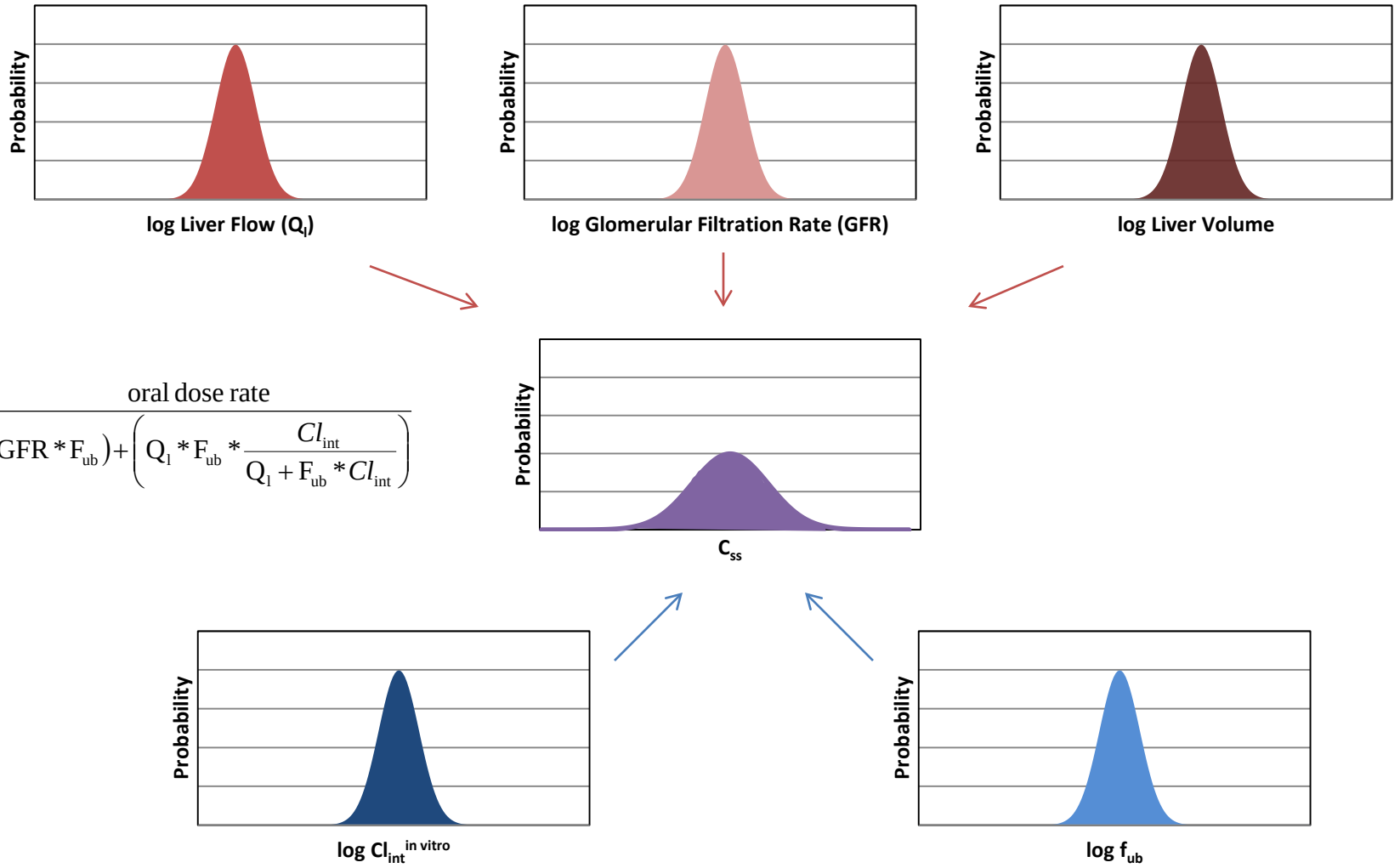
Jamei *et al*. (2009)



$$C_{ss} = \frac{\text{oral dose rate}}{\underbrace{(GFR * F_{ub})}_{\text{(Passive) Renal Clearance}} + \underbrace{\left(Q_l * F_{ub} * \frac{Cl_{int}}{Q_l + F_{ub} * Cl_{int}}\right)}_{\text{Hepatic Clearance (Metabolism)}}}$$

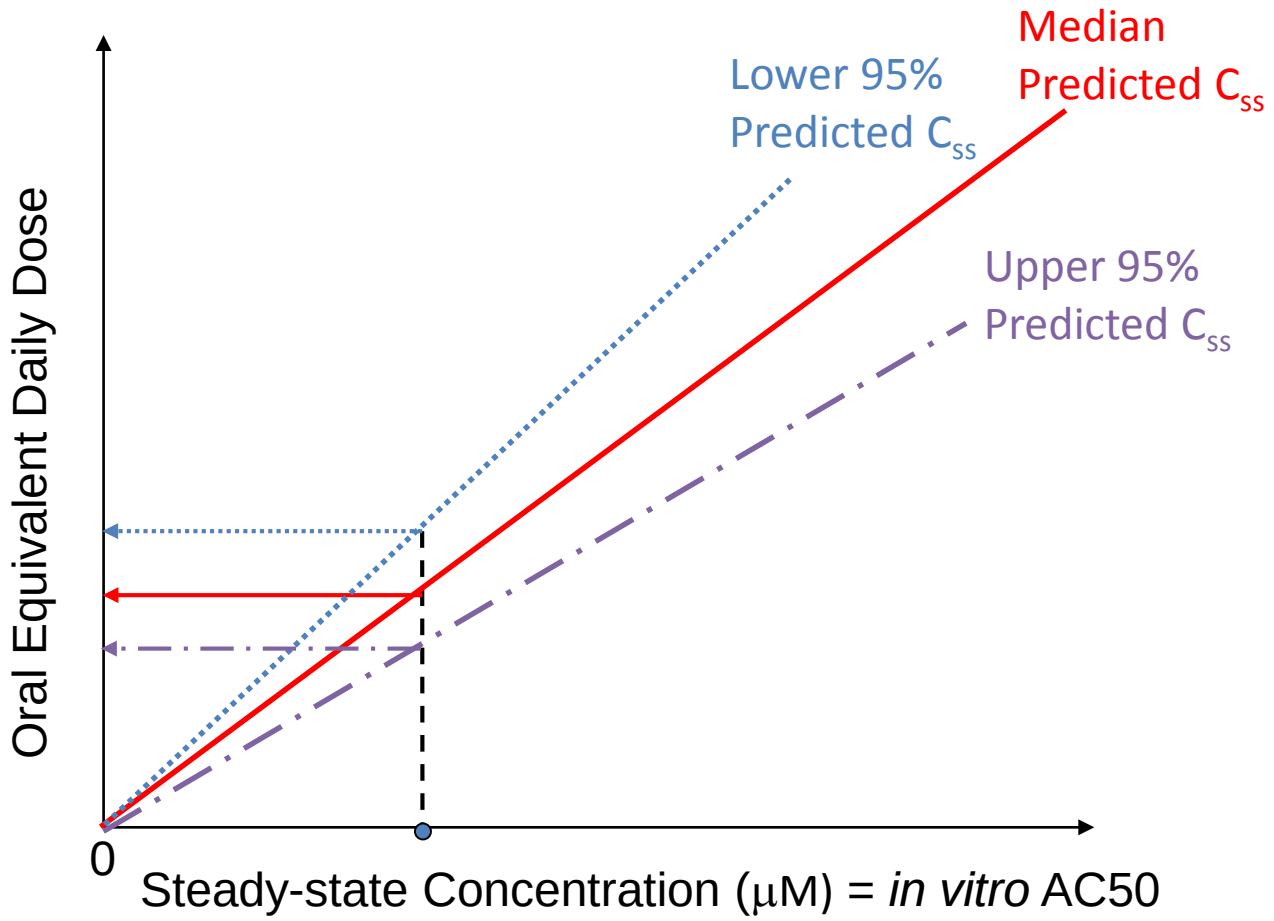
- *In vitro* clearance (µL/min/10^6 hepatocytes) is scaled to a whole organ clearance using the density of hepatocytes per gram of liver and the volume of the liver (which varies between individuals)
- Glomerular filtration rate (GFR) and blood flow to the liver (Q_l) both vary from individual to individual
- Further assume that measured HTTK parameters have 30% coefficient of variation

Monte Carlo (MC) Approach to Variability: SimCYP (Pharma) Approach



Wetmore *et al*. (2012)

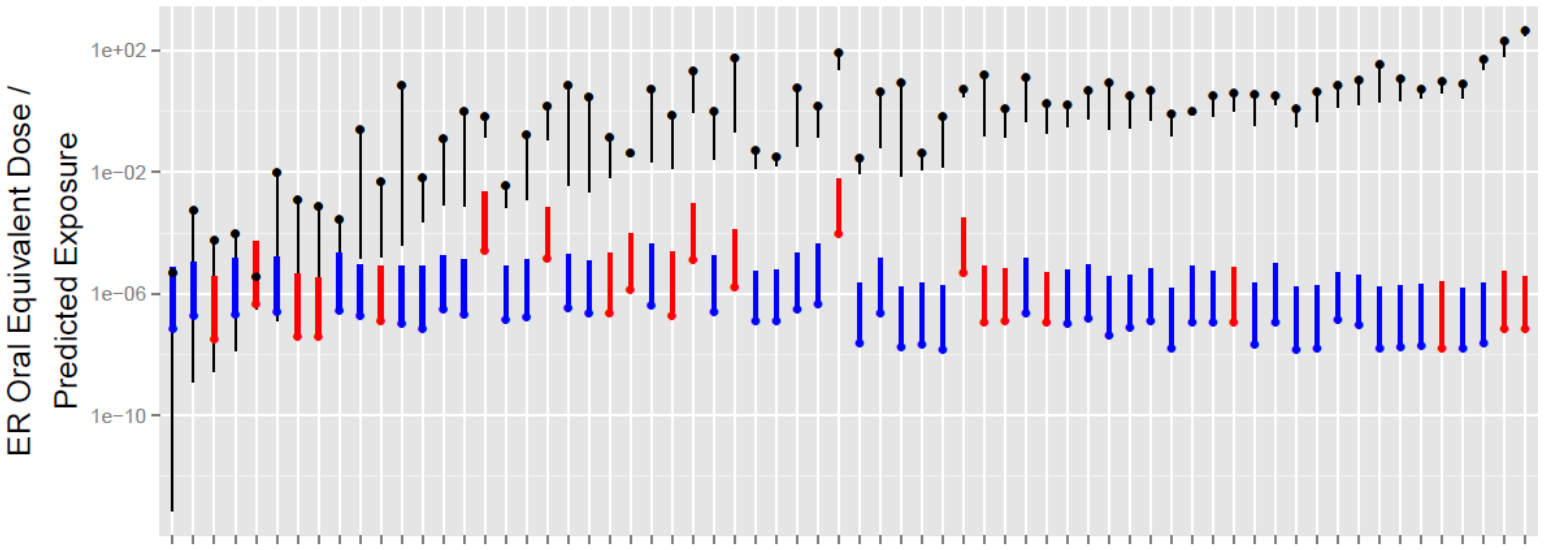
Steady-State In Vitro-In Vivo Extrapolation (IVIVE)



- The higher the predicted C_{ss}, the lower the oral equivalent dose, so the upper 95% predicted C_{ss} from the MC has a lower oral equivalent dose

Dosimetry and Exposure Provides Context for HTS

Endocrine disruption AOP *(Judson et al., in prep.)*



ToxCast Bioactivity Converted to mg/kg/day with HTTK (Wetmore et al., 2012)

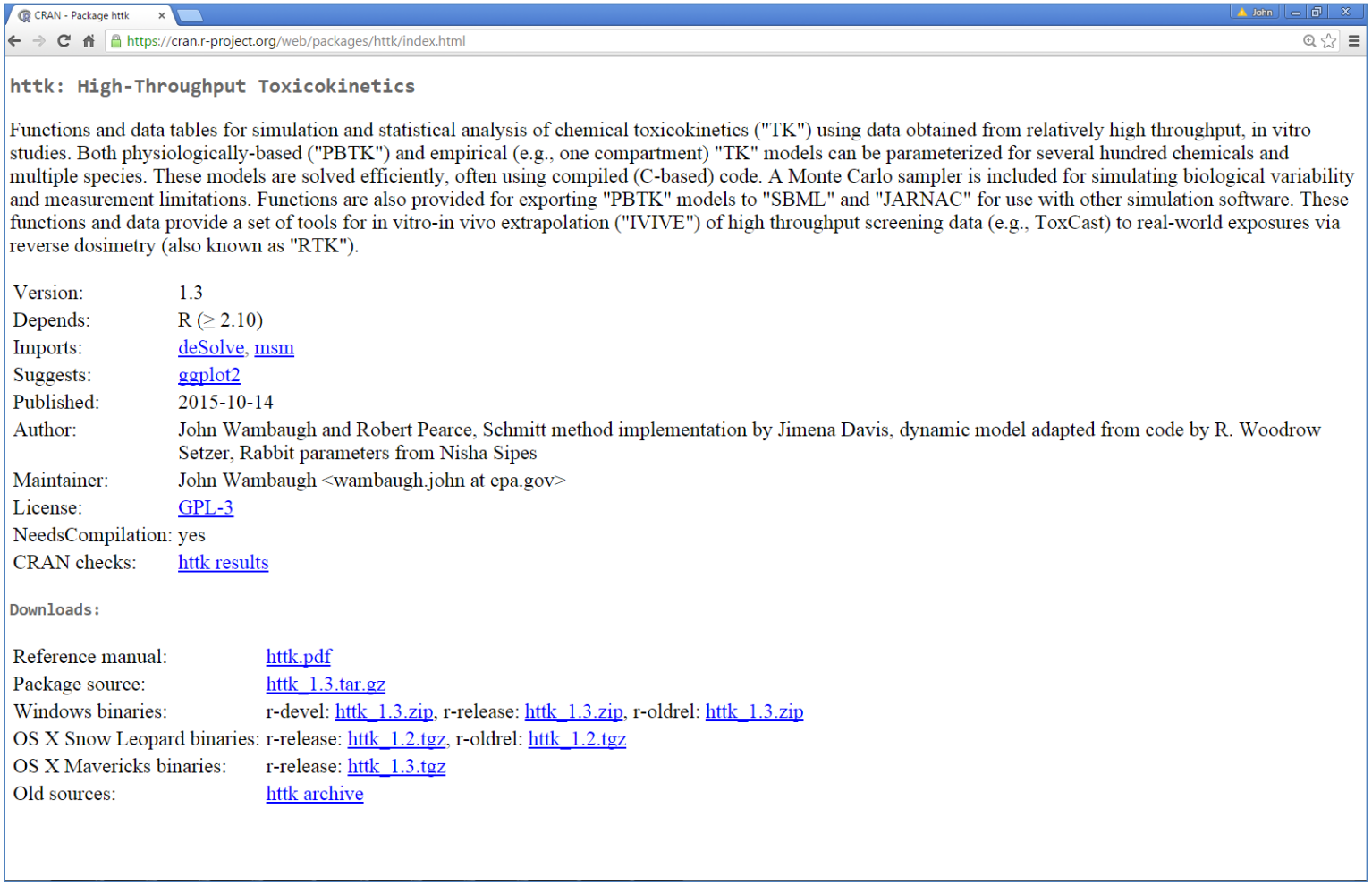
ExpoCast Exposure Predictions (Wambaugh *et al.*, 2014)

ToxCast Chemicals

December, 2015 Panel:
"Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening"

DOCKET NUMBER: EPA–HQ–OPP–2014–0614

Steady State Concentrations with httk R Package


CRAN - Package httk

https://cran.r-project.org/web/packages/httk/index.html

httk: High-Throughput Toxicokinetics

Functions and data tables for simulation and statistical analysis of chemical toxicokinetics ("TK") using data obtained from relatively high throughput, in vitro studies. Both physiologically-based ("PBTK") and empirical (e.g., one compartment) "TK" models can be parameterized for several hundred chemicals and multiple species. These models are solved efficiently, often using compiled (C-based) code. A Monte Carlo sampler is included for simulating biological variability and measurement limitations. Functions are also provided for exporting "PBTK" models to "SBML" and "JARNAC" for use with other simulation software. These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of high throughput screening data (e.g., ToxCast) to real-world exposures via reverse dosimetry (also known as "RTK").

Version:	1.3
Depends:	R (≥ 2.10)
Imports:	deSolve, msm
Suggests:	ggplot2
Published:	2015-10-14
Author:	John Wambaugh and Robert Pearce, Schmitt method implementation by Jimena Davis, dynamic model adapted from code by R. Woodrow Setzer, Rabbit parameters from Nisha Sipes
Maintainer:	John Wambaugh <wambaugh.john at epa.gov>
License:	GPL-3
NeedsCompilation:	yes
CRAN checks:	httk results

Downloads:

Reference manual:	httk.pdf
Package source:	httk_1.3.tar.gz
Windows binaries:	r-devel: httk_1.3.zip, r-release: httk_1.3.zip, r-oldrel: httk_1.3.zip
OS X Snow Leopard binaries:	r-release: httk_1.2.tgz, r-oldrel: httk_1.2.tgz
OS X Mavericks binaries:	r-release: httk_1.3.tgz
Old sources:	httk archive

https://cran.r-project.org/web/packages/httk/

Can access from the R GUI: “Packages” then “Install Packages”

Steady State Concentrations with httk R Package

```
library(httk)

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for human for Acetochlor (published value):
get_wetmore_css(chem.cas="34256-82-1")

# Should produce error:
get_wetmore_css(chem.name="34256-82-1")

#Capitalization shouldn't matter:
get_wetmore_css(chem.name="acetochlor")
get_wetmore_css(chem.name="Acetochlor")

# What's going on?
help(get_wetmore_css)

# What chemicals can I do?
get_wetmore_cheminfo()
```

Steady State Concentrations with httk R Package

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for human for Acetochlor (calculated value):

```
calc_mc_css(chem.cas="34256-82-1")
```

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for rat for Acetochlor (should produce errors since there is no published value, 0.5 quantile only):

```
get_wetmore_css(chem.cas="34256-82-1",species="Rat")
```

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for rat for Acetochlor (calculated value):

```
calc_mc_css(chem.cas="34256-82-1",species="Rat")
```

#Steady-state concentration (uM) for 1 mg/kg/day for 0.5 quantile for rat for Acetochlor (published value):

```
get_wetmore_css(chem.cas="34256-82-1",species="Rat",which.quantile=0.5)
```

#Steady-state concentration (uM) for 1 mg/kg/day for 0.5 quantile for rat for Acetochlor (calculated value):

```
calc_mc_css(chem.cas="34256-82-1",species="Rat",which.quantile=0.5)
```

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for mouse for Acetochlor (should produce error since there is no published value, human and rat only):

```
get_wetmore_css(chem.cas="34256-82-1",species="Mouse")
```

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for mouse for Acetochlor (calculated value):

```
calc_mc_css(chem.cas="34256-82-1",species ="Mouse")
```

Oral Equivalent Doses with with httk R Package

#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.95 quantile, for Acetochlor (published value):

get_wetmore_oral_equiv(0.1,chem.cas="34256-82-1")

#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.95 quantile, for Acetochlor (calculated value):

calc_mc_oral_equiv(0.1,chem.cas="34256-82-1")

#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.05, 0.5, and 0.95 quantile, for Acetochlor (published values):

get_wetmore_oral_equiv(0.1,chem.cas="34256-82-1",which.quantile=c(0.05,0.5,0.95))

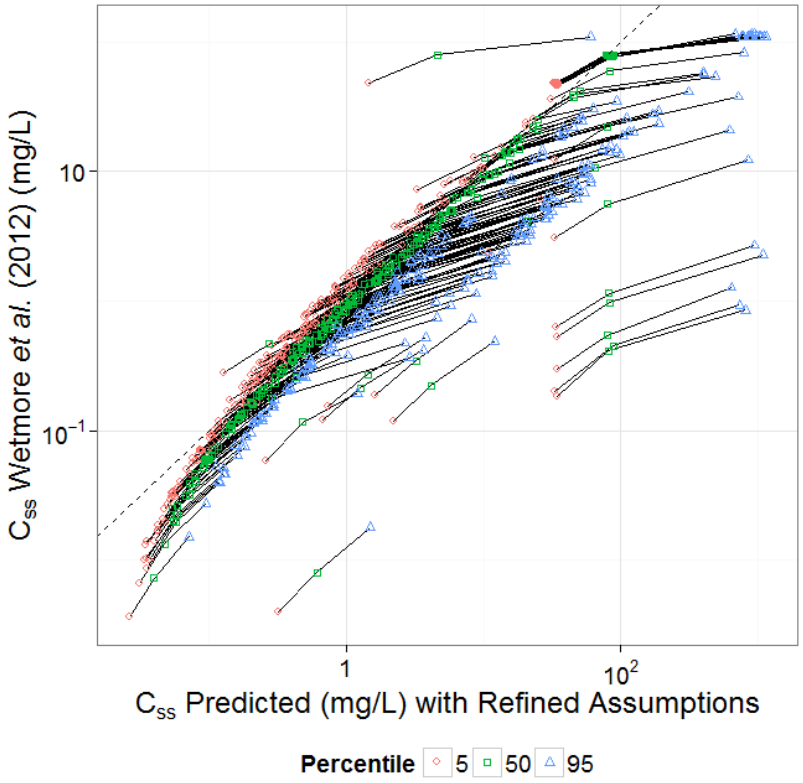
#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.05, 0.5, and 0.95 quantiles, for Acetochlor (calculated value):

calc_mc_oral_equiv(0.1,chem.cas="34256-82-1",which.quantile=c(0.05,0.5,0.95))

#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for rat, 0.95 quantile, for Acetochlor (calculated value):

calc_mc_oral_equiv(0.1,chem.cas="34256-82-1",species="Rat")

Comparison Between httk and SimCYP

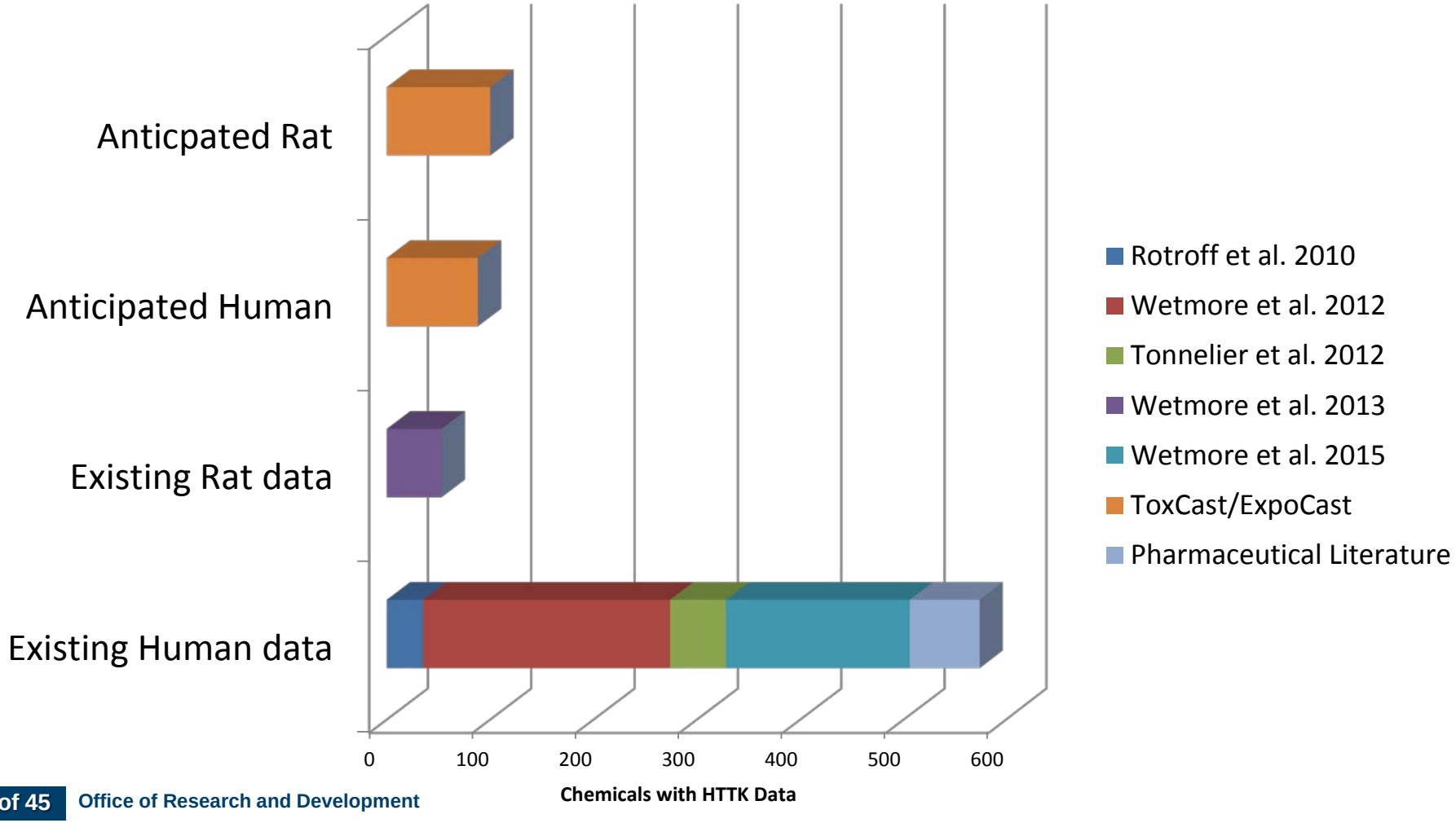


- In the Rotroff et al. (2010) and Wetmore et al. (2010) papers SimCYP was used to predict distributions of C_{ss} from *in vitro* data
  - We show that our new we can reproduce the results from those publications for most chemicals using our implementation of Monte Carlo.
- Any one chemical's median and quantiles are connected by a dotted line.
- Hepatic clearance assays with p-values < 0.05 are considered "good".

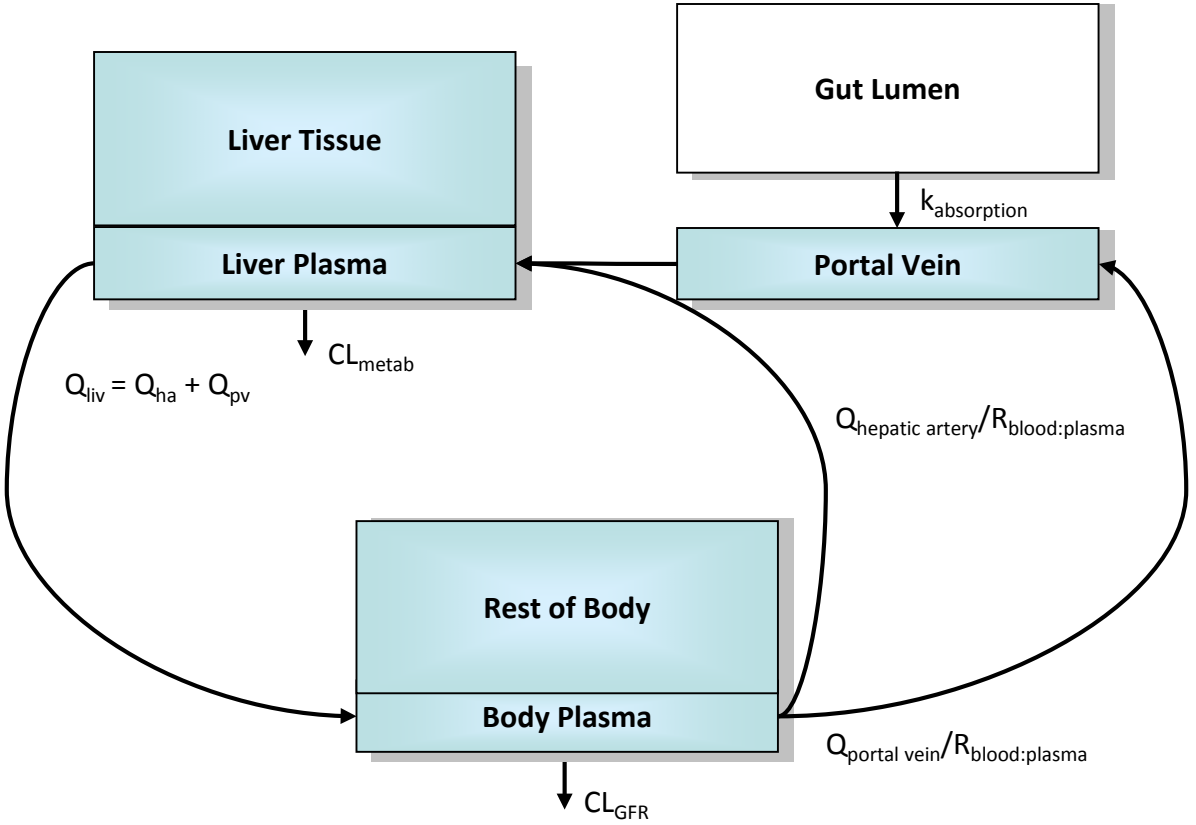
The RED assay for measuring protein binding fails in some cases because the amount of free chemical is below the limit of detection. For those chemicals a default value of 0.5% free was used. We have replaced the default value with random draws from a uniform distribution from 0 to 1%.

Wambaugh et al. (2015)

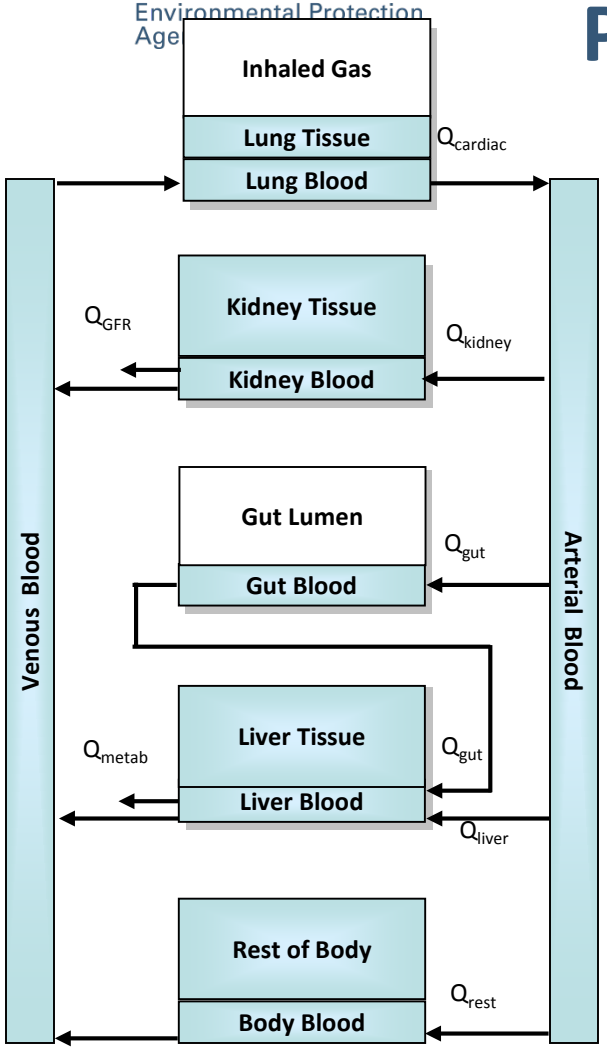
Chemicals with HTTK Data



Three Compartment (SimCYP) Model



A General Physiologically-based Pharmacokinetic (PBPK) Model



Some tissues (e.g. arterial blood) are simple compartments, while others (e.g. kidney) are compound compartments consisting of separate blood and tissue sections with constant partitioning (i.e., tissue specific partition coefficients)

Exposures are absorbed from reservoirs (gut lumen)

Some specific tissues (lung, kidney, gut, and liver) are modeled explicitly, others (e.g. fat, brain, bones) are lumped into the "Rest of Body" compartment.

Blood flows move the chemical throughout the body. The total blood flow to all tissues equals the cardiac output.

The only ways chemicals "leaves" the body are through metabolism (change into a metabolite) in the liver or excretion by glomerular filtration into the proximal tubules of the kidney (which filter into the lumen of the kidney).

Physiological Data

United States Environmental Protection Agency

	Volume (L/kg)					Blood Flow (ml/min/kg)				
Tissue	**Mouse**	**Rat**	**Dog**	**Human**	**Rabbit**	**Mouse**	**Rat**	**Dog**	**Human**	**Rabbit**
Adipose	0.07	0.07	0.05	0.21	0.05	10.80	1.60	3.50	3.71	12.80
Bone	0.05	0.04	0.04	0.07	0.04	23.31	36.11	1.30	3.36	36.11
Brain	0.02	0.01	0.01	0.02	0.01	13.20	5.20	4.50	10.00	5.20
Gut	0.04	0.03	0.04	0.02	0.05	72.50	39.20	23.00	16.43	44.40
Heart	0.00	0.00	0.01	0.00	0.00	14.00	15.60	5.40	3.43	6.40
Kidneys	0.02	0.01	0.01	0.00	0.01	65.00	36.80	21.60	17.71	32.00
Liver	0.05	0.03	0.03	0.02	0.04	90.00	47.20	30.90	20.71	70.80
Lung	0.01	0.00	0.01	0.01	0.01	2.00	6.22	10.56	2.00	6.22
Muscle	0.37	0.39	0.44	0.38	0.54	45.50	30.00	25.00	10.71	62.00
Skin	0.15	0.17	0.17	0.03	0.04	20.50	23.20	10.00	4.29	23.20
Spleen	0.00	0.00	0.00	0.00	0.00	5.50	4.07	1.65	1.10	3.60
Rest	0.03	0.05	0.00	0.05	0.03	110.19	90.00	5.59	2.97	90.00

Volumes and flows from Schmitt (2008) + Nisha Sipes (Rabbit)

Other parameters from Davies and Morris (1993) + Nisha Sipes (Rabbit)

	Units	**Mouse**	**Rat**	**Dog**	**Human**	**Rabbit**
Total Body Water	ml/kg	725.00	668.00	603.60	600.00	716
Plasma Volume	ml/kg	50.00	31.20	51.50	42.86	44
Cardiac Output	ml/min/kg	400.00	296.00	120.00	80.00	212
Average BW	kg	0.02	0.25	10.00	70.00	2.5
Total Plasma Protein	g/ml	0.06	0.07	0.09	0.07	0.057
Plasma albumin	g/ml	0.03	0.03	0.03	0.04	0.0387
Plasma a-1-AGP	g/ml	0.01	0.02	0.00	0.00	0.0013
Hematocrit	fraction	0.45	0.46	0.42	0.44	0.36
Urine	ml/min/kg	0.035	0.139	0.021	0.014	0.0417
Bile	ml/min/kg	0.069	0.063	0.008	0.003	0.0833
GFR	ml/min/kg	14.0	5.2	6.1	1.8	3.12

Schmitt (2008) Tissue Composition Data

	Fraction of total volume[a]		Fraction of cell volume[b]			Fraction of total lipid			
Tissue	Cells	Interstitium	Water	Lipid	Protein	Neutral Lipid[c]	Neutral Phospholipid[c]	Acidic Phospholipid[c]	pH[d]
Adipose	0.86	0.14	0.03	0.92	0.06	1	0.0022	0.0006	7.10
Bone	0.9	0.1	0.26	0.02	0.21	0.85	0.11	0.04	7.00
Brain	1	0.004	0.79	0.11	0.08	0.39	0.48	0.13	7.10
Gut	0.9	0.096	0.78	0.07	0.15	0.69	0.26	0.05	7.00
Heart	0.86	0.14	0.7	0.11	0.19	0.48	0.43	0.09	7.10
Kidneys	0.78	0.22	0.73	0.06	0.21	0.26	0.61	0.13	7.22
Liver	0.82	0.18	0.68	0.08	0.21	0.29	0.59	0.11	7.23
Lung	0.5	0.5	0.74	0.04	0.11	0.51	0.38	0.11	6.60
Muscle	0.88	0.12	0.76	0.01	0.19	0.49	0.42	0.09	6.81
Skin	0.69	0.31	0.47	0.14	0.41	0.9	0.08	0.02	7.00
Spleen	0.79	0.21	0.75	0.02	0.23	0.3	0.54	0.15	7.00
Red blood cells	1	–	0.63	0.01	0.33	0.3	0.59	0.1	7.20

a Values taken from (Kawai et al., 1994). Original values given as fraction of total organ volume were rescaled to tissue volume by subtracting vascular volume

b Values taken from (ICRP, 1975). Original values given as fraction of total tissue mass were rescaled to cellular volume as follows: Water fraction of total tissue reduced by interstitial volume and subsequently all values normalized by cellular fraction.

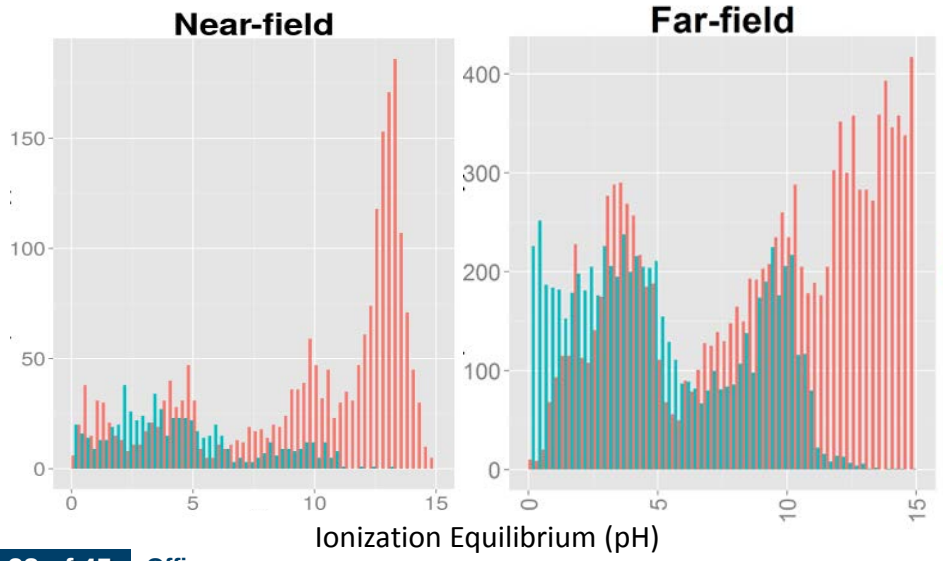
c Data taken from (Rodgers et al., 2005a).

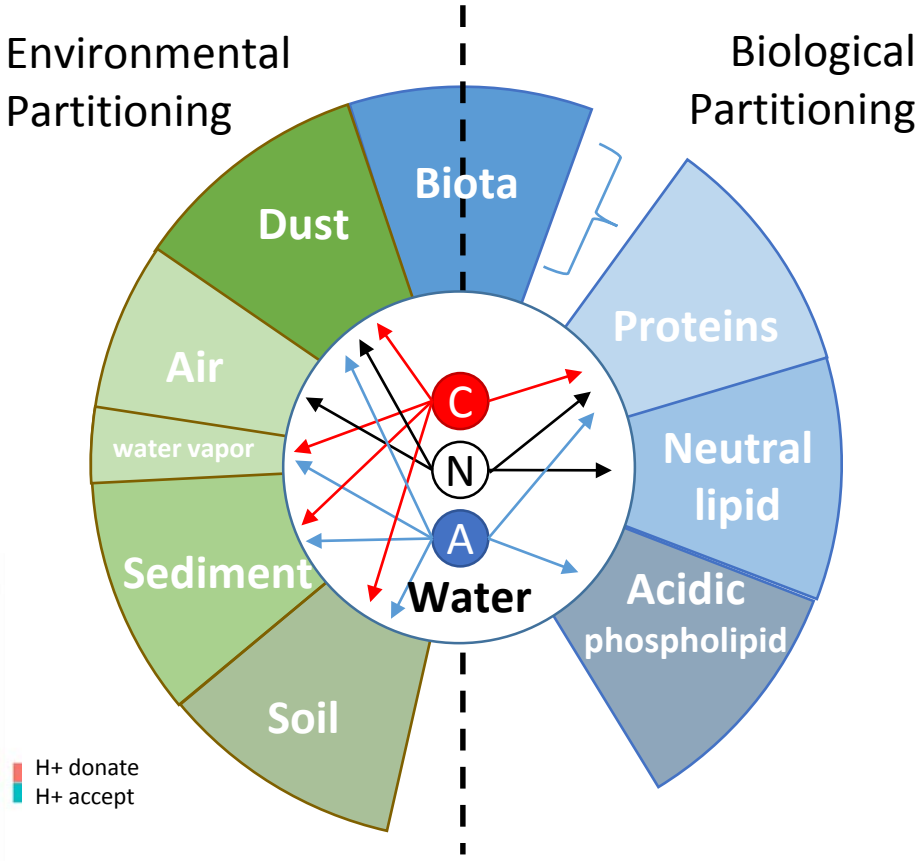
d Values taken from ([Waddell and Bates, 1969], [Malan et al., 1985], [Wood and Schaefer, 1978], [Schanker and Less, 1977], [Harrison and Walker, 1979] and [Civelek et al., 1996]). Mean values were calculated when more than one value was found for the same tissue.

e Data taken from (Gomez et al., 2002).

Prediction of Ionization

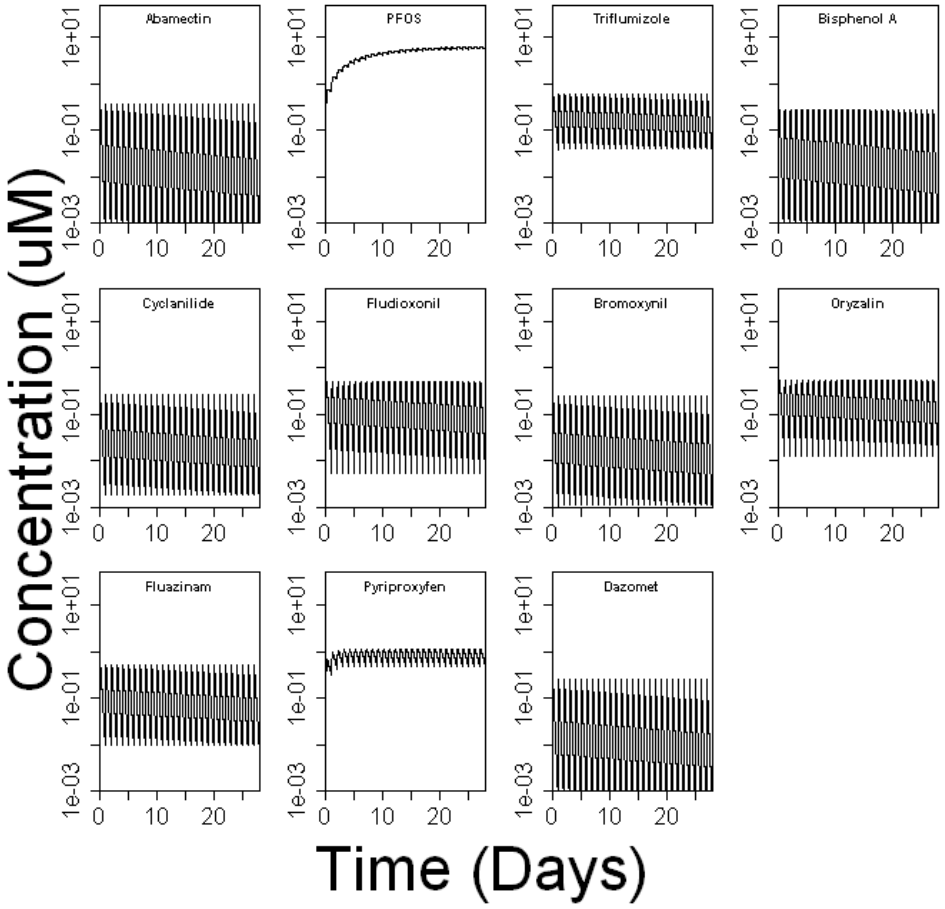
- Neutral and ionized species of the same molecule will partition differently into environmental and biological media
- Better models are needed for predicting pKa at different pH for chemicals





Project lead Cory Strope (Hamner)

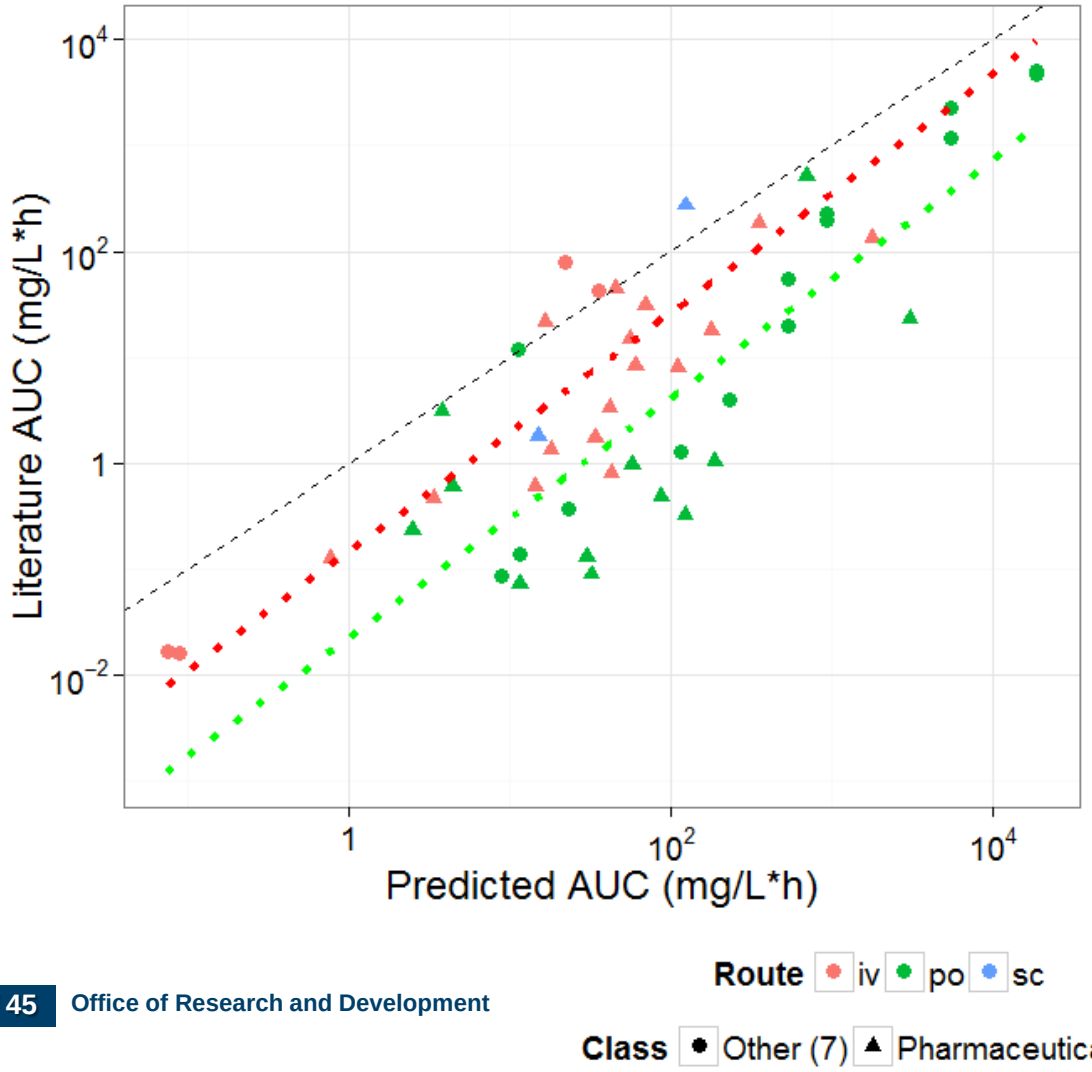
Predicted PK Metrics



Example at left: Human hepatic concentration of various chemicals as a function of 28 daily doses (10 mg/kg/day)

Can predict mean and peak concentration and time integrated area under the curve (AUC) for various tissues

Evaluating HTPBPK Predictions from *In Vitro* Data



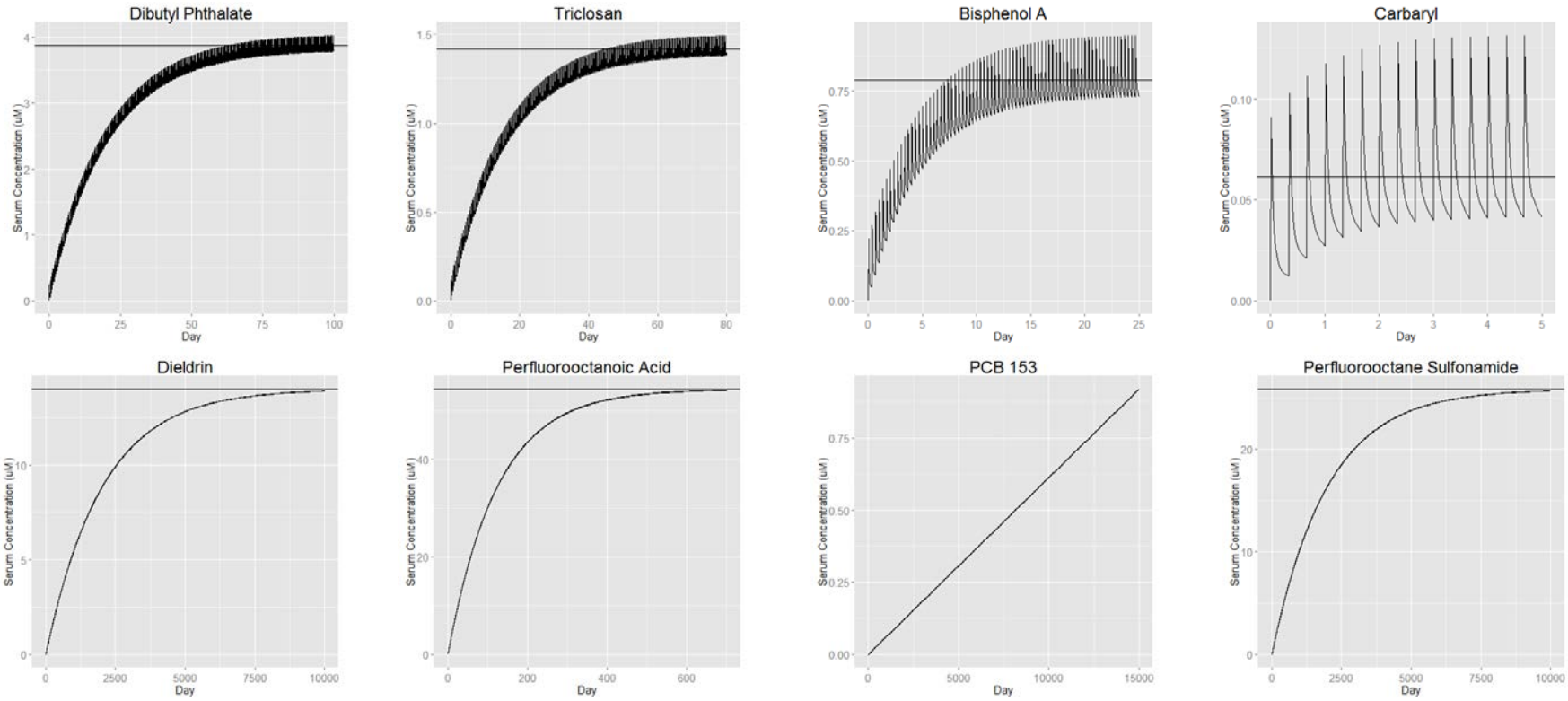
- HTPBPK predictions for the AUC (time integrated plasma concentration or Area Under the Curve)
- *in vivo* measurements from the literature for various treatments (dose and route) of rat.
- Predictions are generally conservative – *i.e.*, predicted AUC higher than measured
- Oral dose AUC ~6.4x higher than intravenous dose AUC

Wambaugh et al. (2015)

calc_stats Examples

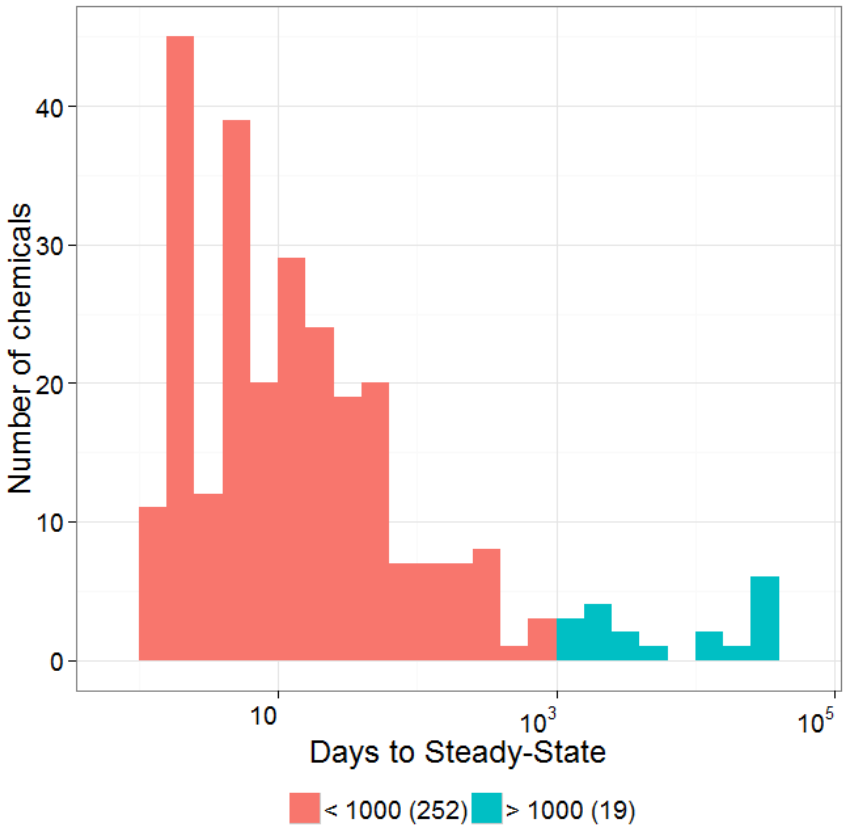
```
library(httk)

#A Function to get PK summary statistics from the PBPK model:
help(calc_stats)
# 28 day human study (20 mg/kg/day) for Abamectin:
calc_stats(days=28,chem.name="bisphenol a", dose=20)
# Units default to µM but can use mg/L:
calc_stats(days=28,chem.name="bisphenol a", dose=20,output.units="mg/L")
# Same study in a mouse:
calc_stats(days=28,chem.name="bisphenol a", dose=20,species="mouse")
```

PBPK Simulated Approach to Steady-State



Figures from Robert Pearce

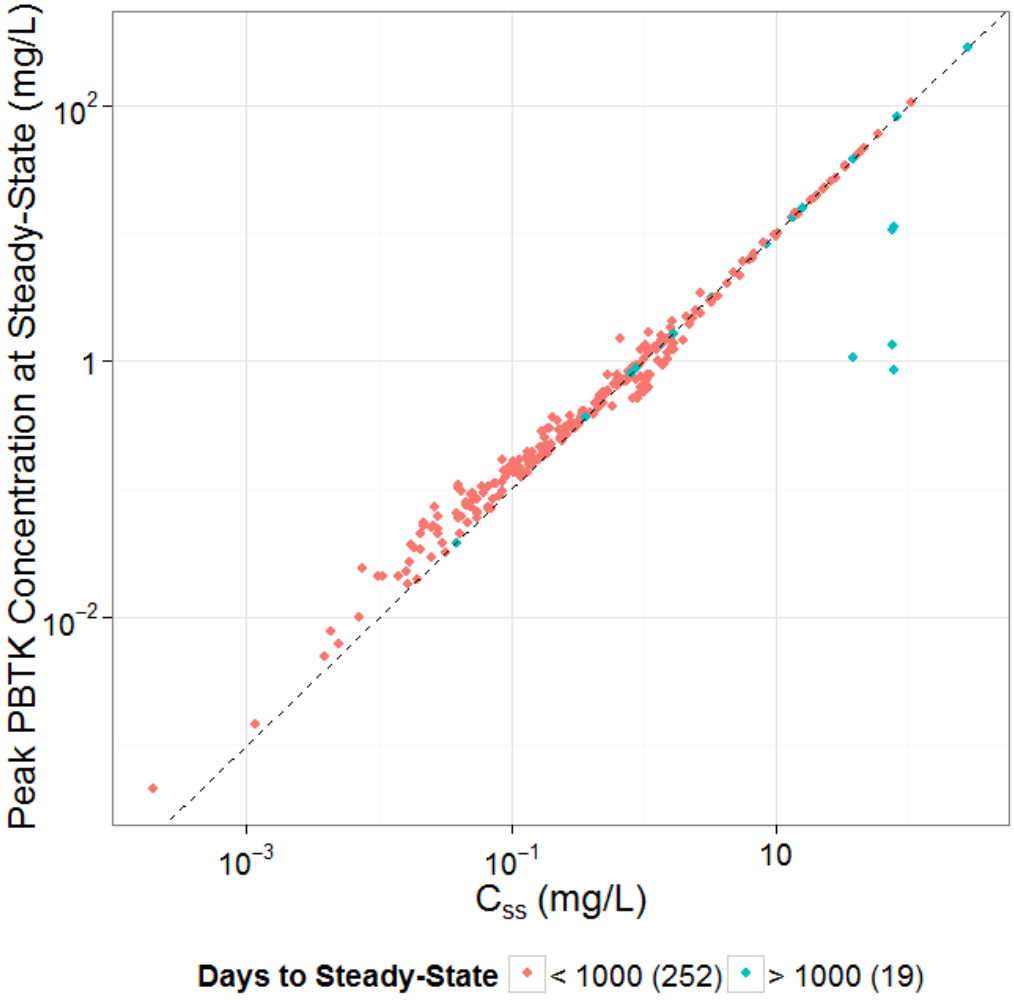
Evaluation of Steady-State Predictions



- Using HTPBTK model and assuming three daily doses (every eight hours)
- This allows us to evaluate the plausibility of the steady-state dosing assumption.
- We find that the majority of chemicals reach steady state in a few weeks
- A second population of chemicals never reach steady state.

Wambaugh et al. (2015)

Peak Concentration vs. C_{ss}



Peak serum concentrations from the HTPBPK model are compared against the steady-state concentration predicted by the three compartment model for a constant infusion exposure (as in Wetmore et al. 2012)

The dashed, identity (1:1) line indicates that for most compounds the peak concentrations are very similar to C_{ss}.

Wambaugh et al. (2015)

In vivo Predictive Ability and Domain of Applicability

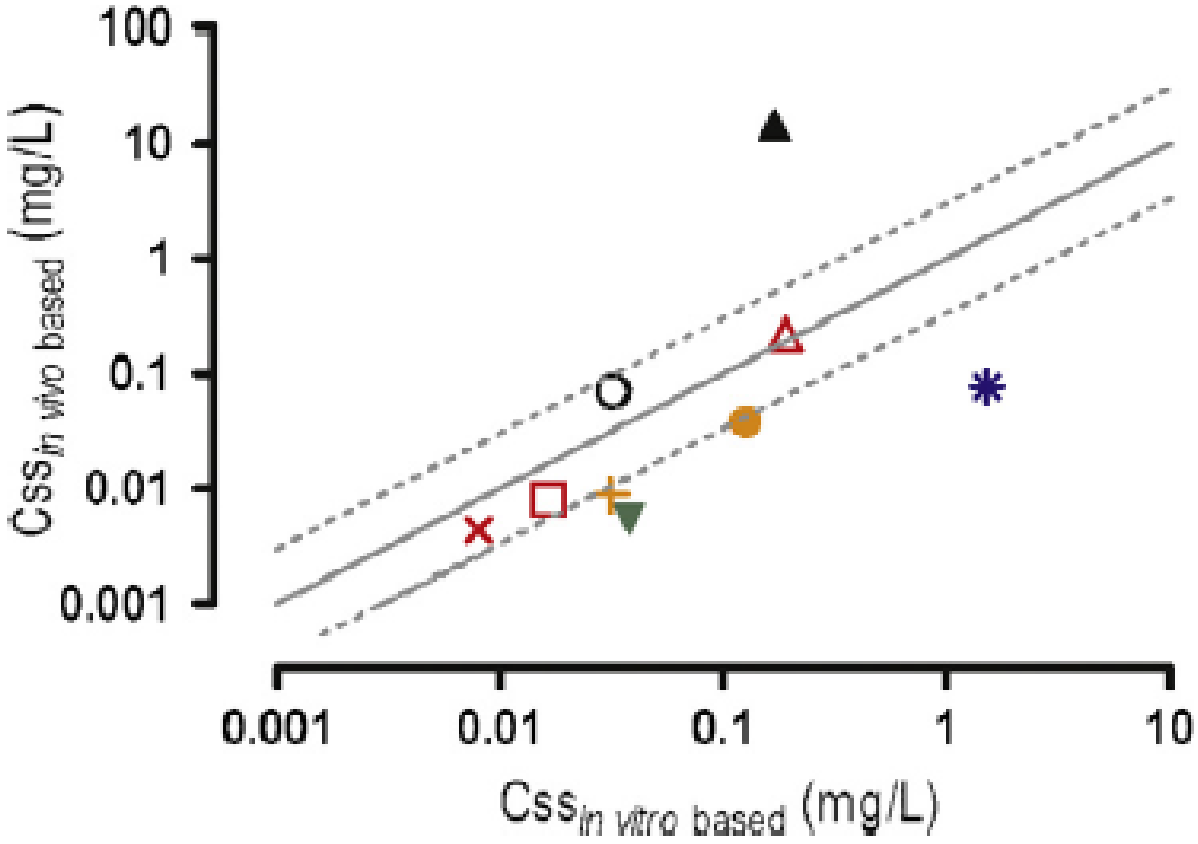
- In drug development, HTTK methods estimate therapeutic doses for clinical studies – predicted concentrations are typically on the order of values measured in clinical trials (Wang, 2010)

- For environmental compounds, there will be no clinical trials

- Uncertainty must be well characterized ideally with rigorous statistical methodology
  - We will use direct comparison to *in vivo* data in order to get an empirical estimate of our uncertainty
  - Any approximations, omissions, or mistakes should work to increase the estimated uncertainty when evaluated systematically across chemicals

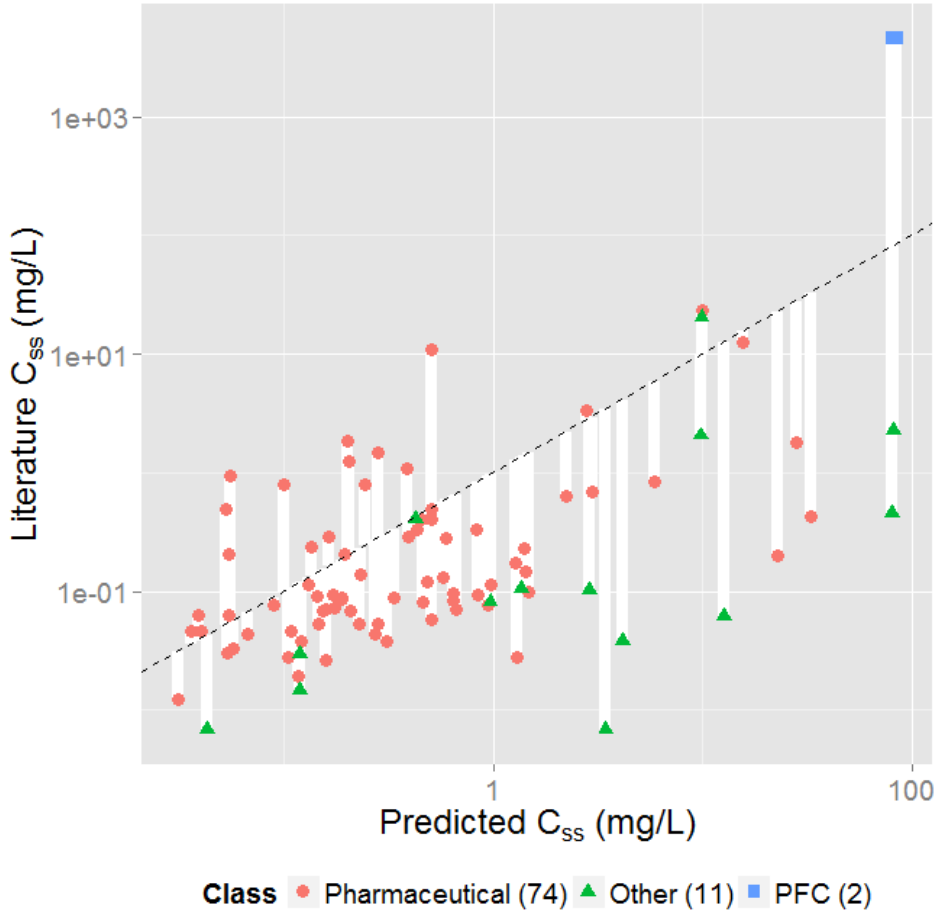
Characterizing Uncertainty in HTTK

Yoon *et al.* (2014): Manual curation of chemical specific PK models allowed direct evaluation of HTTK IVIVE predictions

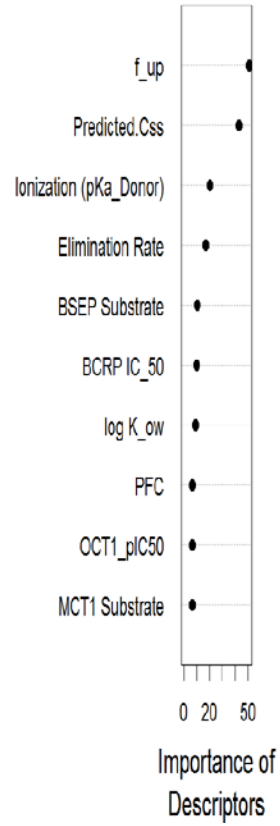


Wang (2010): In vitro predictions typically within a factor of three for pharmaceuticals

Using *in vivo* Data to Evaluate RTK



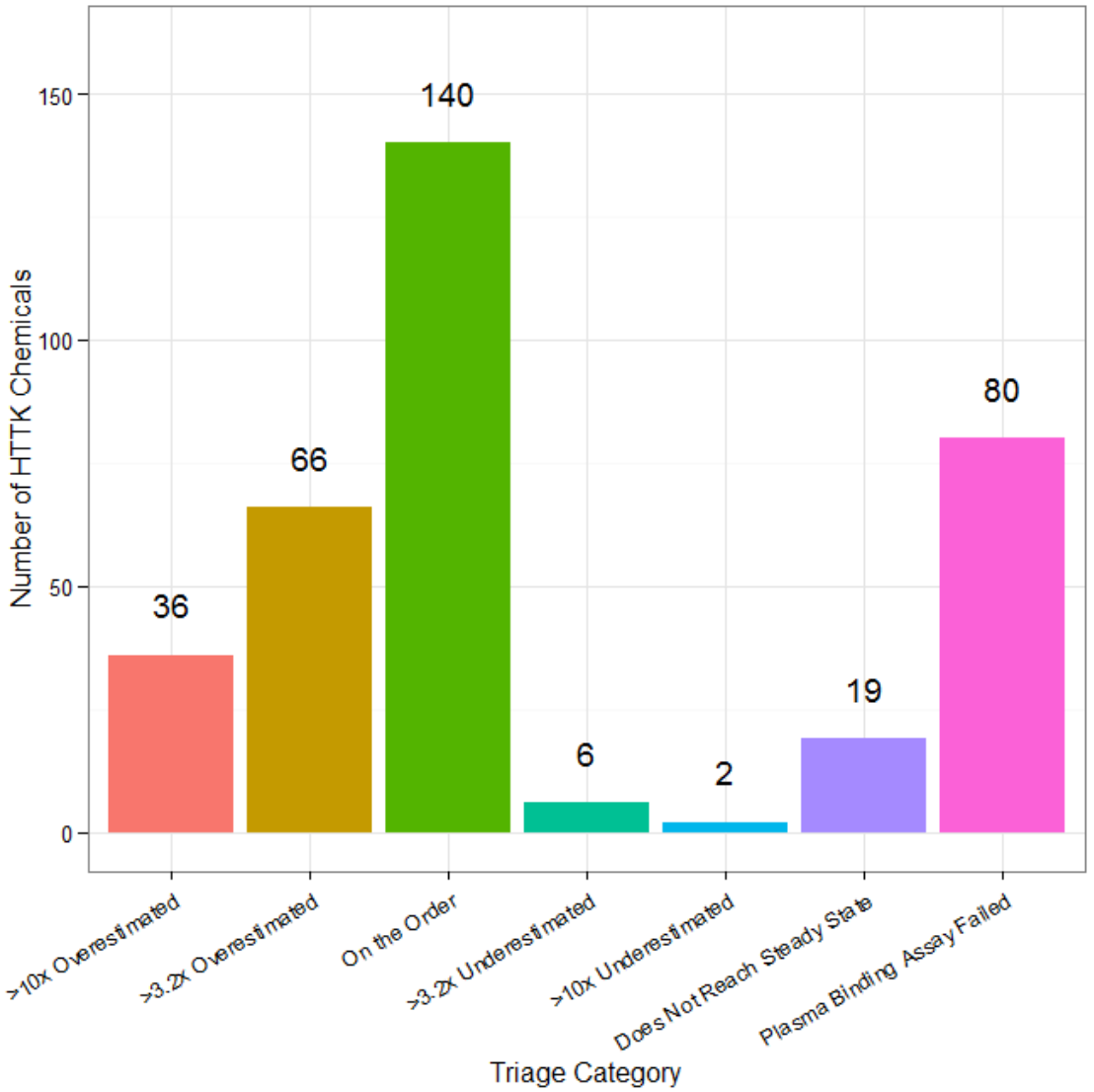
- When we compare the C_{ss} predicted from *in vitro* HTTK with *in vivo* C_{ss} values determined from the literature we find limited correlation (R^2 ~0.34)
- The dashed line indicates the identity (perfect predictor) line:
  - Over-predict for 65
  - Under-predict for 22
- The white lines indicate the discrepancy between measured and predicted values (the residual)



Wambaugh et al. (2015)

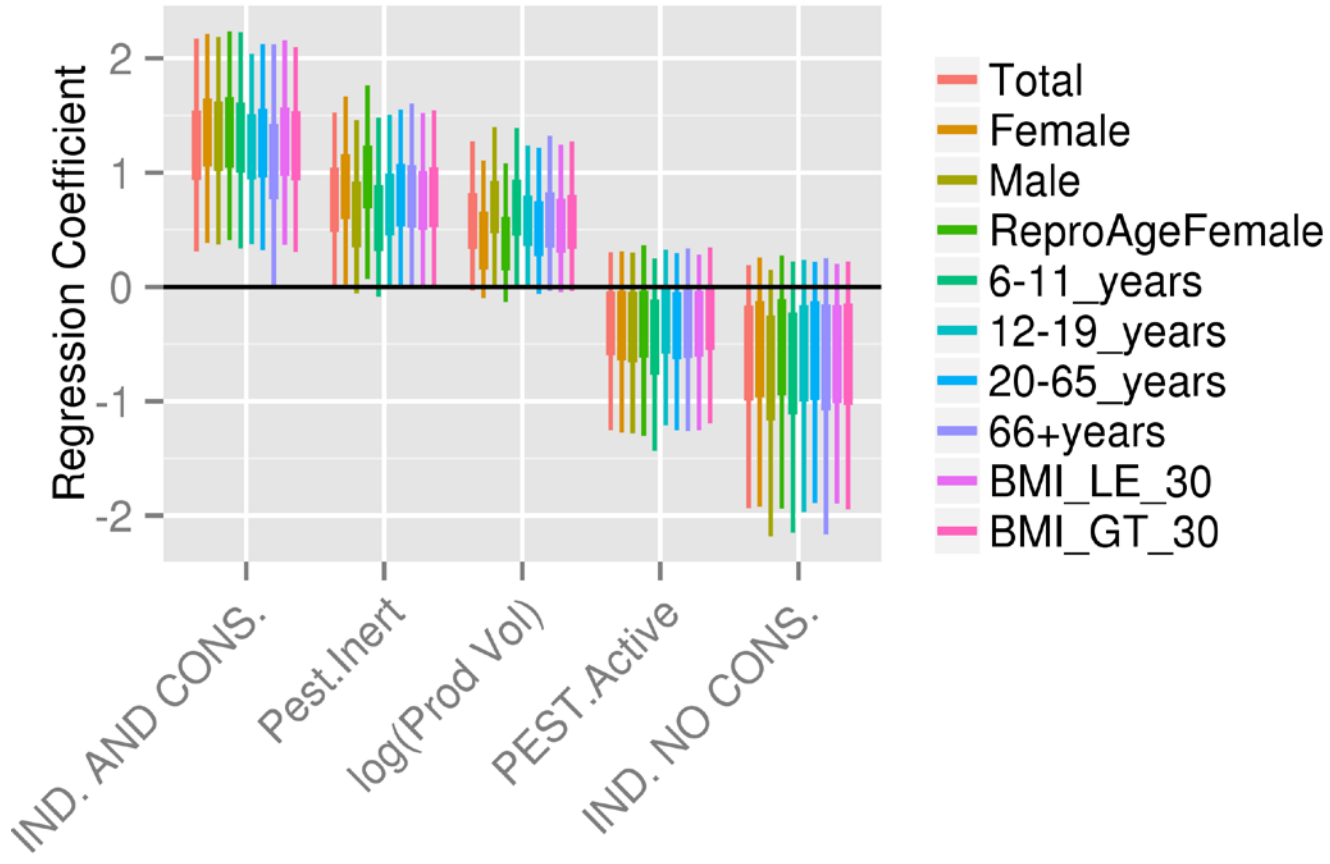
Toxicokinetic Triage

- Through comparison to *in vivo* data, a cross-validated (random forest) predictor of success or failure of HTTK has been constructed
- Add categories for chemicals that do not reach steady-state or for which plasma binding assay fails
- All chemicals can be placed into one of seven confidence categories



Wambaugh et al. (2015)

Calibrated Exposure Predictions for 7968 Chemicals



$R^2 \approx 0.5$ indicates that we can predict 50% of the chemical to chemical variability in **geometric mean NHANES exposure rates** (this does not cover highly exposed individuals)

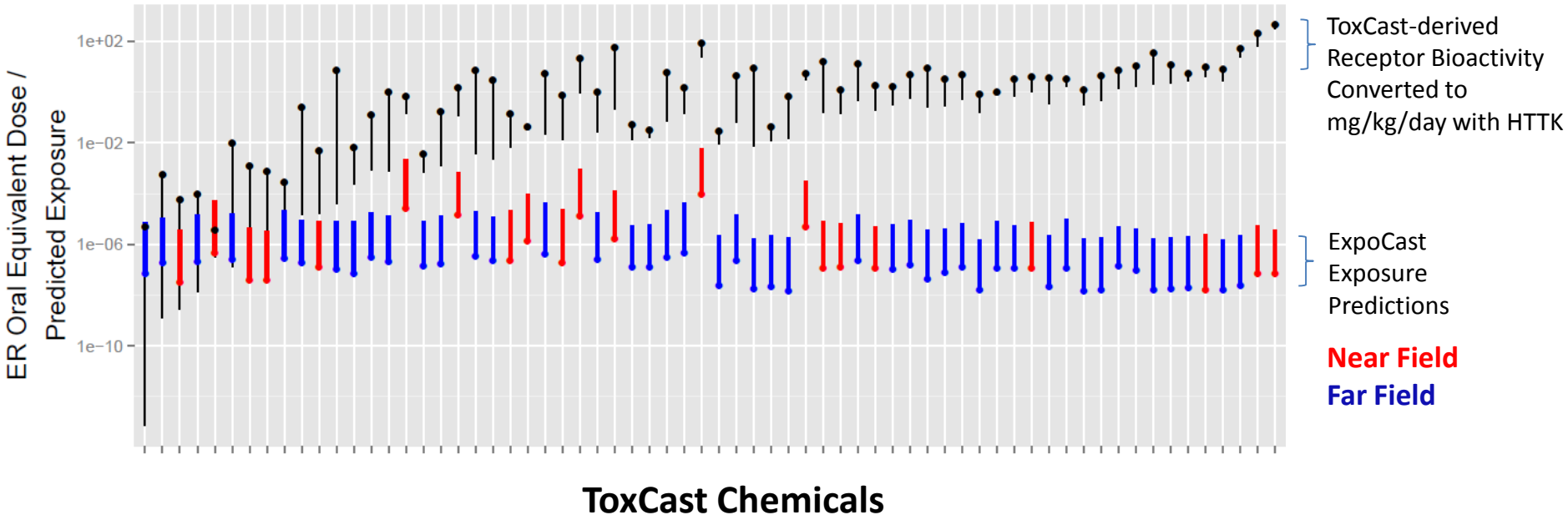
Same five predictors work for all NHANES demographic groups analyzed – stratified by age, sex, and body-mass index:

- Industrial and Consumer use
- Pesticide Inert
- Pesticide Active
- Industrial but no Consumer use
- Production Volume

Wambaugh et al. (2014)

Application to High Throughput Risk Prioritization

Prioritization as in Wetmore *et al*. (2012) Bioactivity, Dosimetry, and Exposure Paper



December, 2014 Panel:
"Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening"

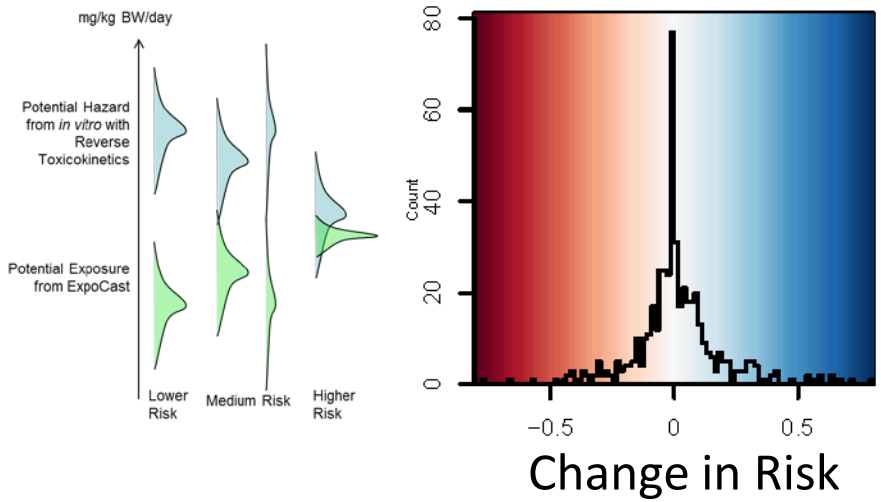
Also see poster "Computational Models to Correlate *In Vitro* to *In Vivo* Activity" by Nisha Sipes and Steve Ferguson, et al.

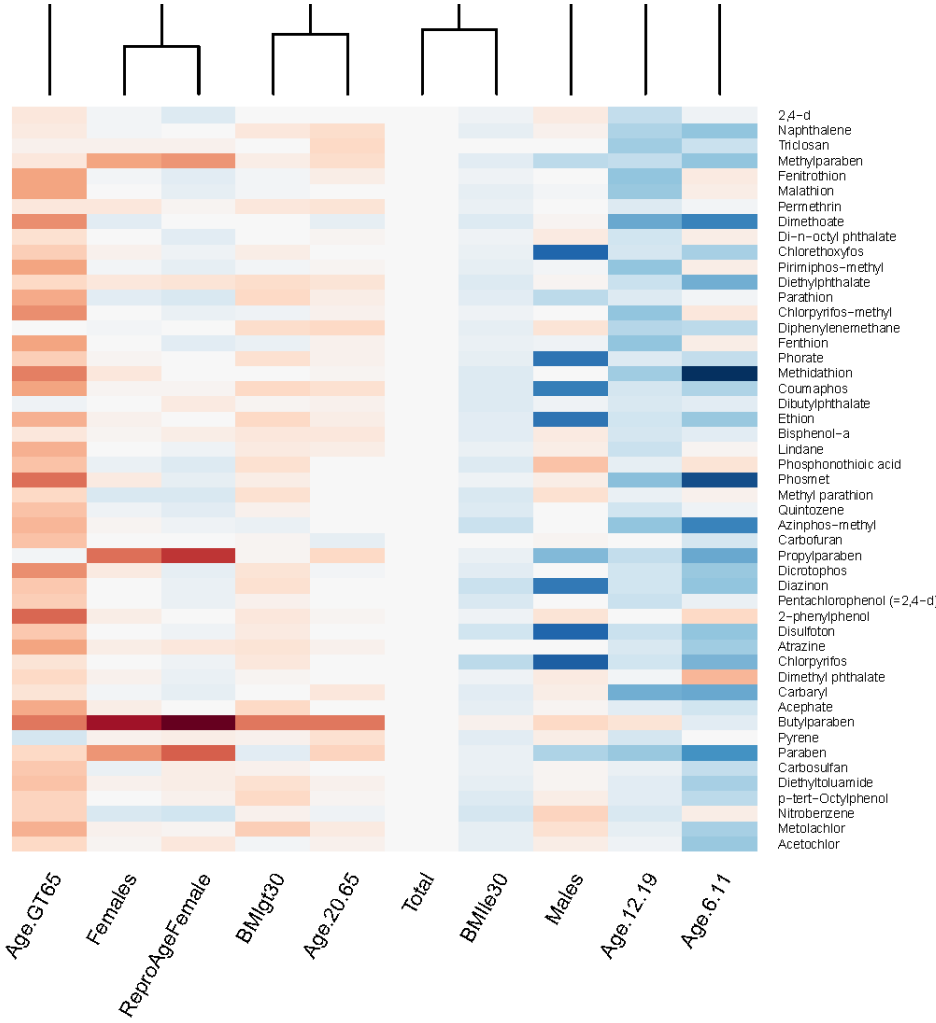
Life-stage and Demographic Specific Predictions

United States Environmental Protection Agency

- Wambaugh *et al.* (2014) predictions of exposure rate for various demographic groups

- New version of httk R package (Ring *et al.*, in preparation) allows prediction of parameters based on actual NHANES biometrics

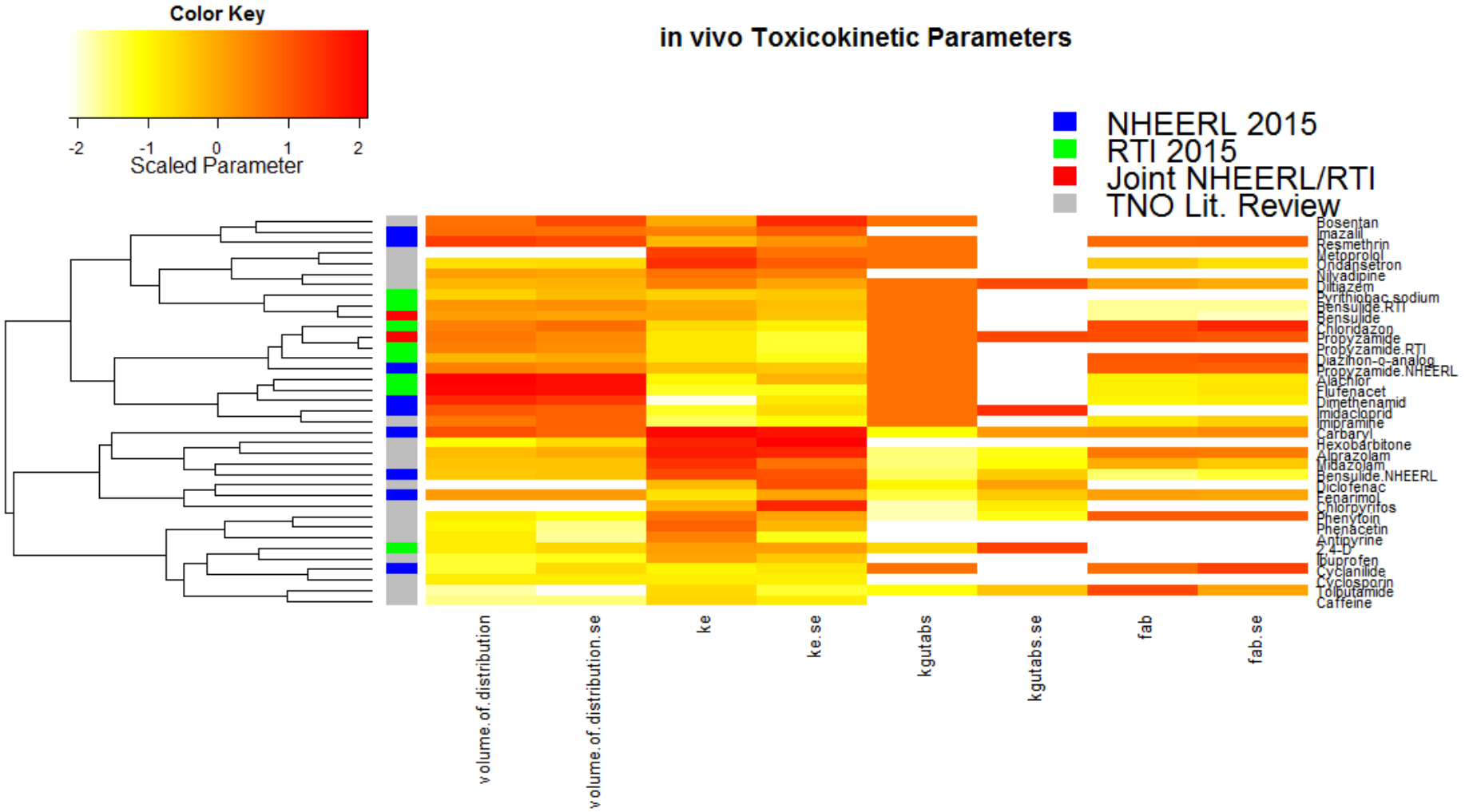




Work by Caroline Ring (NCCT)

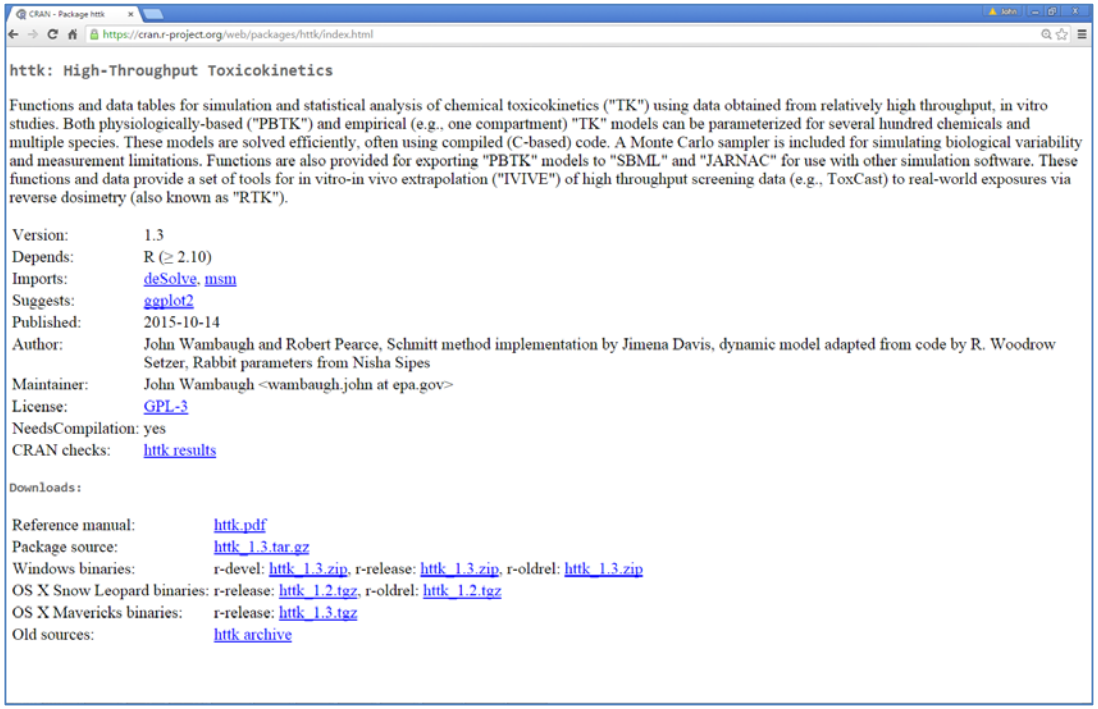
In Vivo TK Library

United States Environmental Protection Agency



Experiment by Mike Hughes, Jane Ellen Simmons (NHEERL) and Tim Fennell (RTI)
Analysis lead by Caroline Ring

httk R Package



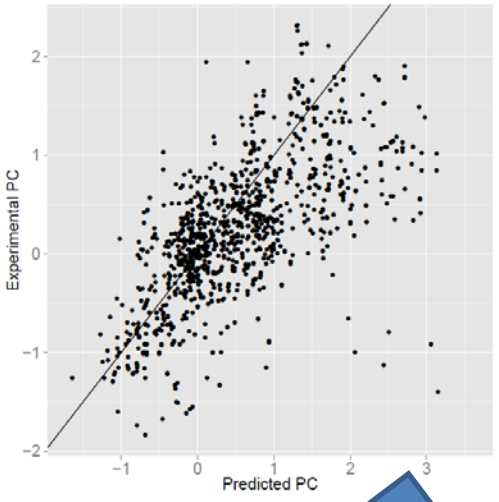
httk: High-Throughput Toxicokinetics

Functions and data tables for simulation and statistical analysis of chemical toxicokinetics ("TK") using data obtained from relatively high throughput, in vitro studies. Both physiologically-based ("PBTK") and empirical (e.g., one compartment) "TK" models can be parameterized for several hundred chemicals and multiple species. These models are solved efficiently, often using compiled (C-based) code. A Monte Carlo sampler is included for simulating biological variability and measurement limitations. Functions are also provided for exporting "PBTK" models to "SBML" and "JARNAC" for use with other simulation software. These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of high throughput screening data (e.g., ToxCast) to real-world exposures via reverse dosimetry (also known as "RTK").

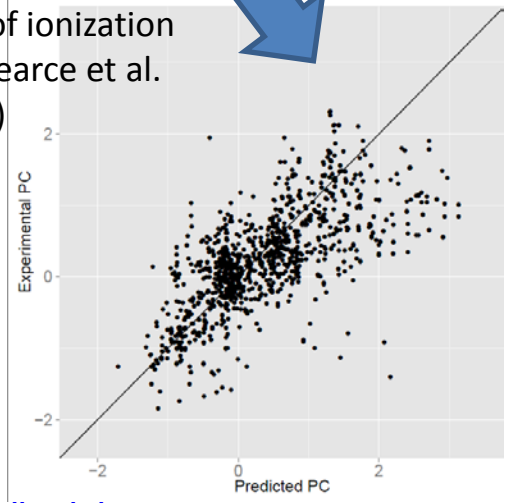
Version:	1.3
Depends:	R (≥ 2.10)
Imports:	deSolve, msm
Suggests:	ggplot2
Published:	2015-10-14
Author:	John Wambaugh and Robert Pearce, Schmitt method implementation by Jimena Davis, dynamic model adapted from code by R. Woodrow Setzer, Rabbit parameters from Nisha Sipes
Maintainer:	John Wambaugh <wambaugh.john at epa.gov>
License:	GPL-3
NeedsCompilation:	yes
CRAN checks:	httk results

Downloads:

Reference manual:	httk.pdf
Package source:	httk_1.3.tar.gz
Windows binaries:	r-devel: httk_1.3.zip, r-release: httk_1.3.zip, r-oldrel: httk_1.3.zip
OS X Snow Leopard binaries:	r-release: httk_1.2.tgz, r-oldrel: httk_1.2.tgz
OS X Mavericks binaries:	r-release: httk_1.3.tgz
Old sources:	httk archive



Ongoing refinements:
High log P, better treatment of ionization (eventual Pearce et al. manuscript)



"httk" R Package
543 Chemicals to date
Lead programmer Robert Pearce
Wambaugh *et al.* (2015), Pearce *et al.* submitted

https://cran.r-project.org/web/packages/httk/

Can access this from the R GUI: "Packages" then "Install Packages"

Version history for the "httk" R Package

The publicly available R package contains code and data that has been part of peer-reviewed publications

- Version 1.1 accompanied "Toxicokinetic Triage for Environmental Chemicals" Wambaugh et al. (2015) Tox. Sci.
- Version 1.2 accompanied "httk: R Package for High-Throughput Toxicokinetics" Pearce et al., submitted to Journal of Statistical Software
- Version 1.3 accompanied "Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted *In Vitro* Bioactivity to Inform Chemical Toxicity Testing" Wetmore et al., (2015) Tox. Sci.
- Version 1.4 is in development to accompany Ring et al., in preparation

We maintain internal versions containing data and code that has yet to be peer reviewed.

Lead programmer Robert Pearce

Summary

- Toxicokinetics (TK) provides a bridge between HTS and HTE by predicting tissue concentrations due to exposure
- HTTK methods developed for pharmaceuticals have been adapted to environmental testing
- A primary application of HTTK is “Reverse Dosimetry” or RTK
  - Can infer daily doses that produce plasma concentrations equivalent to the bioactive concentrations, **but:**
- We must consider domain of applicability
  - Collected new PK data from *in vivo* studies (EPA/NHEERL and Research Triangle Institute)
  - Organizing data from larger, systematic studies (e.g., National Toxicology Program) into computable format
- New R package “httk” freely available on CRAN allows statistical analyses
  - Analysis has been submitted

EPA United States Environmental Protection Agency

Chemical Safety for Sustainability (CSS) Rapid Exposure and Dosimetry (RED) Project

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