Physiologically based pharmacokinetic (PBPK) model reporting template for chemical risk assessment applications

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Society of Toxicology, Biological Modeling Specialty Section webiniar

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

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Regulatory Toxicology and Pharmacology

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

Contemporary Review

PBPK model reporting template for chemical risk assessment applications

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	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					

Executive Summary

- Rationale for conducing the PBPK analysis
- Overview of model development and simulation scenarios, and its applications
- Summary of key conclusions

- This section should clearly convey how the analyses address a specific scientific question in support of a regulatory decision

Introduction/Background

- High-level synopsis of a substance's kinetic properties
- Brief summary of known exposure and toxicity for an environmental chemical, or known dose, toxicity and efficacy of a drug
- Brief regulatory history
- History of previous model submissions for the same chemical, or a chemical analogue
- Summary of relevant studies used for model calibration
- Summary of relevant studies used for model evaluation

Model purpose

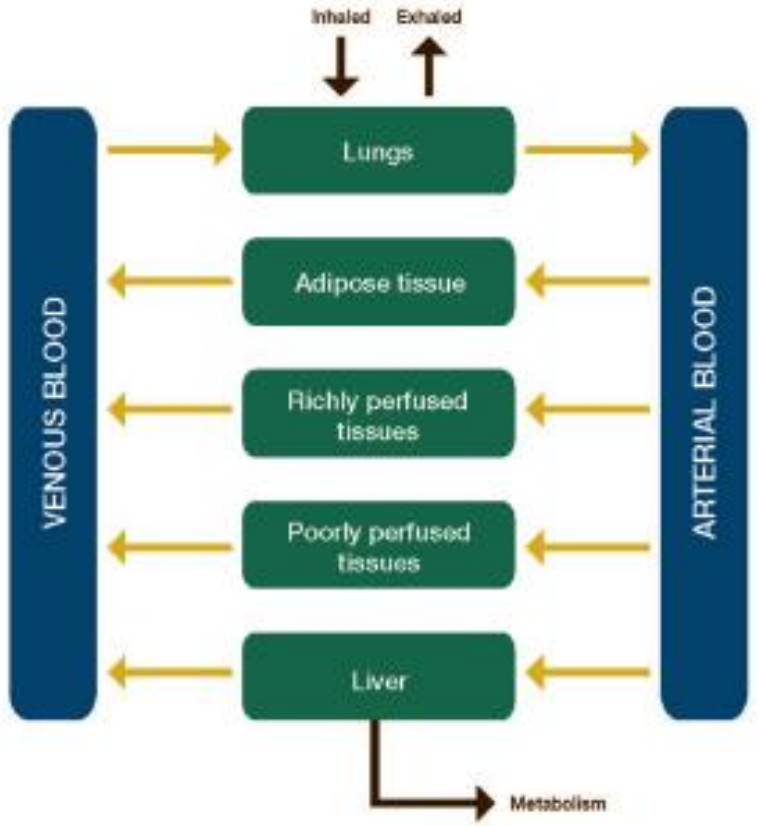
- Clearly articulate the regulatory question(s) the PBPK model is intended to address, such as:
  - Extrapolations
    - Animal to human
    - Human variability
    - Life stage
    - Route to route
  - Design clinical trials or biomonitoring studies
  - Chemical screening and prioritization

Materials and Methods

- Overview of modeling strategies
- Summary of data for model development and evaluation
  - Relevant chemical information, such as physio-chemical properties and relevant exposure routes
  - Toxicity studies that determine mode of action, toxic moiety, dose metric
  - Mass balance studies that inform absorption, distribution, metabolism, excretion
  - Time course of chemical concentrations in plasma/blood and tissues
  - *in vitro* or *in silico* studies used to estimate model parameters

Materials and Methods (cont'd)

- Model development and structure
  - Key assumptions used to determine the model structure
  - A schematic diagram to present the structure
  - Explain whether the model replicates a published model, is refined or modified from an existing model (with justifications), or is a new model



Materials and Methods (cont'd)

- Model equations
  - Parameter names consistent with those in the computational code

$$\frac{\mathrm{d}A_t}{\mathrm{d}t} = Q_t \times \left(Ca - \frac{C_t}{p_t} \right) - \frac{\mathrm{d}A_m}{\mathrm{d}t}$$

  - In some cases, model code is acceptable

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At' = Qt*(Ca-Ct/Pt) – Am'
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- If a commercial PBPK software platform is used, providing model equations may not be necessary. The software, however, must show the ability to predict a specific outcome that is relevant to the submission (EMA, 2018)

Materials and Methods (cont'd)

- Model parameters
  - At a minimum, include parameter names/symbols, meanings, values, units, and sources of values; also include types of probability distributions and parameters for describing distributions for a probabilistic model
  - If a parameter has more than one value from multiple sources, justify the chosen value
  - If ancillary studies are conducted to measure or predict parameters, submit unpublished reports describing these studies as supplemental materials
  - If a commercial PBPK platform is used, export parameter values and provide sources of user-defined values
  - Include methods used to estimate parameters, such as equations for age-dependent changes in physiology
  - Document model optimization process and criteria to evaluate the optimization performance

Parameters	Rat Values	Human Values	Sources
Body weight (kg); BW	0.25	80	Default setting
Cardiac output (L/h/$bw^{0.75}$); QCc	15	15	Brown et al., 1997
Ventilation rate (L/h/$bw^{0.75}$); QPc	15	15	Set to = QCc
Fractional venous blood volume; VVBc	0.056[A]	0.059 [A]	Brown et al., 1997
Blood:Plasma Concentration Ratio; RBP	1	1	Default setting
Fractional liver volume; VLc	0.04	0.026	Brown et al., 1997
Fractional rapidly perfused tissue volume; VRc	0.06[B]	0.05 [B]	Brown et al., 1997
Fractional fat volume; VFc	0.07	0.214	Brown et al., 1997
All Perfused Tissues; VAll	0.865	0.878	Brown et al., 1997
Fractional slowly perfused tissue volume; VSc	0.62	0.71	Calculated from: VAll – (VLc + VRc + VVc + VFc + VAc)
Fractional liver blood flow; QLc	0.18	0.227	Brown et al., 1997
Fractional rapidly perfused tissue blood flow; QRc	0.58	0.333	Brown et al., 1997
Fractional fat blood flow; QFc	0.07	0.052	Brown et al., 1997
Fractional slowly perfused tissue blood flow; QSc	0.24	0.44	Calculated from: 1 – (QLc + QRc + QFc)

[A] Fraction of venous blood was determined as the fraction of body that is blood multiplied by the proportion that is venous or arterial (75% or 25%, respectively; Brown et al., (1997))

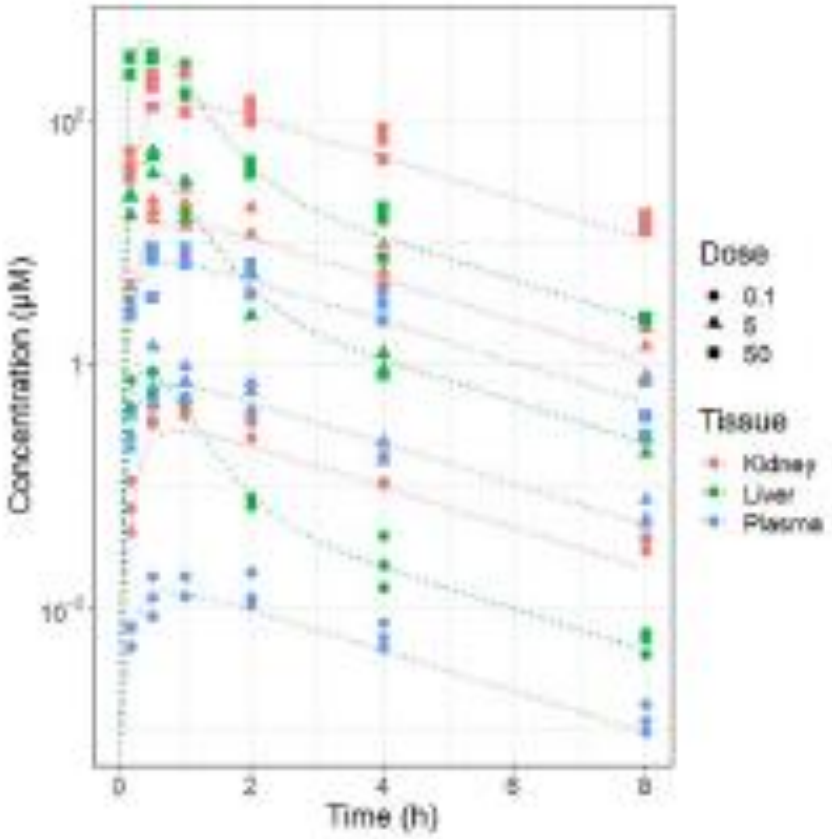
[B] Rapidly perfused tissues: adrenals, brain, kidneys, large intestine, lungs, pancreas, stomach, thyroid, and spleen.

Materials and Methods (cont'd)

- Model simulations
  - Doses
  - Exposure/dosing characteristics, such as routes, time/duration/frequency of exposure, formulation or other physical properties, feeding/fasting status
  - Sample types and time of sample collection
  - Characteristics of the test subjects and the simulated virtual population
  - For probabilistic simulations, describe analytical methods, number of iterations, and associated data involved in the analysis
- Software
  - Name and version of the software
  - Specification of the differential equation solvers, optimization and statistical algorithms

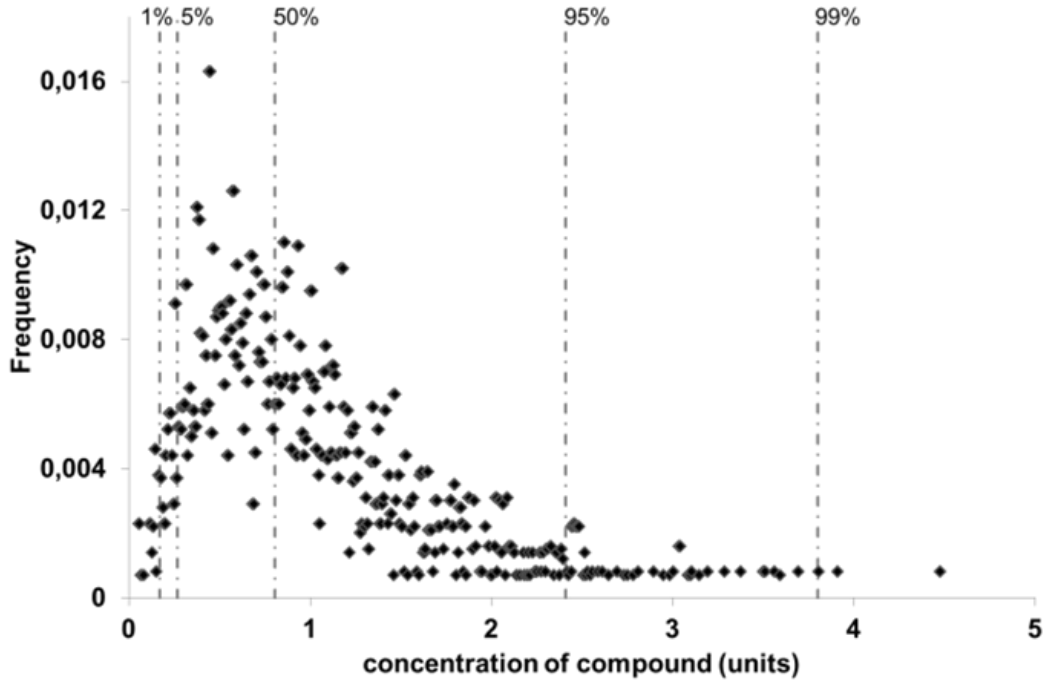
Results

- Present graphical comparisons between model simulations and observed data
- Clearly distinguish the results showing the model fit to training set and the results showing the model's ability to simulate other datasets
- Describe criteria used to evaluate goodness-of-fit
- Discuss model performance in the context of the intended application
  - Levels of confidence, given the uncertainty
  - Model limitations and domains of applicability

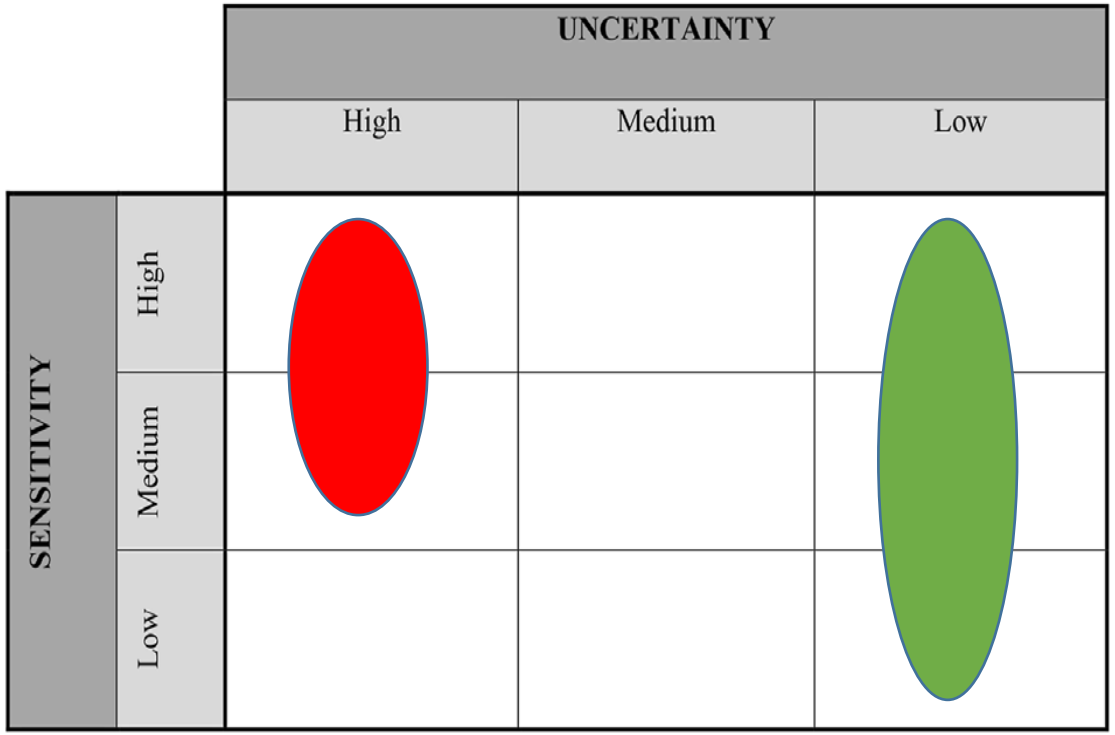


Results (cont'd)

- Sensitivity, uncertainty, and variability analyses



OECD 2021



WHO 2010

Discussion and conclusions

Reiterate the science question(s) or hypothesis

Reiterate why a PBPK model is required or preferred

A summary of modeling analysis, key results and interpretation of these results, uncertainties and limitations of the model

Electronic files and supporting documents

Electronic files, such as model code, metadata

Supporting documents, such as step-by-step instructions to run model simulations, peer review of the modeling analysis, unpublished study reports

Appendices

List of tables

List of figures

Table of acronyms and abbreviations

References

When possible, use hyperlinks in the report to cross-reference tables, figures, and references

Additional uses of the reporting template

Guidance	Communication	Training	Promotion
Provide clear guidance on critical elements evaluated by regulatory agencies	Use to organize modeling analysis for peer-reviewed publications or scientific collaborations	Provide training to new modelers and risk assessors	Facilitate the application of PBPK models and regulatory acceptance of PBPK analysis