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APCRA Case Study:
High Throughput Toxicokinetics for *In Vitro-In Vivo* Extrapolation

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plus, any interested APCRA contributor

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Goals for HTTK Case Study

- We aim to demonstrate that HTTK, with appropriately propagated uncertainty, enhances NAM-based prediction of *in vivo* points of departure to inform regulatory decision making.

- We will describe a framework for decision makers to make use of toxicokinetic (TK) new approach methods that take into consideration chemical space and the decision-making context.

- We will review the quantitative uncertainty in HTTK-based predictions of toxicokinetics.

- Finally, we will perform a gap analysis by identifying, for example, areas of chemical space and routes of exposure in need of further research.

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]

Most chemicals do not have TK Data

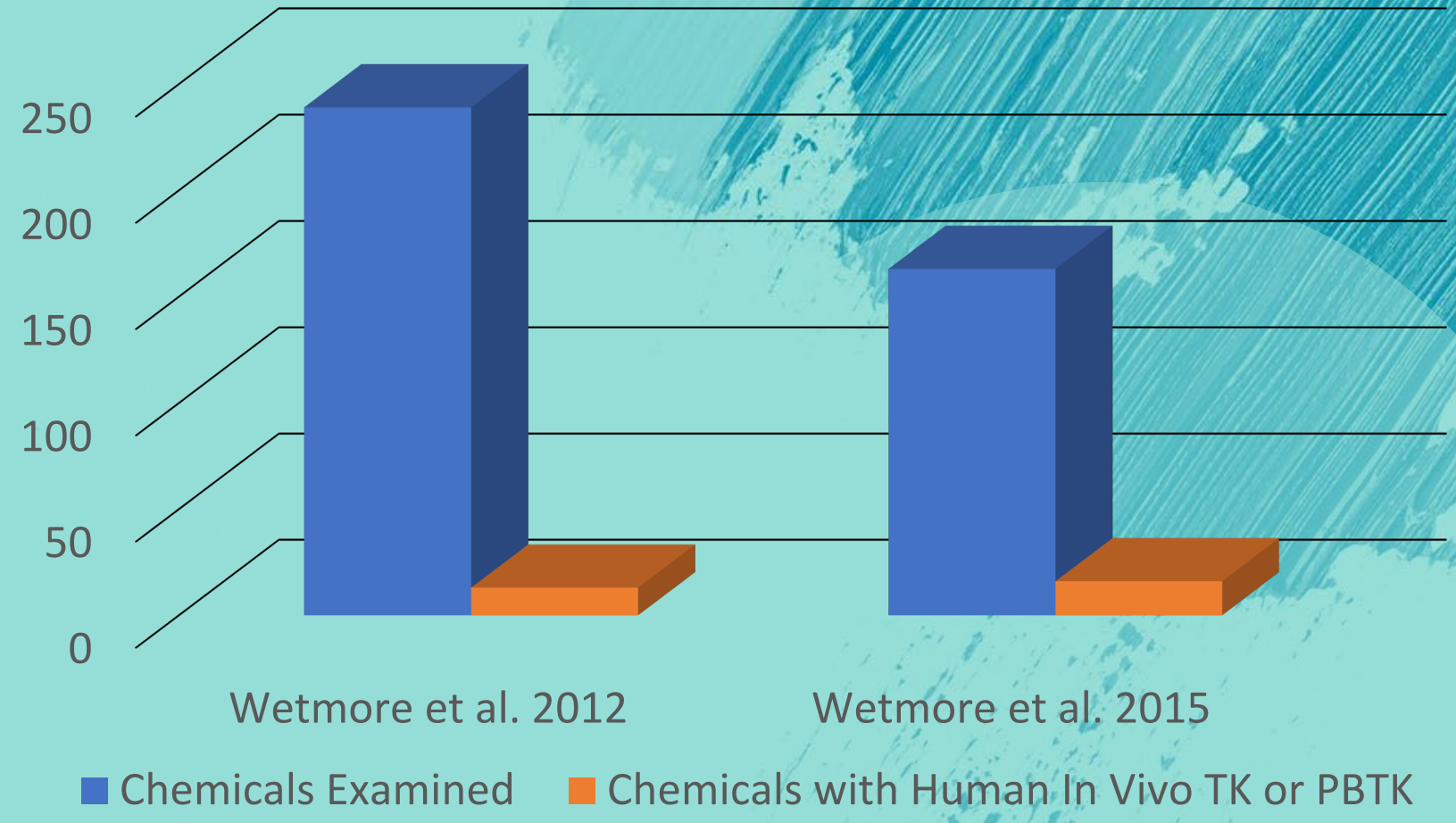

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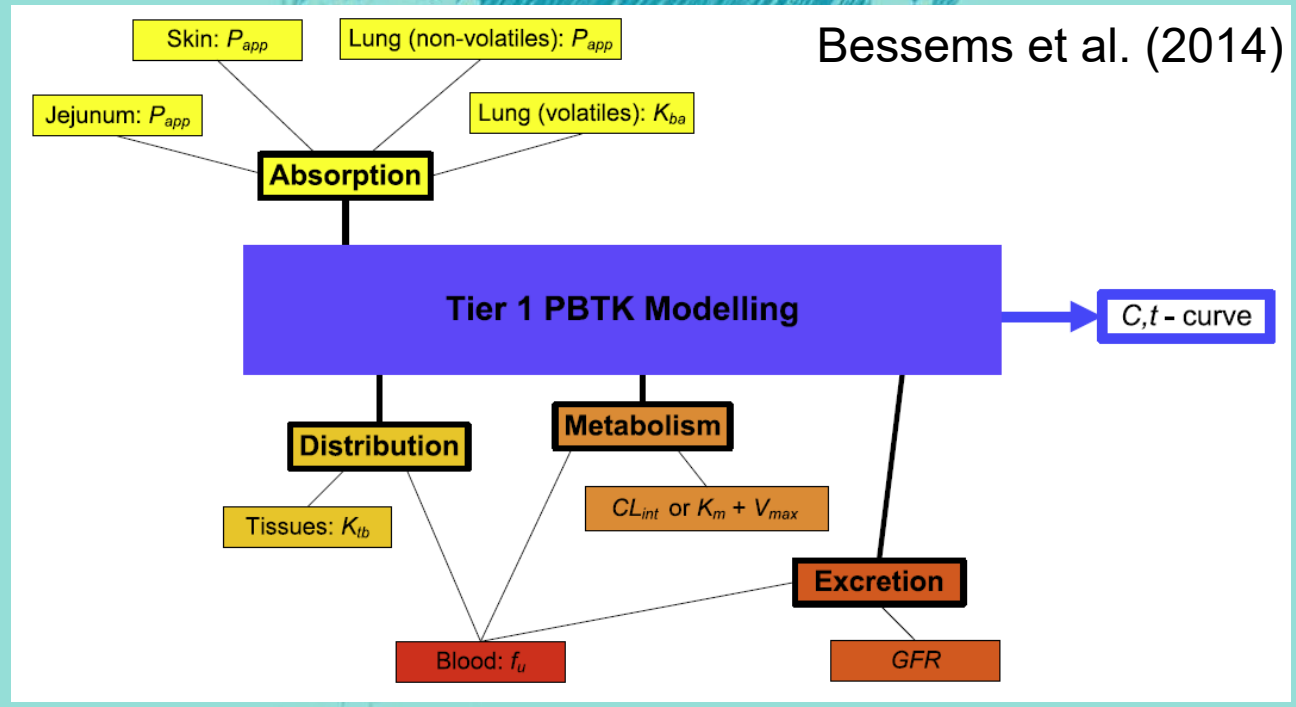
Figure from Bell et al. (2018)

Fit for Purpose Toxicokinetics

- Chiu et al. (2007) "…[P]arsimony in selecting [toxicokinetic] model structures is an important and guiding principle in developing models for use in risk assessments."
  - **Complexity is constrained by limited data** available to calibrate and test the model and the need to justify both the model assumptions and predictions
- Bessems et al. (2014): **We need "a first, relatively quick ('Tier 1'), estimate" of concentration vs. time in blood, plasma, or cell**
  - At the time they suggested that we might neglect active metabolism. Thanks to *in vitro* measurements we can now do better
  - We still neglect transport and other protein-specific phenomena



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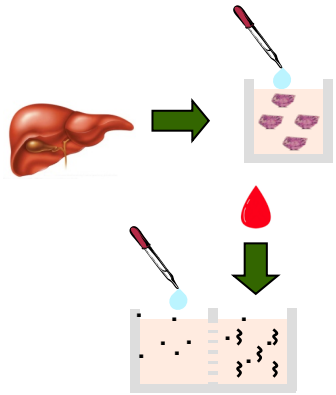
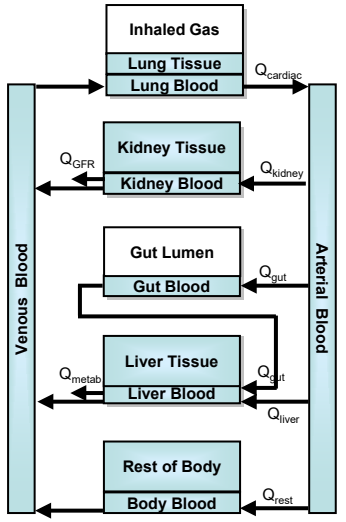
High Throughput Toxicokinetics (HTTK)

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



Intrinsic Hepatic Clearance

Plasma Protein Binding



= *httk*

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Generic PBTK Models

Table 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

A Generic Model is a Hypothesis

- **For pharmaceuticals**, *in vitro* data plus 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

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Decision Trees

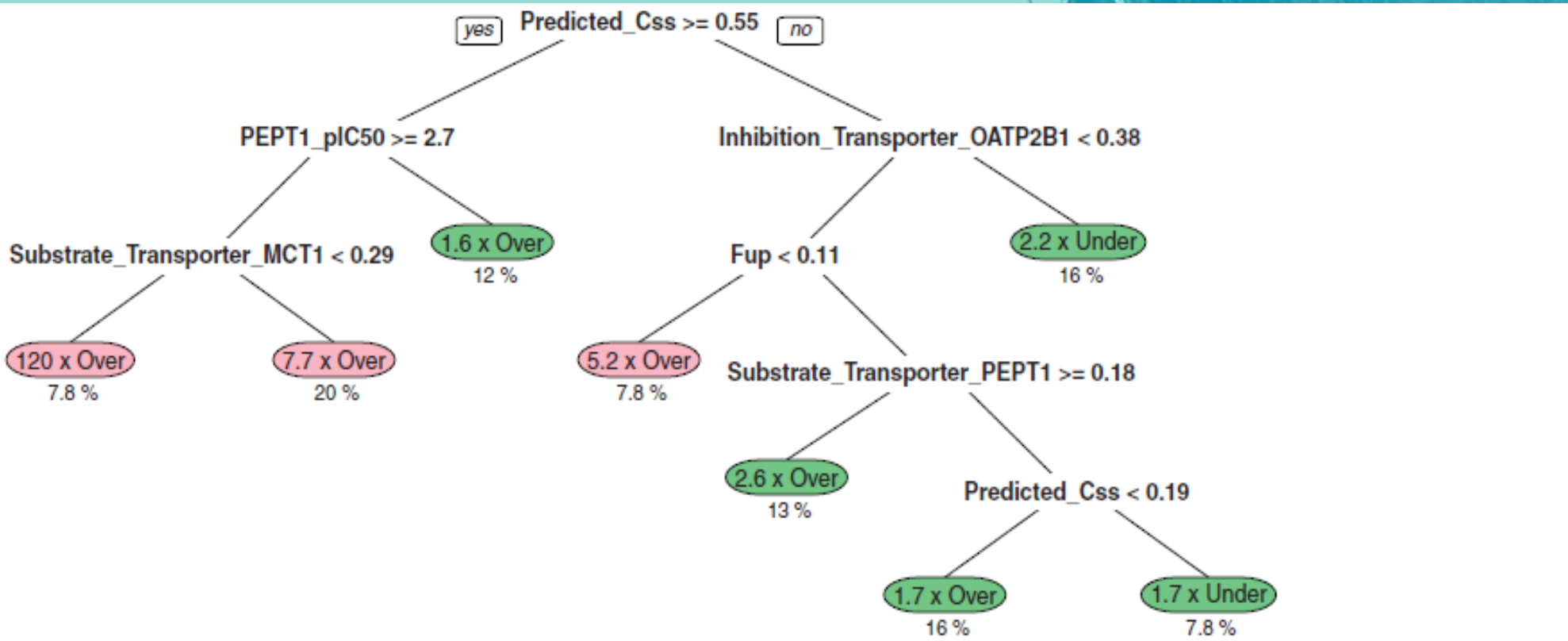

FIG. 5. A recursive partitioning regression tree was used to classify the discrepancy between the C_{ss} predicted from *in vitro* data and the *in vivo* C_{ss} (Obach *et al.*, 2008; Wetmore *et al.*, 2012). Each "leaf" of the tree shows a group of chemicals for which HTTK either overestimates C_{ss} (making conservative predictions) or underestimates C_{ss}. For all but 3 groups, the predictions are on the order of the observed C_{ss} (approximately within a factor of 3.2× greater or lesser). For the other 3 groups, the C_{ss} is 5.2×, 7.7×, and 120× overestimated.

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Figure from Wambaugh et al. (2015)

Decision Trees

We are constructing a decision tree/tiered framework that is two dimensional: Decision context vs. chemical space

- We need to ensure that evaluators can understand and use this information.
- How are you going to use the data? For example, when do you identify the metabolites from the *in vitro* data?
- How do we decide when it is good enough?
- Can we look from exposure side with these decision trees?
- When using a bioactivity:exposure ratio (BER) or margin of exposure approach it would be helpful to have a library of urinary excretion
- There is chemical specific uncertainty in interpreting urine biomonitoring data, can HTTK help?

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Decision Trees

Different levels of certainty needed for prioritization, risk evaluation, susceptible populations

- What is conservative depends on the application (for example, 100% absorption)
- What is the uncertainty associated with chemistry and decision?
- Since *in vitro* experiments are surrogates for reality, do you really get a reduction of uncertainty if you perform a specific measurement?
- Certain chemicals are suitable, others may not be appropriate:
  - For example, what do we do when highly bioaccumulative?
    - If you predict the days to reach steady state to be longer than the exposure period you are trying to model, then steady state is a poor assumption.

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HTTK Measurements

We will develop a table of what we can measure/model

Start with Coecke et al. (2013)?

For each measurement technology describe:

1) decision context
2) applicable chemistry
3) scientific motivation
4) impact on models
5) whether quantitative structure-property relationship (QSPR) models exist and when they are appropriate

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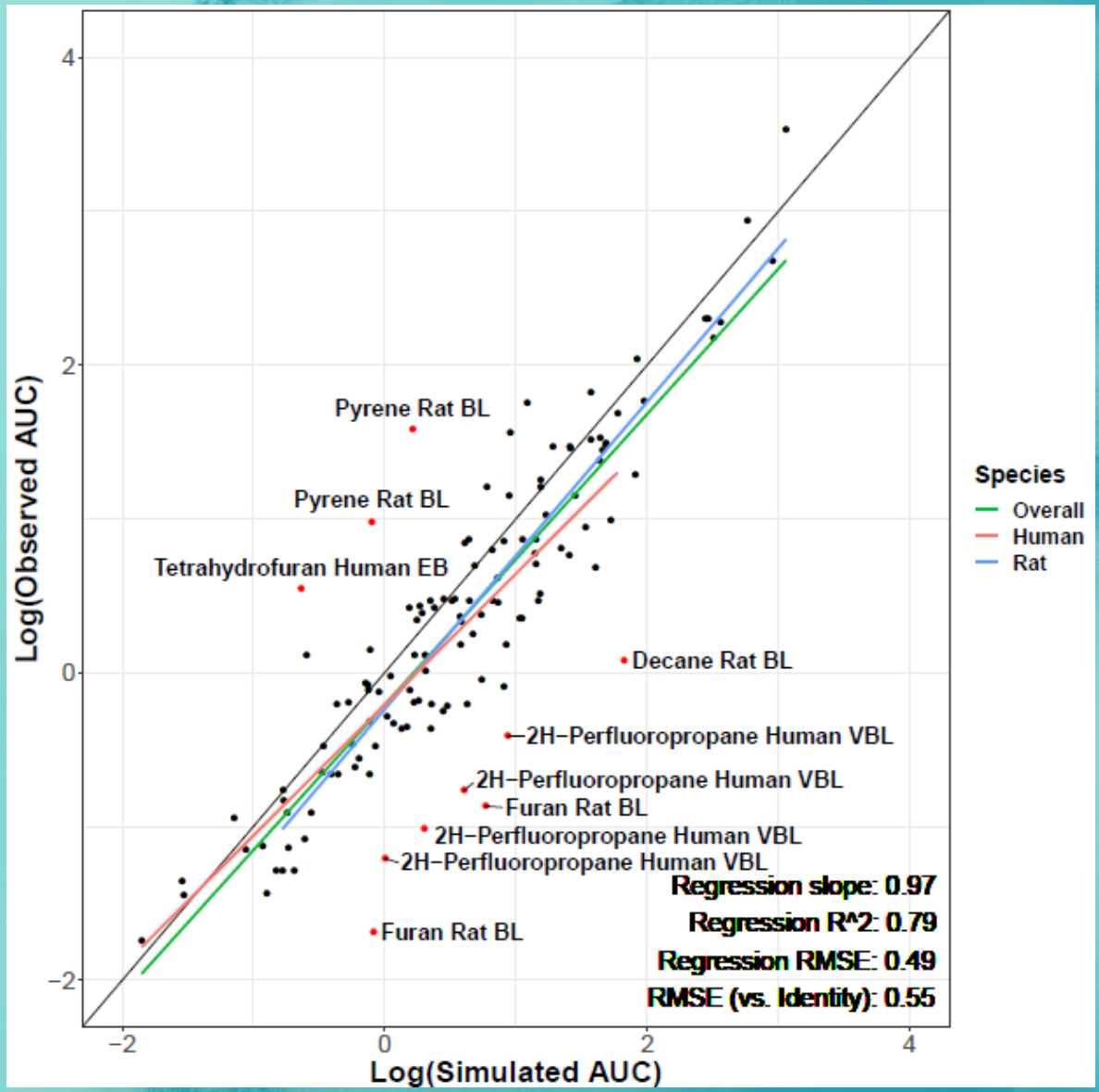
Table 1
Main Alternative Methods Available (adapted from Adler et al. (2011); Supplementary Information).

	Test name		Advantages	Limitations
Absorption	QSAR	*In silico*	• Applicable for dermal and oral exposure • Able to predict overall absorption of a chemical based on available physicochemical parameters • OECD principles for the validation of QSARs for regulatory purposes	• Not available for lung absorption • Active metabolism and transport not yet included
	Artificial intestinal membranes	*In vitro*	• Used for very early screening	• Information only on passive diffusion • Underestimation of the permeability of highly lipophilic drugs
	Skin Preparations	*In vitro* & Ex vivo	• Mainly composed of human source or slaughter sources of animals resembling human (e.g.: pig)	• In Skin preparations, the value of absorption under finite dose is specific for the specific exposure time, concentration and skin load making it difficult as input parameter for PBPK-models
	Cell Cultures	*In vitro*	• Standard procedures that can be incorporated in a medium-throughput test strategy • Allow the study of both absorption and metabolism	• Limited/unspecified correspondence to *in vivo* metabolic and active transport systems
	Ussing chamber & Everted sac	Ex vivo	• Possible to use human sources • Fast and reproducible study of intestinal absorption of molecules across the inserted tissue • Allows the study of both absorption and metabolism	• The bioavailability depends on intestinal section • Limitation on the availability of the test material
Distribution	QSAR / Computerized models	*In silico*	• Methods still under development, but improving	• Predictions not reproducible among different studies • Poor results obtained for charged molecules under physiological conditions and with charged phospholipids
	Ex-vivo methods (Equilibrium dialysis; Ultrafiltration Ultracentrifugation; Vial-equilibration)	*Ex vivo*	• Automation possible for high-throughput • Easy to perform; good precision and reproducibility • Results very close to the ones obtained *in vivo* regarding plasma protein binding	• Routine for plasma protein binding, applications for other tissues/organs under development
	2D and 3D Mixed Cultures	*In vitro*	• Importance of barrier integrity and correlation with *in vivo* permeability (Pe) and transendothelial electrical resistance recognized	• *In vitro* systems still not adequately characterized for reliable predictions
	Human perfused placenta cotyledon	*Ex vivo*	• Minimum number of ethical problems • Up to 48 h perfusions possible	• The term *placenta* may not reflect the placenta during the first months of foetal development
Metabolization	Expert systemsQSARPharmacophore or molecularprotein modelling	*In silico*	• Useful for indicating potential routes and metabolites (but usually overprediction!) • Predictive capability heavily dependent on selected parameters and model compounds	• Developed mostly for pharmaceuticals (drug development tools) • Quantitative predictions still not reliable enough
	2D and 3D Cell Cultures	*In vitro*	• Studies on metabolic stability, metabolic clearance, metabolite formation; metabolic activation; induction of metabolism and inhibitory interactions with probe substrates • High-troughput screening and cocktail methods established • With suitable analytical techniques, covers also elucidation of primary metabolite profile	• Not fully representative of the *in vivo* specific activities • Correlations between activation and toxic outcomes not well established • Limitation on the availability of primary human cells • Missing methods measuring cellular transport/efflux and bioavailability/nominal concentration
Excretion	Computerized models	*In silico*	• only 4 physico-chemical parameters (charge, molecular weight, lipophilicity, and protein unbound fraction in plasma) are required to predict major excretion pathways	• Still under development • Not standardized • No formal validation studies are known
	Collagen-sandwich cultures of hepatocytes	*In vitro*	• Useful *in vitro* method to differentiate between hepatic sinusoidal and canalicular disposition of conjugates	• Not standardized • No formal validation studies are known

Quantifying Uncertainty in HTTK

- U.S. Air Force and U.S. EPA developed generic gas inhalation physiologically-based toxicokinetic (PBTK) model
- Evaluated HTTK with CvTdb (Sayre et al., 2020): 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)

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Review of HTTK Evaluations

- 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)**

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Breen et al. (2020)

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

Pharm Res (2019) 36: 113
https://doi.org/10.1007/s11095-019-2645-0

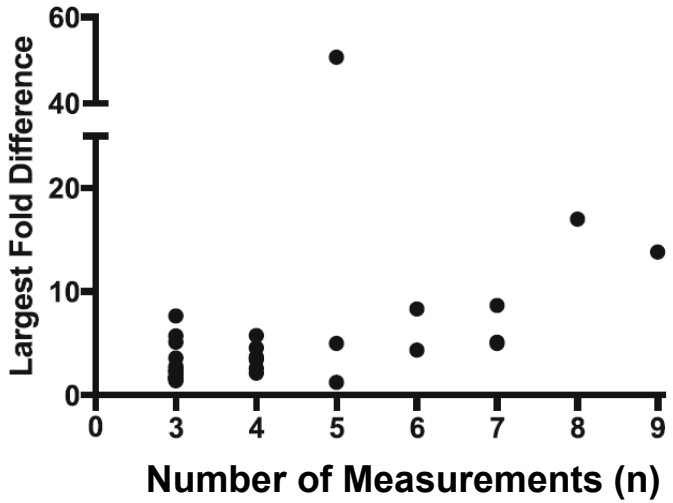
Check for updates

RESEARCH PAPER

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

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

Received: 7 March 2019 / Accepted: 10 May 2019 / Published online: 31 May 2019



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	-	-

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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)

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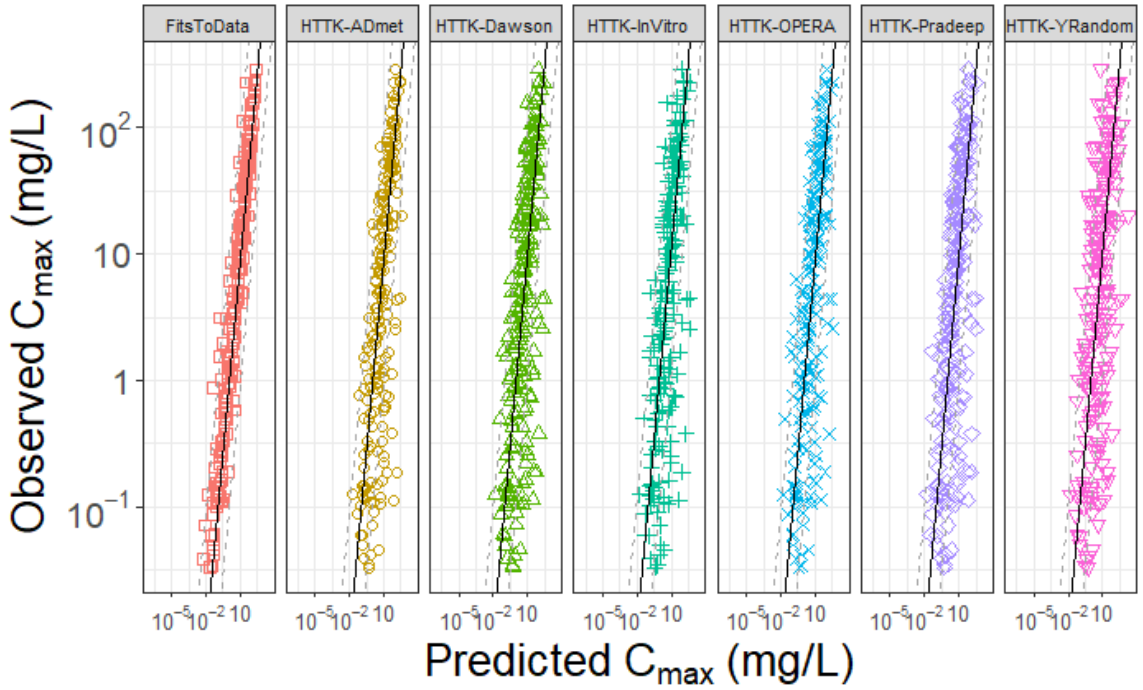
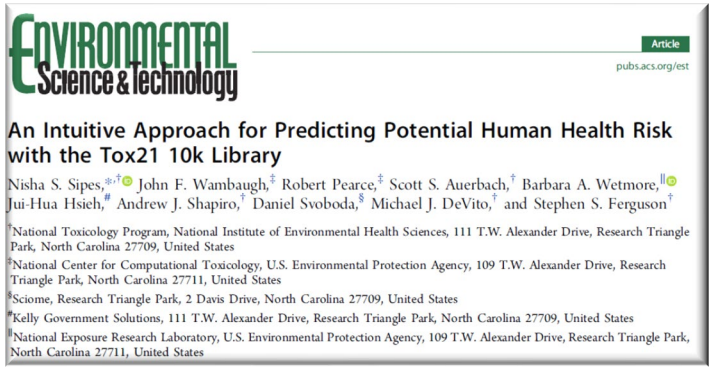
QSPRs for HTTK Parameters

- We may not always need to measure
- Ongoing evaluation of QSPRs for predicting HTTK
  - Presented at QSAR2021 virtual meeting / Manuscript in preparation
- Interpretable machine learning
  - Perhaps we can reduce a machine learning model to a diagram that fits on an index card




Environmental Science & Technology

Article

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An Intuitive Approach for Predicting Potential Human Health Risk with the Tox21 10k Library

Nisha S. Sipes, John F. Wambaugh, Robert Pearce, Scott S. Auerbach, Barbara A. Wetmore, Jui-Hua Hsieh, Andrew J. Shapiro, Daniel Svoboda, Michael J. DeVito, and Stephen S. Ferguson

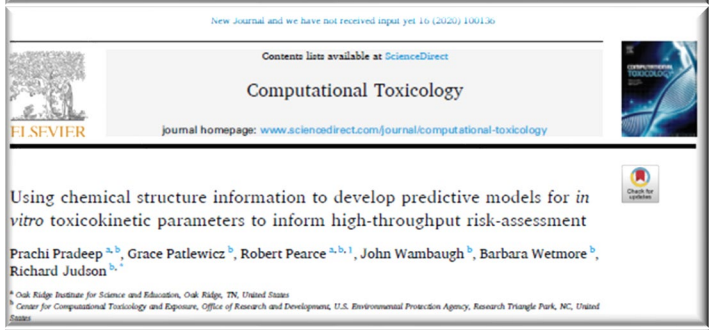

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Development of human biotransformation QSARs and application for PBT assessment refinement

Ester Papa, Alessandro Sangion, Jon A. Arnot, Paola Gramatica


Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.sciencedirect.com/journal/computational-toxicology

Using chemical structure information to develop predictive models for *in vitro* toxicokinetic parameters to inform high-throughput risk-assessment

Prachi Pradeep, Grace Patlewicz, Robert Pearce, John Wambaugh, Barbara Wetmore, Richard Judson


Environmental Science & Technology

pubs.acs.org/est

Article

Designing QSARs for Parameters of High-Throughput Toxicokinetic Models Using Open-Source Descriptors

Daniel E. Dawson, Brandall L. Ingle, Katherine A. Phillips, John W. Nichols, John F. Wambaugh, and Rogelio Tornero-Velez

Cite This: https://doi.org/10.1021/acs.est.0c06117

Read Online

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Case Study Outcome

The decision tree will serve as a "Cheat-sheet" for regulators:

- Why/when to use HTTK?
- What information is available and where?
- How to judge input & output quality?
- What is associated uncertainty?

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HTTK Case Study Path Forward

- Manuscript is not yet complete – skeleton draft just circulated (October 2021)
- Targeting 2022 submission to Environment International

We need:

1) A table of the types of *in vitro* measurements that are currently available and the uncertainties they address
2) A series of decision trees based upon chemical and context
3) A series of case studies/examples walking through the data

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HTTK Case Study Needs

- Contributions of the partners will include:
  - Development of and comment on decision trees
    - Help assess what factors are important depending on chemical, application, regulator, etc.?

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HTTK Case Study Needs

- Partners can also help inform examples (what we will call “case studies” in the manuscript)
  - **Generic vs. Bespoke Model Case Study**
  - **Data Rich Chemical Case Study**
  - **Chemical Class Case Study**
  - **Biomonitoring Case Study**

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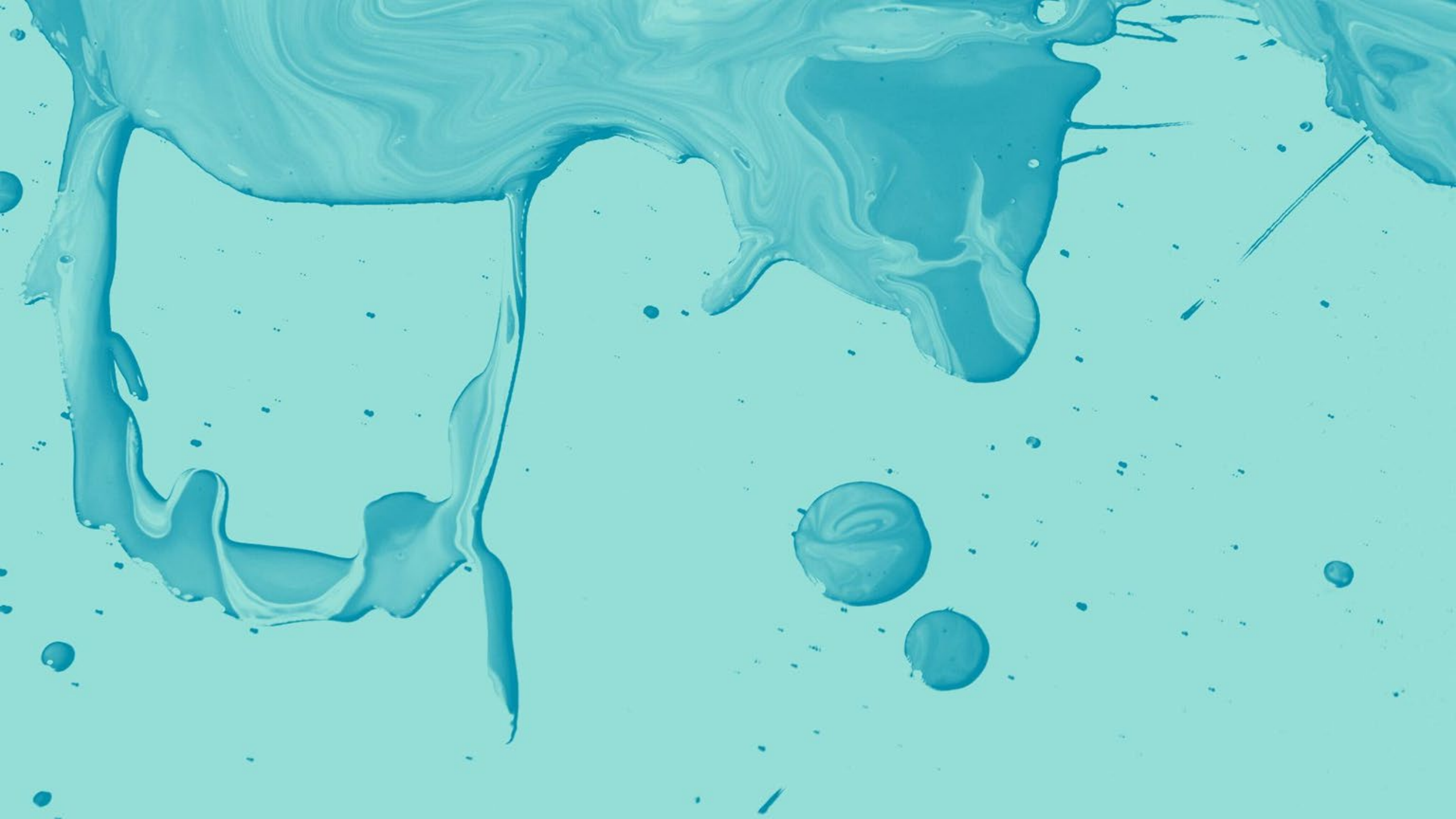

Toxicology in Vitro 27 (2013) 1570–1577

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]

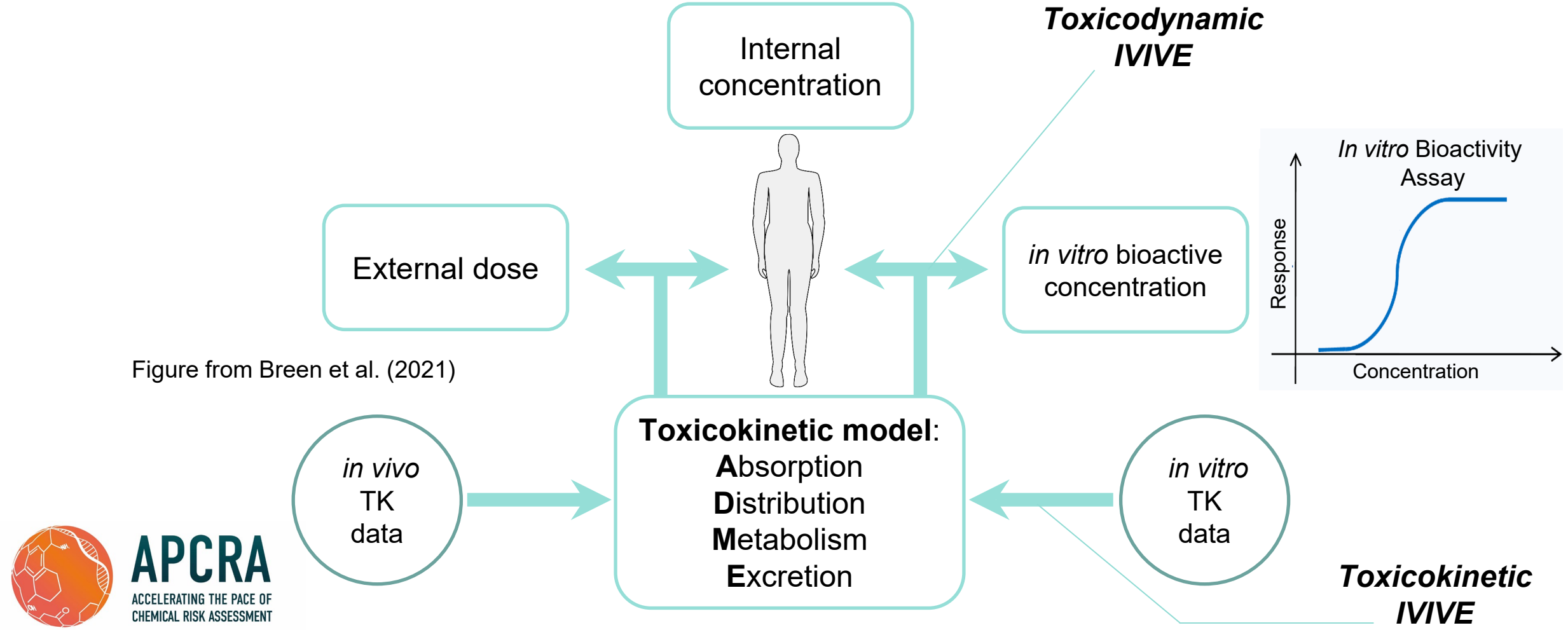

Figure from Breen et al. (2021)

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HTTK Measurements Overview

We will develop a table of what we can measure/model:

- For each measurement technology (for example, intrinsic clearance, plasma protein binding) we will describe 1) decision context, 2) applicable chemistry, 3) scientific motivation, 4) impact on models, and 5) whether quantitative structure-property relationship (QSPR) models exist and when they are appropriate
    - We will focus on the needed certainty in a measurement.
    - Do you really get a reduction of uncertainty if you measure X?
    - We will make clear the time and labor for both traditional and new approach measurements.

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Review of HTTK Evaluations

- Armitage et al. (2021) found that the performance of generic PBTK models in “data poor” situations was both “acceptable in qualitative (that is, shape of concentration versus time (CvT) profiles) and quantitative terms for most of the selected chemicals.”

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

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Breen et al. (2020)

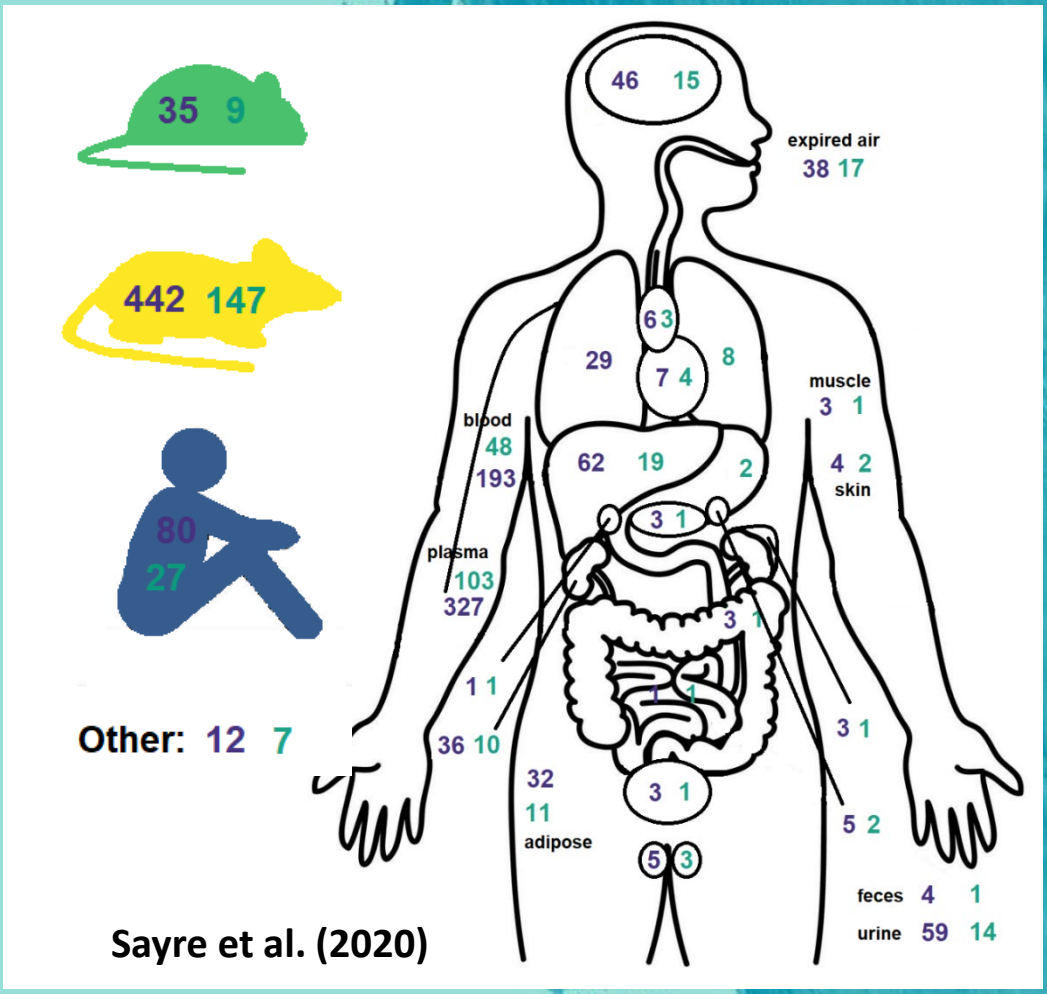
Quantifying Uncertainty in HTTK

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

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

- Curation and development is ongoing, but to date includes:
  - 198 analytes (EPA, National Toxicology Program, 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

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