EPA United States Environmental Protection Agency

62nd Annual Meeting & ToxExpo • Nashville, TN
March 19–23, 2023

Enabling Risk-Based Decisions with Pharmaco- and Toxicokinetic Models while Addressing Transparency and Reproducibility

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Workshop:
Crucial role of Physiologically-Based (Pharmaco-)kinetic (PBK) Modelling in Human Health Risk Assessment in Different Sectors

Tuesday, March 21, 2023

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United States Environmental Protection Agency

Conflict of Interest Statement

The author declares no conflict of interest

US EPA Office of Research and Development

- The Office of Research and Development (ORD) is the scientific research arm of EPA
- 539 peer-reviewed journal articles in 2021
- Research is conducted by ORD's four national centers organized to address:
  - Public health and environmental assessment
  - Computational toxicology and exposure
  - Environmental measurement and modeling
  - Environmental solutions and emergency response
- 13 facilities across the United States
- Research conducted by a combination of Federal scientists, including uniformed members of the **Public Health Service**; contract researchers; and postdoctoral, graduate student, and post-baccalaureate trainees

ORD Facility in
Research Triangle Park, NC

Today's Workshop:
Crucial role of Physiologically-Based (Pharmaco-) kinetic (PBK) Modelling in Human Health Risk Assessment in Different Sectors

- Shi and Zha (2018): Clinical trial failures caused by pharmacokinetics and bioavailability have been reduced due to PBK/PBPK/PBTK
  - "One of the most popular and fast-growing techniques over the past 2 decades, with applications in both drug development and regulatory science."

- Pharmaceutical industry relies on PBPK models for drug lead optimization, design of clinical trials, and extrapolation to sensitive scenarios

- For non-pharmaceutical commercial chemicals and any chemical present in the environment, next generation risk assessment (NGRA) will rely on new approach methodologies (NAMs) to fill critical biological data gaps and inform points of departures

- EPA New Approach Methods Work Plan (2021): Five objectives for reducing animal testing while ensuring that Agency decisions remain fully protective of human health and the environment
  - PBPK models are necessary for extrapolating from data obtained under *in vitro* conditions to *in vivo* scenarios

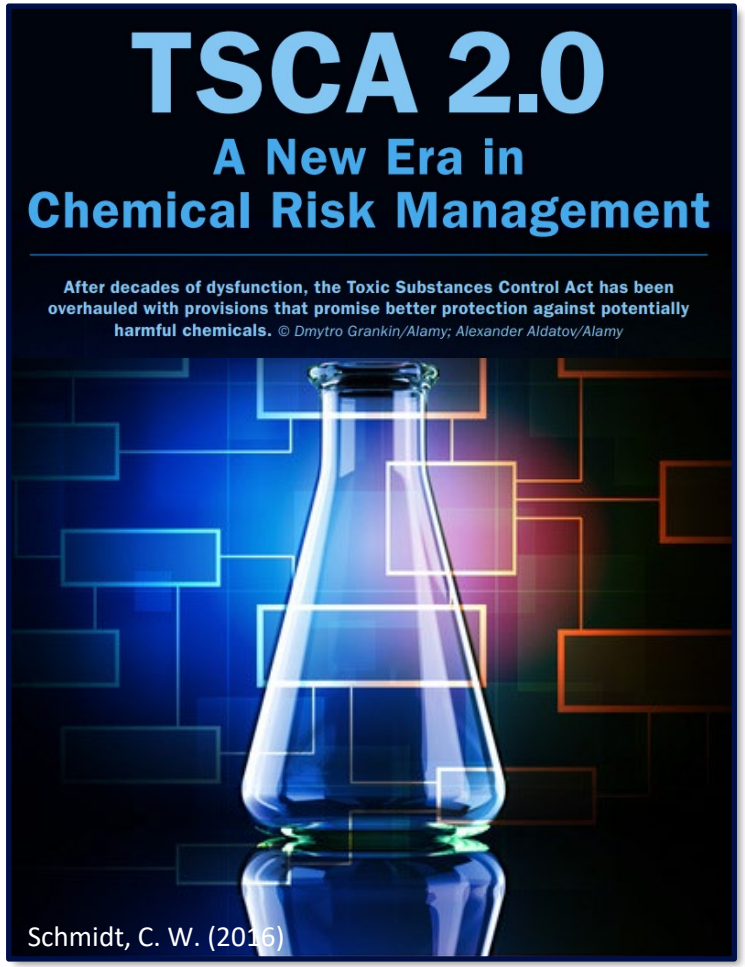
PBK: Physiologically-based kinetic
PBPK: Physiologically-based pharmacokinetic
PBTK: Physiologically-based toxicokinetic

Chemical Regulation in the United States

- A tapestry of laws covers the chemicals to which people are exposed in the United States (Breyer, 2009)

- Chemical safety testing is primarily for food additives, pharmaceuticals, and pesticide active ingredients (NRC, 2007)
  - Therapeutic chemicals are tested in human trials in order to establish beneficial amounts, but potentially harmful chemicals are rarely deliberately tested in humans

- Most other chemicals occuring in commerce and the environment – ranging from industrial waste to dyes to packing materials – are covered by the Toxic Substances Control Act (TSCA)
  - *TSCA is administered by the Environmental Protection Agency*
  - *There are limited or no data for many of these chemicals*
  - *New approach methodologies (NAMs) are being evaluated for their potential to inform risk assessment*



Schmidt, C. W. (2016)

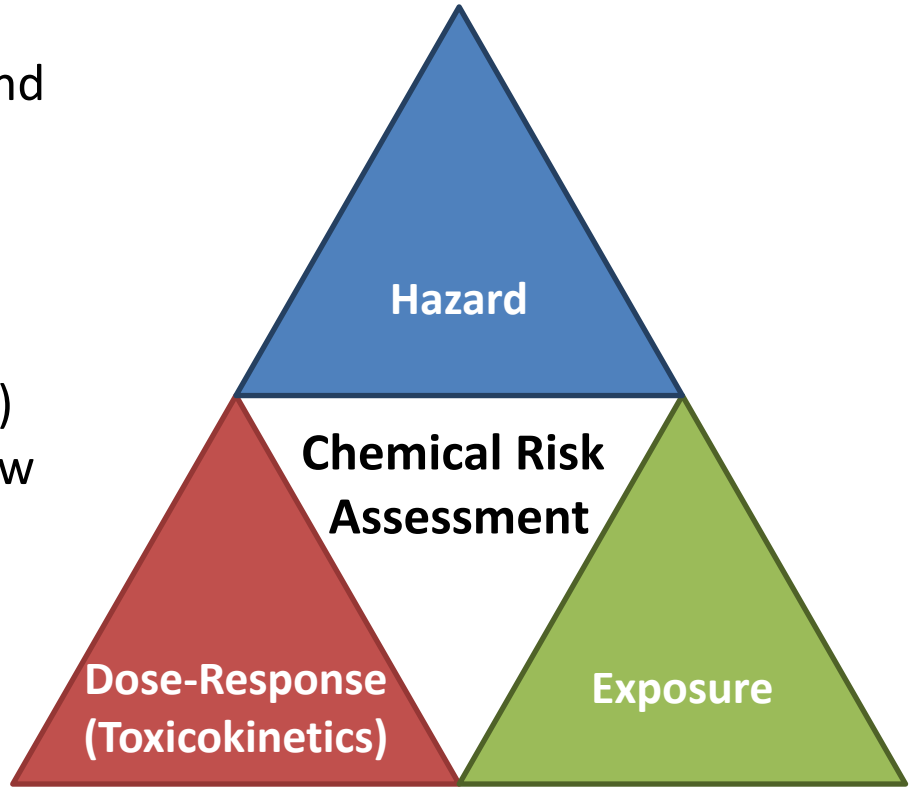
Chemical Risk Assessment Requires Understanding Dose-Response

- NRC (1983): Risk is a function of inherent chemical hazard, extent of exposure, and the dose-response relationship (including toxicokinetics)

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

- Physiologically-Based (Pharmaco- / Toxico-) kinetic (PBK/PBPK/PBTK) models allow quantitative prediction of tissues concentrations in new scenarios (extrapolation)

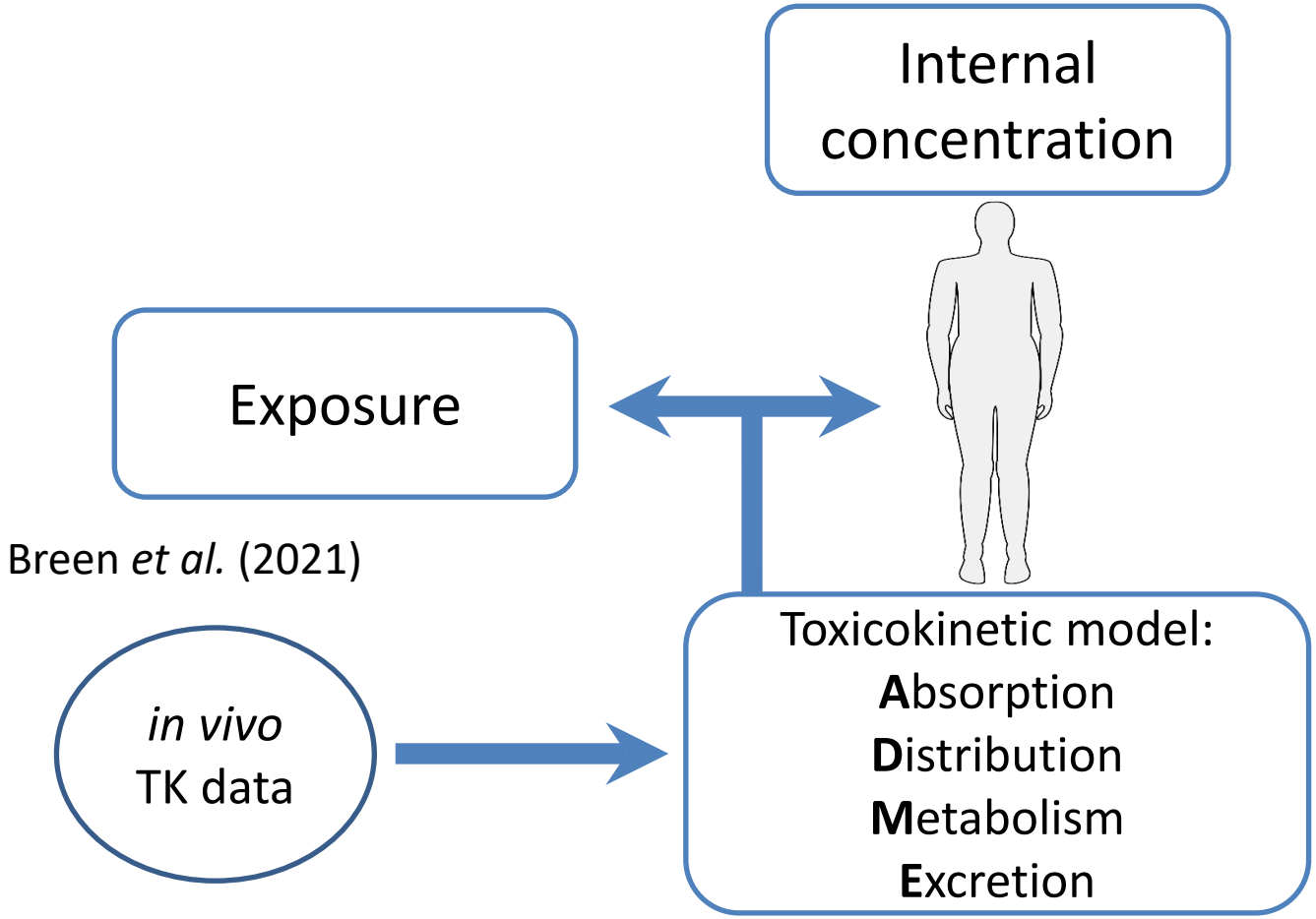
- Next generation risk assessment (NGRA) will require PBTK to extrapolate from NAMs to *in vivo* conditions



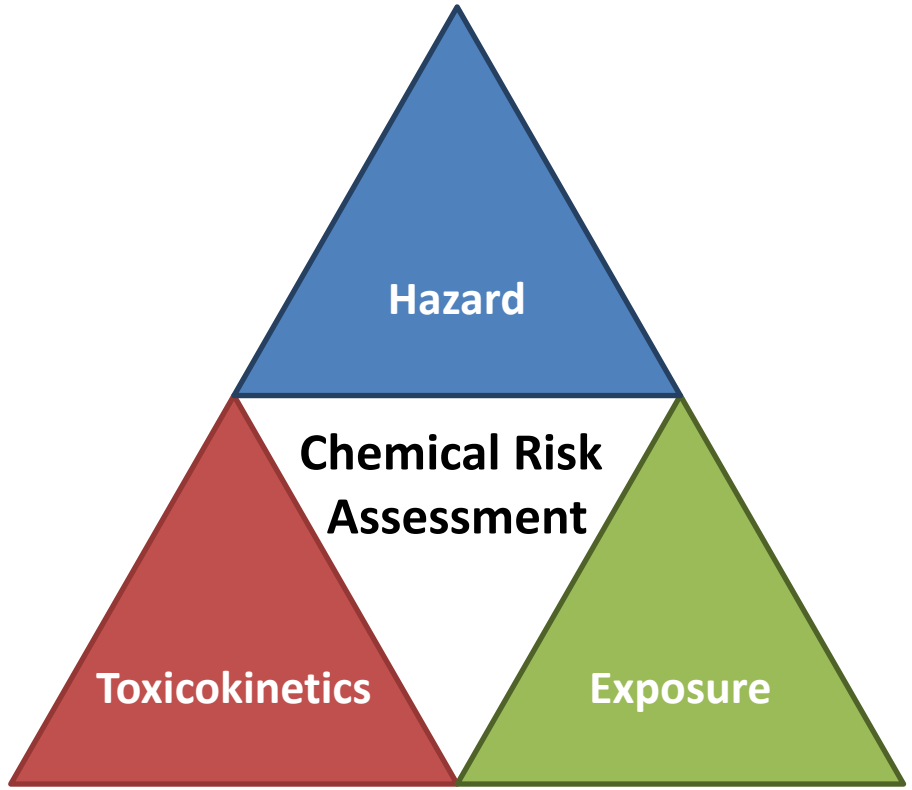
NRC, 1983

Toxicokinetics

- Toxicokinetics describes the absorption, distribution, metabolism, and excretion of a chemical by the body:



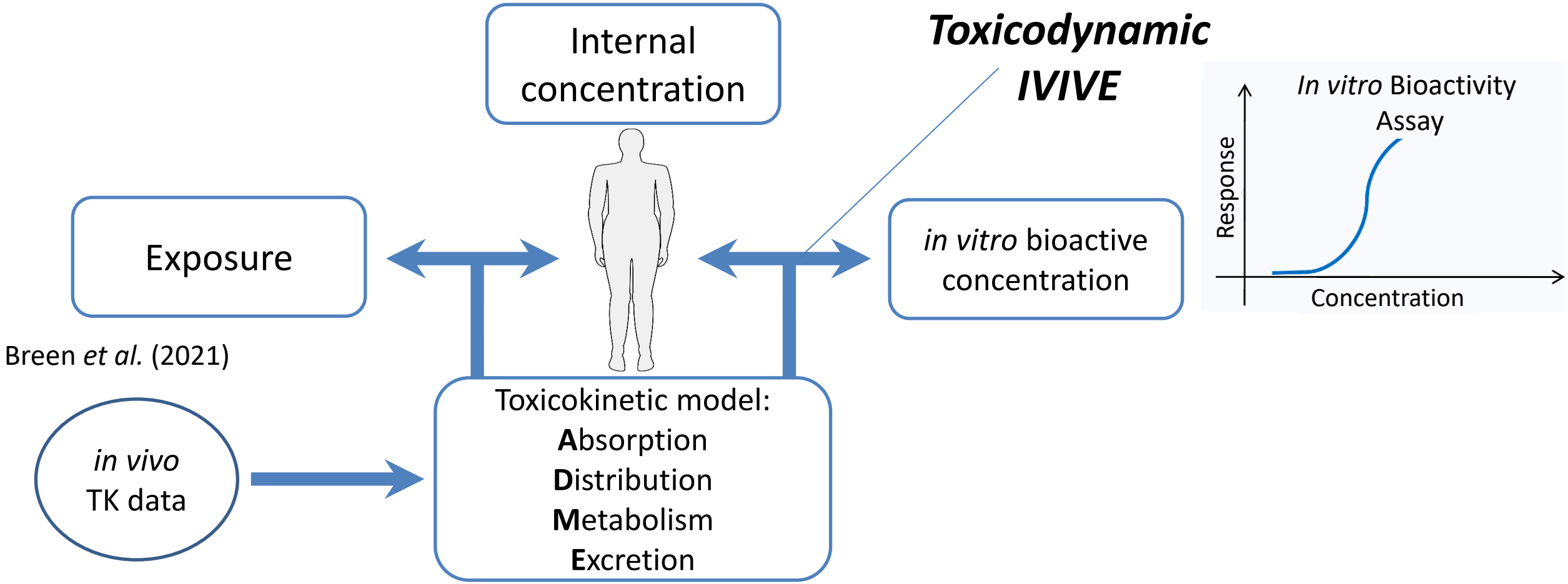
Breen *et al.* (2021)



NRC, 1983

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



PBK/PBPK/PBTK is for Extrapolation

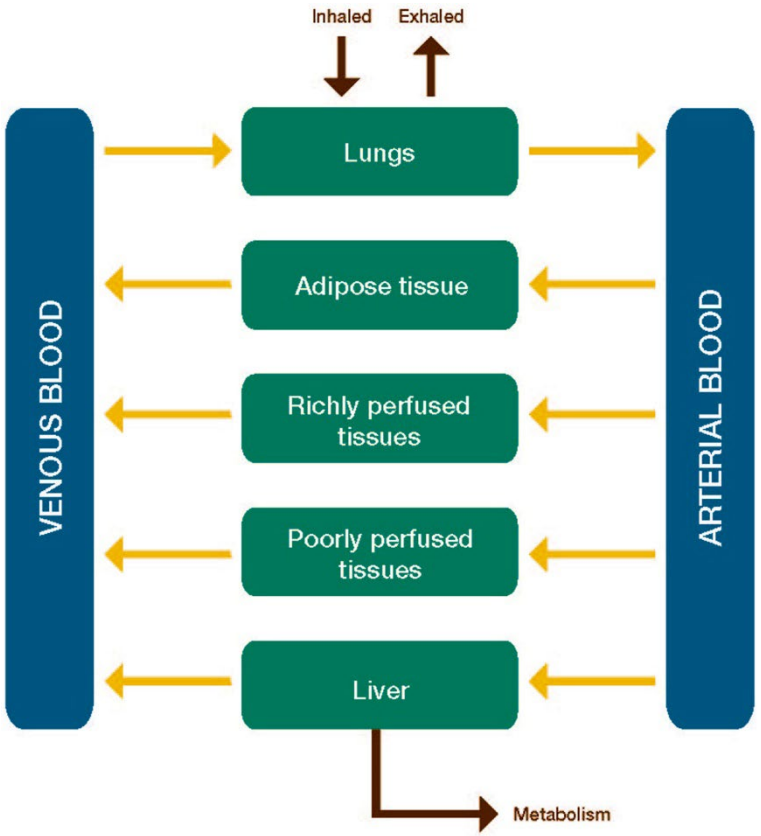
- A PBK/PBPK/PBTK model is used for ***extrapolation***

- We are using our (chemical-independent) knowledge of physiology to constrain the range of possible chemical-related outcomes in a scenario we cannot observe (Chiu et al., 2008)

- For pharmaceuticals extrapolation could be, for example, from non-pregnant adults to pregnancy, children, or drug-drug interactions
  - In drug-drug interactions two pharmaceuticals might compete for the same metabolizing enzyme

- For other chemicals, extrapolation could be from animal species or *in vitro* NAMs

Example of PBTK Model

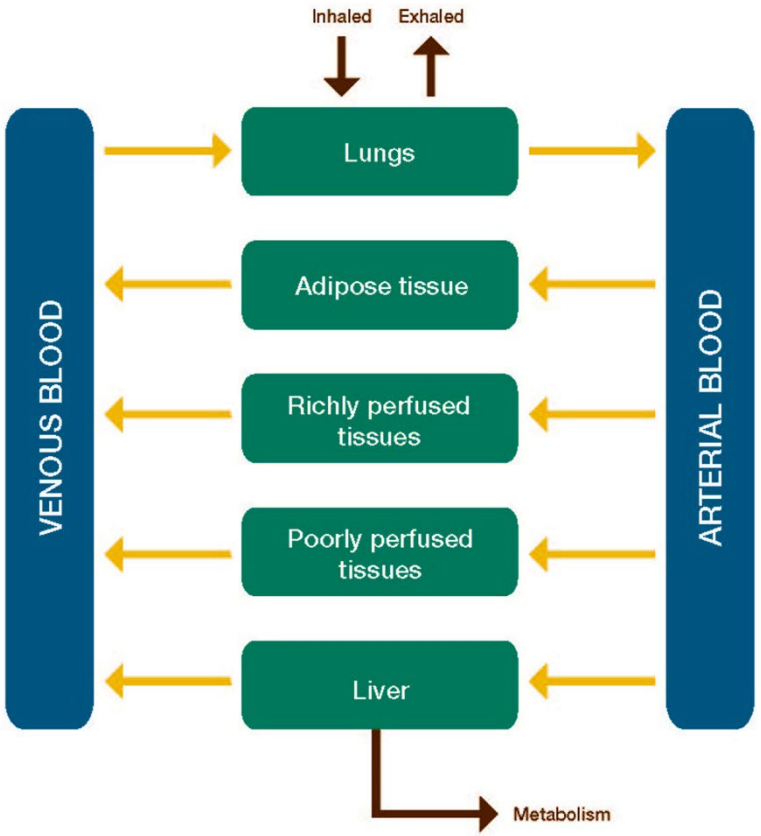


Tan et al. (2020)

PBTK for Pharmaceuticals vs. Other Chemicals in Commerce and the Environment

- We can use PBTK to simulate variability in physiology to assess some aspects of human variability
- Knowledge of metabolizing enzyme allows greater insight to human variability and metabolic pathways involved
- Largely because the available resources are different, we rarely know the chemical-specific metabolizing enzyme for non-pharmaceuticals
  - *In silico* models are currently insufficiently specific to narrow to a single enzyme

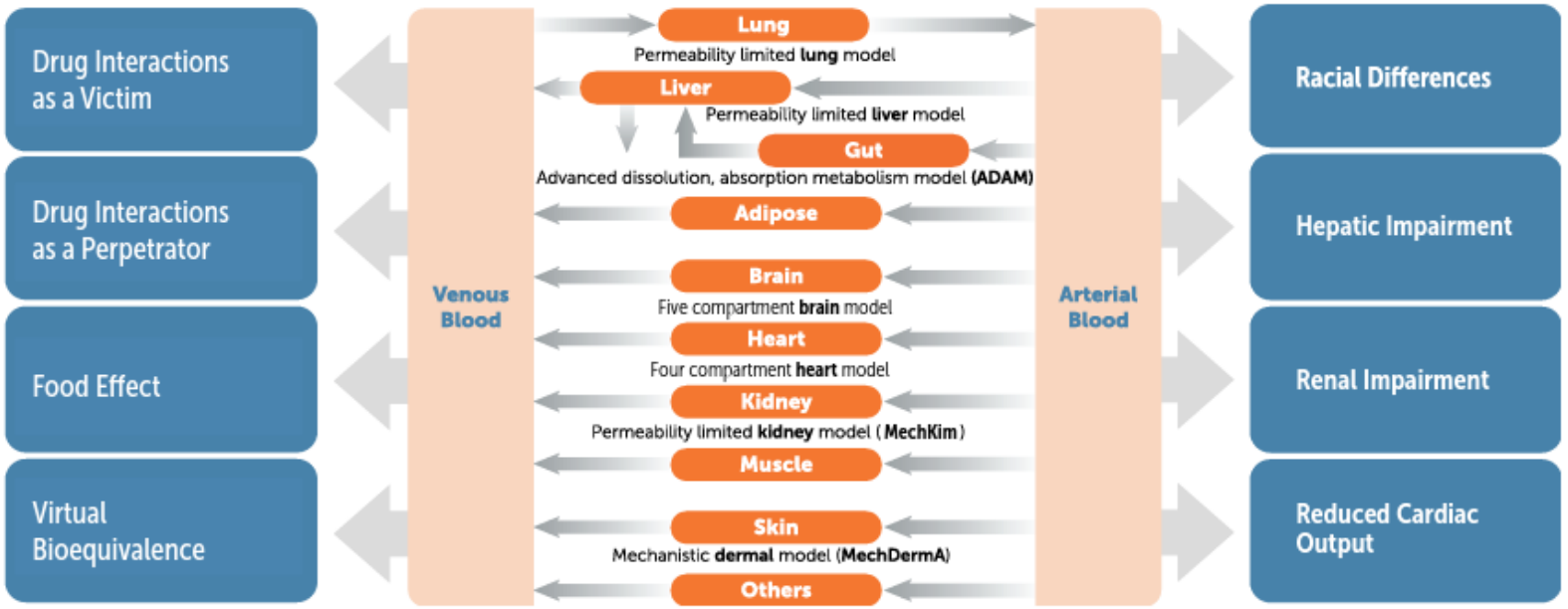
Example of PBTK Model



Tan et al. (2020)

SimCYP

- Simcyp PBPK Simulator for Population-based Modeling is supported by a consortium of pharmaceutical companies
- When parameterized with enzyme-specific *in vitro* data can prospectively evaluate the success of clinical trials and identify potential for drug-drug interactions
- Includes modules for children and toxicological animal species



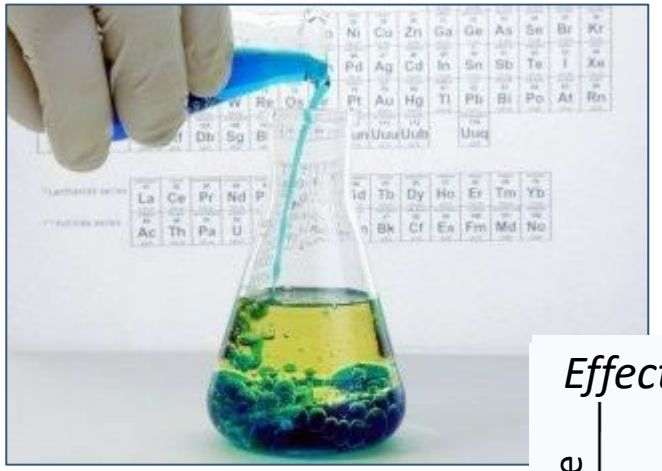
https://www.certara.com/software/simcyp-pbpk/

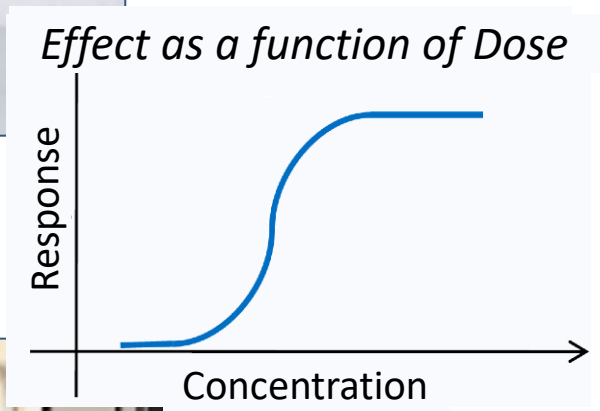
Clinical Trials are the Key Difference

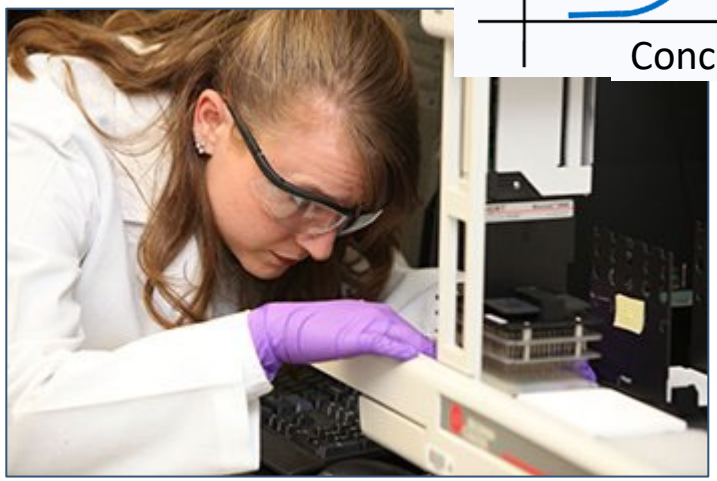
- Therapeutic chemicals are tested in human trials in order to establish beneficial amounts, but potentially harmful chemicals are rarely deliberately tested in humans
  - Some studies with very low-level concentrations were conducted in the past, unlikely going forward

- To estimate the impact of potentially harmful chemicals we use animal and *in vitro* studies and extrapolate to humans
  - For NGRA 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.
  - Route-to-route extrapolation







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

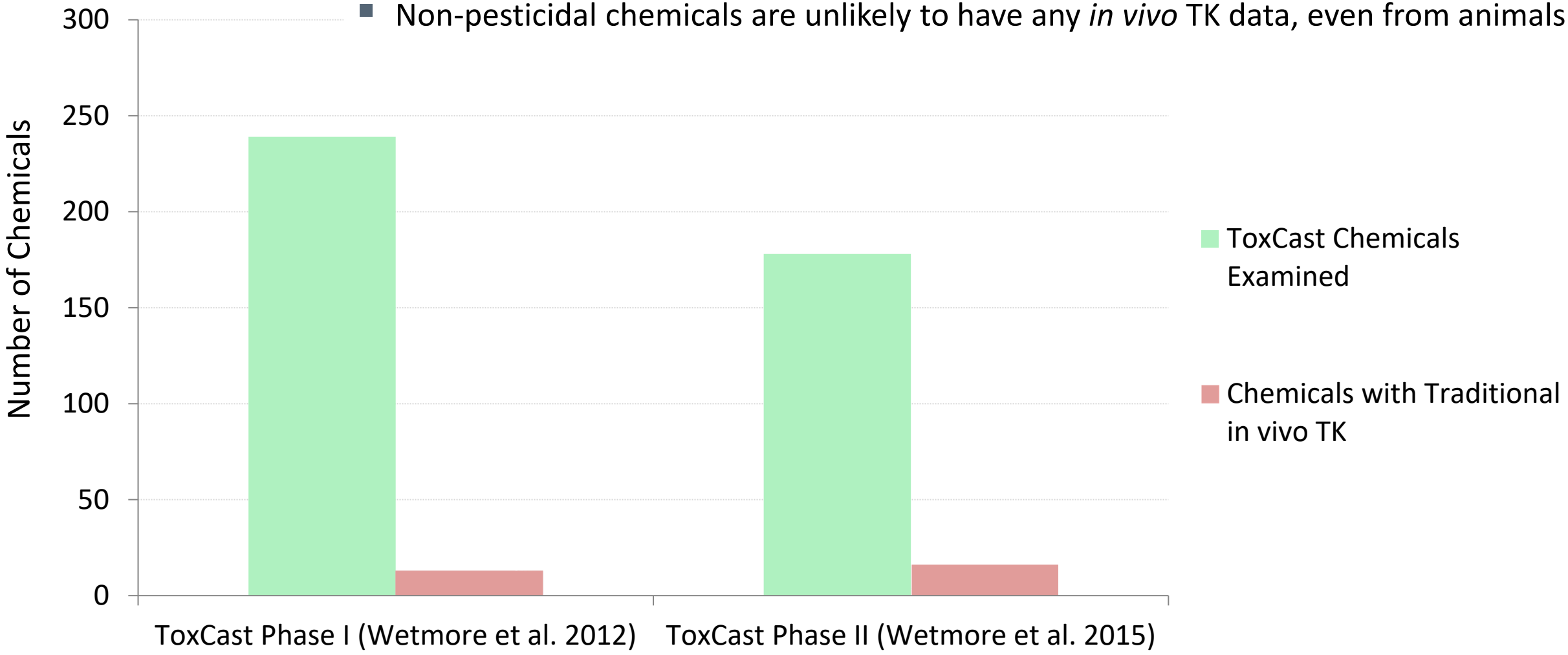


Figure from Bell et al. (2018)

High Throughput Toxicokinetics (HTTK):
A New Approach Methodology (NAM) for Exposure

- 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)
  - In addition to using a standardized (generic) model, this approach also standardizes the parameters and *in vitro* measurements needed to describe a chemical
- HTTK can provide **open-source data and models** for evaluation and use by the broader scientific community (Pearce et al, 2017)
- While there is more data for pharmaceuticals, these data are often proprietary

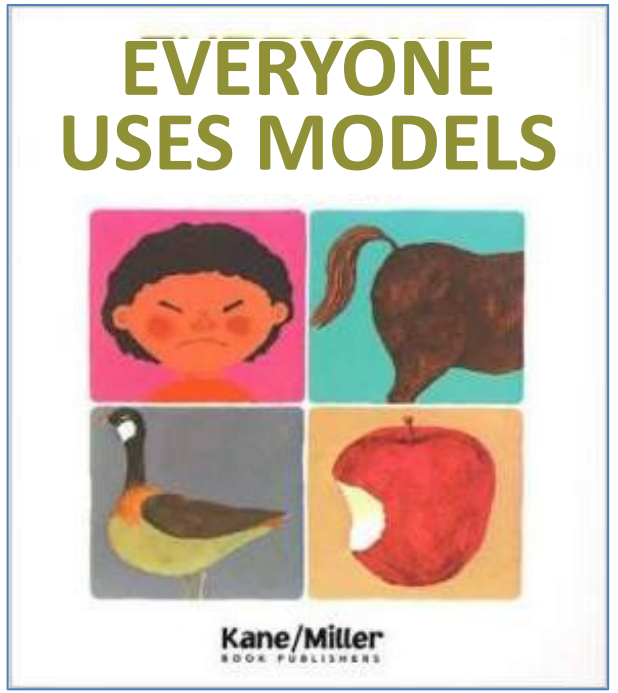
How do We Extrapolate with Confidence?

- 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
  - Toxicology has long relied upon model animal species

- Mathematical models offer some significant advantages:
  - Reproducible
  - Can (and should) be transparent

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

  "…cunningly chosen parsimonious models often do provide remarkably useful approximations… **The only question of interest is 'Is the model illuminating and useful?'**"
  George Box



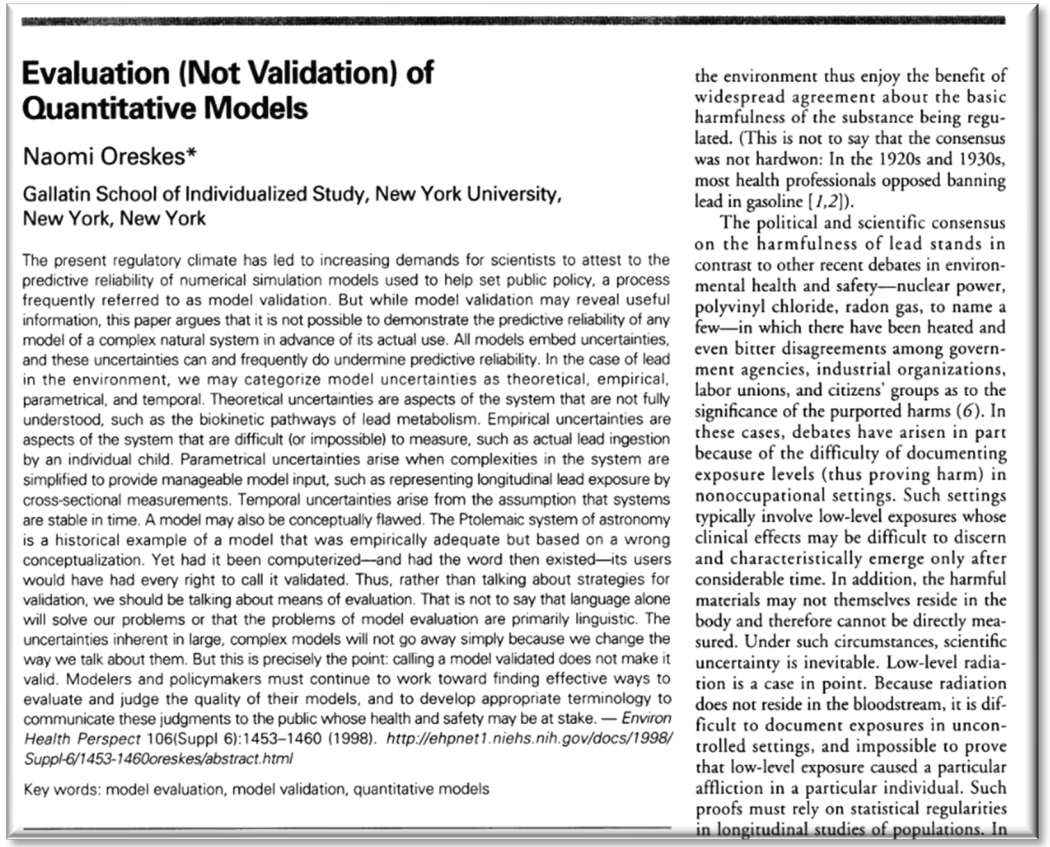
How Do We Evaluate Models?

- If we accept that to be useful our model omits some processes, then we must evaluate how well it works

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)



Evaluation (Not Validation) of Quantitative Models

Naomi Oreskes*

Gallatin School of Individualized Study, New York University, New York, New York

The present regulatory climate has led to increasing demands for scientists to attest to the predictive reliability of numerical simulation models used to help set public policy, a process frequently referred to as model validation. But while model validation may reveal useful information, this paper argues that it is not possible to demonstrate the predictive reliability of any model of a complex natural system in advance of its actual use. All models embed uncertainties, and these uncertainties can and frequently do undermine predictive reliability. In the case of lead in the environment, we may categorize model uncertainties as theoretical, empirical, parametrical, and temporal. Theoretical uncertainties are aspects of the system that are not fully understood, such as the biokinetic pathways of lead metabolism. Empirical uncertainties are aspects of the system that are difficult (or impossible) to measure, such as actual lead ingestion by an individual child. Parametrical uncertainties arise when complexities in the system are simplified to provide manageable model input, such as representing longitudinal lead exposure by cross-sectional measurements. Temporal uncertainties arise from the assumption that systems are stable in time. A model may also be conceptually flawed. The Ptolemaic system of astronomy is a historical example of a model that was empirically adequate but based on a wrong conceptualization. Yet had it been computerized—and had the word then existed—its users would have had every right to call it validated. Thus, rather than talking about strategies for validation, we should be talking about means of evaluation. That is not to say that language alone will solve our problems or that the problems of model evaluation are primarily linguistic. The uncertainties inherent in large, complex models will not go away simply because we change the way we talk about them. But this is precisely the point: calling a model validated does not make it valid. Modelers and policymakers must continue to work toward finding effective ways to evaluate and judge the quality of their models, and to develop appropriate terminology to communicate these judgments to the public whose health and safety may be at stake. — *Environ Health Perspect* 106(Suppl 6):1453–1460 (1998). *http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-6/1453-1460oreskes/abstract.html*

Key words: model evaluation, model validation, quantitative models

the environment thus enjoy the benefit of widespread agreement about the basic harmfulness of the substance being regulated. (This is not to say that the consensus was not hardwon: In the 1920s and 1930s, most health professionals opposed banning lead in gasoline [*1,2*]).

The political and scientific consensus on the harmfulness of lead stands in contrast to other recent debates in environmental health and safety—nuclear power, polyvinyl chloride, radon gas, to name a few—in which there have been heated and even bitter disagreements among government agencies, industrial organizations, labor unions, and citizens' groups as to the significance of the purported harms (*6*). In these cases, debates have arisen in part because of the difficulty of documenting exposure levels (thus proving harm) in nonoccupational settings. Such settings typically involve low-level exposures whose clinical effects may be difficult to discern and characteristically emerge only after considerable time. In addition, the harmful materials may not themselves reside in the body and therefore cannot be directly measured. Under such circumstances, scientific uncertainty is inevitable. Low-level radiation is a case in point. Because radiation does not reside in the bloodstream, it is difficult to document exposures in uncontrolled settings, and impossible to prove that low-level exposure caused a particular affliction in a particular individual. Such proofs must rely on statistical regularities in longitudinal studies of populations. In

Oreskes (1998)

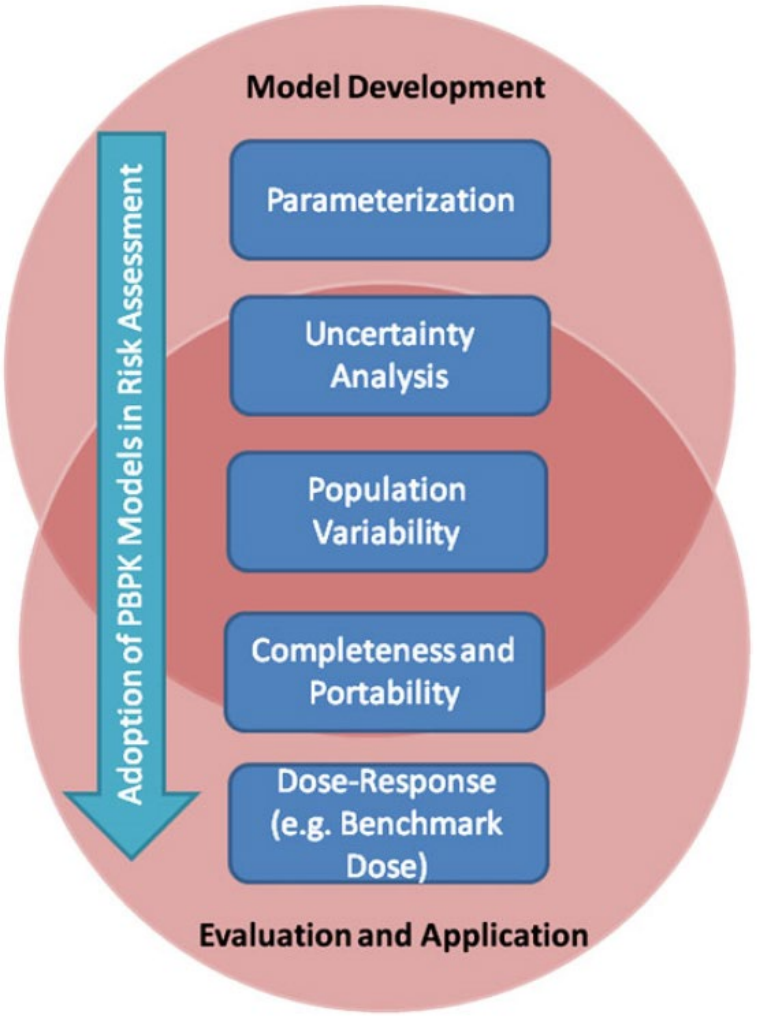
Open Source, Verifiable, Reproducible

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]"



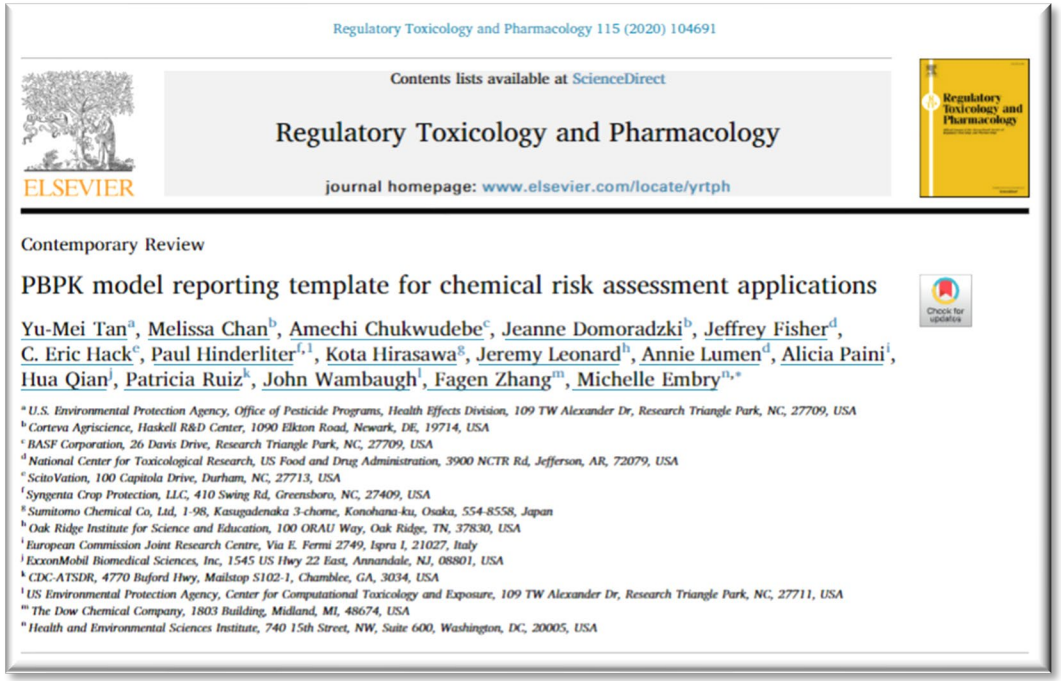
Key considerations during PBTK model development, evaluation, and applications for Human Health Risk Assessment

Model Documentation Templates

- Tan et al. (2020):
  While the development of PBPK model shave grown steadily since their emergence, only a handful of models have been accepted to support regulatory purposes due to obstacles such as the lack of a standardized template for reporting PBPK analysis.”

- Harmonized reporting template provides guidance for submitting PBPK-related studies for publication and other model sharing application

- What should be documented and how



Regulatory Toxicology and Pharmacology 115 (2020) 104691

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Contemporary Review

PBPK model reporting template for chemical risk assessment applications

Yu-Mei Tan[a], Melissa Chan[b], Amechi Chukwudebe[c], Jeanne Domoradzki[b], Jeffrey Fisher[d], C. Eric Hack[e], Paul Hinderliter[f,1], Kota Hirasawa[g], Jeremy Leonard[h], Annie Lumen[d], Alicia Paini[i], Hua Qian[j], Patricia Ruiz[k], John Wambaugh[l], Fagen Zhang[m], Michelle Embry[n,*]

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Runnable Model Templates

- Bernstein et al. (2021, 2023) provide a PBPK model template capable of replicating published model results for several chemical-specific PBPK models (using R and MCSim)
  - They were able to reproduce several published model simulation results
- Also showed that the template can be a useful tool for identifying potential model errors.
- The model template allows for faster evaluation and review of published PBPK models
- Scripts and relevant data files are available through the U.S. Environmental Protection Agency's Environmental Dataset Gateway https://doi.org/10.23719/1520081

OXFORD SOT Society of Toxicology
academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 182(2), 2021, 215–228
doi: 10.1093/toxsci/kfab063
Advance Access Publication Date: 2 June 2021
Research Article

A Model Template Approach for Rapid Evaluation and Application of Physiologically Based Pharmacokinetic Models for Use in Human Health Risk Assessments: A Case Study on Per- and Polyfluoroalkyl Substances

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Disclaimer: The views expressed in this manuscript are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.

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See poster presentation Bernstein et al. "Speed Isn't Everything: "Comparing the Speed of Simulations Using Stand-Alone and PBPK Model Template Implementations of PBPK Models". Abstract 4317, Poster P182, Wednesday Morning

Runnable Template Relies on a Standardized PBTK Model Structure

OXFORD SOT Society of Toxicology academic.oup.com/toxsci

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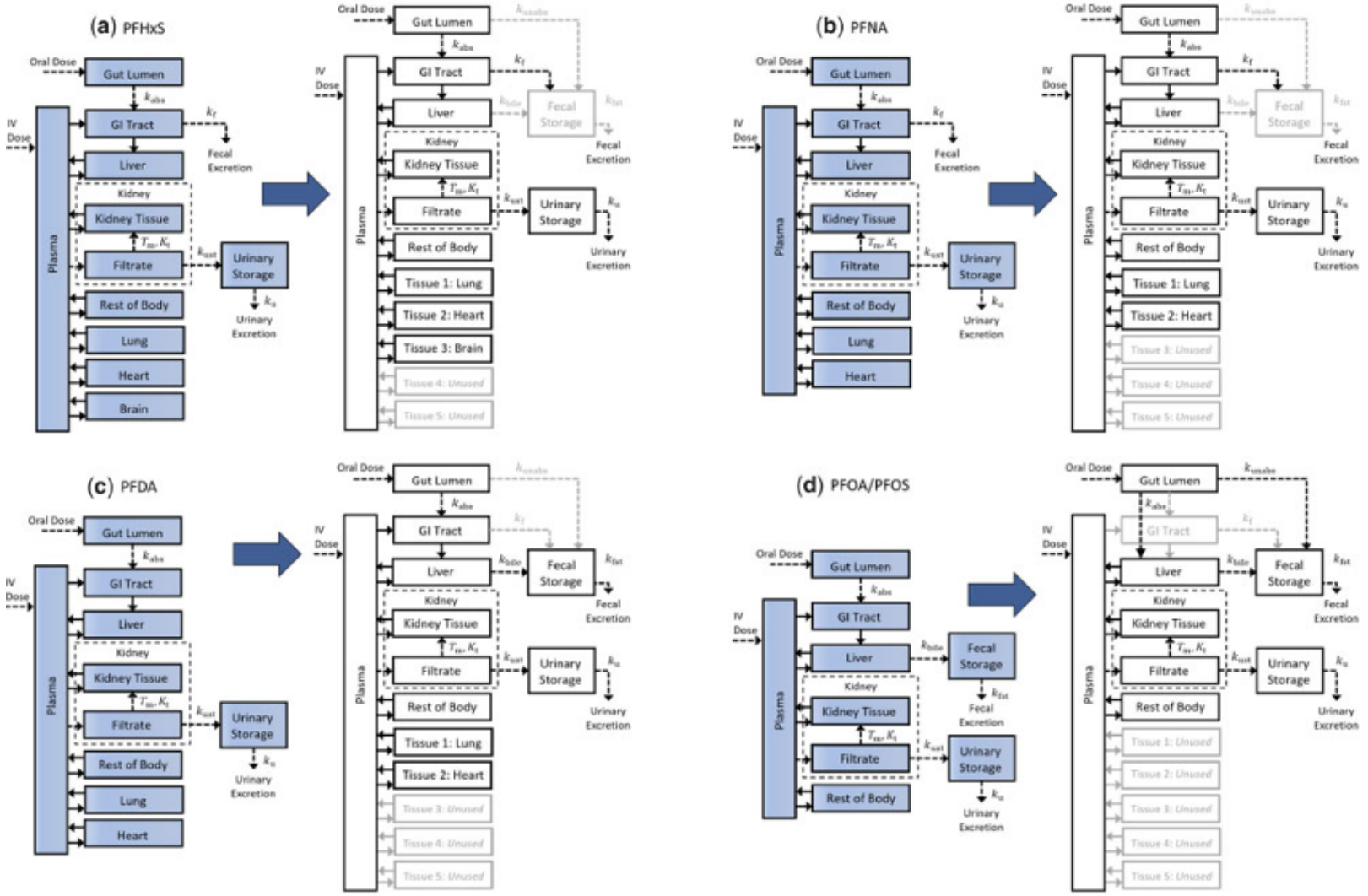
- As with SimCYP the equations for the model template only need to be reviewed once
- Application to a specific chemical only requires reviewing input parameters.



Bespoke vs. Generic PBK/PBPK/PBTK

Bespoke, Tailored, Custom…
Requires specific measurements

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

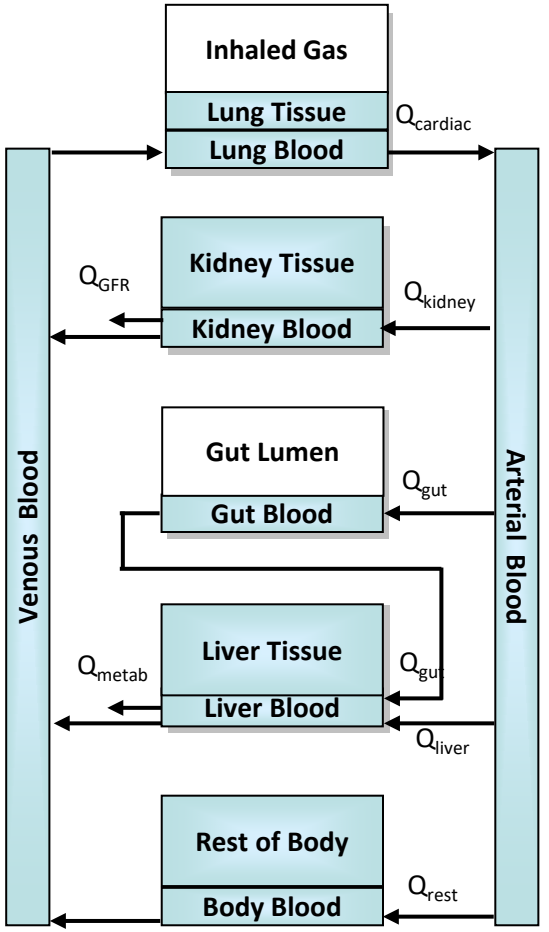
Generic PBTK Tools

	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

from Breen et al. (2021)

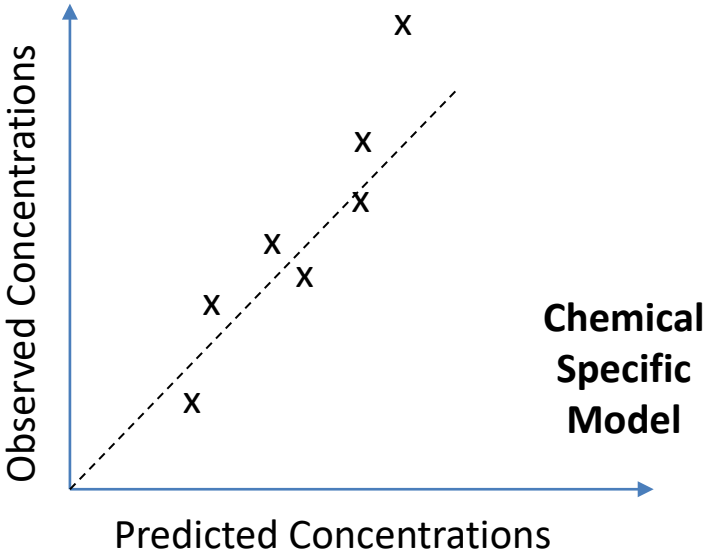
Generic PBK/PBPK/PBTK Models

- 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



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

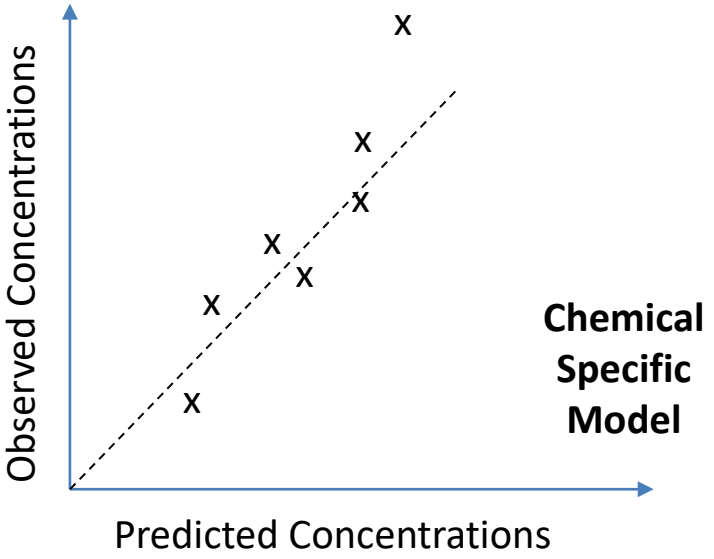


Cohen Hubal et al. (2019)

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



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
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- We can parameterize a **generic TK model**, and evaluate that model for as many chemicals as we do have data
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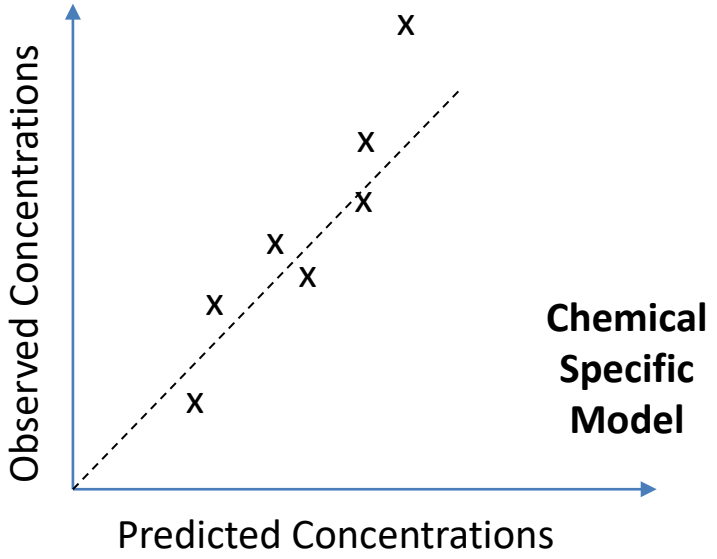

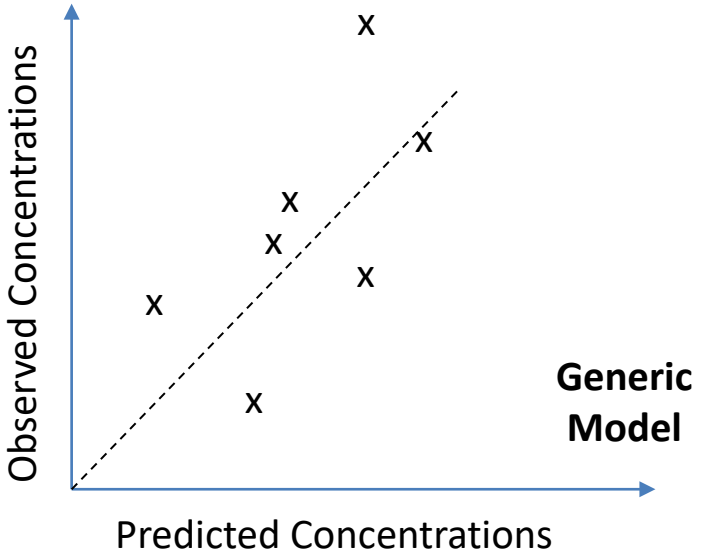

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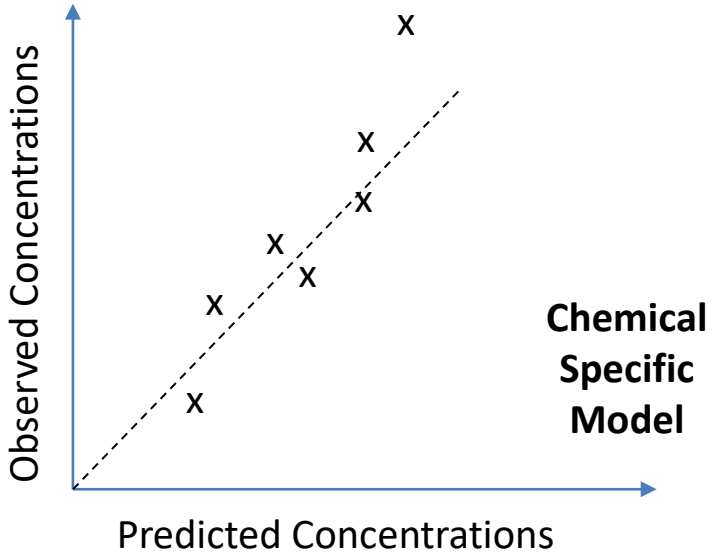

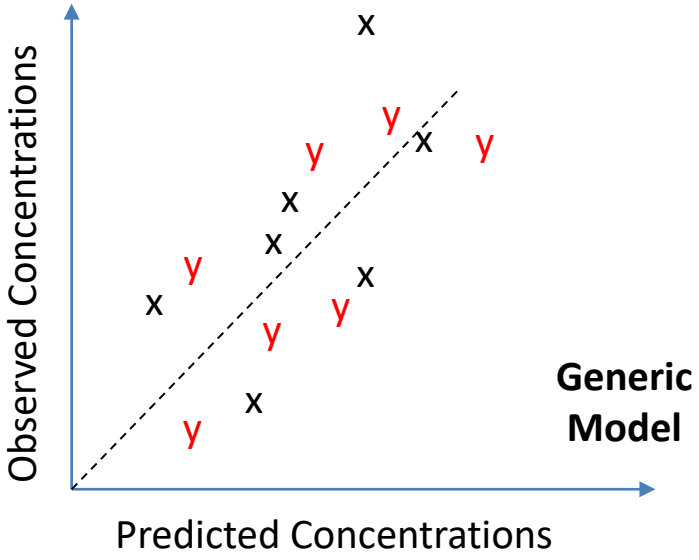

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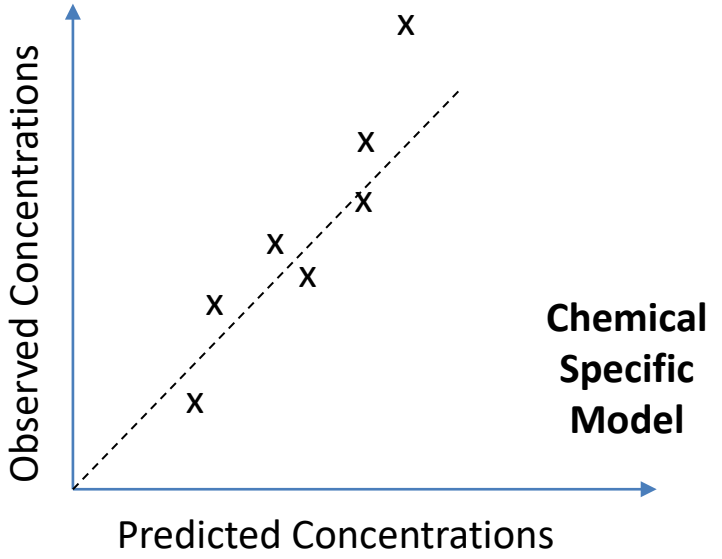
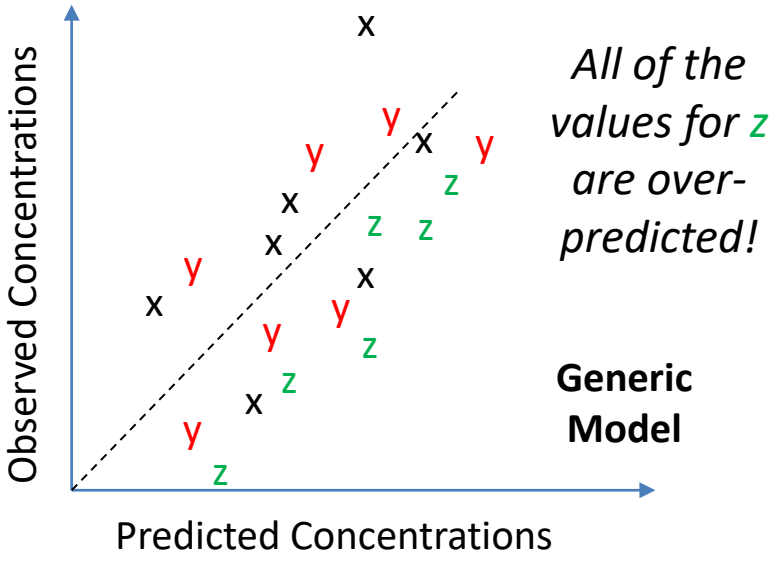


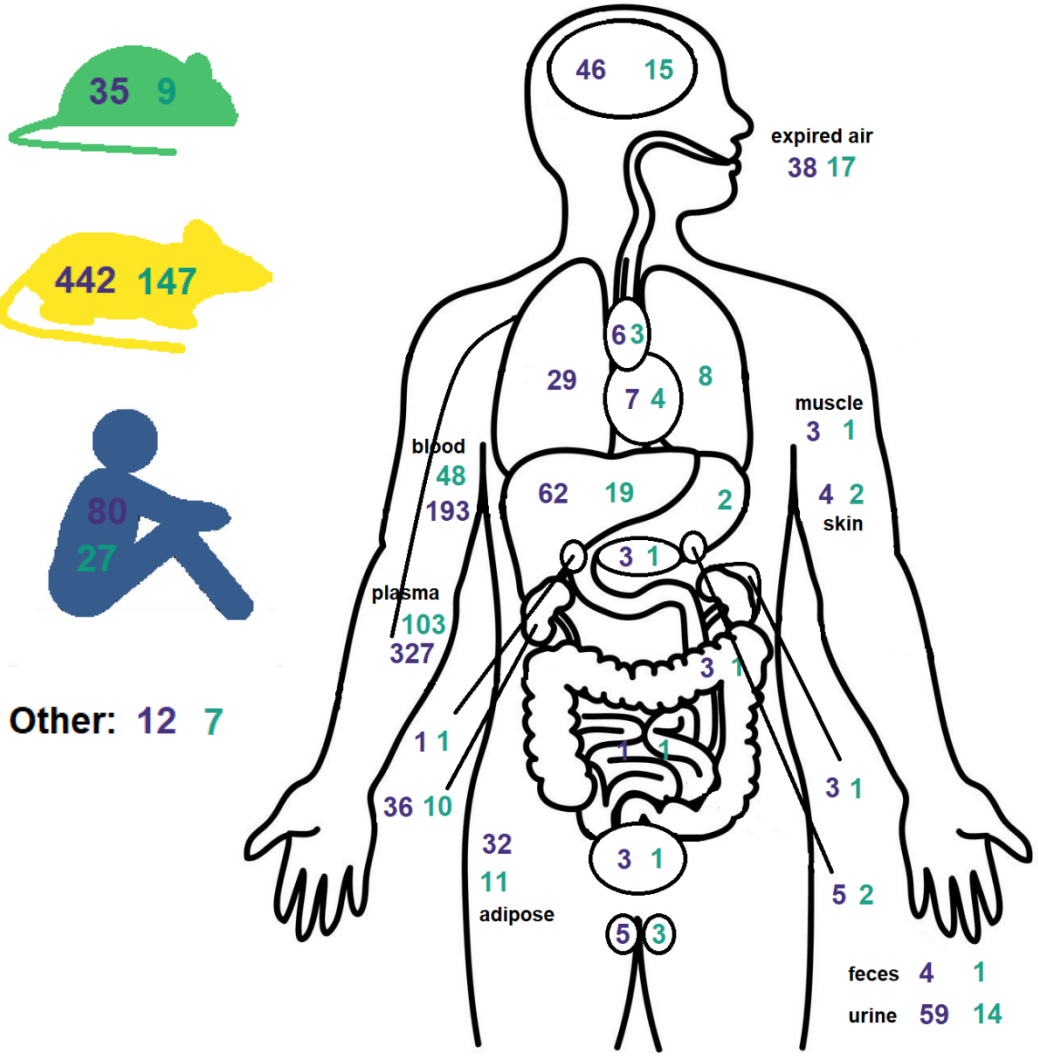


Cohen Hubal et al. (2019)

CvtDB: An In Vivo TK Database

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

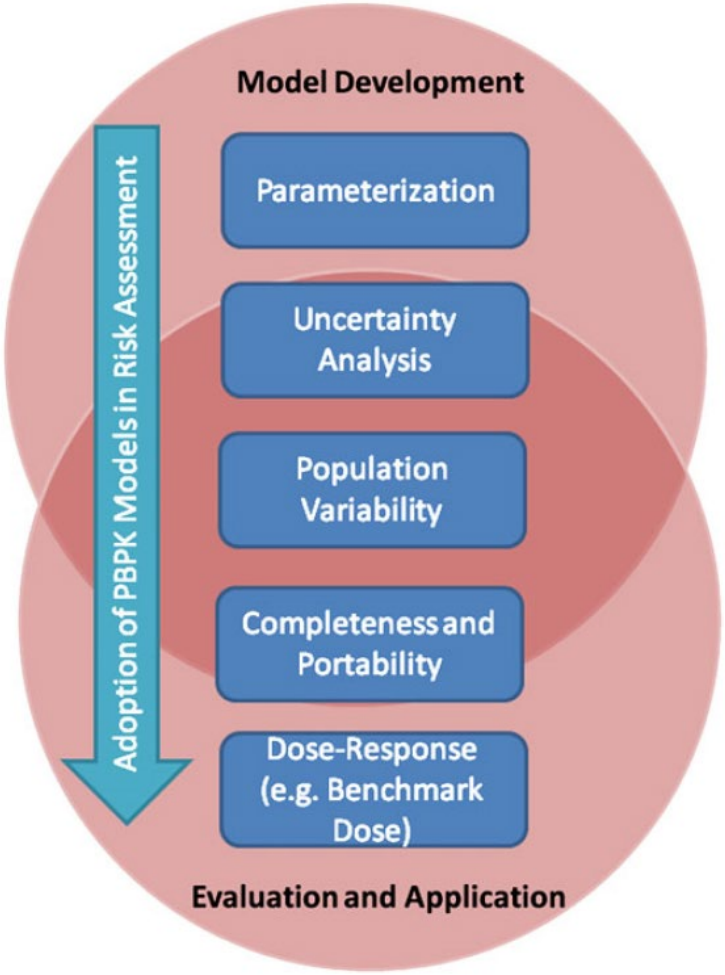
- The most important thing for evaluating PBK/PBPK/PBTK is evaluation data
- EPA has developed a **public database** of **concentration vs. time data** for building, calibrating, and evaluating TK models
- Curation and development is ongoing, but to date includes:
  - >200 analytes (EPA, National Toxicology Program, Showa Pharmaceutical University, 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)

Conclusions

- Toxicokinetics links exposure with internal concentrations
- Physiologically-based toxicokinetic (PBTK) models allow extrapolation
- Including *in vitro-in vivo* extrapolation (IVIVE)
- 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



McLanahan et al. (2012)

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

United States Environmental Protection Agency

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