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Simulation of blood and urine levels of chemicals and their metabolites after inhalation or dermal exposure with a generic PBTK-model running in Excel

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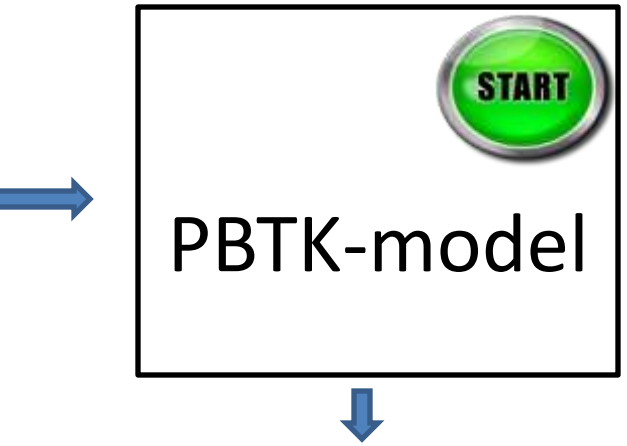
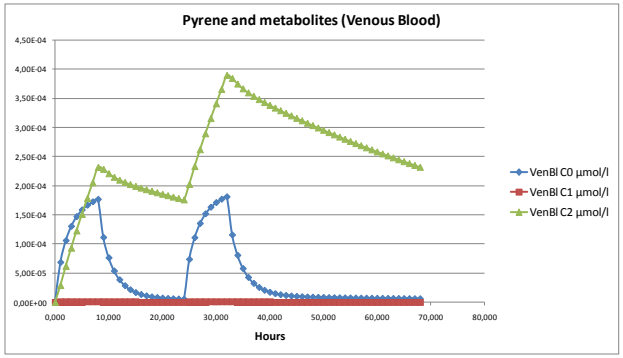
Overview of the PBTK-model IndusChemFate

Exposure scenario
- Three routes of uptake:
  - Inhalation - concentration
  - Dermal – dose rate
  - Oral - dose
- Duration of exposure
- Personal Protective Equipment
- Physical activity level (rest/ light)

Compound data
- Physical-chemical properties:
  - Density
  - Molecular weight
  - Vapour pressure
  - Log(K_{ow}) at pH 5.5 and 7.4
  - Water Solubility
- Biochemical parameters :
  - Metabolism (k_M and V_{max})
  - Renal tubulair resorption
  - Enterohepatic circulation ratio





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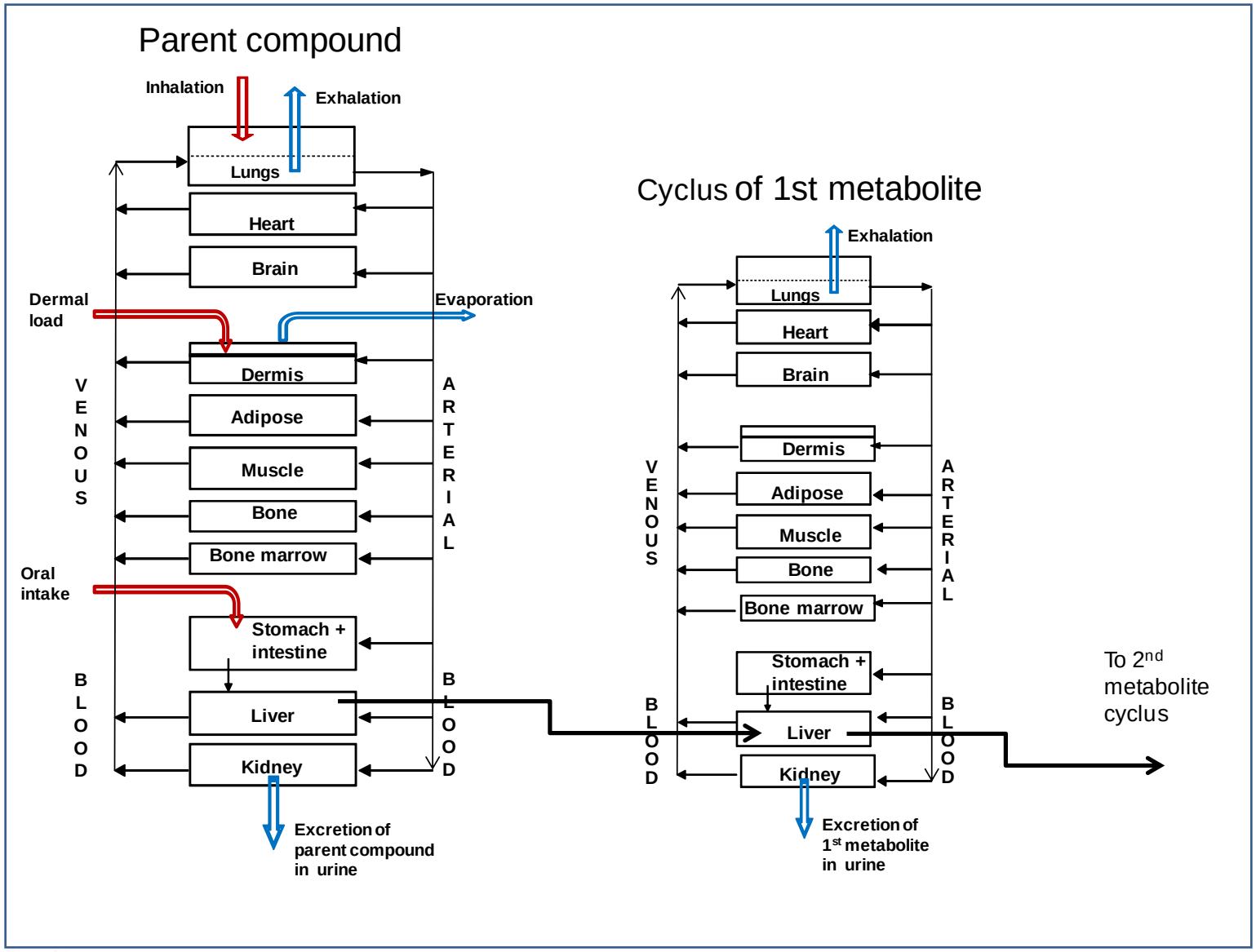
What is a PBTK-model?

- PBTK-model = Physiologically Based ToxicoKinetic model
- A PBTK-model is a mathematical description for predicting the absorption, distribution, metabolism and excretion (ADME) of a chemical in the body of experimental animals or humans
- Compartments corresponds to predefined organs or tissues, with interconnections corresponding to blood
- A system of differential equations is used to estimate the concentration or amount of substance in each compartment

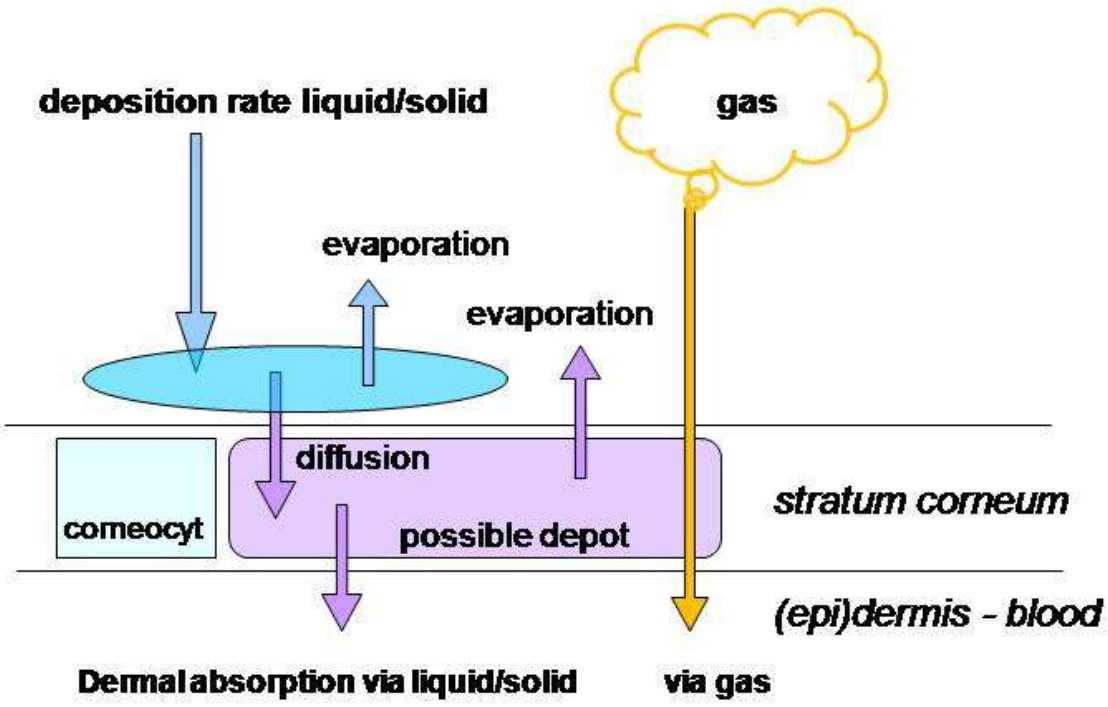
Scheme of the physiology of the PBTK-model



Routing of chemicals in the PBTK-model

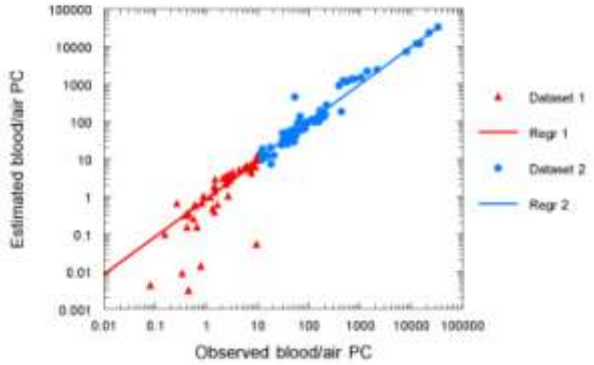
- Absorption
  - Inhalation
  - Oral uptake
  - Dermal uptake
- Distribution over the body
  - QSPR algorithm for blood:air partition coefficient
  - QSPR algorithm for tissue:blood partition coefficient
- Metabolism
  - Saturable metabolism according to Michaelis-Menten kinetics
  - Default in liver, other tissues might also have capacity to metabolise
- Excretion
  - Urine
  - Exhaled air

Dermal absorption module of the model



Distribution over compartments in the body

- Blood:air partition coefficient
  - Algorithm for estimation of blood:air partitioning based on Henry coefficient and K_{oa}



- Blood:tissue partition coefficient
  - Algorithm for estimation of blood:tissue partitioning taken from De Jong et al (1997), based on lipid content and K_{ow}

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The PBTK-model is build as application in MS-Excel

- The differential equations of the PBTK-model are written in visual basic
- The Excel-file is named IndusChemFate and has 4 sheets:
    1. Tutorial with instructions in short
    2. Worksheet
        - For data entry (exposure scenario, properties of chemical under study)
        - For numerical output
    3. Database of phys-chemical and biochemical properties of various chemicals
    4. Graphical output sheet

Example 1:
Simulation of experimental observation

- 1-hydroxypyrene was measured in urine of an operator of a creosote impregnating plant during 7-days
- Creosote oil = a timber protective agent that contains PAH
- Pyrene is metabolised to 1-hydroxypyrene

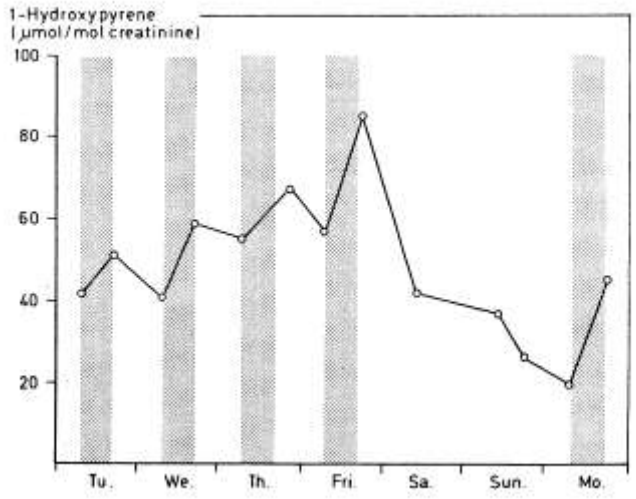
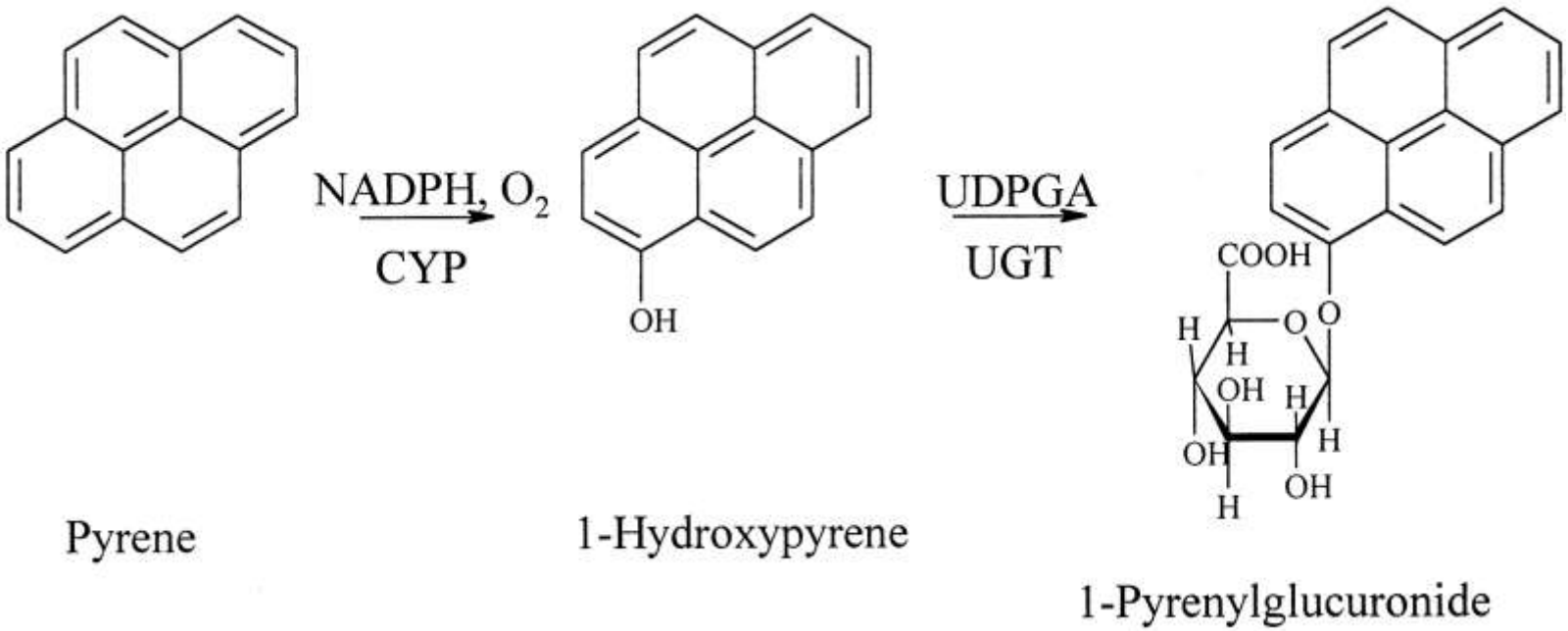


Figure 3-1A. Excretion of 1OHP in urine of a creosote impregnating worker (Jongeneelen et al, 1988)

How to simulate this excretion pattern?

Example 1

Metabolism of pyrene



Pyrene

1-Hydroxypyrene

1-Pyrenylglucuronide

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Example 1

Enter data

- ✓ Enter phys-chemical properties and biochemical properties of parent compound and two metabolites under study

- ✓ Enter exposure conditions
  - Inhalation: concentration and duration
  - Dermal: dose rate and duration
  - Oral: bolus dose

Example 1

Properties of parent chemical and metabolites

Pyrene

1-OH-Pyrene

1-OH-Pyrene-glucuronide

Parent Compound	Pyrene
CAS	129-00-0
Density (mg/cm3 or grams/litre)	1270
Molecular weight	202,26
Vapour Pressure (Pa)	0,0106
Log[Kow) at skin pH 5.5	4,88
Log[Kow) at blood pH 7.4	4,88
Water solubility (mg/litre)	0,135
Resorption tubuli (y/n/?)	Y
Enterohepatic removal (relative to liver venous blood)	0
Vmax Liver (parent[total] µmol/kg tissue/hr)	360
Km Liver (parent[total] µmol/litre)	4,5
Vmax Liver (parent[specif] µmol/kg tissue/hr)	180
Km Liver (parent[specif] µmol/litre)	4,5
1st metabolite	Hydroxypyrene
CAS	5315-79-7
Density (mg/cm3 or grams/litre)	1000
Molecular weight	218,28
Vapour Pressure (Pa)	0,000022
Log[Kow) at skin pH 5.5	
Log[Kow) at blood pH 7.4	4,45
Water solubility (mg/litre)	4
Resorption tubuli (y/n/?)	Y
Enterohepatic removal (relative to liver venous blood)	0
Vmax Liver (1st metab[total] µmol/kg tissue/hr)	6900
Km Liver (1st metab[total] µmol/litre)	7,7
Vmax Liver (1st metab[specif] µmol/kg tissue/hr)	6900
Km Liver (1st metab[specif] µmol/litre)	7,7
2nd metabolite	Hydroxypyrene Glucuronide
CAS	154717-05-2
Density (mg/cm3 or grams/litre)	1000
Molecular weight	394
Vapour Pressure (Pa)	3,2E-17
Log[Kow) at skin pH 5.5	
Log[Kow) at blood pH 7.4	-2,12
Water solubility (mg/litre)	40000
Resorption tubuli (y/n/?)	n
Enterohepatic removal (relative to liver venous blood)	0,8
Vmax Liver (2nd metab[total] µmol/kg tissue/hr)	
Km Liver (2nd metab[total] µmol/litre)	
Vmax Liver (2nd metab[specif] µmol/kg tissue/hr)	
Km Liver (2nd metab[specif] µmol/litre)	

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Example 1

Exposure scenario of the creosote plant operator

Airborne exposure

Dermal exposure

Oral intake

Parameters Airborne Exposure	
Concentration parent compound (mg/m3)	0,003
Start of airborne exposure (hours)	0
Duration of airborne exposure (hours)	8
Respiratory protection factor (=> 1)	1
Dermal protection factor (air tight clothing => 1)	1
Parameters Dermal exposure to parent compound	
Skin deposition pure substance (mg/cm2/hour)	0,000006
Start of skin exposure (hours)	0
Duration of skin exposure (hours)	8
Skin temperature (centigrade)	25
Affected skin area (cm2)	7500
Parameters of oral absorption	
Bolusdose to stomach of parent compound (mg/kg bwt)	0
Time of application (time in hours)	0
Absorption rate into intestinal tissue (1/hour)	3
Selection of model parameters	
Select model (1=hum. rest, 2=hum. light act. 3=mouse 4=rat)	2
Repeating exposure for how many days?	5
Observation settings	
Start of observation (time in hours)	0
End of observation (time in hours)	168
Number of steps per hour	1000
Report times per hour	1

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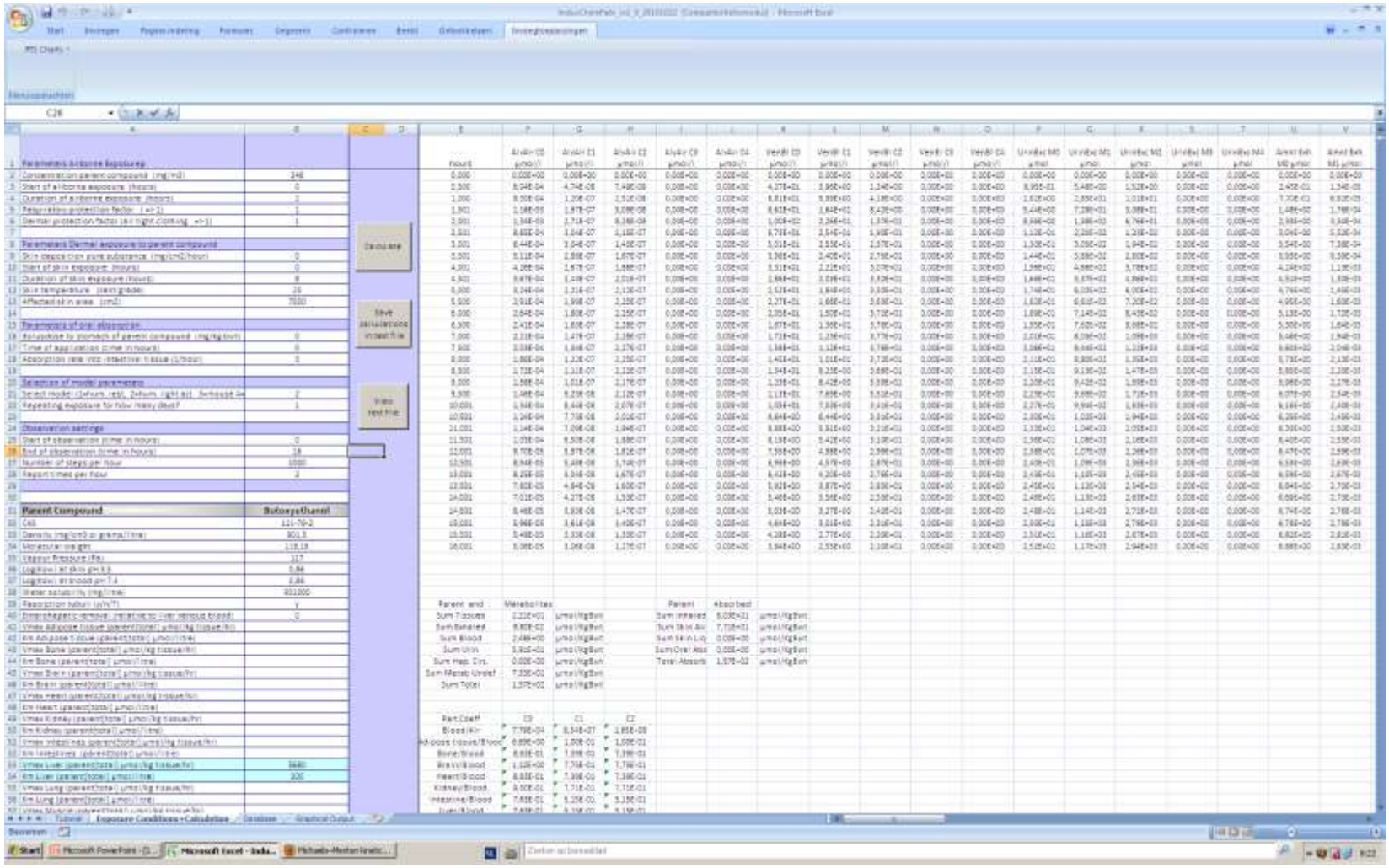
Example 1

Results of simulation: numerical data



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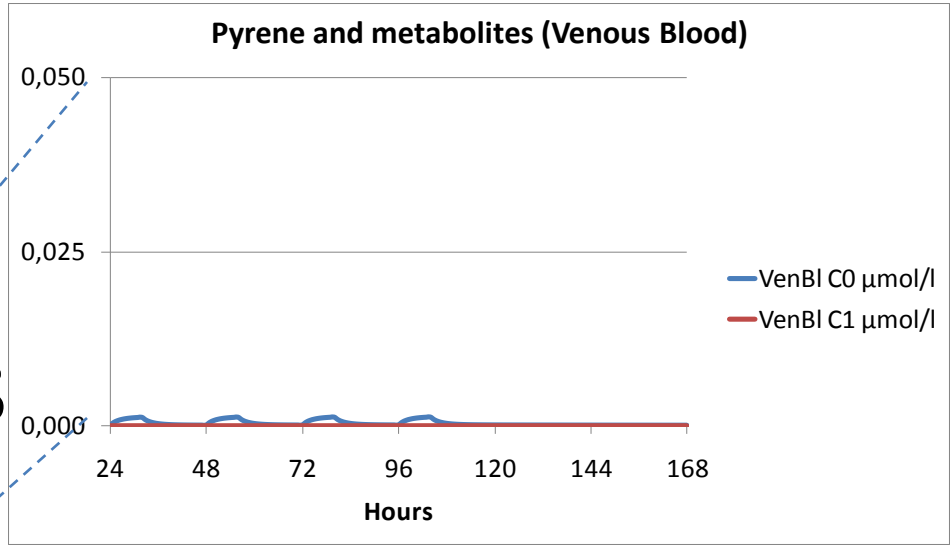
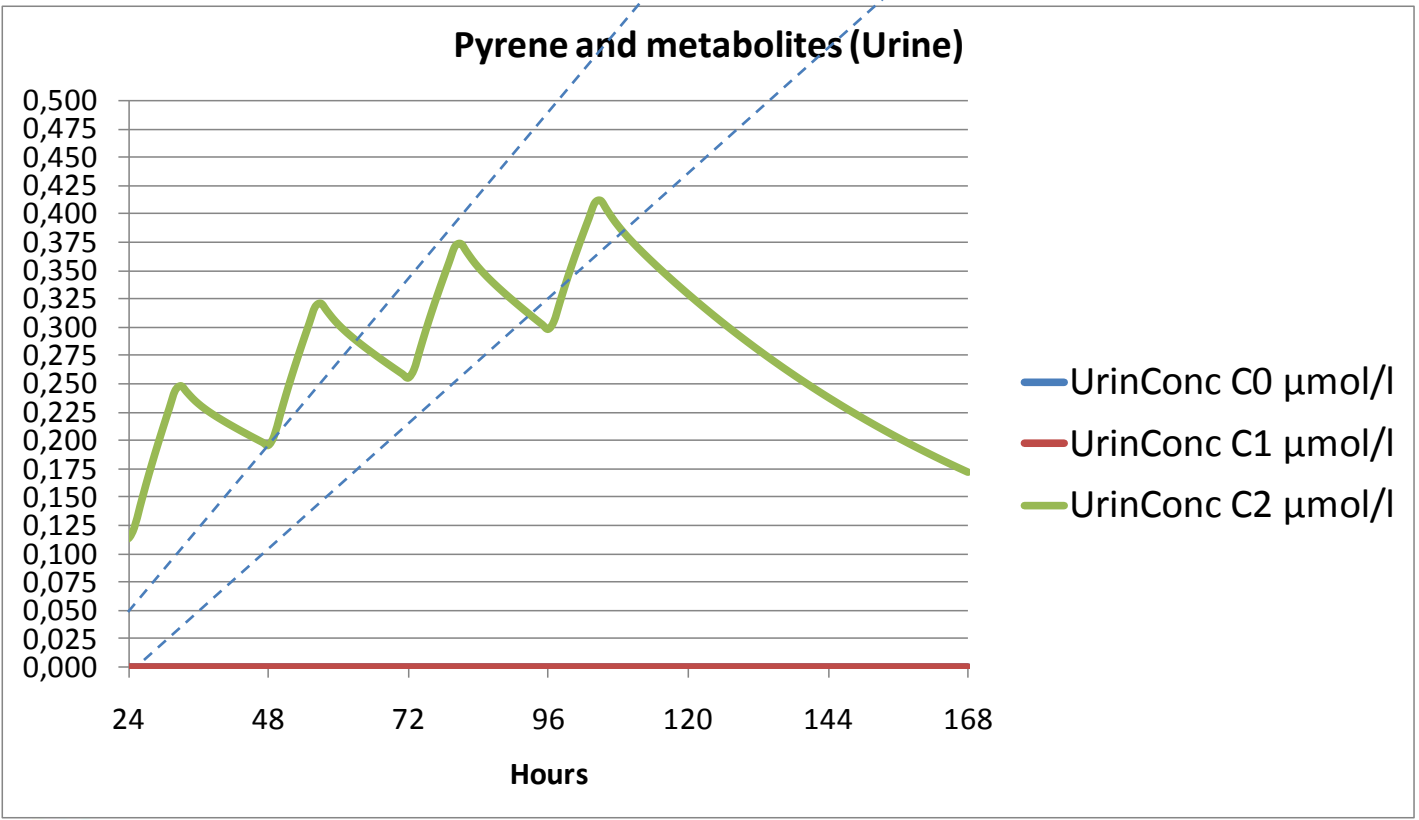
Example 1

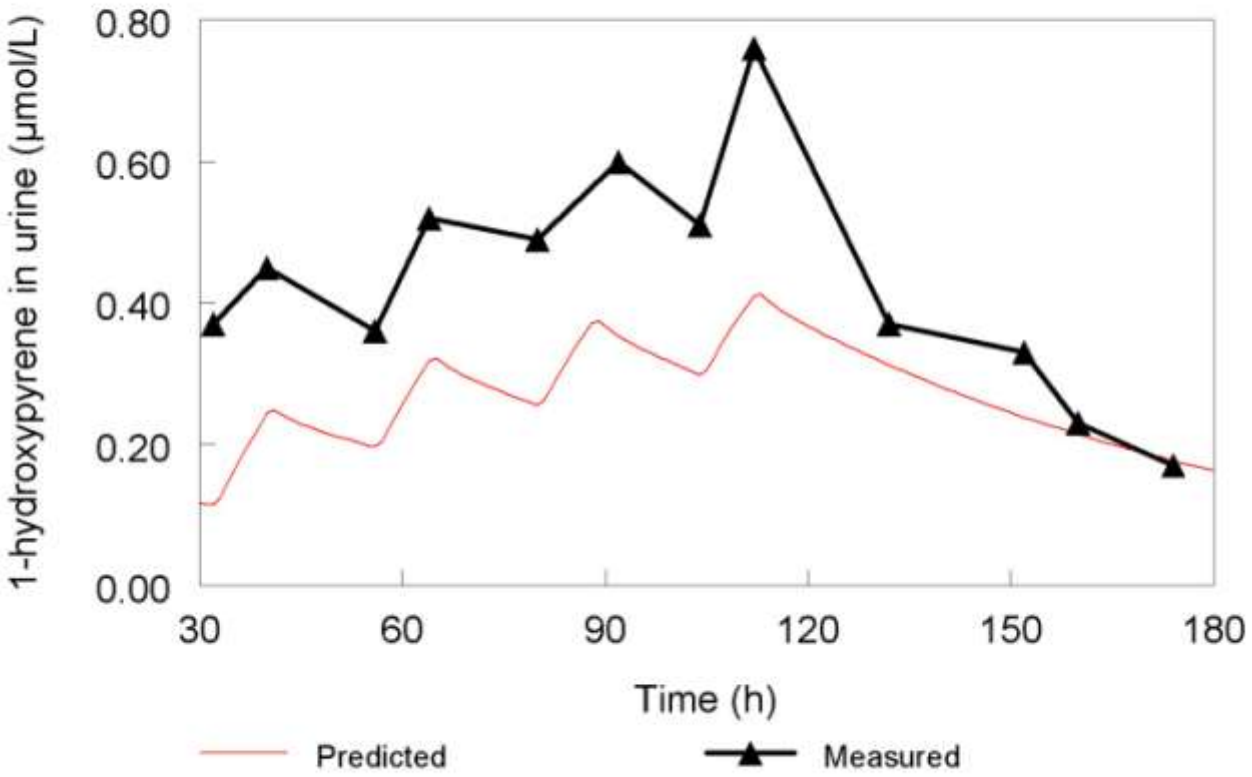
Results of simulation: graphs





Example 1

Comparison of measured and model-predicted level of 1-hydroxypyrene in urine of creosote operator



Note: the measured and the predicted level is the sum of free 1-OHP and 1-OHP-glucuronide

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Example 2:

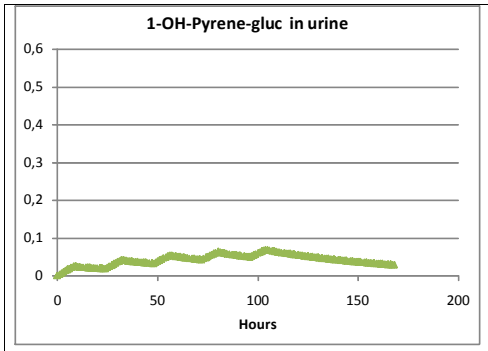
What is the contribution of dermal exposure to the body burden of the operator?

- Creosoting operator is exposed via inhalation and by dermal uptake
- What is relative contribution of each route?

Do simulations with single route exposure!

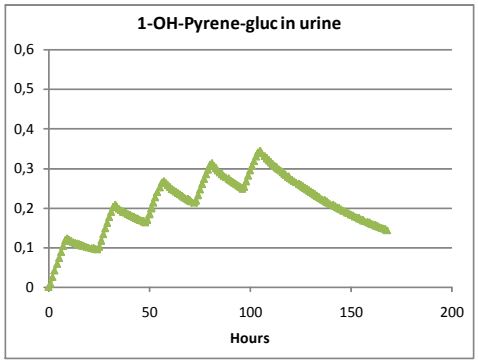
Example 2

Simulation of single route exposure of the creosoting operator



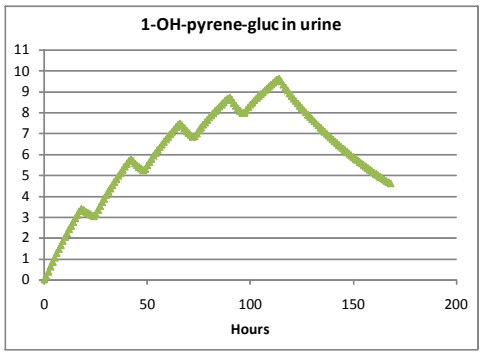
4A: Predicted excretion assuming only inhalation of 3 μg/m^3

Only inhalation



4B: Predicted excretion assuming only dermal exposure of 6 ng/cm2/h over 7500 cm^2.

Only dermal exposure



4C: Predicted excretion assuming only dermal exposure at a 30-fold increased skin deposition rate (= 180 ng/cm^2/h)

Only dermal exposure, but 30-fold increased

PBTK-Simulations can give insight in the relevance of exposure routes

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Comparisons of experimental results with simulations

Nr.	Compound	Exposure route	Exposure scenario	Measured parameter	Refer-ence
A	Ethanol	Dermal	10 times disinfection of hands and arms with ethanol. Rubbing during 80 min. Volunteer study	Ethanol in blood	Kramer, 2007
B	N-Methyl-Pyrrolidone (NMP)	1-Inhalation + dermal and 2 -Dermal only (as vapour)	16 Volunteers exposed to 80 mg/m^3 for 2*4h	NMP and two metabolites in urine (5-HNMP and 2-HMSI)	Bader, 2008

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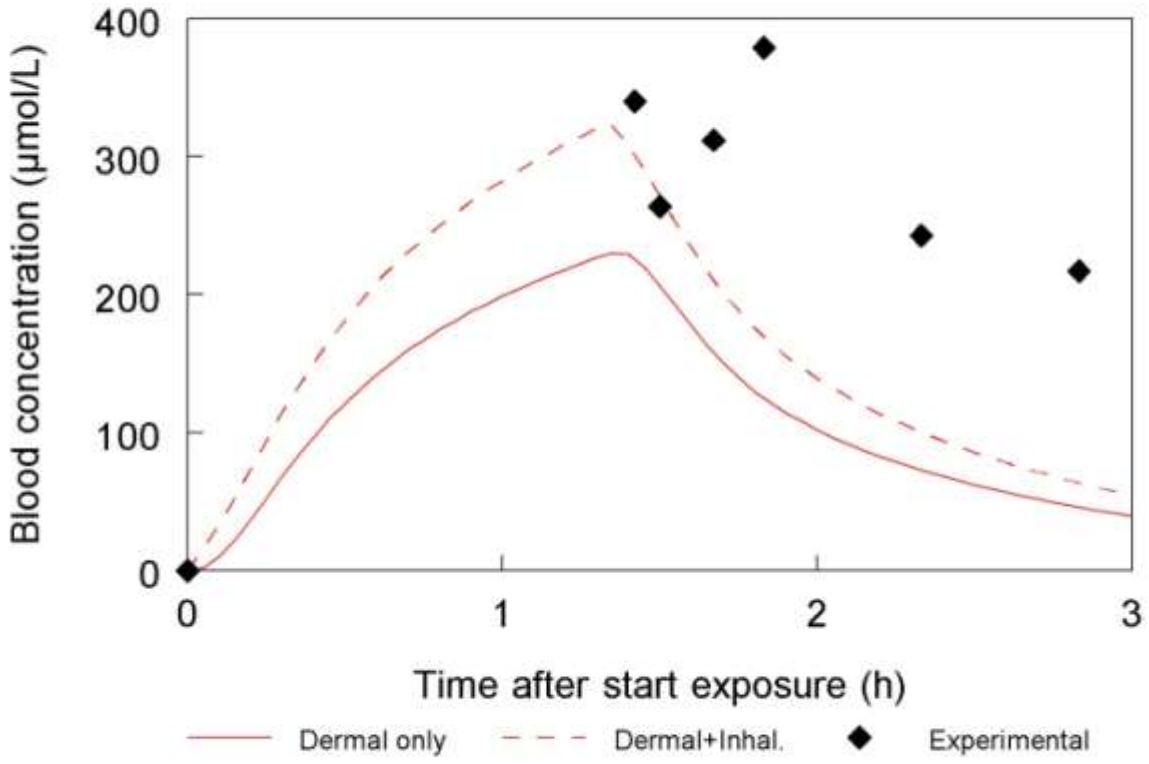
Comparison A

Ethanol in blood after disinfecting of hands and arms (Kramer et al, 2007)



Additional inhalation of evaporated ethanol might occur!

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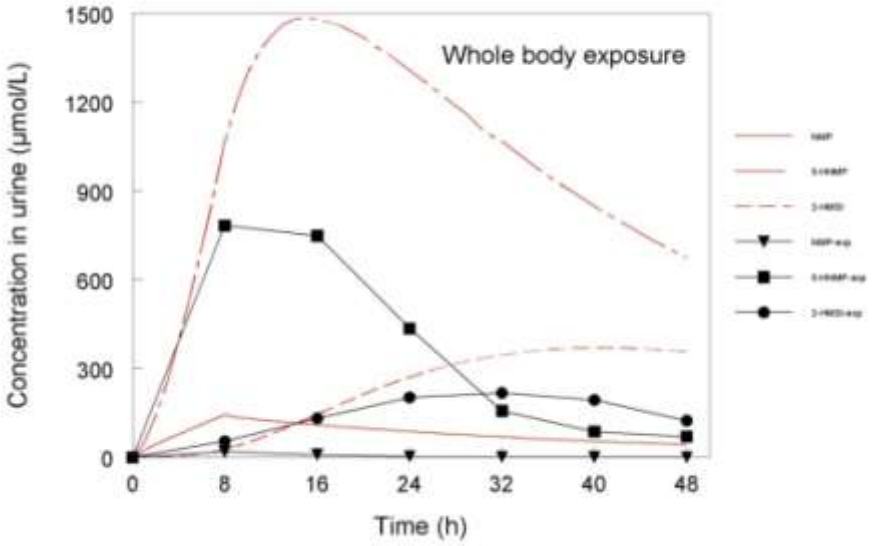
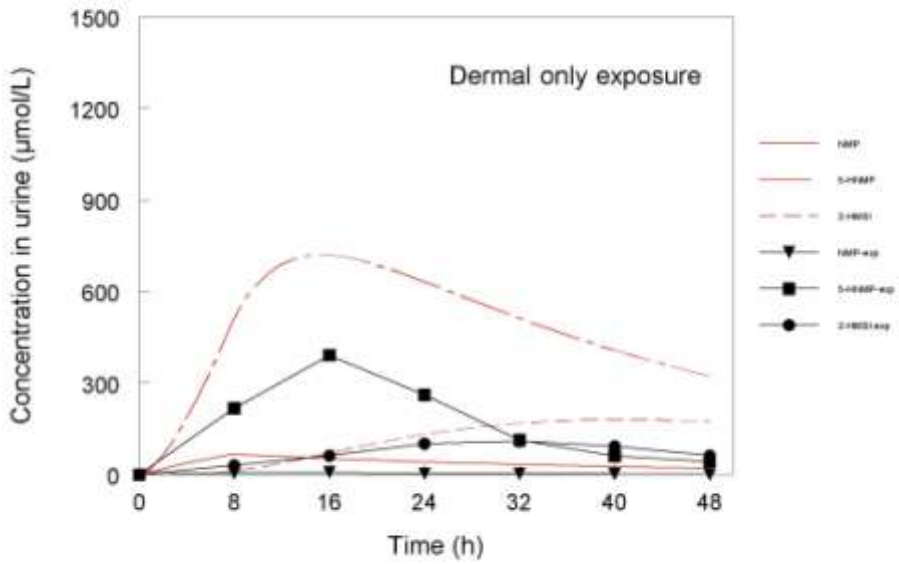
Comparison B

NMP + two metabolites in urine after exposure of volunteers to 80 mg/m^3 for 2*4h (Bader et al, 2008)





- Dermal vapour uptake is approximately 50%
- 5-HNMP is main metabolite in urine
- Level of parent NMP in urine is overestimated

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Conclusions

- This generic PBTK-model can be used for simulations of multiple chemicals
- Vapor and liquid dermal uptake can be estimated with his model
- Accuracy of predictions of body fluid concentrations is within an order of magnitude
- Specific software for PBTK-modeling is not necessary; simulations can be done with EXCEL-application of the model

Suggested application domain for this PBTK-model IndusChemFate

- ✓ Exploration/understanding of biomonitoring results
- ✓ Estimation of contribution of exposure via different routes to total internal body burden
- ✓ Testing of fate of data-poor substances in human body
- ✓ First tier estimation of biological equivalent guidance value (BEGV) as equivalent to external exposure limit
- ✓ Educational purposes to understand toxicokinetics of chemicals in human body

Where to get more info?

- Download the EXCEL-file IndusChemFate and user manual from the Website CEFIC LRI, on page IndusChemFate

  http://www.cefic-lri.org/lri-toolbox/induschemfate

  (The software application is free of charge)

- 1stPaper is submitted to ***Annals of Occupational Hygiene ,*** 2nd paper to ***Int Arch Occup Environ Health***

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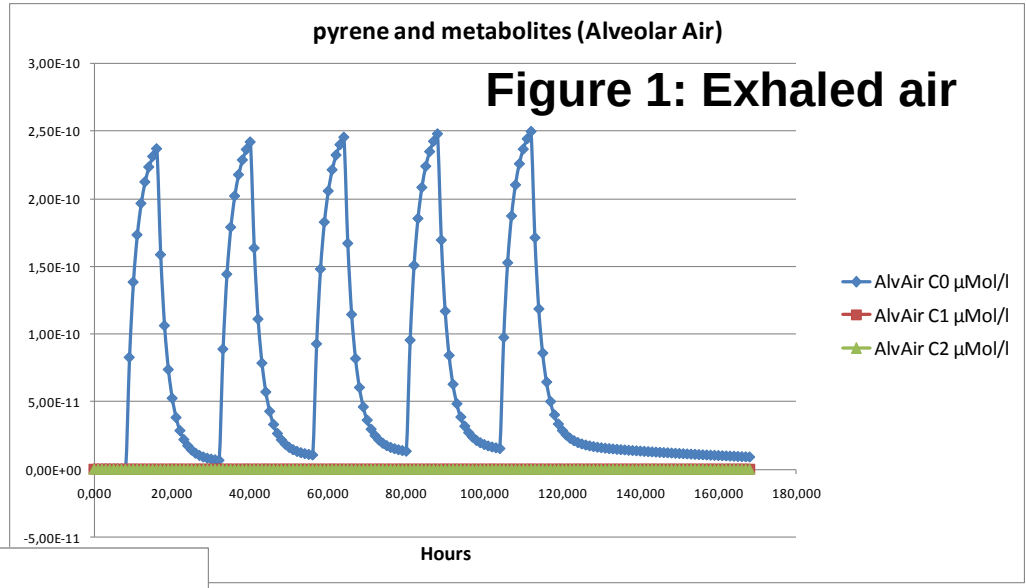
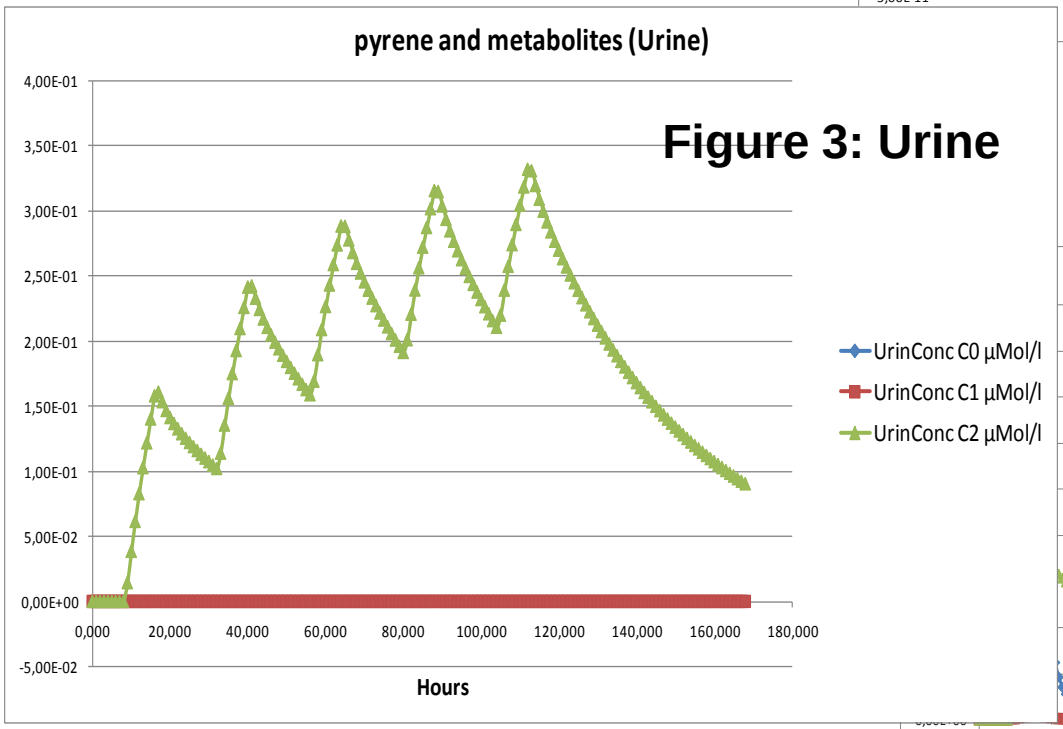
Acknowledgements

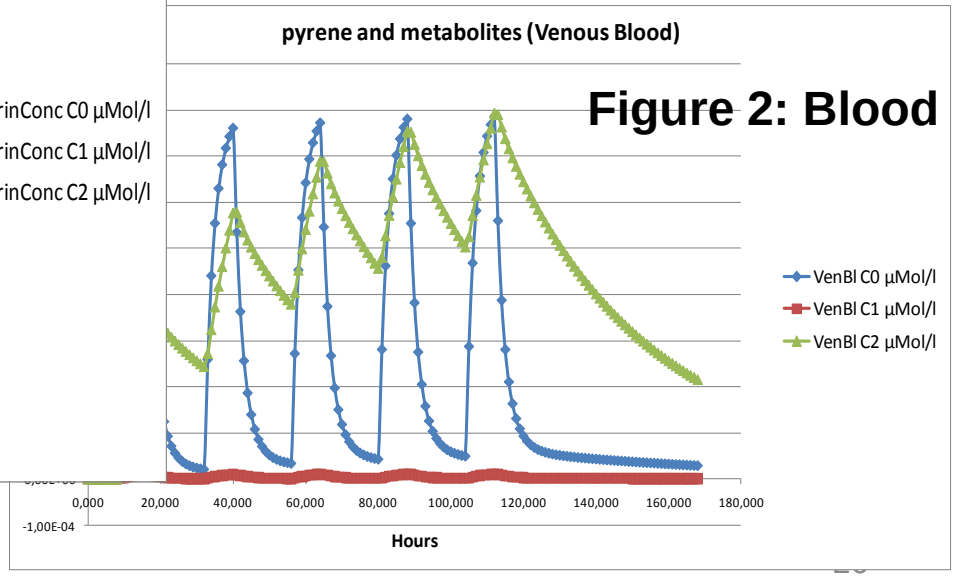
Funding from CEFIC-LRI

Example 1

Results of simulation – graphs-2







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