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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LRI Annual workshop 2011, 16-17 November 2011

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. Patent protected PBTK-software.

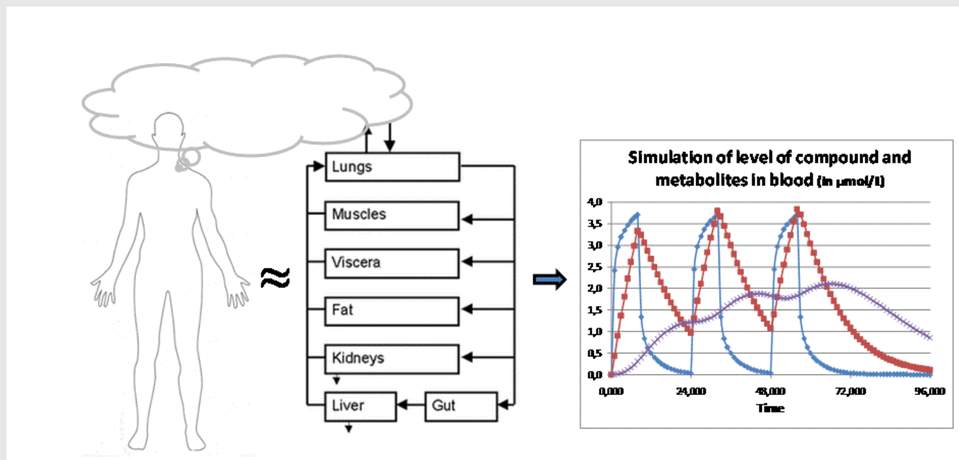

Figure 1. Scheme of a PBTK-model

In order to overcome these barriers we used algoritmes (QSPRs = Quantitative Structure-Property Relationships) for the cross-chemical prediction of blood:tissue parttioning.
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 a 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 QSPRs (= 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 a open source code.

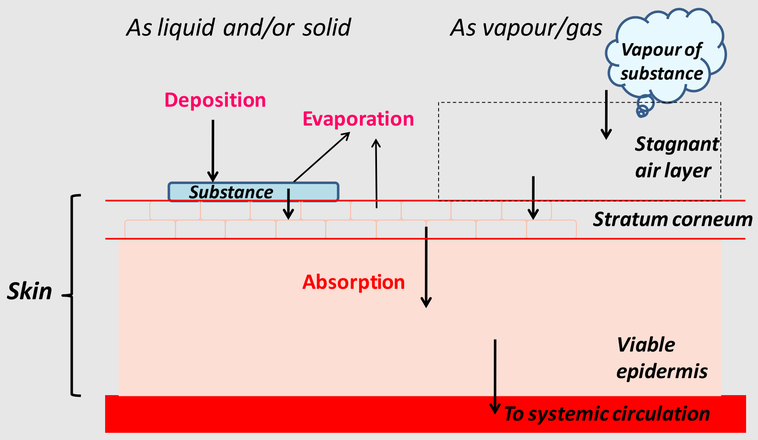

Figure 2. Scheme of dermal uptake pathways

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.

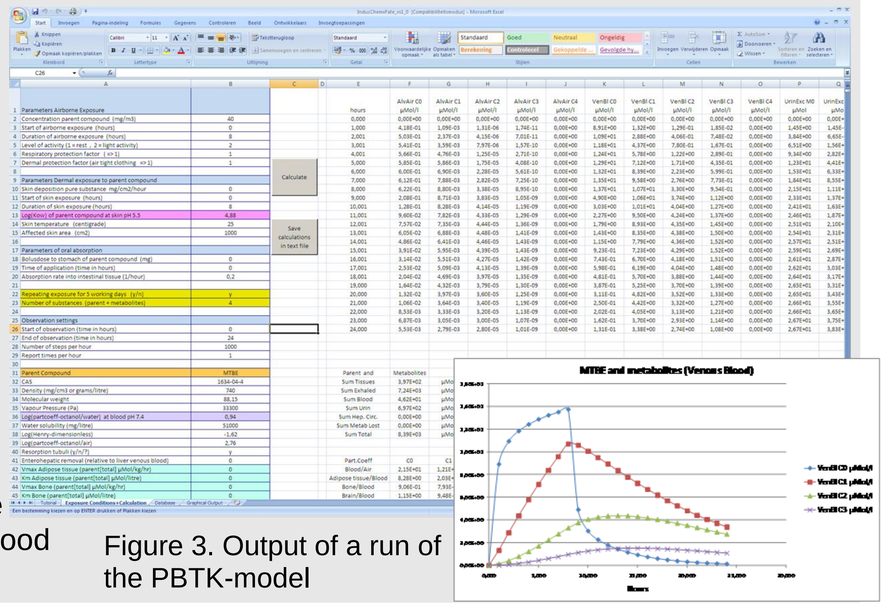

Figure 3. Output of a run of the PBTK-model

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-Hydroxypyrene in urine after inhalation and dermal exposure of a creosote facility operator

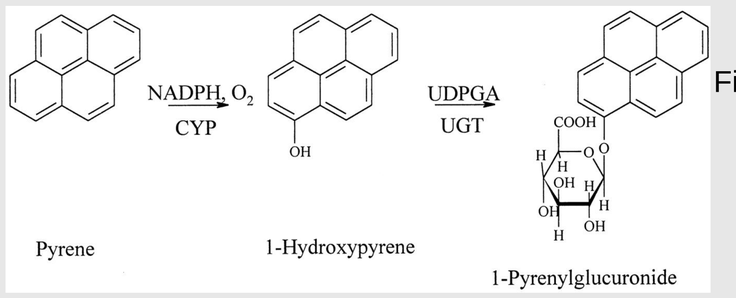

Fig. 4: Metabolism of pyrene.

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 µg/m^3 pyrene and with 8h dermal exposure of a skin surface of 5000 cm^2 to pyrene at a rate of 5 ng/cm^2/h.

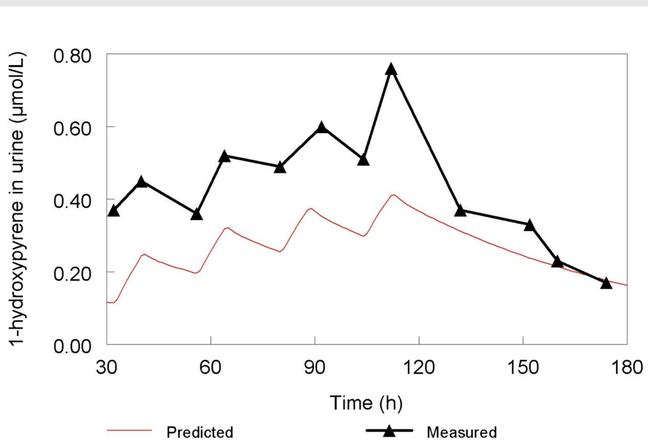

Fig.5: The measured level of free and conjugated 1-OHP in urine of a creosote impregnating operator worker = black line (from: Jongeneelen et al 1988).
The model-predicted level is indicated as the red line.

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

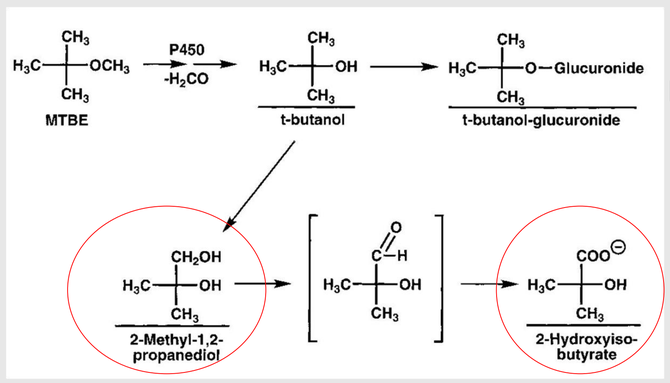

Fig 6: Metabolism of MTBE.

The exposure scenario of the volunteers was: 4h of inhalation of 150 mg/m^3 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).

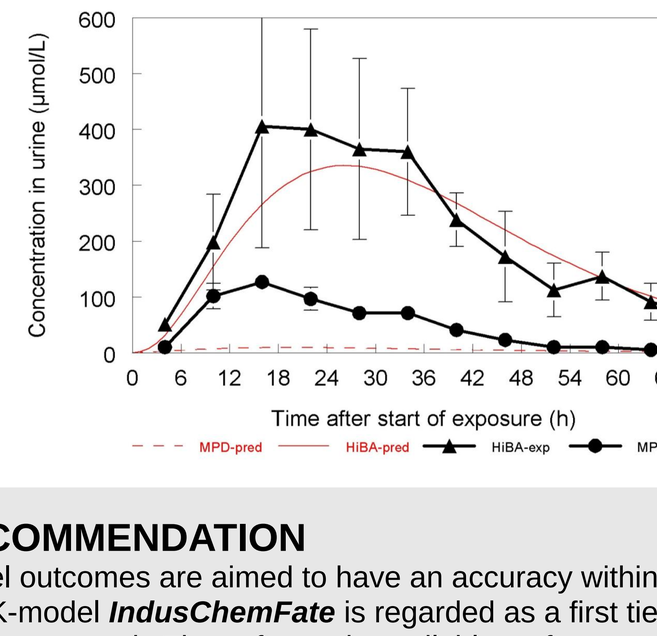

Fig. 7: The measured levels of the two metabolites 2-MPD and 2 -HiBA in urine of volunteers = black lines (from: Amberg et al, 1999).
The model-predicted levels of the metabolites of MTBE in urine are the red lines.

RECOMMENDATION

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/lri-toolbox/induschemfate

ACKNOWLEDGEMENT

The work has been funded by CEFIC-LRI.

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.