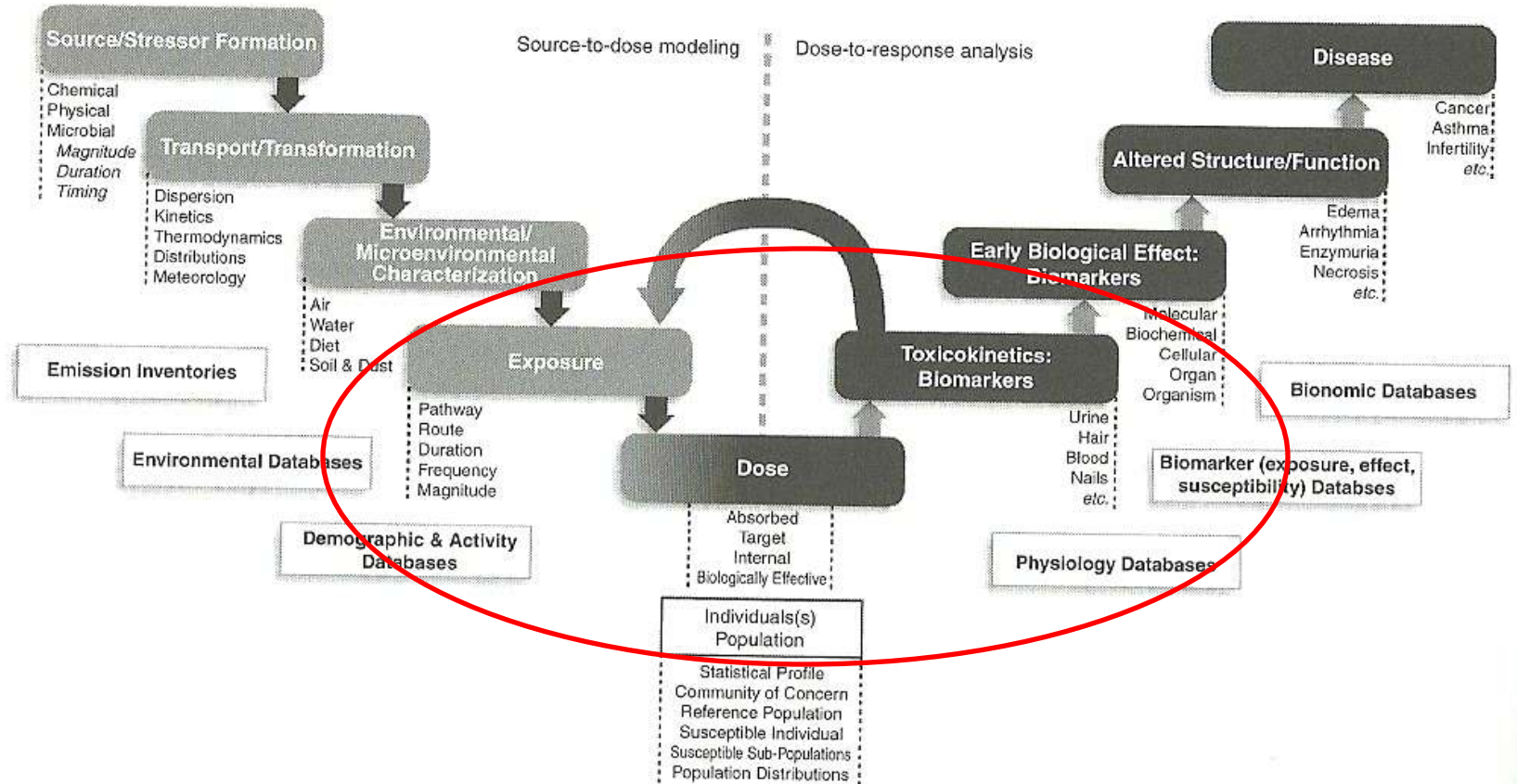


IndusTox

A generic, cross-chemical predictive PBTK-model

Frans Jongeneelen & Wil ten Berge

PBTK-model in exposure/dose assessment



Schematic from: Georgopoulos

What were the demands for our generic PBTK-model?

➤ Simple and easy model

- To be used for occupational and/or environmental exposures (*Variability of environmental exposure is higher than biological variability*)
- 1st tier estimate accuracy (one order of magnitude)
- Minimum of data input
- Free open source model

➤ Choices made

- QSPR prediction of partitioning
- metabolism data of in vitro metabolism kinetics
- MS Excel software platform
- Species: man (in rest or light activity), rat, mouse

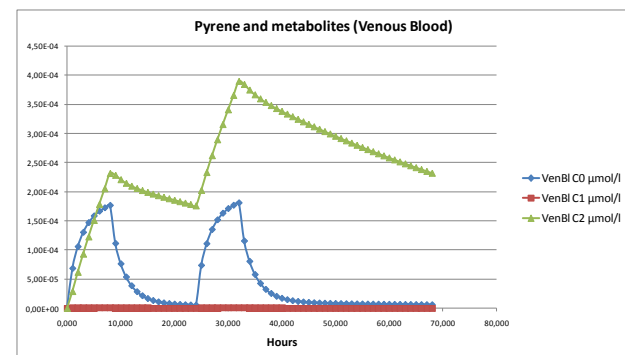
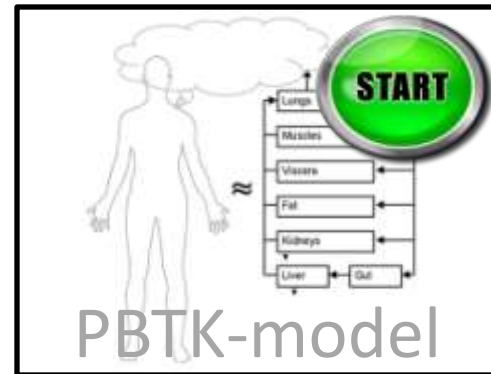
Result: Overview of the PBTK-model IndusChemFate

Compound data

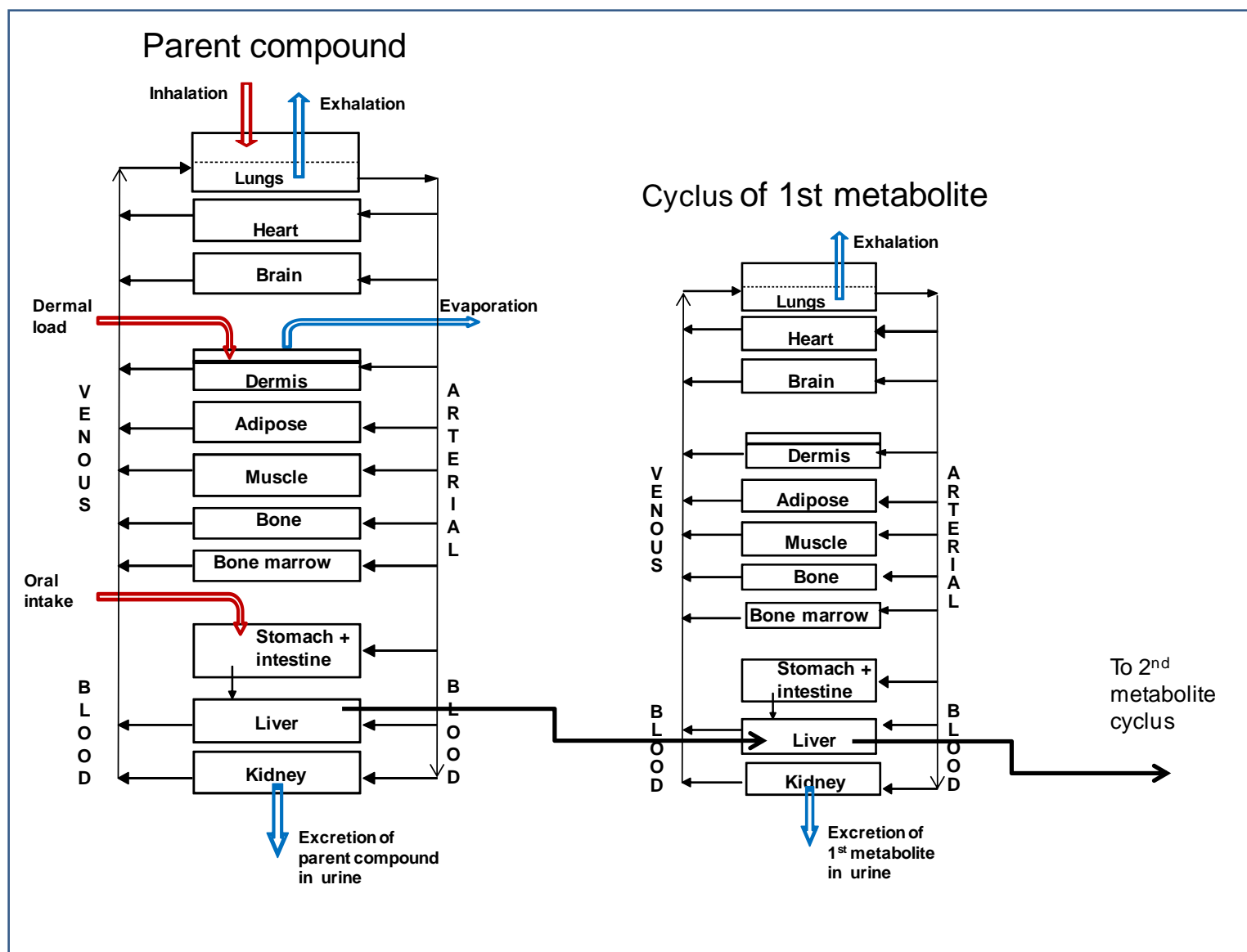
- Physical-chemical properties:
 - Density
 - Molecular weight
 - Vapour pressure
 - $\text{Log}(K_{ow})$ at pH 5.5 and 7.4
 - Water Solubility
- Biochemical parameters :
 - Metabolism (k_M and V_{max})
 - Renal tubular resorption
 - Enterohepatic circulation ratio

Exposure scenario

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



Scheme of the physiology of the PBTK-model



Routing of chemicals and metabolites in the PBTK-model

- Absorption

- Inhalation
- Oral uptake
- Dermal uptake

- Distribution over the body

- QSPR algorithm for estimate of blood:air partitioning
- QSPR algorithm for estimate of tissue:blood partitioning

- Metabolism

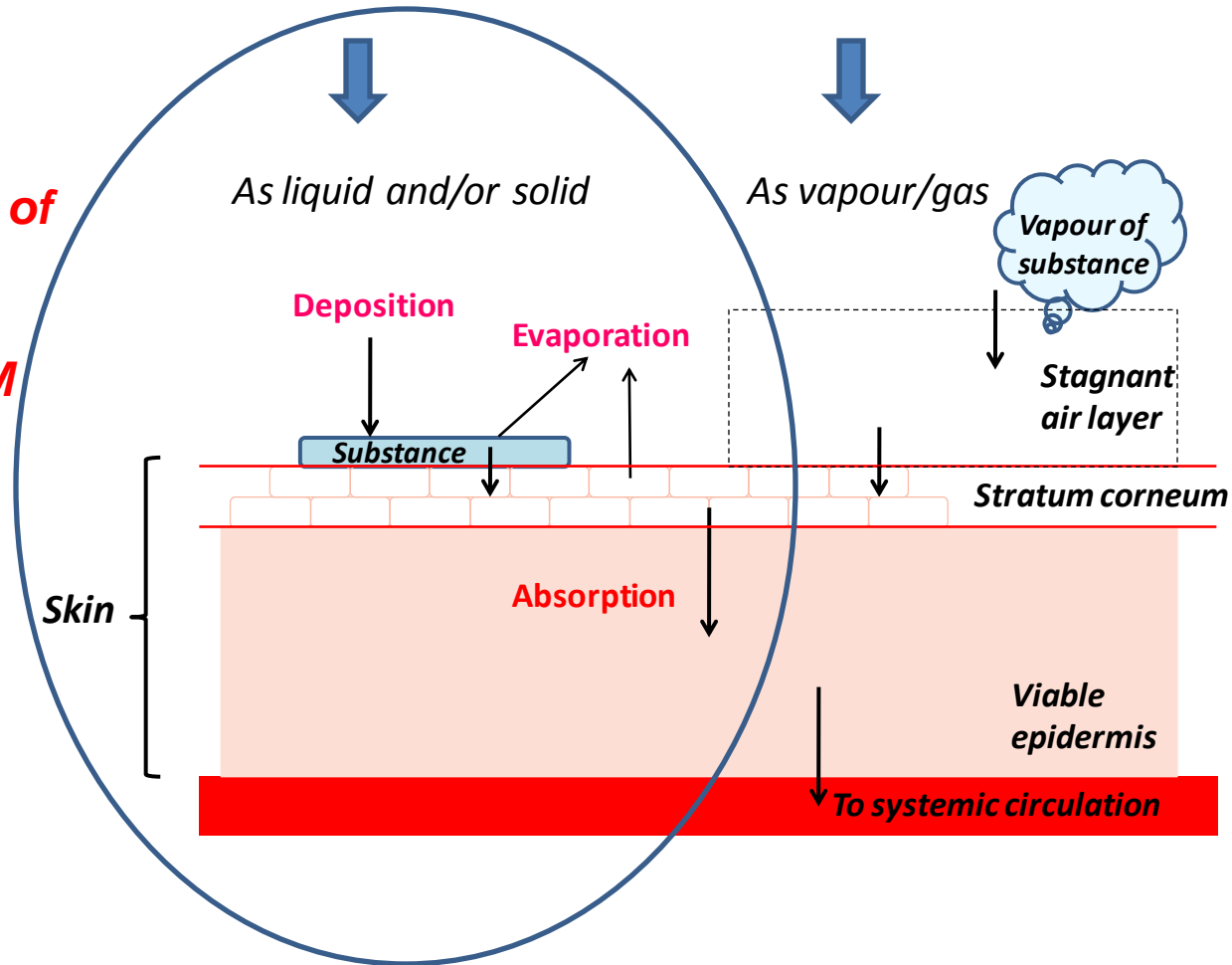
- Saturable metabolism according to Michaelis-Menten kinetics

- Excretion

- Urine
- Exhaled air

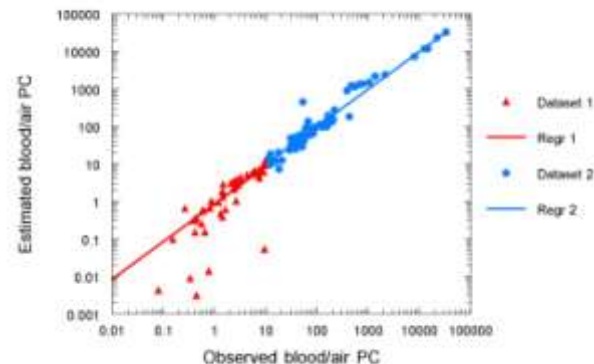
Dermal absorption module of the model

**= New model of
AIHA-EASC
named
IH SKINPERM**



Distribution over compartments in the body

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



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

Metabolism

- Metabolism can be modeled in all tissues
- Default is metabolism in liver only
- Sequential metabolism
 - Parent, 1st metabolite, 2nd metabolite and so on
- Stoichiometric yield in every step
 - Rate of loss of parent and appearance of metabolite
 - Difference gives stoichiometric yield of specific metabolite
- K_M and V_{max} from in experiments in microsomal liver fraction or hepatocytes
 - Scaled to liver weight of individual/species

Other aspects

- Excretion in urine and alveolar air
- With enterohepatic circulation
 - fase 2 metabolites

The PBTK-model is build as application in MS-Excel, called IndusChemFate

- The differential equations of the PBTK-model are written in spreadsheet syntax (visual basic)
- The file IndusChemFate contains 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

Simulation example 1

Average and individual variation in workers

Paper: Inhaled dosimetry and biomonitoring of coal liquefaction workers (Quinlan et al, 1995)

- At coal liquefaction plants PAH occur as pollutants
- 5 workers were followed during 4 shift on and 96h off work
- Average pyrene in breathing zone was **1.3 $\mu\text{g}/\text{m}^3$ pyrene.**
- 1-hydroxypyrene in urine was measured during 8 days = 192 h

Simulation example 1

Metabolism of pyrene

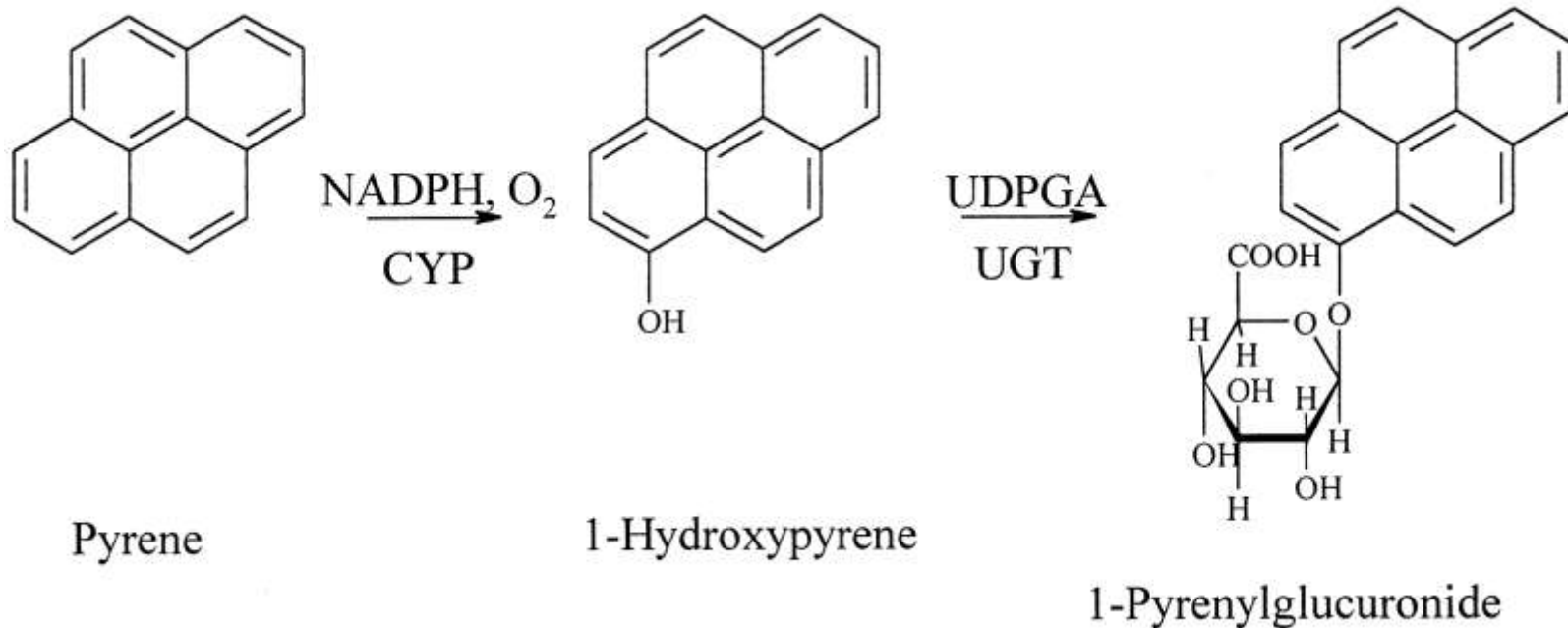


Figure taken from: Luukkanen et al, 2001

Simulation example 1

Kinetics of in vitro metabolism of pyrene in human hepatic fractions

Step	Tissue	Parameter and value	ref
Pyrene to 1-OH-pyrene	Hepatic 9000*g fraction of 12 individuals	$V_{\max} = 180 \mu\text{mol/hr/kg}$ tissue $K_M = 4.4 \mu\text{M}$	Jongeneelen (1987)
1-OH-Pyrene to 1-OH-pyrene- glucuronide	Hepatic microsomal fraction of 3 individuals	$V_{\max} = 6,900 \mu\text{mol/hr/kg}$ tissue $K_M = 7.7 \mu\text{M}$	Luukkanen et al (2001)

Simulation example 1

Modeling: Data to be entered

- 1) Enter **phys-chemical properties** and **biochemical parameters** of parent compound and metabolites under study

- 2) Enter **exposure scenario**
 - 1) Inhalation: concentration and duration
 - 2) Dermal: dose rate and duration
 - 3) Oral: bolus dose

Simulation example 1

Entering properties & biochem data of pyrene and metabolites

Pyrene

1-OH-Pyrene

1-OH-Pyrene-glucuronide

Parent Compound	Pyrene
CAS	129-00-0
Density (mg/cm ³ 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/cm ³ 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/cm ³ 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)	0,3
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)	

Simulation example 1

Entering exposure scenario of the coal liquefaction workers

Airborne exposure scenario

Parameters Airborne Exposure _{ej}	
Concentration parent compound (mg/m ³)	0,0013
Start of airborne exposure (hours)	0
Duration of airborne exposure (hours)	12
Respiratory protection factor (⇒ 1)	1
Dermal protection factor (air tight clothing ⇒ 1)	1

Dermal exposure scenario

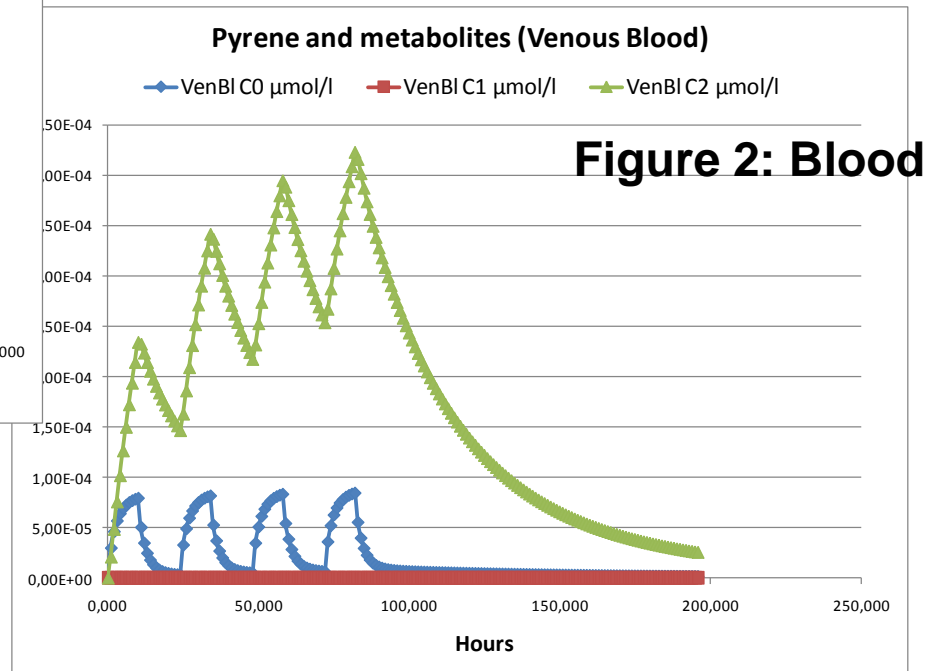
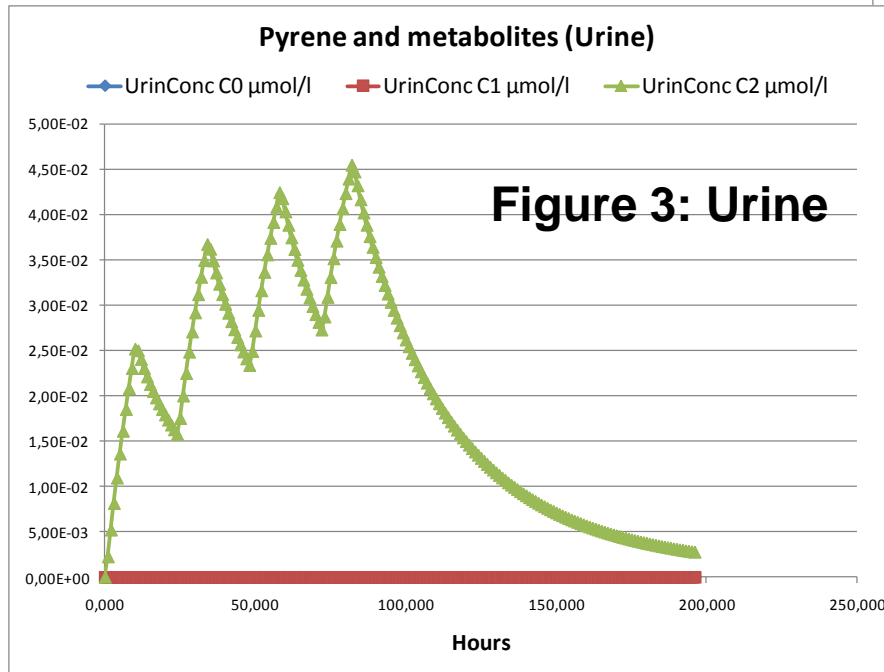
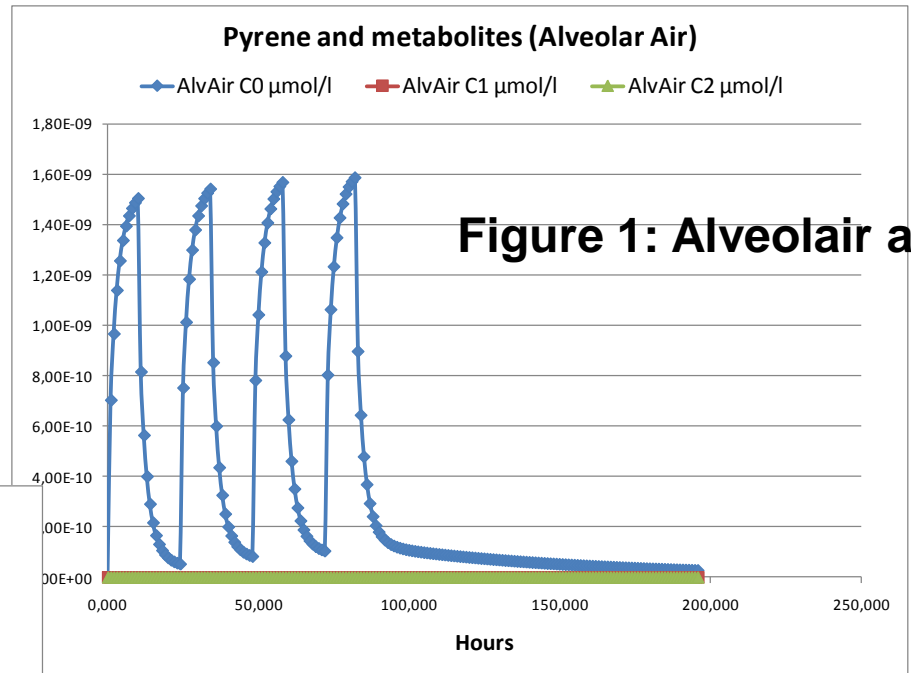
Parameters Dermal exposure to parent compound	
Skin deposition pure substance (mg/cm ² /hour)	0
Start of skin exposure (hours)	0
Duration of skin exposure (hours)	8
Skin temperature (centigrade)	25
Affected skin area (cm ²)	5000

Oral intake scenario

Parameters of oral absorption	
Bolus dose to stomach of parent compound (mg/kg bwt)	0
Time of application (time in hours)	0
Absorption rate into intestinal tissue (1/hour)	3

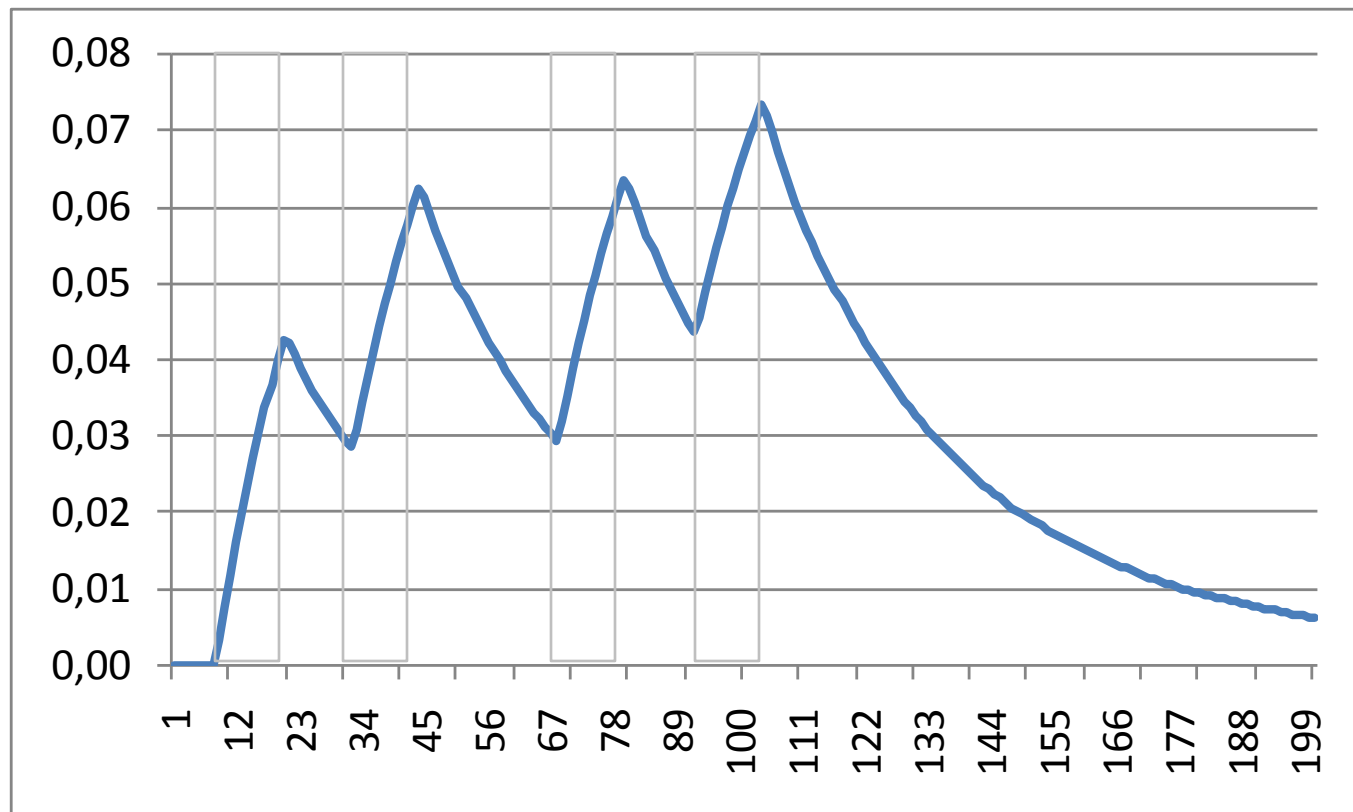
Simulation example 1

Run program- Results as graphs



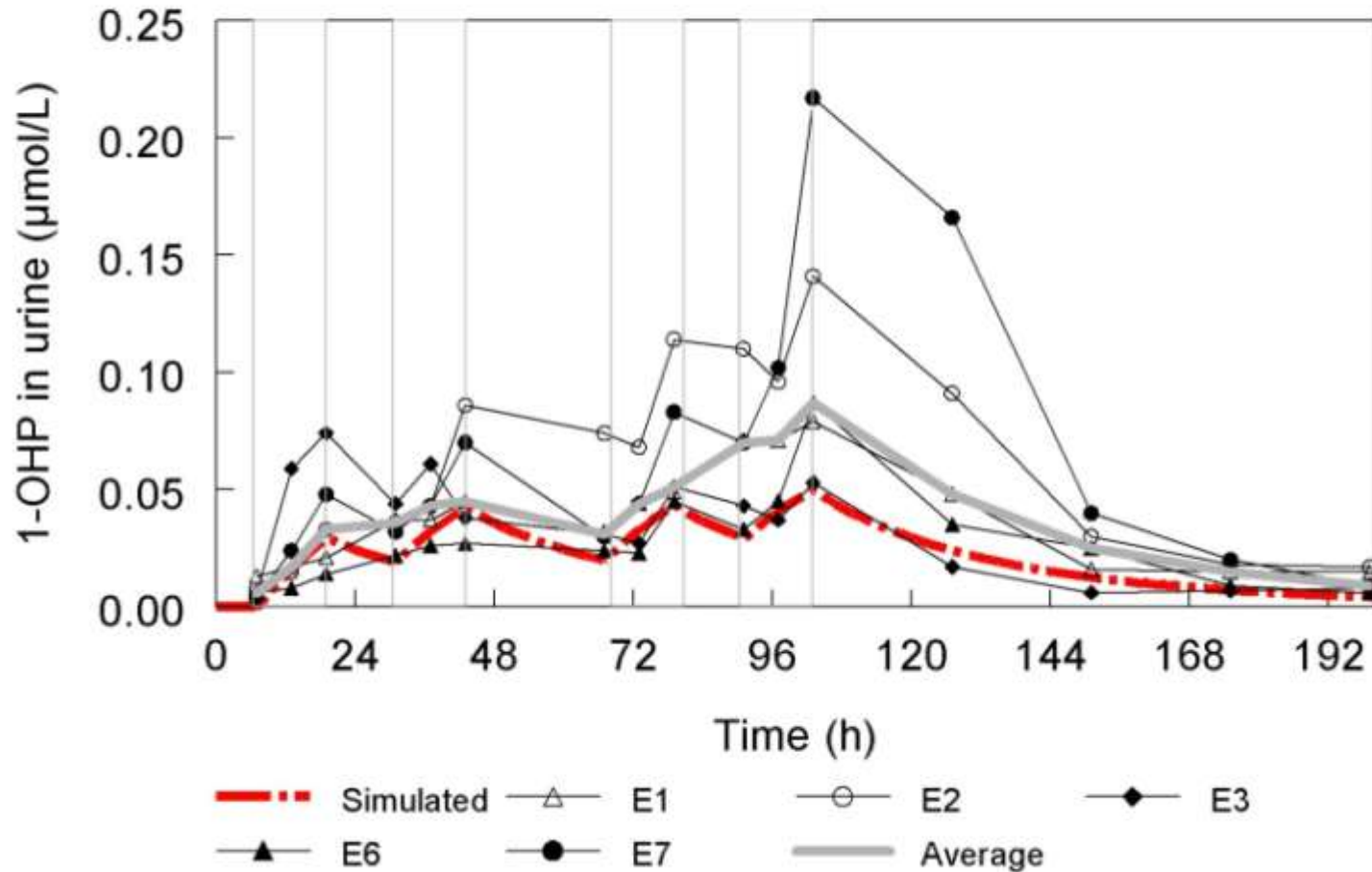
Simulation Example 1

Result: predicted concentration total 1-OHP in urine of the coal liquefaction workers (in $\mu\text{mol/L}$)



Simulation example 1

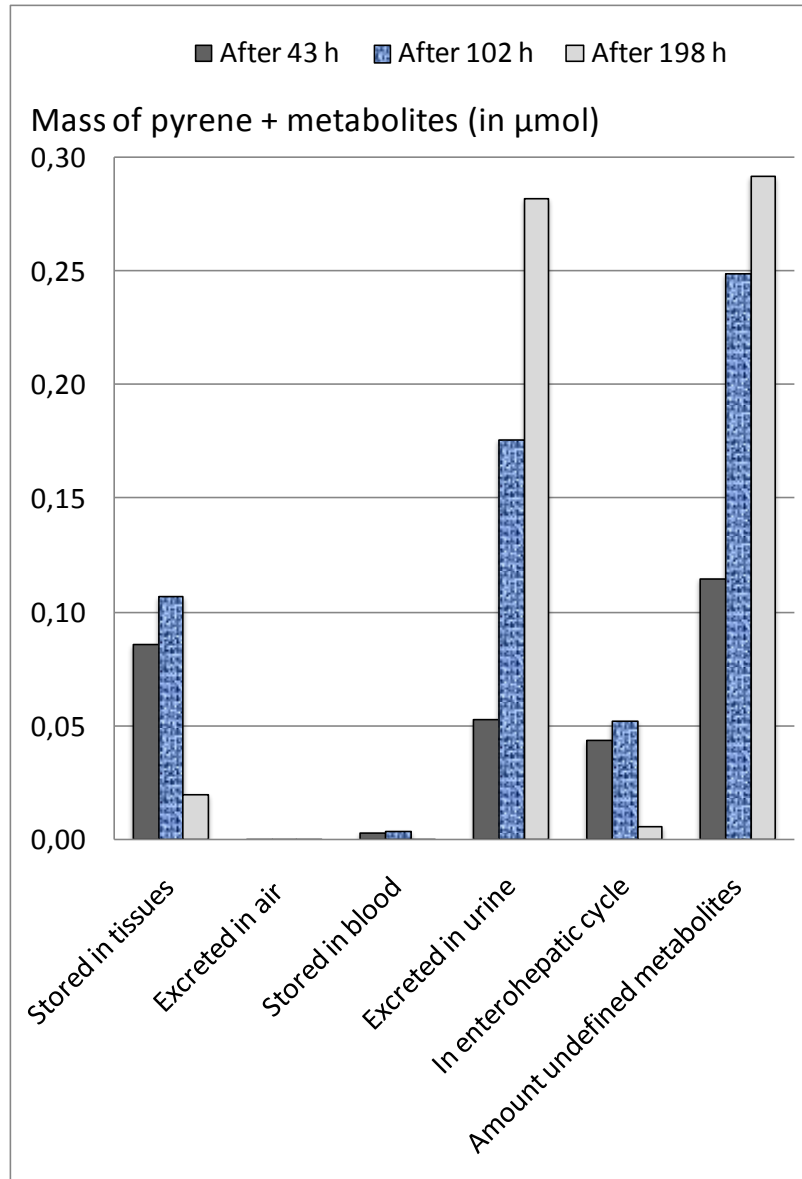
Comparison measured 1-OHP in urine versus predicted



Note: Dermal exposure was not measured and set at zero in simulation

Simulation Example 1

Result: Estimated fate of mass of pyrene + metabolites



Simulation example 1

Conclusion

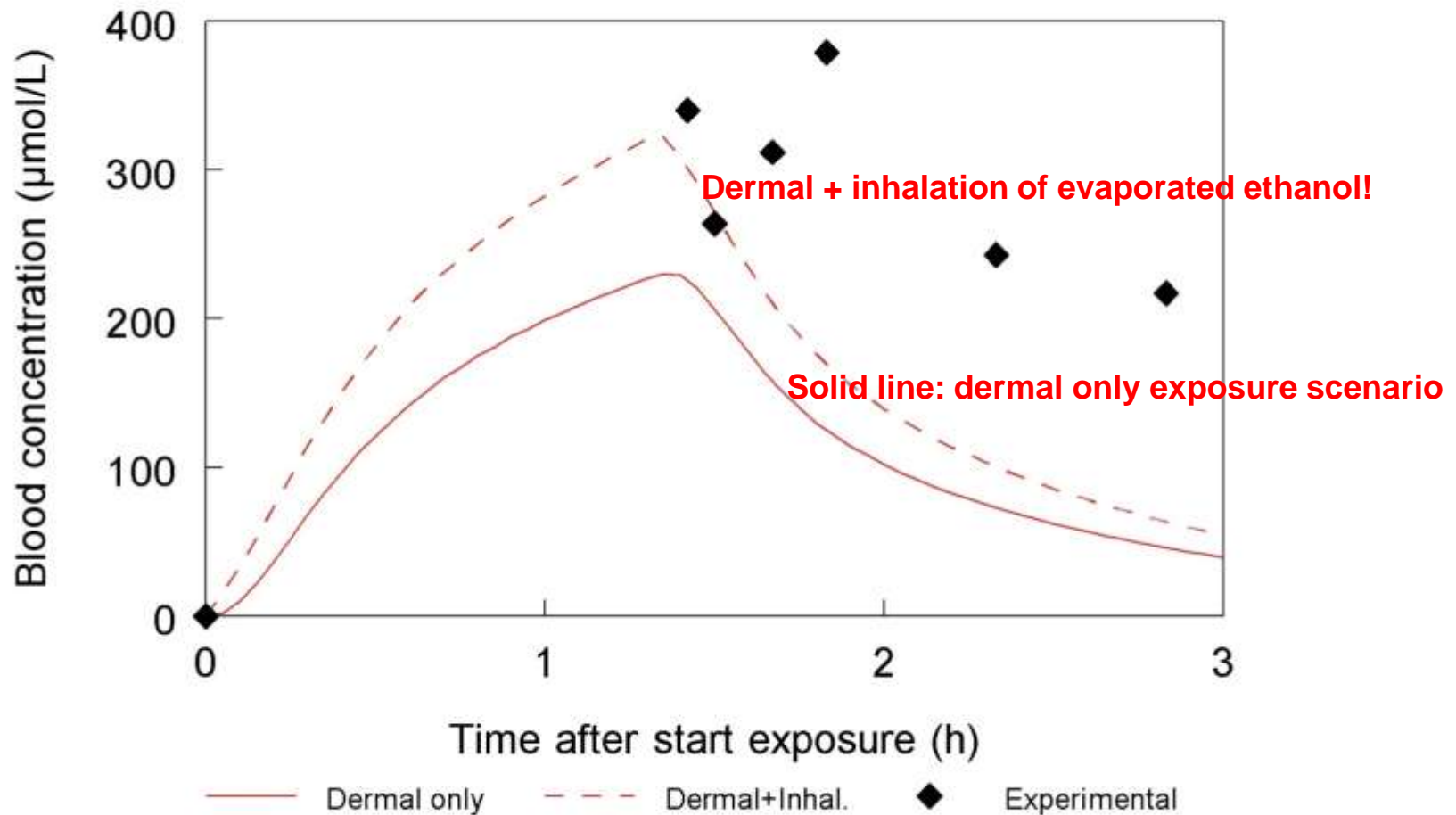
- ✓ The average level of hydroxypyrene can be predicted when the exposure scenario is known
- ✓ A rough predictive model does when we realise that differences of external exposure between workers are large

Simulation example 2: dermal uptake after disinfection of hands with ethanol

Nr.	Compound	Type of study	Exposure route	Exposure scenario	Reference
1	Pyrene	Observational study of workers	Inhalation + dermal	4*12 on work, 96 hr off work	Quinlan, 1995
2	Ethanol	Volunteer study	Application on skin, dermal	10 times disinfection of hands and arms. Rubbing during 80 min.	Kramer, 2007

Simulation example 2

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



Simulation example 2

Conclusion

- ✓ Dermal uptake of ethanol can be predicted
- ✓ Evaporation of ethanol seems to be a significant extra route of uptake of ethanol after handrubbing

What are the differences between this PBTK-model and other PBTK-models?

- **GENERIC MODEL**

- Distribution of the chemical/metabolite in the body is estimated by algorithms, thus model can easily be used for many different volatile and semi-volatile chemicals

- **RUNS IN WIDELY AVAILABLE SOFTWARE**

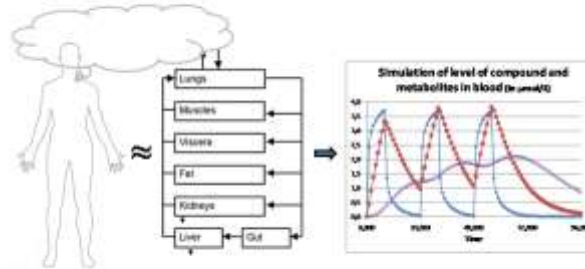
- The software application is running in MS EXCEL, a software platform that is widely available

Suggested application of this PBTK-model IndusChemFate

- ✓ *Chemical health risk assessors*
 - Volatile and semi-volatile compounds
 - *A priori* (= 1st tier) estimation of concentration in body tissues and/or body fluids at specific exposure scenarios
 - Screening of absorption and fate of data-poor substances in the human body
 - In vivo extrapolation of in vitro ADME data
 - Comparisons of toxicokinetics in different species (in-vivo to in vivo extrapolation)
 - Assessment of contribution of dermal uptake to body burden
- ✓ Student and non-experts
 - Educational tool to understand toxicokinetics of chemicals in human body in relation to phys-chem properties

Where to get more info?

- Download **EXCEL-application file** and **user manual**:
 - Website CEFIC LRI, webpage IndusChemFate
- <http://www.cefic-lri.org/lri-toolbox/induschemfate>



- Read **Paper** (in Annals Occupational Hygiene 2011)
- See at our website: www.industox.nl
- Ask us to do a **live-demonstration**

Acknowledgement

Funding from CEFIC-LRI



Thank you

Any questions?