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United States Environmental Protection Agency

ECETOC Workshop on the best use of generic in vitro – in vivo extrapolation (IVIVE) models

EPA's HTTK Research:
In vitro Data and Generic TK Models for IVIVE

John Wambaugh, Barbara Wetmore, Katie Paul-Friedman, Sarah Davidson, Michael Devito, Caroline Ring, Miyuki Breen, Dustin Kapraun, Marina Evans, and Russell Thomas

Office of Research and Development
Center for Computational Toxicology and Exposure
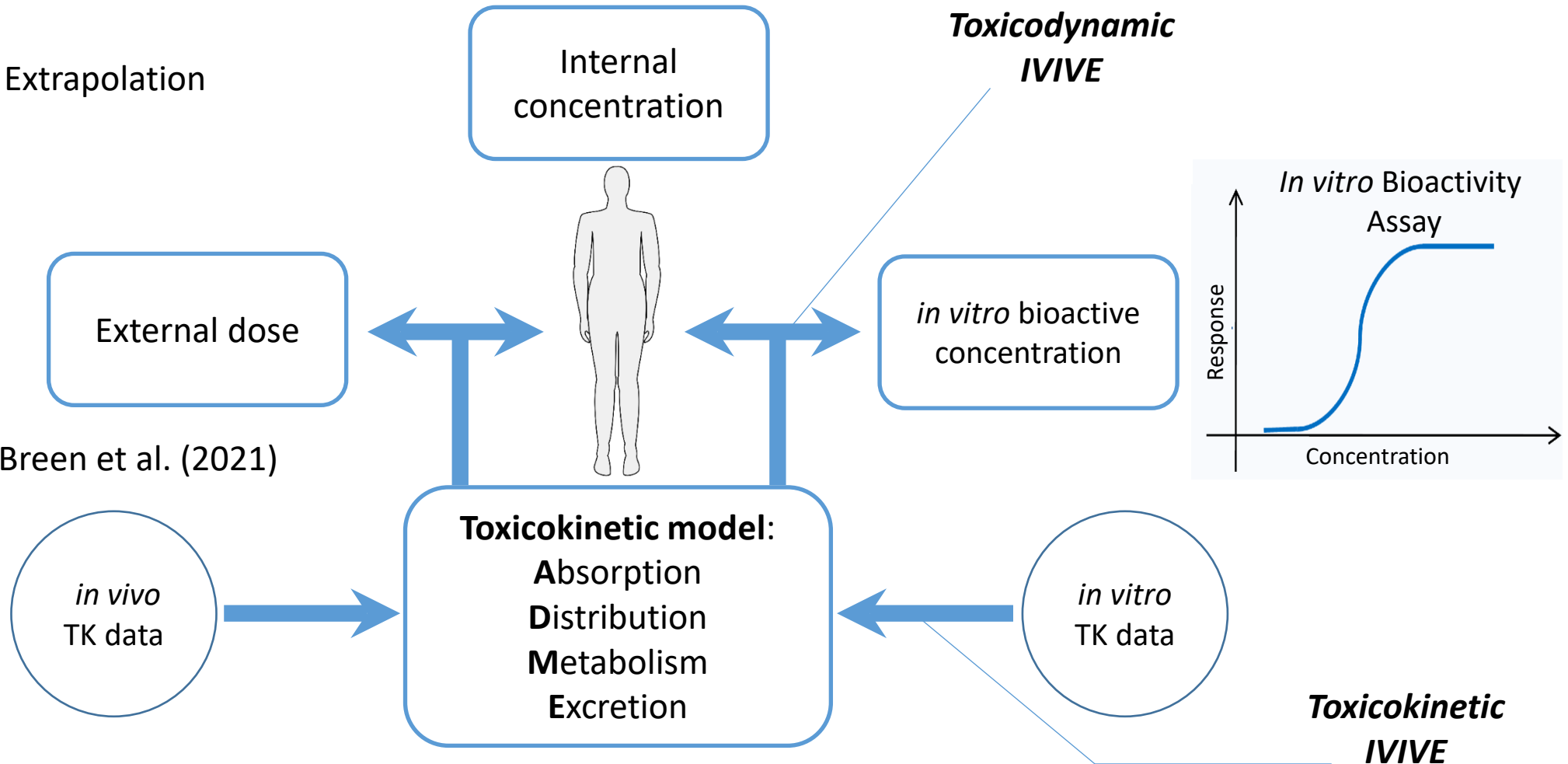
November 9, 2021

Toxicology in Vitro 27 (2013) 1570–1577

Toxicokinetics as a key to the integrated toxicity risk assessment based primarily on non-animal approaches ☆

Sandra Coecke [a], Olavi Pelkonen [b,*], Sofia Batista Leite [a,c], Ulrike Bernauer [d], Jos GM Bessems [e], Frederic Y. Bois [f], Ursula Gundert-Remy [g], George Loizou [h], Emanuela Testai [i], José-Manuel Zaldívar [j]

IVIVE:
In Vitro-In Vivo Extrapolation

Figure from Breen et al. (2021)

Toxicodynamic IVIVE

Internal concentration

In vitro Bioactivity Assay

External dose

in vitro bioactive concentration

Toxicokinetic model:
Absorption
Distribution
Metabolism
Excretion

in vivo TK data

in vitro TK data

Toxicokinetic IVIVE

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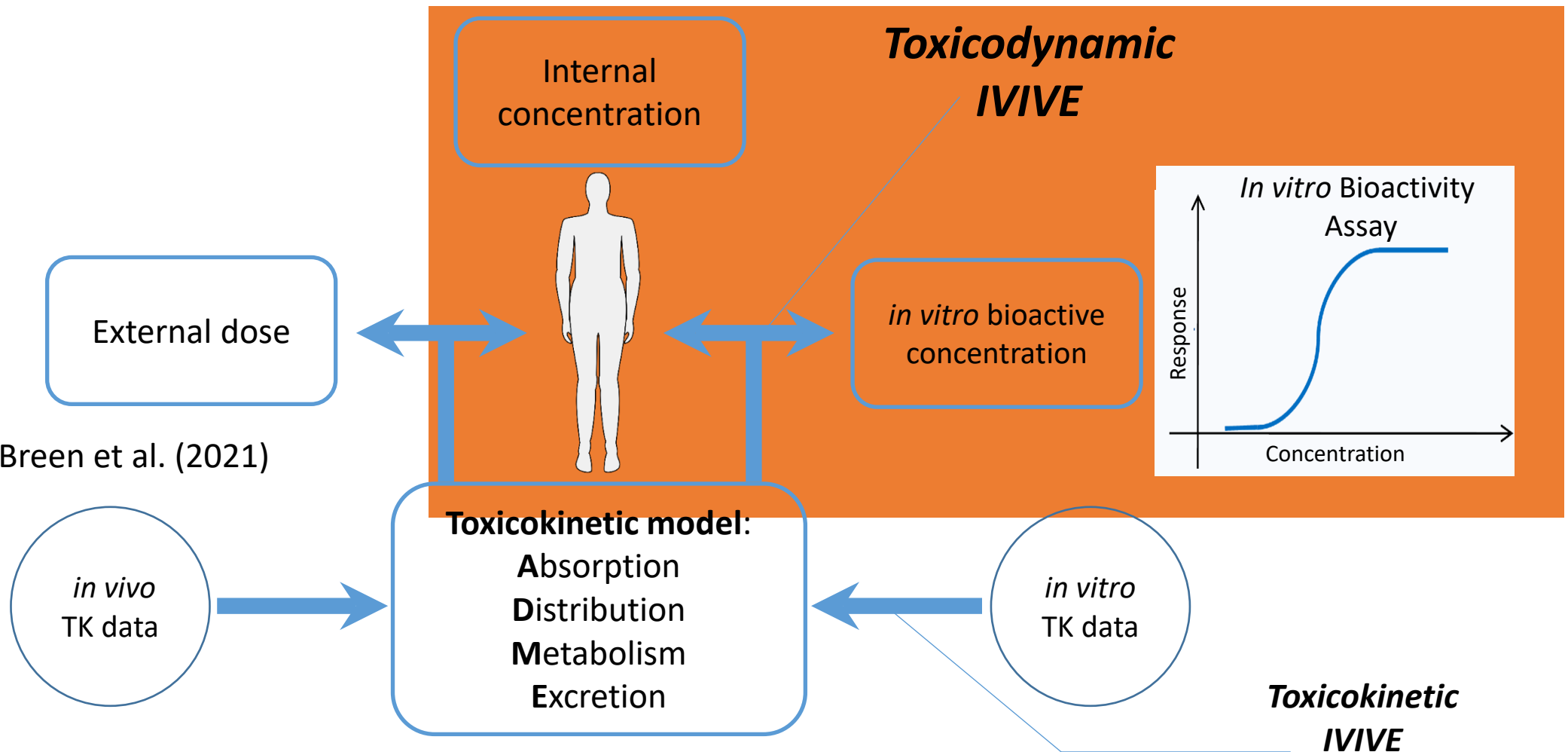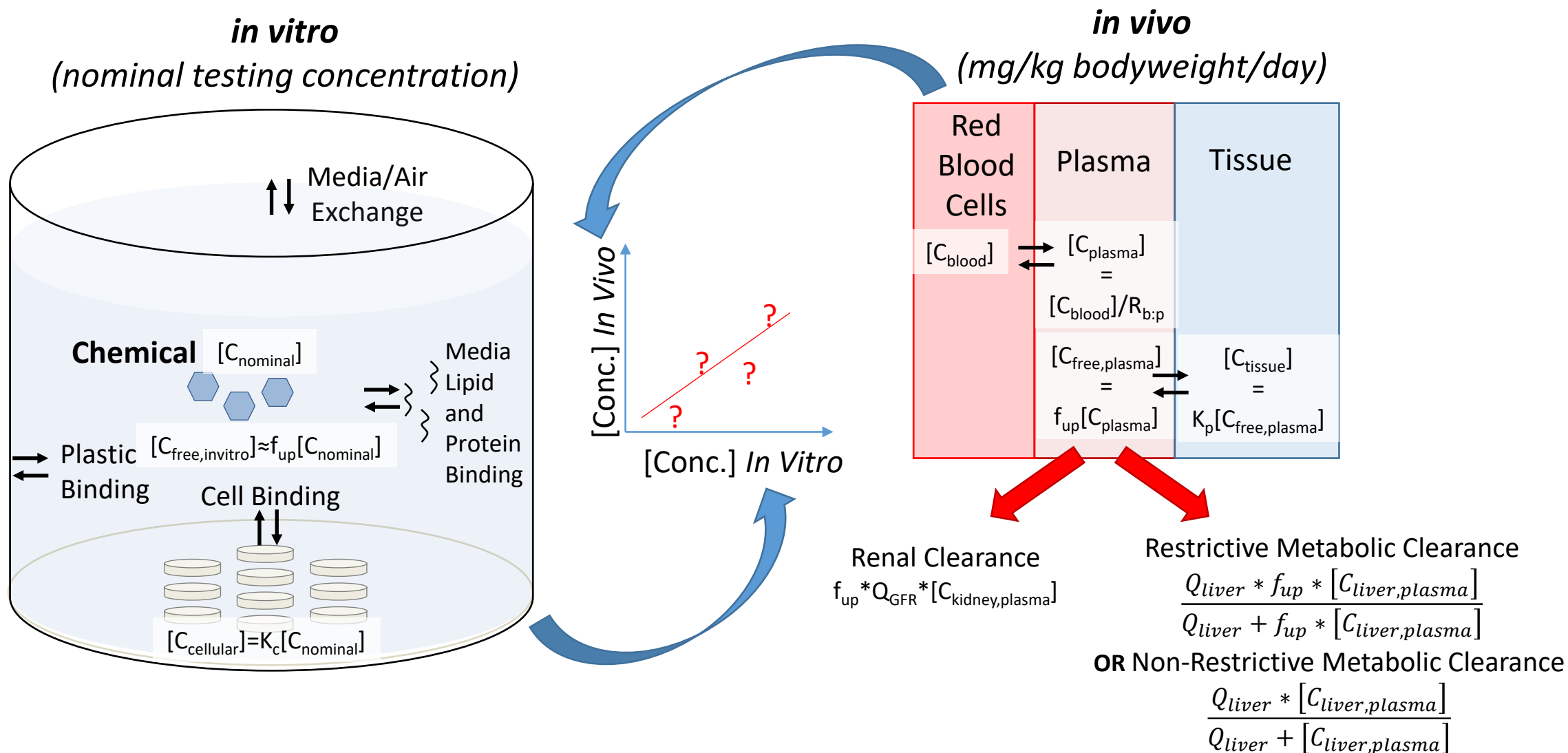

Figure from Breen et al. (2021)

How do you select the appropriate *in vitro* and *in vivo* concentrations for extrapolation?

Impact of IVIVE Assumptions

Honda et al. (2019)

Different combinations of assumptions, for example:

res-tot-vein-mean = restrictive metabolism, total chemical, venous concentrations, mean concentration during tox study

Count of Times Selected as Best Model

Forward Dosimetry

res.-tot.-vein-mean
(*httk* v1.8 default)
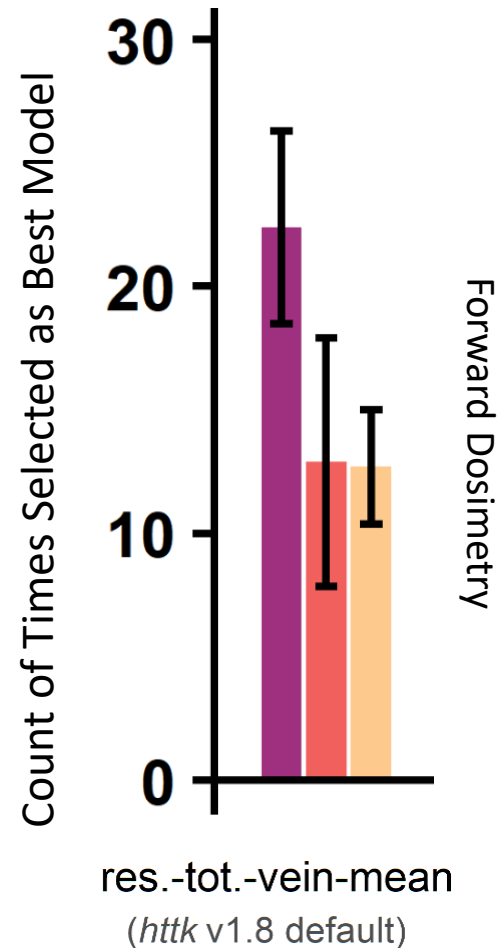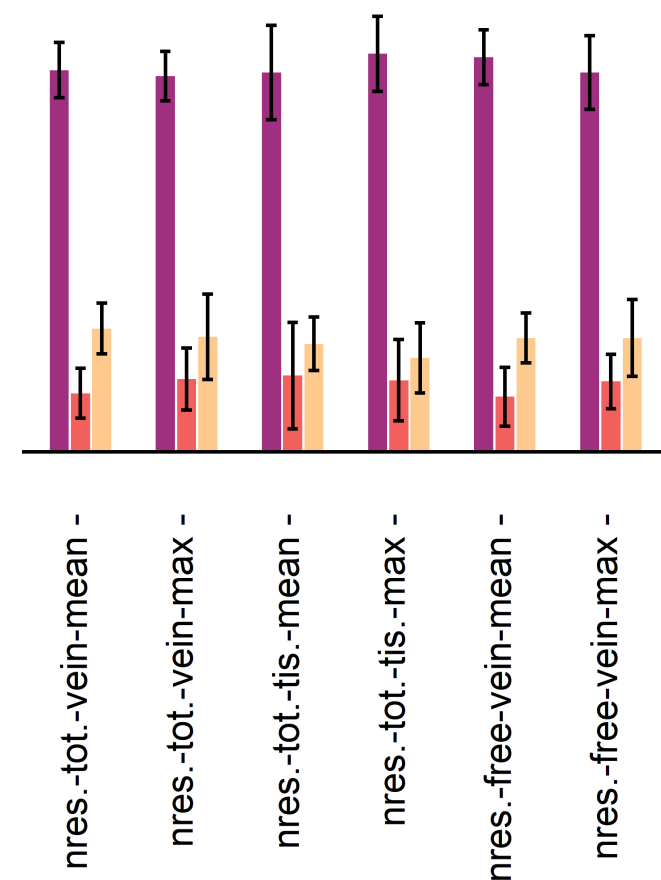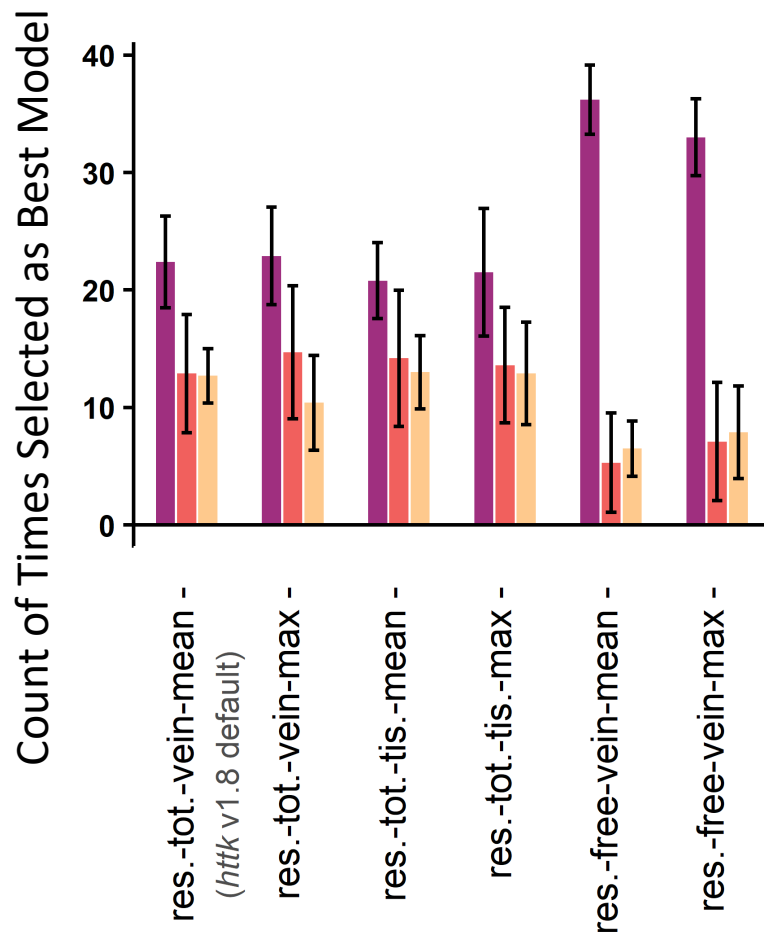
PBTK   Random   Dose

Impact of IVIVE Assumptions

Different combinations of assumptions, for example:

Honda et al. (2019)

"res-tot-vein-mean" = restrictive metabolism, total chemical, venous concentrations, mean concentration during tox study

"nres-tot-tis-max" = non-restrictive metabolism, total chemical, tissue concentrations, max conc. during tox study
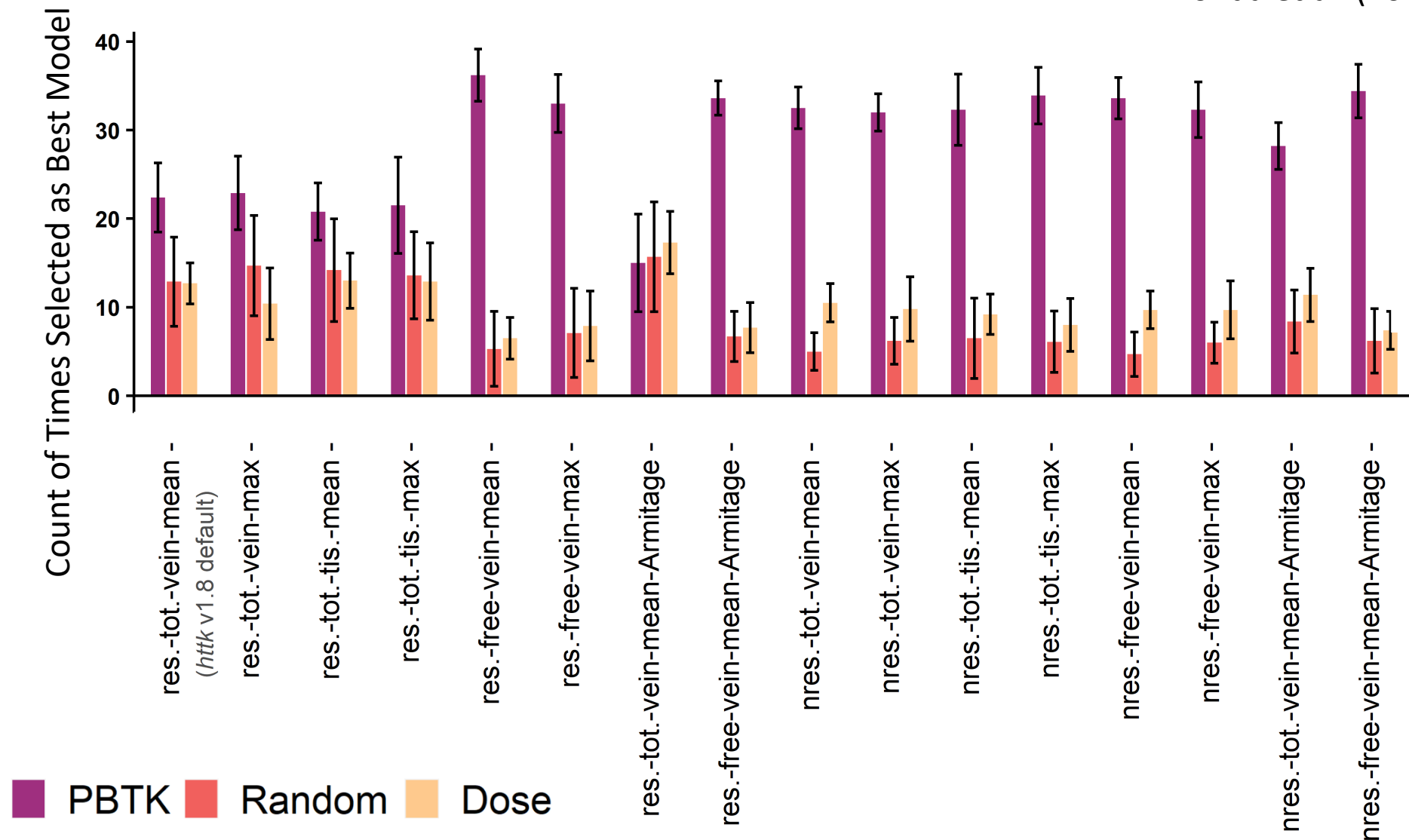
Impact of IVIVE Assumptions

Different combinations of assumptions, for example:
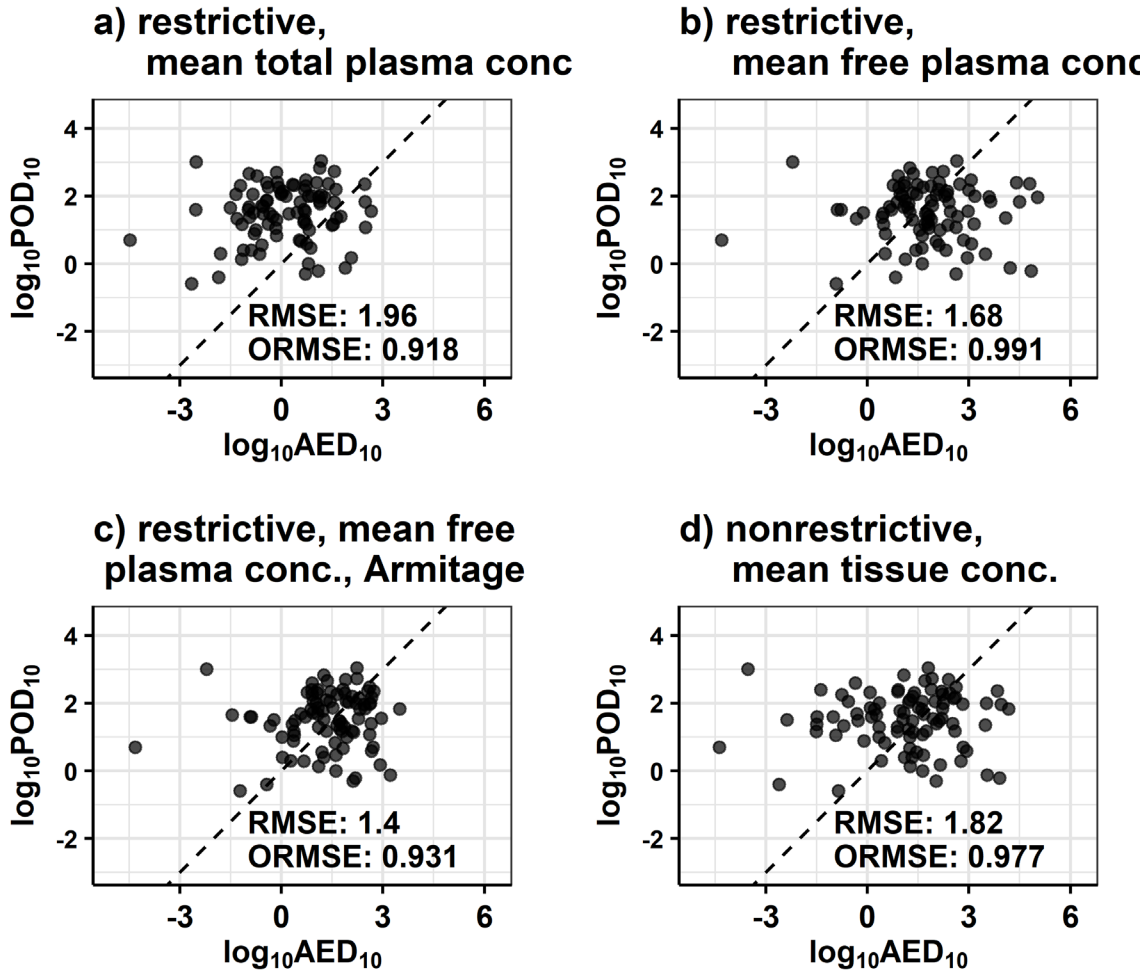
Honda et al. (2019)

"Armitage" indicates that the Armitage et al. (2014) *in vitro* disposition model was used to adjust for free concentration

# Comparing Traditional and IVIVE Points of Departure

Honda et al. (2019)

Paul-Friedman et al. (2019)

In vivo Point of Departure (POD)

a) restrictive, mean total plasma conc

RMSE: 1.96
ORMSE: 0.918

b) restrictive, mean free plasma conc

RMSE: 1.68
ORMSE: 0.991

c) restrictive, mean free plasma conc., Armitage

RMSE: 1.4
ORMSE: 0.931

d) nonrestrictive, mean tissue conc.

RMSE: 1.82
ORMSE: 0.977

NAM-derived POD

Conservatism of NAM-POD depends on choices made for generic PBTK and *in vitro* disposition
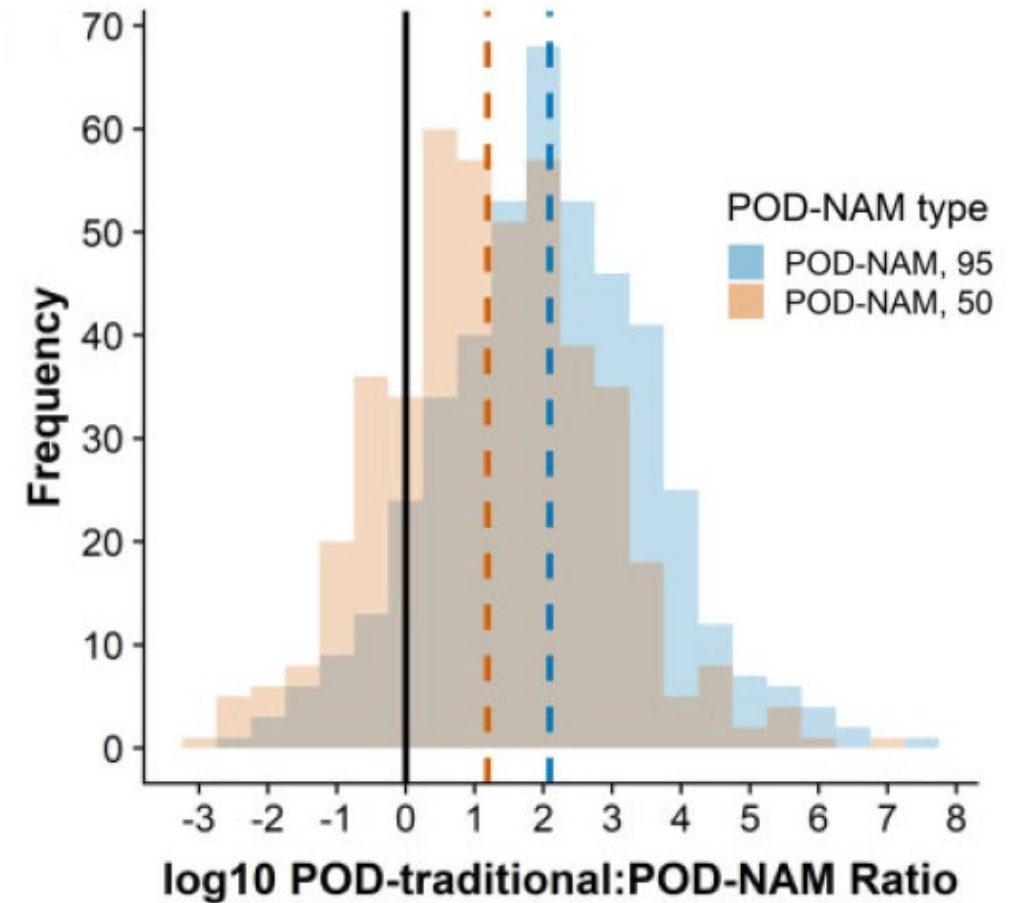
New Approach Methodology (NAM)-derived point of departure (POD) from ten to one hundred times more conservative than traditional methods

Toxicokinetics as a key to the integrated toxicity risk assessment based primarily on non-animal approaches ☆

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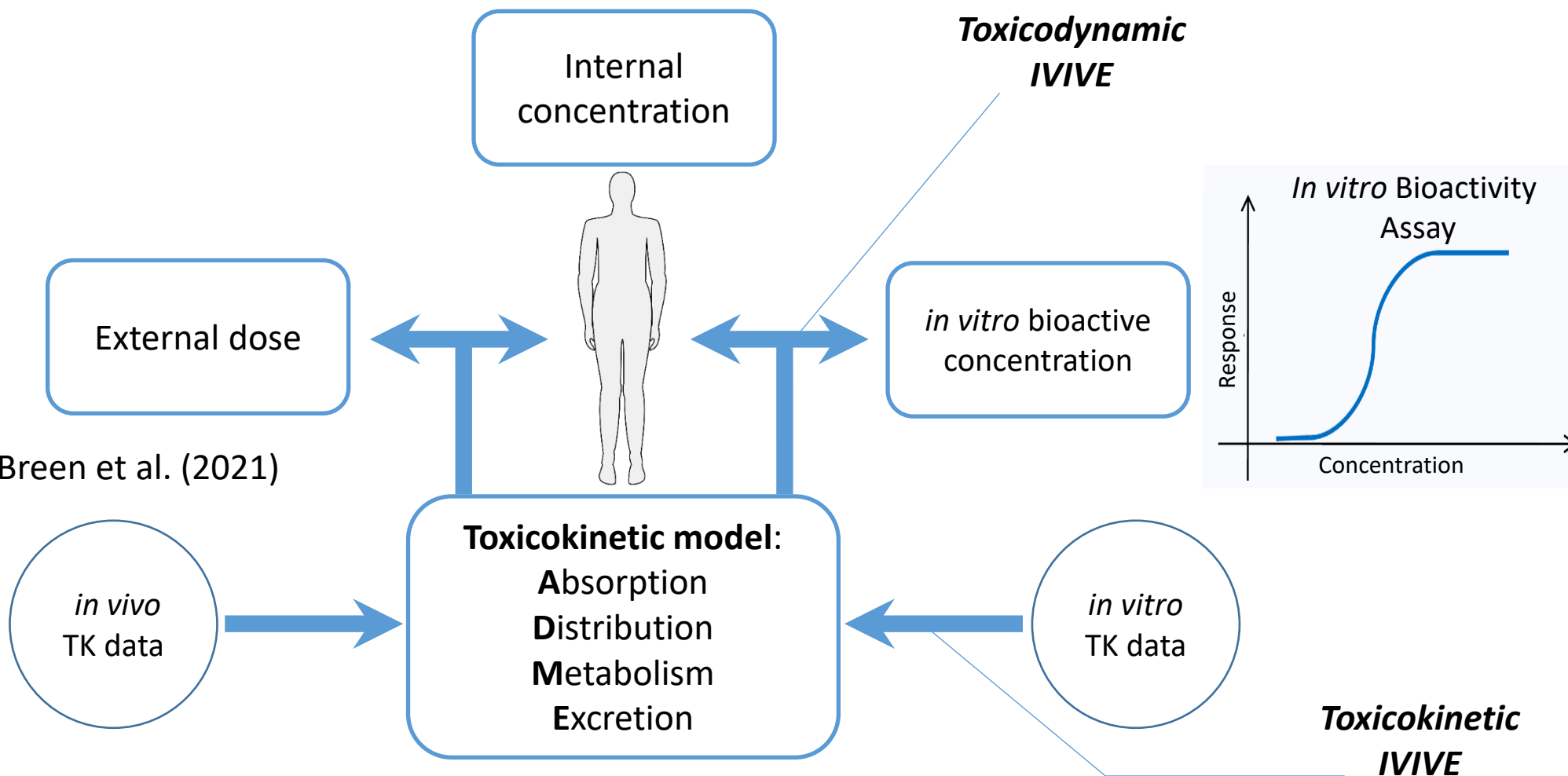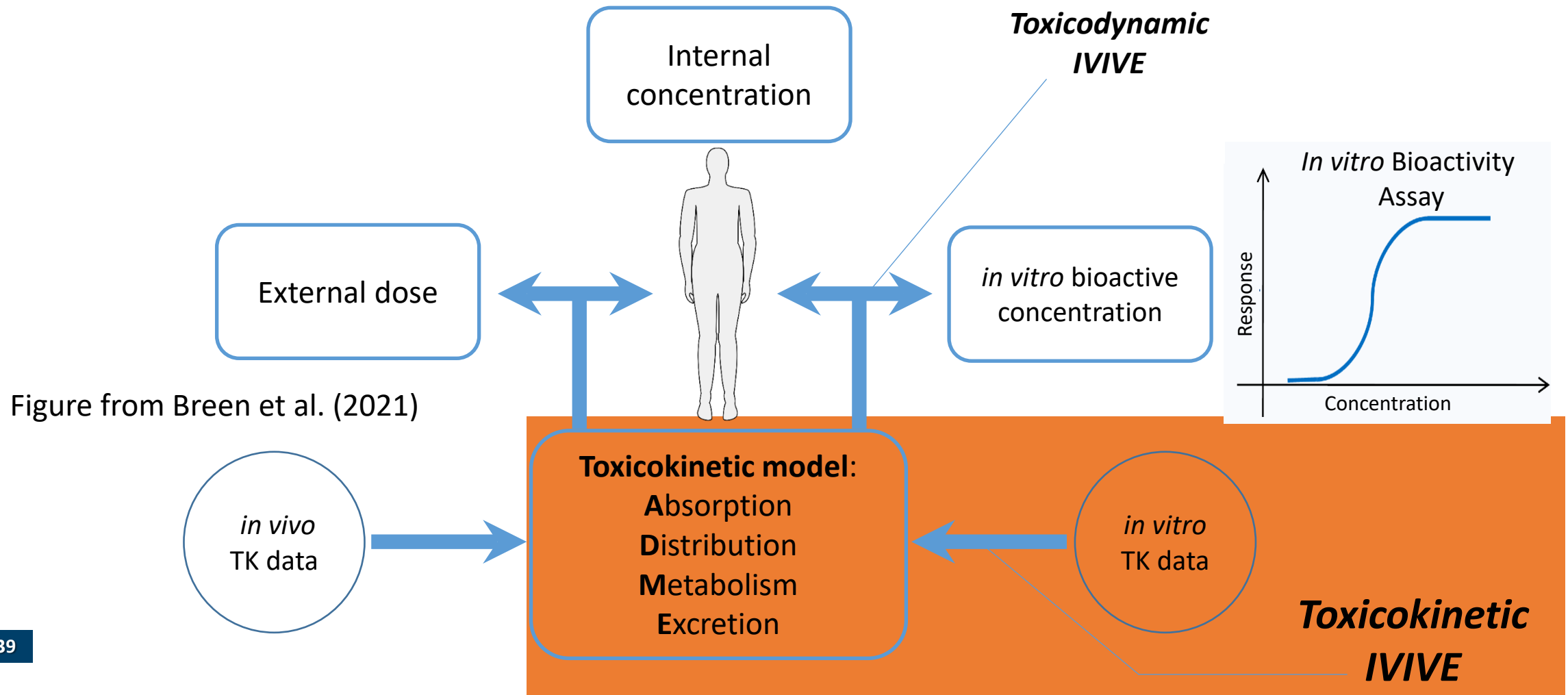

Figure from Breen et al. (2021)

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Internal concentration

In vitro Bioactivity Assay

External dose

in vitro bioactive concentration

Response

Concentration

Figure from Breen et al. (2021)

Toxicokinetic model:
Absorption
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Metabolism
Excretion

in vivo TK data
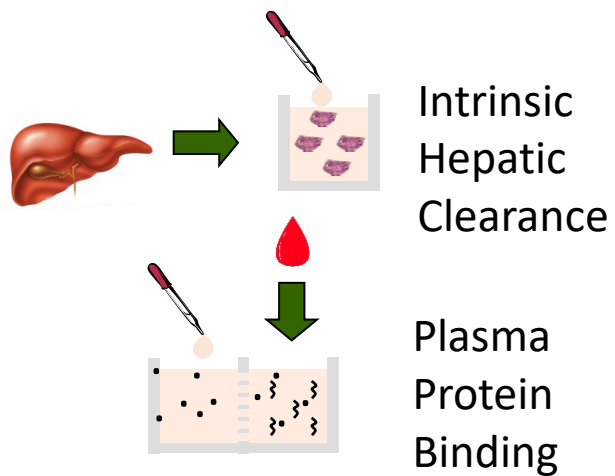
in vitro TK data

Toxicokinetic IVIVE

HTTK: A NAM for Exposure

- We collect *in vitro*, high throughput toxicokinetic (HTTK) data to provide toxicokinetics for large numbers of chemicals (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)

Wambaugh, et al. "New Approach Methodologies for Exposure Science."
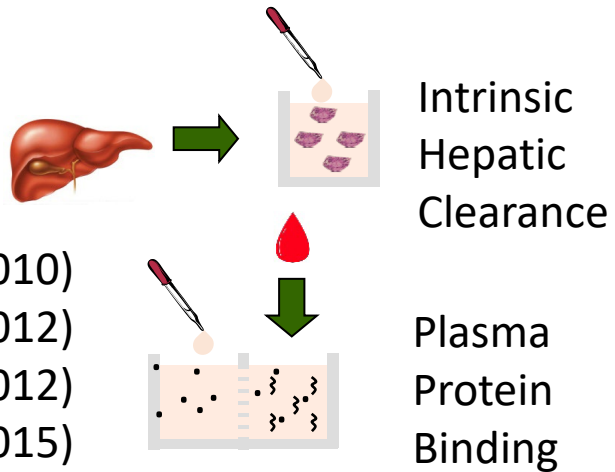*Current Opinion in Toxicology 15 (2019): 76-92.*

High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data

Intrinsic Hepatic Clearance

Plasma Protein Binding

Breen et al. (2021)

High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data

Intrinsic
Hepatic
Clearance

Plasma
Protein
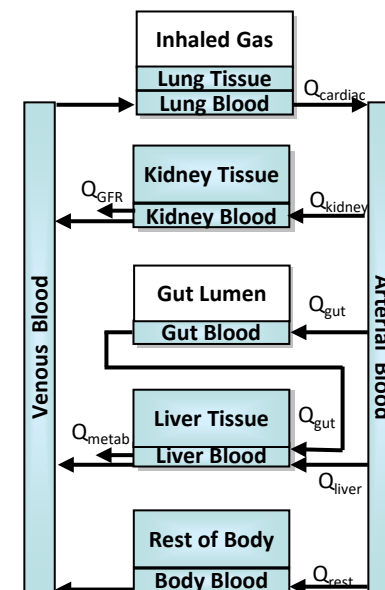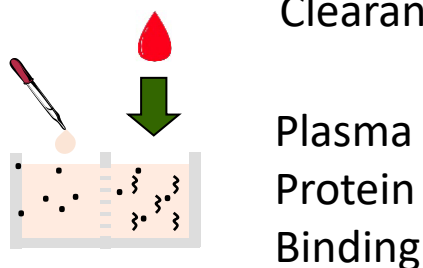Binding

Rotroff et al. (2010)
Wetmore et al. (2012)
Tonnelier et al. (2012)
Wetmore et al. (2015)
Wambaugh et al. (2019)
Paini et al. (2020)

Breen et al. (2021)

High Throughput Toxicokinetics (HTTK)

In vitro toxicokinetic data + generic toxicokinetic model

Intrinsic Hepatic Clearance

Plasma Protein Binding
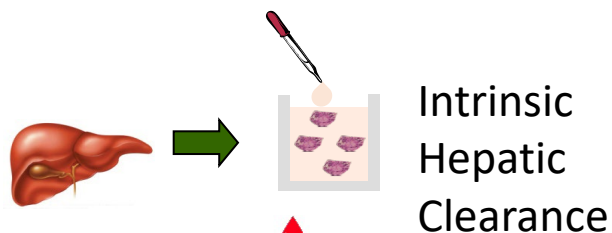
Rotroff et al. (2010)
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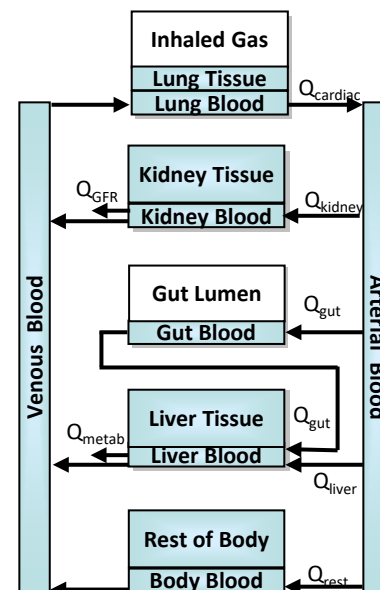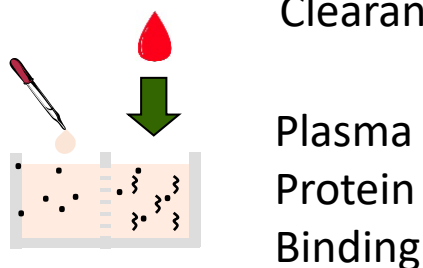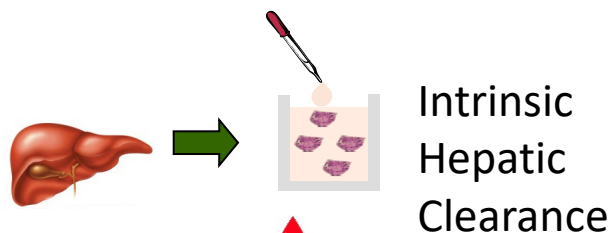Wambaugh et al. (2019)
Paini et al. (2020)

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

Breen et al. (2021)

High Throughput Toxicokinetics (HTTK)

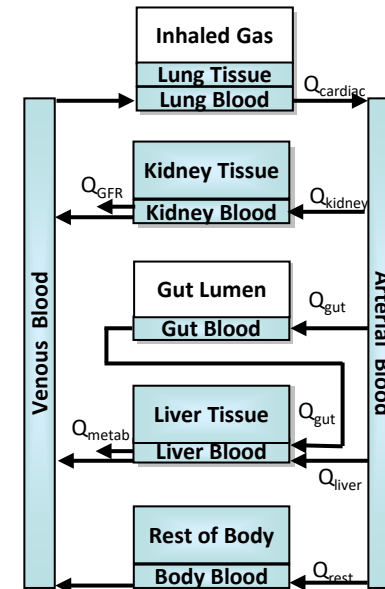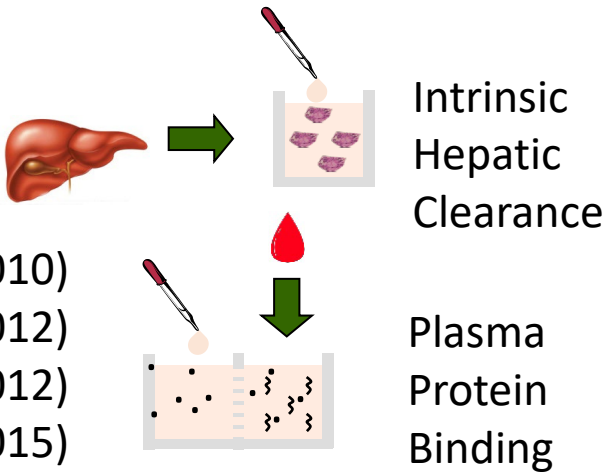## *In vitro* toxicokinetic data + generic toxicokinetic model = high(er) throughput toxicokinetics

Rotroff et al. (2010)
Wetmore et al. (2012)
Tonnelier et al. (2012)
Wetmore et al. (2015)
Wambaugh et al. (2019)
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Intrinsic Hepatic Clearance

Plasma Protein Binding

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

= *httk*

Breen et al. (2021)

A Generic Model is a Hypothesis

- **For pharmaceuticals**, *in vitro* data combined with a generic TK model including hepatic metabolism and passive glomerular filtration (kidney) are often enough to make predictions **within a factor of 3** of *in vivo* data (Wang, 2010)

- For other chemicals there may be complications

- We can add additional processes only if there is some way **to parameterize the process for most chemicals** – otherwise we are back to tailoring the model to a chemical

Why Build Another Generic PBTK Tool?

from Breen et al. (2021)

	SimCYP	ADMET Predictor / GastroPlus	PK-Sim	IndusChem Fate	pbktool	G-PBTK	httk
References	Jamei (2009)	Parrott (2009)	Eissing (2011)	Jongeneelen (2011)	Punt (2020)	Armitage (2021)	Pearce (2017)
Availability	License, but inexpensive for research	License, but inexpensive for research	Free	Free	Free	Free	Free
Open Source	**No**	**No**	**GitHub**	**No**	**GitHub**	**Planned Release**	**CRAN and GitHub**
Default PBTK Structure	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Population Variability	Yes	Yes	Yes	No	No	No	Yes
Data Needs	High/Low	High/Low	High	High	Low	Low	Low
Typical Use Case	Drug Discovery	Drug Discovery	Drug Discovery	Environmental Assessment	Food and Drug Safety Evaluation	Environmental Assessment	Screening
Batch Mode	Yes	Yes	Yes	No	No	No	Yes
Graphical User Interface	Yes	Yes	Yes	Excel	No	Excel	No
Built-in Chemical-Specific Library	Many Clinical Drugs	No	Many pharmaceutical-specific models available	15 Environmental Compounds	No	No	Pharmaceuticals and ToxCast: 998 human, 226 rat
Oral Bioavailability Modeling	Yes	Yes	No	No	No	No	No (Will be available in the future version)
In Vitro Distribution	SIVA VIVD	No	No	No	No	No	Armitage Model
Exposure Route	Oral, IV	Oral, IV	Oral, IV	Oral, Gas Inhalation, Dermal	Oral	Oral, IV, Inhalation	Oral, IV, Gas Inhalation (Dermal, Aerosol, and Fetal forthcoming)
Ionizable Compounds	Yes	Yes	Yes	No	No	Yes	Yes
Export Function	No	No	Matlab and R	No	No	No	SBML and Jarnac
R Integration	**No**	**No**	**Yes (2017)**	**No**	**Yes**	**Yes**	**Yes**
Reverse Dosimetry	Yes	Yes	Yes	No	No	No	Yes

*Both **PLETHEM** (Pendse et al., 2020) and **Web-ICE** (Bell et al., 2020) provide GUI's to HTTK and other models
Pre-computed HTTK results are also available at https://comptox.epa.gov/dashboard

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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 998 chemicals
- Described in Pearce et al. (2017a) and Breen et al. (2020)

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, and inhalation (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)

Table from Breen et al. (2021)

Building Confidence in TK Models

- To evaluate a **chemical-specific TK model** for "chemical x" you can compare the predictions to *in vivo* measured data
  - Can estimate bias
  - Can estimate uncertainty
  - Can consider using model to extrapolate to other situations (dose, route, physiology) where you have no data

Observed Concentrations (y-axis)
Predicted Concentrations (x-axis)

Chemical Specific Model

Cohen Hubal et al. (2019)

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Cohen Hubal et al. (2019)

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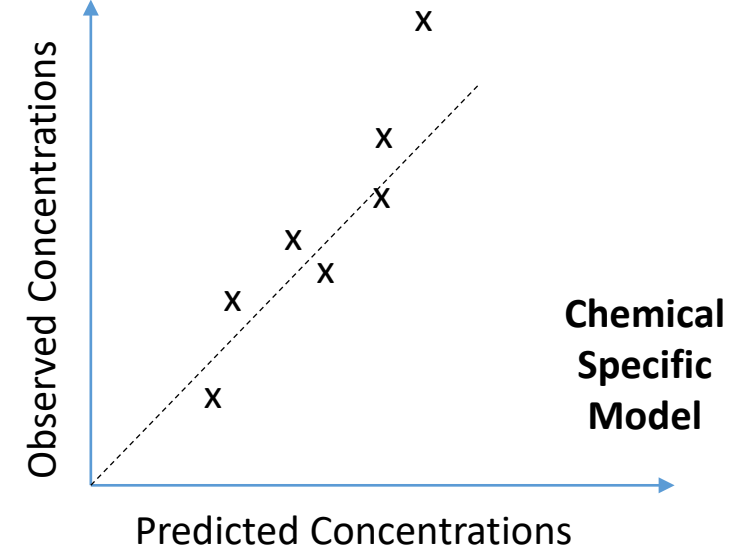
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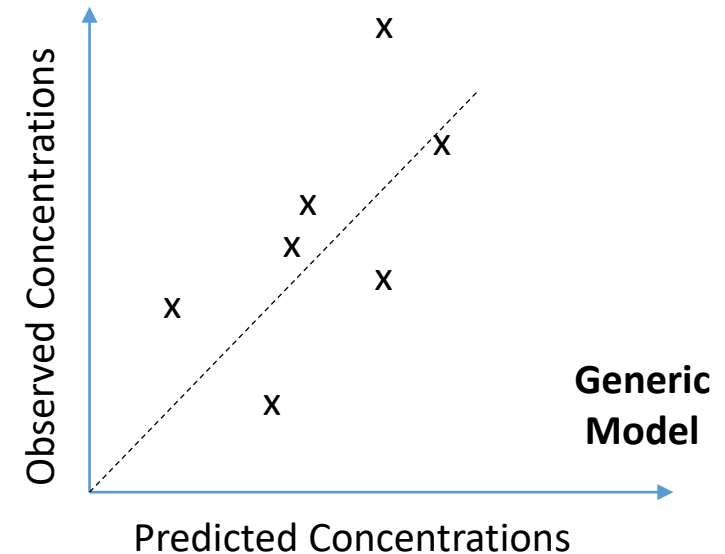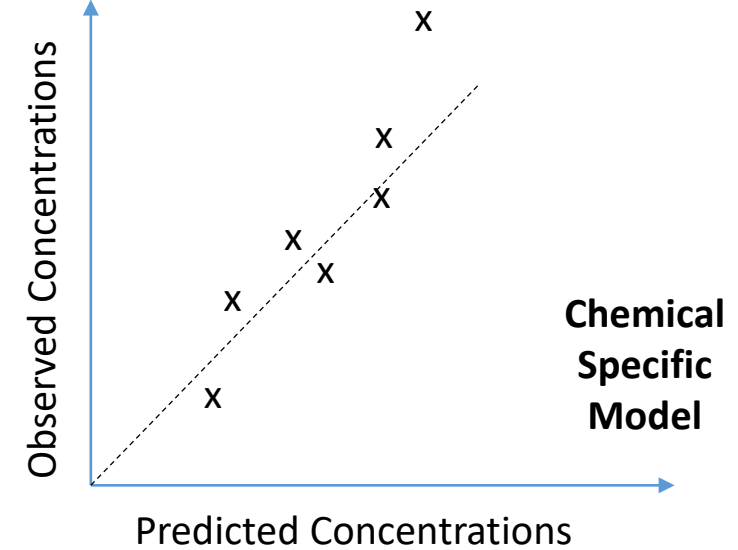
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Chemical Specific Model

Generic Model

Cohen Hubal et al. (2019)

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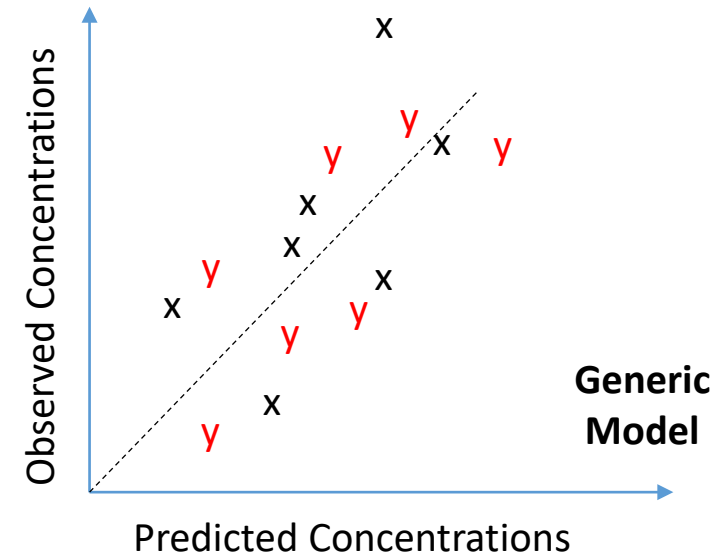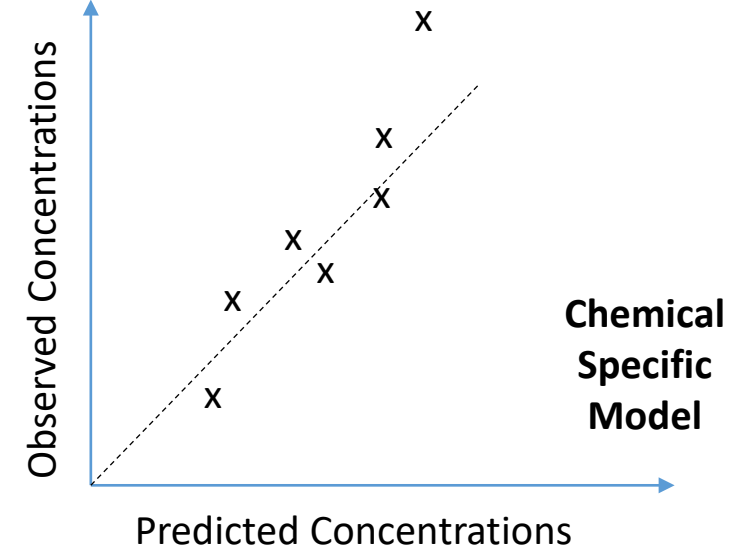
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Cohen Hubal et al. (2019)

CvTdb: An *In Vivo* TK Database

https://github.com/USEPA/CompTox-PK-CvTdb

- EPA has developed a **public database** of **concentration vs. time data** for building, calibrating, and evaluating TK models

- Curation and development is ongoing, but to date includes:
  - 198 analytes (EPA, National Toxicology Program, open literature)
  - Routes: Intravenous, dermal, oral, sub-cutaneous, and inhalation exposure

- Standardized, open-source curve fitting software invivoPKfit used to calibrate models to all data:

  https://github.com/USEPA/CompTox-ExpoCast-invivoPKfit

Studies
Test Substances

Other: 12 7
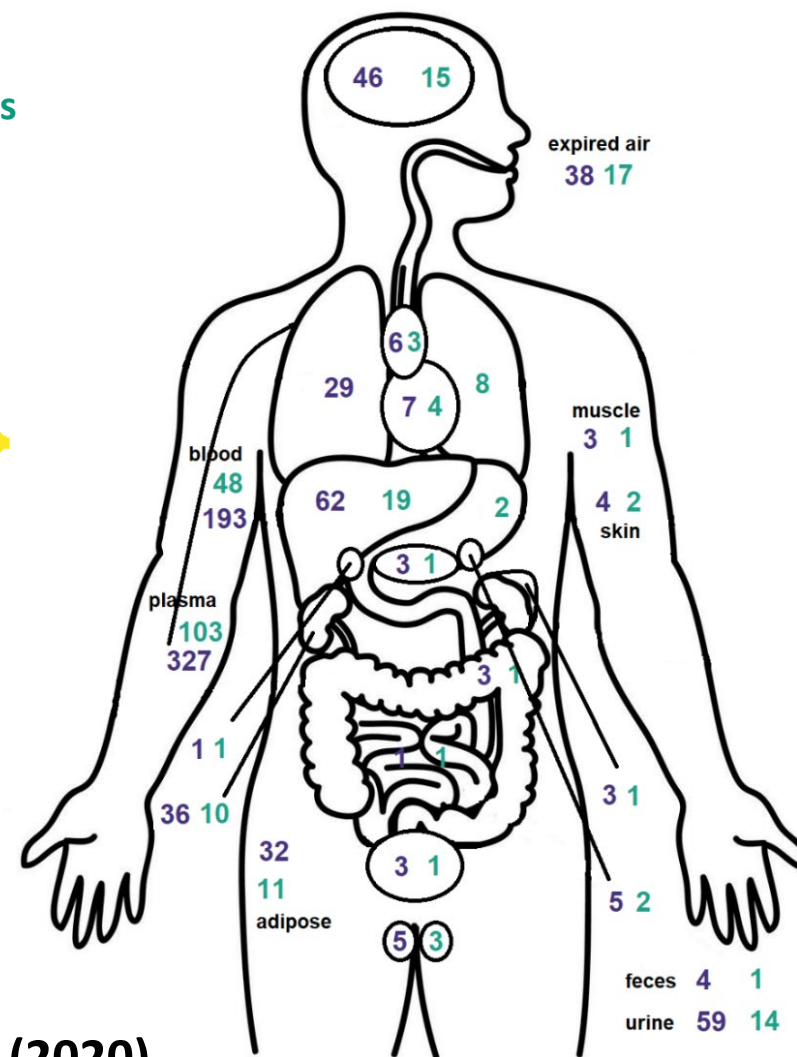
Sayre et al. (2020)

Developing Models with the CvT Database

- USAF and EPA developed a generic gas inhalation physiologically-based toxicokinetic (PBTK) model

- Evaluated HTTK with CvTdb: 142 exposure scenarios across 41 volatile organic chemicals were modeled and compared to published *in vivo* data for humans and rat

- R^2 was 0.69 for predicting peak concentration

- R^2 was 0.79 for predicting time integrated plasma concentration (Area Under the Curve, AUC)

Linakis et al. (2020)

- World Health Organization (2010): PBTK models are "adequate" when predictions "are, on average, **within a factor of 2** of the experimental data"

Breen et al. (2021)

Review of HTTK Evaluations

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- Predictions of full concentration vs. time curve (that is, all time points for all chemicals):
    - Linakis et al. (2020): For forty volatile, non-pharmaceutical chemicals root mean squared error (RMSE) of 1.11 (on a log10 scale, therefore **a factor of 13x**) and a coefficient of determination (R^2) of 0.47

Breen et al. (2021)

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  - Linakis et al. (2020): For forty volatile, non-pharmaceutical chemicals root mean squared error (RMSE) of 1.11 (on a log10 scale, therefore **a factor of 13x**) and a coefficient of determination (R^2) of 0.47

- Prediction of TK summary statistics such as peak concentration and time-integrated ("area under the curve" or AUC) concentration:
  - Wang (2010): For 54 pharmaceutical clinical trials the predicted AUC differed from observed by **2.3x**
  - Linakis et al. (2020): RMSE = 0.46 or **2.9x for peak concentration** and RMSE = 0.5 or **3.2x for AUC**
  - Wambaugh et al. (2018): For 45 chemicals of both pharmaceutical and non-pharmaceutical nature, RMSE of **2.2x for peak** and **1.64x for AUC**
  - Pearce et al. (2017b):The calibrated method for predicting tissue partitioning that is included in httk similarly predicted human volume of distribution with a RMSE of 0.48 **(3x)**

Breen et al. (2021)

Coordinating Ongoing Data Collection

- U.S. EPA maintains a list of chemicals that already have *in vitro* TK measurements (Cl_{int}, f_{up}, CACO-2, etc.) tested and those that are being considered for testing

- **We are happy to share this list with others upon request** (wambaugh.john@epa.gov)

- **We would appreciate any lists of chemicals you plan to test** or are testing to minimize duplication unless intended for cross-laboratory evaluations

- You do not need to share your data, but we'd always love to have your data

- EPA distributes HTTK data via R package httk (https://cran.r-project.org/package=httk) and CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard). Also see U.S. NICEATM Web-ICE (https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox/ct-ivive/ivive.html)

Documenting, Standardizing, and Assessing *In Vitro* Measurements

- Multiple governments and organizations continuing to collect *in vitro* data for HTTK

- Various approaches, including R package "httk", try to summarize these data

- EPA is interested in standardizing data analysis

  - Working on new R package "invitroTKstats"

  - Ensure all necessary measurements and metadata are recorded

  - Structure data to support potential future databases

RESEARCH PAPER

Interlaboratory Variability in Human Hepatocyte Intrinsic Clearance Values and Trends with Physicochemical Properties

Christine M. Bowman[1] · Leslie Z. Benet[1]

Check for updates
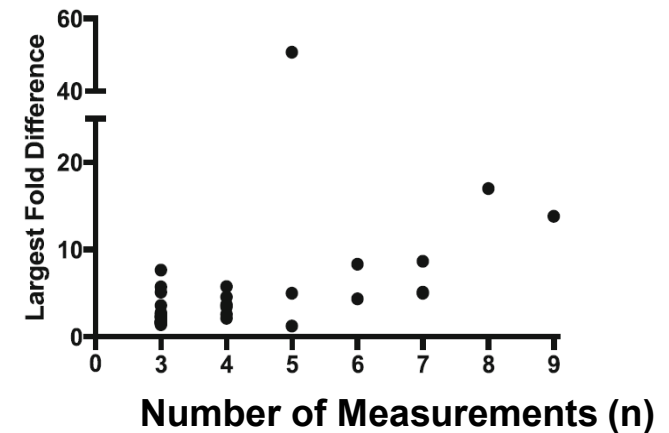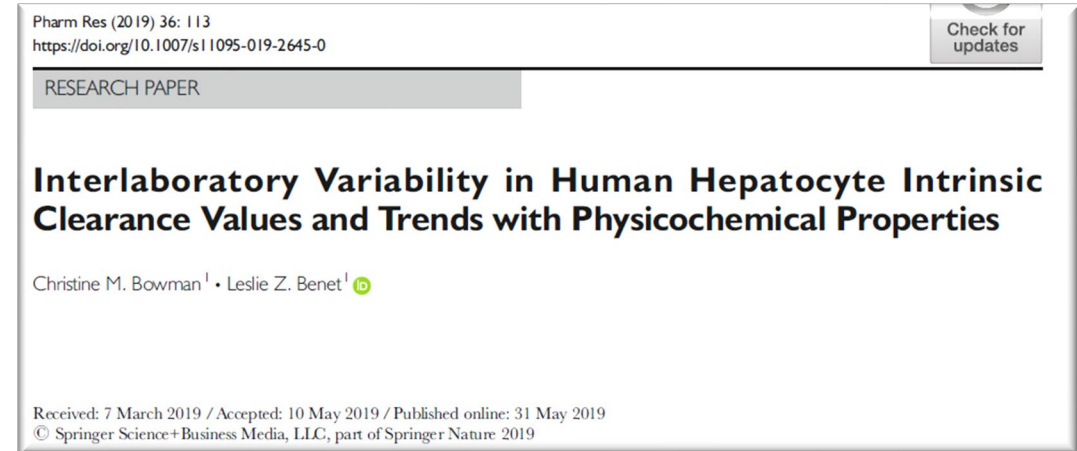
n	3	4	5	6	7	8	9
# values	17	6	3	2	3	1	1
Mean Largest Dif.	2.8	3.7	19	6.3	6.3	17	14
SD	1.8	1.3	28	2.8	2.1	-	-

QSPRs for HTTK Parameters

- We may not always need to measure
- There is a separate collaborative evaluation of QSPRs for predicting HTTK
  - Presented at QSAR2021 virtual meeting
  - Manuscript in preparation
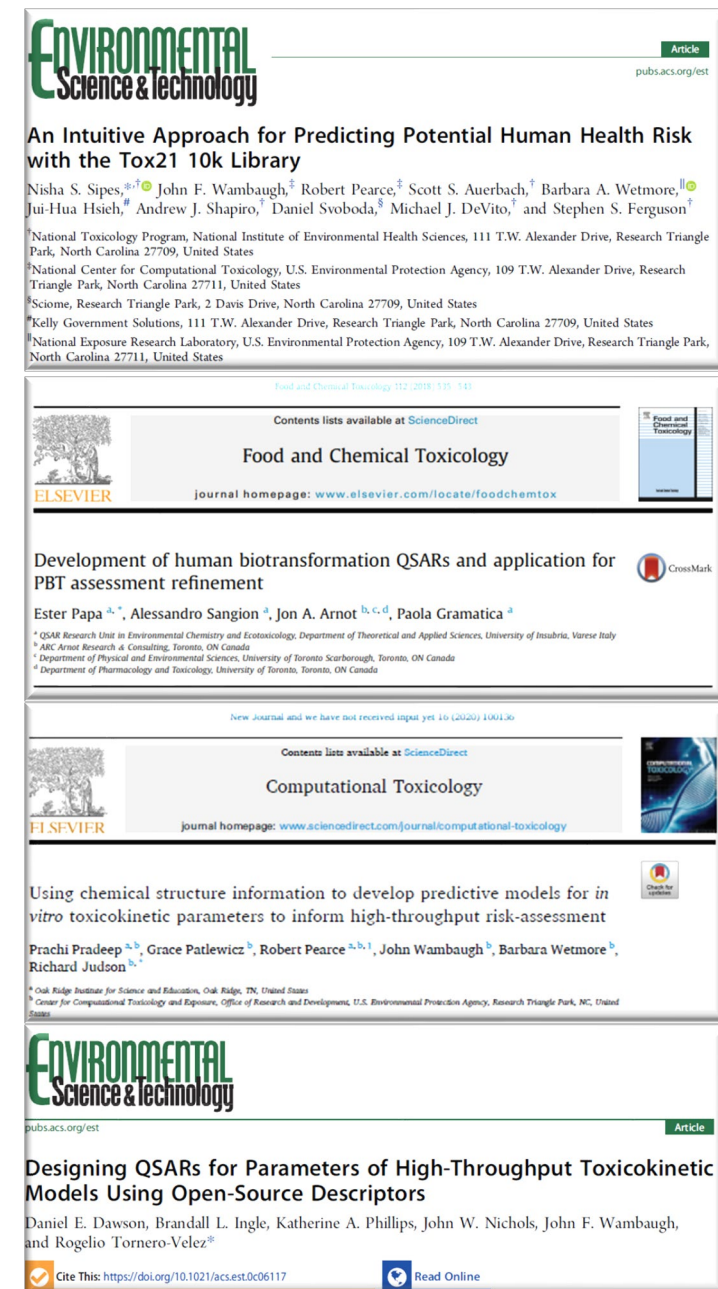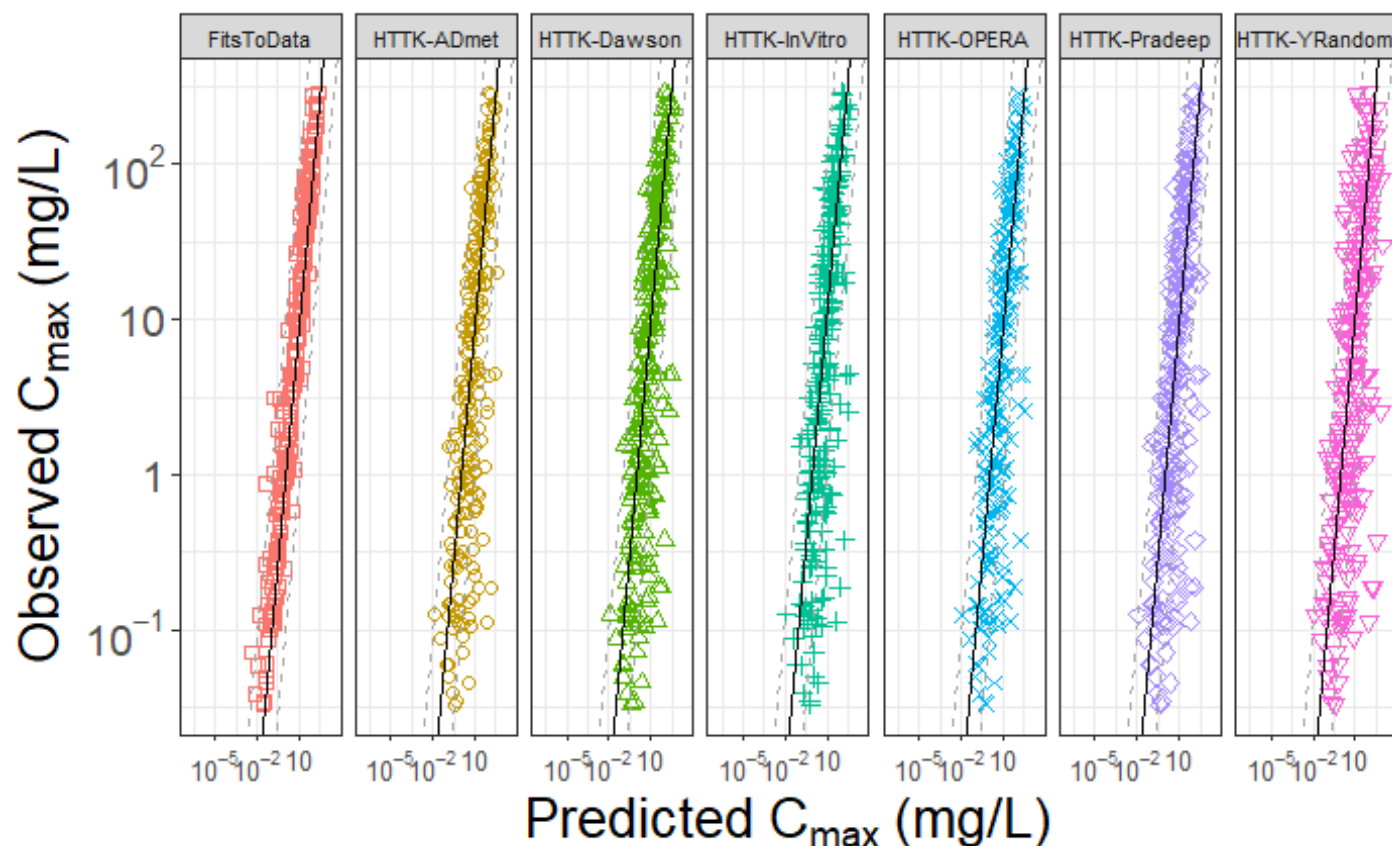
Adding Models to HTTK

- The R package "httk" provides a library of peer-reviewed, published chemical-specific data and a suite of tools for parameterizing and evaluating TK models

- The open-source language "MCsim" (Bois,) is used to describe models for compartmental and PBTK. "MCsim" converts the model descriptions into high-speed C computer code

- With the addition of a model documentation file in the R language, the C model code is then integrated into the "httk" environment using the open-source R package development functionality

- We have described in detail how to add models to the "httk" suite and how to take advantage of the pre-existing data and functionality of the "httk" environment.

  Draft manuscript:
  Developing Generic Toxicokinetic Models with R Package "httk" for Enhanced Reporting Accuracy and Statistical Evaluation

  Expected EPA clearance (public availability) and submission to journal in January 2022

Gas Inhalation Exposure Route
Linakis et al. (2020)
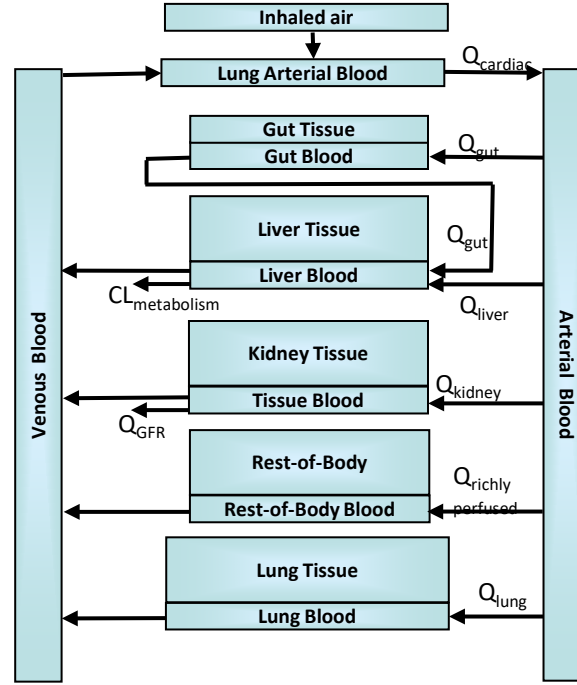
Aerosol Inhalation Exposure Route (including APEX model)
EPA, USAF

Standard httk 2.0.3 PBTK Model

Dermal Exposure Route
EPA, Unilever

Human Gestational Model
EPA, FDA (based on Kapraun et al, 2019)

Fetus

Mother

Evaluating Generic Human Maternofetal Model

In Vivo data collected by Dallmann et al.
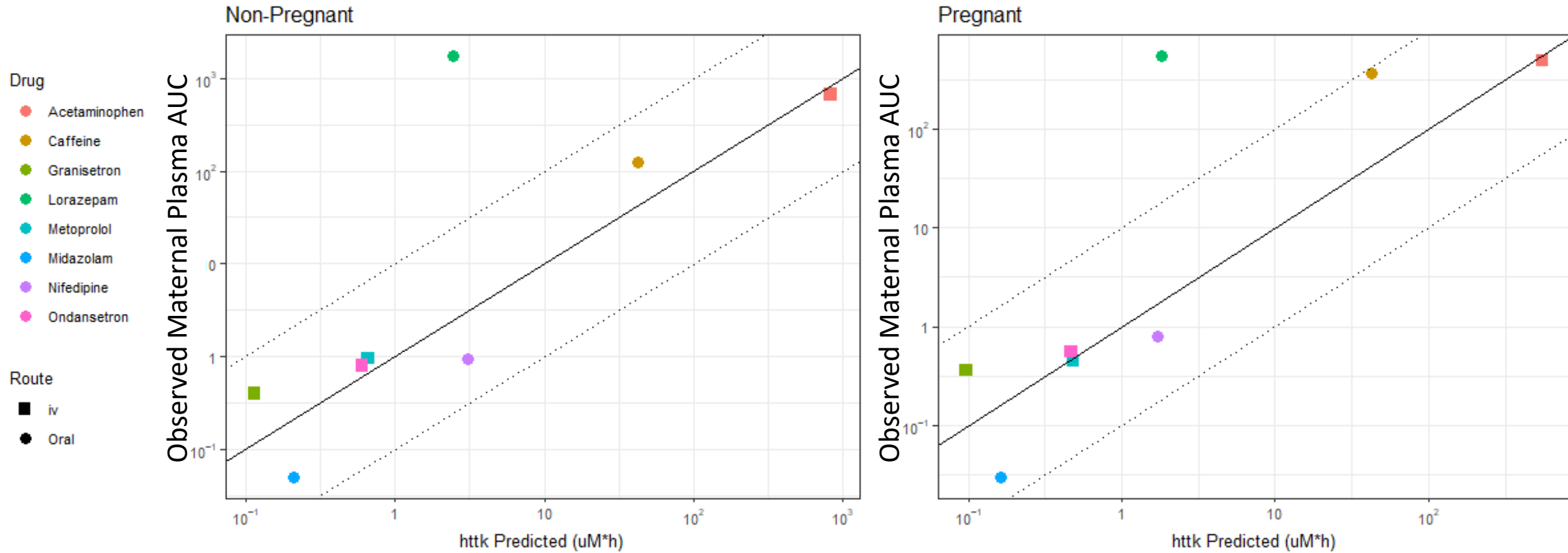
Work led by Dustin Kapraun with Mark Sfeir, Robert Pearce, Annie Lumen, Lesa Aylward, André Dallmann, and Richard Judson

Conclusions

- IVIVE for points of departure requires models of biological pathway, *in vitro* disposition, and toxicokinetics
  - Conservatism depends upon assumptions used

REVIEW

High-throughput PBTK models for *in vitro* to *in vivo* extrapolation

Miyuki Breen[a], Caroline L Ring[a], Anna Kreutz[b], Michael-Rock Goldsmith[a] and John F Wambaugh[a]

- Generic PBTK models evaluated across multi-chemical databases provide a degree of statistical evaluation that is often otherwise unobtainable for non-therapeutic chemicals
  - CvTdb (Sayre et al., 2020) provides key tool for statistical evaluation of TK models
- EPA provides peer reviewed data (>1000 chemicals for human, >200 for rat) and models via the R package "httk"
  - New guidance (papers, R packages) in development for adding new TK data and models to "httk" in an open, transparent format

Office of Research and Development
Center for Computational Toxicology and Exposure

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
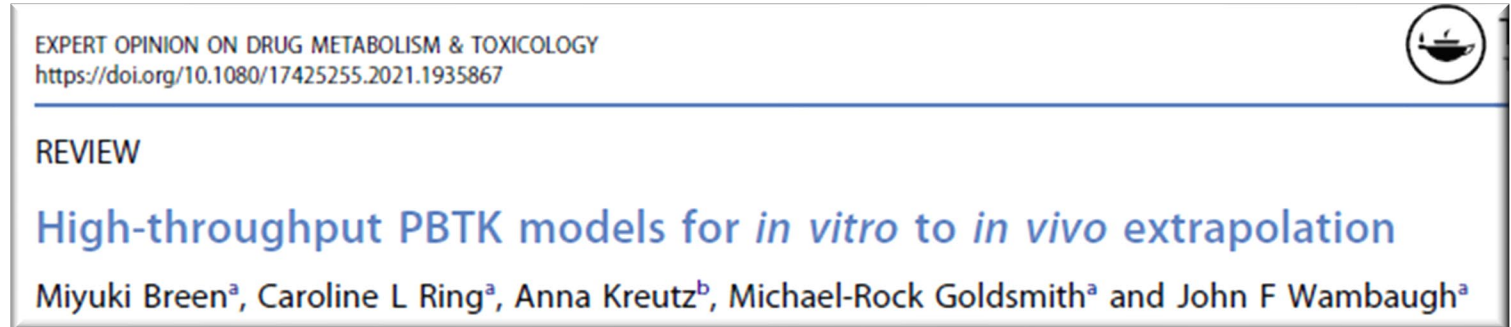
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