Systematic Evaluations of Physiologically-Based Pharmacokinetic Models for Human Health Risk Assessment

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Background

- Physiologically-based pharmacokinetic (PBPK) models are tools for estimating absorption, distribution, metabolism, and elimination (ADME) of chemicals in the body.
- Quantity internal (tissue/orGAN) dose vs exposure
- Facilitate dose-response analysis/human extrapolation
- Use chemical- and species-specific data (unlike default BW44 allometric scaling)
- Multiple alternative models or analyses in literature
- “Being published is not enough”: EPA thoroughly evaluates models based on scientific and technical criteria prior to use in an assessment
- IRIS uses a structure approach to evaluate quality and usability
- The evaluation process stresses: (1) clarity in the documentation of model purpose, structure, and biological characterization; (2) validation of mathematical descriptions, parameter values, and computer implementation; and (3) evaluation of each plausible dose metric.
- NAS (2014) recommendations addressed
  - Develop and expand use of formal quantitative methods in data integration for dose-response assessment and derivation of toxicity values
  - Develop tools for assessing risk of bias in different types of studies

Identification and Inventory of PBPK Models

- A thorough literature search is conducted to identify existing PBPK models
- A summary report is prepared of available models and their possible utility for use (scoping)
- This work is conducted by the Pharmacokinetics Workgroup (PKWG)*, in conjunction with information specialists
- Table 1 outlines typical summary information presented for each model at the scoping phase

Table 1. Example animal PBPK inventory table for model scoping

<table>
<thead>
<tr>
<th>Author</th>
<th>Contact Email</th>
<th>Code Available</th>
<th>Effort to Recreate Model</th>
<th>Math Evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith</td>
<td><a href="mailto:eecox@email.com">eecox@email.com</a></td>
<td>YES</td>
<td>COMPLETE</td>
<td>YES</td>
</tr>
<tr>
<td>Davis</td>
<td><a href="mailto:dox@email.com">dox@email.com</a></td>
<td>YES</td>
<td>SIGNIFICANT</td>
<td>YES</td>
</tr>
<tr>
<td>Brown</td>
<td><a href="mailto:bro@email.com">bro@email.com</a></td>
<td>YES</td>
<td>COMPLETE</td>
<td>NO</td>
</tr>
</tbody>
</table>

PBPK Model Scoping Criteria

PBPK Model Scoping Criteria A
- An evaluation of a model is required before accepting it for use in an assessment
- Many models contain errors with varying degrees of impact on model predictions
- Initial judgments on the suitability of a model are separated into two categories: scientific and technical (Table 2)

Evaluation of PBPK Models

PBPK Evaluation Example: Chloroform

- Chloroform is a trihalomethane present in drinking water as a byproduct of disinfection
- Kidney and liver are target organs
- Effects induced via production of reactive metabolites
- A PBPK model (left) was obtained during scoping and satisfied Criteria A
- Issues identified during in-depth technical evaluation:
  - Metabolic parameter derivation for the kidney cortex contained a units error, and the calculation was not performed consistently for humans and rodents
- The volume ratio for kidney cortex and medulla was reversed in the code, and did not match the reported value or original reference

Selected references


In-Depth Technical Evaluation: Criteria B
- Primary address computational implementation and technical issues
- Only conducted on models that pass review for Criteria A
- Model equations and parameters in computer codes match those in the manuscript or original reference
- Published figures/tables of model simulations are reproducible using the available code (within 10% of the publication)
- Errors in model code or parameters are found and corrected, the revised model must still be in agreement with data. Errors must be small enough to not invalidate the model, parameters, or assumptions
- Model predictions outside the range of the data are allowed to change by more than 10% of the original model or publication, since this would be considered a model correction

Resource Considerations for PBPK Model Revision or Development: Criteria C
- If existing models fail Criteria A or B, the potential value in implementing a PBPK in a risk assessment must be weighed against the time, effort, and possible expenses required to address model shortcomings.

The revised PBPK model allows for improved quantitative dose-response modeling and data integration. Kidney endpoints can be evaluated across different routes of exposure and different species (Nagano et al., 2006, and Yamamoto et al., 2002). The figures above illustrate dose-responses for rats from multiple exposure routes (inhalation, oral, and combined inhalation/oral) on basis of PBPK-derived kidney dose.