http://orcid.org/0000-0002-4024-534X

United States Environmental Protection Agency

# *Toxicokinetic New Approach Methodologies (NAMs)*

# Generic TK models: Parameterization and Evaluation

John Wambaugh

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

**Office of Research and Development**
Center for Computational Toxicology and Exposure

**October 29, 2021**

United States Environmental Protection Agency

# Overview

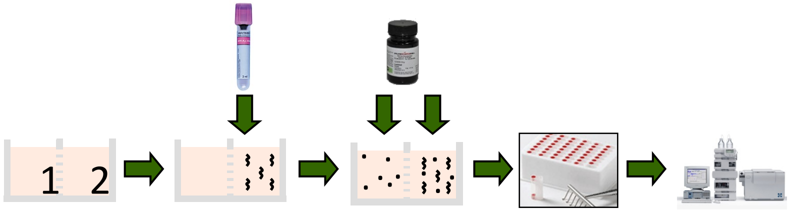
- Generic vs. bespoke PBTK models
- Models available within R package "httk"
- Model parameterization
  - Physiologic parameters
  - Chemical-specific parameters
- Model evaluation
  - The Concentration vs. Time Database (CvTdb)

# HTTK: A NAM for Exposure

- Toxicokinetics is the predictive description of the absorption, distribution, metabolism, and elimination (ADME) of a chemical compound
- We collect *in vitro*, high throughput toxicokinetic (HTTK) data to provide toxicokinetics for larger 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)

## High Throughput Toxicokinetics (HTTK)

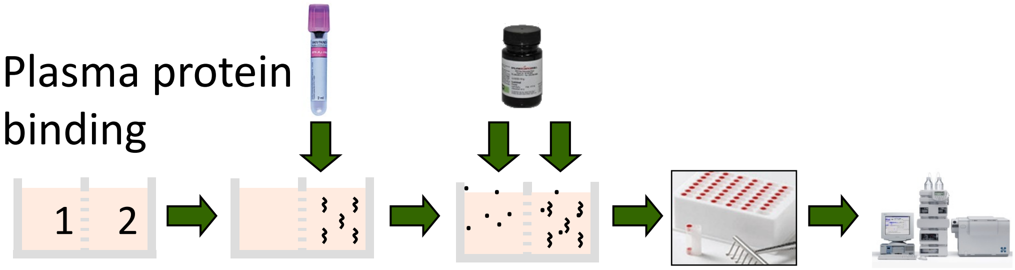
# *In vitro* toxicokinetic data



# *In vitro* toxicokinetic data

Intrinsic hepatic clearance

Plasma protein binding




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

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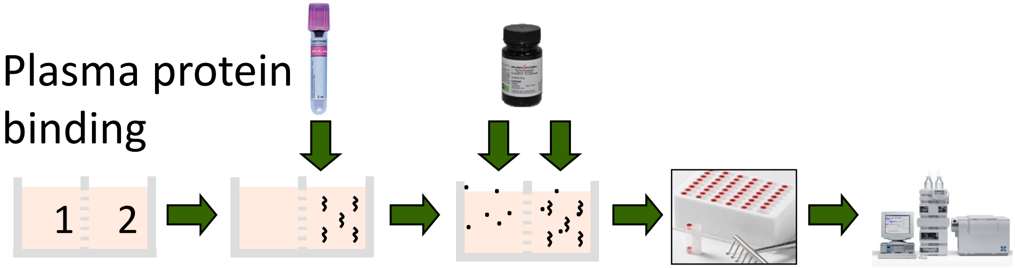
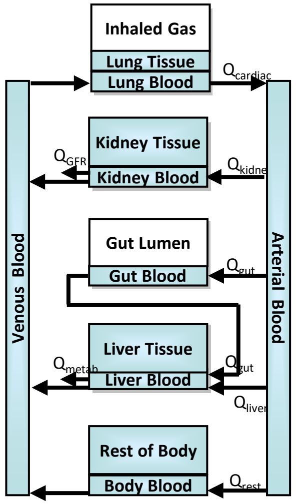
# High Throughput Toxicokinetics (HTTK)

## *In vitro* toxicokinetic data + generic toxicokinetic model

Intrinsic hepatic clearance

Plasma protein binding

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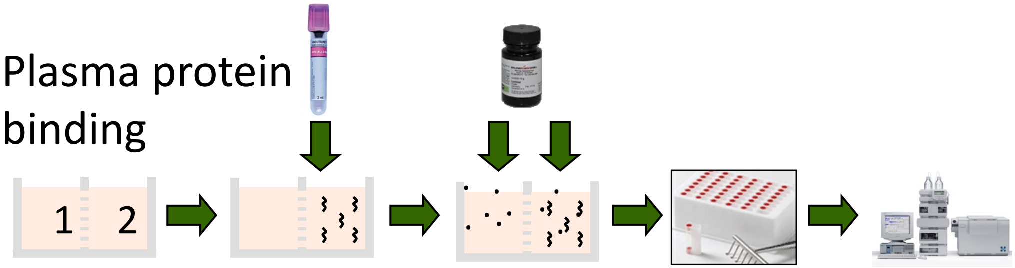


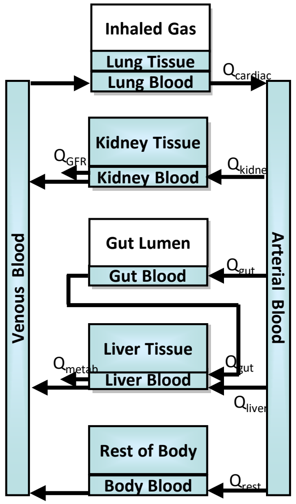


Rotroff et al. (2010)
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Wambaugh et al. (2015)
Pearce et al. (2017)
Ring et al. (2017)
Linakis et al. (2020)

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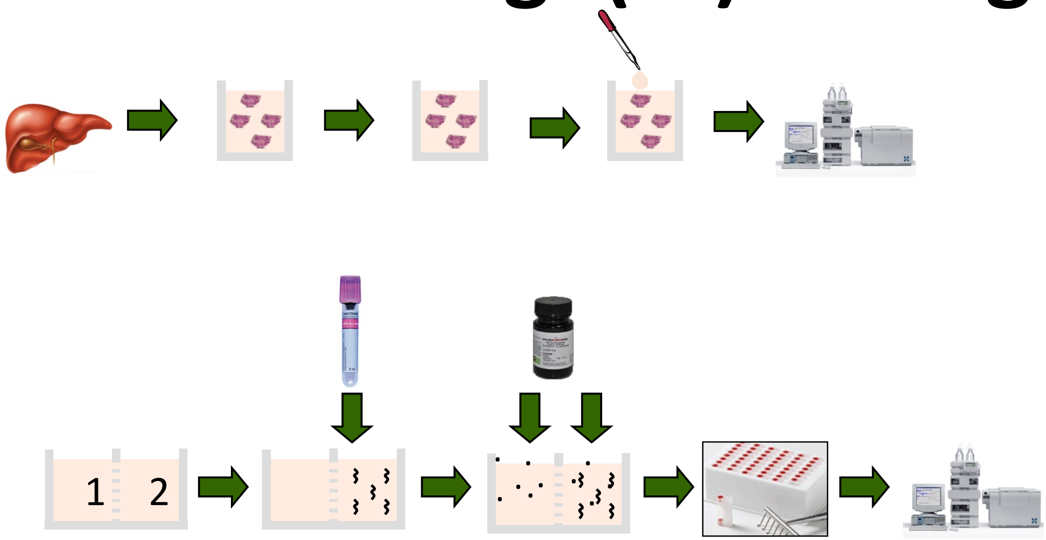
# High Throughput Toxicokinetics (HTTK)

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

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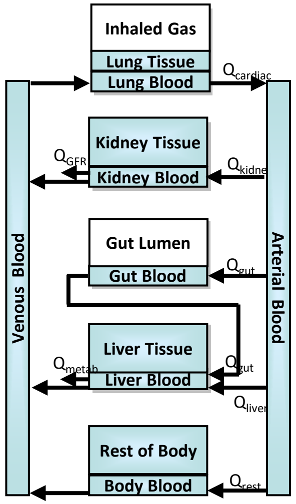


= *httk*

Wambaugh et al. (2015)
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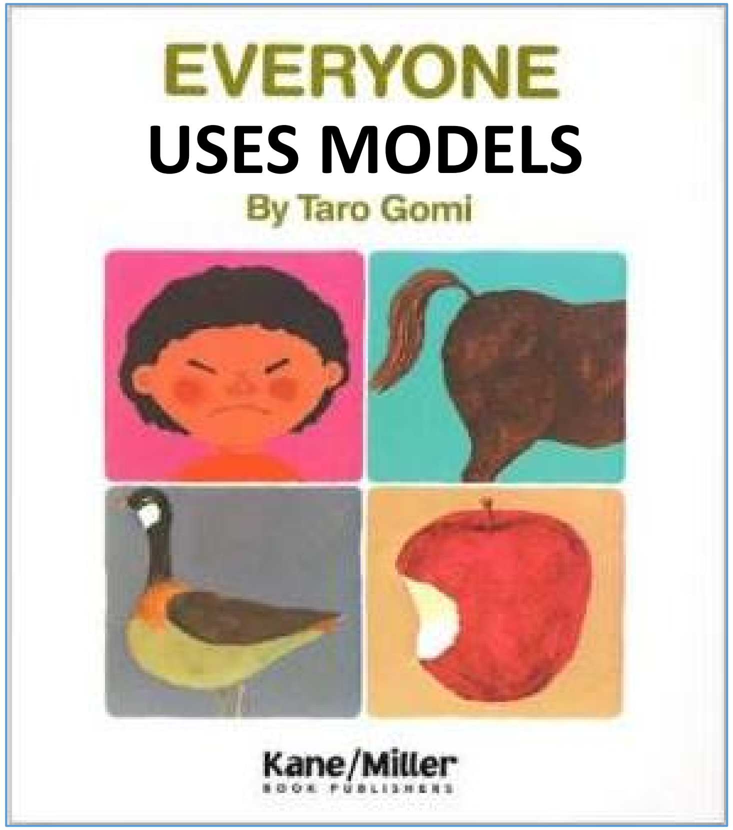
# Generic vs. bespoke PBTK models

# 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.

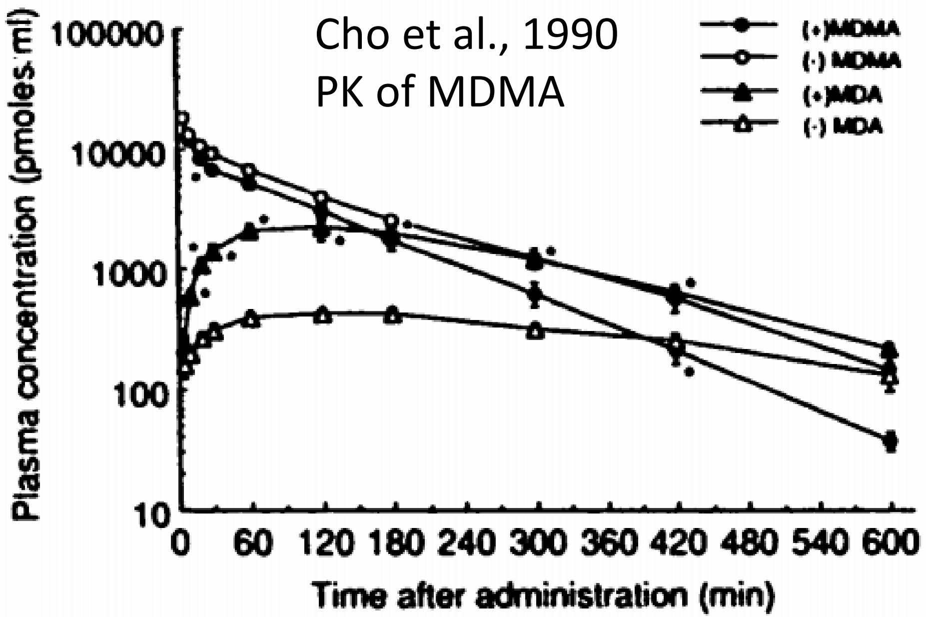
  - How do I drive to a place I've never been before?

# Complexity should match the data…

“Since all models are wrong the scientist cannot obtain a ‘correct’ one by excessive elaboration. On the contrary, following William of Occam, they should seek an economical description of natural phenomena.”

George Box

**We choose to make the complexity of the model and the number of physiological processes appropriate given the data and the decision context**



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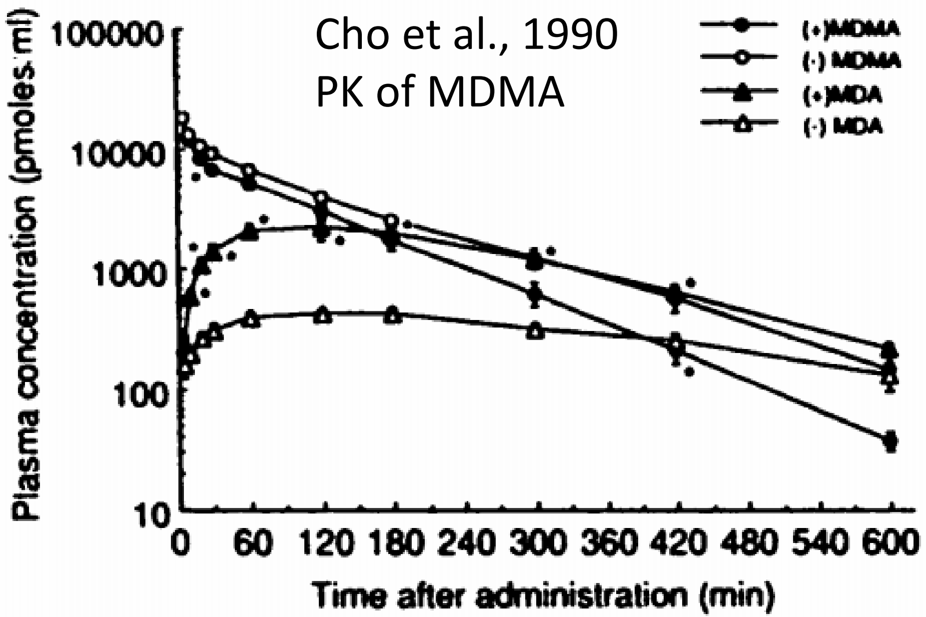
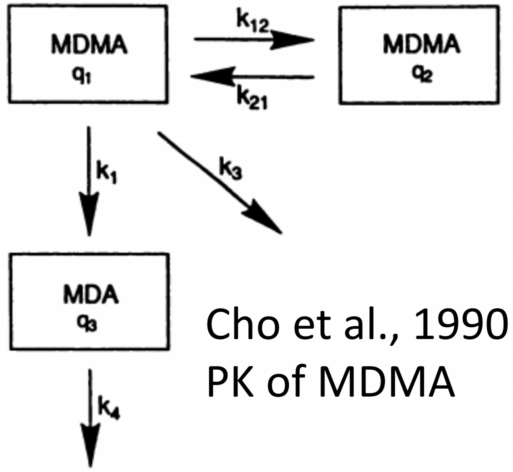
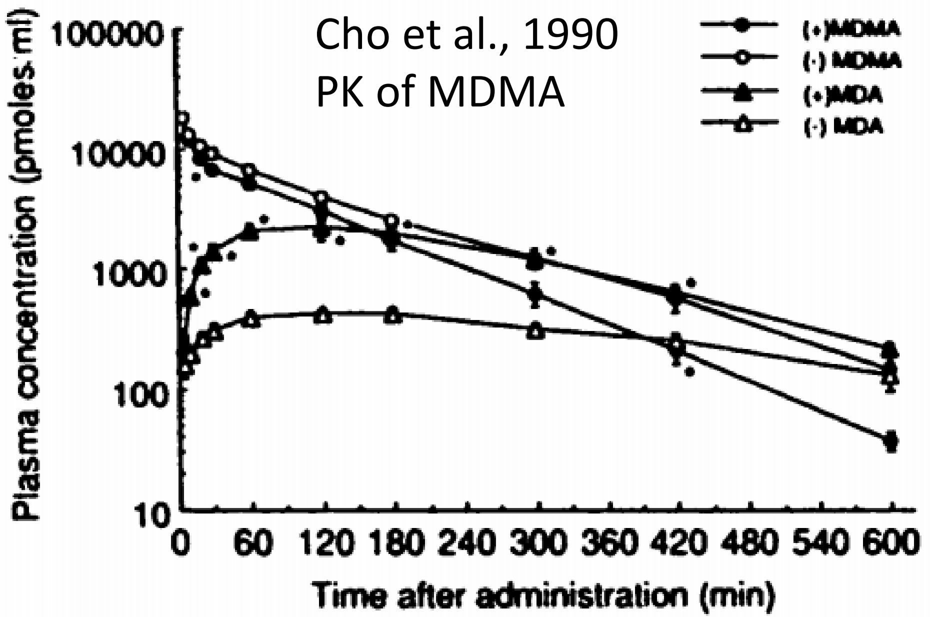



Cho et al., 1990
PK of MDMA

# Complexity should match the data…

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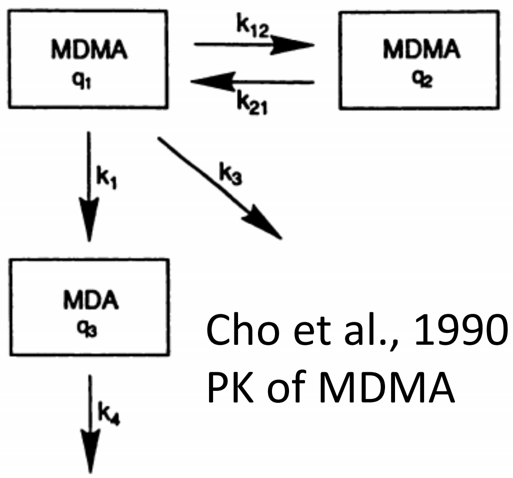


Cho et al., 1990
PK of MDMA

Jones et al., 2012
PK of Statins

In this case they had transporter-specific data

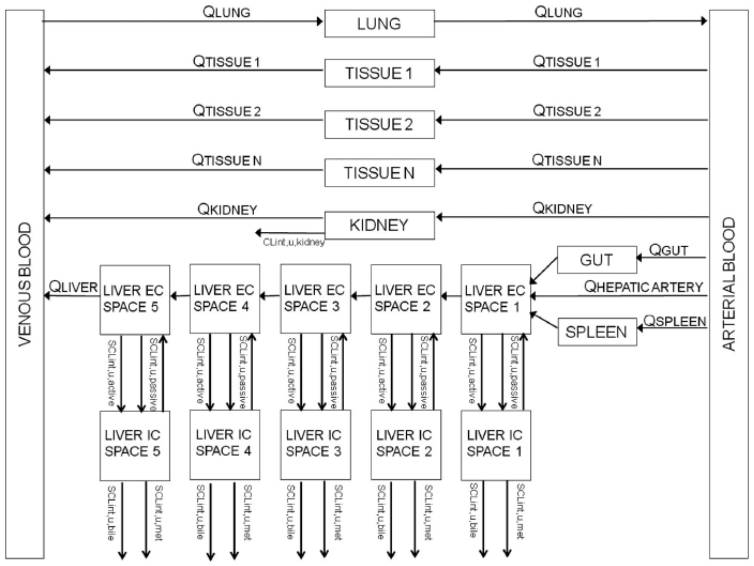


FIG. 2. Schematic diagram of the in vivo PBPK model. EC, extracellular; IC, intracellular.

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# Lex Parsimoniae
# "Law of Parsimony"

"Among competing hypotheses, the one with the fewest assumptions should be selected."
William of Occam

"While Occam's razor is a useful tool in the physical sciences, it can be a very dangerous implement in biology. It is thus very rash to use simplicity and elegance as a guide in biological research. "
Francis Crick

"With four parameters I can fit an elephant, and with five I can make him wiggle his trunk."
John von Neumann

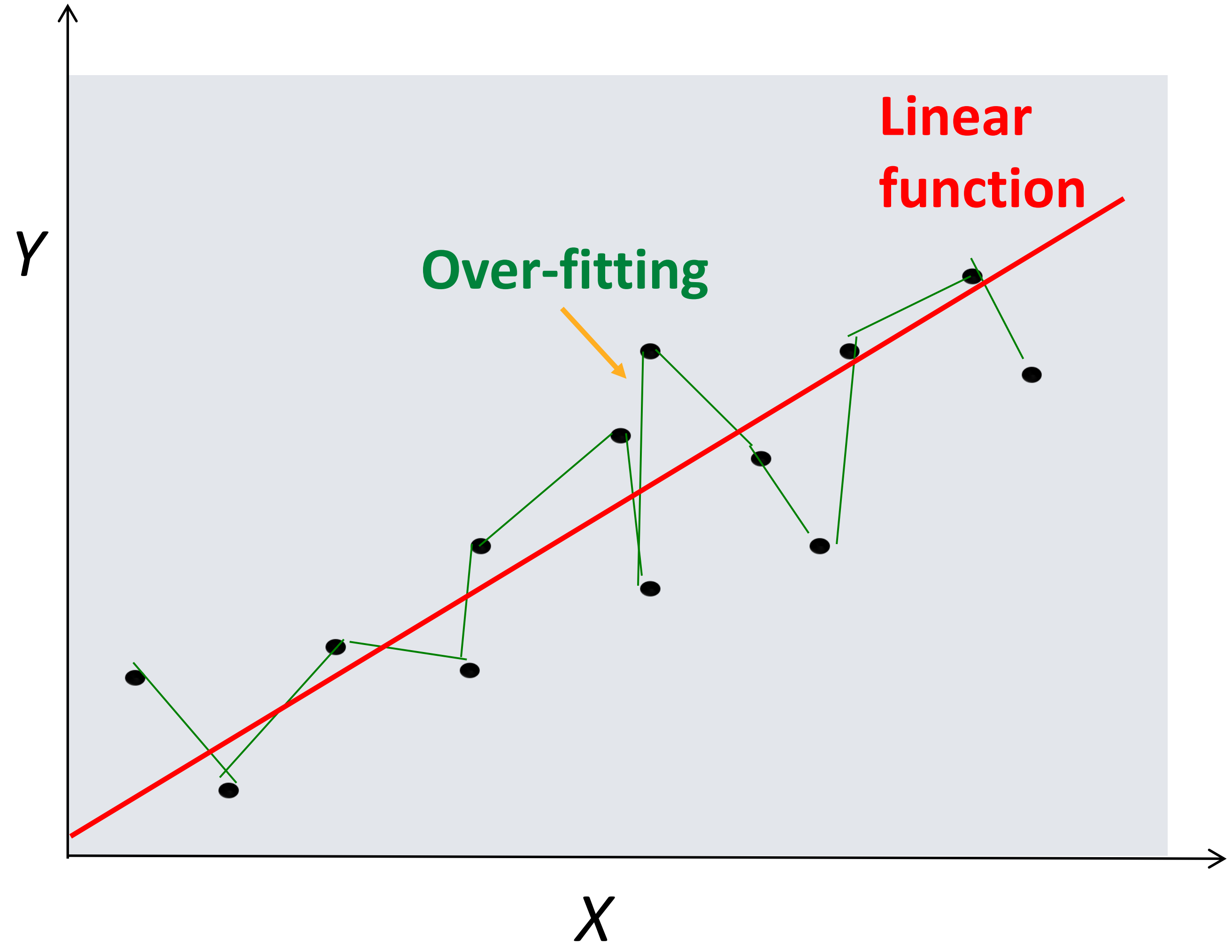
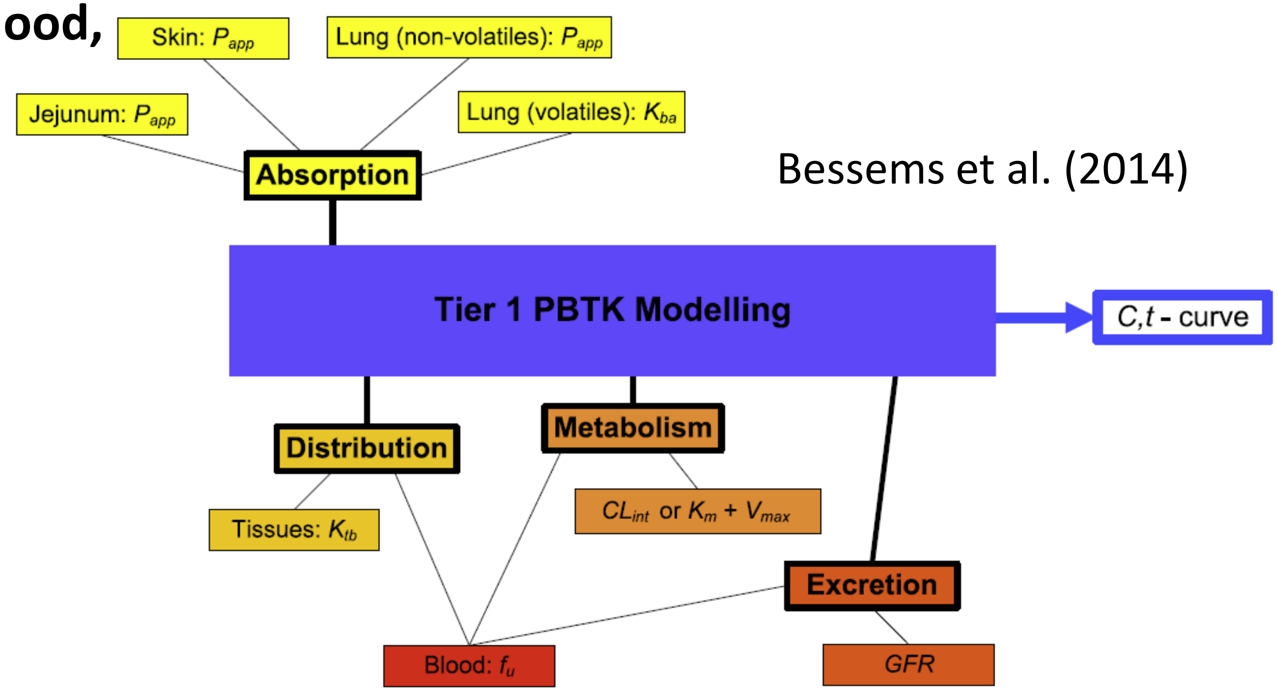



*Figure from Anran Wang*

# 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 the limited data** available to calibrate and test TK models 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




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*

# Exquisite Systems

"Although NASA has always partnered with industry, the nature of that relationship is changing. **Historically, NASA would design an exquisite system or spacecraft,** select a commercial contractor to build it, oversee its construction in detail while sometimes changing its requirements, then own and operate the result. The government was the sole buyer/owner."

After retirement of the Space Shuttle, NASA began working with multiple contractors who may provide their services to multiple customers. Once "…certified, the manufacturers would deliver cargo for NASA—and any other customer the company could engage in the growing LEO commercial marketplace. **Rather than building, owning, and operating a luxury sedan, NASA now essentially hails a taxi**."



From: https://www.nasa.gov/directorates/heo/scan/services/nasas_commercial_communications_services

# Why Use Generic Models?

- Each of the models provided by the R package "httk" is a generic model
  - Each model is designed to used standardized chemical-specific *in vitro* measurements (fraction unbound in plasma, intrinsic hepatic clearance)

**high(er) throughput toxicokinetics =**

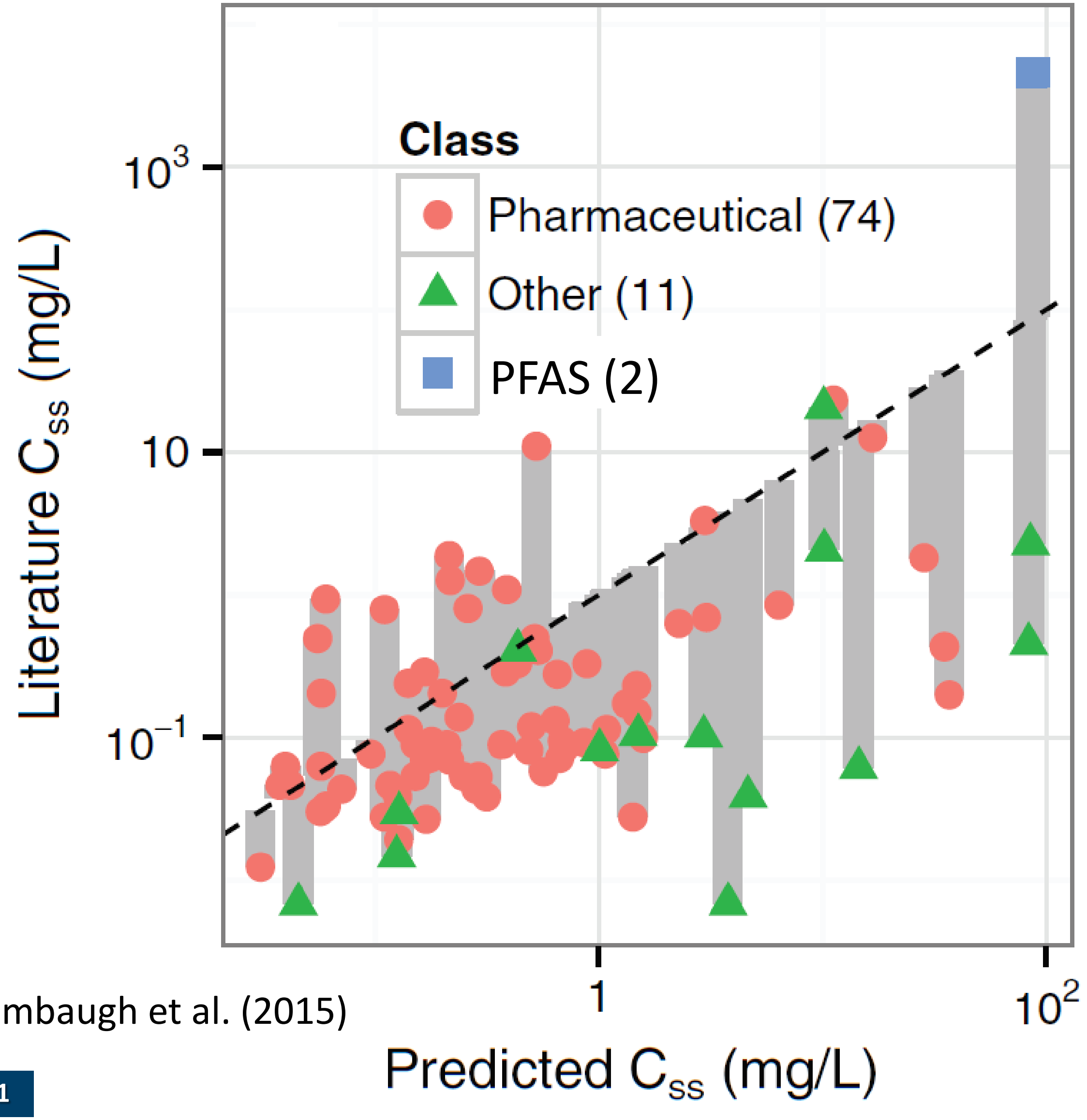
***In vitro* toxicokinetic data + generic toxicokinetic model**

- 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

- 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)

- We can estimate the accuracy of a generic model for a new chemical using performance across multiple chemicals where data happen to exist

# 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 to HTTK (that is, add a new 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

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# Generic PBTK Models

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

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*Int. J. Mol. Sci.* **2011**, *12*, 7469-7480; doi:10.3390/ijms12117469

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International Journal of
**Molecular Sciences**
**ISSN 1422-0067**
www.mdpi.com/journal/ijms

*Review*

**Development of a Human Physiologically Based Pharmacokinetic (PBPK) Toolkit for Environmental Pollutants**

**Patricia Ruiz [1,*], Meredith Ray [2], Jeffrey Fisher [3] and Moiz Mumtaz [1]**

1 Computational Toxicology and Methods Development Laboratory, Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, Atlanta, GA 3033 USA; E-Mail: mgm4@cdc.gov
2 Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of S Carolina, Columbia, SC 29208, USA; E-Mail: mere2110@yahoo.com
3 USFDA, National Center for Toxicological Research, Jefferson, AR 72079, USA; E-Mail: jeffrey.fisher@fda.hhs.gov

* Author to whom correspondence should be addressed; E-Mail: pruiz@cdc.gov; Tel.: +1-770-488-3348; Fax: +1-770-488-3470.

*Received: 20 September 2011; in revised form: 13 October 2011 / Accepted: 24 October 2011 / Published: 31 October 2011*

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*Ann. Occup. Hyg.*, Vol. 55, No. 8, pp. 841–864, 2011
© The Author 2011. Published by Oxford University Press on behalf of the British Occupational Hygiene Society
doi:10.1093/annhyg/mer075

**A Generic, Cross-Chemical Predictive PBTK Model with Multiple Entry Routes Running as Application**
… of

Clinical Pharmacokinetics
October 2006, Volume 4

Development
Based Pharm

Authors | Authors and affiliations

Andrea N. Edginton, Walter Schmitt, Stefan Willmann

Technology Evaluation

**Expert Opinion**

1. Introduction
2. The programming language
3. The platform structure
4. Applications of the simulator
5. Discussion
6. Expert opinion

**The Simcyp® Population-based ADME Simulator**

Masoud Jamei†, Steve Marciniak, Kairui Feng, Adrian Barnett, Geoffrey Tucker & Amin Rostami-Hodjegan
†*Modelling & Simulation Group, Simcyp Limited, Blades Enterprise Centre, John Street, Sheffield, S2 4SU, UK*

The Simcyp® population-based absorption, distribution, metabolism and excretion simulator is a platform and database for 'bottom-up' mechanistic modelling and simulation of the processes of oral absorption, tissue distribution, metabolism and excretion of drugs and drug candidates in healthy and disease populations. It combines experimental data generated routinely during preclinical drug discovery and development from *in vitro* enzyme and cellular systems and relevant physicochemical attributes of compound and dosage form with demographic, physiological and genetic information on different patient populations. The mechanistic approach implemented in the Simcyp Simulator allows simulation of complex absorption, distribution, metabolism and excretion outcomes, particularly those involving multiple drug interactions, parent drug and metabolite profiles and time- and dose-dependent phenomena such as auto-induction and auto-inhibition.

phthalate and di(2-e
as metabolites. Tiss
ronmental exposure
properties, reaction

Received 8 April 2005, Revised 25 May

# 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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# Regulatory Acceptance

TOXICOLOGICAL SCIENCES 126(1), 5–15 (2012)
doi:10.1093/toxsci/kfr295
Advance Access publication November 1, 2011

## Physiologically Based Pharmacokinetic Model Use in Risk Assessment—Why Being Published Is Not Enough

Eva D. McLanahan,*,[1] Hisham A. El-Masri,† Lisa M. Sweeney,‡ Leonid Y. Kopylev,|| Harvey J. Clewell,§ John F. Wambaugh,¶ and P. M. Schlosser||

"Although publication of a PBPK model in a peer-reviewed journal is a mark of good science, subsequent evaluation of published models and the supporting computer code is necessary for their consideration for use in [Human Health Risk Assessments]"

**The White House**
Office of the Press Secretary

For Immediate Release May 09, 2013

## Executive Order -- Making Open and Machine Readable the New Default for Government Information

EXECUTIVE ORDER

\- - - - - - -

MAKING OPEN AND MACHINE READABLE THE NEW DEFAULT FOR GOVERNMENT INFORMATION

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. General Principles. Openness in government strengthens our democracy, promotes the delivery of efficient and effective services to the public, and contributes to economic growth. As one vital benefit of open government, making information resources easy to find, accessible, and usable

"…the default state of new and modernized Government information resources shall be open and machine readable."

# 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 |
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Pre-computed HTTK results are also available at https://comptox.epa.gov/dashboard

# Models available within R package "httk"

# Open Source Tools and Data for HTTK

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

CRAN - Package httk

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

Apps | CompTox Chemical... | Article Request | Absence Request | Travel Forms | EHP | Change Password | FAITAS | Reading list

**httk: High-Throughput Toxicokinetics**

Generic models and chemical-specific data for simulation and statistical analysis of chemical toxicokinetics ("TK") as described by Pearce et al. (2017) <doi:10.18637/jss.v079.i04>. Chemical-specific in vitro data have been obtained from relatively high throughput experiments. Both physiologically-based ("PBTK") and empirical (for example, one compartment) "TK" models can be parameterized with the data provided for thousands of chemicals, multiple exposure routes, and various species. The models consist of systems of ordinary differential equations which are solved using compiled (C speed. A Monte Carlo sampler is included, which allows for simulating human biological variability (Ring et al., 2017 <doi:10.1016/j.envi propagating parameter uncertainty. Calibrated methods are included for predicting tissue:plasma partition coefficients and volume of distri 2017 <doi:10.1007/s10928-017-9548-7>). These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of hi screening data (for example, Tox21, ToxCast) to real-world exposures via reverse dosimetry (also known as "RTK") (Wetmore et al., 2015 <doi:10.1093/toxsci/kfv171>).

| | |
|---|---|
| Version: | 2.0.4 |
| Depends: | R (≥ 2.10) |
| Imports: | deSolve, msm, data.table, survey, mvtnorm, truncnorm, stats, graphics, utils, magrittr, purrr, methods |
| Suggests: | ggplot2, knitr, rmarkdown, R.rsp, GGally, gplots, scales, EnvStats, MASS, RColorBrewer, TeachingDemos, classInt, reshape2, gdata, viridis, CensRegMod, gmodels, colorspace, cowplot, ggrepel, dplyr, forcats, smatr, gtools, gridExtra, |
| Published: | 2021-05-10 |
| Author: | John Wambaugh [aut, cre], Robert Pearce [aut], Caroline Ring [aut], Greg Honda [aut], Mark Sfeir [aut], Sarah Davidson [aut], Miyuki Breen [ctb], Shannon Bell [ctb], Xiaoqing Chang [ctb], Jimena Davi [ctb], Nisha Sipes [ctb], Barbara Wetmore [ctb], Woodrow Setzer [ctb] |
| Maintainer: | John Wambaugh <wambaugh.john at epa.gov> |
| BugReports: | https://github.com/USEPA/CompTox-ExpoCast-httk |
| License: | GPL-3 |
| Copyright: | This package is primarily developed by employees of the U.S. Federal government as part of their official duties and i domain. |
| URL: | https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research |
| NeedsCompilation: | yes |
| Citation: | httk citation info |
| Materials: | NEWS |
| CRAN checks: | httk results |

Downloads:

Reference manual: httk.pdf

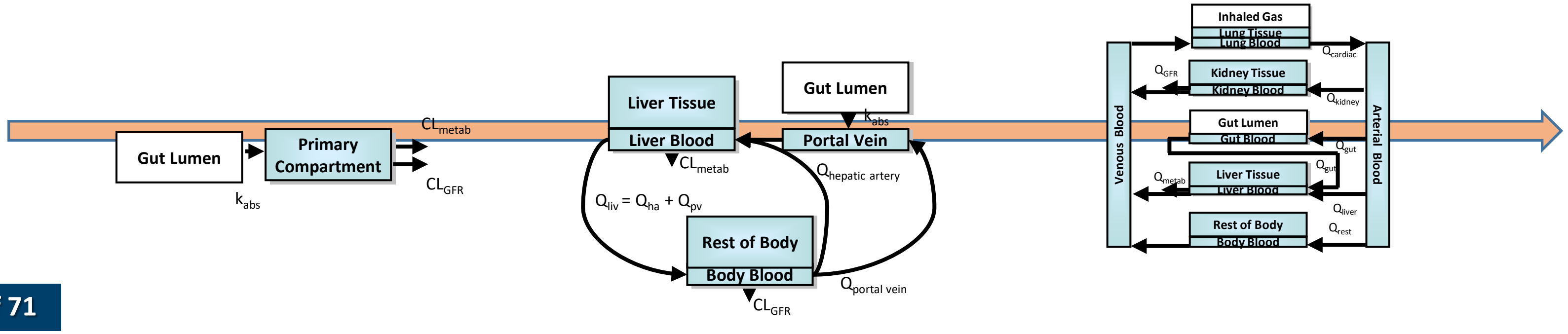
downloads 1071/month

## 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)

# HTTK Models Range in Complexity

| Model | Hepatic clearance | Partition coefficients | Fraction unbound | Hematocrit | Molecular weight | Ratio of blood to plasma | Elimination rate[1] | Volume of distribution[2] | Dynamic prediction | Steady state prediction |
|---|---|---|---|---|---|---|---|---|---|---|
| pbtk | Yes | Yes | Yes | Yes | Yes | Yes | **No** | **No** | Yes | Yes |
| Gas_pbtk | Yes | Yes | Yes | Yes | Yes | Yes | **No** | **No** | Yes | Coming Soon |
| 1compartment | **No** | **No** | **No** | **No** | Yes | **No** | Yes | Yes | Yes | Yes |
| 3compartment | Yes | Yes | Yes | Yes | Yes | Yes | **No** | **No** | Yes | Yes |
| 3compartmentss | Yes | **No** | Yes | **No** | Yes | **No** | **No** | **No** | **No** | Yes |




[1]Partition coefficients are needed in calculating $V_{dist}$

[2]Clearances and *fup* are needed in calculating $k_{elim}$

Adapted from Pearce et al. (2017a)

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# HTTK Models Range in Complexity

| Model | Hepatic clearance | Partition coefficients | Fraction unbound | Hematocrit | Molecular weight | Ratio of blood to plasma | Elimination rate[1] | Volume of distribution[2] | Dynamic prediction | Steady state prediction |
|---|---|---|---|---|---|---|---|---|---|---|
| pbtk | Yes | Yes | Yes | Yes | Yes | Yes | **No** | **No** | Yes | Yes |
| Gas_pbtk | Yes | Yes | Yes | Yes | Yes | Yes | **No** | **No** | Yes | Coming Soon |
| 1compartment | **No** | **No** | **No** | **No** | Yes | **No** | Yes | Yes | Yes | Yes |
| 3compartment | Yes | Yes | Yes | Yes | Yes | Yes | **No** | **No** | Yes | Yes |
| 3compartmentss | Yes | **No** | Yes | **No** | Yes | **No** | **No** | **No** | **No** | Yes |

- The simplest models often allow predictions with a single equation
- More complex models often require numerical solvers to determine the solution to a system of differential equations as a function of exposure (dose) and time



Adapted from Pearce et al. (2017a)

United States Environmental Protection Agency

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| Model | Hepatic clearance | Partition coefficients | Fraction unbound | Hematocrit | Molecular weight | Ratio of blood to plasma | Elimination rate[1] | Volume of distribution[2] | Dynamic prediction | Steady state prediction |
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| 1compartment | **No** | **No** | **No** | **No** | Yes | **No** | Yes | Yes | Yes | Yes |
| 3compartment | Yes | Yes | Yes | Yes | Yes | Yes | **No** | **No** | Yes | Yes |
| 3compartmentss | Yes | **No** | Yes | **No** | Yes | **No** | **No** | **No** | **No** | Yes |

- At steady-state all compartments are at equilibrium and the concentrations can be predicted with a single equation, **but**:
  - The exposure (dose) must be constant
  - Enough time must pass to reach equilibrium

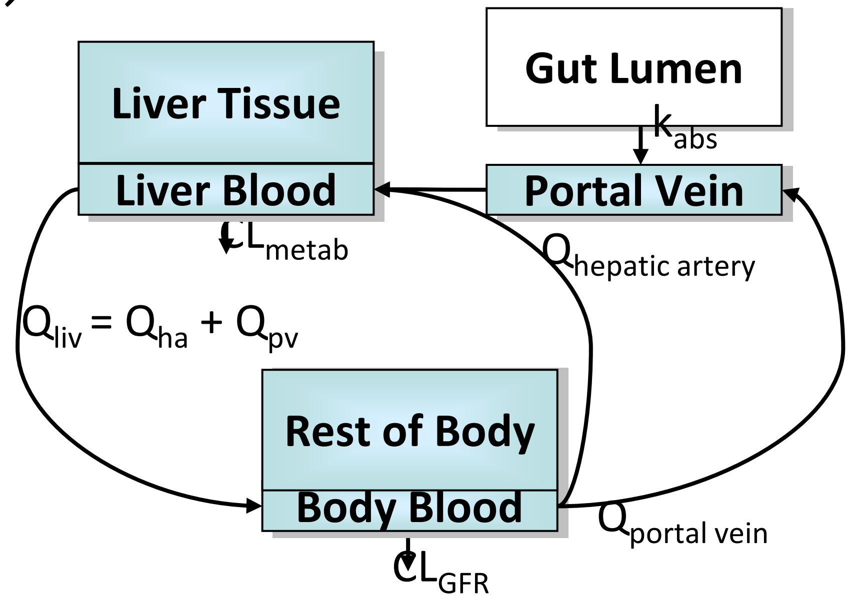


Adapted from Pearce et al. (2017a)

# Simple Model for Steady-State Plasma Concentration ($C_{ss}$)

- This equation is the steady-state solution for a three-compartment model (3compartmentss):

$$C_{ss} = \frac{oral\ dose\ rate\ * F_{hepfirstpass}}{(GFR * f_{up}) + \left(Q_l * f_{up} * \frac{Cl_{hepatic}}{Q_l + f_{up} * Cl_{hepatic}}\right)}$$




Wilkinson and Shand (1975)

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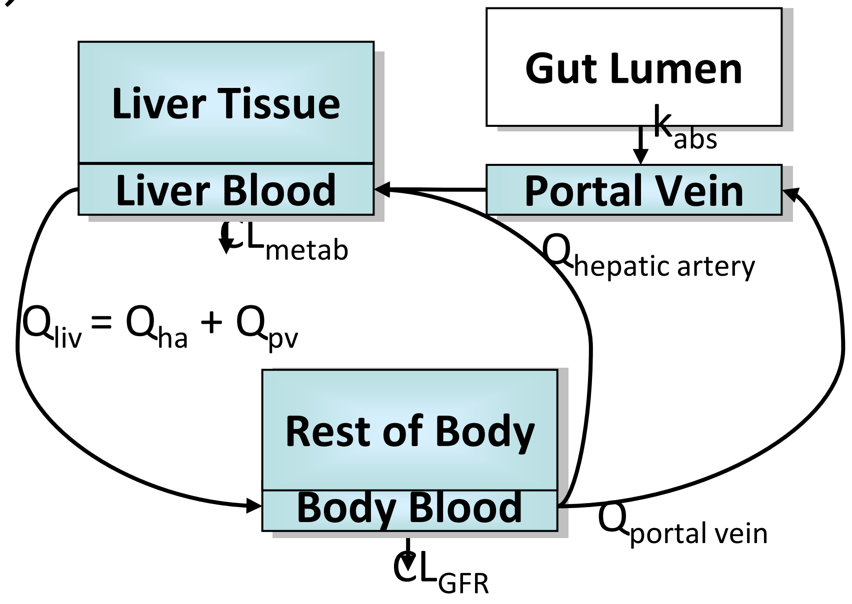
Estimated fraction not metabolized in first pass through liver before systemic circulation




Wilkinson and Shand (1975)

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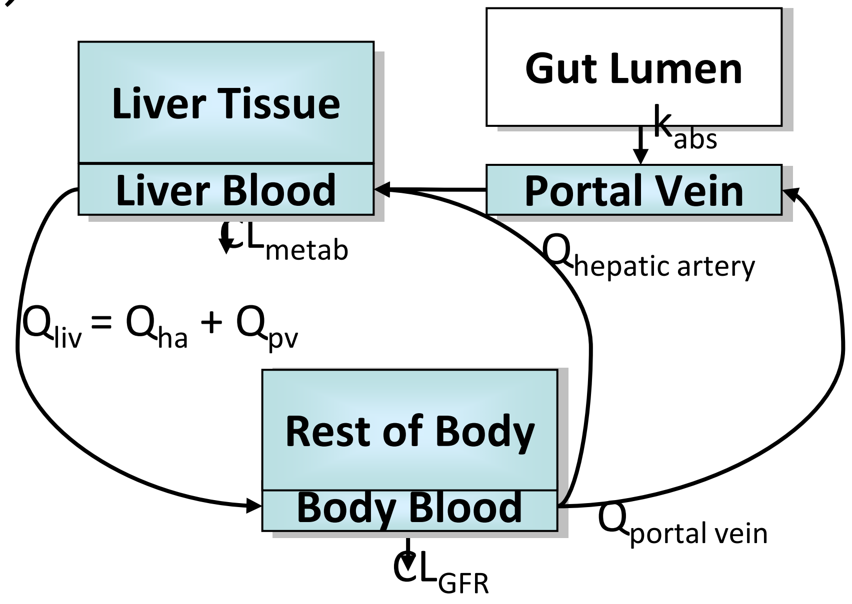
Passive Renal Clearance (GFR: Glomerular filtration rate
$f_{up}$: fraction unbound in plasma)

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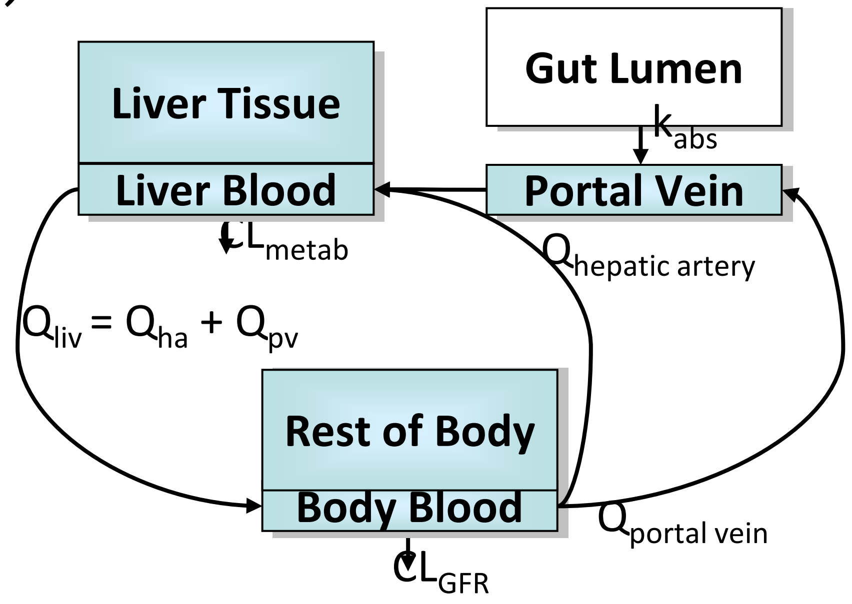
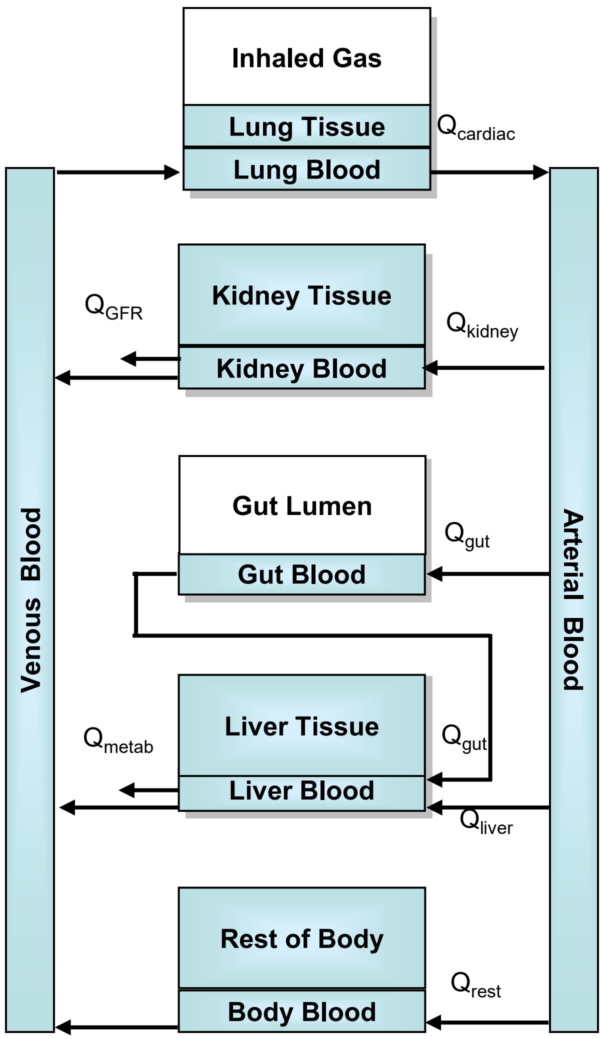
Hepatic Metabolism
($Cl_{hepatic}$: Scaled hepatic clearance
$Q_l$: Blood flow to liver)




Wilkinson and Shand (1975)

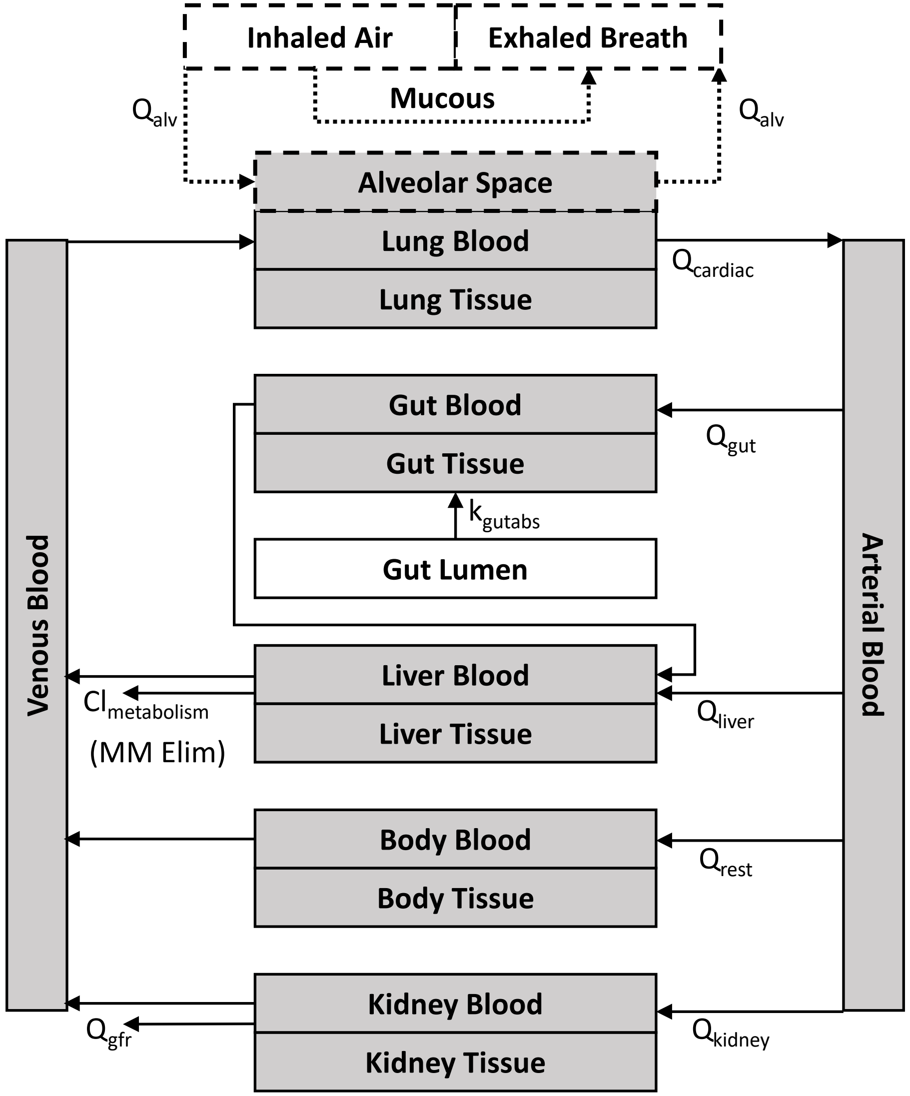
# The "httk" General Physiologically-based Toxicokinetic (PBTK) Model




Pearce et al. (2017a)

- Tissues are modeled by compartments:
  - Some tissues (for example, arterial blood) are simple compartments
  - Others (for example, kidney) are compound compartments consisting of separate blood and tissue sections with constant partitioning (that is, tissue specific tissue:plasma partition coefficients)
  - Remaining tissues (for example, fat, brain, bones) are lumped into the "Rest of Body" compartment
- Clearance from the body depends on two processes:
  - Metabolism in the liver (estimated from *in vitro* clearance and binding)
  - Excretion by glomerular filtration in the kidney (estimated from *in vitro* binding)
- 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

# Generic Gas Inhalation Model




Linakis et al. (2020)

- Inhalation is an important route of exposure, particularly for occupational settings
- The structure of the inhalation model was developed from two previously published physiologically-based models from Jongeneelen *et al.* (2011) and Clewell *et al*. (2001)
- The model can be parameterized with chemical-specific *in vitro* data from the HTTK package for 917 chemicals in human and 181 chemicals in rat
- Model was made publicly available with the release of httk v2.0.0 in February 2020

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# Model parameterization

# 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 (scaled to kg body weight) | 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) |

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



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
  - Users can choose to add new species to HTTK by providing this information

| 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 |


- Davies, Brian, and Tim Morris. "Physiological parameters in laboratory animals and humans." Pharmaceutical research 10.7 (1993): 1093-1095.
- Brown, Ronald P., et al. "Physiological parameter values for physiologically based pharmacokinetic models." Toxicology and industrial health 13.4 (1997): 407-484.
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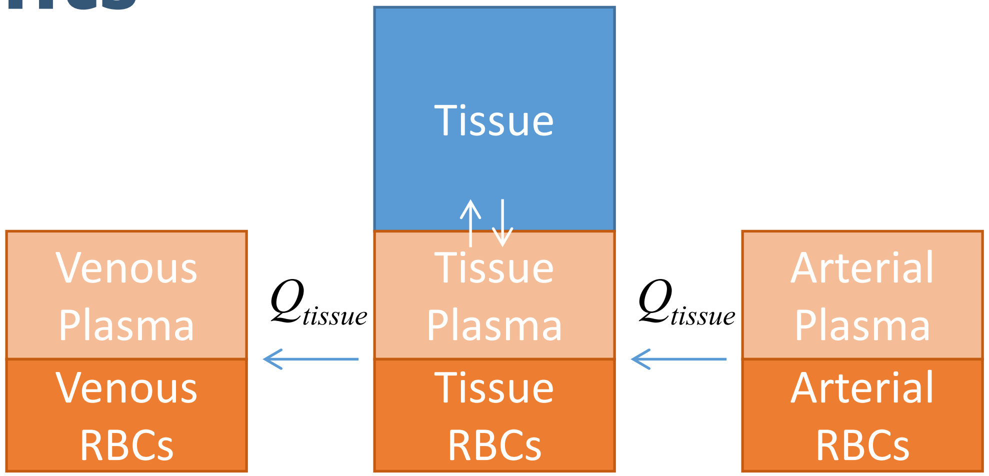
# PBTK Partition Coefficients

- 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)**

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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

*Received 4 M*

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Available online at www.sciencedirect.com
ScienceDirect
Toxicology in Vitro 22 (2008) 457–467
Toxicology in Vitro
www.elsevier.com/locate/toxinvit

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


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

*Receive*
*Publish*

Toxicology and Applied Pharmacology 249 (2010) 197–207
Contents lists available at ScienceDirect
ELSEVIER
Toxicology and Applied Pharmacology
journal homepage: www.elsevier.com/locate/ytaap

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

Thomas Peyret[a], Patrick Poulin[b], Kannan Krishnan[a,*]
[a] *DSEST, Université de Montréal, Canada H3T 1A8*
[b] *Consultant, 4009 rue Sylvia Daoust, Québec City, Québec, Canada G1X 0A6*

# Schmitt's Method (2008)

- Depending on its structure a chemical partitions differently into water, fats, and charged materials
- Schmitt's method predicts chemical affinity based on the composition of a tissue
  - Users can choose to add new tissue to HTTK by providing this information

| | Fraction of total volume | | Fraction of cell volume | | | Fraction of total lipid | | | |
|---|---|---|---|---|---|---|---|---|---|
| Tissue | Cells | Interstitium | Water | Lipid | Protein | Neutral Lipid | Neutral Phospholipid | Acidic Phospholipid | pH |
| Adipose | 0.86 | 0.14 | 0.02 | 0.93 | 0.05 | 0.94 | 0.06 | 0.01 | 7.10 |
| Bone | 0.90 | 0.10 | 0.26 | 0.02 | 0.21 | 0.85 | 0.11 | 0.04 | 7.00 |
| Brain | 1.00 | 0.01 | 0.80 | 0.11 | 0.08 | 0.37 | 0.46 | 0.17 | 7.10 |
| Gut | 0.90 | 0.10 | 0.78 | 0.07 | 0.15 | 0.69 | 0.26 | 0.05 | 7.00 |
| Heart | 0.75 | 0.25 | 0.70 | 0.14 | 0.17 | 0.89 | 0.08 | 0.03 | 7.10 |
| Kidney | 0.84 | 0.17 | 0.77 | 0.06 | 0.17 | 0.64 | 0.29 | 0.07 | 7.22 |
| Liver | 0.77 | 0.23 | 0.72 | 0.09 | 0.18 | 0.72 | 0.23 | 0.05 | 7.23 |
| Lung | 0.80 | 0.20 | 0.80 | 0.01 | 0.18 | 0.30 | 0.56 | 0.14 | 6.60 |
| Muscle | 0.85 | 0.15 | 0.80 | 0.02 | 0.18 | 0.54 | 0.38 | 0.08 | 6.81 |
| Skin | 0.40 | 0.60 | 0.43 | 0.28 | 0.29 | 0.36 | 0.50 | 0.14 | 7.00 |
| Spleen | 0.75 | 0.26 | 0.77 | 0.04 | 0.19 | 0.53 | 0.39 | 0.07 | 7.00 |
| Red blood cells | 1.00 | 0.00 | 0.66 | 0.01 | 0.33 | 0.40 | 0.50 | 0.10 | 7.20 |

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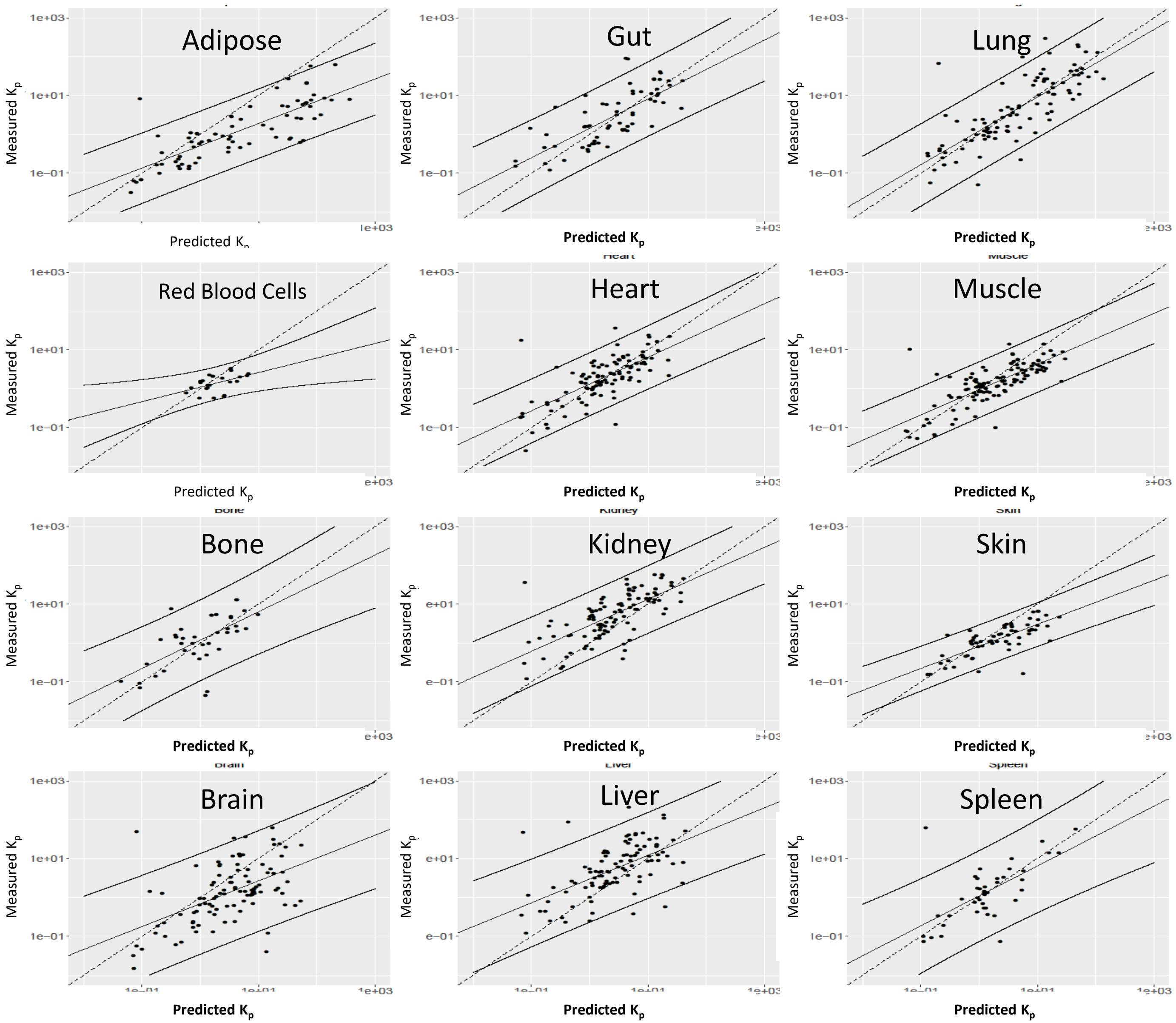
# HTTK Partition Coefficients

- We use a modified Schmitt (2008) method with elements of Peyret et al. (2010)
- Pearce et al. (2017b) analyzed literature measurements of chemical-specific partition coefficients (PC) in rat
  - 945 tissue-specific PC
  - 137 unique chemicals
  - Mostly pharmaceuticals
- We use tissue-specific calibrations for the *in silico* predictors
- Pearce et al. (2017b) evaluated with human measured volumes of distribution for 498 chemicals from Obach (2008) – root mean squared error was 0.48

Pearce et al. (2017b)



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# Review: HTTK 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 | |

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# 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)

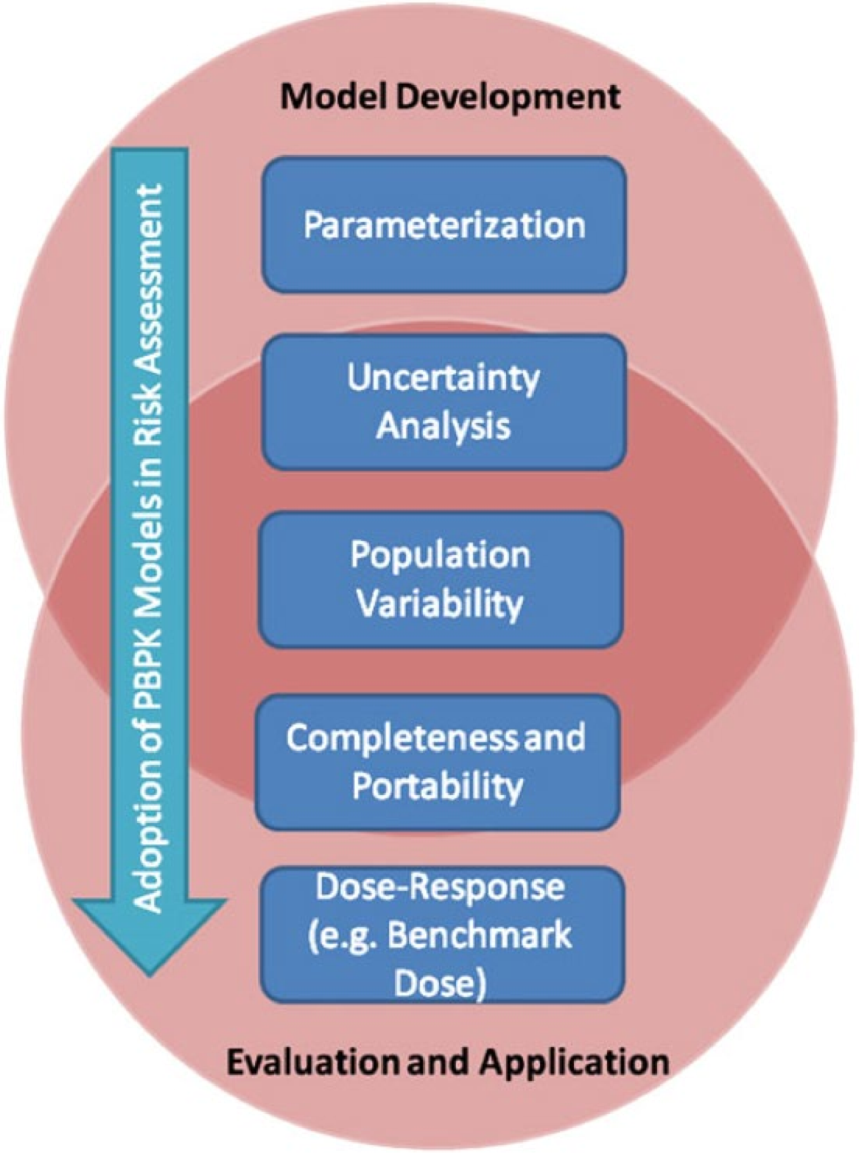



**FIG. 1.** This figure shows examples of key considerations during model development, evaluation, and application that are necessary before a PBPK model may be adopted for use in a HHRA.

McLanahan et al. (2012)

# 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

# Statistical Analysis with HTTK

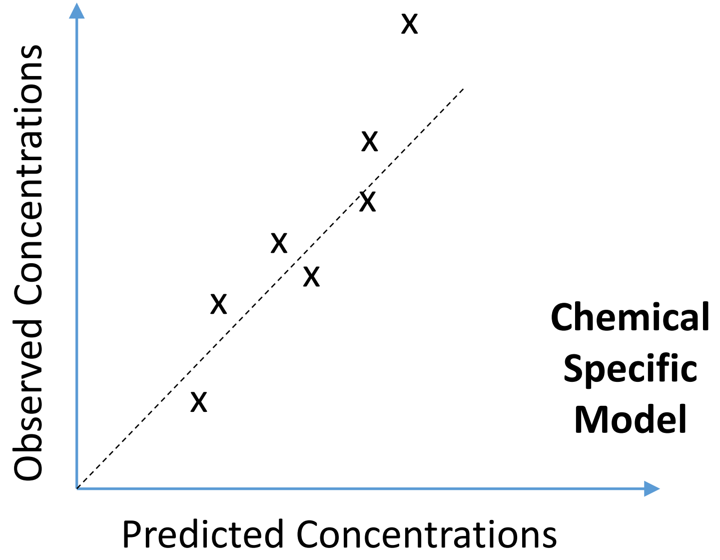
- If we are to use HTTK, then we need confidence in its predictive ability

- In drug development, HTTK methods estimate therapeutic doses for clinical studies – predicted concentrations are typically on the order of values measured in clinical trials (Wang, 2010)
  - For most compounds in the environment there will be no clinical trials

- Uncertainty must be well characterized
  - We compare to *in vivo* data to get **empirical estimates of HTTK uncertainty**
  - ORD has both compiled existing (literature) TK data (Wambaugh *et al*., 2015) and conducted new experiments in rats on chemicals with HTTK *in vitro* data (Wambaugh *et al*., 2018)
  - Any approximations, omissions, or mistakes should work to increase the estimated uncertainty when evaluated systematically across chemicals

# 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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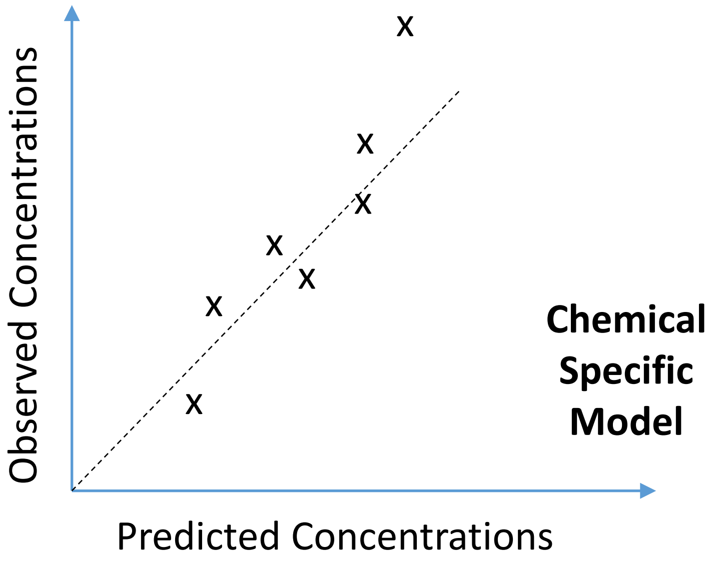
- However, we do not typically have TK data

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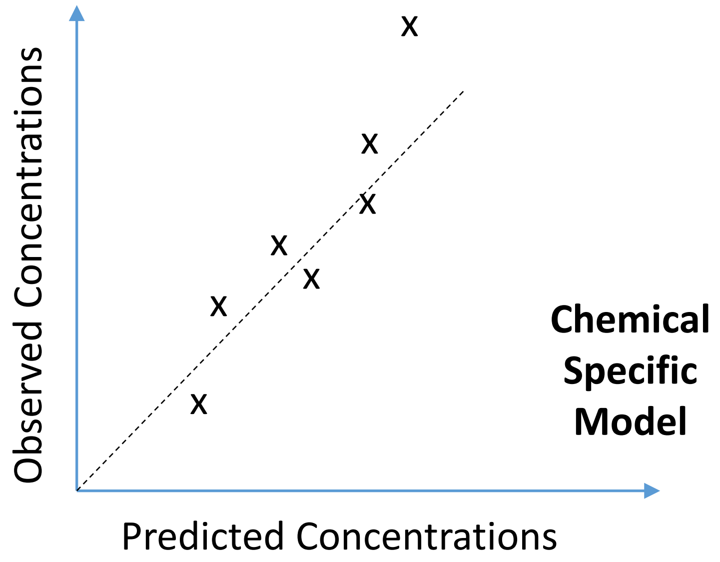
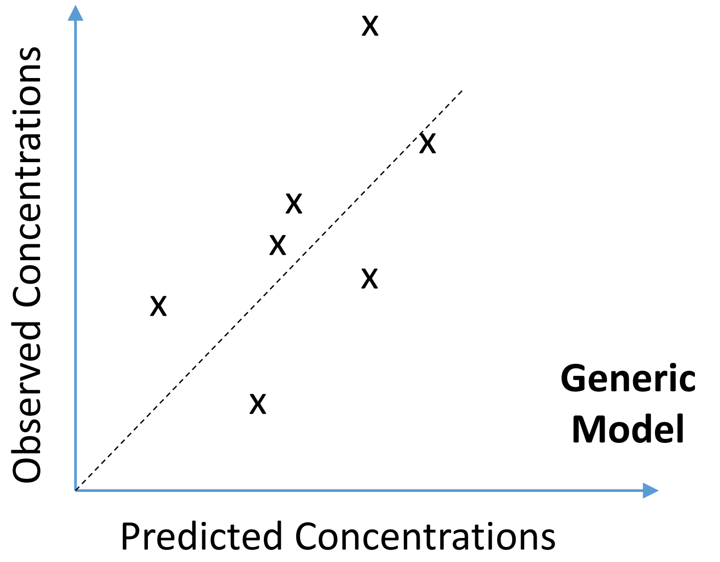
- However, we do not typically have TK data

- 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)

# Building Confidence in TK Models

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  - Can estimate bias
  - Can estimate uncertainty
  - Can consider using model to extrapolate to other situations (dose, route, physiology) where you have no data

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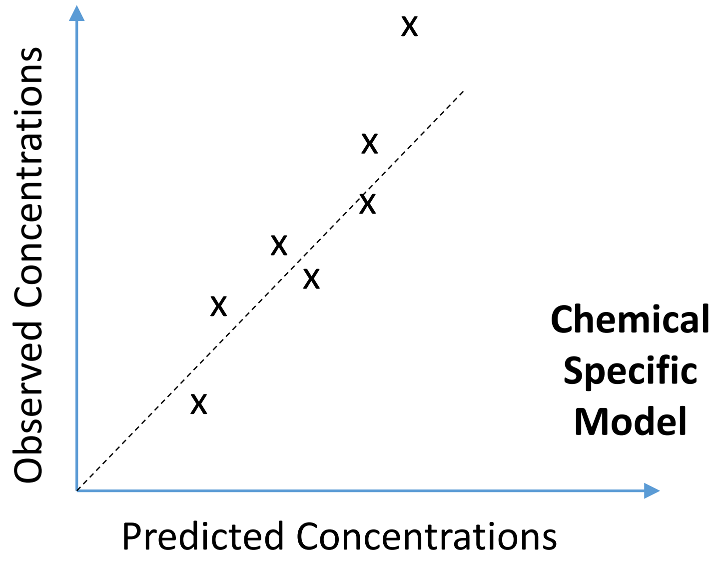
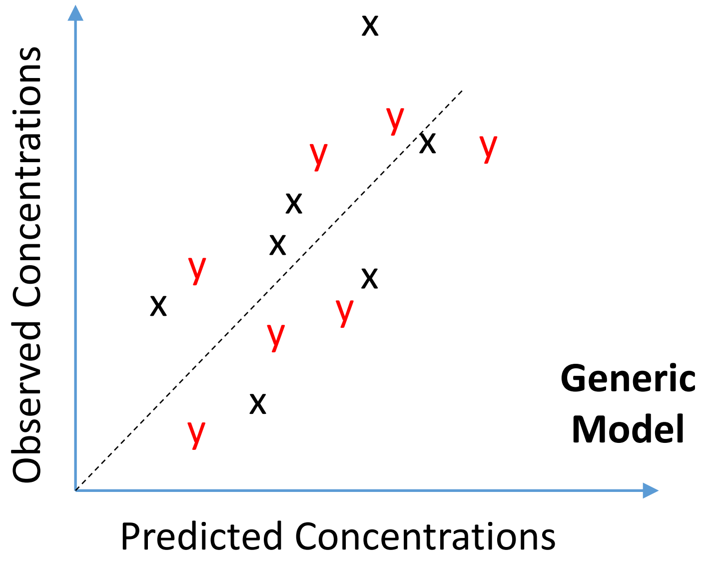
  - We do expect larger uncertainty, but also greater confidence in model implementation
  - Estimate bias and uncertainty, and try to correlate with chemical-specific properties
  - Can consider using model to extrapolate to other situations (chemicals without *in vivo* data)



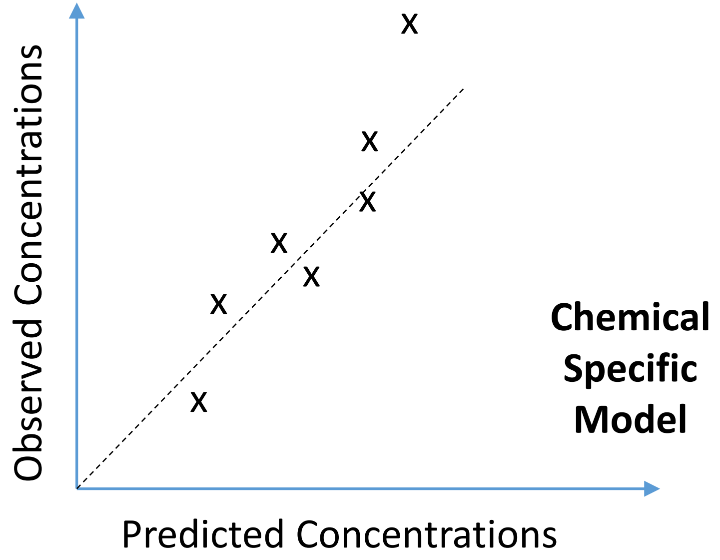

Cohen Hubal et al. (2019)

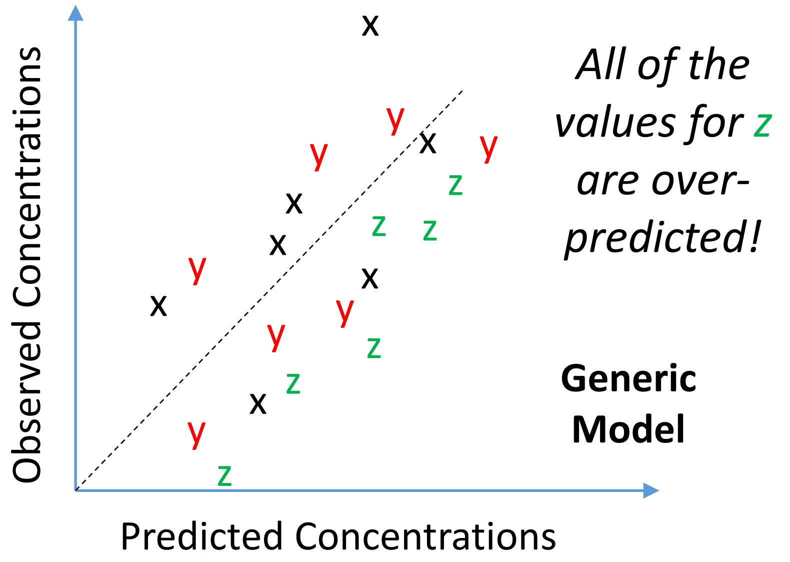
# Building Confidence in TK Models

- 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

- However, we do not typically have TK data

- 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
  - Can consider using model to extrapolate to other situations (chemicals without *in vivo* data)



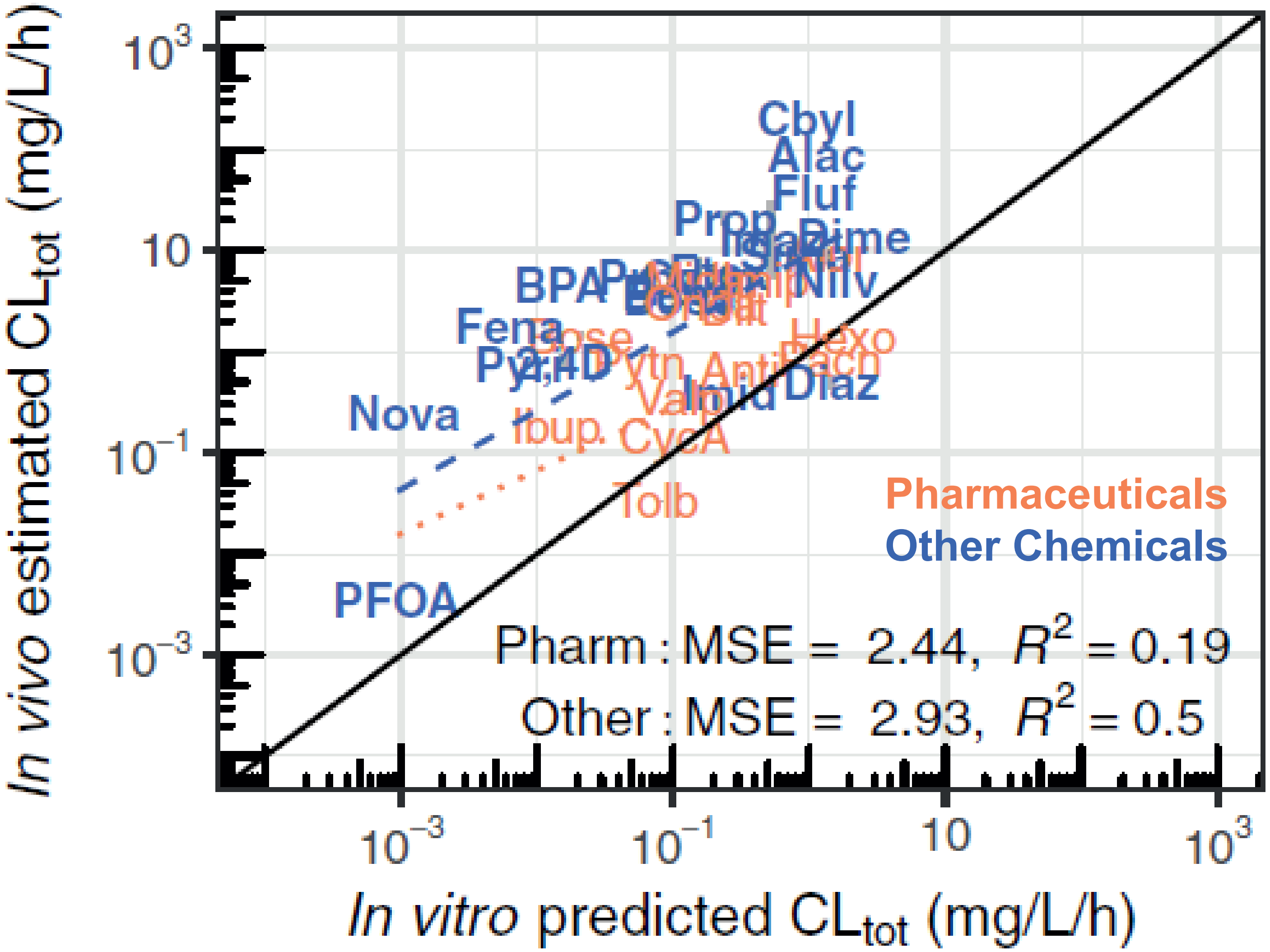

Cohen Hubal et al. (2019)

# 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

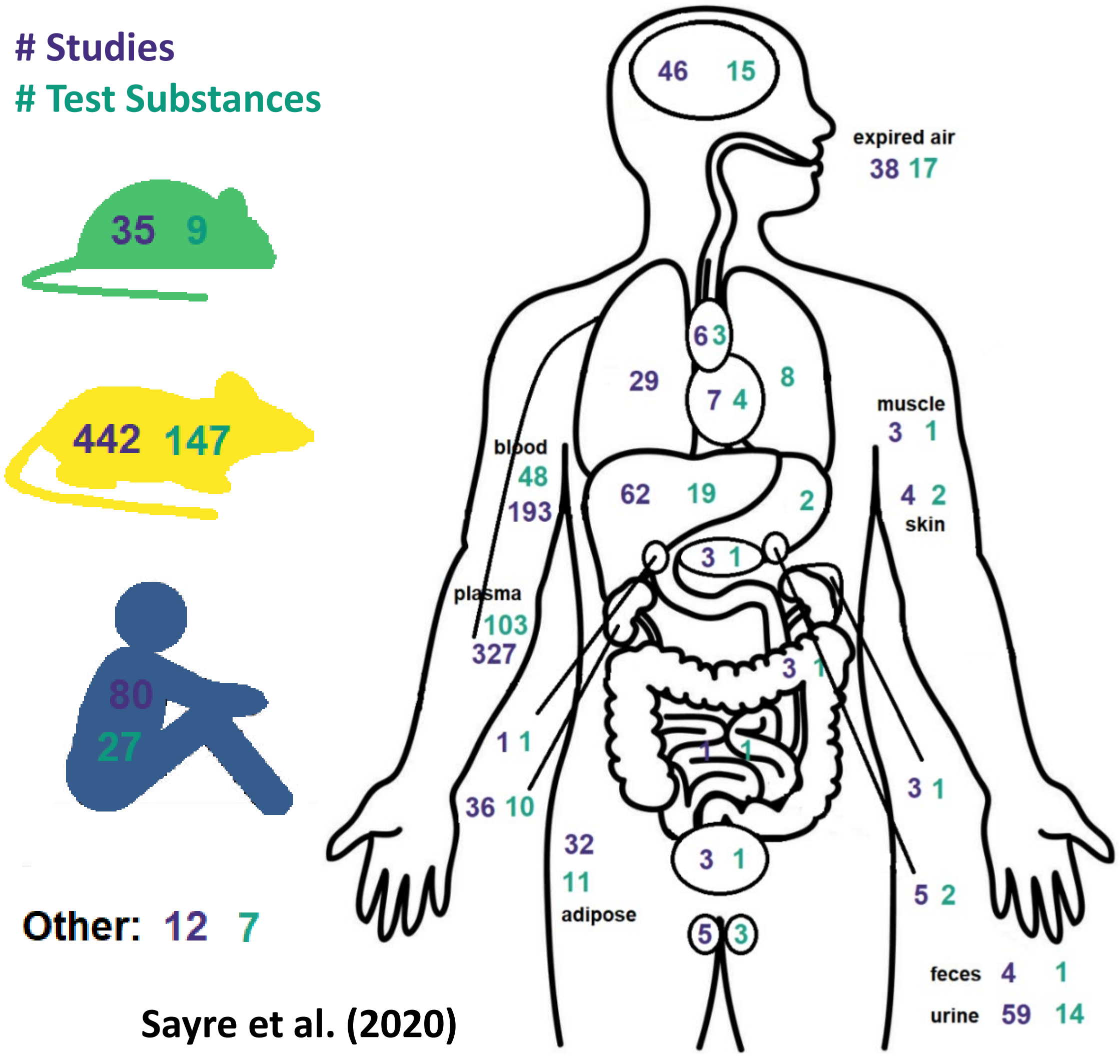
https://github.com/USEPA/CompTox-PK-CvTdb

- 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:

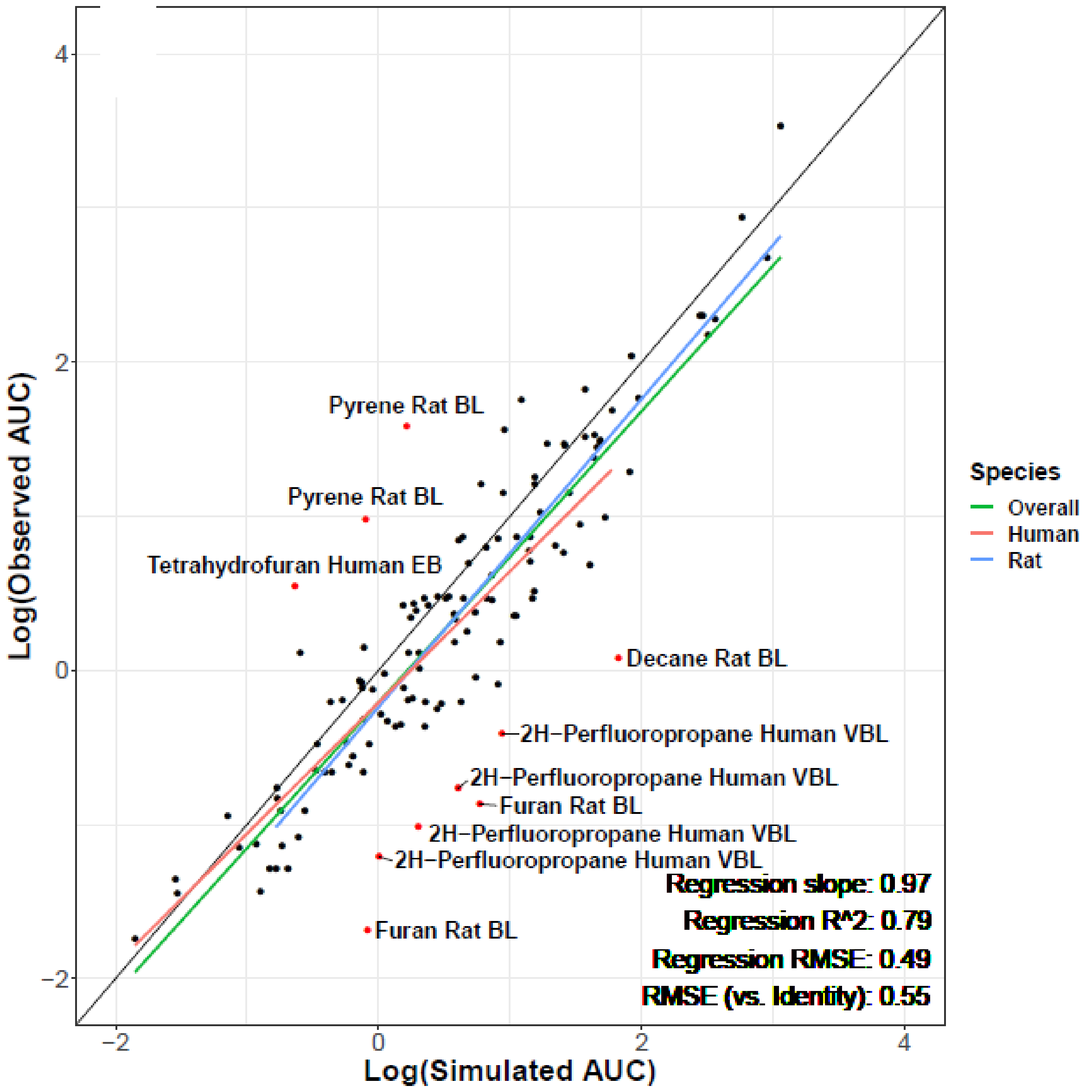
https://github.com/USEPA/CompTox-ExpoCast-invivoPKfit




Sayre et al. (2020)

# Developing Models with the CvT Database

- USAF and EPA developed 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)

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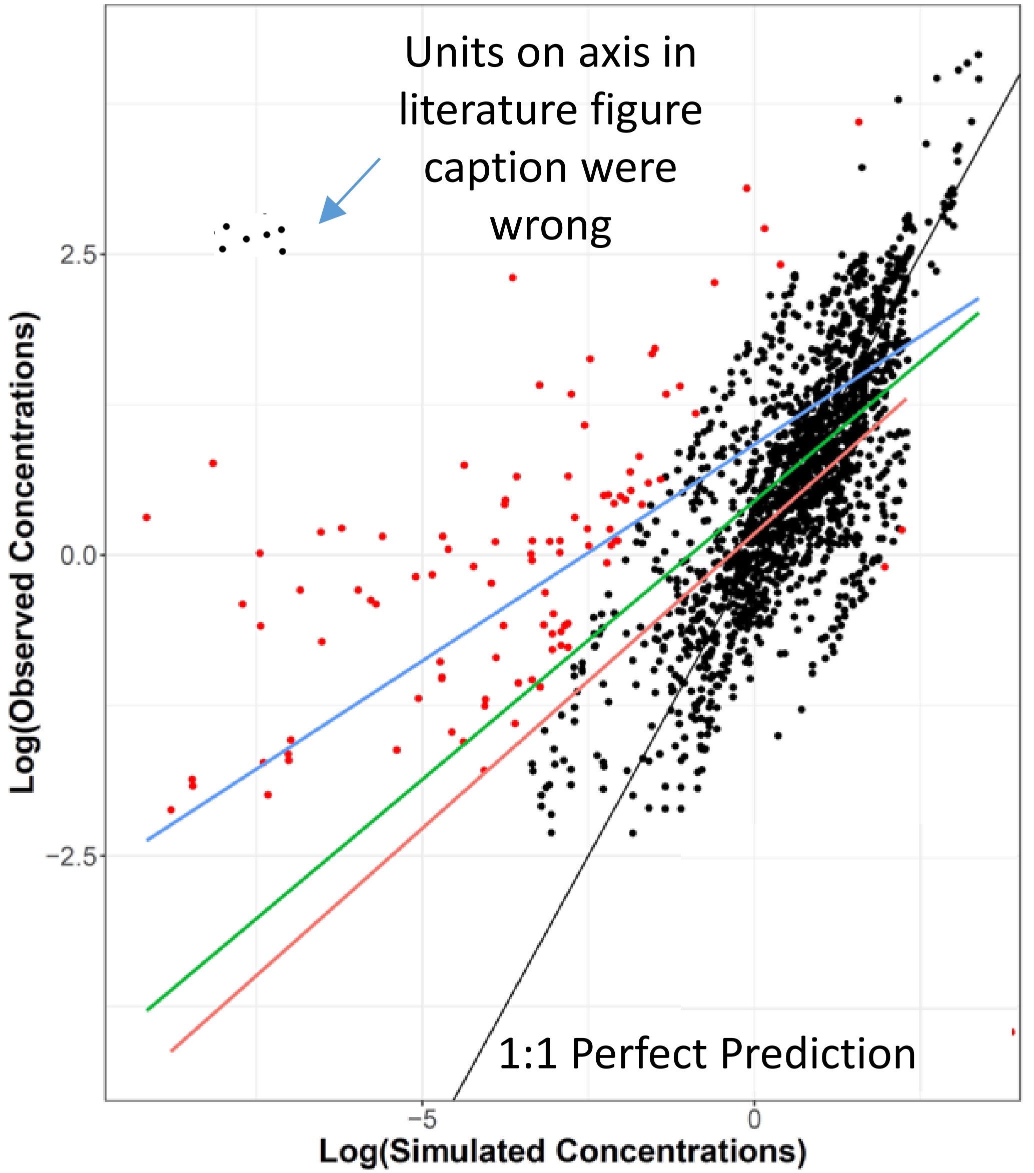
# Developing Models with the CvT Database

- Access to *in vivo* concentration vs. time data made it easier to identify coding and other modeling errors
- **Access to *in vivo* concentration vs. time data also made it easier to find fault with specific data sets**




Linakis et al. (2020)

# Review of HTTK Evaluations

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

- 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

- 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. (2020)

# Conclusions

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# Verifying the HTTK R Package

| | Clark et al. (2004) Process for the Evaluation of PBPK Models | Evaluation of HTTK R Package |
|---|---|---|
| | Assessment of Model Purpose | |
| | Assessment of Model Structure and Biology | |
| | Assessment of Mathematical Descriptions | |
| | Assessment of Computer Implementation | |
| | Parameter Analysis and Assessment of Model Fitness | |
| | Assessment of any Specialized Analyses | |

# Verifying the HTTK R Package

| | Clark et al. (2004)<br>Process for the Evaluation of PBPK Models | Evaluation of HTTK R Package |
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| √ | Assessment of Computer Implementation | Open-source code available from GitHub (https://github.com/USEPA/CompTox-ExpoCast-httk) and CRAN (https://CRAN.R-project.org/package=httk) where bugs can be reported and patched |
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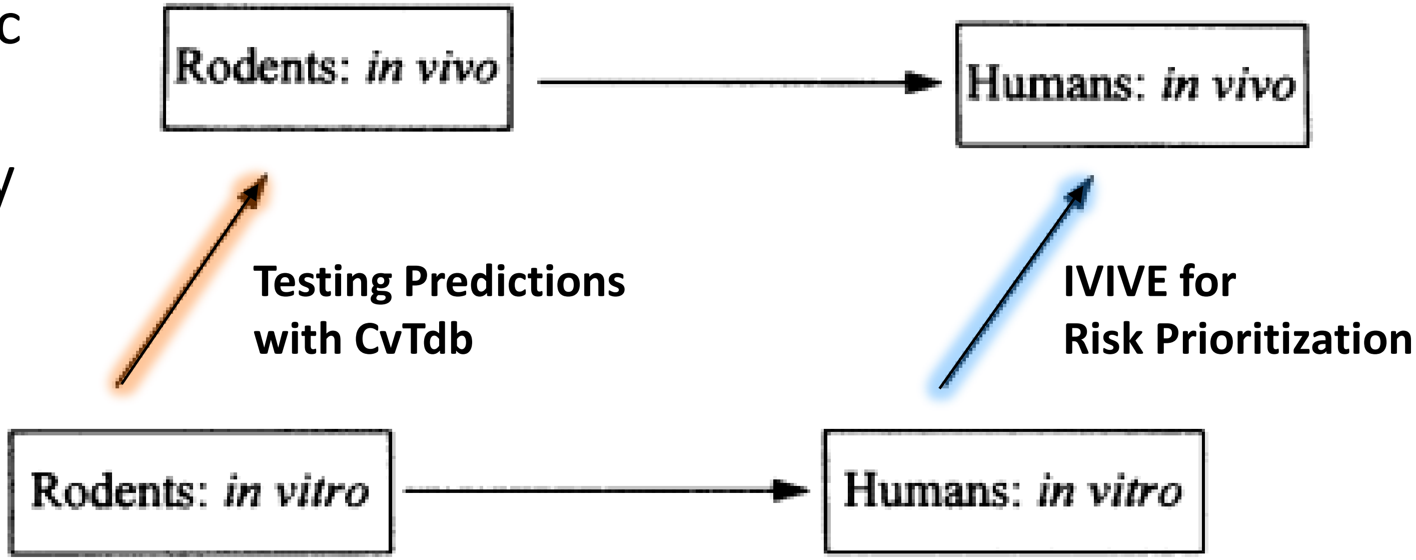
| √ | Parameter Analysis and Assessment of Model Fitness | Model fitness quantified through comparison with CvTdb |
| √ | Assessment of any Specialized Analyses | Population variability simulator httk-pop has been published (Ring et al., 2017) and is being revised with most recent NHANES biometrics (Breen et al., in prep.) |

# Conclusions

- The *in vitro*-measured chemical specific parameters may be used to build a variety of models ranging in complexity from steady-state to full PBTK
- Chemical-independent information on physiology and tissue composition allow predictions of chemical distribution




- Generic models allow for verification of model implementation
- Comparing model predictions for chemicals with *in vivo* data allows estimation of confidence in predictions for chemicals without *in vivo* data

# There is time for questions now followed by a BREAK

## Talk Three will begin at 2:00 PM EST

# Feel free to contact me at: wambaugh.john@epa.gov

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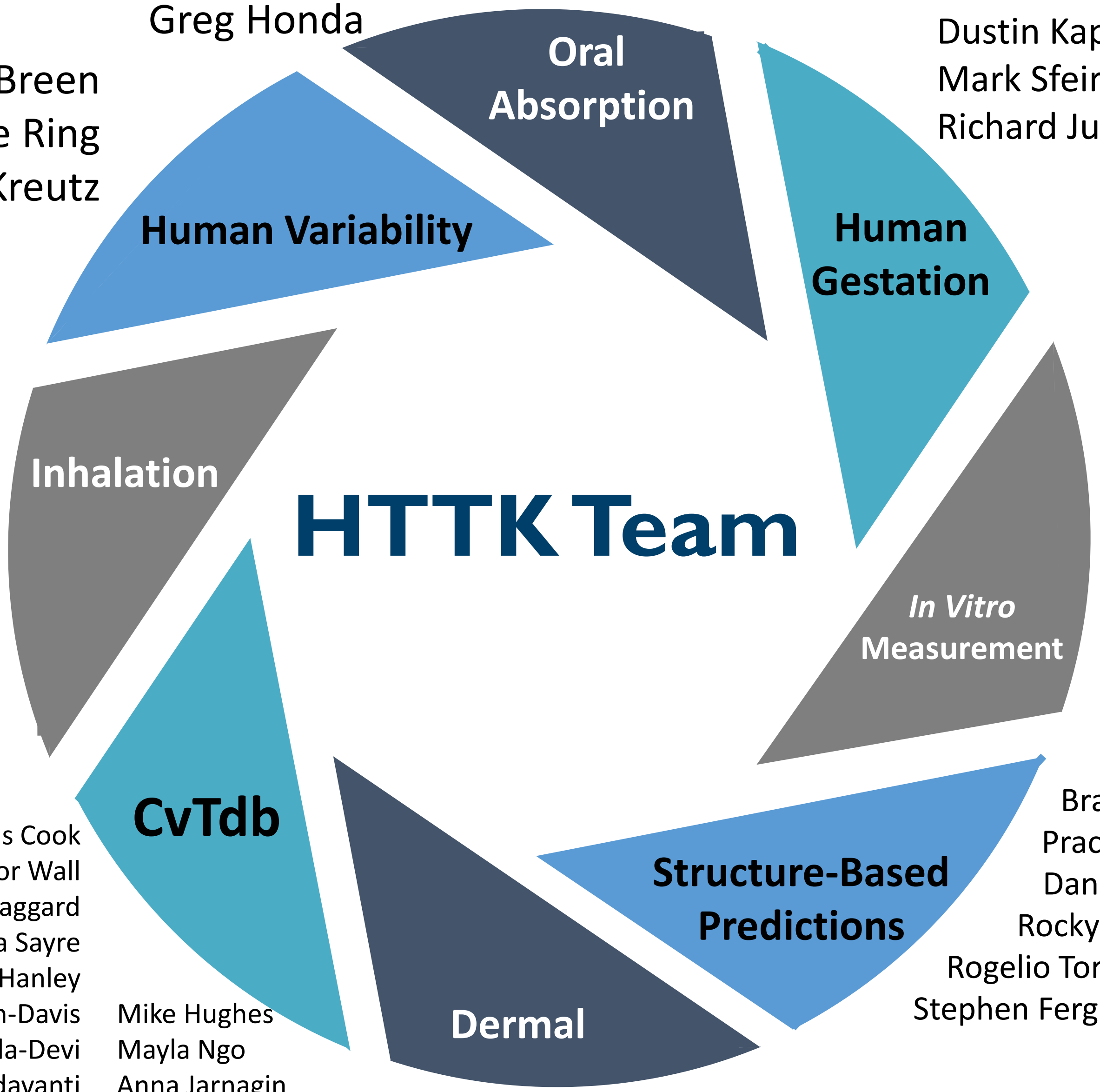
Evgenia Korol-Bexell
Greg Honda

Miyuki Breen
Caroline Ring
Anna Kreutz

Dustin Kapraun
Mark Sfeir
Richard Judson

Tom Knudsen
Annie Lumen (FDA)

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**Janice Lau**
David Ayres

Roger Dinallo
Chris Strock

EPA

Anna Kreutz
Marci Smeltz
Evgenia Korol-Bexell

Lucas Albrecht
**Barbara Wetmore**

Matt Linakis (Ramboll)
Heather Pangburn (USAF)
Jeffery Gearhart (USAF)
Kristin Isaacs
Marina Evans
Miyuki Breen

**Sarah Davidson**
Russell Thomas
Mike Devito
Katie Paul-Friedman
David Murphy
Katherine Coutros
Ann Richard
Tony Williams

Chris Cook
Taylor Wall
Derik Haggard
Risa Sayre
Nancy Hanley
Karen Herbin-Davis
Tirumala-Devi Kodavanti
Evgenia Korol-Bexell
**Showa Pharmaceutical Universitay**

Mike Hughes
Mayla Ngo
Anna Jarnagin
Lucas Albrecht
Anna Kreutz

Marina Evans
Longjian Chen (Unilever)

Tom Moxon (Unilever)
Beate Nicol (Unilever)

Brandall Ingle
Prachi Pradeep
Daniel Dawson
Rocky Goldsmith
Rogelio Tornero-Velez
Stephen Ferguson (NTP)

Richard Judson
Jon Arnot (ARC)
Ester Papa
Kamel Mansouri (NIH)
Michael Lawless (Simulations Plus)

***Alumni***

Robert Pearce
Woody Setzer
Mark Sfeir
Nisha Sipes

Greg Honda
Chantel Nicolas
Cory Strope
Jimena Davis

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