

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



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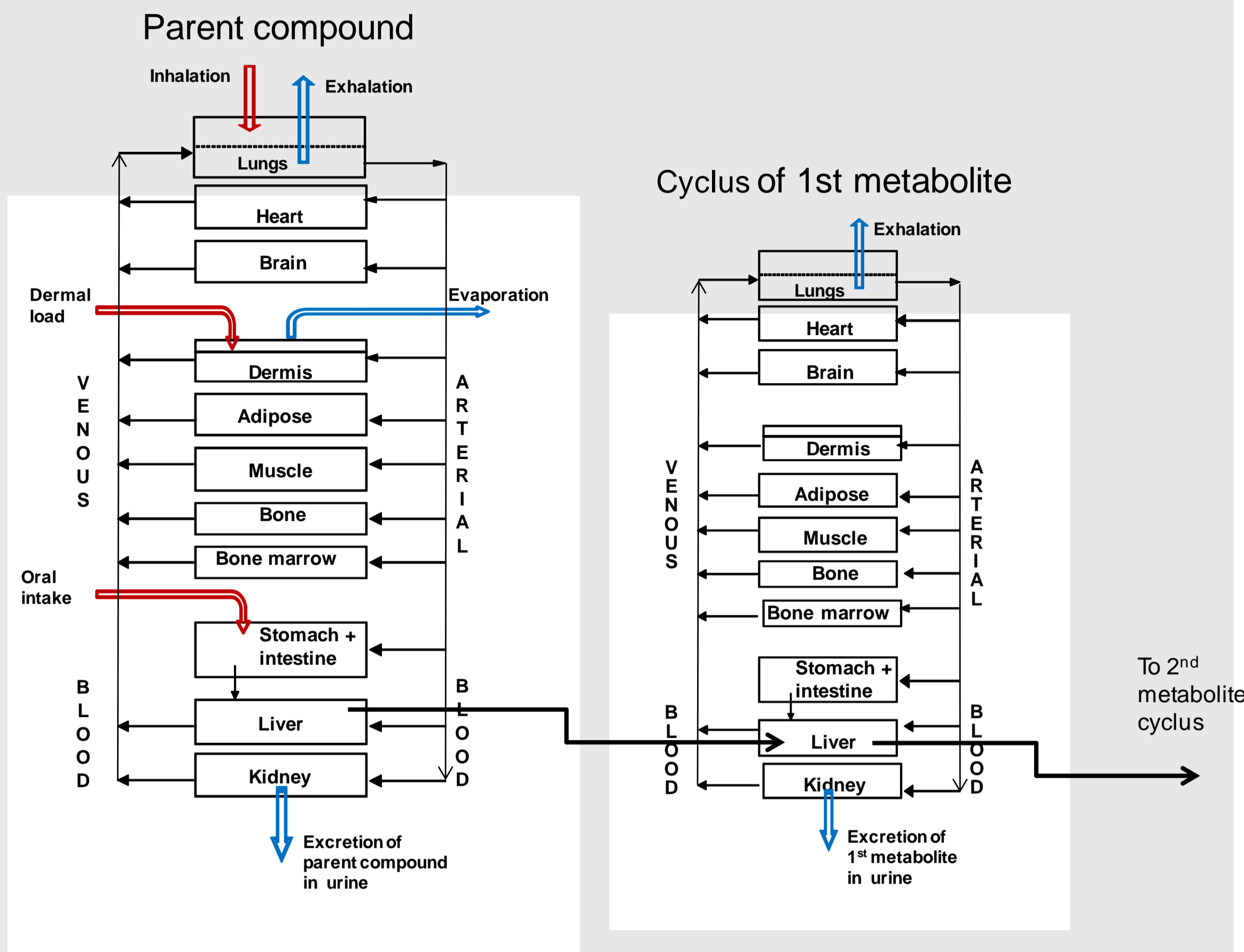
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## INTRODUCTION

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



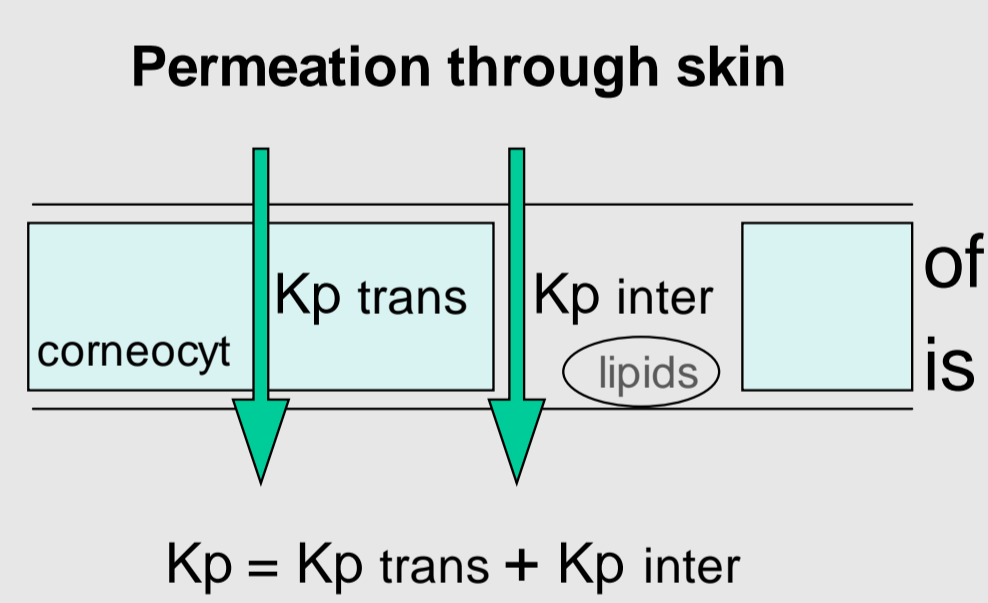
In addition, we developed algorithms for the cross-chemical prediction of blood:tissue:air partitioning. These routines have been built in a generic model, named **IndusChemFate**. It is a Physiologically Based Toxicokinetic model (= PBTK-model) for a 70 kg man that considers three uptake routes (inhalation, dermal and/or oral, see figure 1). The model is written 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 deposition. Moreover, evaporation during skin contact 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 free-ware with a open source code.



## RUNNING THE PROGRAM

### STEP 1: Input of data

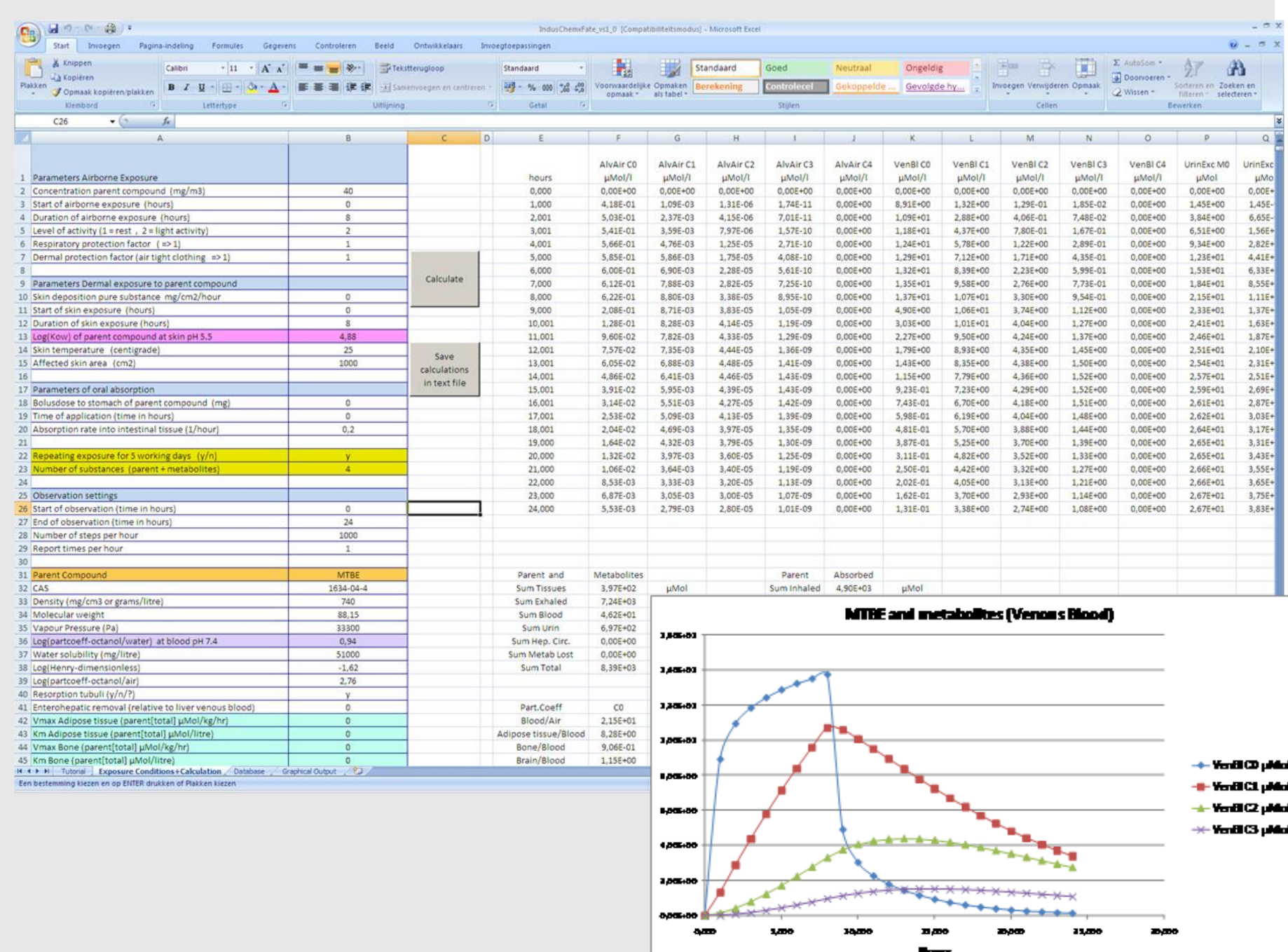
- Phys-chem properties
- In vitro metabolism data

### STEP 2: Enter exposure scenario

### STEP 3: Run program

### STEP 4: Review results

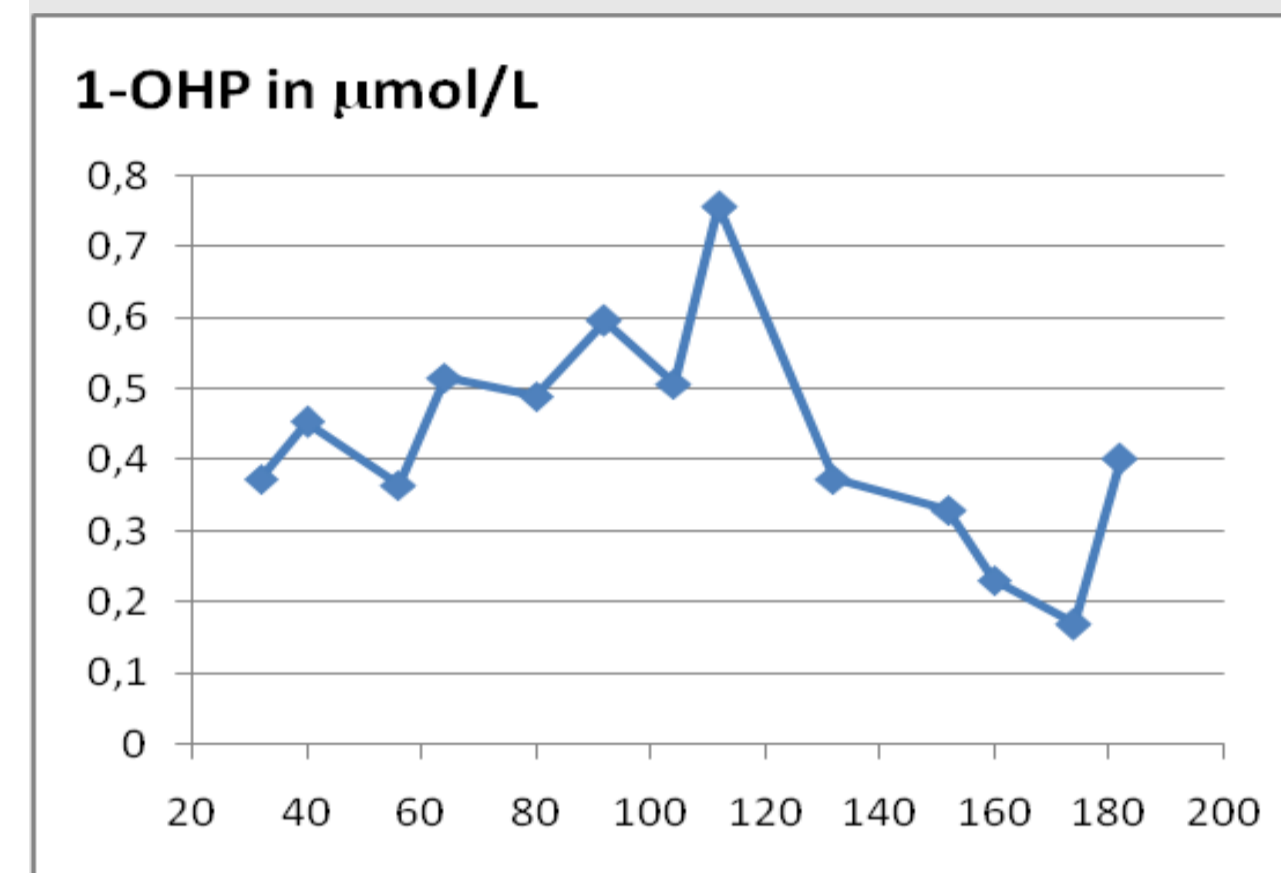
- + Listing of amount and concentration of compound and metabolites over time;
- + Mass balance;
- + Partitioning coefficients;
- + Graphs of time course of concentrations in blood and urine.



## COMPARING MEASURED WITH MODEL-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. The exposure scenario was: Tuesday to Friday work with 8h inhalation of 20 µg/m<sup>3</sup> pyrene and with 8h dermal exposure of a skin surface of 5000 cm<sup>2</sup> to pyrene at a rate of 5 ng/cm<sup>2</sup>/h.

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

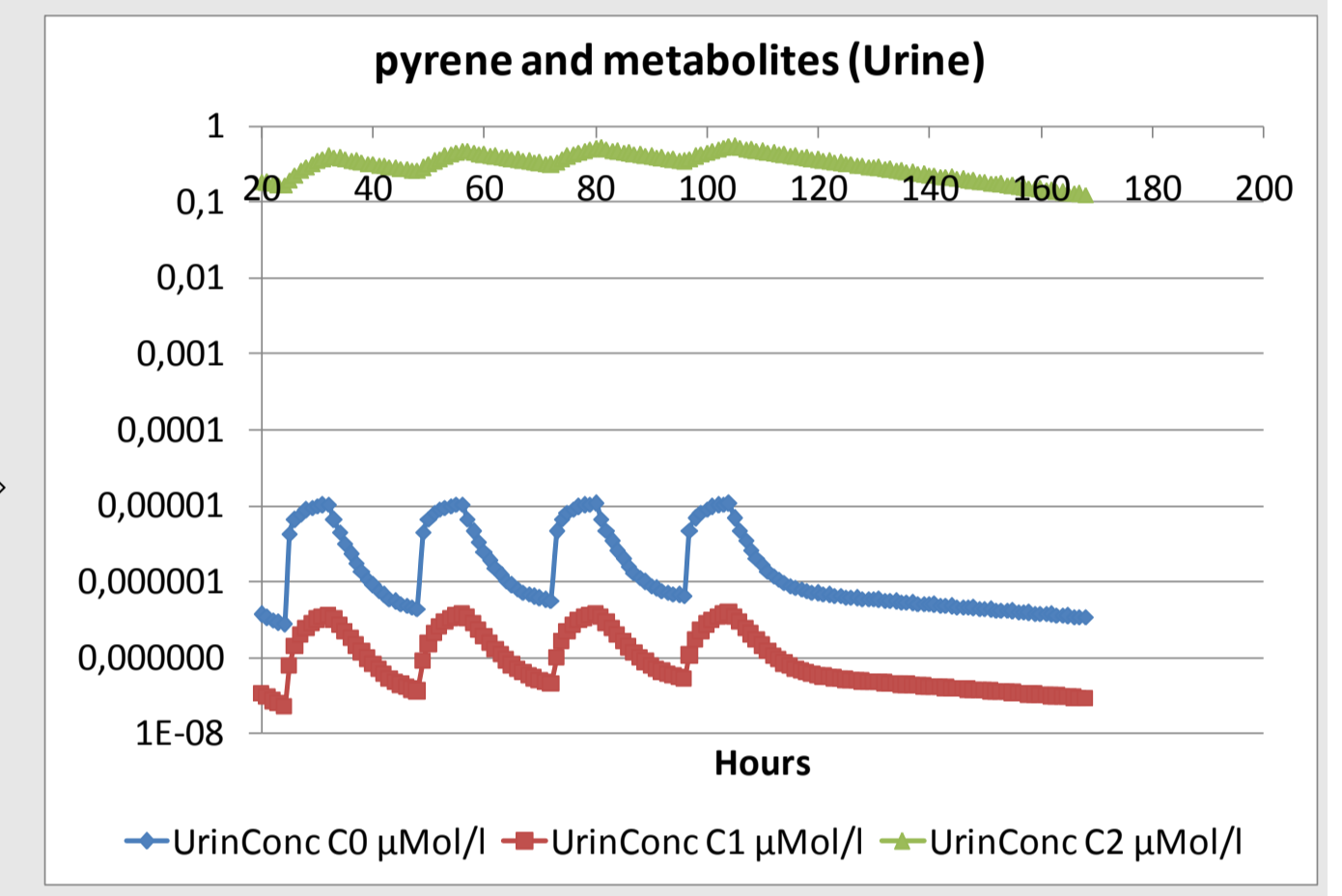
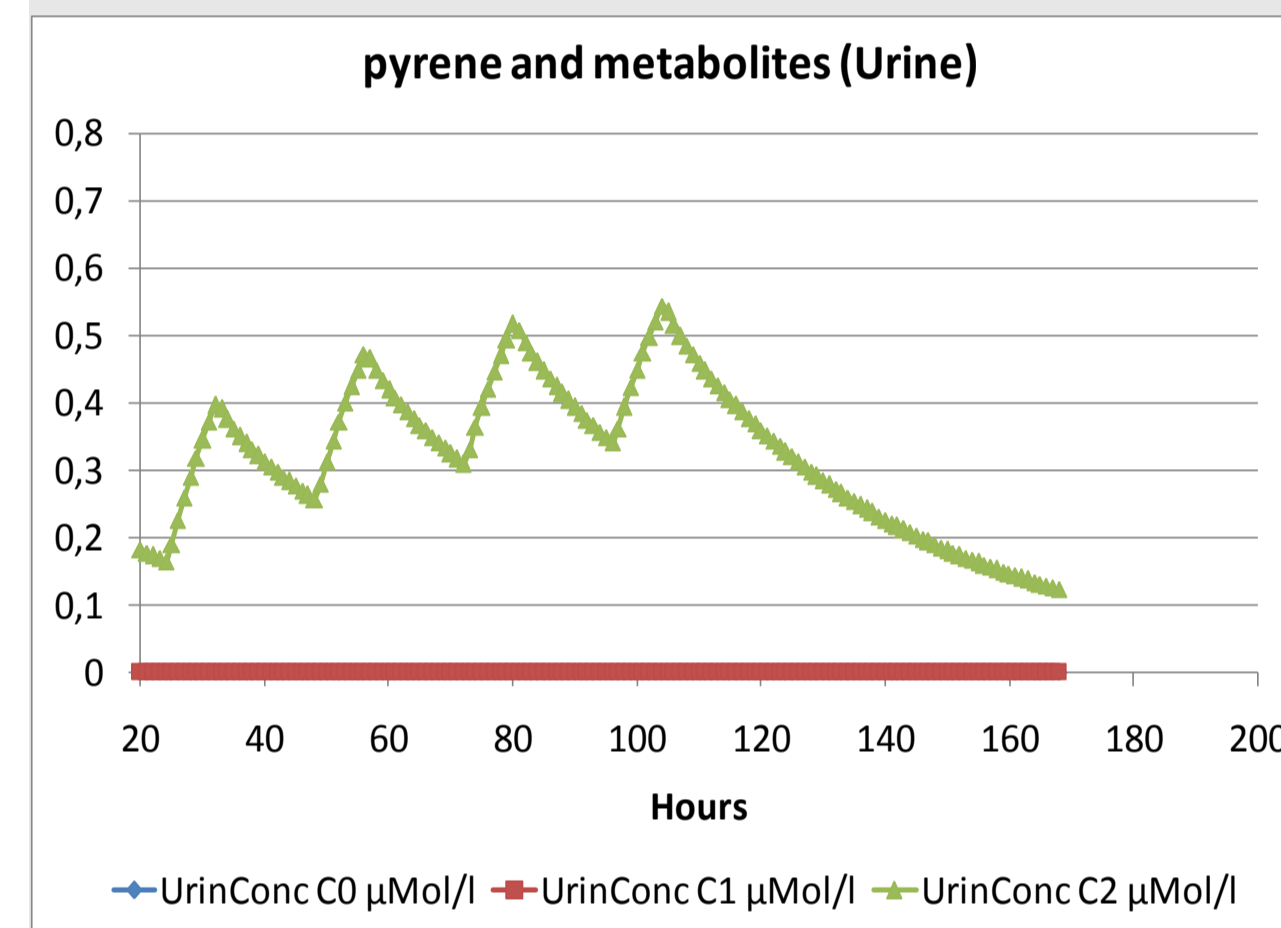


Figure 5a. Simulated concentration in urine of pyrene (C0), 1-OHP (C1) and 1-OHP-glucuronide (C2)

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

### Comparison 2: Urinary MTBE-metabolites after inhalation

Metabolism of MTBE:

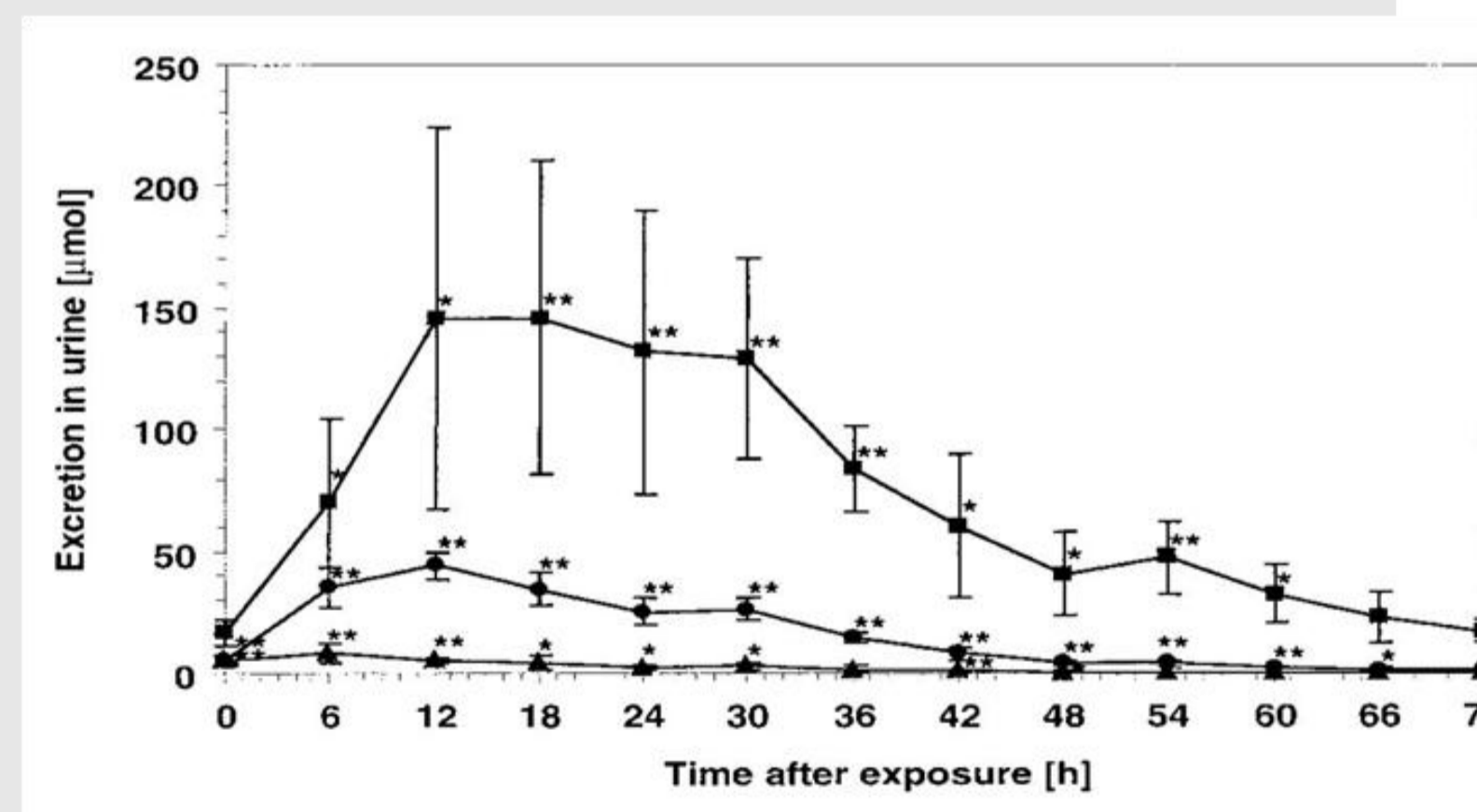
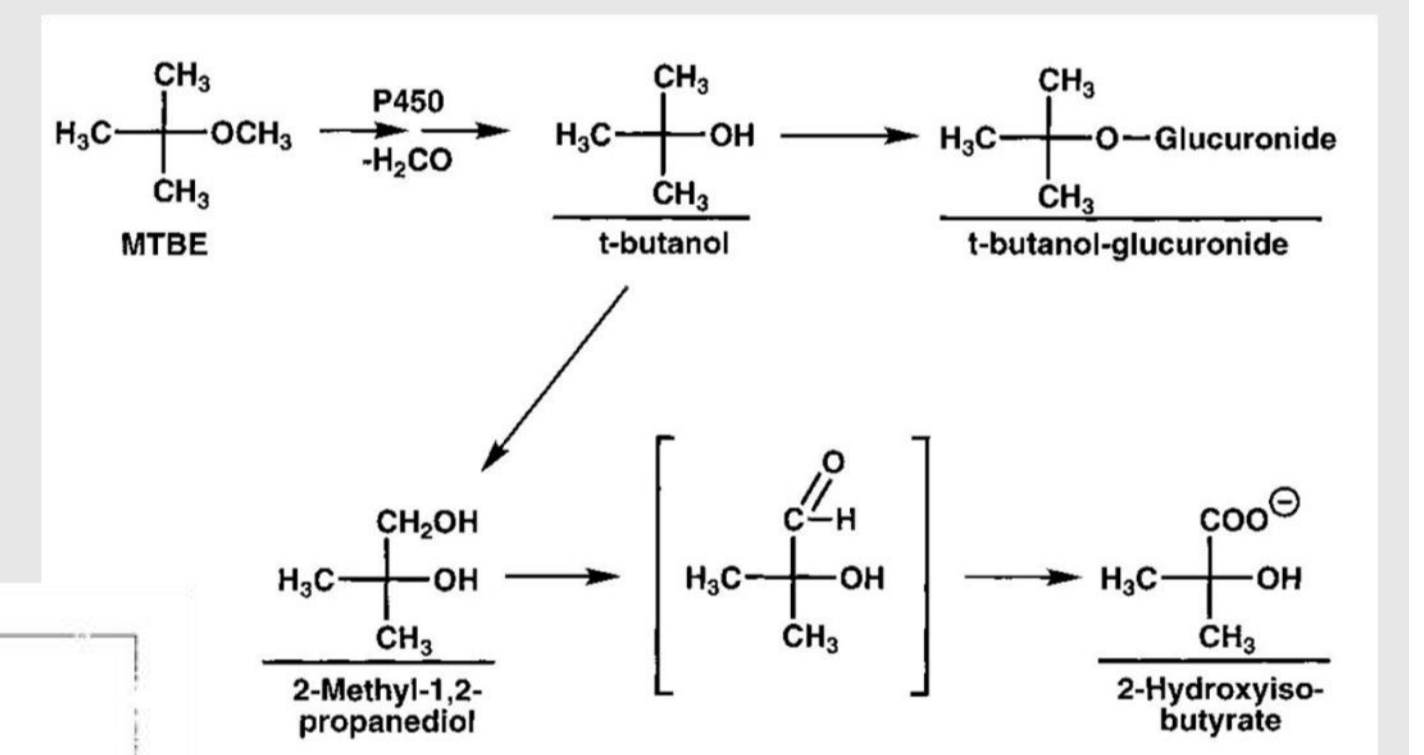
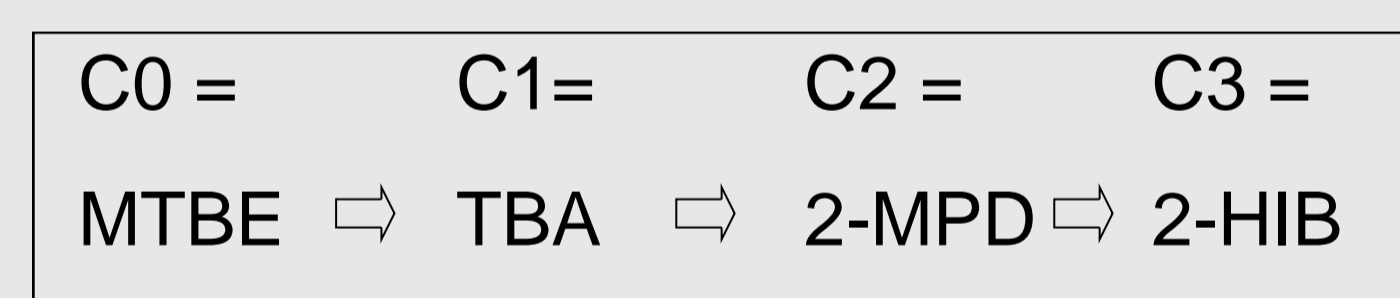


Figure 6: Measured urinary concentrations in volunteers after exposed for 4 h to 150 mg/m<sup>3</sup> MTBE (Amberg et al, 1999)

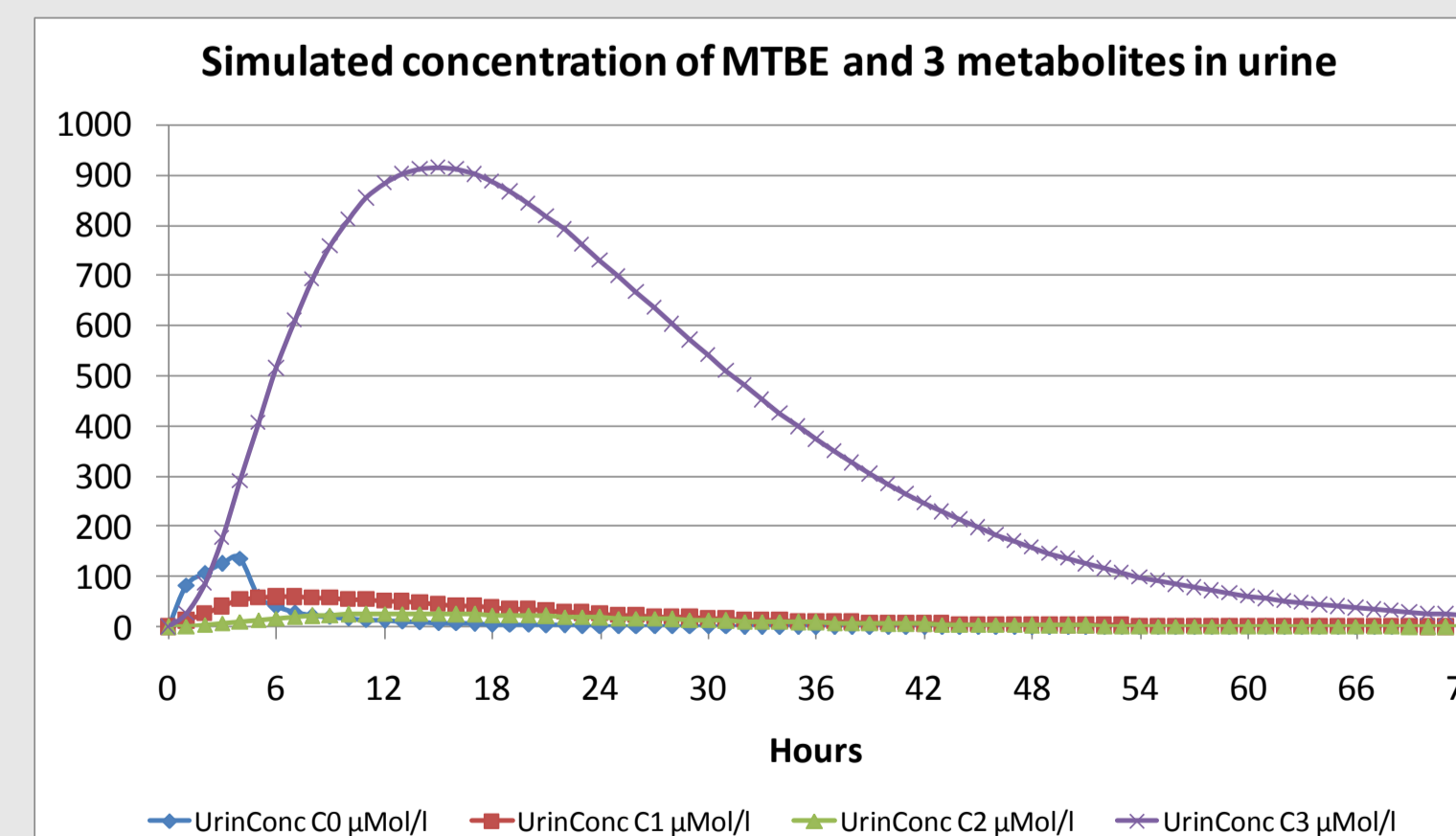


Figure 7: Simulated concentration of MTBE and metabolites in urine: C0=MTBE, C1=TBA, C2=2MPD, C3=2-HIB

## 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](http://www.cefic-lri.org/lri-toolbox/induschemfate)

## ACKNOWLEDGEMENT

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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 simplic-

