The Rapid Generation of Physiologically Based Pharmacokinetic Models using MEGen

Martin Spendiff, George Loizou and Alex Hogg
Health and Safety Laboratory, Buxton SK17 9JN; email: martin.spendiff@hsl.gov.uk

HEALTH & SAFETY LABORATORY
An agency of the Health and Safety Executive

Introduction

A reliable, scientifically based and quantitative chemical risk assessment technique is the goal of governments and industry worldwide. Physiologically based pharmacokinetic (PBPK) (Fig. 1) modelling is a powerful means of simulating the factors that determine tissue dose within any biological organism and consequently, correlation with health effects. The value of PBPK models is that they are tools for integrating *in vitro* and *in vivo* mechanistic, pharmacokinetic and toxicologic information through their explicit mathematical description of important anatomical, physiological and biochemical determinants of chemical uptake, disposition and elimination. Thus, PBPK modelling is a potential tool for use in risk assessment. However, PBPK models are perceived as complex, data hungry, resource intensive and time consuming. In addition, model validation and verification are hindered by the relative complexity of the equations. To address these issues a system for the rapid construction of PBPK models has been developed.

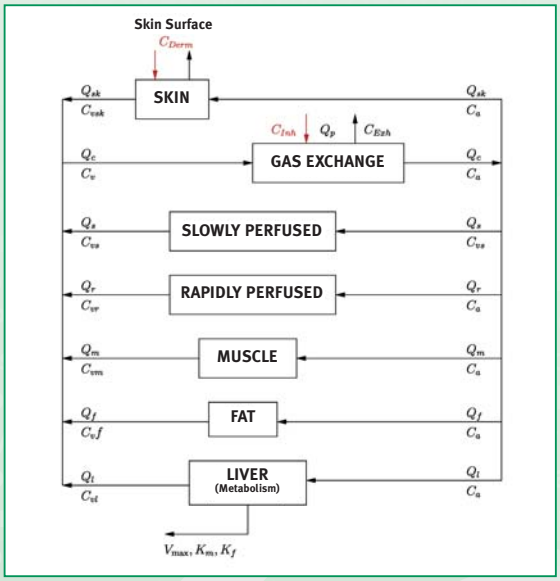
The modelling capability comprises two main components :

1. The PBPK parameter database
2. Model Equation Generator

The PBPK Database

The anatomical, physiological, biochemical and physicochemical data required to build PBPK models reside in a specifically designed electronic database. Different values for parameters are stored along with their source making selection of all the parameters for a model easy, rapid and transparent. The database can be used in isolation or as part of model building in the Model Equation Generator (MEGen).

Figure 1. Schematic representation of a PBPK model.



MEGen - The Model Equation Generator

MEGen is a code generator that eliminates the need to formulate and code a set of equations. The user is engaged in a dialogue relating to the details of the physiology of the system to be modelled and the biochemistry and physicochemistry of the compound of interest. On the basis of this information, a script is produced in XML. The XML can be transformed into alternative markup (e.g. MathML) or plain text for use in modelling software packages such as Berkeley Madonna, MCSim, ACSL and MATLAB. This greatly reduces development time (from days to minutes) and removes the need for any mathematical expertise (Fig. 2).

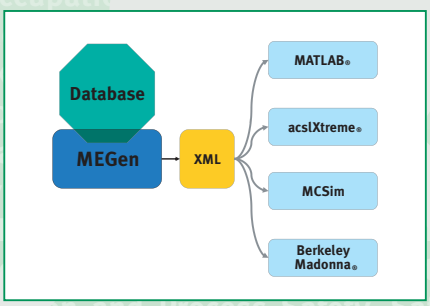


Figure 2. Overview of the model generation process.

Figure 3 is a montage of screenshots showing two property pages from MEGen, the underlying XML code and mathematics in MathML viewed in separate browser windows. The compartment volumes, blood perfusion rates, partition coefficients and metabolic rate constants are listed as the model is being constructed. MEGen transforms the mathematical equations and all other necessary operators into model code.

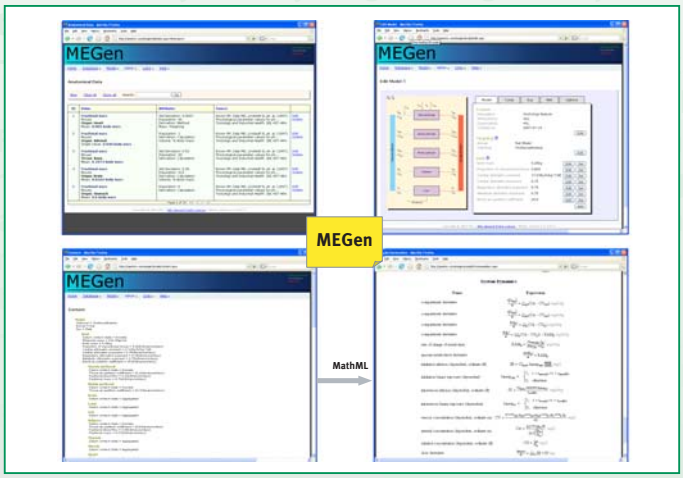


Figure 3. Montage of MEGen screenshots (parameters and model structure property page) and outputs (XML and MathML).

The code is saved in a format (native syntax) which is run using a commercial simulation package where it may be visualised and exercised (Fig. 4).

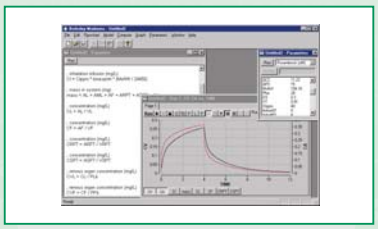


Figure 4. Visualisation and exercise of model in a commercial simulation package.

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Summary

- Currently able to quickly generate and analyse standard PBPK models
- Provides full model transparency and reproducibility
- Shifts focus from mathematics to biology
- Saves time and money
- Massive scope for development

Future Developments

Phase II of development will broaden the applicability of MEGen by adding

1. An extended library of governing equations, including diffusion-limited compartments, enhanced oral uptake model, micturition model, wash-in/wash-out inhalation route and other functional forms requested by the partners.
2. Built in QSAR algorithms and state of the art in vitro to in vivo scaling for the use of experimentally derived partition coefficients and metabolic rate constants in PBPK models.
3. Software facility for the addition of new governing equations into the model library as MathML.
4. Output template that provides a standard document with model information that has been established as pertinent to regulators.
5. Population modelling module that allows the deterministic PBPK model to be used in a population simulation that includes the specification of covariance between parameters.

Phase I of the development of MEGen was a Joint Industry-Government project funded by a number of partners including the CEFIC LRI. Other contributors were the UK Health & Safety Executive, UK Department of the Environment Food and Rural Affairs/Pesticide Safety Directorate and Unilever.