Simulation of blood and urine levels with a cross-chemical predictive Physiologically Based ToxicoKinetic (PBTK) model

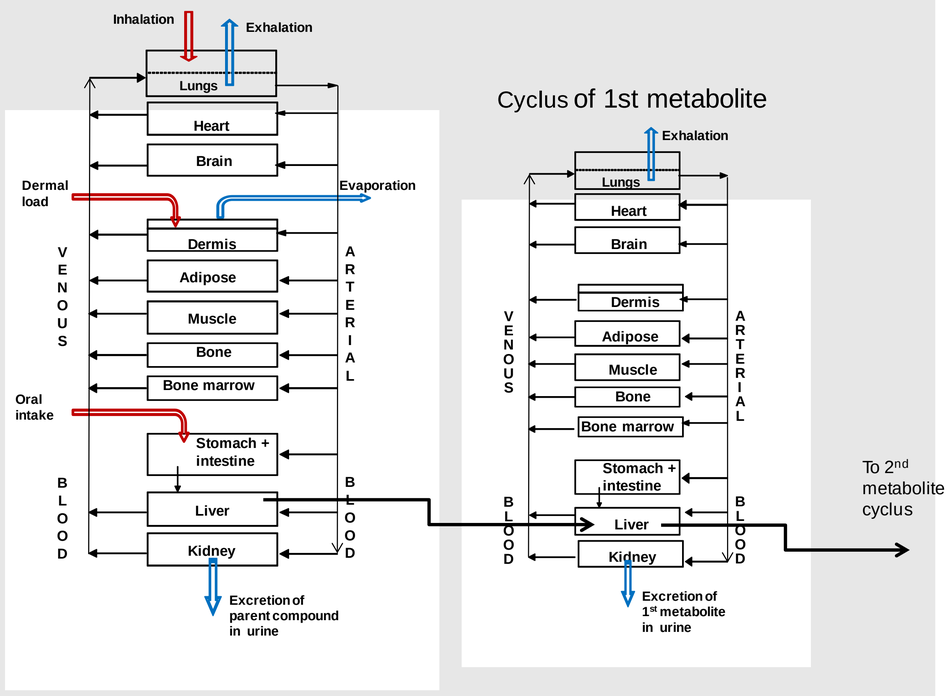
Frans J. Jongeneelen [1] and **Wil F. ten Berge** [2]
[1] IndusTox Consult, Netherlands (E-mail: frans.jongeneelen@industox.nl)
[2] Santoxar, Netherlands (E-mail: wtberge@planet.nl)
Web: www.industox.nl

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.

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



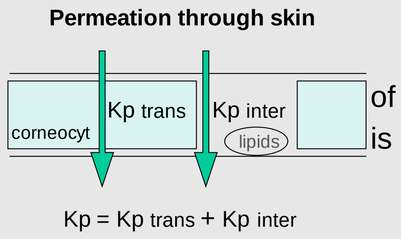
In addition, we developed algorithms for the cross-chemical prediction of blood tissue:air partitioning. These routines have been build in a generic model, named ***IndusChemFate.*** It is a Phsyologically Based ToxicoKinetic model (= PBTK-model) for a 70 kg man that considers three uptake routes (inhalation, dermal and/or oral, see figure 1). The model is written in the general available software Microsoft Excel.

AIM

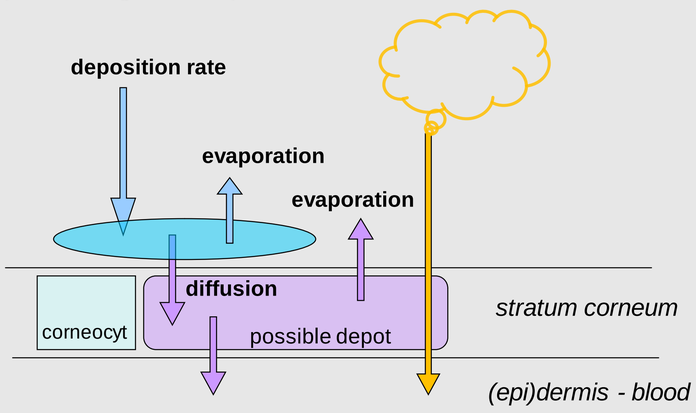
Development of a generic model that can predict the concentration of multiple chemicals and its metabolites in blood and urine of various exposure scenarios.

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 model ***IndusChemFate*** are written in Visual Basic and the model runs as an application in MS Excel.
- The program is provided as freeware with a open source code.



Skin absorption processes

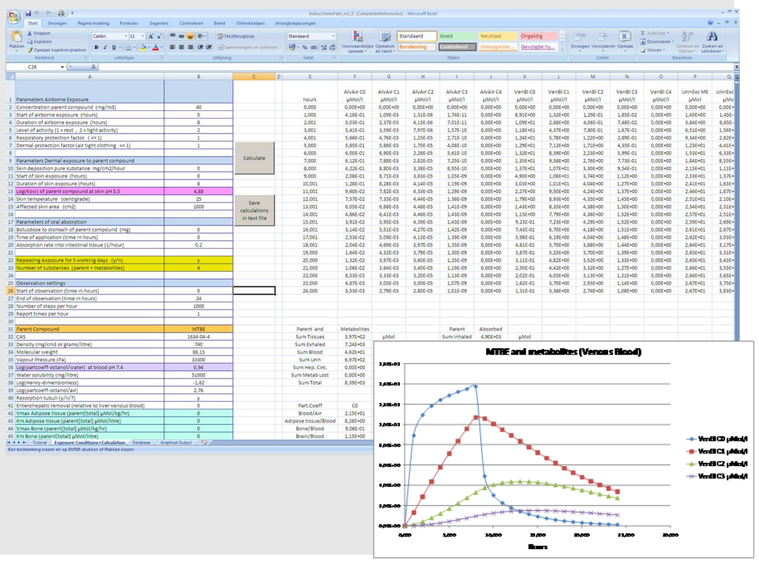
RUNNING THE PROGRAM

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.

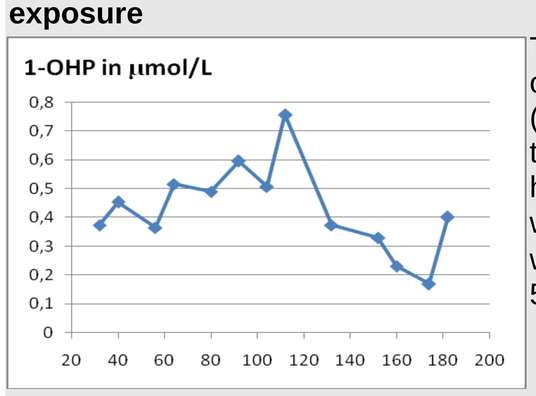


HBM conference, 27-28 October

COMPARING MEASURED WITH MODEL-SIMULATED

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: Urinary 1-hydroxypyrene excretion after inhalation and dermal exposure



The sum of free and conjugated 1-OHP in urine of a creosote impregnating operator worker (Jongeneelen et al, 1988) was compared with the simulated data. T
he exposure scenario was: 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.

Figure 4. Measured level in urine of 1-OH-pyrene as sum of free 1-OHP and 1-OHP-glucuronide.

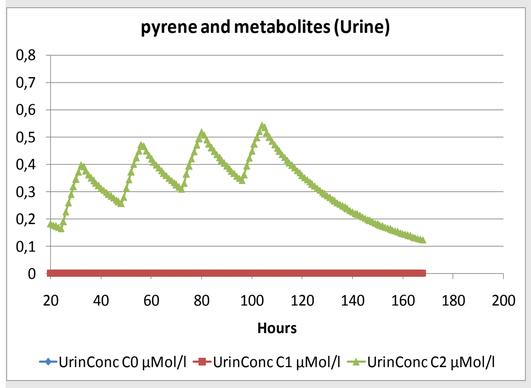


Figure 5a. Simulated concentration in urine of pyrene (C0), 1-OHP (C1) and 1-OHP-glucuronide (C2)

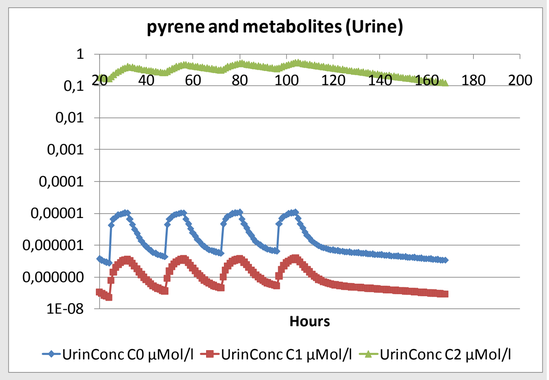
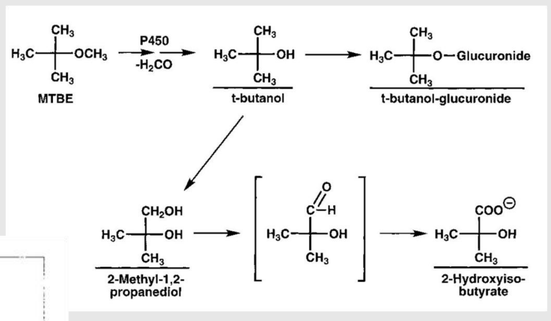


Figure 5b. Simulated concentration in urine of Pyrene (C0), 1-OHP (C1) and 1-OH-P-glucuronide (C2). Vertical scale = log 10 scale

Comparison 2: Urinary MTBE-metabolites after inhalation

Metabolism of MTBE:

C0 =	C1=	C2 =	C3 =
MTBE ⇨	TBA ⇨	2-MPD ⇨	2-HIB



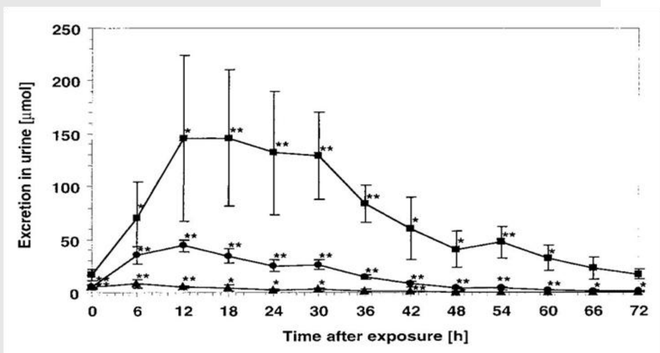


Figure 6:
Measured urinary concentrations in volunteers after exposed for 4 h to 150 mg/m^3 MTBE (Amberg et al, 1999)

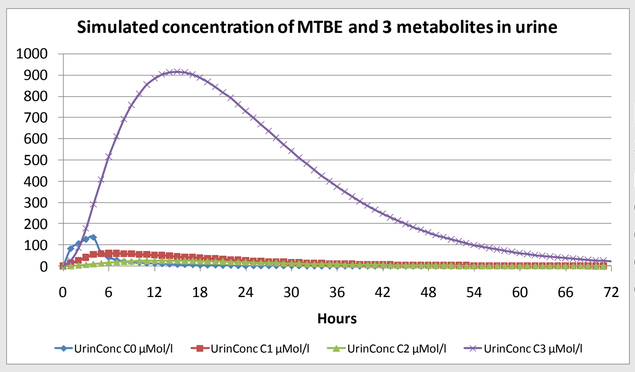


Figure 7:
Simulated concentration of MTBE and metabolites in urine:
C0=MTBE
C1=TBA
C2=2MPD
C3=2-HIB

RECOMMENDATION

Model outcomes are aimed to have an accuracy within an order of magnitude. The 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 is available on 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 simplic-