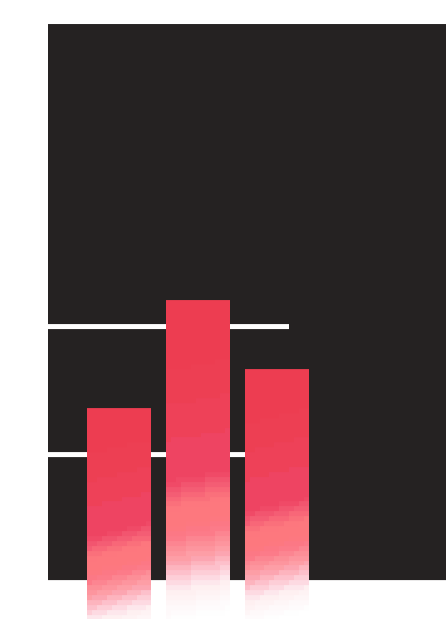


# Simulation of blood and urine levels with a newly developed generic Physiologically Based Toxicokinetic (PBTK) model



**IndusTox**

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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 published algorithms (QSPRs = Quantitative Structure-Property Relationships) for the prediction of blood:tissue partitioning. In addition, we developed algorithms for tissue:air partitioning. With that we developed the generic model *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 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 syntax of the model *IndusChemFate* is written in Visual Basic and the model runs in the program MS Excel.
- The program is provided as freeware with a open source code.

## RUNNING THE PROGRAM

### STEP 1: Input of data

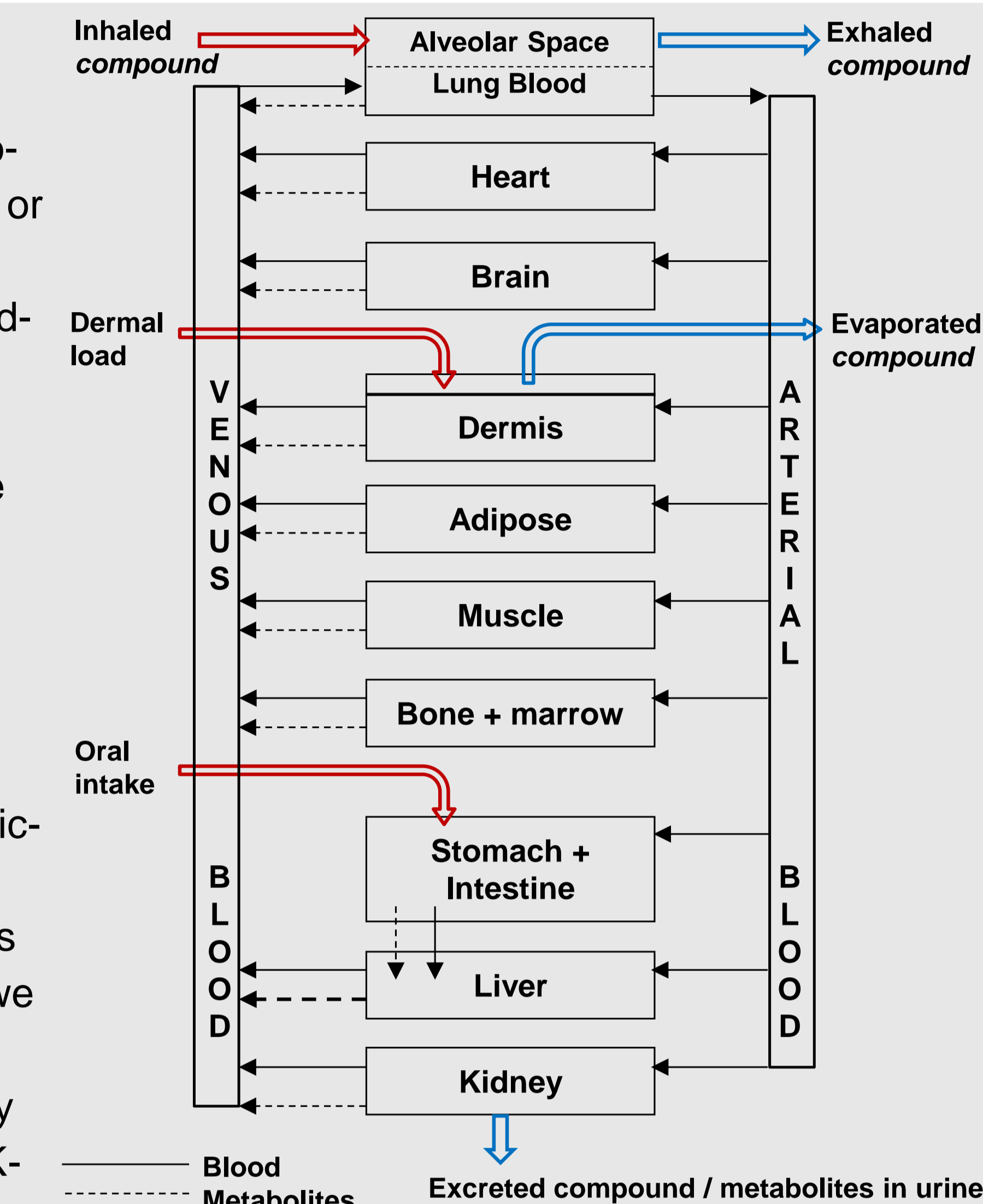
- Phys-chem properties
- In vitro metabolism data

### STEP 2: Enter exposure scenario

### STEP 3: Run program

### STEP 4: Take output data

- 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.

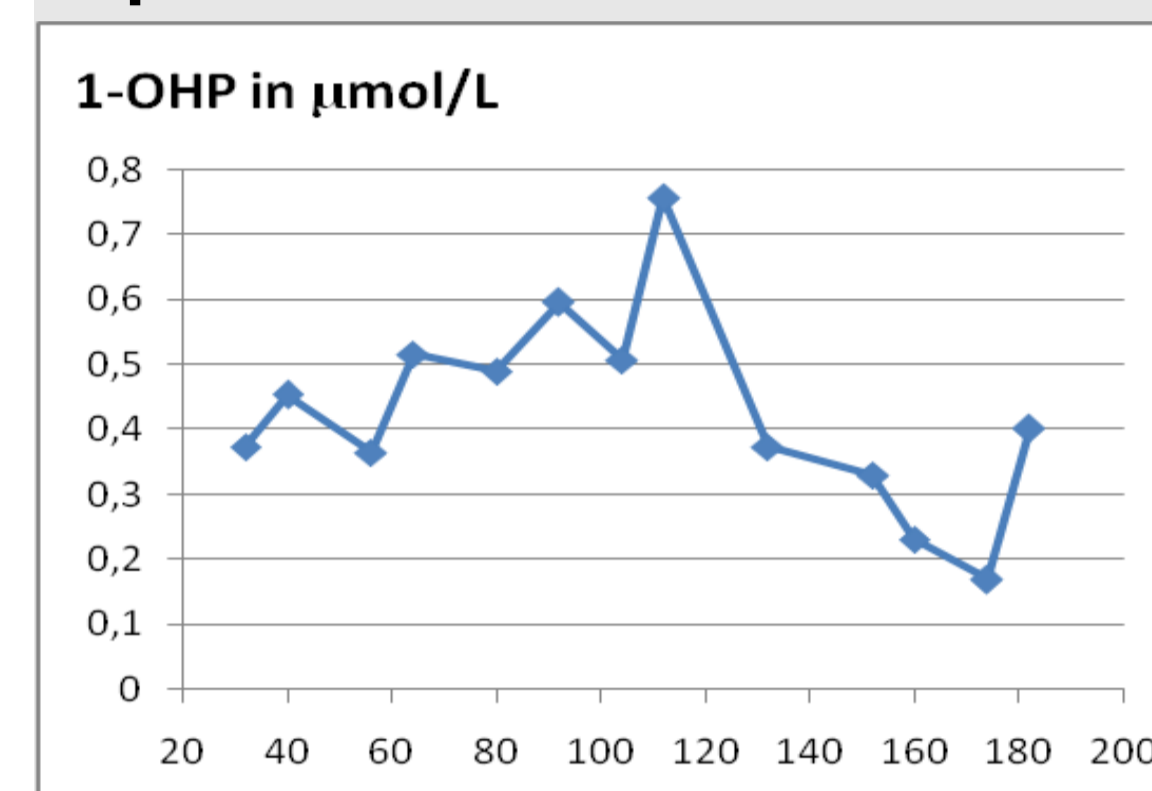


The model is written in the general available software Microsoft Excel.

## 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 major metabolism pathway of pyrene is to 1-hydroxypyrene (1-OHP) and then to 1-OHP-glucuronide. Published data of the level of 1-OHP in urine of a creosote impregnating operator worker (Jongeneelen et al, 1988) were compared with the model simulated data.

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

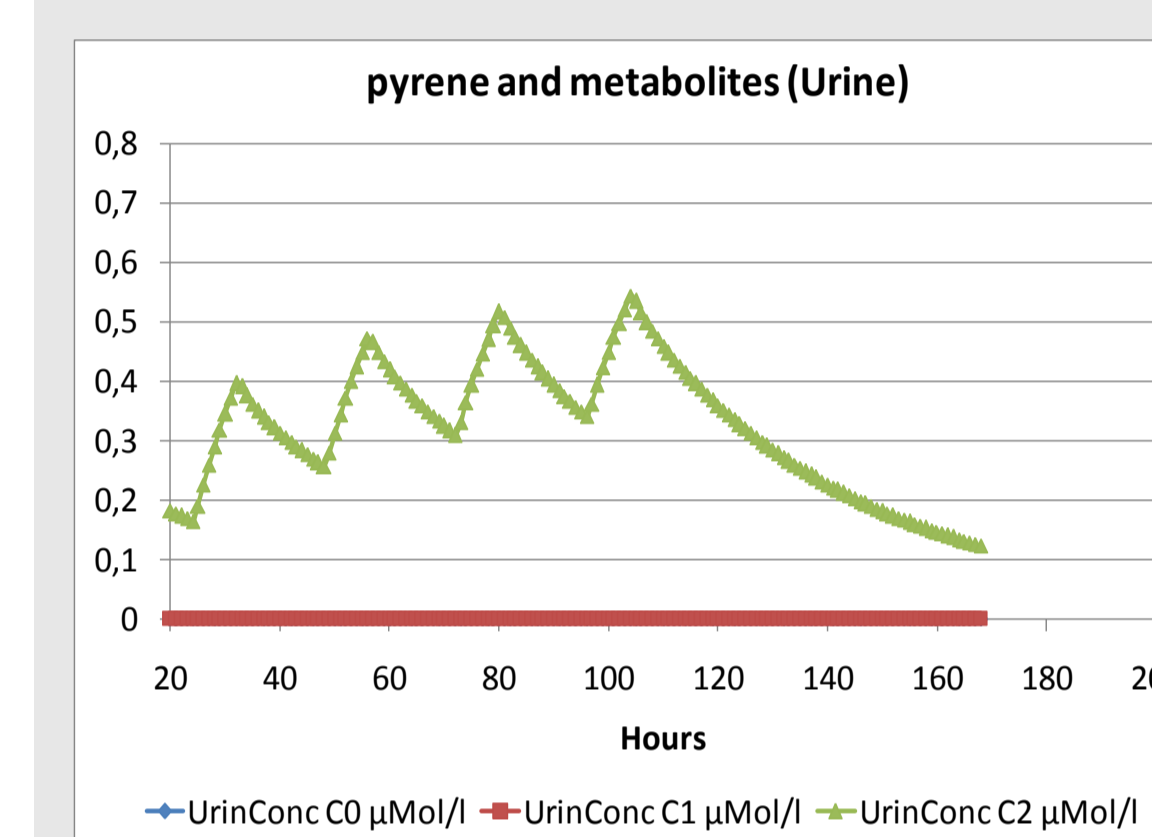


Figure 5a. Simulated concentration in urine of pyrene, 1-OHP and 1-OHP-glucuronide

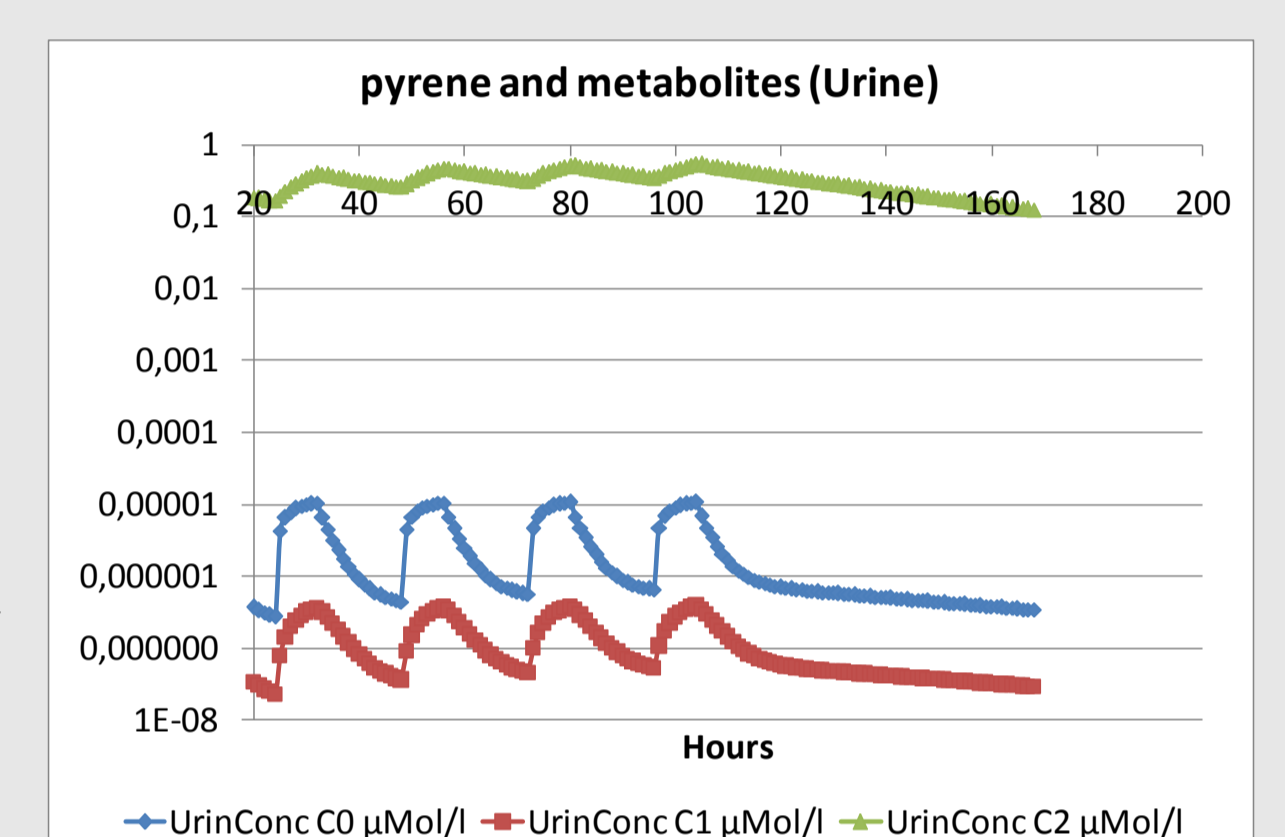


Figure 5b. Simulated concentration in urine of pyrene, 1-OHP and 1-OHP-glucuronide (vertical scale = log 10 scale)

The adopted exposure scenario was: 5 days of exposure 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.

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

Metabolism of MTBE:

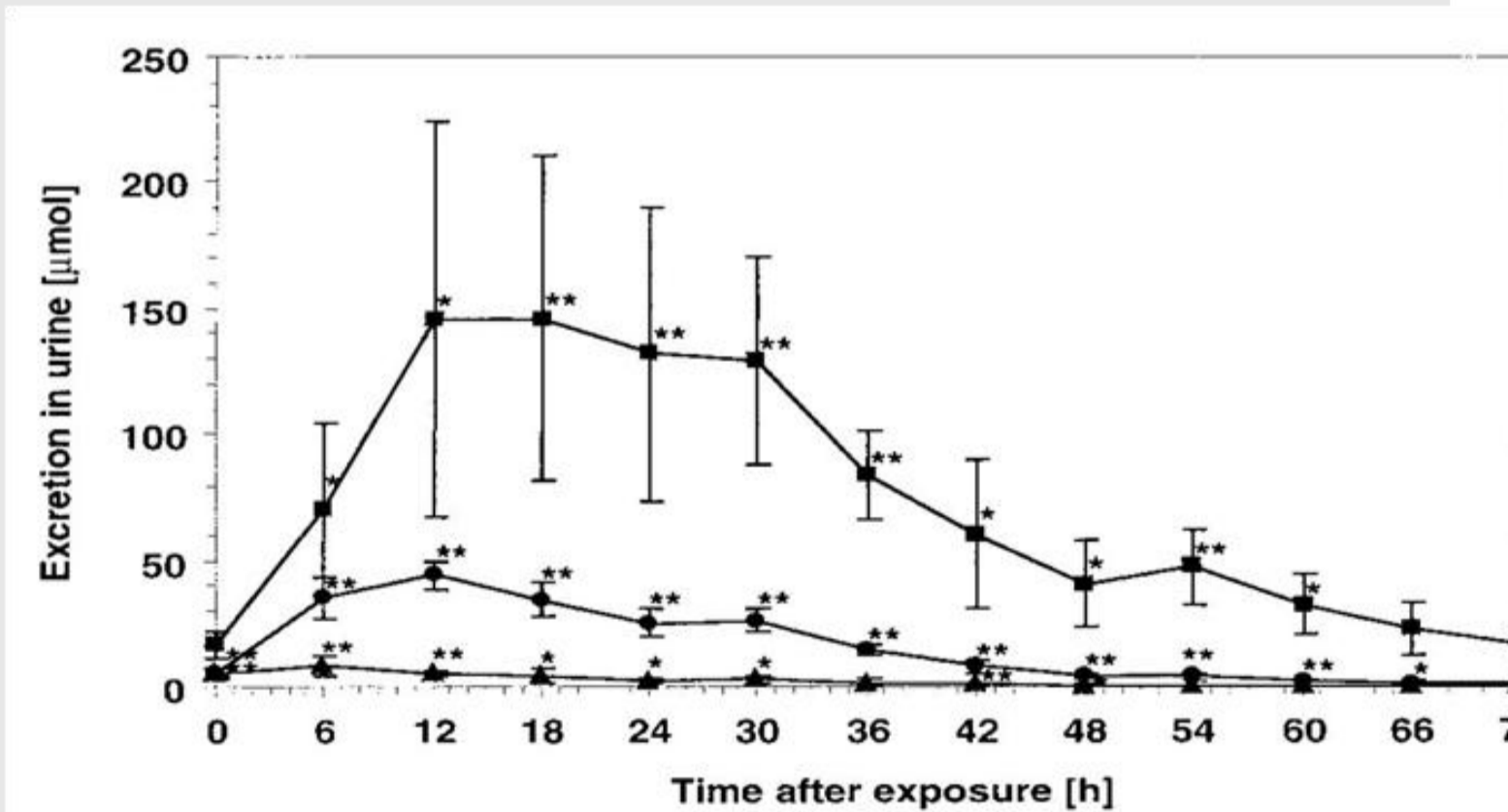
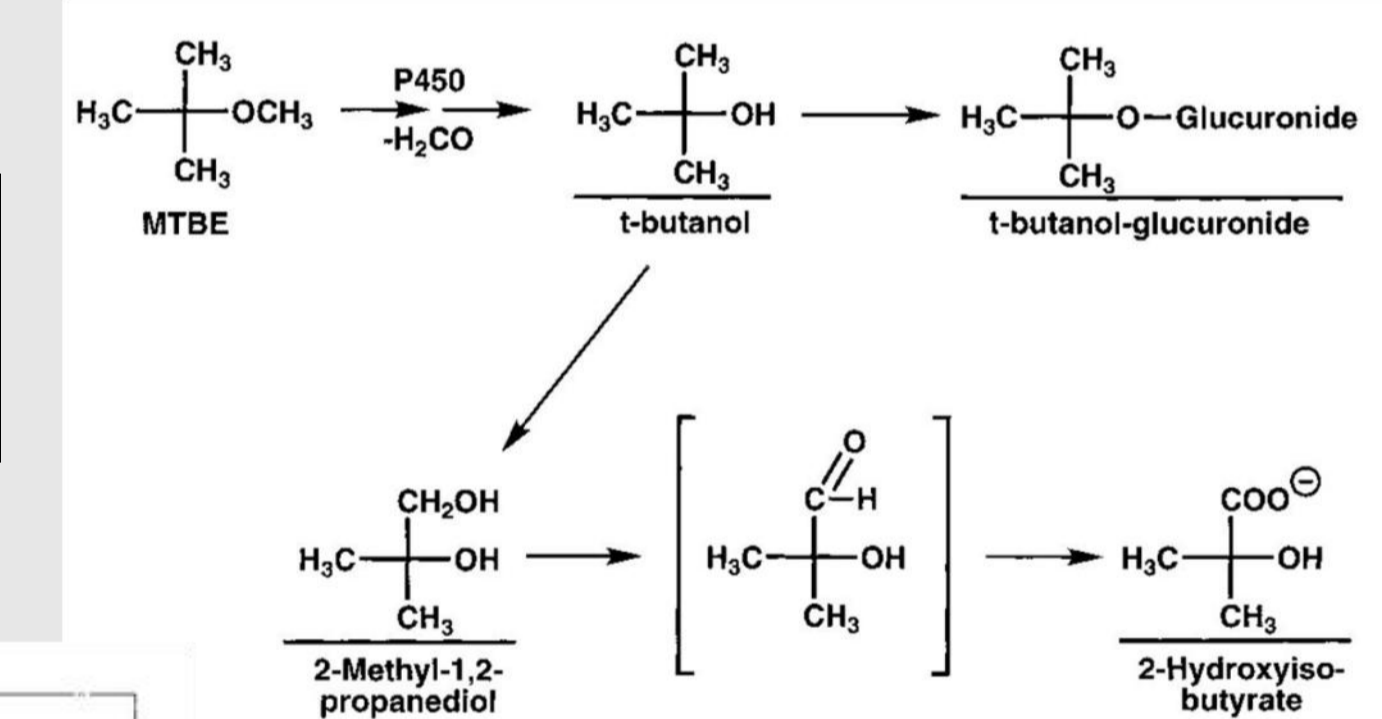
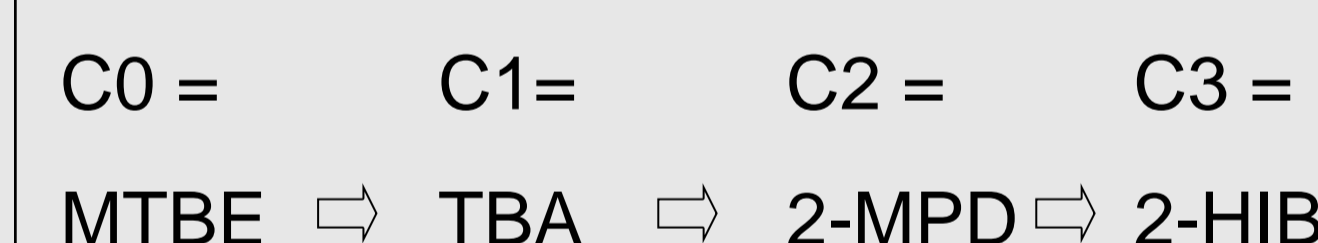


Figure 6: Measured urinary concentrations in volunteers after exposed for 4 h to 150 mg/m<sup>3</sup> MTBE (ref)

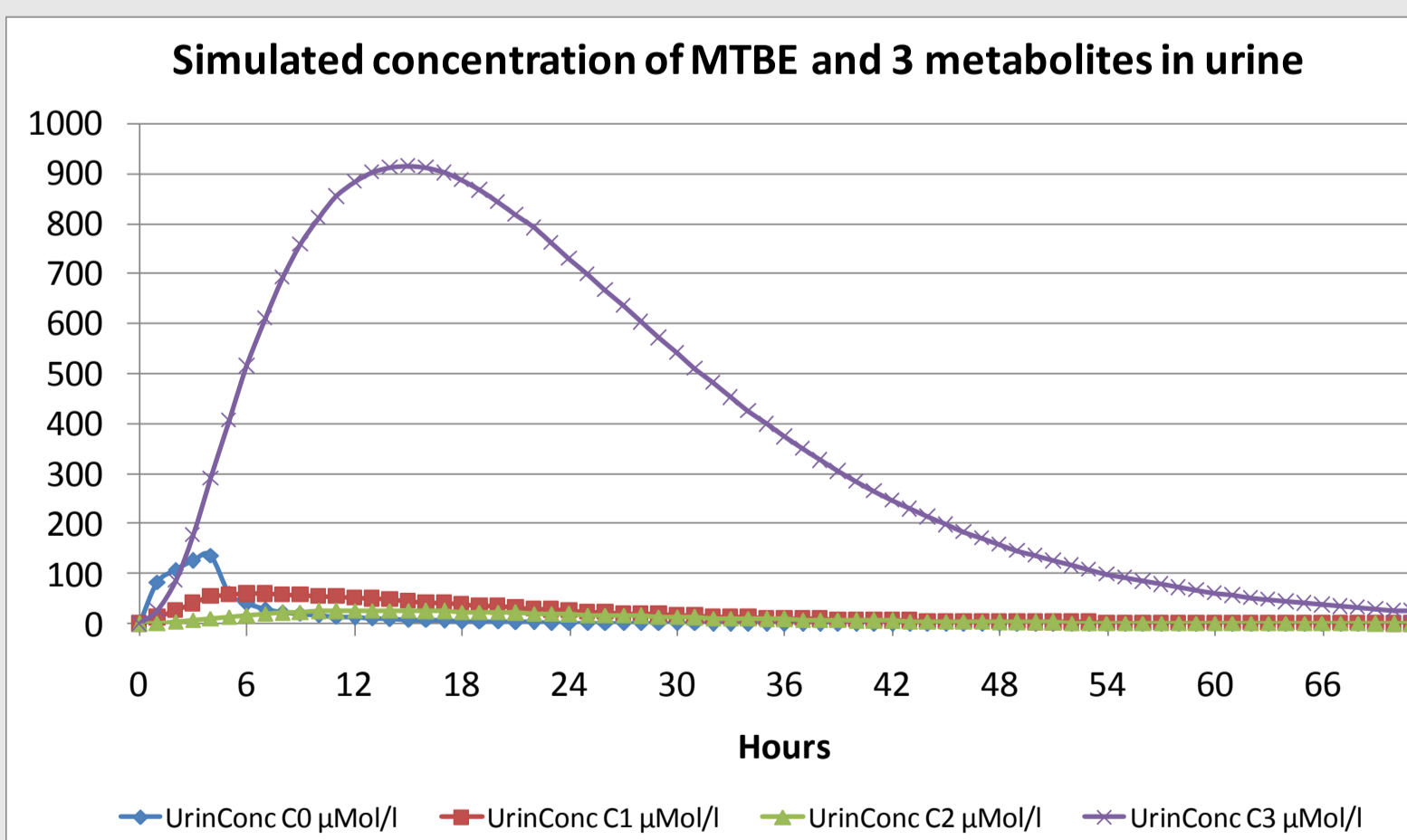


Figure 7: Simulated concentration of MTBE and metabolites in urine: C0=MTBE, C1=TBA, C2=2MPD, C3=2-HIB

## 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 simplicity and transparency of the program and the predictive simulations.

