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

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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

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

FDA (2018)

EMA (2018)
Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

OECD (2021)
Guidance document on the characterisation, validation and reporting of Physiologically Based Kinetic (PBK) models for regulatory purposes
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<td><strong>Executive Summary</strong></td>
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<td><strong>Background Introduction</strong></td>
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<td><strong>Model Purpose</strong></td>
<td>Included in Introduction</td>
<td>Included in Executive Summary</td>
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<tr>
<td><strong>Materials &amp; Methods</strong></td>
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<td></td>
<td>Called “Model characterization”</td>
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<td><strong>Results</strong></td>
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<td>Called “Identification of uncertainties Peer engagement”</td>
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<td><strong>Discussion &amp; Conclusions</strong></td>
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<td><strong>References</strong></td>
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<tr>
<td><strong>Electronic files and Supporting Materials</strong></td>
<td>Included in Materials and Methods</td>
<td>Included in Qualification of PBPK platform</td>
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<td><strong>Appendices</strong></td>
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</table>
Executive Summary

• Rationale for conducting 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
    \[ \frac{dA_t}{dt} = Q_t \times \left( Ca - \frac{C_t}{p_t} \right) - \frac{dA_m}{dt} \]
  • In some cases, model code is acceptable
    \[ At' = Qt^* (Ca-Ct/Pt) - Am' \]

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

^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
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**

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