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PBPK and Toxicokinetic Modeling

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OpenTox 2022
PBPK and Toxicokinetics Modeling (Part 1)
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Office of Research and Development
Center for Computational Toxicology and Exposure

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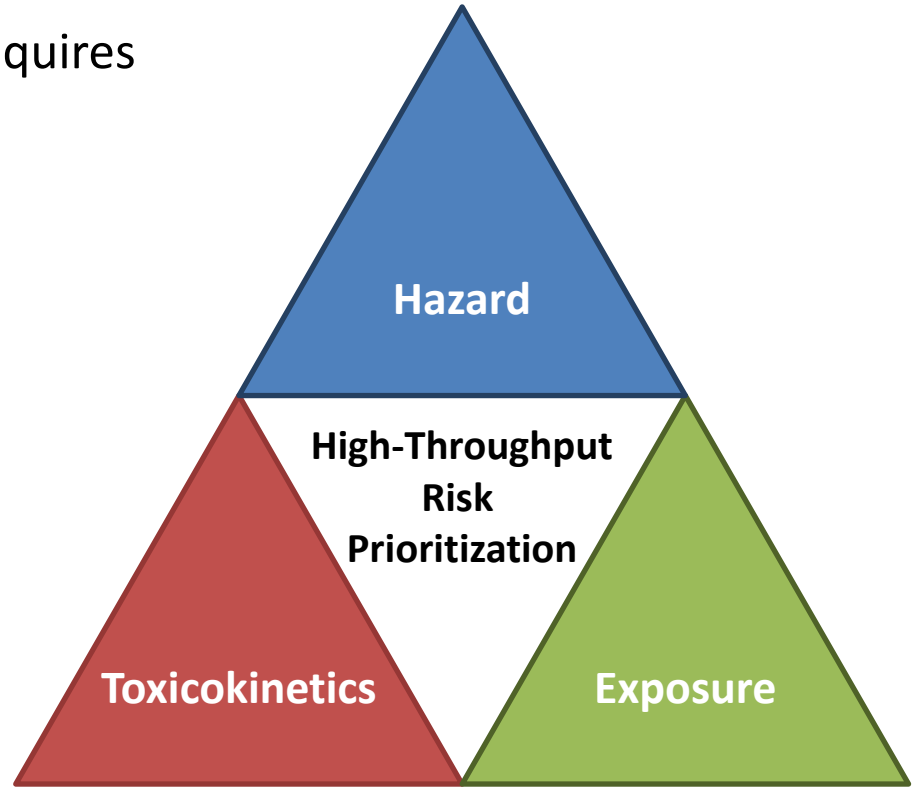
Overview

- Generic vs. bespoke PBTK models
- High Throughput Toxicokinetics (HTTK)
- Model parameterization
  - Physiologic parameters
  - Chemical-specific parameters
- Model evaluation

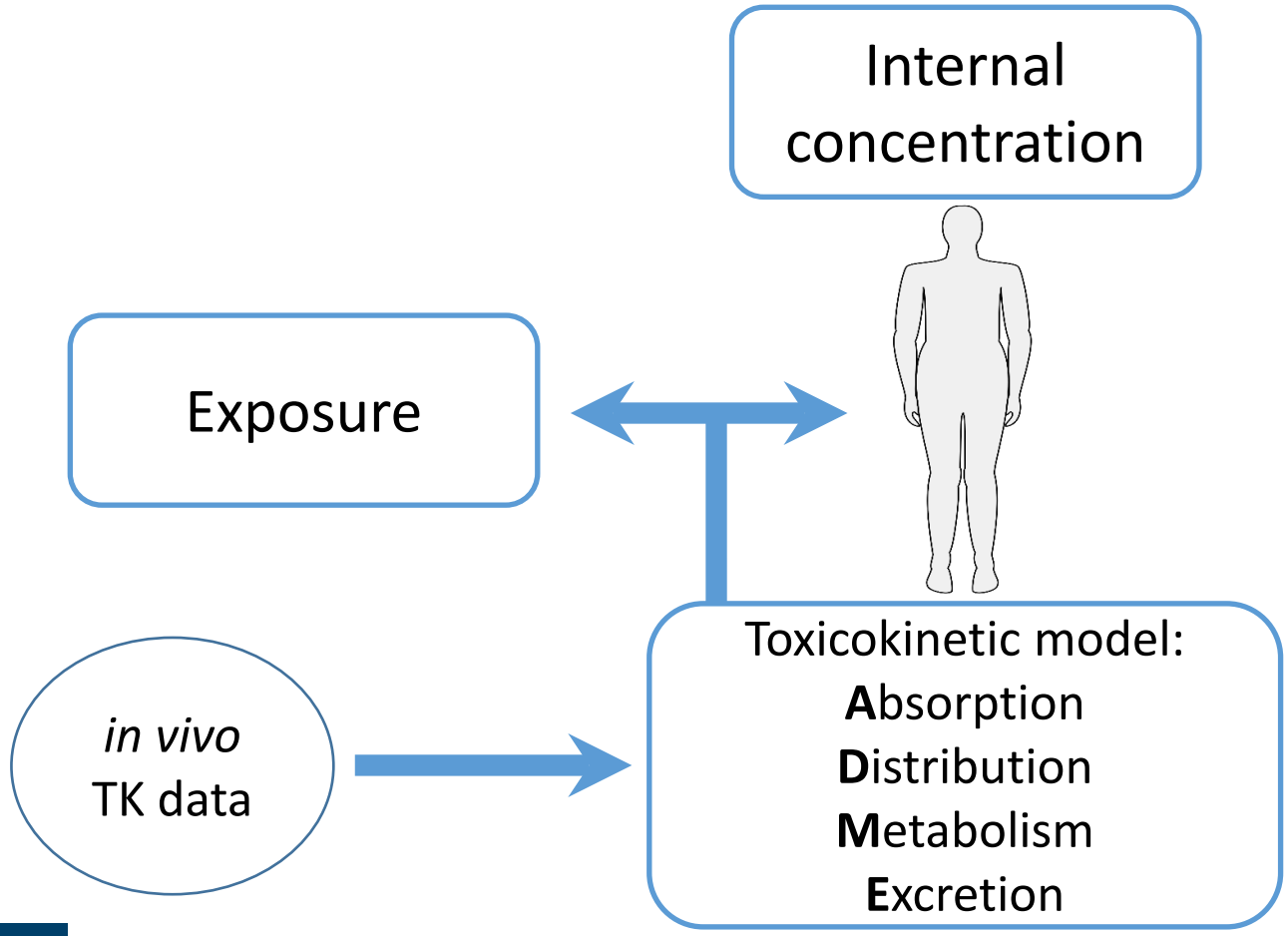
Estimating Chemical Risk

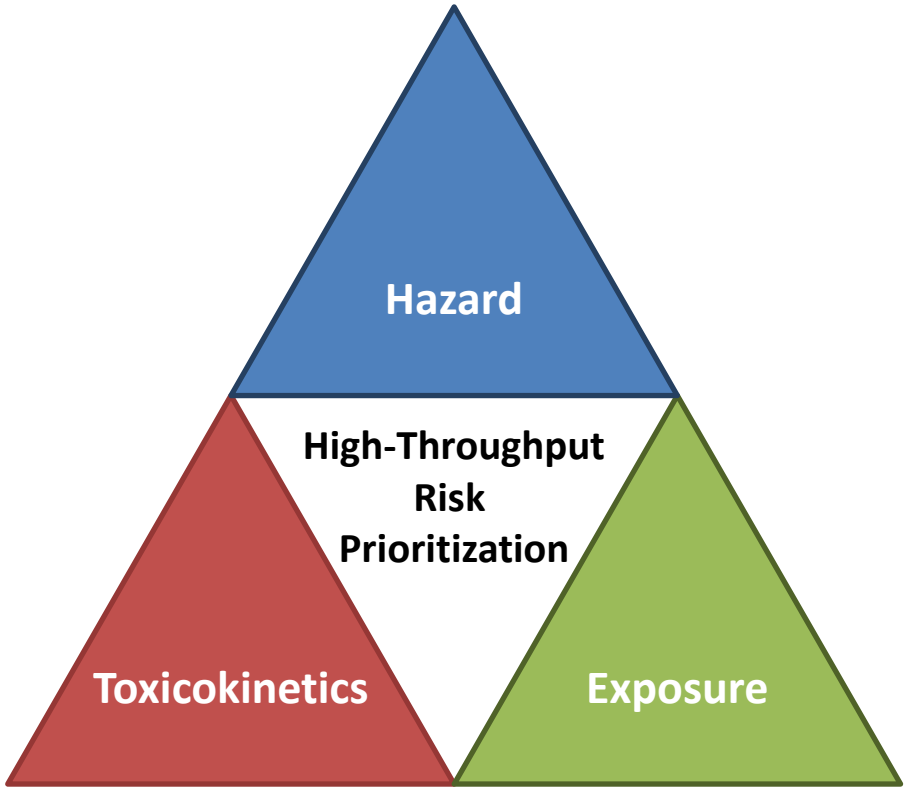
- NRC (1983): Risk is a function of inherent chemical hazard, extent of exposure, and the dose-response relationship (including toxicokinetics)
- High throughput risk prioritization based upon *in vitro* screening requires comparison to exposure
- Data obtained *in vitro* must be placed in an *in vivo* context: *in vitro-in vivo* extrapolation (IVIVE)
- Information must be relevant to the scenario, for example, consumer, ambient, or occupational exposure.



Toxicokinetics

- Toxicokinetics describes the absorption, distribution, metabolism, and excretion of a chemical by the body:
  - Chemical-specific
  - Links exposure with internal concentrations

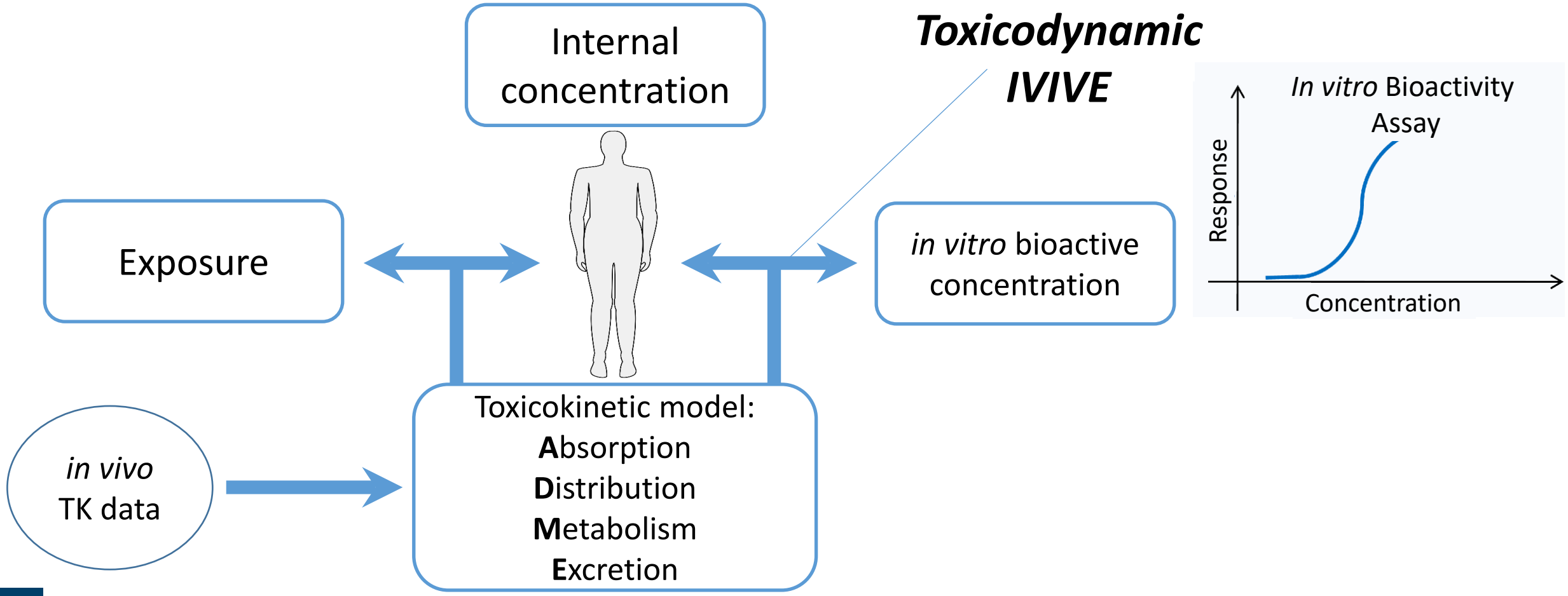




Breen *et al.* (2021)

In Vitro-In Vivo Extrapolation (IVIVE)

- Translation of *in vitro* high throughput screening requires chemical-specific toxicokinetic models for anywhere from dozens to thousands of chemicals



Breen *et al.* (2021)

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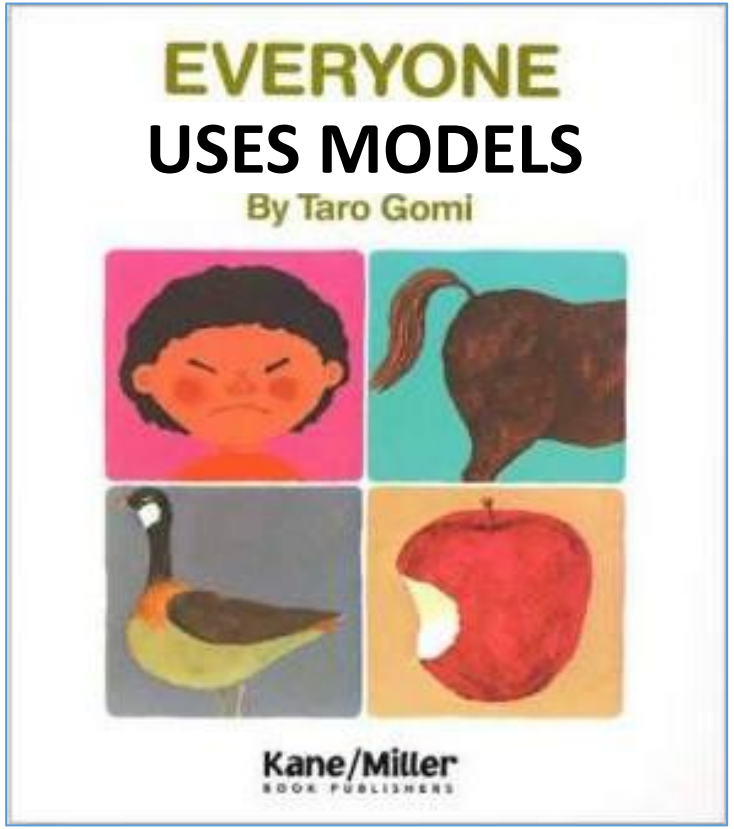
Generic vs. bespoke PBTK models

Everyone Uses Models

- Toxicology has long relied upon model animal species
- People rely on mental models every day
  - For example, with repetitive activities like driving home from work
- Mathematical models offer some significant advantages:
  - Reproducible
  - Can (and should) be transparent
- …with some disadvantages:
  - Sometimes reality is complex
  - Sometimes the model doesn't always work well
  - How do we know we can extrapolate?
- …that can be turned into advantages:
  - If we have evaluated confidence/uncertainty and know the "domain of applicability" we can make better use of mathematical models



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Fit for Purpose Models

- A “fit for purpose” model is an abstraction of a complicated problem that allows us to reach a decision.

  “Now it would be very remarkable if any system existing in the real world could be *exactly* represented by any simple model. However, cunningly chosen parsimonious models often do provide remarkably useful approximations… **The only question of interest is ‘Is the model illuminating and useful?’**”
  George Box

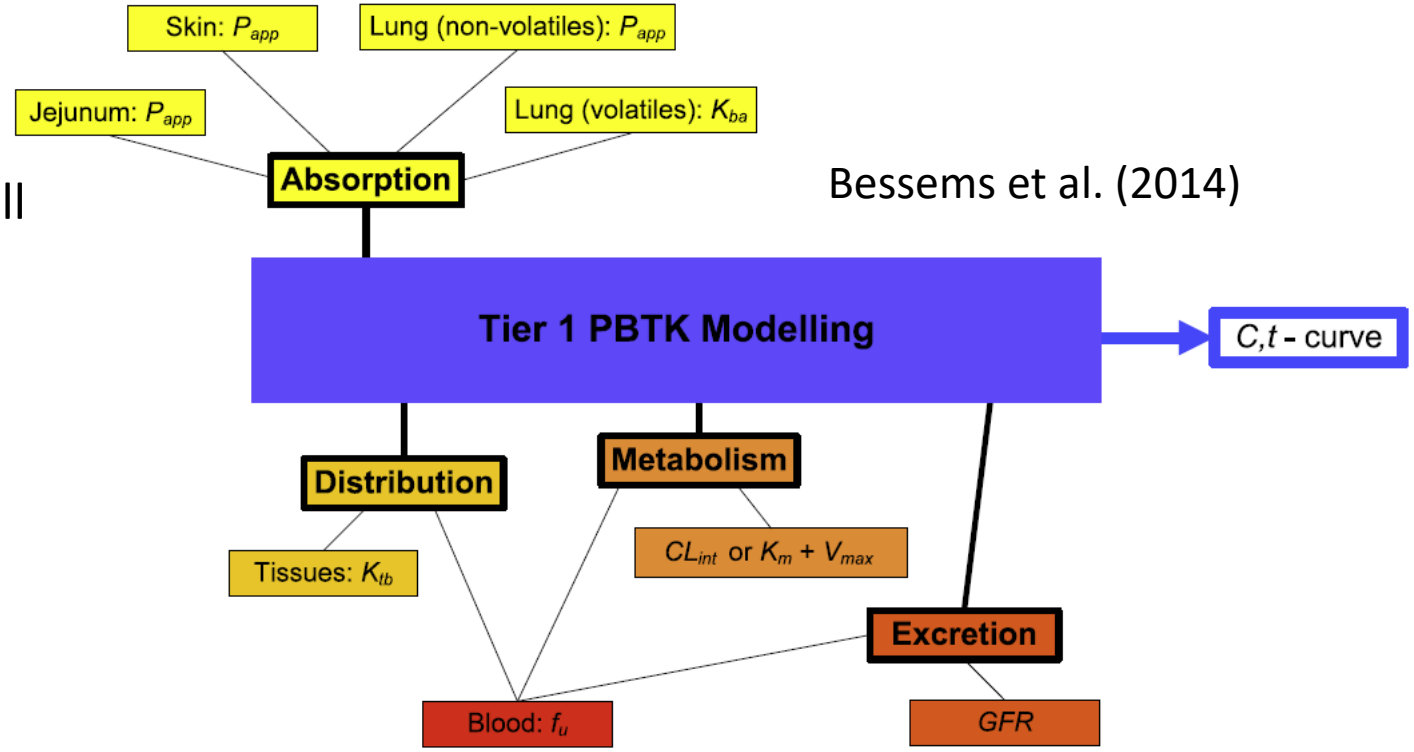
- A fit for purpose model is defined as much by what is omitted as what is included in the model.

- We must accept that there will always be areas in need of better data and models – our knowledge will always be incomplete, and thus we wish to extrapolate.

  - How do I drive to a place I’ve never been before?

Fit for Purpose Toxicokinetics

- Chiu et al. (2007) "…[P]arsimony in selecting 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
  - They suggested that we neglect active metabolism. But thanks to *in vitro* measurements we can now do better
  - We still neglect transport and other protein-specific phenomena



Bessems et al. (2014)

Bespoke vs. Generic

Bespoke, Tailored, Custom…
Requires specific measurements

Generic, Off-the-Shelf/Rack, One-Size-Fits-Most
Approximately fits certain categories

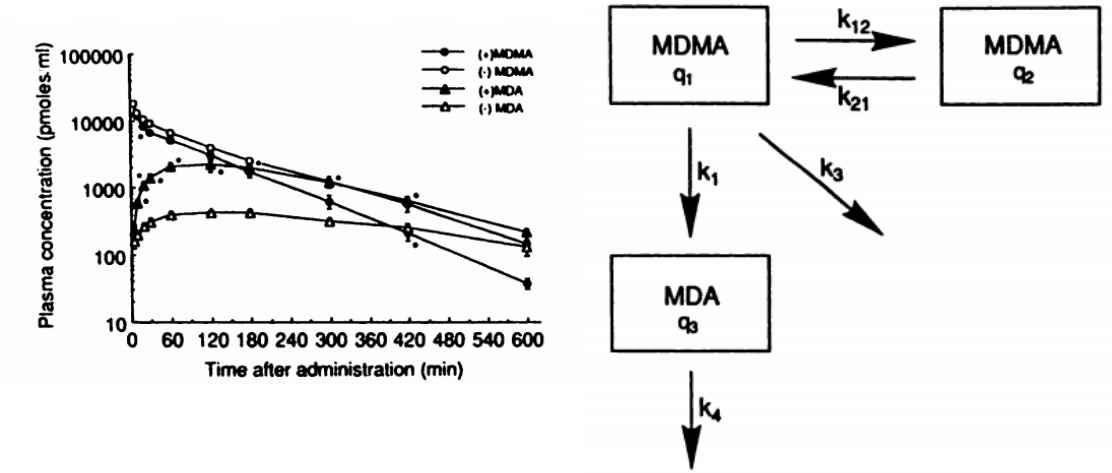
Bespoke Models

- Toxicokinetic (and pharmacokinetic) models are traditionally developed using *in vivo* data
  - These data could be from clinical trials (increasing the relevance but limiting the measurements) or possibly animal studies (allowing tissues to be sampled)
  - Potentially resource-intensive

- Physiologically-based toxicokinetic (PBTK) models allow extrapolation between species and routes of administration
  - Physiological information augments chemical-specific data

- Can choose to make the complexity of the model and the number of physiological processes appropriate given the data and the decision context
  - This is how we "tailor" the model

Cho et al., 1990
PK of MDMA



Jones et al., 2012
PK of Statins

In this case they had transporter-specific data

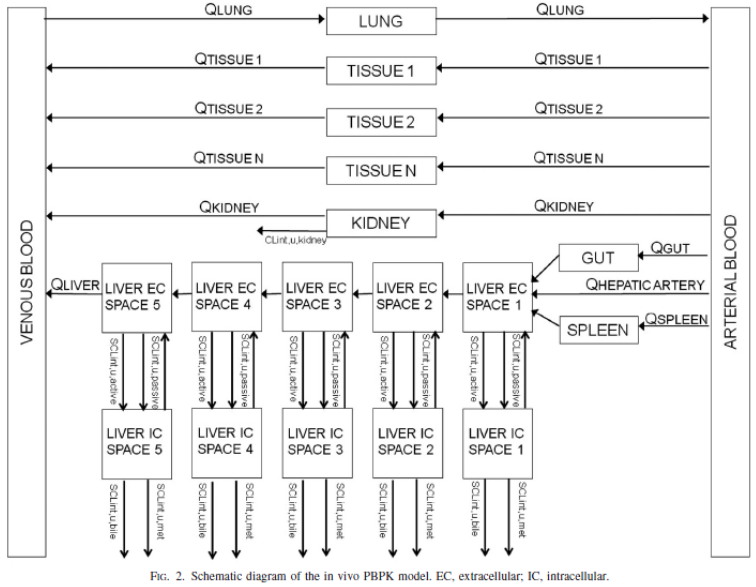
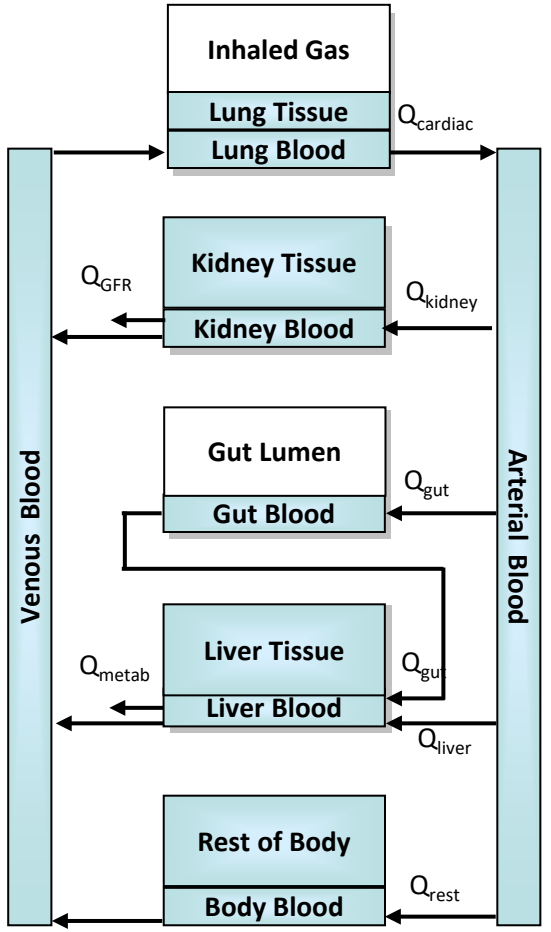


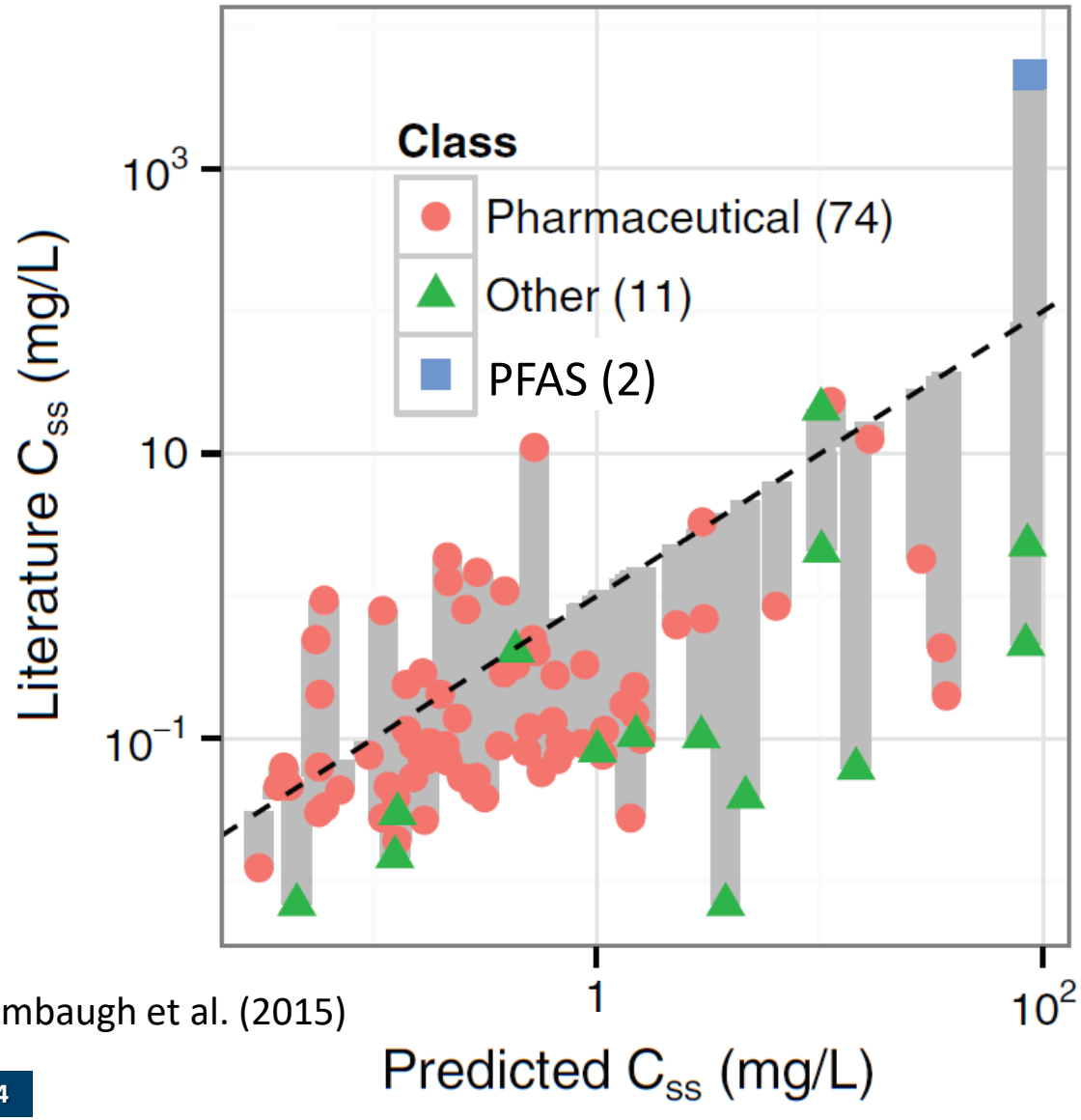
FIG. 2. Schematic diagram of the in vivo PBPK model. EC, extracellular; IC, intracellular.

Generic Models

- A standardized physiology is assumed, regardless of chemical:
  - The same parameters such as volumes, flows, and rates are used
  - The same processes are included (hepatic metabolism, glomerular filtration) or omitted
- A fixed set of descriptors (such as rate of metabolism and protein binding) are varied from chemical to chemical and potentially measured in vitro
- The generic model is implemented once, reducing the likelihood of coding errors and enhancing documentation
- We can estimate the accuracy of a generic model for a new chemical using performance across multiple chemicals where data happen to exist
- The generic model is a hypothesis
  - If we have evaluation data then we can check if we need to elaborate the model (for example, create a bespoke model)



Generic Models as a Hypothesis

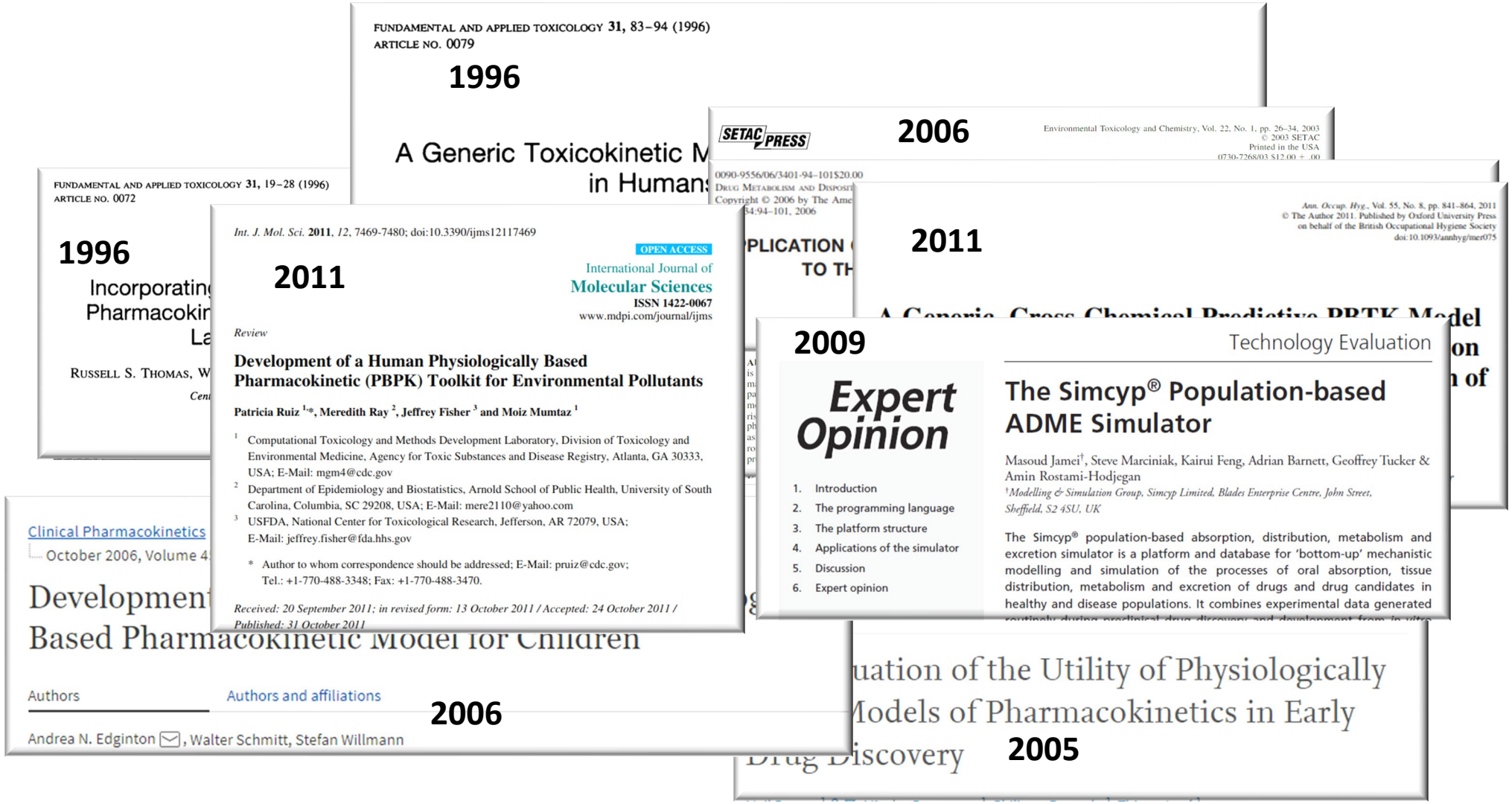


Wambaugh et al. (2015)

- For pharmaceuticals, *in vitro* data plus a 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, for example, there is thought to be (Andersen et al. 2006) active transport of some per- and poly-fluorinated alkyl substances (PFAS) in the kidney
- We could add a renal resorption process (that is, modify the generic model) only if there was some way to parameterize the process for most chemicals – otherwise we are back to tailoring the model to a chemical

Generic PBTK Models

The idea of generic PBTK has been out there for a while…



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High Throughput Toxicokinetics

Most Chemicals Lack Toxicokinetic Data

- Most non-pharmaceutical chemicals – for example, flame retardants, plasticizers, pesticides, solvents – do not have human *in vivo* TK data.
- Non-pesticidal chemicals are unlikely to have any *in vivo* TK data, even from animals

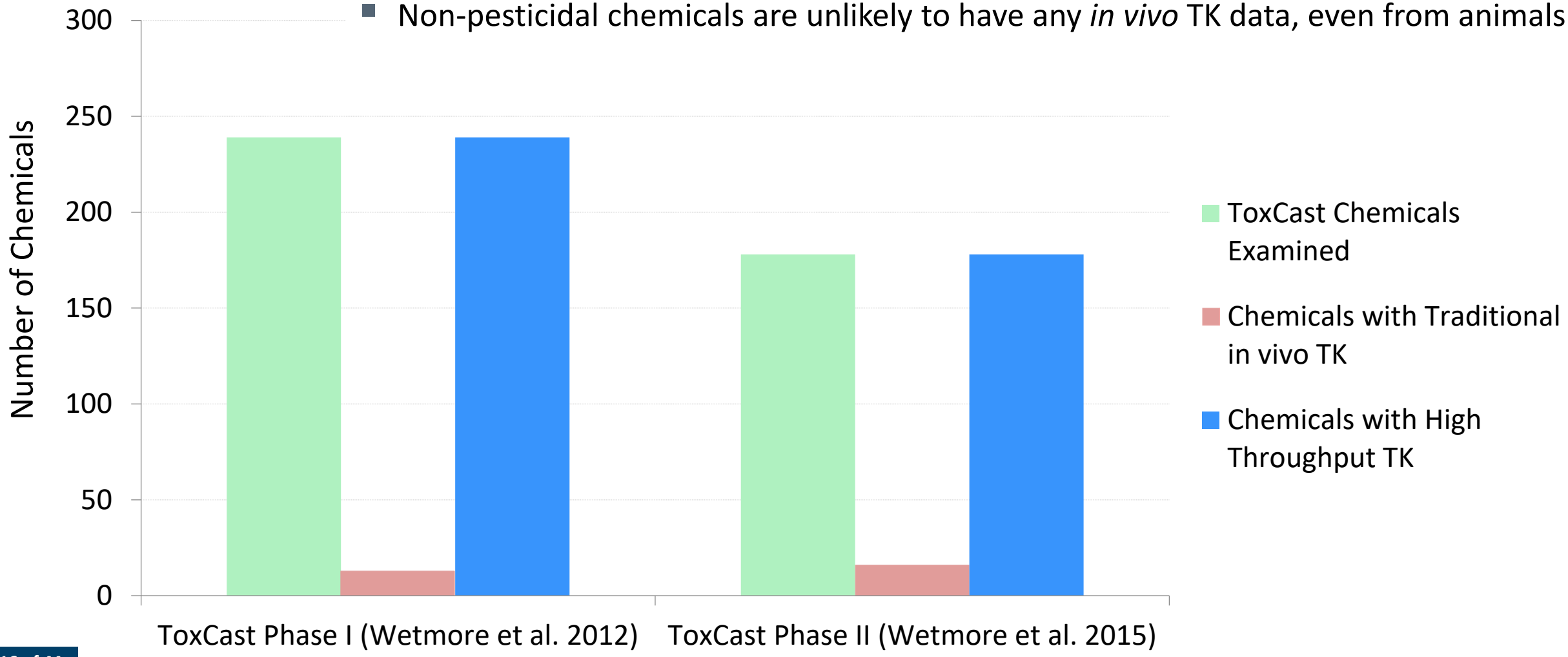


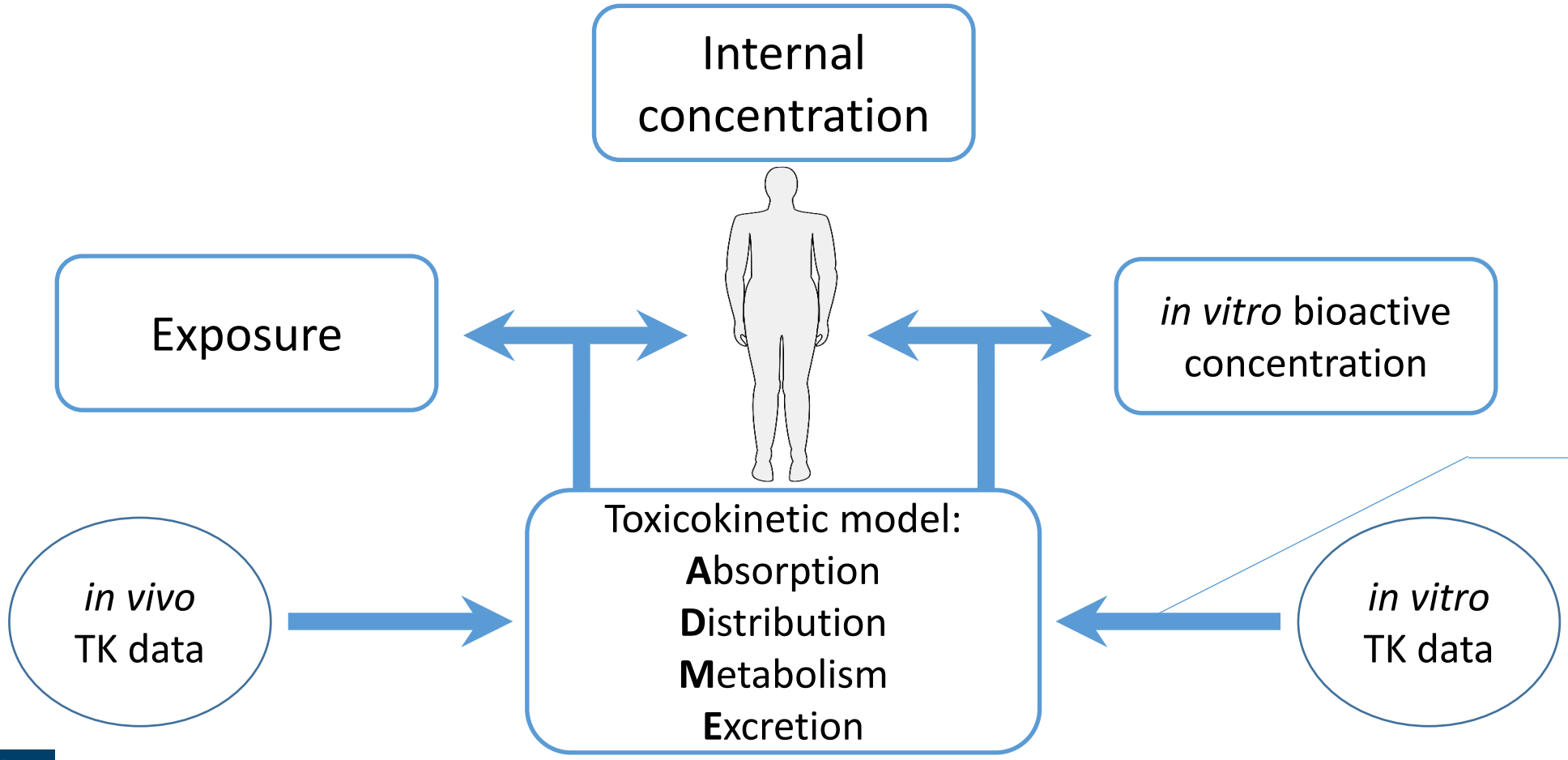
Figure from Bell et al. (2018)

HTTK: A NAM for Exposure

- *In vitro* high throughput toxicokinetic (HTTK) methods can provide toxicokinetic data for larger numbers of chemicals
(for example, Rotroff et al., 2010, Wetmore et al., 2012)
- 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 concentrations from high throughput screening (that is*, in vitro-in vivo* extrapolation, or **IVIVE**) (for example, Wetmore et al., 2015)
- A **secondary goal** is to provide **open-source data and models** for evaluation and use by the broader scientific community (Pearce et al, 2017)

In Vitro-In Vivo Extrapolation (IVIVE)

- Translation of *in vitro* high throughput screening requires chemical-specific toxicokinetic models for anywhere from dozens to thousands of chemicals



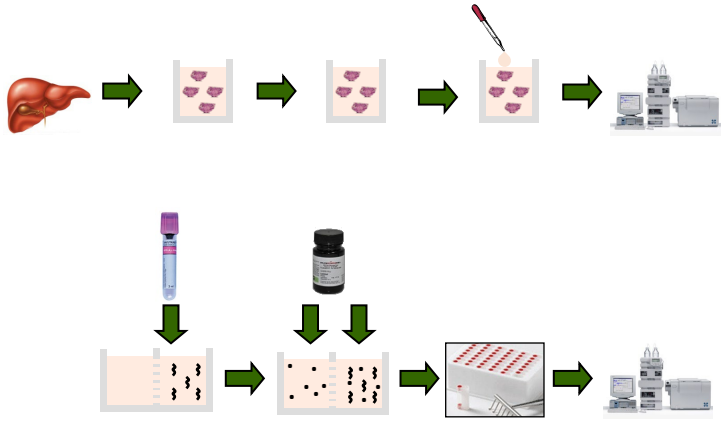
Toxicokinetic IVIVE

Chemical-specific data are steadily being generated by ORD laboratories (Barbara Wetmore), EPA contractors and collaborators

Breen et al. (2021)

What is High Throughput Toxicokinetics (HTTK)?

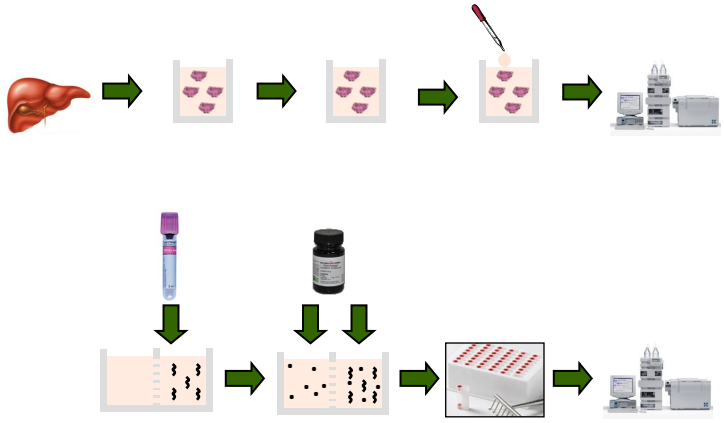
In vitro toxicokinetic data



What is High Throughput Toxicokinetics (HTTK)?

In vitro toxicokinetic data

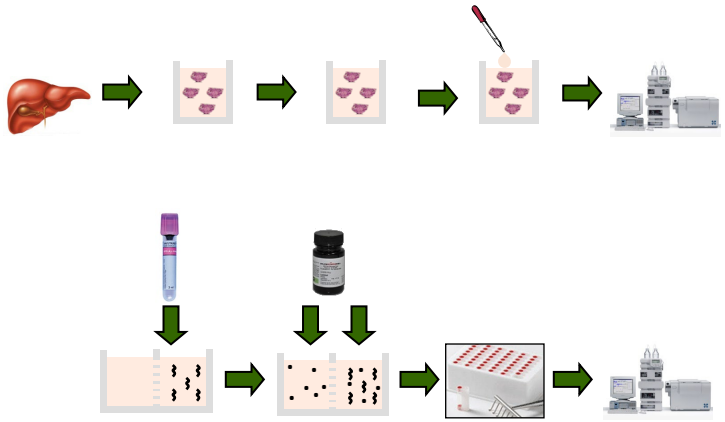
Typically, intrinsic hepatic clearance
and fraction unbound in plasma

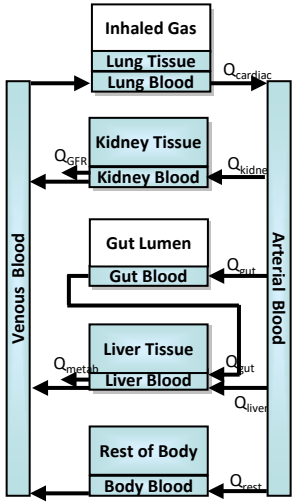


Rotroff et al. (2010)
Wetmore et al. (2012)
Wetmore et al. (2015)
Wambaugh et al. (2019)

What is High Throughput Toxicokinetics (HTTK)?

In vitro toxicokinetic data + generic toxicokinetic model





Rotroff et al. (2010)
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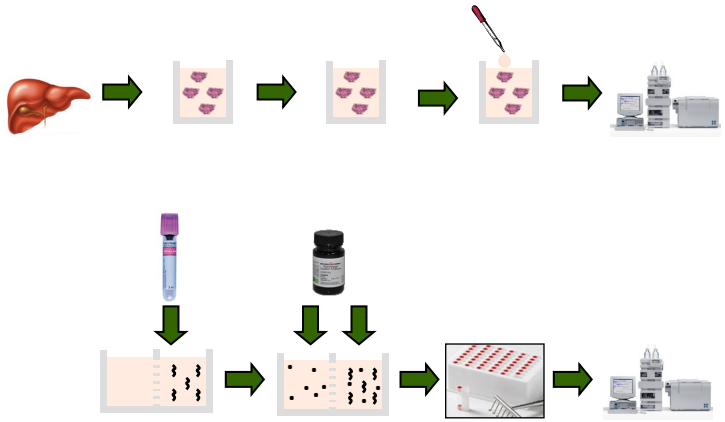
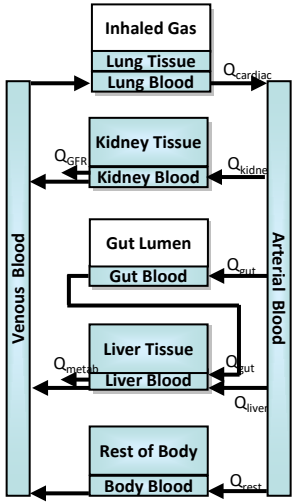
What is High Throughput Toxicokinetics (HTTK)?

In vitro toxicokinetic data + generic toxicokinetic model





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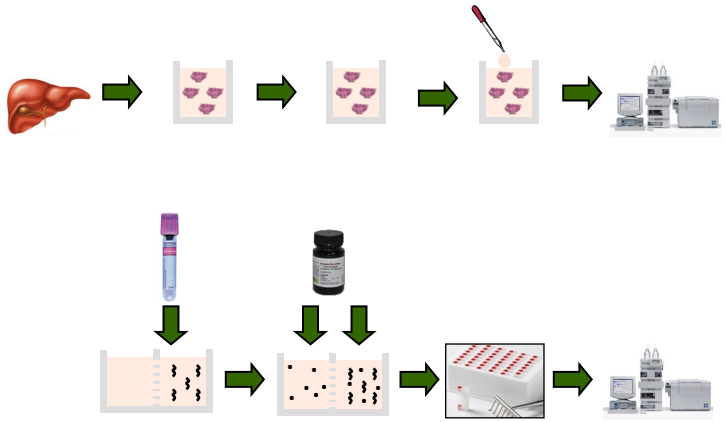
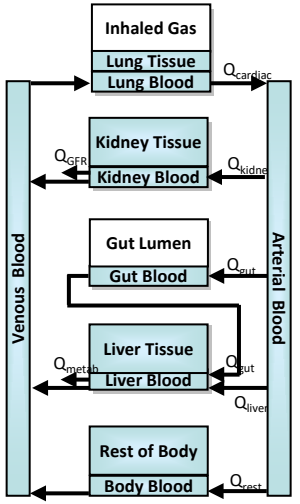
Wambaugh et al. (2015)
Pearce et al. (2017)
Ring et al. (2017)
Linakis et al. (2020)

What is High Throughput Toxicokinetics (HTTK)?

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





= *httk*

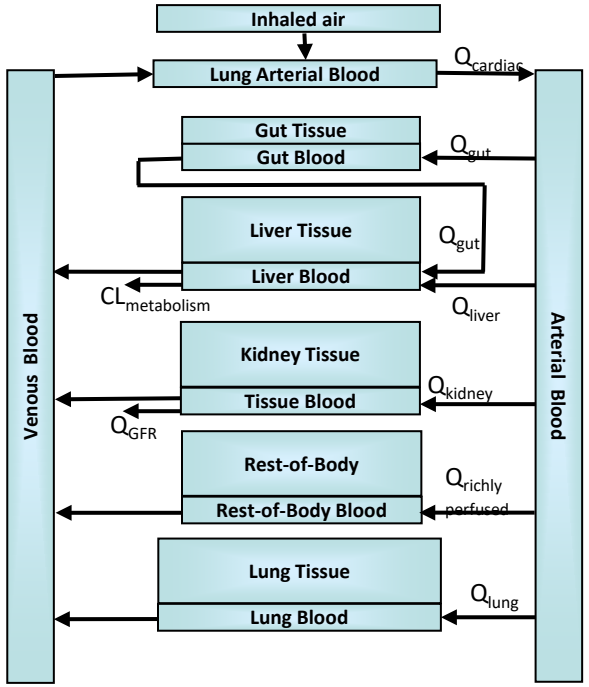
Rotroff et al. (2010)
Wetmore et al. (2012)
Wetmore et al. (2015)
Wambaugh et al. (2019)

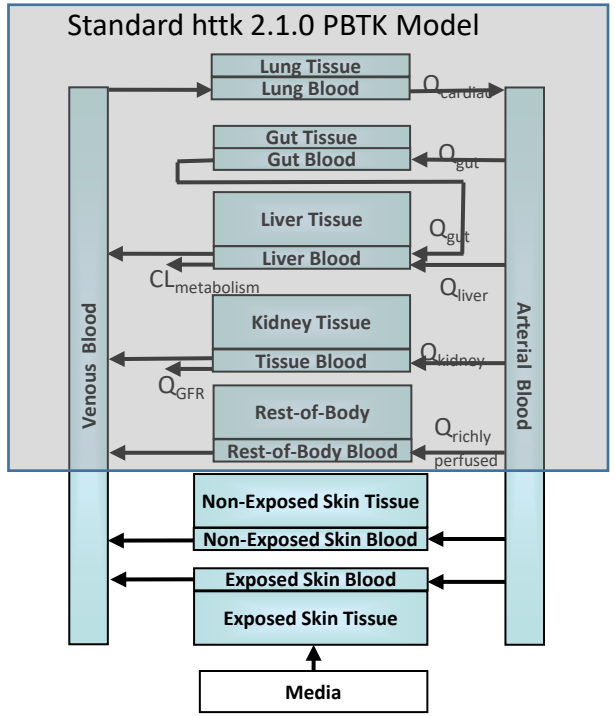
Wambaugh et al. (2015)
Pearce et al. (2017)
Ring et al. (2017)
Linakis et al. (2020)

New HT-PBTK Models

Gas Inhalation Exposure Route

Linakis et al. (2020)



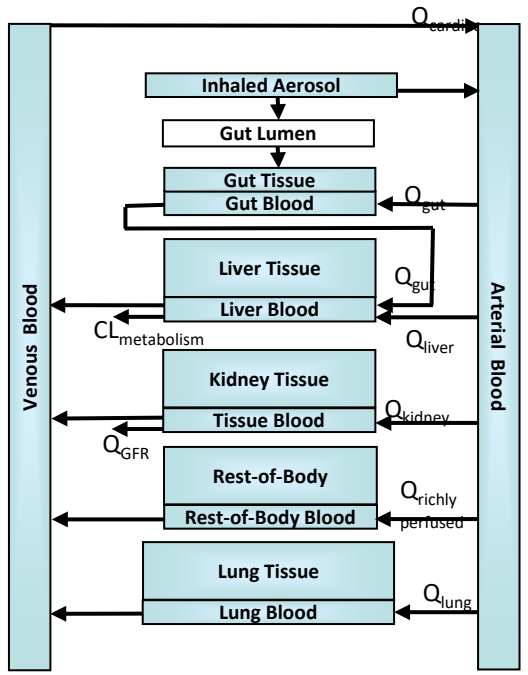


Dermal Exposure Route

EPA, Unilever

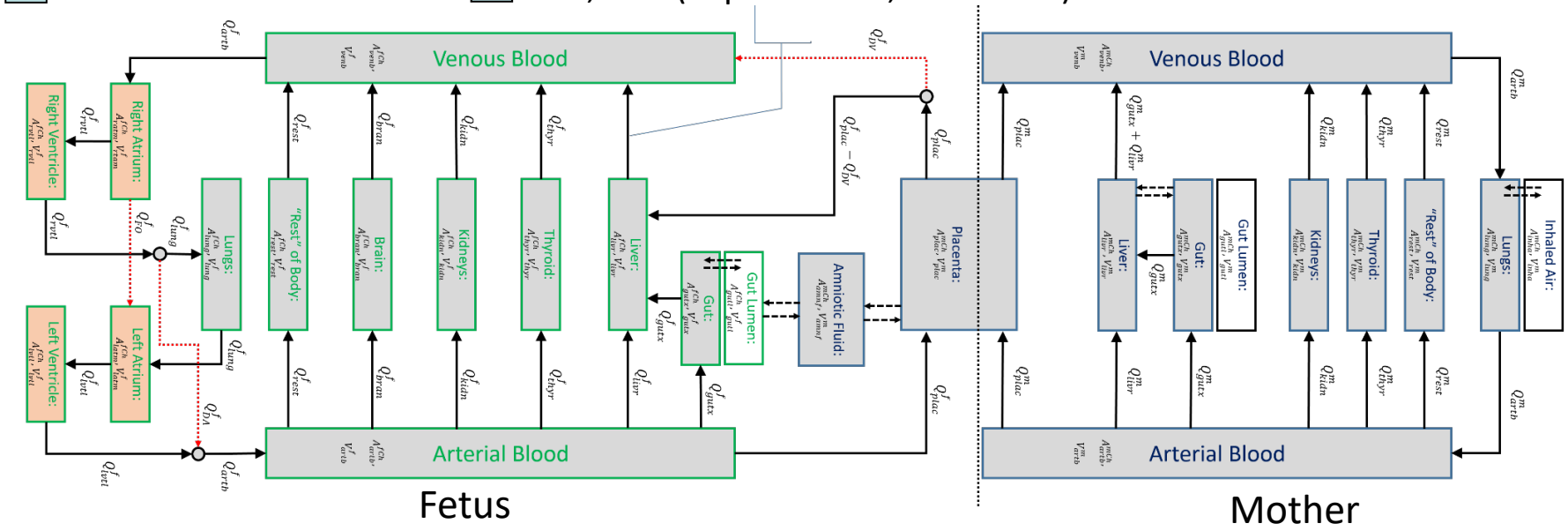
Aerosol Inhalation Exposure Route (including APEX model)

EPA, USAF



Human Gestational Model

EPA, FDA (Kapraun et al, submitted)



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Model parameterization

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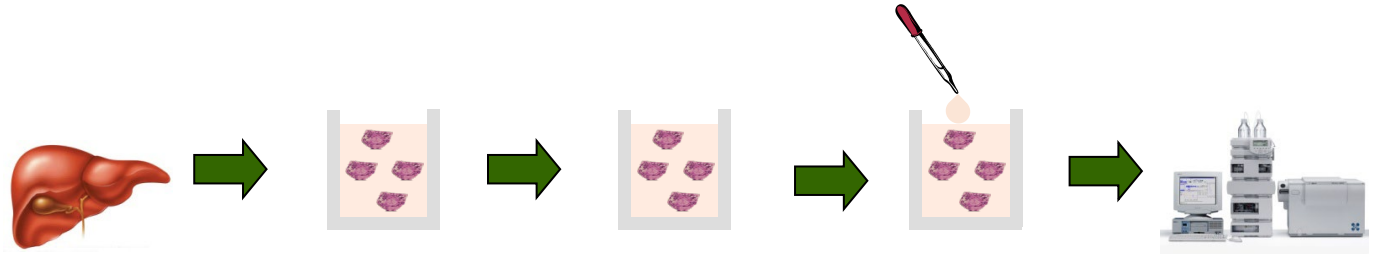
Model Parameters

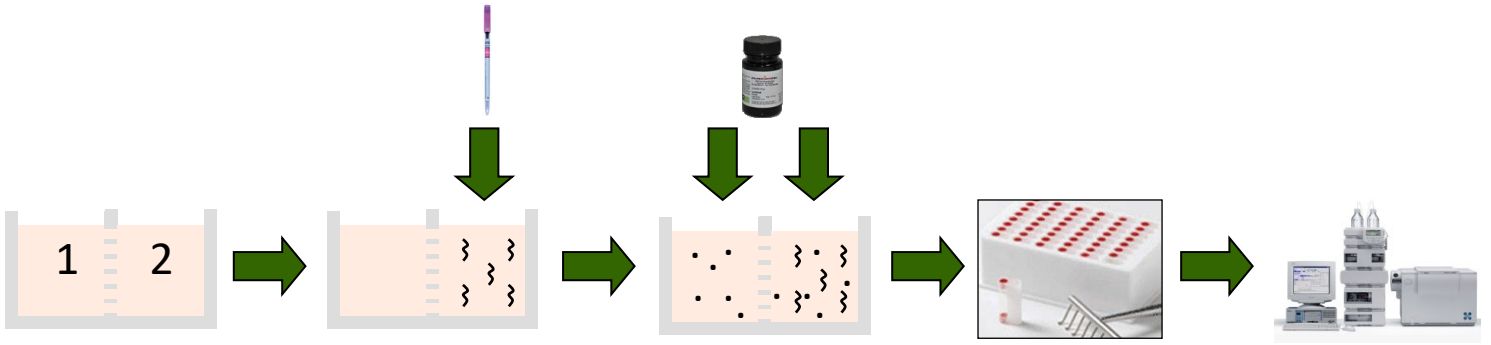
Chemical-specific parameters	
Intrinsic hepatic clearance rate (CL_{int})	Measured in HT *in vitro* assays (Rotroff *et al.* 2010; Wetmore *et al.* 2012, 2014, 2015; Wambaugh *et al.* 2019) or predicted *in silico* (Sipes *et al.* 2017)
Fraction unbound to plasma protein (F_{up})	
Tissue:blood partition coefficients (for compartmental models)	Predict from phys-chem properties and tissue properties (Pearce et al., 2017)
Physiological parameters	
Tissue masses (including body weight)	Gathered from data available in the published literature [Wambaugh et al. 2015; Pearce et al. 2017a]
Tissue blood flows	
Glomerular filtration rate (passive renal clearance)	
Hepatocellularity	

Chemical-Specific *In Vitro* Measurements for TK

Cryo-preserved hepatocyte suspension Shibata *et al.* (2002)



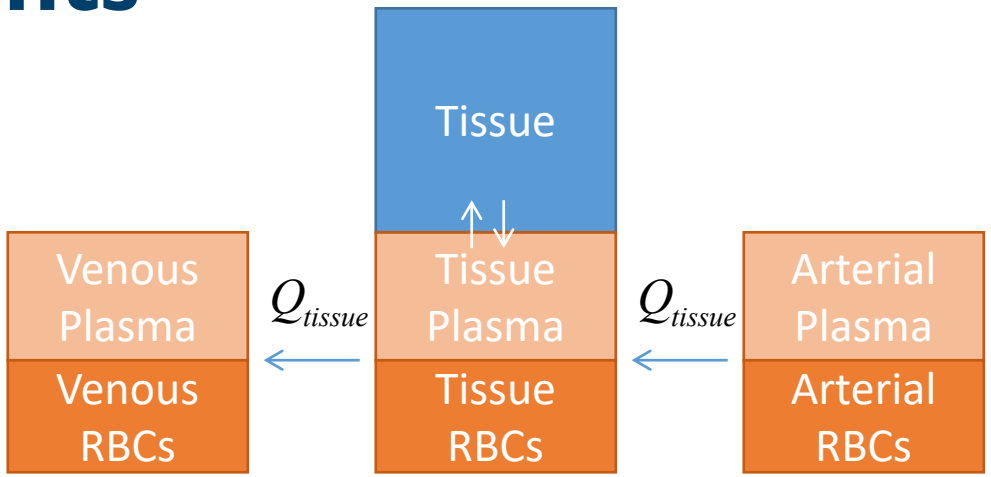
Rapid Equilibrium Dialysis (RED) Waters *et al.* (2008)



- 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)

PBTK Partition Coefficients

- Although in our model there are really three separate concentrations (C) that describe a tissue, we assume that they are related to each other by constants
- We assume that the ratio between the blood and plasma ($R_{blood:plasma}$) is a uniform constant throughout the body



$$C_{compartment,blood} = R_{blood:plasma} C_{compartment,plasma}$$

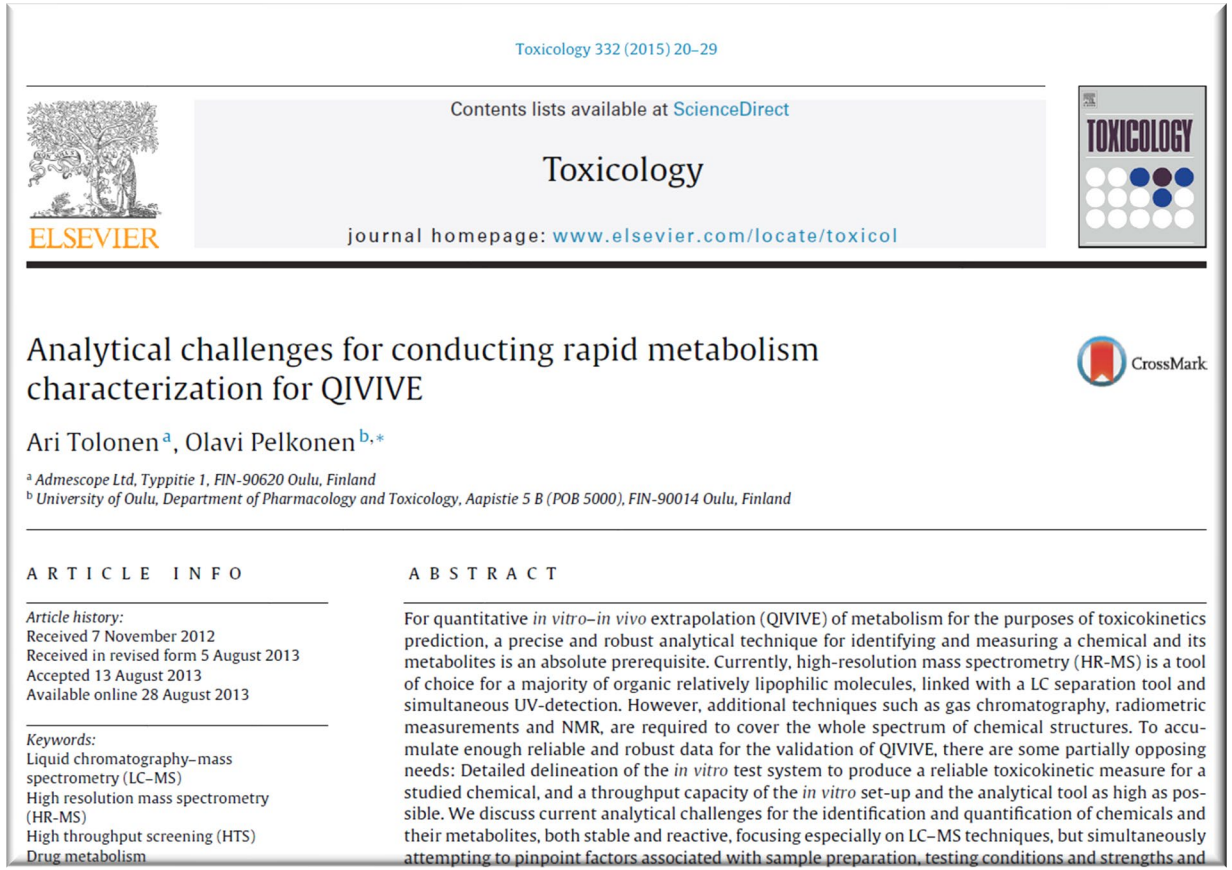
- We assume that all the tissues are "perfusion limited", which means that the tissue concentration instantly comes to equilibrium with the free fraction in plasma (concentration is limited by flow to the tissue)

$$C_{compartment,tissue} = K_{tissue:plasma} * f_{up} * C_{compartment,plasma}$$

$K_{tissue:plasma}$ is the tissue partition coefficient which we either measure experimentally or predict *in silico* (*for example* Schmitt's method)

Development of Analytical Chemistry Method is a Rate Limiting Step

- **The HTTK *in vitro* assays need to measure differences in chemical concentration**
- Historically, methods cannot be developed for all chemicals
- Different chemicals require different instruments and methods, for example liquid vs. gas chromatography mass spectrometry (LC vs. GC MS)



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Analytical challenges for conducting rapid metabolism characterization for QIVIVE

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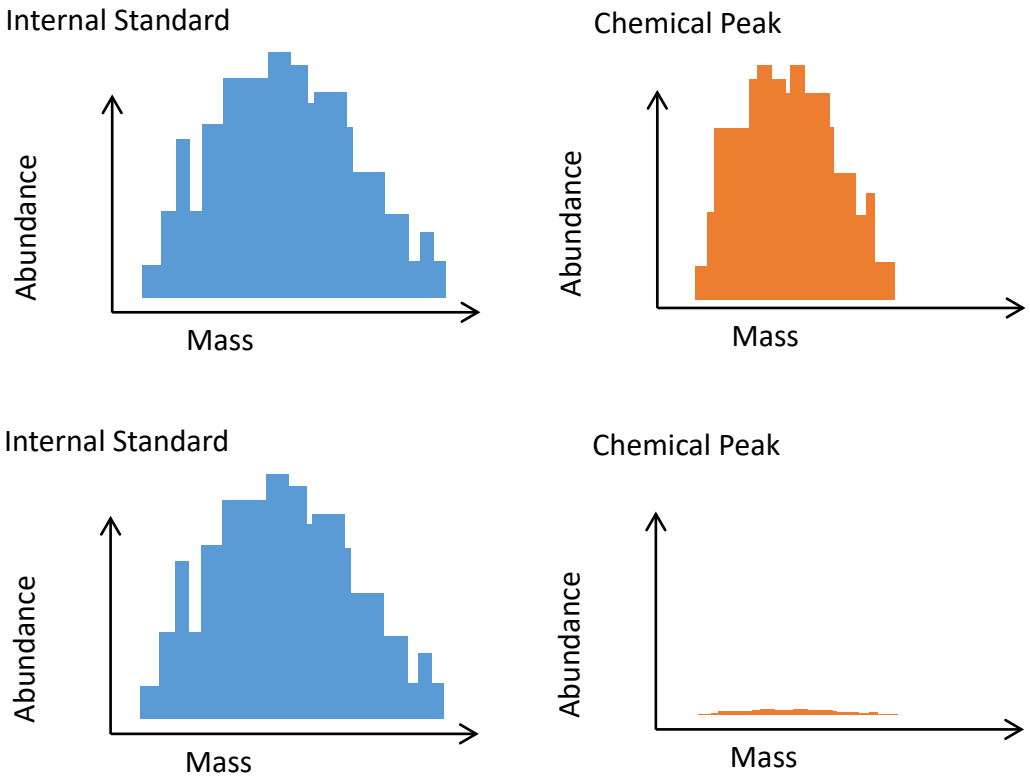
Drug metabolism

ABSTRACT

For quantitative *in vitro–in vivo* extrapolation (QIVIVE) of metabolism for the purposes of toxicokinetics prediction, a precise and robust analytical technique for identifying and measuring a chemical and its metabolites is an absolute prerequisite. Currently, high-resolution mass spectrometry (HR-MS) is a tool of choice for a majority of organic relatively lipophilic molecules, linked with a LC separation tool and simultaneous UV-detection. However, additional techniques such as gas chromatography, radiometric measurements and NMR, are required to cover the whole spectrum of chemical structures. To accumulate enough reliable and robust data for the validation of QIVIVE, there are some partially opposing needs: Detailed delineation of the *in vitro* test system to produce a reliable toxicokinetic measure for a studied chemical, and a throughput capacity of the *in vitro* set-up and the analytical tool as high as possible. We discuss current analytical challenges for the identification and quantification of chemicals and their metabolites, both stable and reactive, focusing especially on LC–MS techniques, but simultaneously attempting to pinpoint factors associated with sample preparation, testing conditions and strengths and

Development of Analytical Chemistry Method is a Rate Limiting Step

- **The HTTK *in vitro* assays need to measure differences in chemical concentration**
- Area of the internal standard (ITSD) at a known, fixed concentration fluctuates with time, depends on instrument and methodology
- Analytical chemist must find a peak that corresponds to chemical of interest, and then follow the ratio R of the chemical peak to the ITSD
- Ability to resolve peak depends on the matrix (for example, blood vs. DMSO)



Key Physiological Parameters for *In Vitro-In Vivo* Extrapolation

Model parameters are either:

- **Physiological:** determined by species and potentially varied via Monte Carlo (including HTTK-pop, Ring et al. 2017)
- **Chemical-specific**: physico-chemical properties (Mansouri et al., 2018) and equilibrium partition coefficients plus plasma binding and metabolism rates that are determined from *in vitro* measurements or potentially predicted from structure

Parameter	Definition	Value (Mean)	Units	Reference
Q_{liverc}	Total blood flow to liver (arterial, gut)	3.6	1/h/kg BW	Davies and Morris (1993)
Q_{GFR}	Flow to glomerulus (glomerular filtration rate)	0.32	1/h/kg BW	Davies and Morris (1993)
$n_{cell\_density}$	Hepatocellularity	110	Millions of cells / g Liver	Carlile et al. (1997)
V_{liverc}	Liver volume	0.0245	1/kg BW	Davies and Morris (1993)
d_{liver}	Liver density	1.05	g/ml	International Commission on Radiological Protection (1975)
Hematocrit	Fraction of blood that is red blood cells	0.43	Unitless	Davies and Morris (1993)
$C_{protein}$	Concentration of protein used in f_{up} assay	5	µM	Wambaugh et al. (2019)

$$Cl_{hepatic} = n_{cell\ density} \times V_{liverc} \times d_{liver} \times Cl_{int}$$

Breen et al. (2021)

Species-Specific Physiological Parameters for Physiologically-Based Toxicokinetics

- Rates, volumes, and tissue-specific information (not shown) are needed for a species

Parameter	Units	Mouse	Rat	Dog	Human	Rabbit	Monkey
Total Body Water	ml/kg	725.000	668.000	603.600	600.000	40.812	693.000
Plasma Volume	ml/kg	50.000	31.200	51.500	42.857	110.000	44.800
Cardiac Output	ml/min/kg^(3/4)	150.424	209.304	213.394	231.401	266.576	324.790
Average BW	kg	0.020	0.250	10.000	70.000	2.500	5.000
Total Plasma Protein	g/ml	0.062	0.067	0.090	0.074	0.057	0.088
Plasma albumin	g/ml	0.033	0.032	0.026	0.042	0.039	0.049
Plasma a-1-AGP	g/ml	0.013	0.018	0.004	0.002	0.001	0.002
Hematocrit	fraction	0.450	0.460	0.420	0.440	0.360	0.410
Urine Flow	ml/min/kg^(3/4)	0.013	0.098	0.037	0.040	0.042	0.151
Bile Flow	ml/min/kg^(3/4)	0.026	0.044	0.015	0.010	0.083	0.004
GFR	ml/min/kg^(3/4)	5.265	3.705	10.901	5.165	3.120	2.080
Average Body Temperature	C	37.000	38.700	38.900	37.000	39.350	38.000
Plasma Effective Neutral Lipid Volume Fraction	unitless	0.004	0.002	0.001	0.007	0.002	0.007
Plasma Protein Volume Fraction	unitless	0.060	0.059	0.090	0.070	0.057	0.070
Pulmonary Ventilation Rate	l/h/kg^(3/4)	24.750	24.750	24.750	27.750	24.750	27.750
Alveolar Dead Space Fraction	unitless	0.330	0.330	0.330	0.330	0.330	0.330

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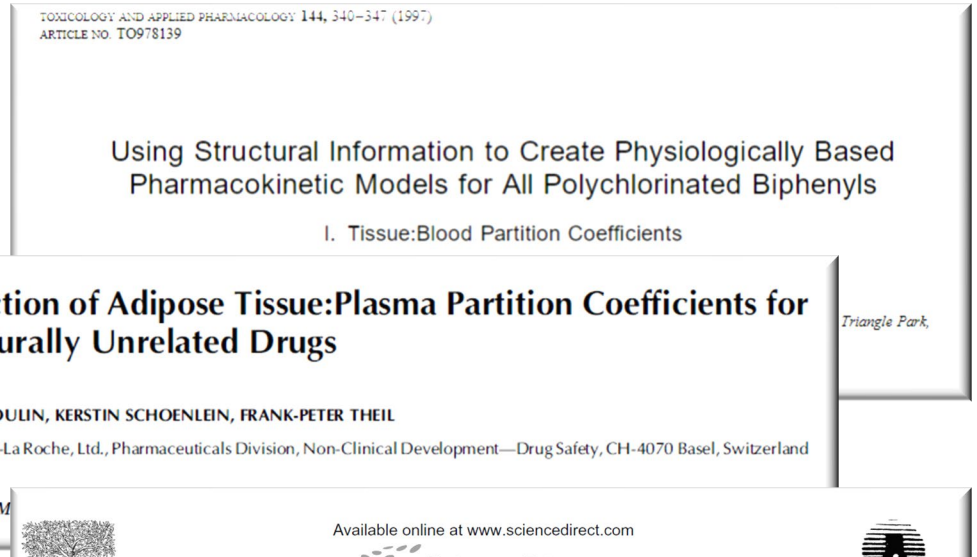
Tools for Chemical-Specific PBTK Parameters

Physiological parameters depend on species, but we must also make chemical-specific estimates of tissue partitioning…


TOXICOLOGY AND APPLIED PHARMACOLOGY 144, 340–347 (1997)
ARTICLE NO. TO978139

Using Structural Information to Create Physiologically Based Pharmacokinetic Models for All Polychlorinated Biphenyls

I. Tissue:Blood Partition Coefficients

Triangle Park,

Prediction of Adipose Tissue:Plasma Partition Coefficients for Structurally Unrelated Drugs

PATRICK POULIN, KERSTIN SCHOENLEIN, FRANK-PETER THEIL

F. Hoffmann-La Roche, Ltd., Pharmaceuticals Division, Non-Clinical Development—Drug Safety, CH-4070 Basel, Switzerland

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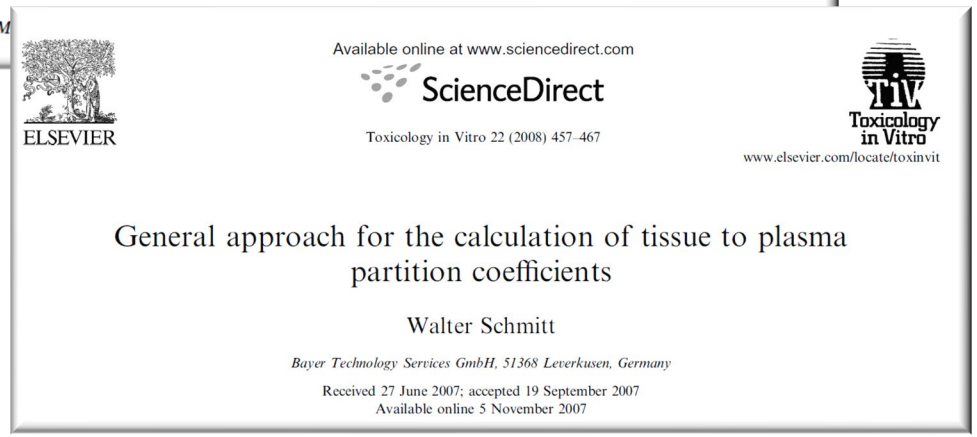
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General approach for the calculation of tissue to plasma partition coefficients

Walter Schmitt

Bayer Technology Services GmbH, 51368 Leverkusen, Germany

Received 27 June 2007; accepted 19 September 2007
Available online 5 November 2007


Arch Toxicol (1997) 72: 17–25 © Springer-Verlag 1997

TOXICOKINETICS

Joost DeJongh · Henk J.M. Verhaar
Joop L.M. Hermens

A quantitative property-property relationship (QPPR) approach to estimate in vitro tissue-blood partition coefficients of organic chemicals in rats and humans

Physiologically Based Pharmacokinetic Modeling 1: Predicting the Tissue Distribution of Moderate-to-Strong Bases

TRUDY RODGERS,[1] DAVID LEAHY,[2] MALCOLM ROWLAND[1]

[1]Centre for Applied Pharmacokinetic Research, School of Pharmacy and Pharmaceutical Sciences, University of Manchester, United Kingdom

[2]Cyprot

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A unified algorithm for predicting partition coefficients for PBPK modeling of drugs and environmental chemicals

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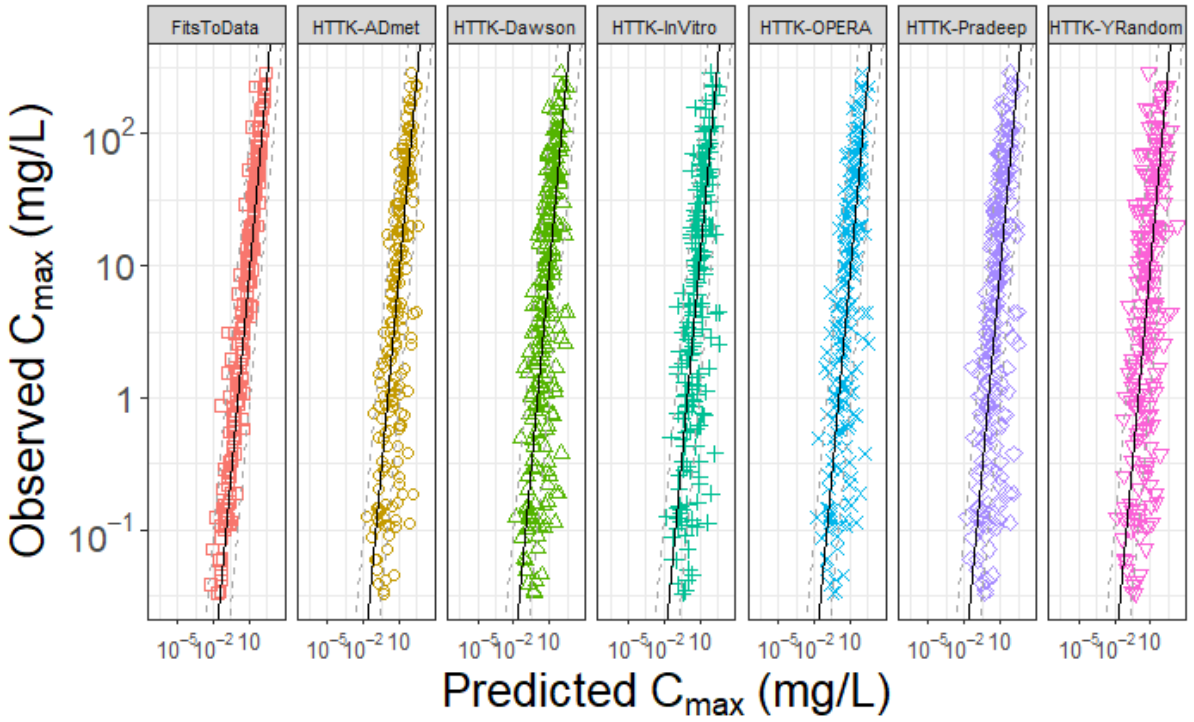
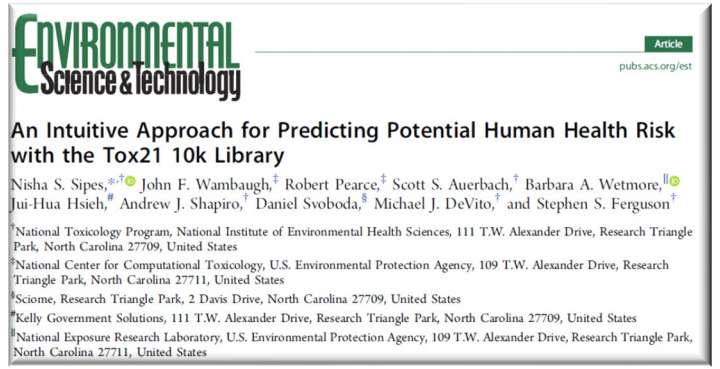
[b] Consultant, 4009 rue Sylvia Daoust, Québec City, Québec, Canada G1X 0A6

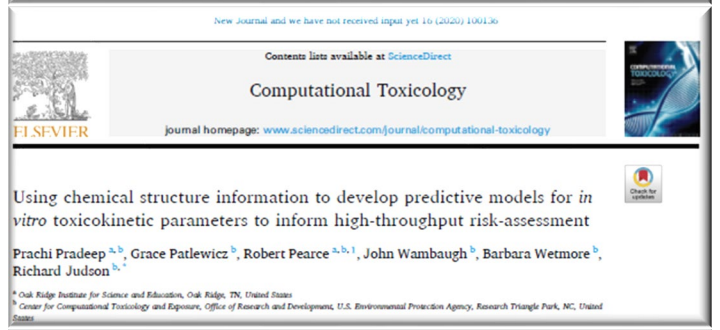
Collaborative Evaluation of QSPRs (Quantitative Structure-Property Relationships) for HTTK

- Open-source QSPR predictions currently available for thousands of chemicals, including full Tox21 library

- EPA is leading an international collaborative evaluation of various QSPRs trained to both pharma and non-pharma chemicals for predicting HTTK







EPA United States Environmental Protection Agency

Model evaluation

Verifying PBTK Models

Process for the Evaluation of PBPK Models

1. Assessment of Model Purpose
2. Assessment of Model Structure and Biological Characterizations
3. Assessment of Mathematical Descriptions
4. Assessment of Computer Implementation
5. Parameter Analysis and Assessment of Model Fitness
6. Assessment of any Specialized Analyses

Clark et al. (2004)

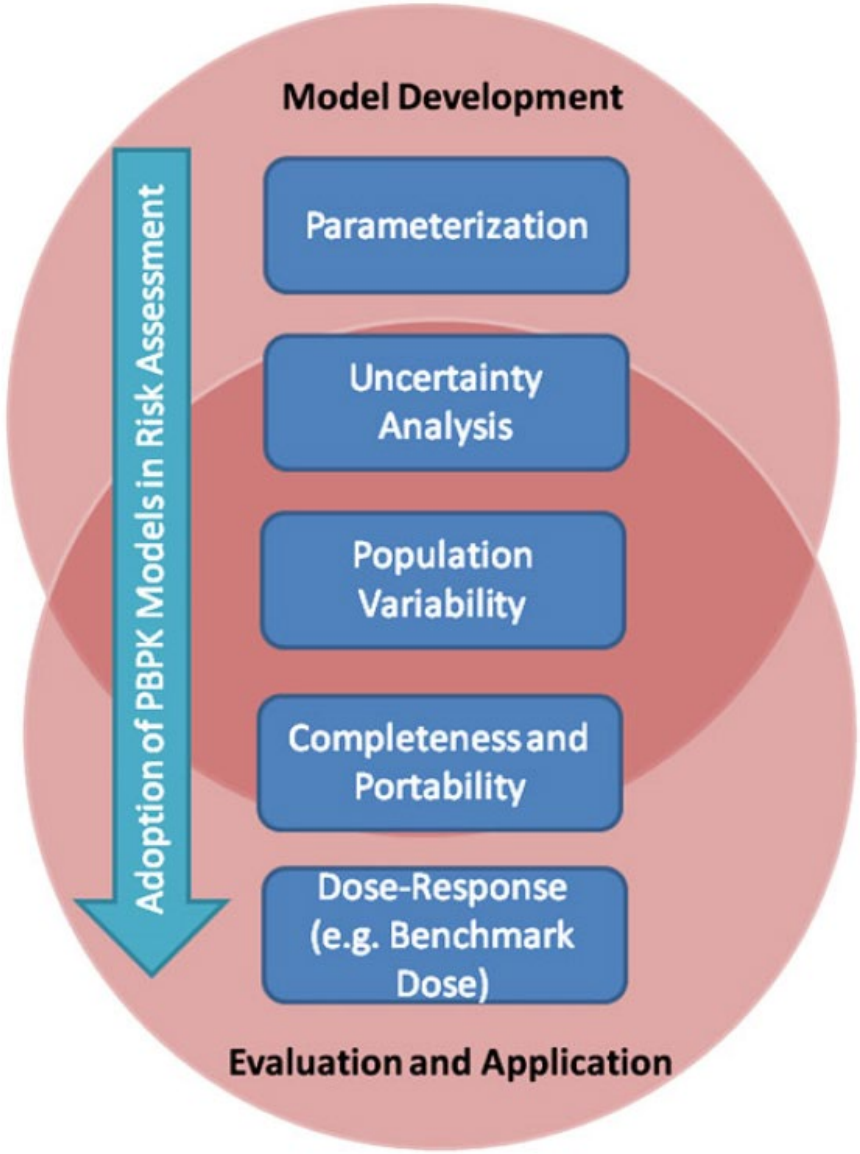
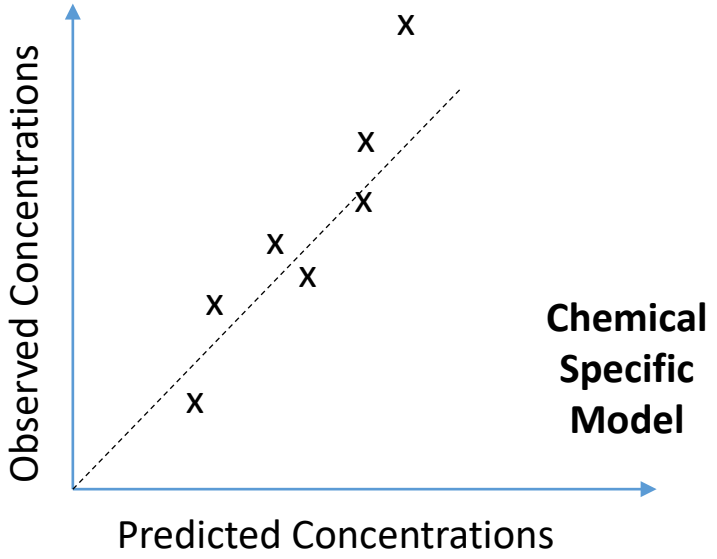


FIG. 1. This figure shows examples of key considerations during model development, evaluation, and application that are necessary before a PBPK model may be adopted for use in a HHRA.

McLanahan et al. (2012)

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



Cohen Hubal et al. (2019)

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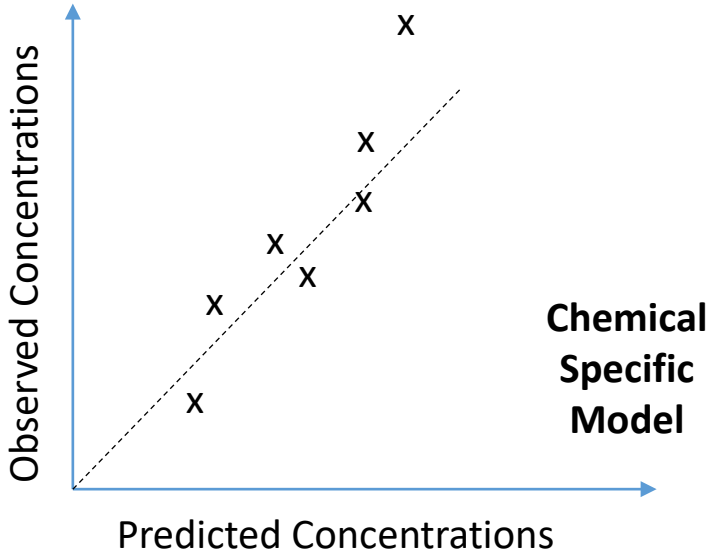
- However, we do not typically have TK data



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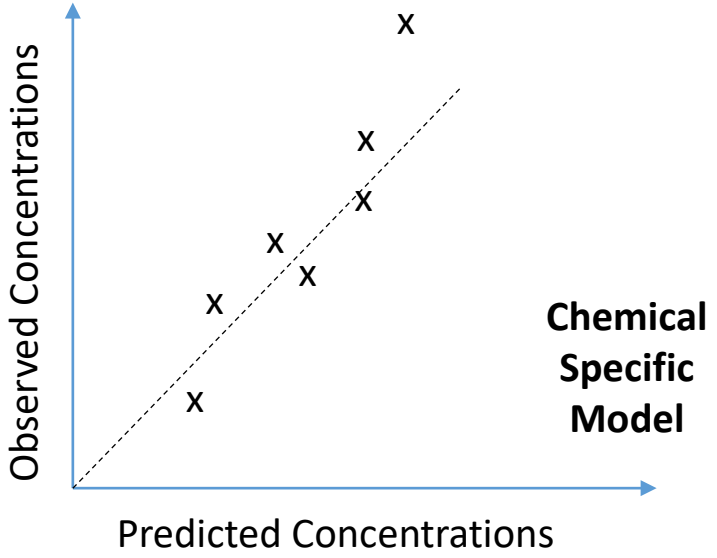
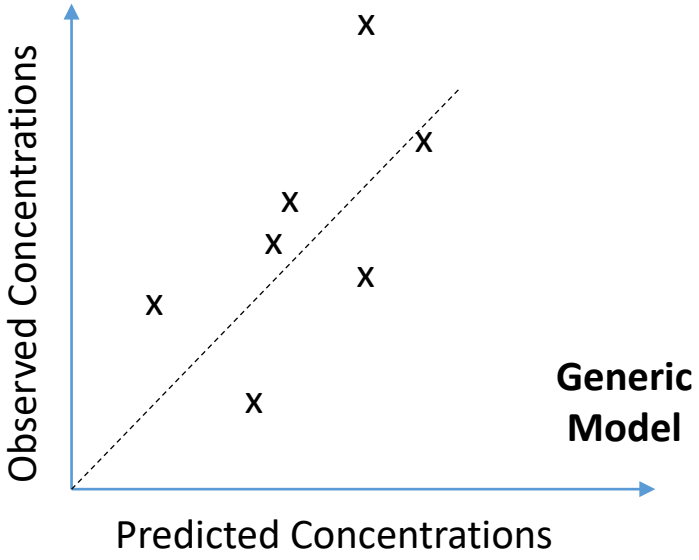
- We can parameterize a **generic TK model**, and evaluate that model for as many chemicals as we do have data
  - We do expect larger uncertainty, but also greater confidence in model implementation
  - Estimate bias and uncertainty, and try to correlate with chemical-specific properties





Cohen Hubal et al. (2019)

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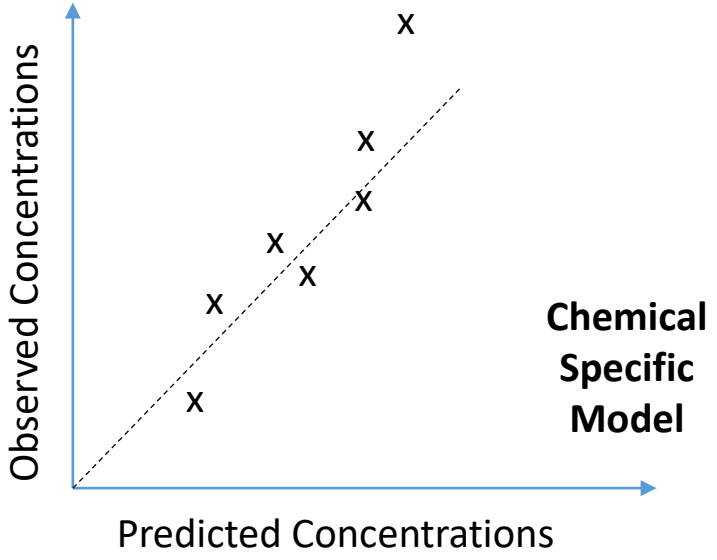

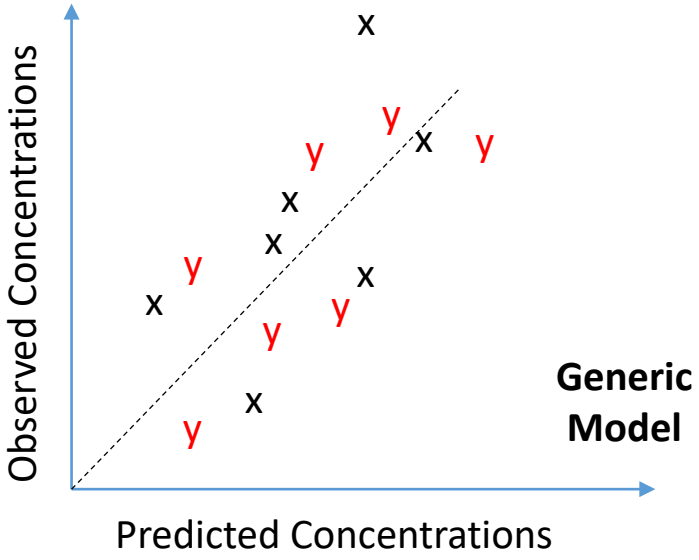

Cohen Hubal et al. (2019)

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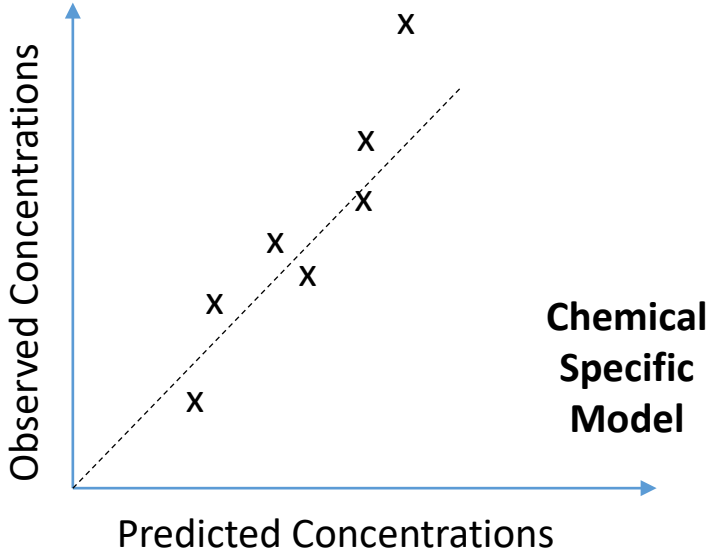
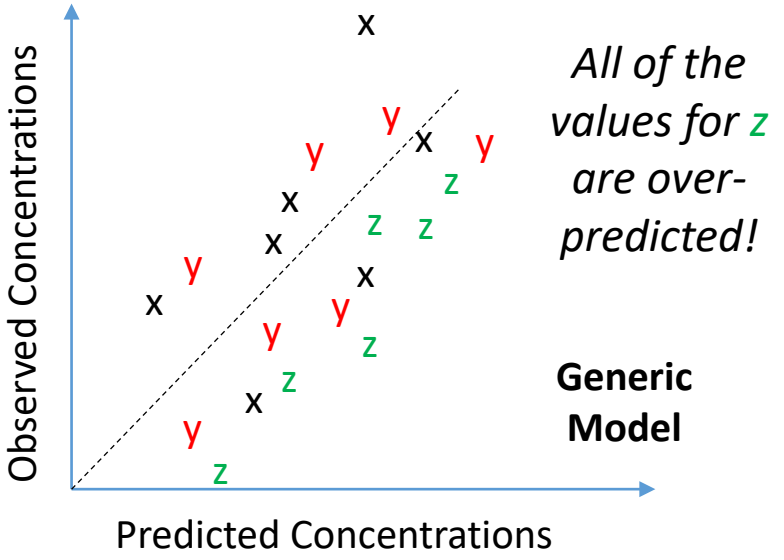
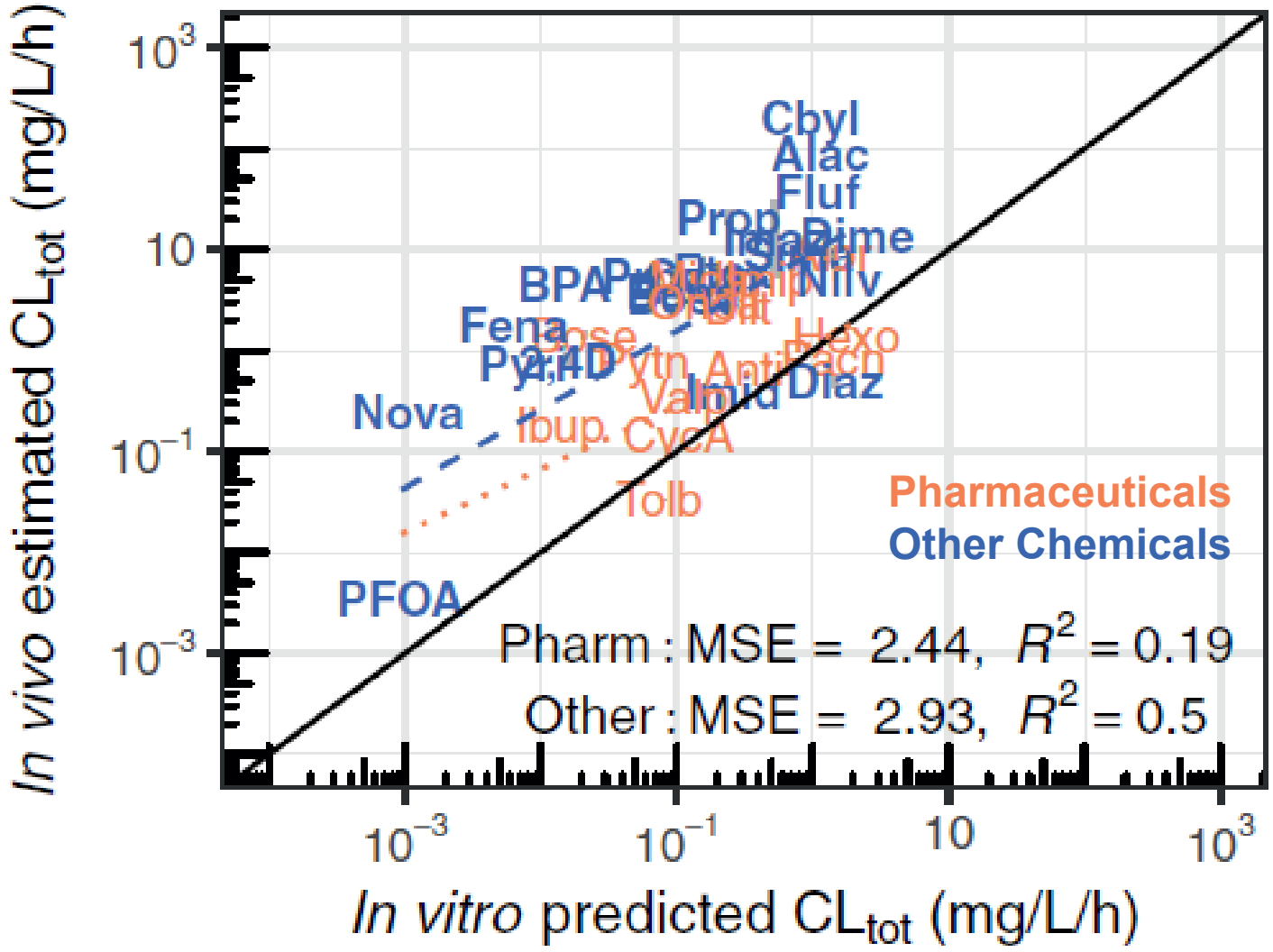




Cohen Hubal et al. (2019)

Evaluation Example: Observed Total Clearance

- We estimate clearance from two processes – hepatic metabolism (liver) and passive glomerular filtration (kidney)
- This appears to work better for pharmaceuticals than other chemicals:
  - ToxCast chemicals are overestimated
- Non-pharmaceuticals may be subject to extrahepatic metabolism and/or active transport



Wambaugh et al. (2018)

CvTdb: An *In Vivo* TK Database

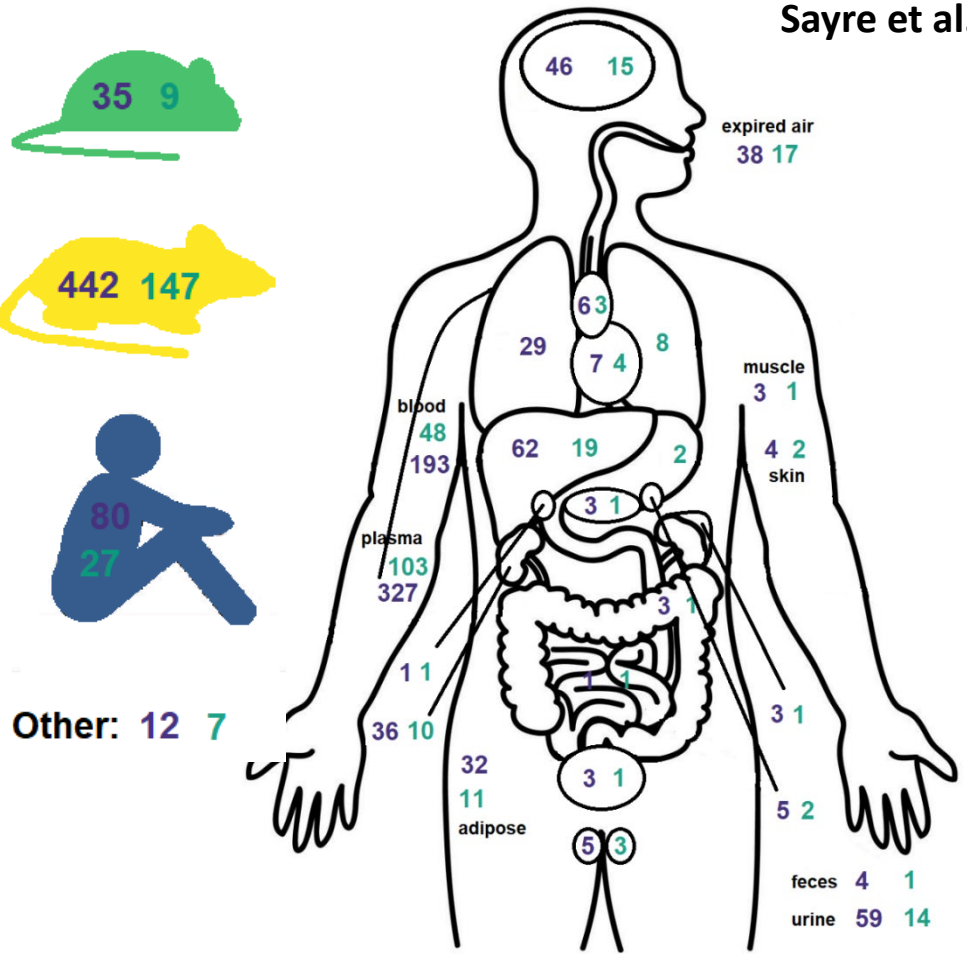
https://github.com/USEPA/CompTox-PK-CvTdb

- 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, literature)
  - Routes: Intravenous, dermal, oral, sub-cutaneous, and inhalation exposure

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

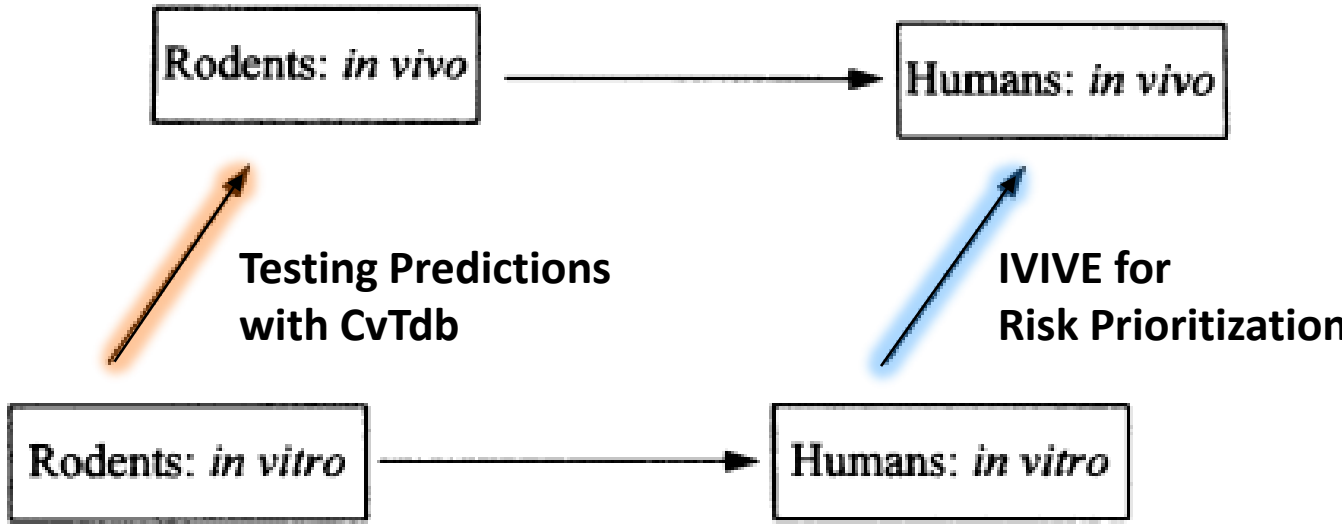
Sayre et al. (2020)



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

Conclusions

- Toxicokinetics links exposure with internal concentrations
- Physiologically-based toxicokinetic (PBTK) models allow extrapolation, including *in vitro-in vivo* extrapolation (IVIVE)
- PBTK models can be generic or bespoke



- Generic models allow for verification of model implementation
- High throughput toxicokinetics (HTTK) allow *in vitro* parameterization of generic PBTK models
- Comparing model predictions for chemicals with *in vivo* data allows estimation of confidence in predictions for chemicals without *in vivo* data

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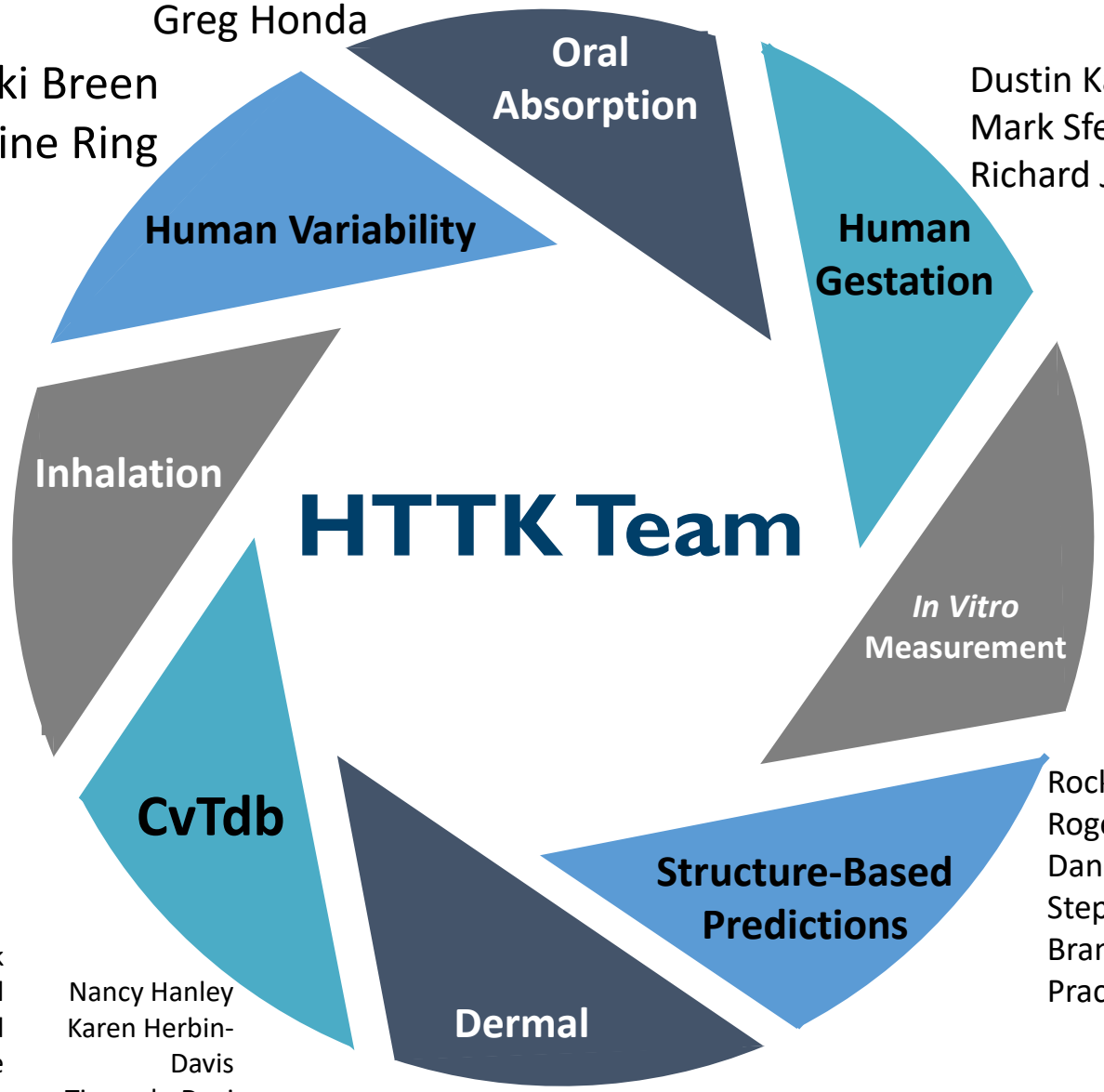

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