Evaluating New Approach Methodologies for Toxicokinetics

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The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA

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Evaluating High-Throughput New Approach Methods (NAM) for Exposure
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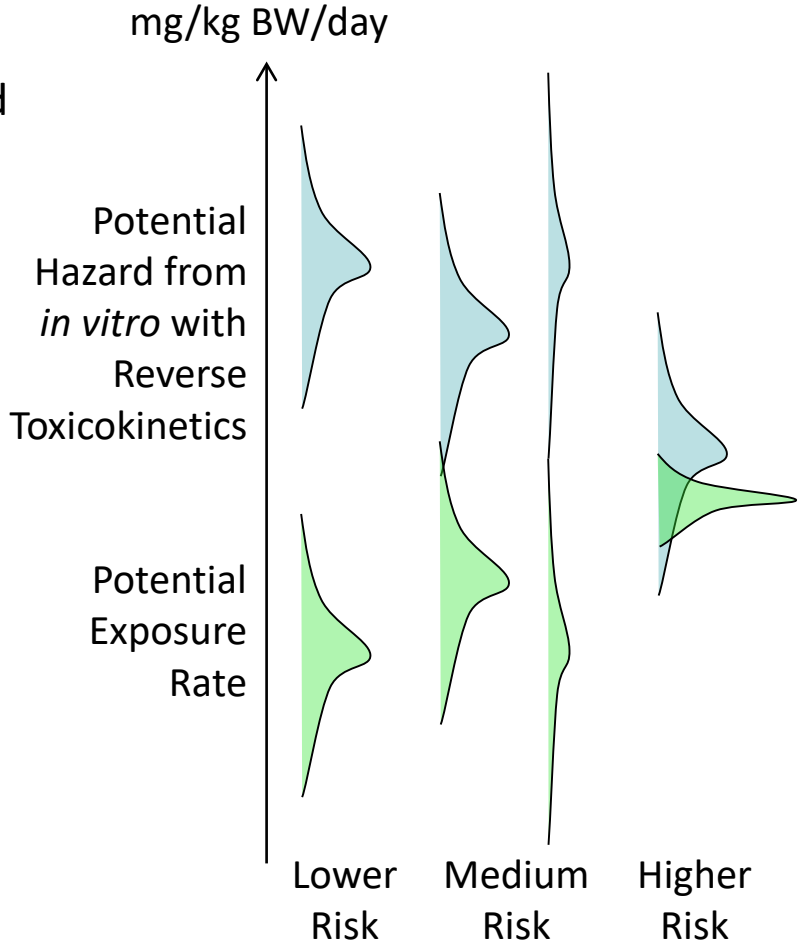
Chemical Risk = Hazard x Exposure

- National Research Council (1983) identified chemical risk as a function of both inherent hazard and exposure

- To address thousands of chemicals, we need new approach methodologies that can prioritize those chemicals most worthy of additional study

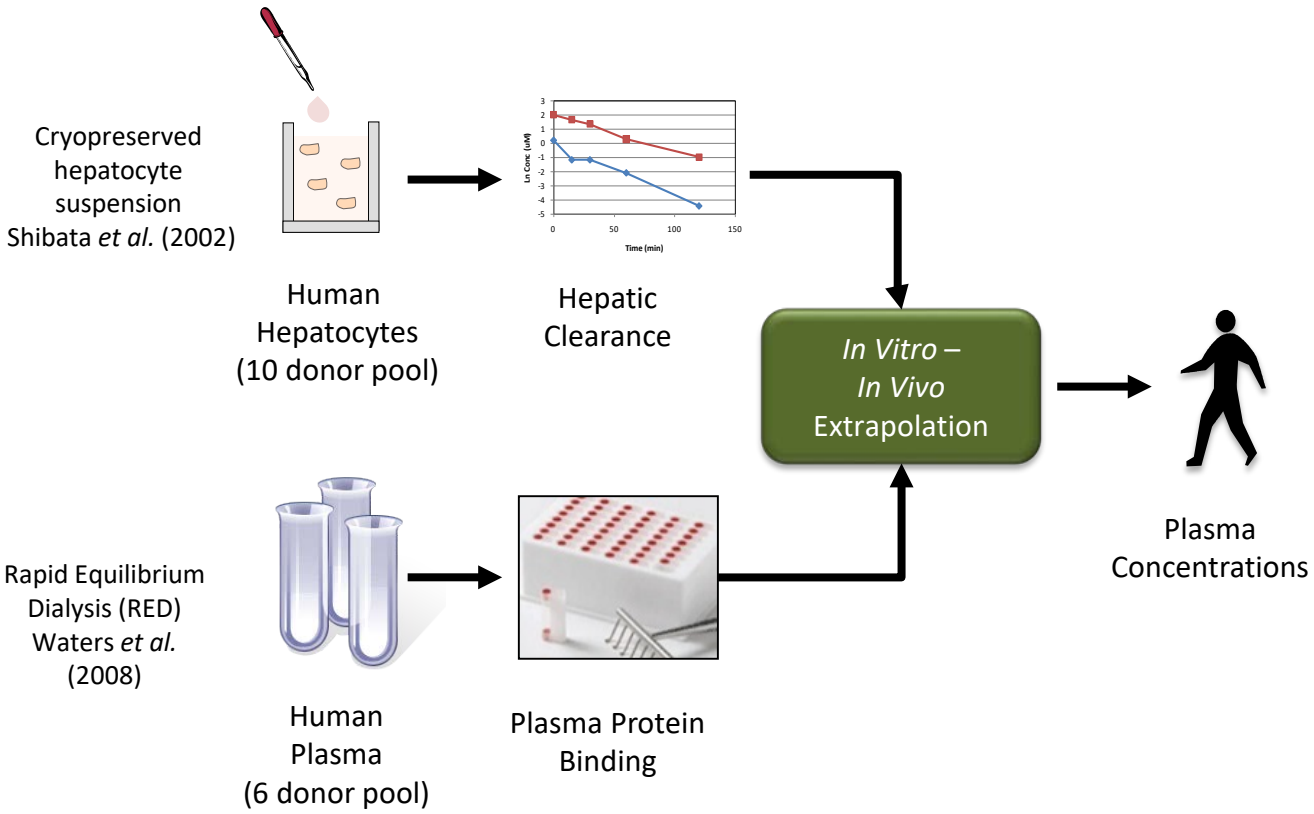
- High throughput risk prioritization needs:

1. high throughput hazard characterization (Dix et al., 2007, Collins et al., 2008)
2. high throughput exposure forecasts (Wambaugh et al., 2013, 2014)
3. high throughput toxicokinetics (i.e., dose-response relationship) linking hazard and exposure



High-Throughput Toxicokinetics (HTTK) for *In Vitro-In Vivo* Extrapolation (IVIVE)

United States Environmental Protection Agency



- **Most chemicals do not have TK data** – we use *in vitro* HTTK methods adapted from pharma to fill gaps
- In drug development, HTTK methods allow IVIVE to estimate therapeutic doses for clinical studies – predicted concentrations are typically on the order of values measured in clinical trials (Wang, 2010)

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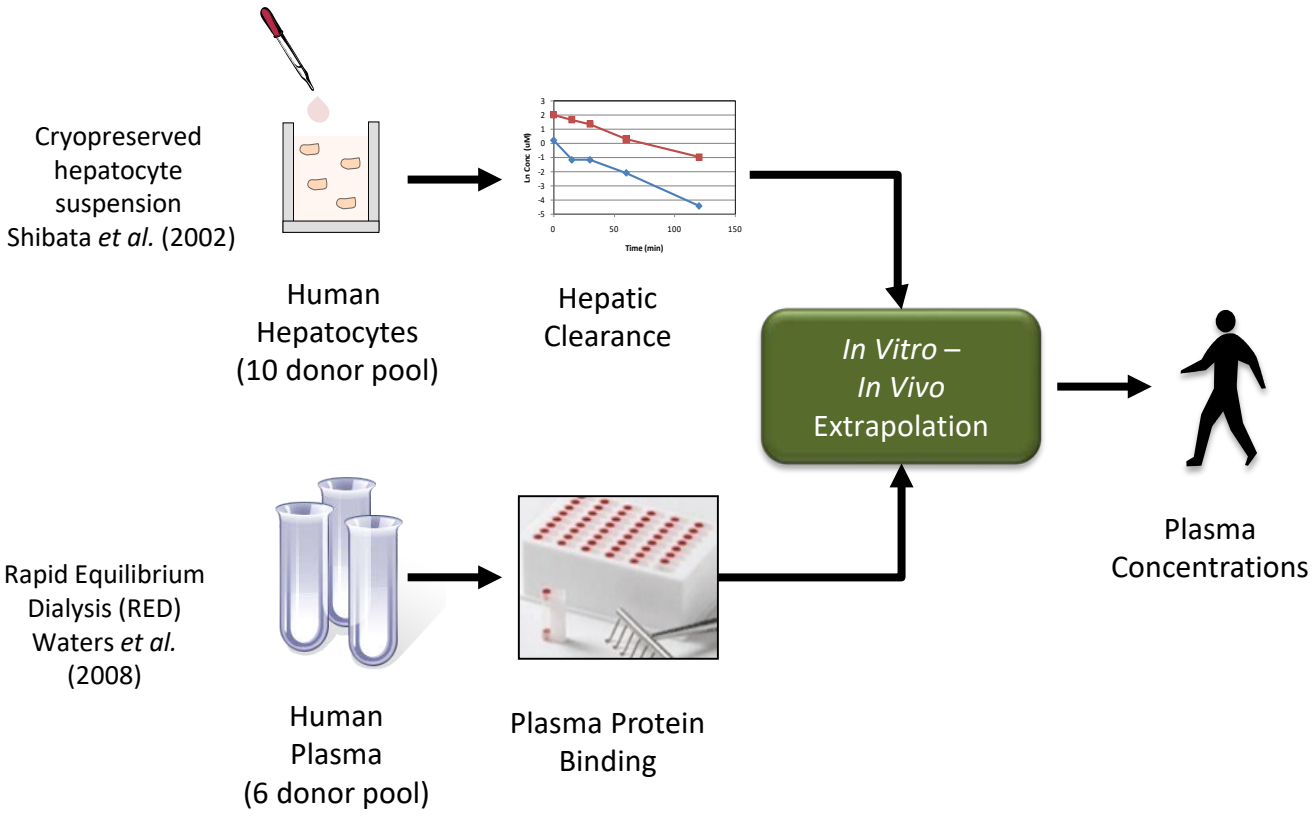

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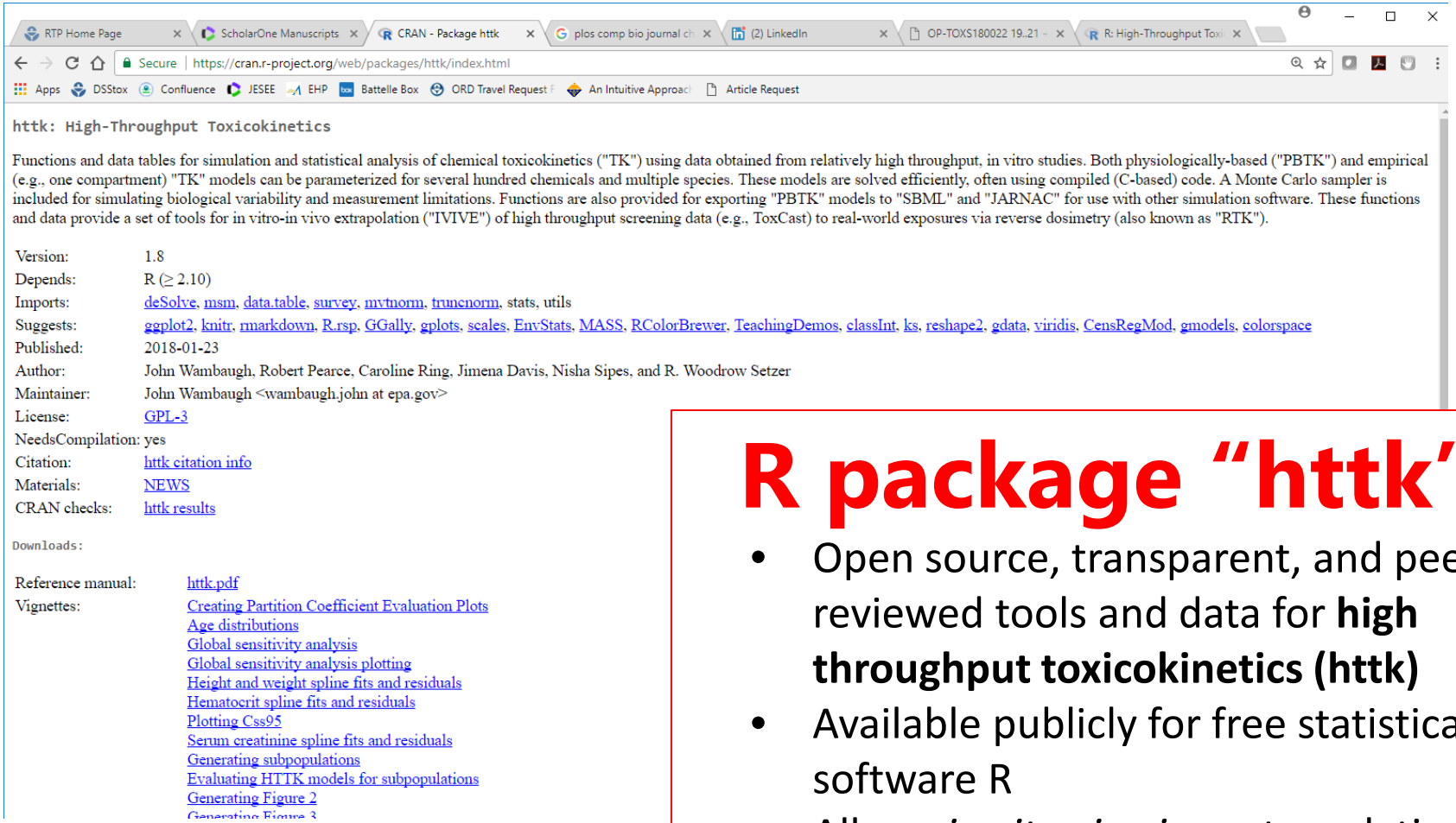
Environmental chemicals:

Rotroff et al. (2010) 35 chemicals
Wetmore et al. (2012) +204 chemicals
Wetmore et al. (2015) +163 chemicals
Wambaugh et al. (in prep.) + ~300 chemicals

Open Source Tools and Data for HTTK

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



RTP Home Page | ScholarOne Manuscripts | CRAN - Package httk | plos comp bio journal ch | (2) LinkedIn | OP-TOXS180022 19..21 | R: High-Throughput Toxi

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

Apps | DSStox | Confluence | JESEE | EHP | Battelle Box | ORD Travel Request | An Intuitive Approach | Article Request

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:	1.8
Depends:	R (≥ 2.10)
Imports:	deSolve, msm, data.table, survey, mvtnorm, truncnorm, stats, utils
Suggests:	ggplot2, knitr, rmarkdown, R.rsp, GGally, gplots, scales, EnvStats, MASS, RColorBrewer, TeachingDemos, classInt, ks, reshape2, gdata, viridis, CensRegMod, gmodels, colorspace
Published:	2018-01-23
Author:	John Wambaugh, Robert Pearce, Caroline Ring, Jimena Davis, Nisha Sipes, and R. Woodrow Setzer
Maintainer:	John Wambaugh <wambaugh.john at epa.gov>
License:	GPL-3
NeedsCompilation:	yes
Citation:	httk citation info
Materials:	NEWS
CRAN checks:	httk results

Downloads:

Reference manual:	httk.pdf
Vignettes:	Creating Partition Coefficient Evaluation Plots
	Age distributions
	Global sensitivity analysis
	Global sensitivity analysis plotting
	Height and weight spline fits and residuals
	Hematocrit spline fits and residuals
	Plotting Css95
	Serum creatinine spline fits and residuals
	Generating subpopulations
	Evaluating HTTK models for subpopulations
	Generating Figure 2
	Generating Figure 3

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-base toxicokinetics (PBTK)

High-Throughput Toxicokinetics (HTTK) for *In Vitro-In Vivo* Extrapolation (IVIVE)

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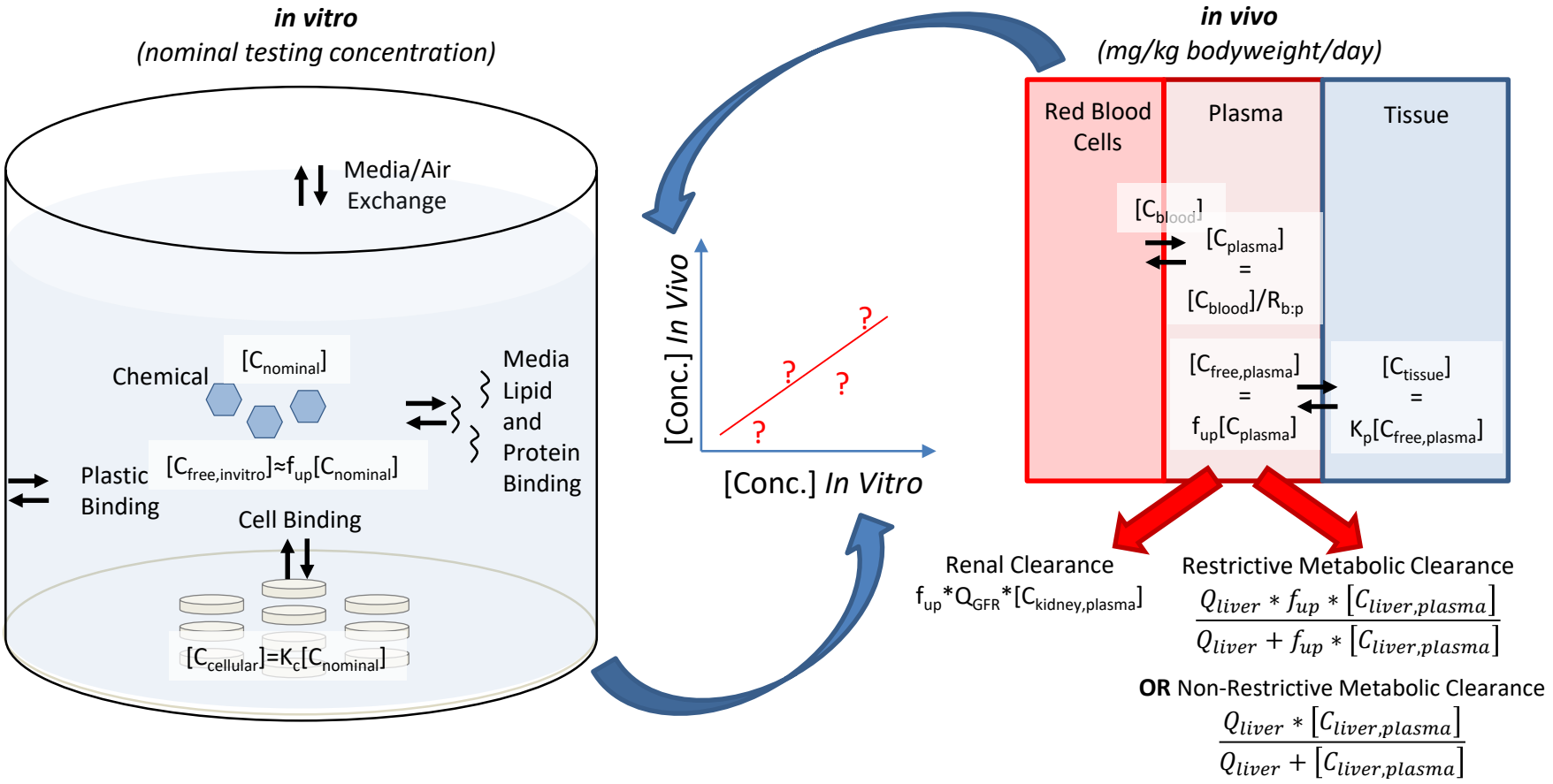


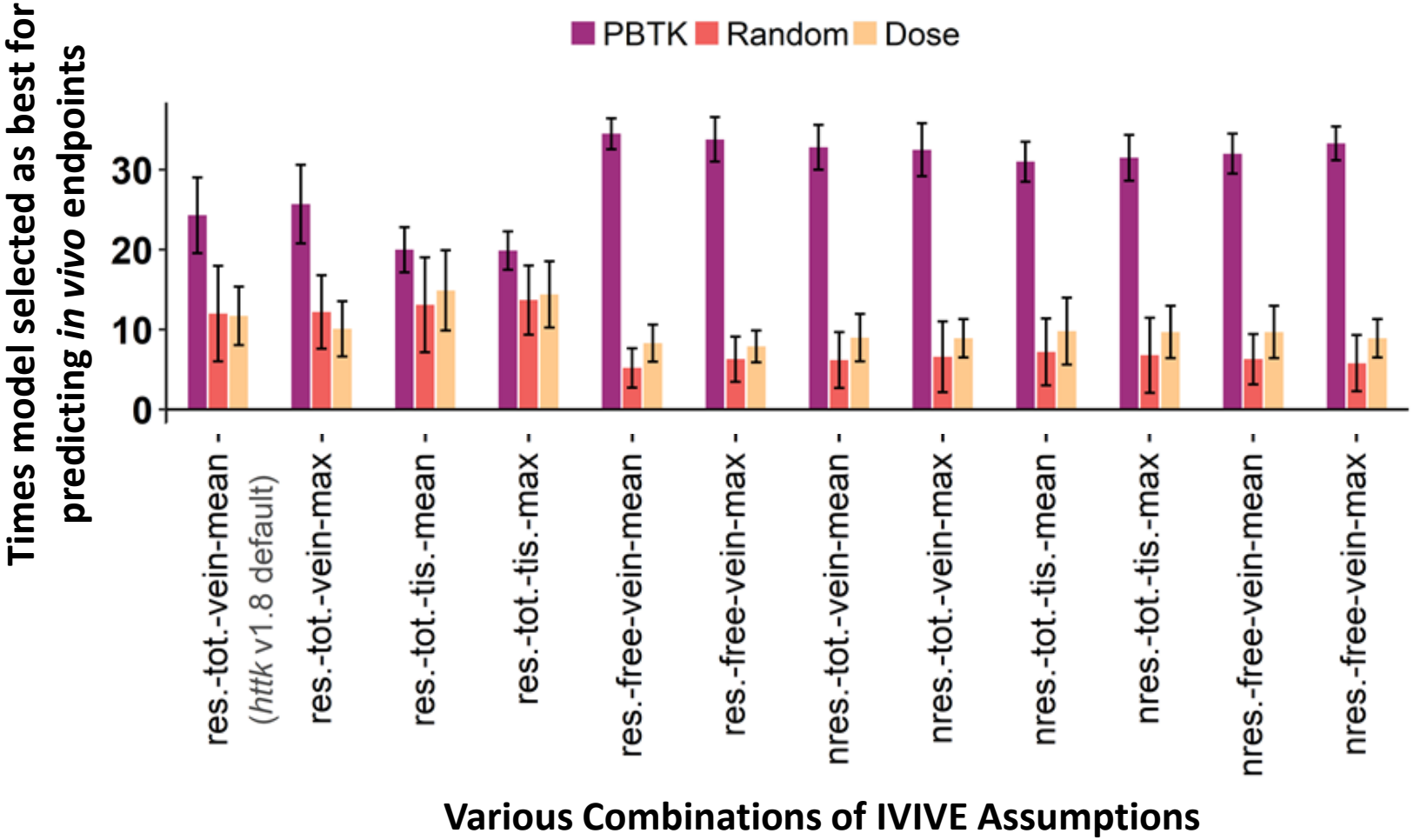
$$\frac{Q_{liver} * f_{up} * [C_{liver,plasma}]}{Q_{liver} + f_{up} * [C_{liver,plasma}]}$$

$$\frac{Q_{liver} * [C_{liver,plasma}]}{Q_{liver} + [C_{liver,plasma}]}$$

Selecting the appropriate *in vitro* and *in vivo* concentrations for extrapolation

Honda et al, in prep.

Optimizing HTTK-based IVIVE

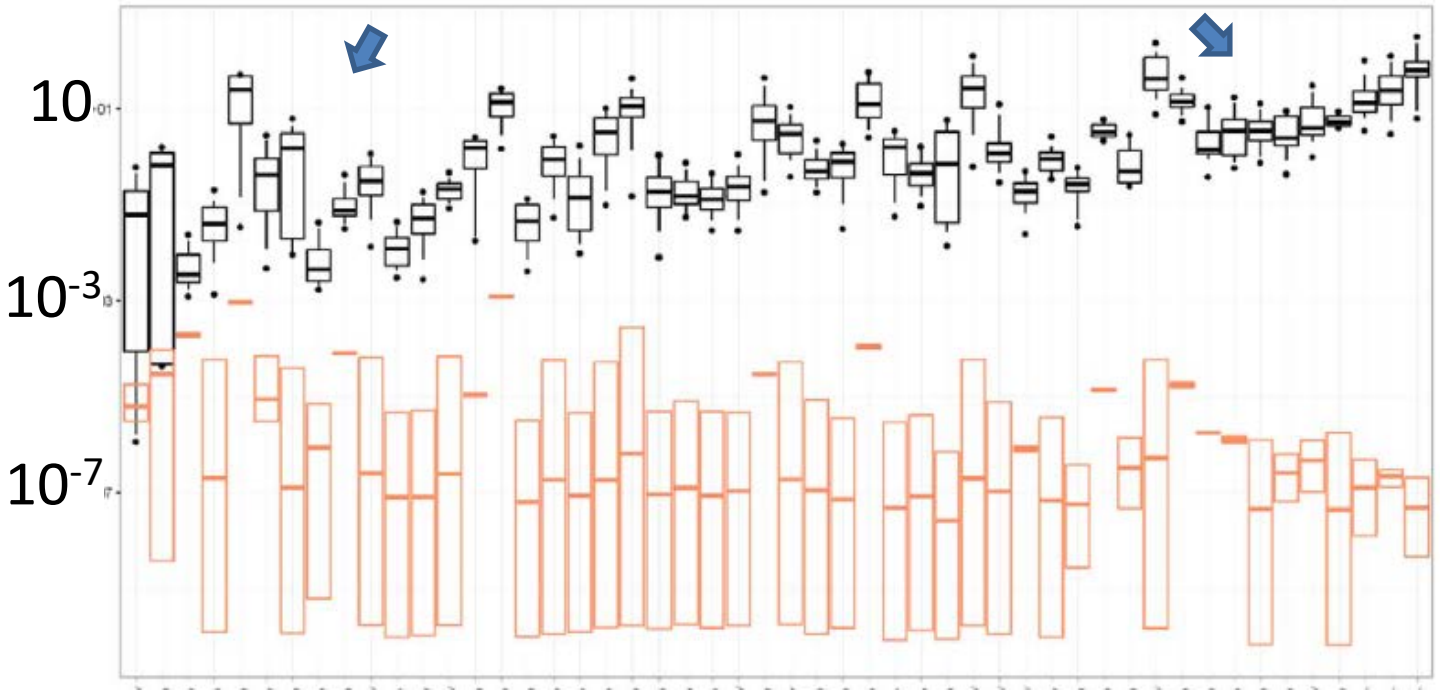


Honda et al, in prep.

High Throughput Risk Prioritization

United States Environmental Protection Agency

High Throughput Screening + HTTK can estimate doses needed to cause bioactivity (Wetmore, et al., 2012, 2015)



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

National Health and Nutrition Examination Survey (NHANES) is an ongoing survey that covers ~10,000 people every two years

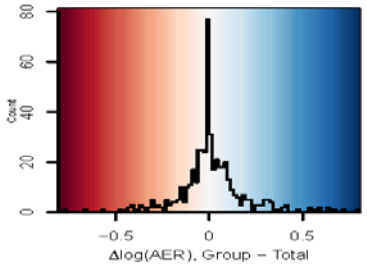
Most NHANES chemicals do not have traditional PK models (Strope et al., 2018)

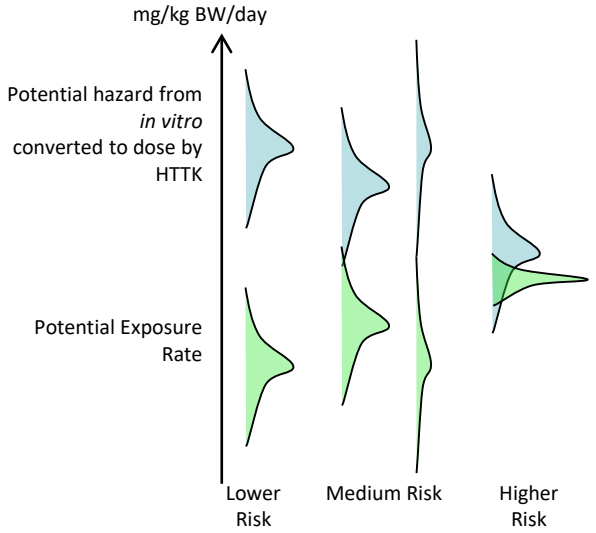
Ring *et al*. (2017)

Life-stage and Demographic Specific Predictions

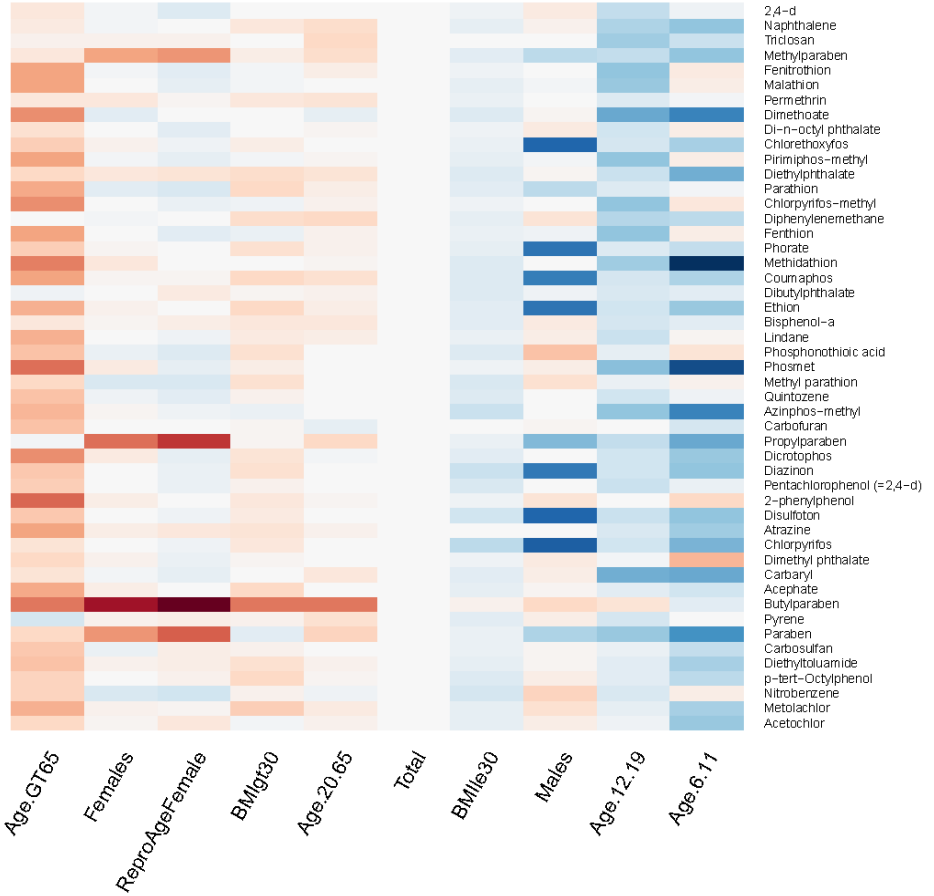
United States Environmental Protection Agency

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





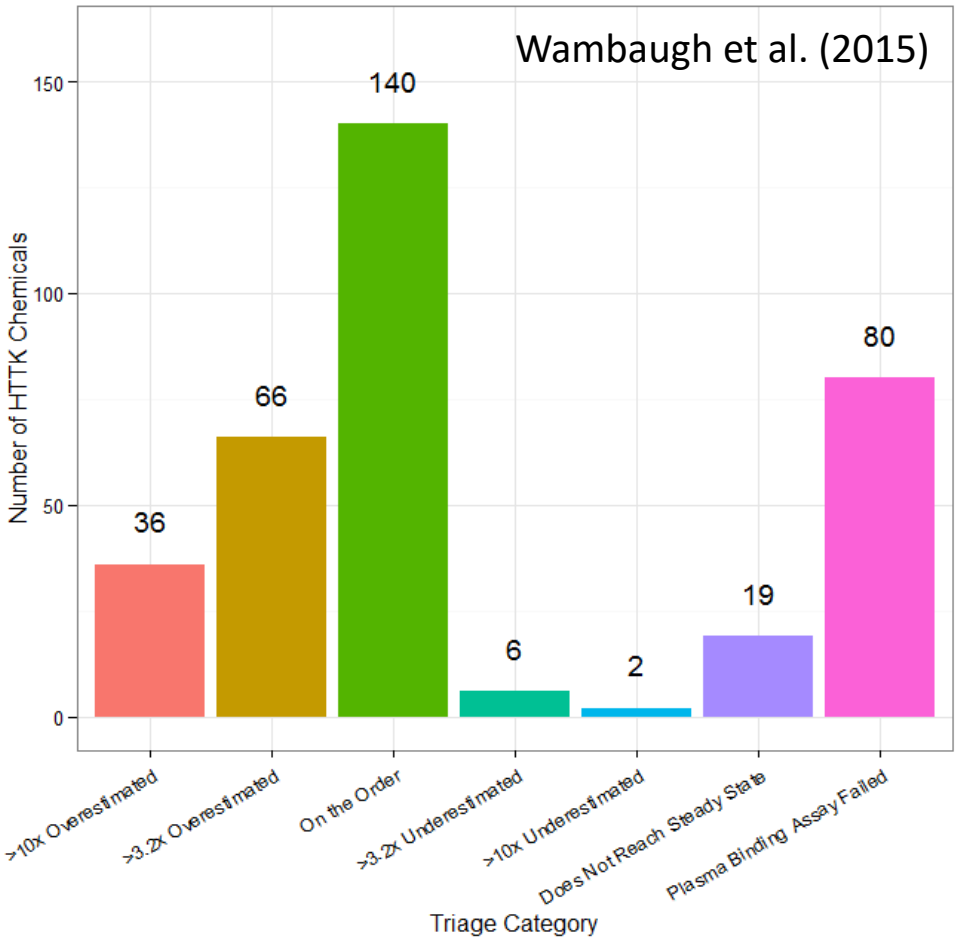
Change in Activity : Exposure Ratio



Ring *et al*. (2017)

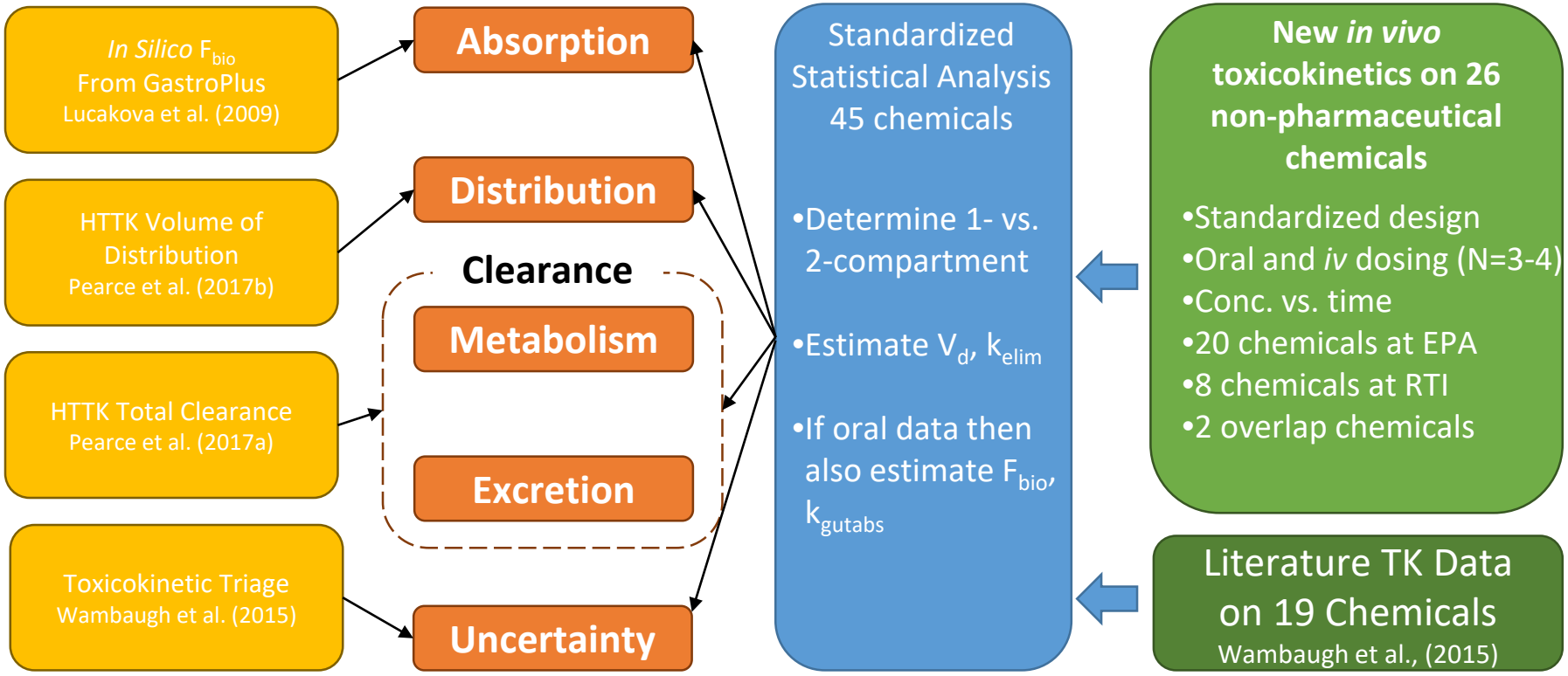
Toxicokinetic Triage

- Through comparison to existing *in vivo* data, a cross-validated (random forest) predictor of success or failure of HTTK was constructed
- We added 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
- Plurality of chemicals end up in the "on the order" bin (within a factor of 3.2x) which is consistent with Wang (2010)



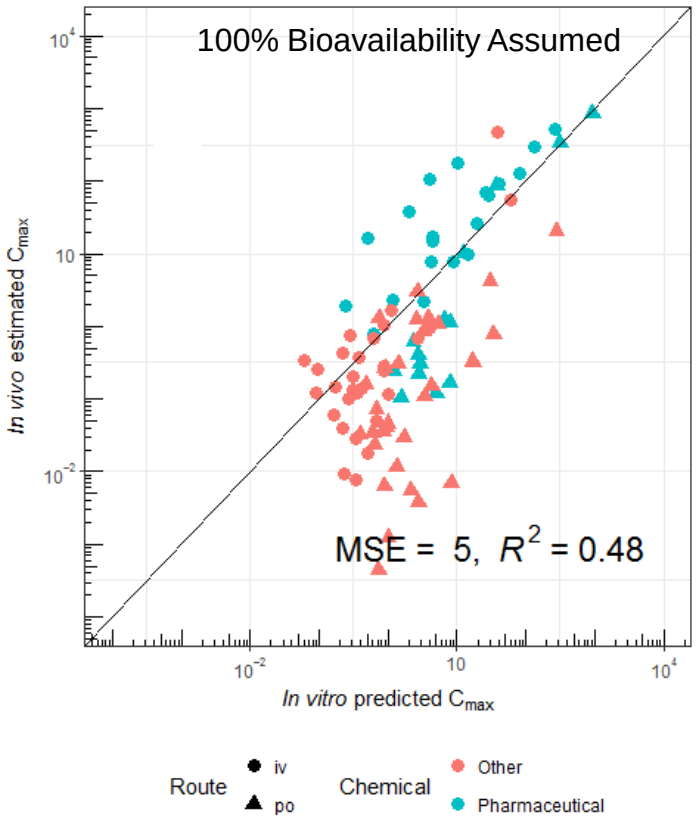
New Data for Evaluation

Available literature *in vivo* TK evaluation data was heavily biased toward pharmaceuticals



Wambaugh et al. (2018)

Evaluating HTTK

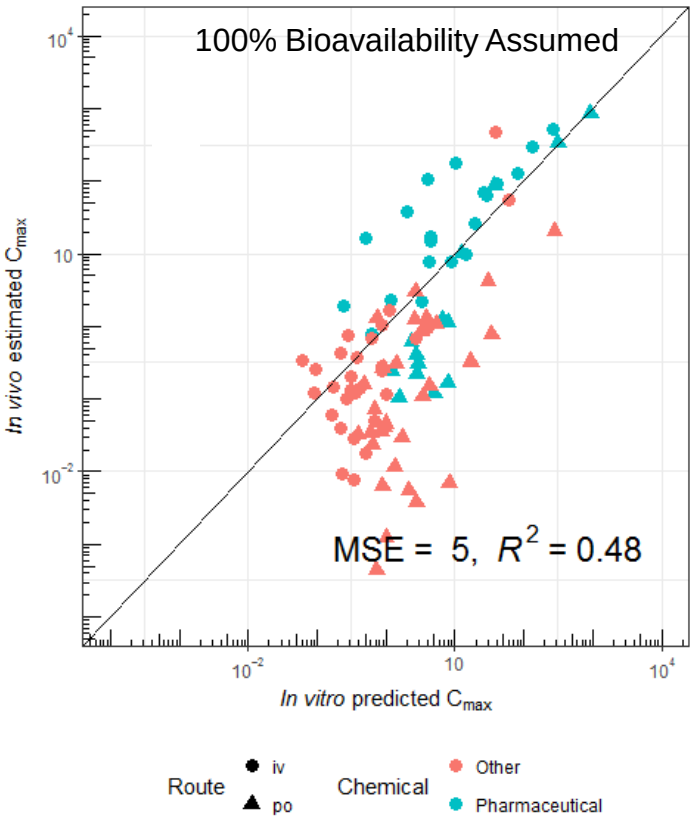


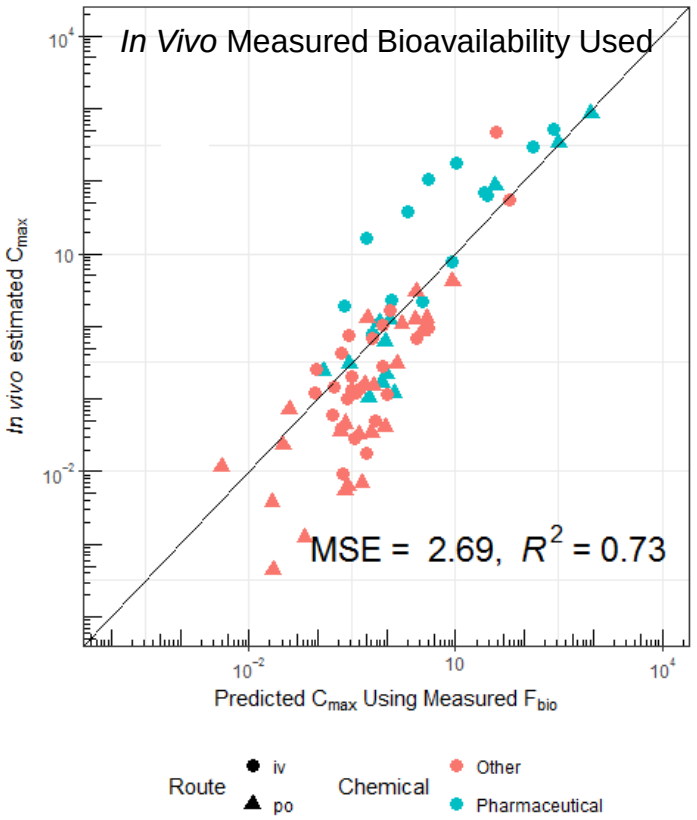
We evaluate HTTK by comparing predictions with observations for as many chemicals as possible

Wambaugh et al. (2018)

Evaluating HTTK

Impact of Oral Bioavailability Data





Wambaugh et al. (2018)

Evaluating HTTK

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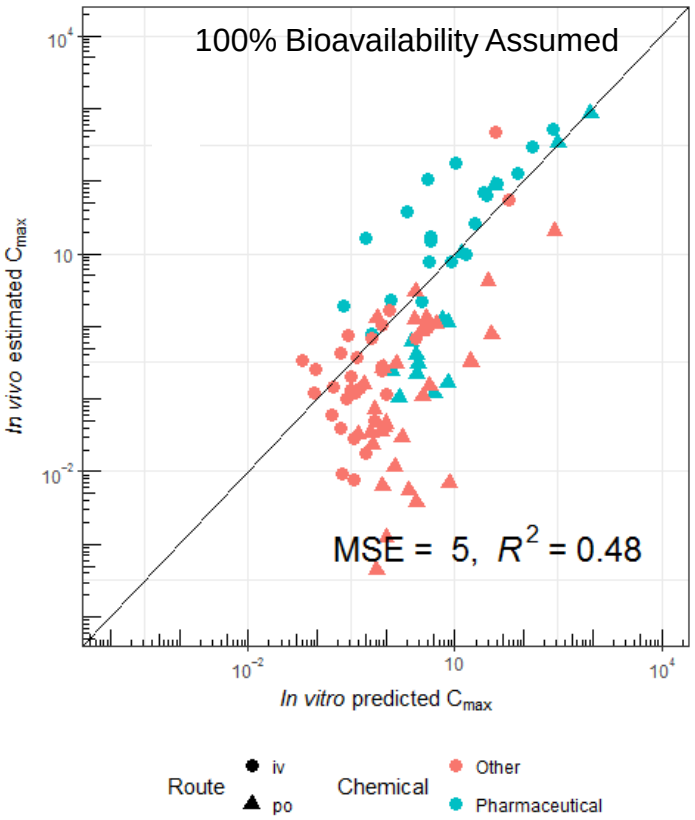
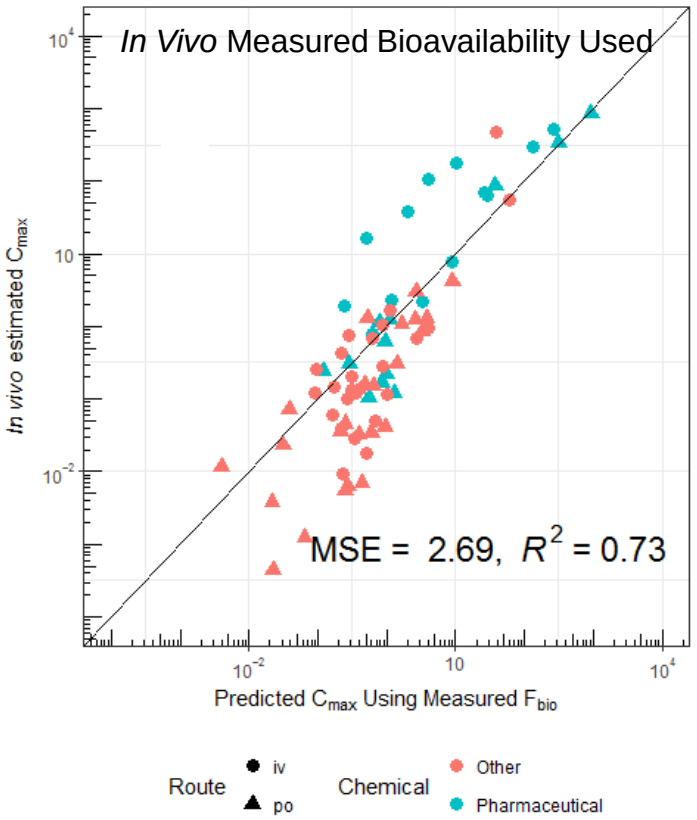
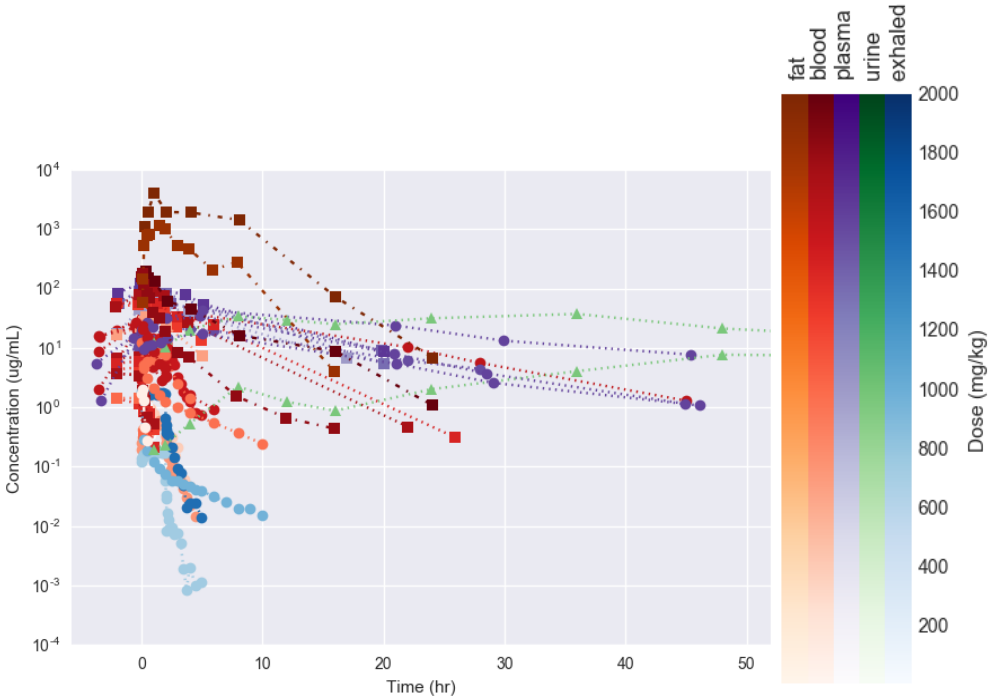




Greg Honda (NCCT) made a SOT2018 presentation on using Caco2 *in vitro* data to predict absorption for ~300 ToxCast chemicals

In Vivo TK Database

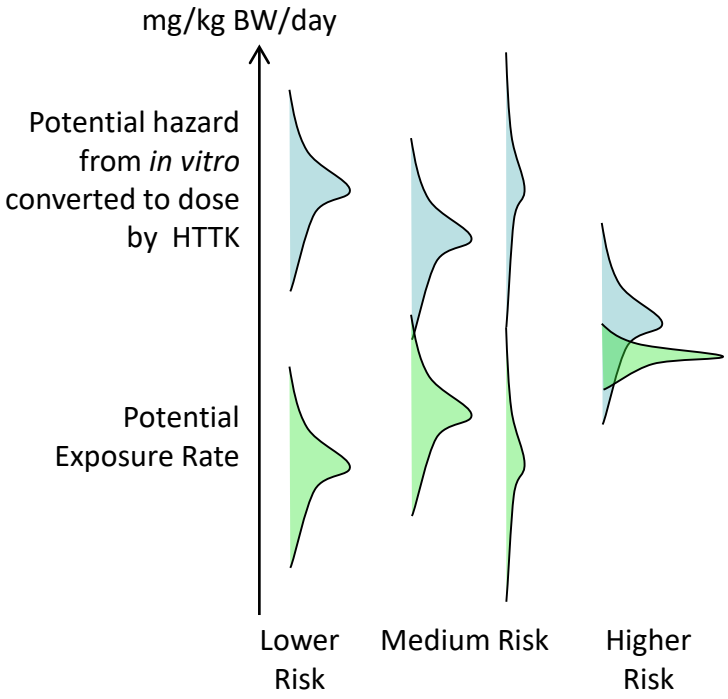
- EPA is developing a public database of concentration vs. time data for building, calibrating, and evaluating TK models
- Curation and development ongoing, but to date includes:
  - 175 analytes (EPA, National Toxicology Program, literature)
  - Routes: Intravenous, dermal, oral, sub-cutaneous, and inhalation exposure



- Database will be made available through web interface and through the “httk” R package
- Standardized, open source curve fitting software invivoPKfit used to calibrate models to all data:
  https://github.com/USEPA/CompTox-ExpoCast-invivoPKfit

Work led by Risa Sayre and Chris Grulke

Conclusions



- We would like to know more about the risk posed by thousands of chemicals in the environment – which ones should we start with?
- HTTK NAMs are being evaluated through 1) uncertainty analysis and 2) comparison between in vitro predictions and in vivo measurements of both plasma concentrations and doses associated with the onset of effects (i.e., "points of departure").
- Comparison between HTTK predicted time course concentrations in plasma and in vivo data indicate that some properties (e.g. average and maximum concentration) can be predicted with confidence.
- Comparison between in vitro bioactivity data and HTTK-adjusted internal dose predictions for in vivo points of departure has refined assumptions of the HTTK NAMs.
- NAMs for TK allow risk-based prioritization of large numbers of chemicals.

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Chemical Safety for Sustainability (CSS) Research Program

Rapid Exposure and Dosimetry (RED) Project

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