Abstract

Physiologically based toxicokinetic (PBTK) modeling offers a rational basis for the extrapolation of toxicokinetic data from acute, high dose experiments in animals, to chronic, low dose exposures in humans. A general drawback of PBPK exposure modeling is that it requires the estimation of extensive sets of parameters. Physiological, anatomical and physicochemical parameters are often typical values, or mean values available in the literature, and are assumed fixed for model development and application. PBPK models are often also optimized by adjusting certain parameters to experimental data while "fixing" others, many of which are not known with accuracy in vitro. This approach does not incorporate physiological and biochemical uncertainties and the presence of inter- and intra-individual variability.

The present study aims to incorporate estimates of this variability in the formulation of a PBPK model for chloroform. There are many datasets available that describe variability of physiological and anatomical attributes within the general population. Age and gender dependent mathematical regression models are typically used for population exposure modeling. However, there is no simple way to describe variability in biokinetic processes, due to the lack of data on this data. Bayesian methods can be applied to partially overcome limited availability of biokinetic data.

In this case study, two sets of time-series of exhaled breath measurements from six subjects (three male and three female) were used to assess inhaled and dermal exposures from the use of chlorinated drinking water. A chloroform-PBPK model with distributed parameter descriptions of dermal transport was used to incorporate inter- and intra-individual variability by developing posterior distributions of metabolism-related parameters, using a Markov Chain Monte Carlo (MCMC) method with new data sets. Age and gender dependent deterministic equations and subject-specific information were used to calculate physiological parameters.

Methodology

Offers a rational basis for the extrapolation of breath concentration for toxicokinetic data from acute, high dose experiments in animals, to chronic, low dose inhalation only chloroform exposures in humans. A general drawback of PBPK exposure modeling is that it requires the estimation of extensive sets of parameters. Physiological, anatomical and physicochemical parameters are often typical values, or mean values available in the literature, and are assumed fixed for model development and application. PBPK models are often also optimized by adjusting certain parameters to experimental data while “fixing” others, many of which are not known with accuracy in vitro. This approach does not incorporate physiological and biochemical uncertainties and the presence of inter- and intra-individual variability.

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Table 1. List of PBPK model parameters, showing the scaling functions and initial literature parameters used to predict the exhaled concentrations in Figures 1 and 2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Scaling Function</th>
<th>Initial Literature Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>MECI</td>
<td>Exhaled concentration</td>
<td>( \text{MEC}_i )</td>
<td>( \text{MEC}_i^{(0)} )</td>
</tr>
<tr>
<td>PK</td>
<td>Partition coefficient</td>
<td>( \text{PK} )</td>
<td>( \text{PK}^{(0)} )</td>
</tr>
</tbody>
</table>

References


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