PBPK regulatory applications

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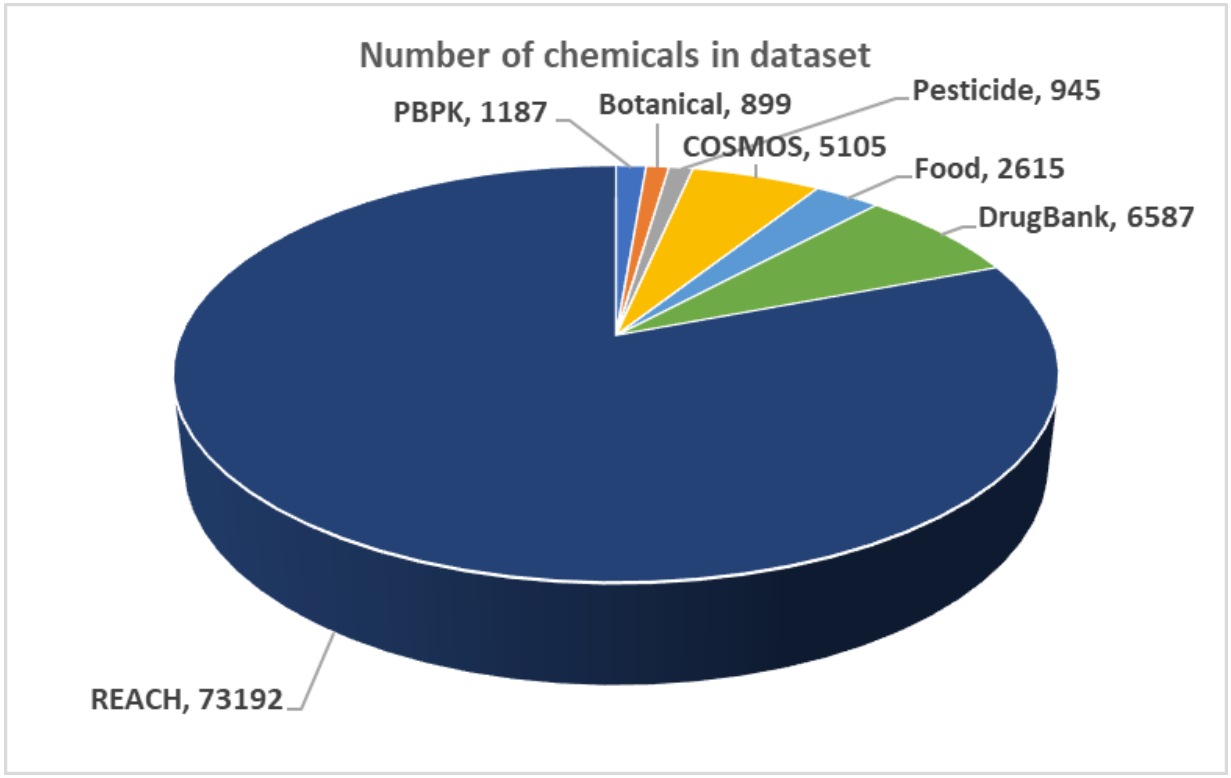
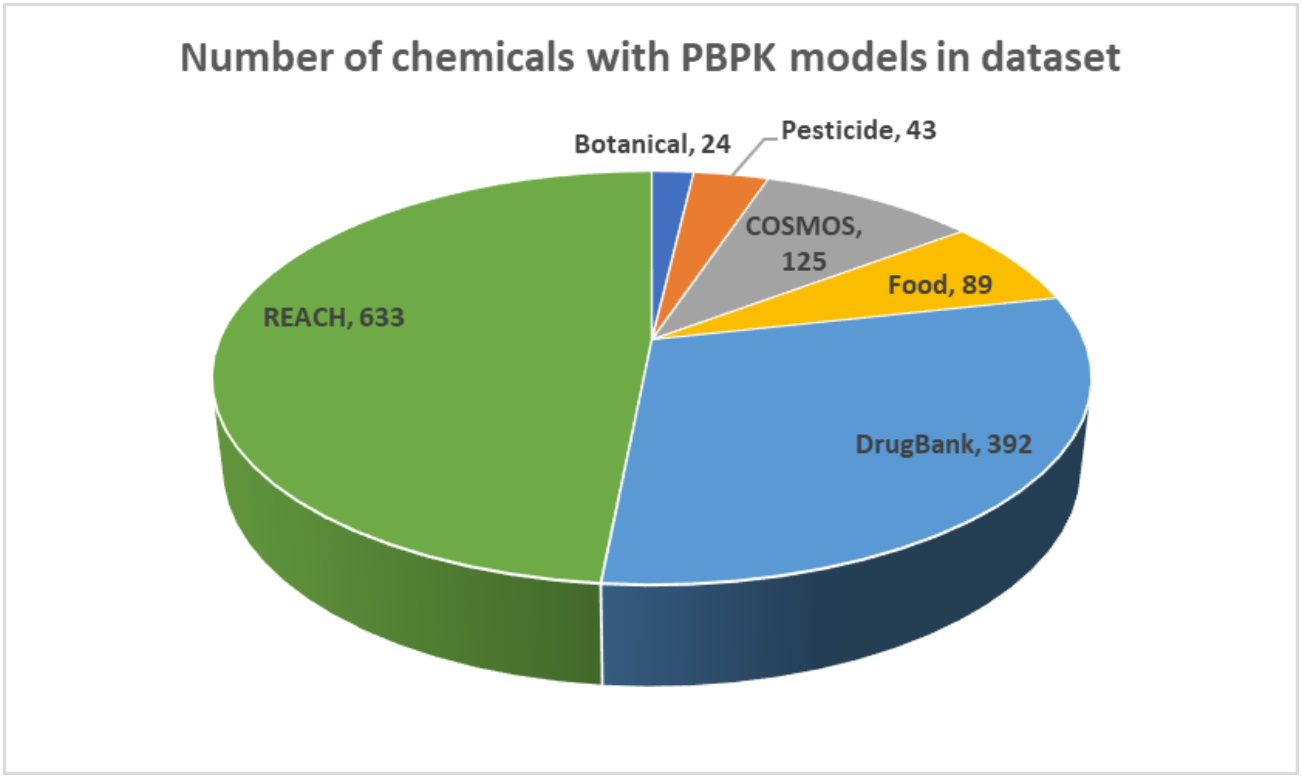
Outline

- Common PBPK applications to support assessing human risks from exposure to environmental chemicals
- Common challenges encountered by modelers and users
- Recommendations to address common challenges

PBPK models available for ~1150 chemicals





~1-6% of chemicals in other datasets have published PBPK models

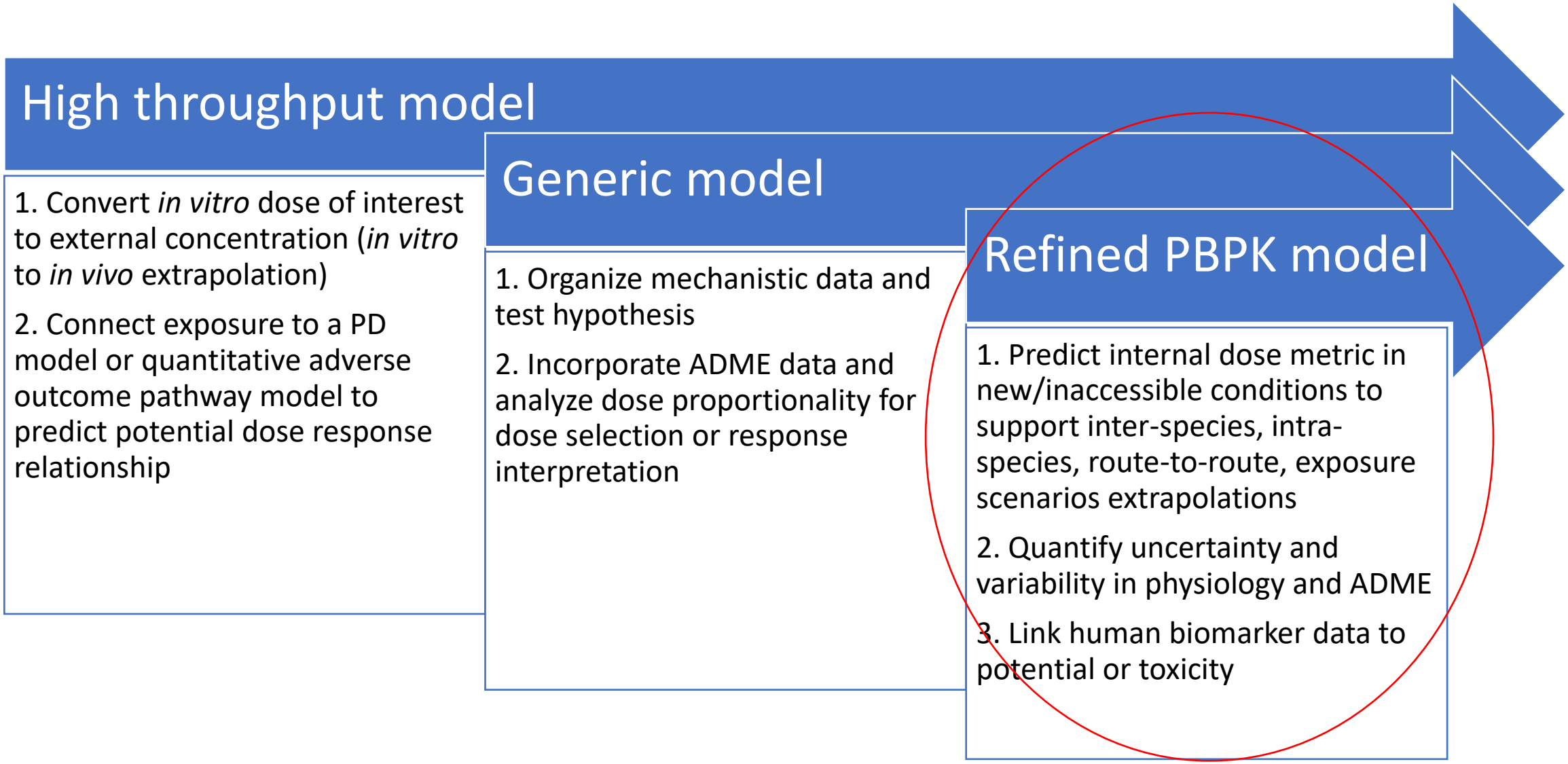
Thompson et al. (2021) Alternatives to Laboratory Animals 49(5):197-208, doi:10.1177/02611929211060264

An example: how often are PBPK models used in regulatory applications?

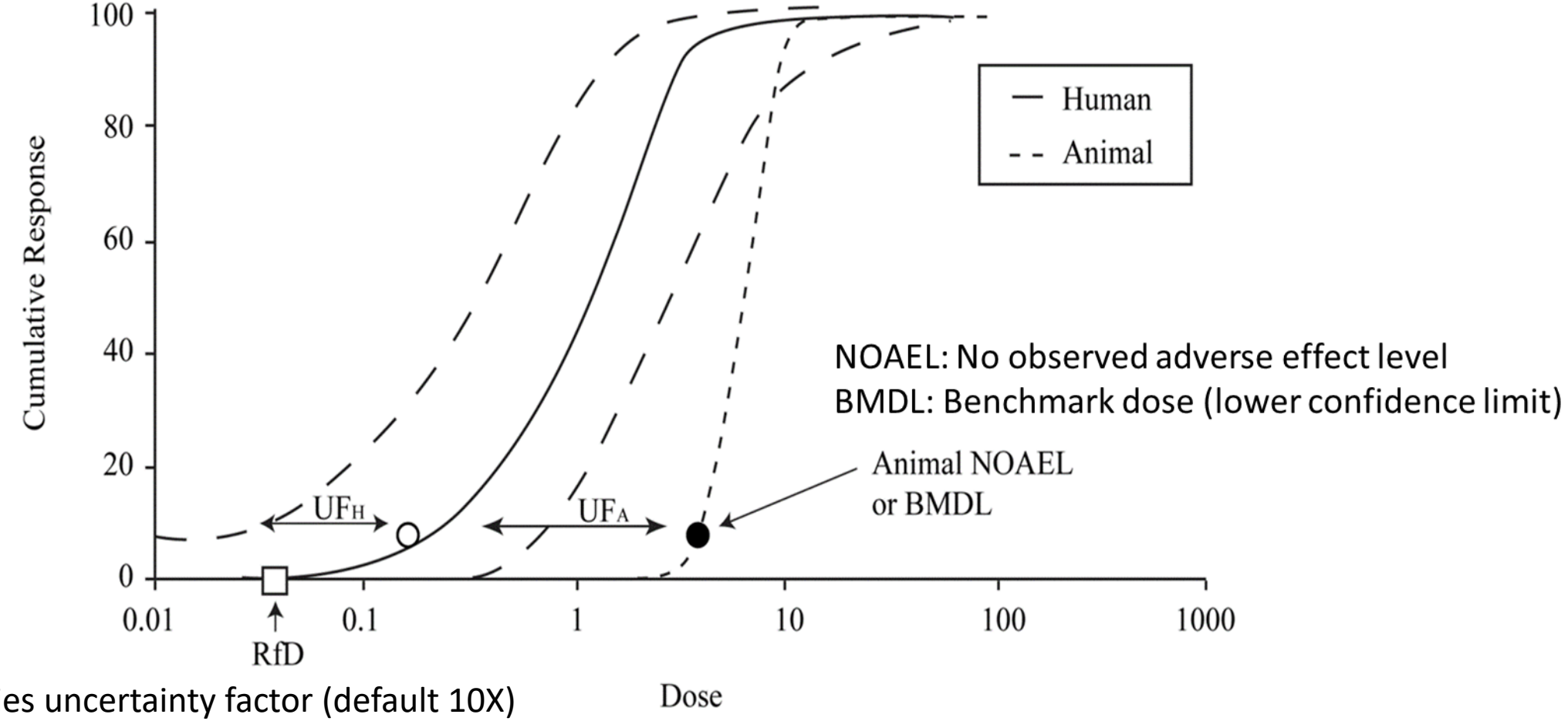
US Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) program provides human Reference Concentrations or Reference Doses for health effects resulting from chronic exposure to chemicals

	Completed IRIS assessment	Assessment in progress
Chemicals in database	571	18
Chemicals with published PBPK models	147	10
PBPK models considered in risk assessment	22	
PBPK models used in risk assessment	14	

Common PBPK applications



Chemical risk assessment is mostly based on animal toxicity data (human data are rare)



UF_A: Inter-species uncertainty factor (default 10X)
UF_H: Intra-species uncertainty factor (default 10X)
RfD: Reference Dose

PBPK can be used to refine default uncertainty factors

- “If enough scientific information exists about the differences in the metabolism or mode of action of a chemical in animal versus in humans, then scientifically derived extrapolation factors can be used rather than the defaults” (IOM, 2013)

- “PBPK model analysis is accepted as a scientifically sound approach to estimating the internal dose of a chemical at a target site and as a means to evaluate and describe the uncertainty in risk assessment” (EPA, 2006)

IOM (2013) Environmental Decisions in the Face of Uncertainty
EPA (2006) Approaches for the Application of Physiologically Based Pharmacokinetic Models and Supporting Data in Risk Assessment

Refined PBPK models

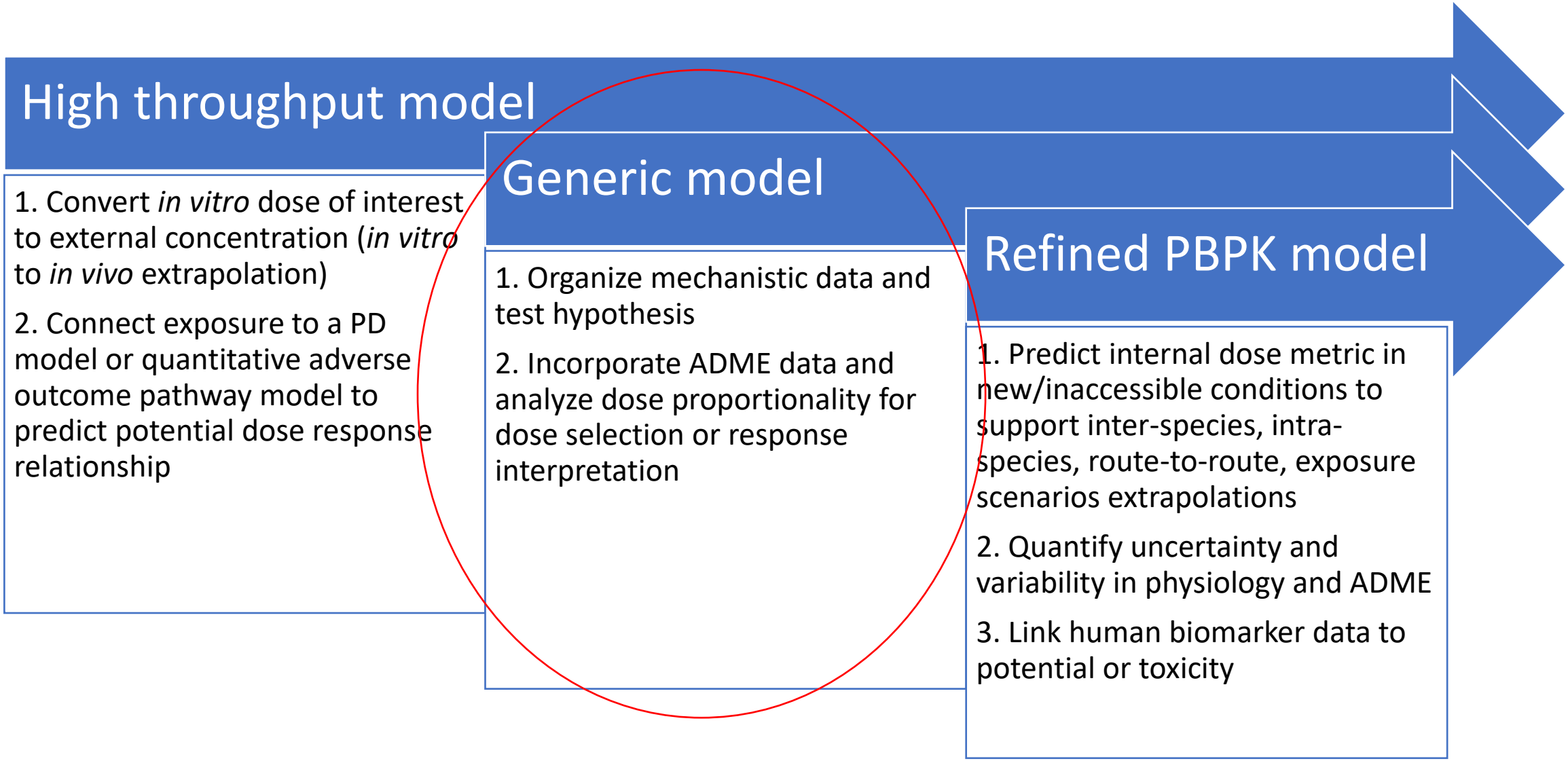
- At a minimum, a chemical-specific model should contain a compartment that is either identified with the target tissue, contains the target tissue, or is identified as an appropriate surrogate for the target tissue
- A model has defensible physiological parameter values that are within the known plausible range
- A model has undergone a thorough evaluation for their structure, implementation, and predictive capability
  - Model verification: Checking for correctness, retracing the model development to understand the model well enough for application
  - Model validation/evaluation: examining a model to accurately predict the general behavior of the animal data in the intended application, and whether any discrepancy between predictions and data is significant enough to affect conclusions derived from the model

EPA (2006) Approaches for the Application of Physiologically Based Pharmacokinetic Models and Supporting Data in Risk Assessment

Examples of applying refined PBPK models in the IRIS assessment

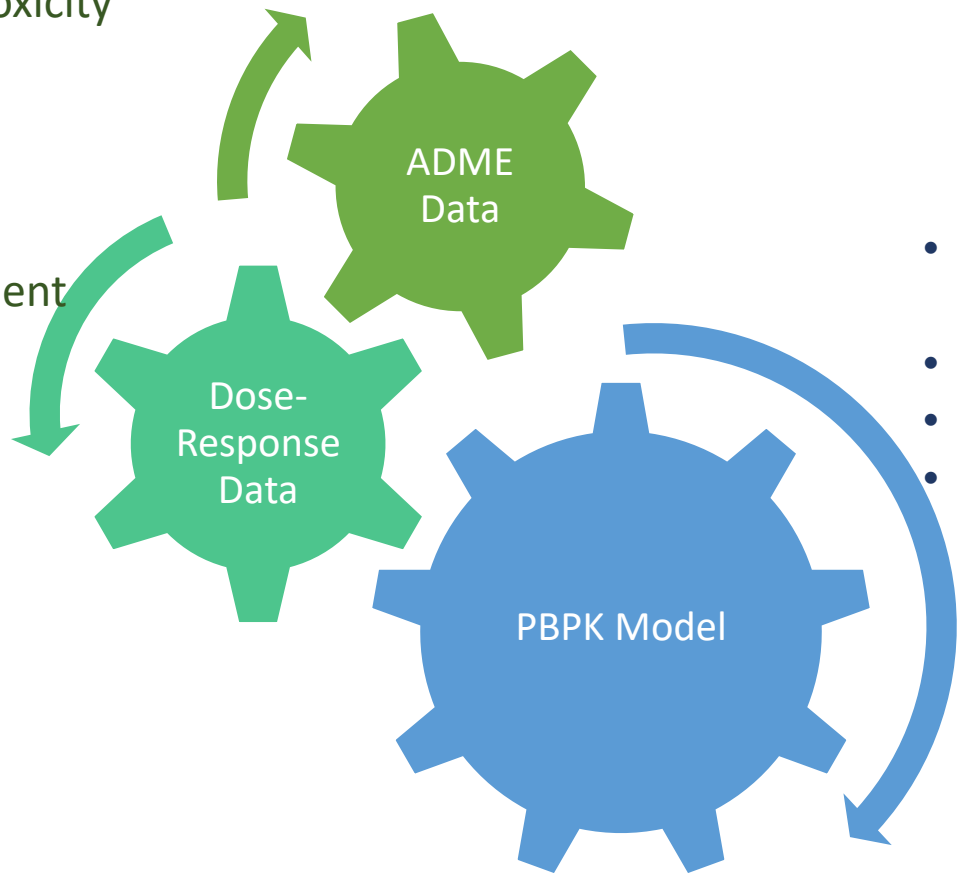
- A PBPK model for *tert*-butanol in rats was used to estimate an inhalation POD from an oral POD based on increases in severity of nephropathy (route to route extrapolation).
- An equivalent human POD was estimated based on a rat POD using PBPK
  - for carbon tetrachloride based on average rate of metabolism in the liver
  - for ethylene glycol monobutyl ether based on the peak blood conc of a metabolite
- A PBPK model for dichloromethane was used to extrapolate rat PODs to human PODs, and to account for PK variability in humans (inter- and intra-species extrapolations)
- A PBPK model for 1,1,1-trichloroethane was used to extrapolate from a one-hour exposure at the LOAEL to other exposure durations
- A PBPK model for methylmercury was used to estimate intra-species variability and compare with ranges predicted by 1-comp models

Common PBPK applications



Using PBPK modeling in an iterative process in a chemical safety testing program

- Acute oral, inhalation, dermal toxicity
- *in vitro* mammalian cell assay
- ADME radioactivity study
- Primary eye, dermal irritation
- Dermal sensitization
- 90-day feeding, rodent/non-rodent
- 90-day dermal, inhalation
- Developmental toxicity
- Acute/delayed neurotoxicity
- Reproduction toxicity
- Chronic feeding, rodent
- Carcinogenicity, rodent



- Organize ADME data to gain insight on PK behaviors
- Identify data gaps
- Optimize study design
- Simulate alternative internal dose metrics to correlate with toxic responses
  - Identify potential toxic moiety
  - Characterize relationships between potential dose metrics and early biochemical response
  - Propose possible mode of action
- Interpret dose-response data

An example of a retrospective analysis on 2,4D

- Saghir et al. (2013) hypothesized that kidney toxicity observed in rats may be due to saturation of renal clearance
- Saghir et al. (2013) analyzed AUC data to interpret shorter-term toxicity data and guide dose selection for longer-term toxicity studies

Male rat 28 day

Dose (mkd)	Fold difference	AUC (ug/h/mL)	Fold difference
5	1X	14	1X
21	4X	60	4X
41	8X	147	11X
67	13X	179	13X
79	15X	579	41X

Female rat 29 day

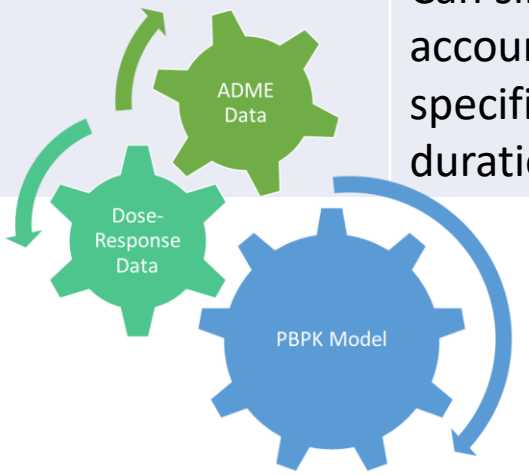
Dose (mkd)	Fold difference	AUC (ug/h/mL)	Fold difference
6	1X	26	1X
14	2X	68	3X
26	4X	220	10X
41	6X	651	31X
54*	8X	1100	39X
75*	12X	4139	160X

*Significant kidney weight changes

Toxicol Sci (2013), 136:kf212

A biologically based approach: use PBPK to test whether data are better explained by linear or nonlinear assumption

Non PBPK approach (such as fold difference)	PBPK approach
Assume a linear relationship between external and internal concentration at the lowest dose group • PK may be nonlinear at the lowest dose group • Rely on one data point	The shape of the external-internal concentration curve is determined by the data, and any *a priori* assumption is made based on available ADME data/knowledge
Subjectively distinguish tested dose groups into linear vs. nonlinear	Simulate an external-internal concentration curve
Use only the average values	Use individual animal data
Consider only one dataset	Can simultaneously analyze multiple datasets by accounting for PK (such as sex-specific, life stage specific) differences and exposure (such as route, duration, frequency) differences

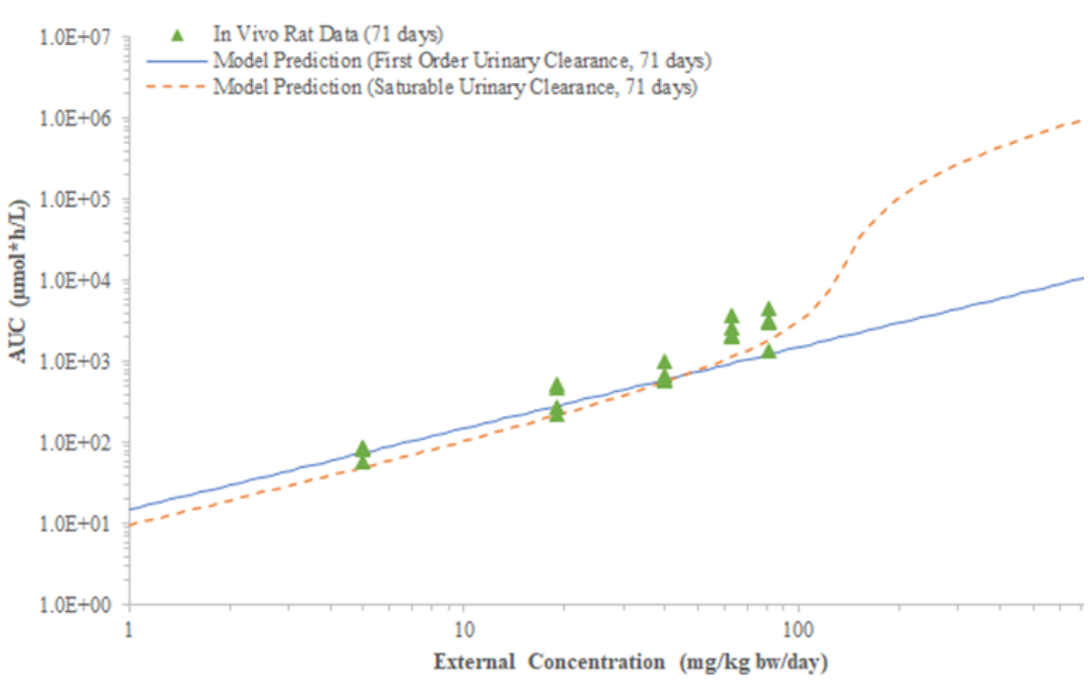


Model assumptions

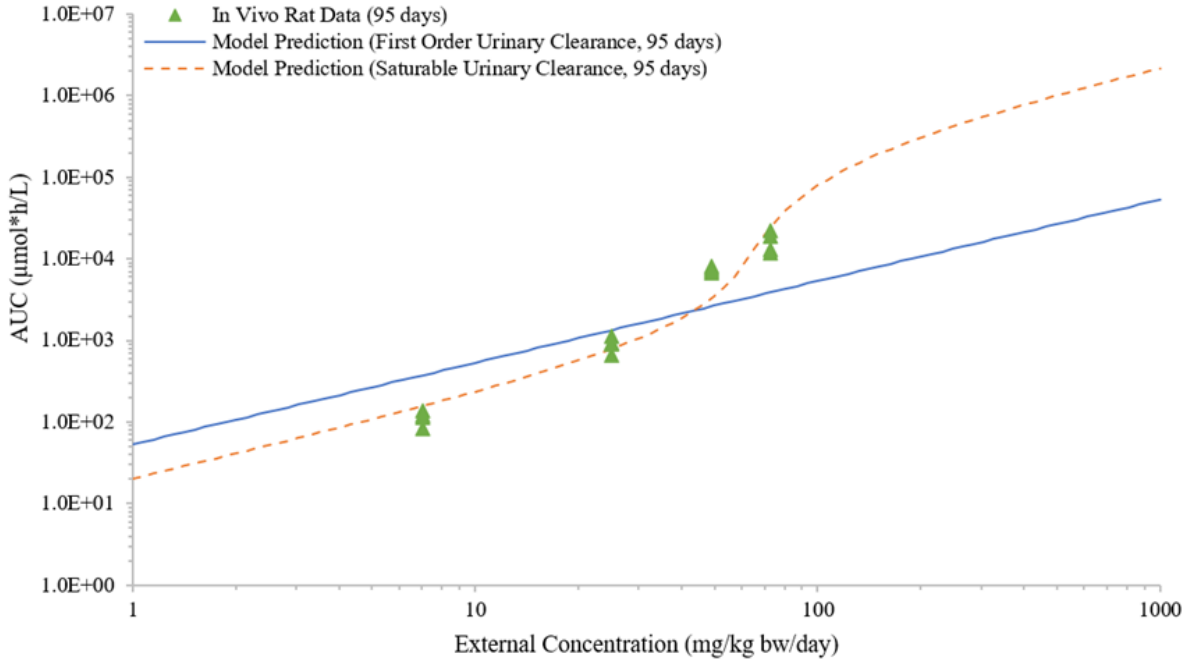
- Literature data suggested that 2,4D is virtually unmetabolized, and is eliminated via renal clearance
- Thus, a PBPK model was used to test whether linear or saturable renal clearance of 2,4D fit the data better
- Plasma AUC data for female rats from 29 and 95-day dietary exposure were used to fit saturable renal clearance parameters (Vmax and Km) or first order renal clearance rate
- Plasma AUC data for male rats from 28 and 71-day dietary exposure were used to fit Vmax (Km set to the female value) or first order renal clearance rate

Non-linear PK assumption results in better fit

Male rats, 71-day exposure

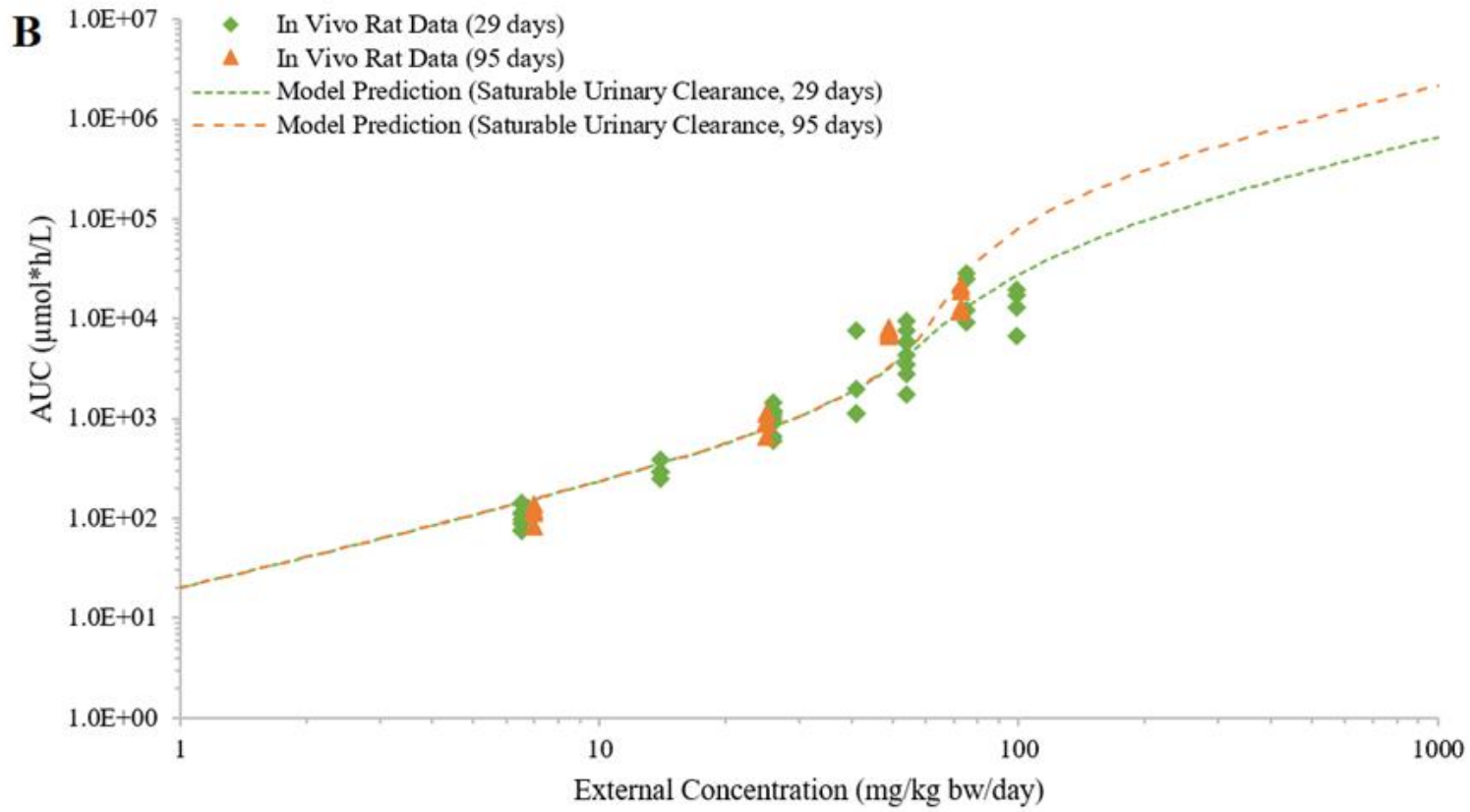


Female rats, 95-day exposure



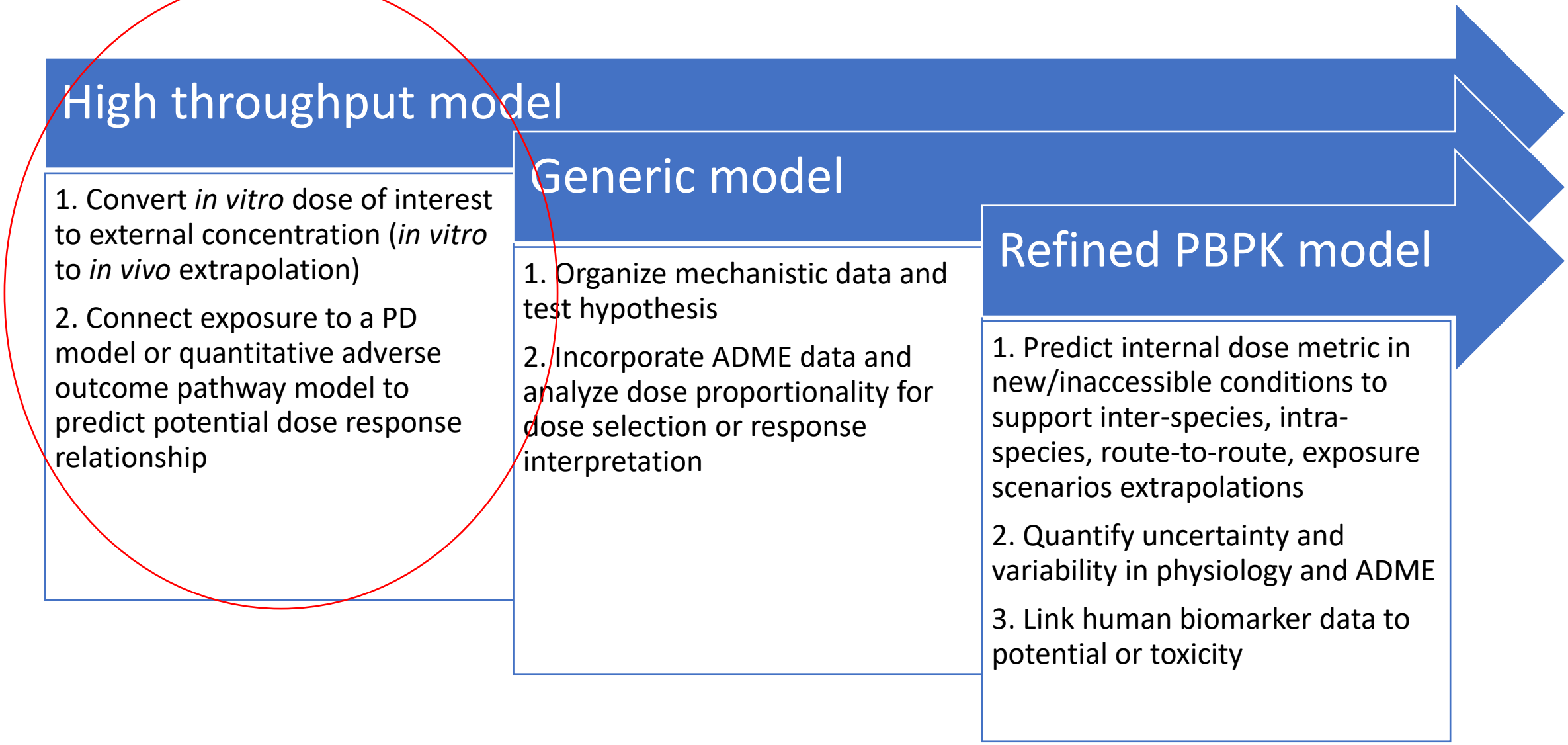
Data at the top dose group were not available due to excessive toxicity observed in female rats

Fitting data from different exposure durations



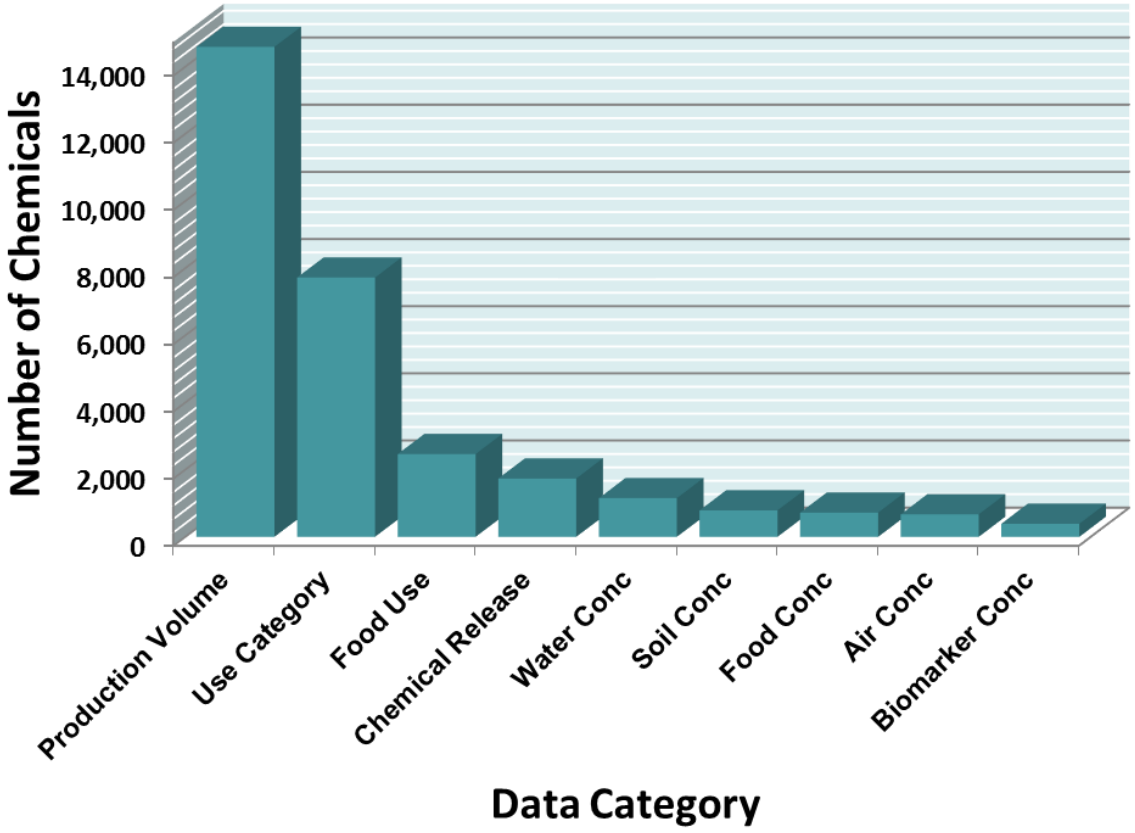
If a PBPK model was used to design a sub-chronic study, the top dose may be selected at a lower level, avoiding the exclusion of the top dose group due to excessive toxicity

Common PBPK applications



Limited data on environmental chemicals

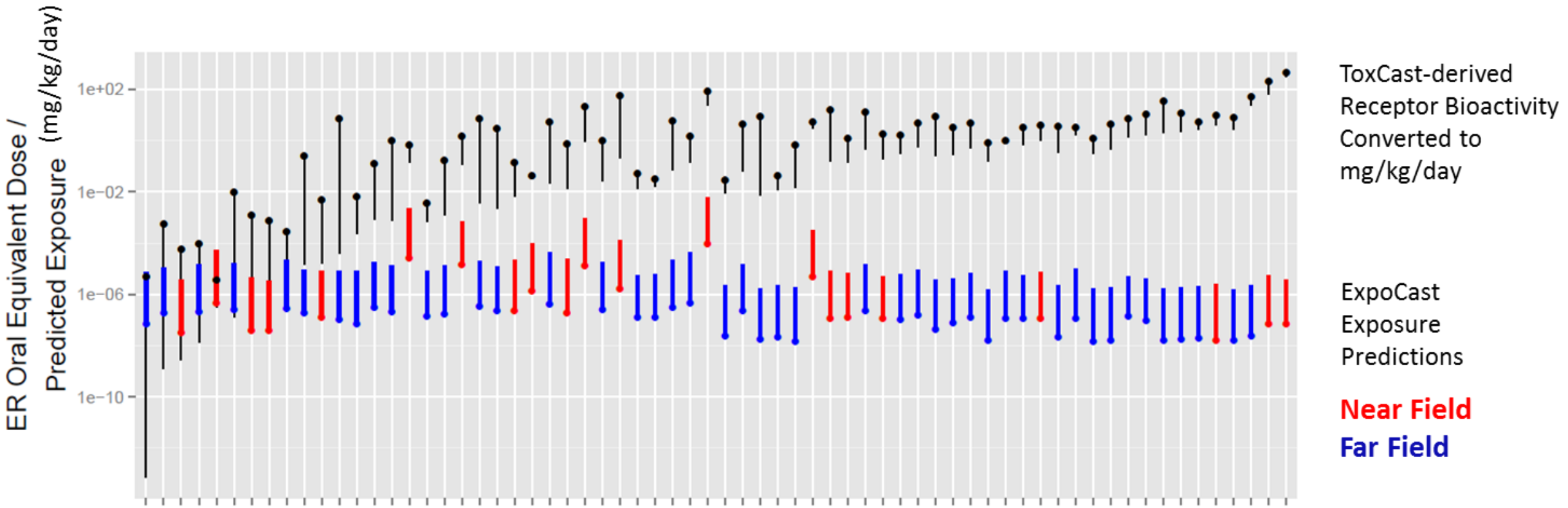
- The vast majority of chemicals in commerce:
  - Are unmeasured in the environment
  - Have unknown environmental fate and exposure potential
  - Have non-quantified human and ecosystem health impacts
- Resource and technological limits preclude any radical enlargement of these numbers



P.P. Egeghy et al. / Science of the Total Environment 414 (2012) 159–166

Courtesy of P Egeghy

High throughput risk prioritization



https://cran.r-project.org/web/packages/httk/

Can access this from the R GUI: “Packages” then “Install Packages”

Courtesy of J Wambaugh

Common reasons for not using PBPK models (IRIS examples)

- Model predictions not validated with human data
- Available model not adequate for calculation of internal dose metrics
- Route-specific model not available
- Available model cannot explain the route-specific difference in dose-response relationship
- Model still in development at the time of assessment
- Available PK data suggested that humans are not more sensitive than rats, so model or inter-species uncertainty factor is not needed

Challenges encountered by modelers/users

Perspectives from modelers	Perspectives from users
Expertise needed within regulatory agencies to recognize the value and limitations of PBPK models, or to review modeling analysis	Expertise needed within the agencies and among peer reviewers
Need a user-friendly software/platform for non-programmers to test a model	Need a user-friendly software/platform for non-programmers to test a model; some agencies require a model to be coded in an open-source platform
Validation of a model requires data that are not available	Validation of a model requires data that are not available
Difference in acceptance criteria between agencies and countries	Need a defensible, transparent model that fits specific purposes
Model development and evaluation processes can take a long time	Reproducing or repurposing a model may be difficult

PBPK expertise

- Limited training opportunities exist through specialized workshops, continuing education courses, academic courses, workshops offered by software companies, but are unlikely to offer sufficient training for
  - A modeler who needs to shepherd a modeling project from problem formulation stage to final submission stage
  - A reviewer who needs to understand PK concepts, PBPK modeling, risk assessment to evaluate the validity of conclusions from PBPK analysis in a timely manner
- Provide PBPK training to users, and risk assessment training to modelers
- How does the community facilitate sustainable growth in the field?

PBPK model evaluation

- “If a complete PK data set were available for the exposure scenarios and species of interest, there would be no need to develop a PBPK model” (WHO 2010)
- “All PBPK models are simplified representations of biological systems of varying complexities. Parsimony is an important and guiding principle in developing models for use in risk assessment” (EPA 2006)
- No published criteria or well-defined standards for model evaluation, but several guidance documents have addressed good modeling practices and approaches for evaluating and documenting PBPK models intended for risk assessment

WHO (2010) Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment

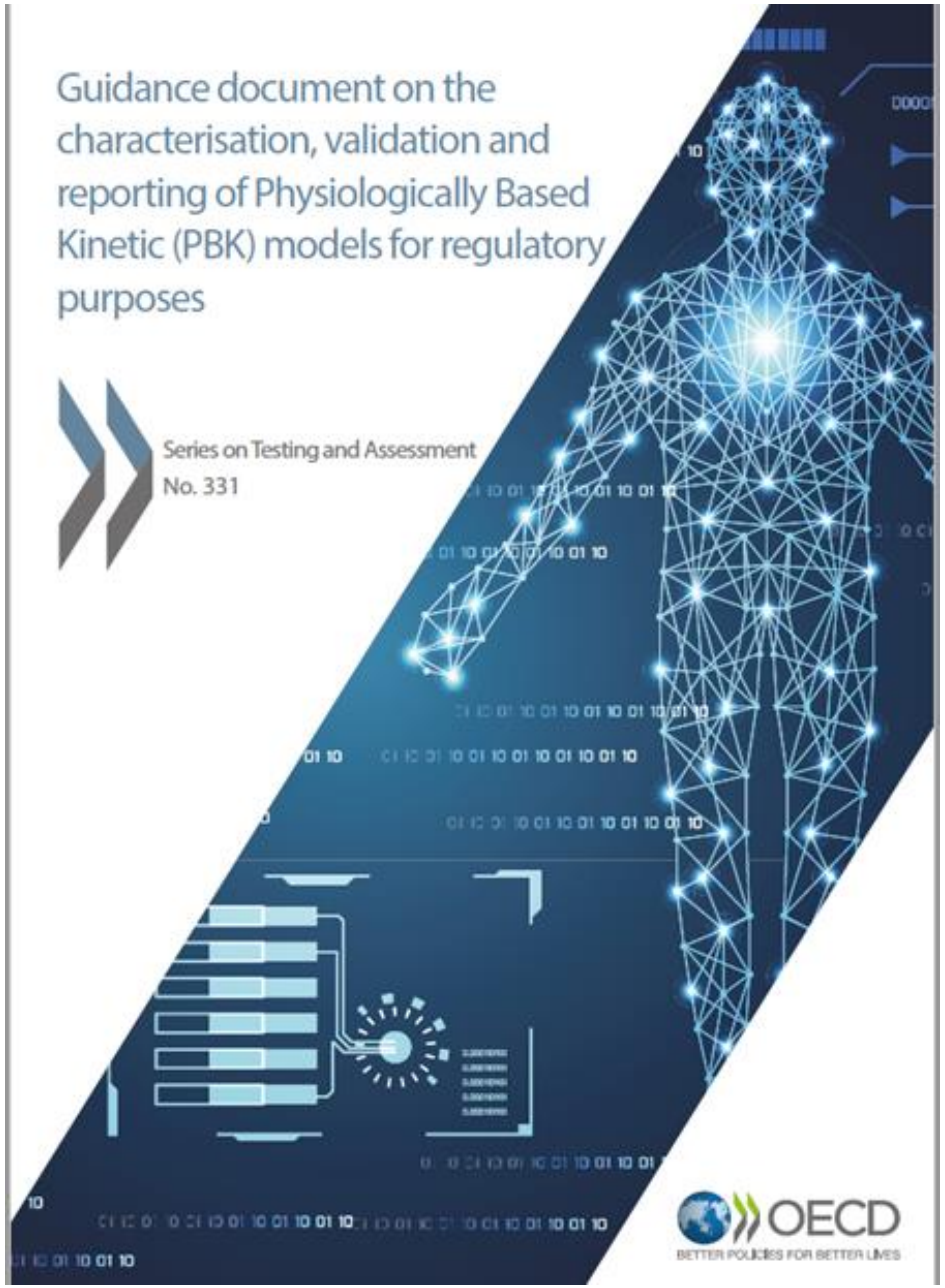
PBPK guidances

IPCS
INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY
WHO
IPCS Harmonization Project

Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment

U.S. Environmental Protection Agency (2006)

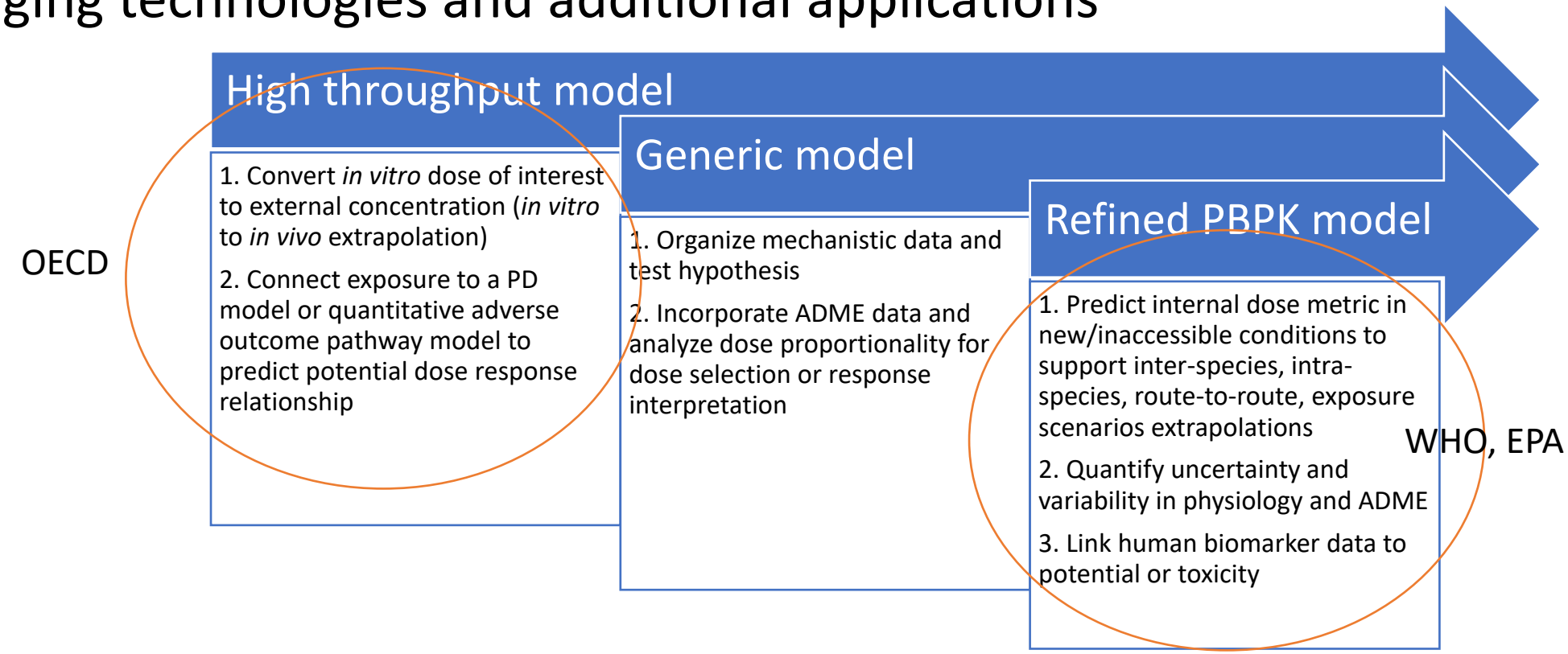
Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment



	EPA, 2006	WHO, 2010	OECD 2021
Introduction			
PK Data and Model Needs in Risk Assessment			
Model Characterization and Documentation			
Model Evaluation			
Model Application			
Process Considerations			
Examples or Case Studies			

Updating PBPK guidance

- Update current best practices based on lessons learned from published models, e.g., how to obtain human values for chemical-specific parameters
- Include emerging technologies and additional applications



Model reporting template

The format and content of PBPK model analysis submitted to regulatory agencies significantly vary

Harmonizing the format of a PBPK analysis report

- reduces the burden of preparing different reports on the same analysis for different agencies
- facilitates more efficient review and timely decision-making
- provides a general format that can be customized to meet specific needs of different agencies

Available templates

IPCS
INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY
WHO
IPCS Harmonization Project

Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment

WHO (2010)

Guidance document on the characterisation, validation and reporting of Physiologically Based Kinetic (PBK) models for regulatory purposes

Series on Testing and Assessment
No. 331

OECD (2021)

FDA (2018)

Physiologically Based Pharmacokinetic Analyses — Format and Content
Guidance for Industry

EMA (2018)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

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,*]

	WHO, 2010	US FDA, 2018	EMA, 2018	HESI PBPK Committee 2020	OECD 2021
Executive Summary					
Background Introduction					
Model Purpose	Included in Introduction	Included in Executive Summary			
Materials & Methods					
Results					Called “Model characterization”
Discussion & Conclusions					Called “Identification of uncertainties Peer engagement”
References					
Electronic files and Supporting Materials		Included in Materials and Methods	Included in Qualification of PBPK platform		
Appendices					

Computing software

- Some agencies require models to be coded in open-source software
- Preferably, a PBPK package should be reviewed by biologists/toxicologists, risk assessors, mathematicians/modelers/programmers, and the last one is often hard to recruit
- Modeler’s choice of computing software is based on the preference, familiarity, or accessibility; and not the reviewer’s choice of software
- Models coded in legacy software platforms will need to be recoded or may not be accessible

User-friendly software for non-programmer to test model behaviors or simulate additional scenarios

Model equations for non-programmer to examine the accuracy of mathematical representation

Computational Implementation

Data exchange format, e.g., extensible markup language (XML), coupled with formal ontologies may help model documentation and translation

Open-source software allows reviewers to have access to the model code. The qualification of a PBPK modeling platform for its intended purpose should be justified

Reproducing or repurposing a model

- Models developed for academic interest are often not directly usable by regulatory agencies because model scope, assumptions, and inputs/outputs are not tailored to the specific risk assessment needs
- Model template code that contains commonly used equations and logic can facilitate more efficient code review, or be used to quickly implement models (Bernstein et al., 2021)
- Modelers are encouraged to engage users early in the model development process to ensure that the final product meets the specific needs of the users

Food for thought

- Meeting training needs
- Expanding model applications
- Updating current guidance/best practices
- Developing templates to harmonize model development and review
- Encouraging more dialogues between modelers and users