Simulation of blood and urine levels after exposure

Prediction with a chemical across predictive Physiologically Based Toxico-Kinetic (PBTK) model available as application in MS Excel

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INTRODUCTION

The absorption, distribution, metabolism and excretion of environmental or industrial chemicals is often poorly known. Applying of toxicokinetic modeling is often not easy due to two sorts of barriers:

1. Missing data on partitioning of the chemical and metabolite;
2. Patented PBTK-software.

In order to overcome these barriers we used algorithms (OSPRs = Quantitative Structure-Property Relationships) for the cross-chemical prediction of blood/tissue partitioning. In addition, we developed algorithms for the cross-chemical prediction of blood tissue:air partitioning. These routines have been build in a generic, multi-chemical model. It is a Physiologically Based ToxicoKinetic model (= PBTK model) for 70 kg man that considers three uptake routes (inhalation, dermal and/or oral, see figure 1). The model is written as an application in the general available software Microsoft Excel.

AIM

Development of a generic model that can predict the concentration of multiple chemicals and its metabolites in blood and urine of various exposure scenarios.

MODEL FEATURES

- The OSPRs (= Quantitative Structure-Property Relationships) for blood:air and tissue:blood partitioning makes that the model can be used even when experimental partition characteristics of a compound are lacking.
- Dermal uptake is estimated by the use of a novel module that considers dermal deposition rate and duration of deposition. Moreover, evaporation during skin contact is fully accounted for and related to the volatility of the substance.
- Michaelis-Menten saturable metabolism is incorporated in the model. Metabolism can be modeled in any of 11 organs/tissues or in liver only.
- Two exercise levels are available (rest or light work).
- Tubular resorption is dependent on the (log) octanol:water partition coefficient.
- Enterohepatic circulation is optional at a user-defined rate.
- The differential equations of the PBTK-model are written in Visual Basic and the model runs as an application in MS Excel.
- The program is called IndusChemFate and is available as freeware with an open source code.

RUNNING THE PROGRAM

**STEP 1: Input of data**
- Phys-chem properties
- In vitro metabolism data

**STEP 2: Enter exposure scenario**

**STEP 3: Run program**

**STEP 4: Review results**
- Listing of amount and concentration of compound and metabolites over time;
- Mass balance;
- Partitioning coefficients;
- Graphs of time course of concentrations in blood and urine.

COMPARING MEASURED WITH MODEL-PREDICTED

A series of published studies of inhalatory and/or dermal exposure was used to test the prediction of concentrations in blood and urine with the IndusChemFate model. Comparisons of model-simulations with data of published studies of exposed volunteers and/or workers were made after inhalation and dermal exposure. Two comparisons are shown:

**Comparison 1:** 1-Hydroxyppyrone in urine after inhalation and dermal exposure of a creosote facility operator

![Figure 1. Scheme of a PBTK-model](image1.png)

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![Figure 2. Scheme of dermal uptake pathways](image2.png)

**Figure 2. Scheme of dermal uptake pathways**

Urine samples of a creosote impregnator were sampled pre- and post shift over 6 days. The exposure of the creosote operator was: From Tuesday to Friday work with 8h inhalation of 20 mg/m³ pyrene and with 8h dermal exposure of a skin surface of 5000 cm² to pyrene at a rate of 5 ng/cm²/h.

**Comparison 2:** MTBE-metabolites in urine of volunteers after inhalation

![Figure 3. Output of a run of the PBTK-model](image3.png)

**Figure 3. Output of a run of the PBTK-model**

The exposure scenario of the volunteers was: 4h of inhalation of 150 mg/m³ MTBE. Urine of exposed volunteers was sampled every 5-6 h over 70 h. Two metabolites were measured in urine samples: 2-methyl-1,2-propanediol (2-MPD) and 2-hydroxyisobutyrate (2-HIBA).

![Figure 4. Metabolism of pyrene](image4.png)

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![Figure 5. The measured level of free and conjugated 1-OHP in urine of a creosote impregnating operator worker – black line](image5.png)

**Figure 5: The measured level of free and conjugated 1-OHP in urine of a creosote impregnating operator worker – black line** (from: Jongeneelen et al 1999). The model-predicted level is indicated as the red line.

![Figure 6. Metabolism of MTBE.](image6.png)

**Figure 6: Metabolism of MTBE.**

The model outcomes are aimed to have an accuracy within an order of magnitude. The PBTK-model IndusChemFate is regarded as a first tier tool or screening tool for data-poor compounds. The software is available as freeware. The program and user manual are downloadable from the CEFIC-LRI site: www.cefic-lri.org/toolbox/induschemfate

RECOMMENDATION

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ASK FOR LAPTOP DEMONSTRATION!

Real-time simulations of various chemicals with the program IndusChemFate will be demonstrated to give an impression of the simplicity and transparency of the program and the predictive simulations.