

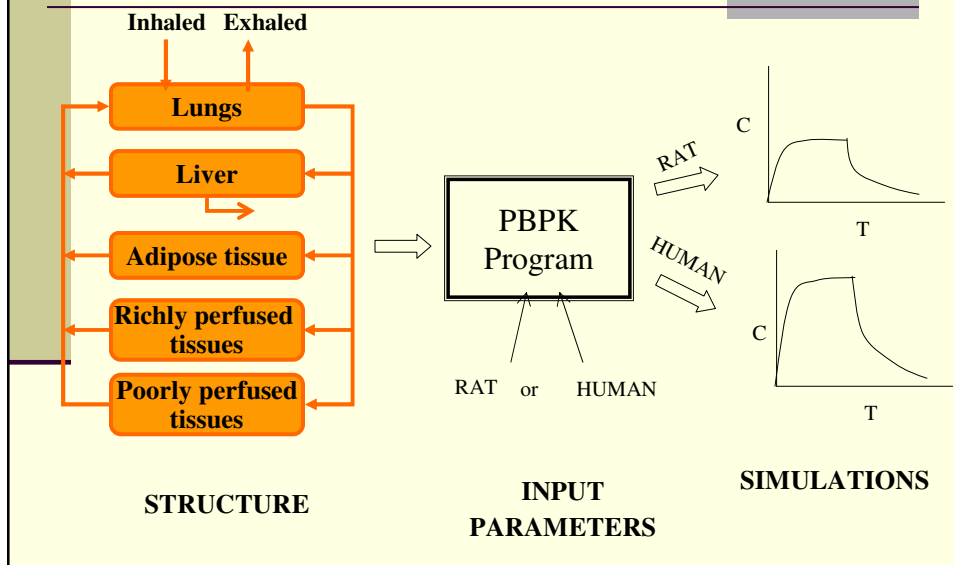
# Species extrapolation with PBPK models

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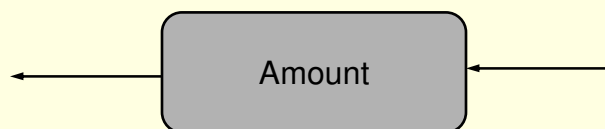
## Outline

- Introduction
- Rat-Human extrapolation
  - Single chemicals
  - Mixtures
  - QSARs
- Rat-Fish extrapolation
  - PBPK modeling
  - QSARs
- Conclusions

## PBPK Models and Interspecies Extrapolation



## Functional Representation



$$\frac{dA_t}{dt} = \text{Input} - \text{Output}$$

Blood flow to tissue, volume, partition coefficient

## Functional Representation Metabolic Clearance

$$\frac{V_{\max} \cdot C}{K_m + C}$$

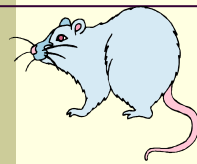
$V_{\max}$  = maximum velocity of metabolism

$K_m$  = Michaelis-Menten constant

$C$  = concentration of chemical

Metabolizing enzyme, its levels, tissue volume

## Interspecies extrapolation of PK of chemicals



### Species SPECIFIC:

- Blood:air PC
- Flows
- Volumes
- [P-450]

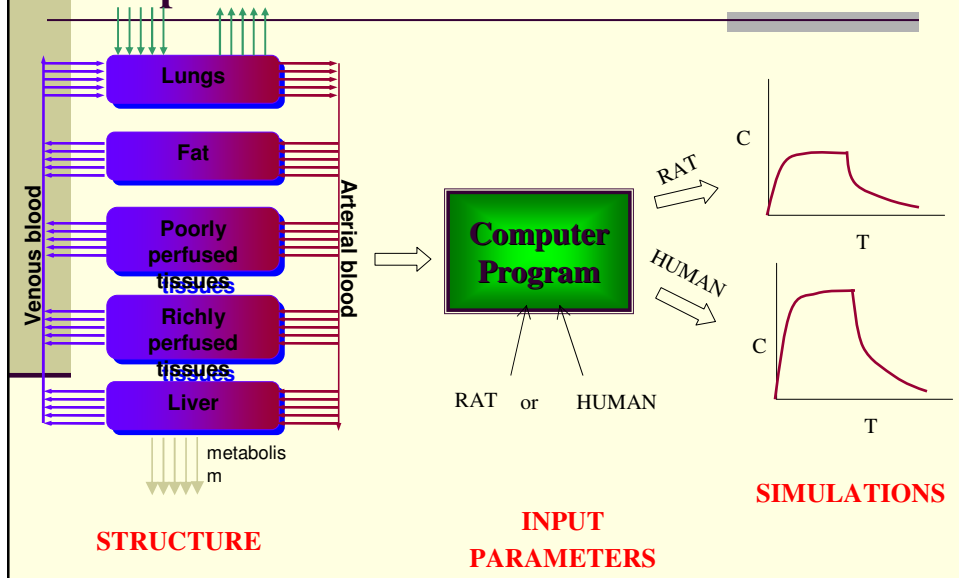
### INVARIANT:

- $V_{\max_c}$
- $K_m$
- Tissue:air PC

### Species SPECIFIC:

- Blood:air PC
- Flows
- Volumes
- [P-450]

## Mixture PBPK Models and Interspecies Extrapolation



## QSARs for PBPK Parameters

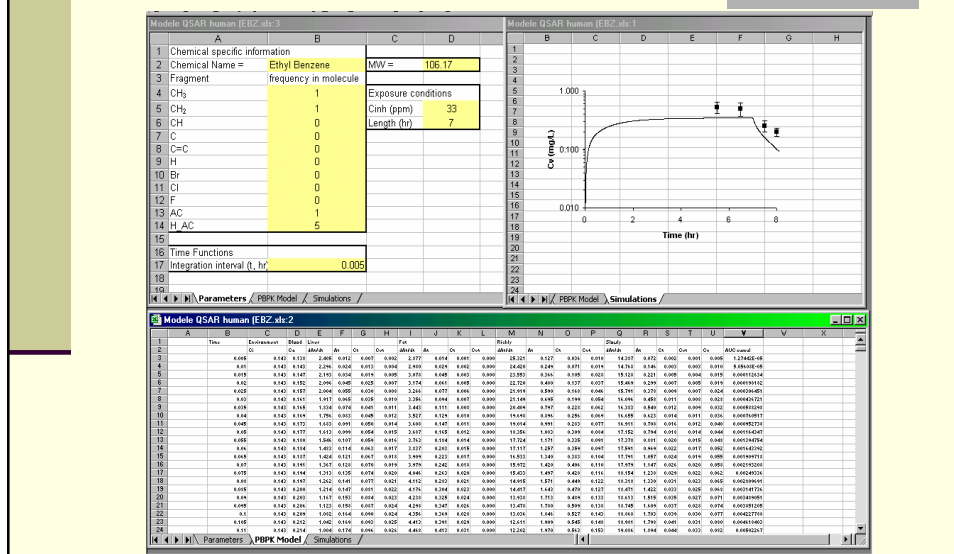
- Fragment constant approach
  - $P_{pbpk} = \sum n_f \cdot C_f$
- Multilinear regression (SPSS®)
- 46 VOCs, Fragments: CH<sub>3</sub>, CH<sub>2</sub>, CH, C, C=C, H, Cl, Br, F, B-ring, 2 E1 substrates
- Cross-validation, external validation

Chemical specific information										Physiological Parameters											
1	Chemical Name =	Ethyl Benzene	MW =	106.17						Tissue fraction V(L)	fraction Q(L/V(L))	Q(L/hr)	Q(L/hr)								
2	Fragment	frequency in molecule								Body (c)	18	70	417.48								
3	CH <sub>3</sub>	1	Exposure conditions						Lung (p)	18											
4	CH <sub>2</sub>	1	Cin (ppm)	33						Liver (l)	0.026	0.26	1.82	108.55							
5	CH	0	Length (hr)	7						Fat (f)	0.19	0.05	13.3	20.87							
6	C	0								Richly (r)	0.05	0.44	3.5	183.70							
7	C=C	0								Slowly (s)	0.62	0.25	4.34	104.25							
8	H	0									0.886	1	62.02	417.49							
9	Br	0																			
10	Cl	0																			
11	F	0																			
12	AC	1																			
13	H <sub>2</sub> AC	5																			
14																					
15																					
16	Time Functions																				
17	Integration interval (t, hr)																				
18																					
19																					
20																					
21																					
22	Contributions to	CH <sub>3</sub>	CH <sub>2</sub>	CH	C	C=C	H	Br	Cl	F	AC	H <sub>2</sub> AC	Sum of contrib	Value							
23	Log P <sub>1</sub>	-4.82E-02	0.136	2.62E-01	-0.193	-0.116	5.73E-02	0.585	0.316	0	3.05	-0.347	1.403	25	93						
24	Log P <sub>2</sub>	1.55E-02	0.234	0.359	3.18E-02	0.257	-3.05E-03	0.7	0.384	-0.113	3.76	-0.408	1.970	29	29						
25	Log P <sub>3</sub>	-1.97E-02	0.122	0.266	-0.105	-7.07E-02	8.13E-02	0.622	0.322	-8.11E-02	3.65	-0.446	1.522	33	33						
26	Log P <sub>4</sub>	0.366	0.435	0.33	-0.295	0.327	0.155	1.17	0.735	7.52E-02	2.92	-5.98E-02	3.442	2767	2767						
27	CL <sub>50</sub>	45.5	10.1	-14.3	-73.7	-16	19.5	42.4	29.2	0	-211	49.3	91.00	91.00	91.00						
28																					
29	Cin <sub>h</sub> (mg/L)																				
30																					
31																					
32	Tissue	Pta	Ptb																		
33	Blood	25.2813349	3.887																		
34	Liver	93.21804703	109.846																		
35	Fat	2766.941645	3.887																		
36	Richly	93.21804703	3.887																		
37	Slowly	33.28894258	1.317																		
38																					
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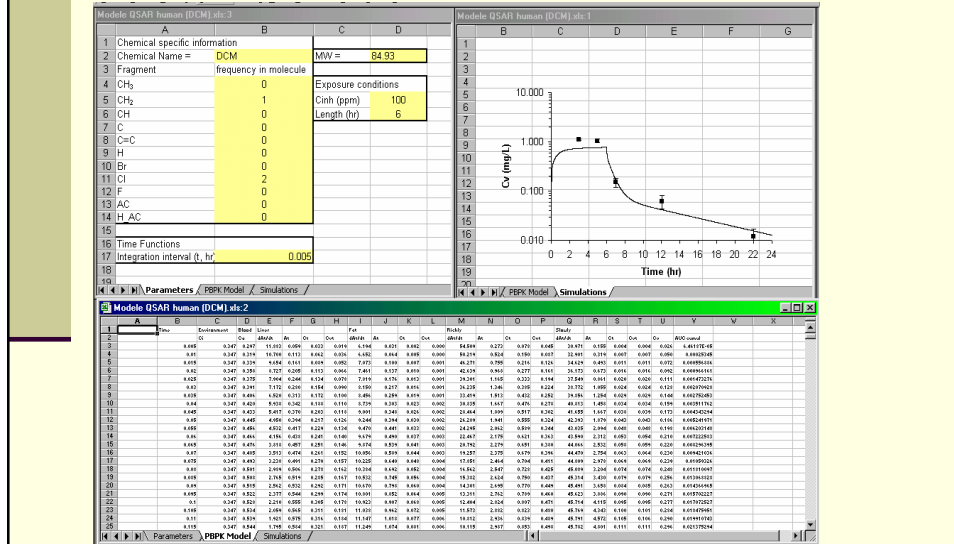
**Exposure Condition**  
**Structure Input @Chemical**

**Yellow Indicates User Input**

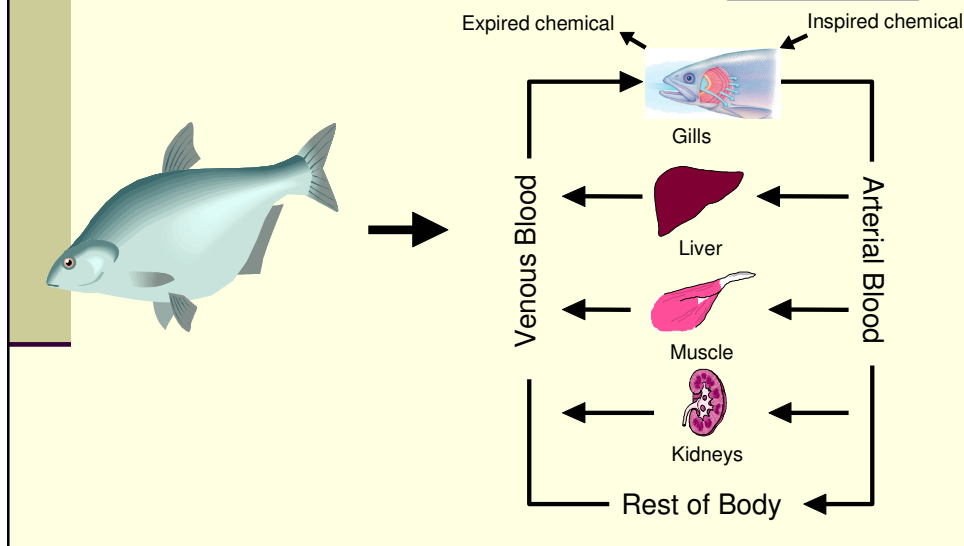
## QSAR/PBPK model – Ethyl benzene

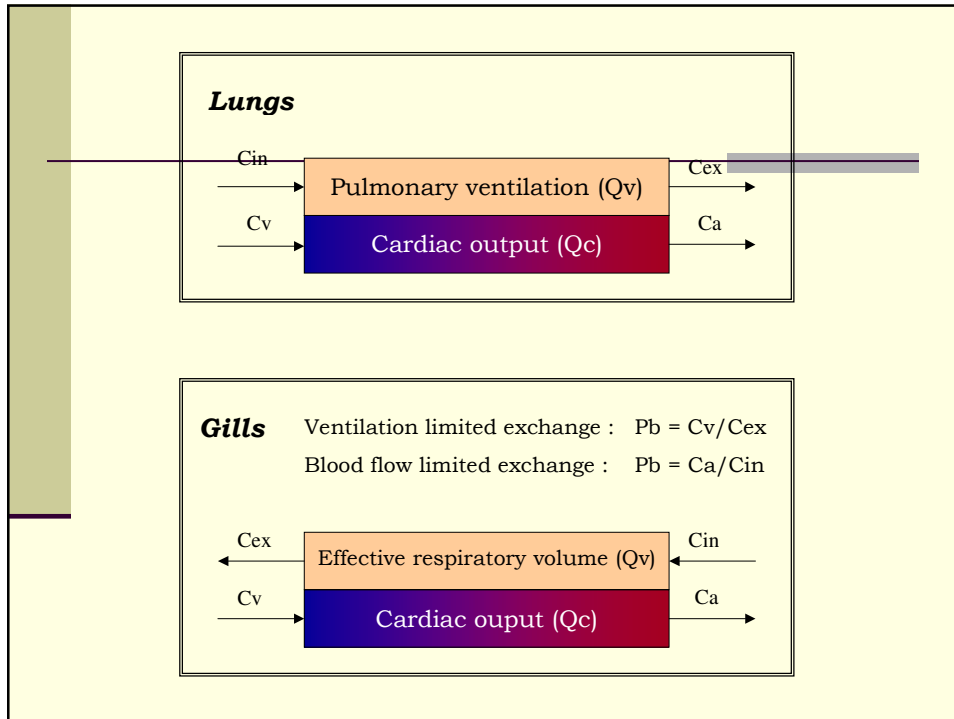


# QSAR/PBPK model: Dichloromethane



# Conceptual Representation





## Partition Coefficients

- Tissue:water PCs
- Determinants of bioconcentration factors
- May vary between species (rat vs fish), if the composition of tissues change from one species to another
- Tissue components: lipids, water, proteins
- Lipids (neutral, phospho) + water

## Tissue composition based Computation of PCs

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$$P_{t:e} = P_{o:e} (F_{nt} + 0.3 F_{pt}) + (F_{wt} + 0.7 F_{pt})$$

P<sub>o:e</sub> = *n*-octanol:env partition coefficient

P<sub>t:e</sub> = tissue:env partition coefficient

F<sub>nt</sub> = volume fraction of neutral lipids in tissue

F<sub>pt</sub> = volume fraction of phospholipids in tissue

F<sub>wt</sub> = volume fraction of water in tissue

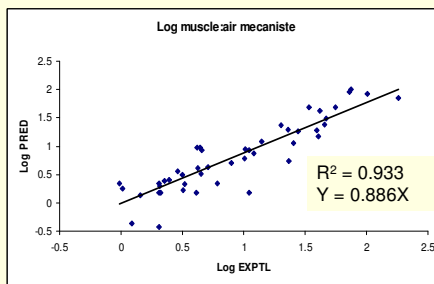
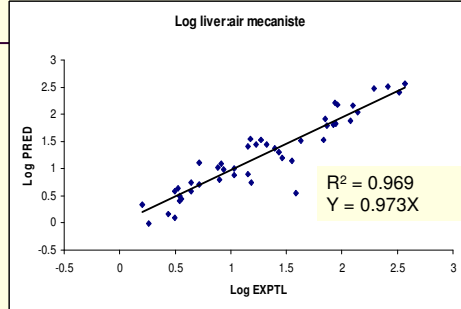
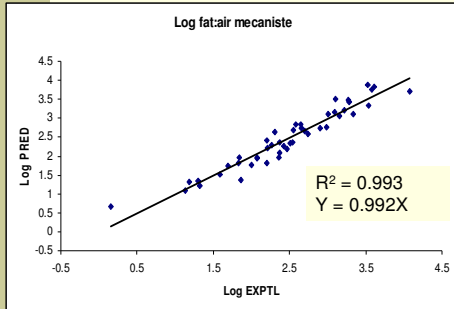
## Interspecies differences in mechanistic determinants (PCs)

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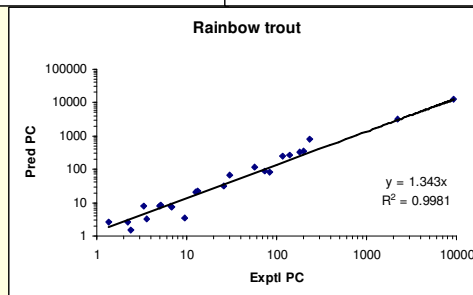
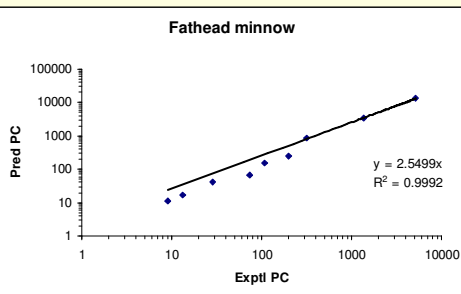
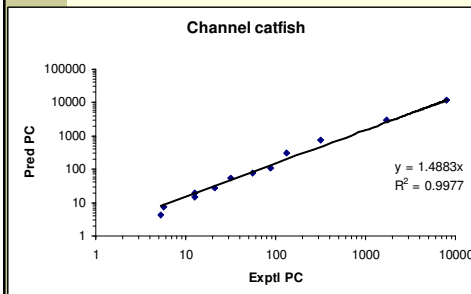
Tissue and species	Neutral lipid eqvt	Water eqvt
Muscle		
Rat	0.0117	0.7471
Human	0.0378	0.7573
Catfish	0.0041	0.7960
FHM	0.0194	0.8116
Trout	0.0244	0.7746



## Interspecies extrapolation of tissue:air partition coefficients (Humans)



## Interspecies extrapolation of tissue:air partition coefficients (Fish)



## Application (chloroethane)

H	H	
H C	C	CL
H	H	

$$\text{Log } P_{oa} = 0.373 + 0.433 + 0.785 = 1.6$$

$$\text{Log } P_{wa} = -0.031 - 0.225 + 0.471 = 0.215$$

$$\text{Rat } P_{la} = 0.0425 * 10^{1.6} + 0.7176 * 10^{0.215} = 2.87$$

$$\text{Trout } P_{la} = 0.0261 * 10^{1.6} + 0.7649 * 10^{0.215} = 2.29$$

## Magnitude of Interspecies Differences in Tissue:Water PCs

$$P_{t:w} \text{ A/B} = \frac{P_{o:w} (AF_{nt} + 0.3AF_{pt}) + (AF_{wt} + 0.7AF_{pt})}{P_{o:w} (BF_{nt} + 0.3BF_{pt}) + (BF_{wt} + 0.7BF_{pt})}$$

$P_{o:w}$  = *n*-octanol:water partition coefficient

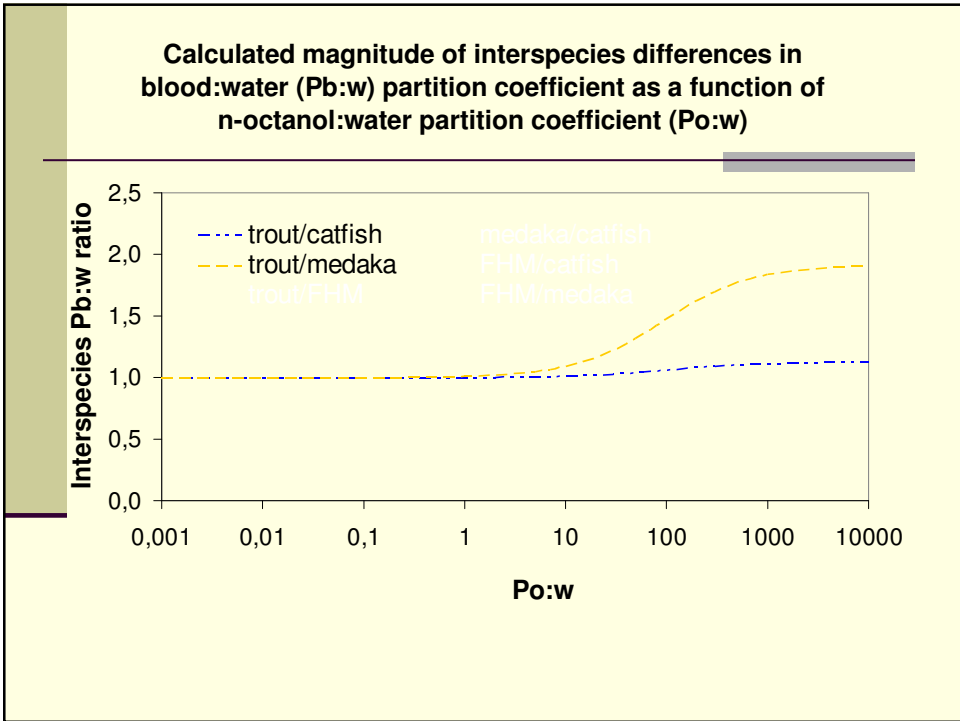
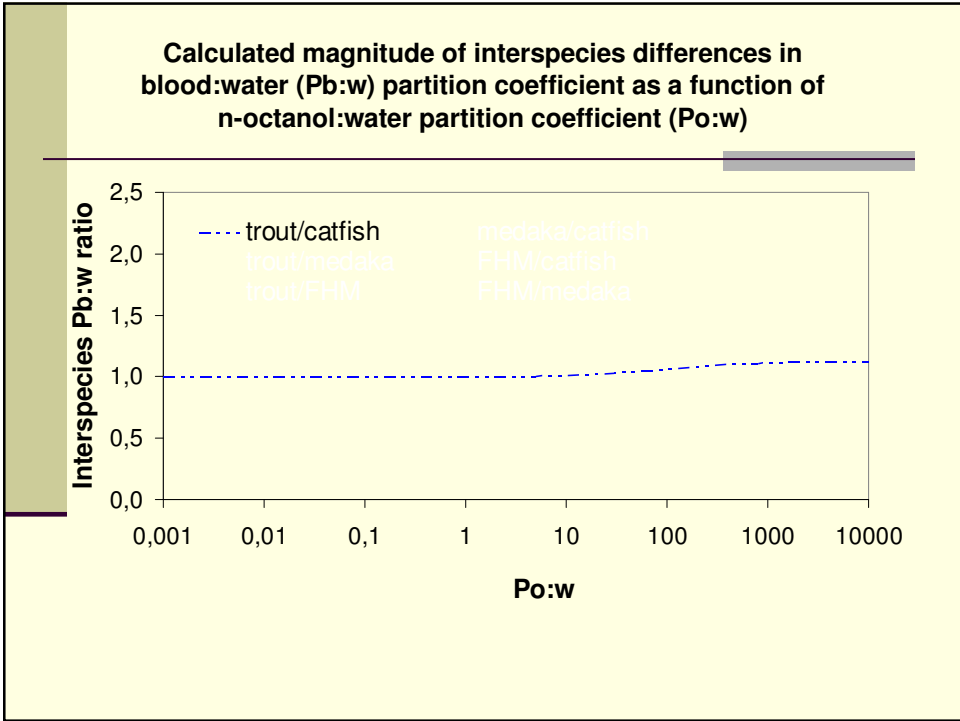
$P_{t:a}$  = tissue:water partition coefficient

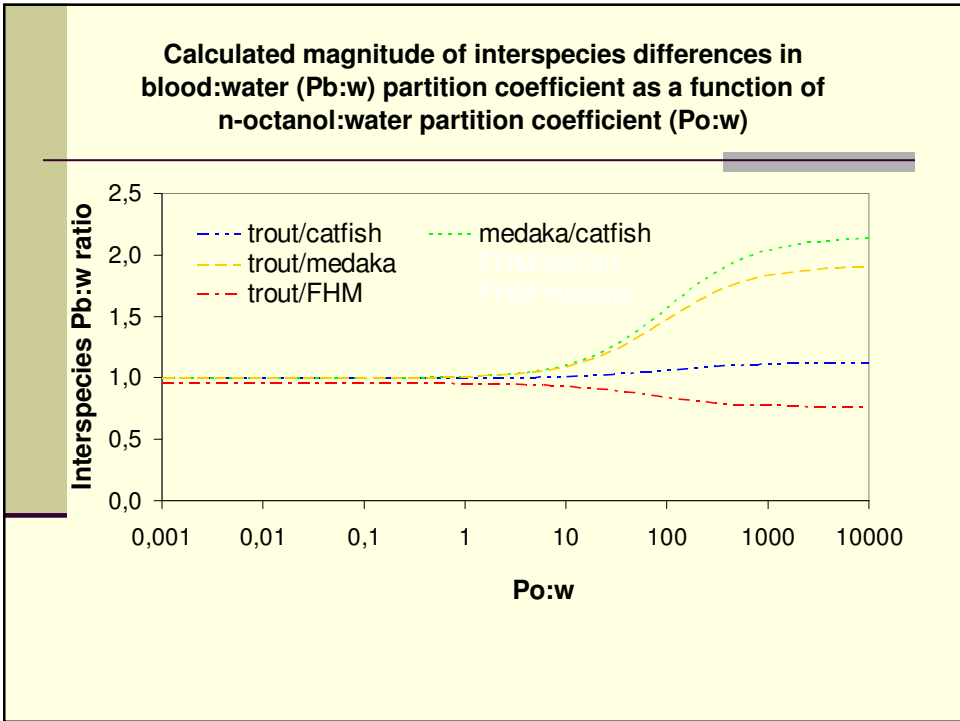
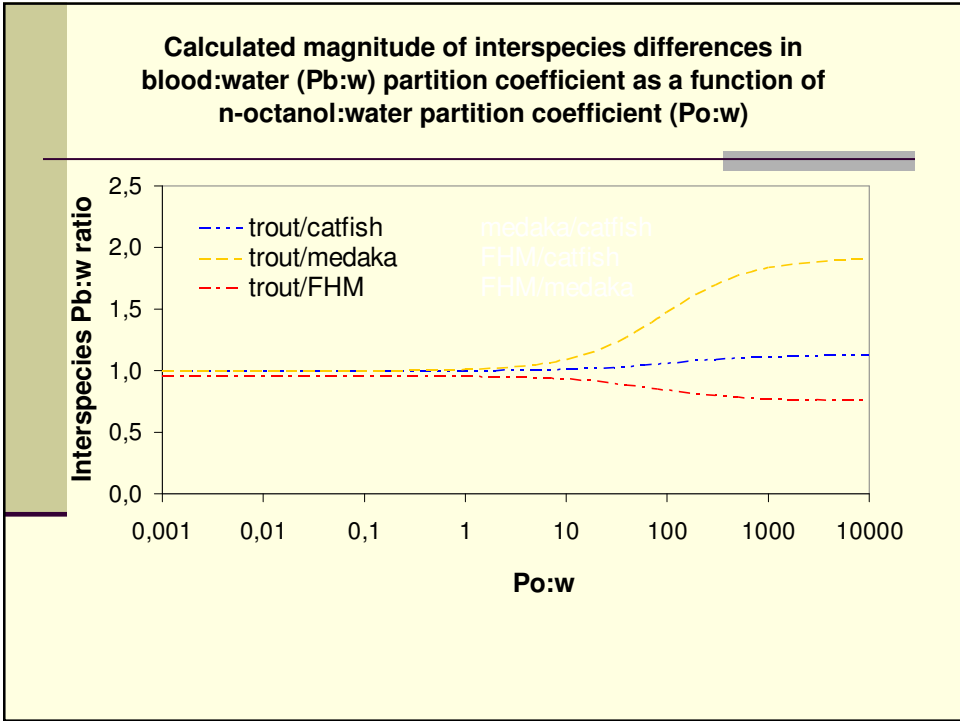
$F_{nt}$  = volume fraction of neutral lipids in tissue

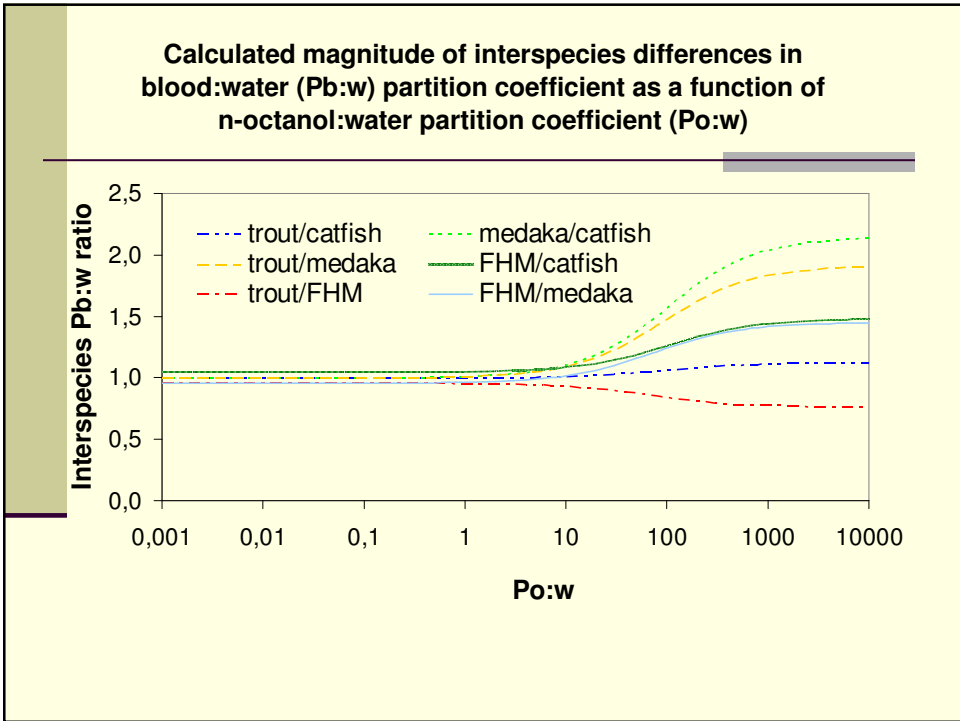
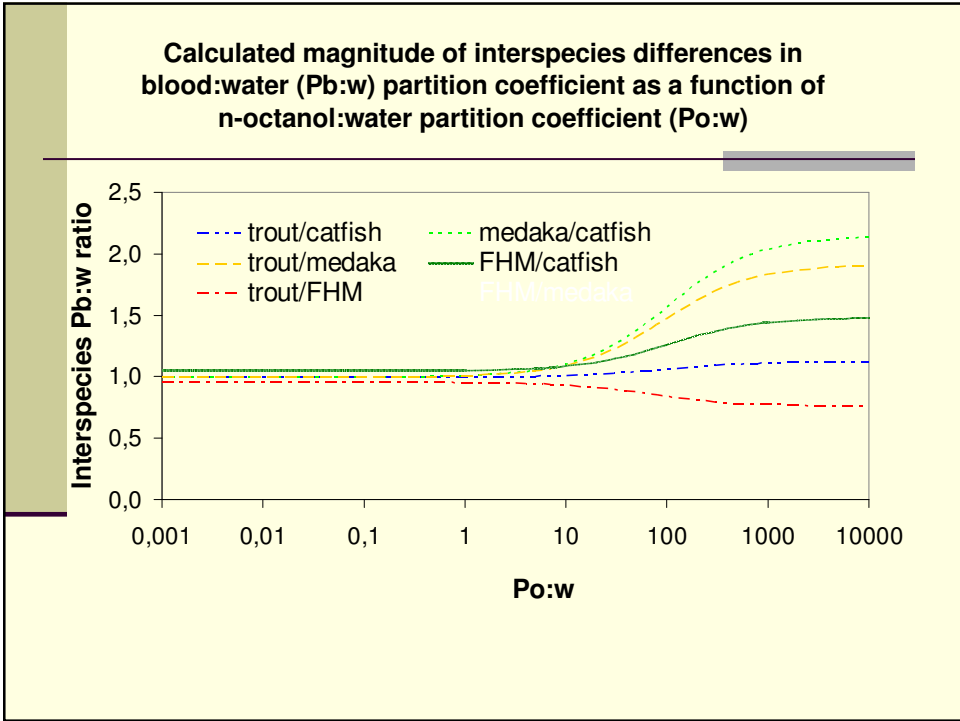
$F_{pt}$  = volume fraction of phospholipids in tissue

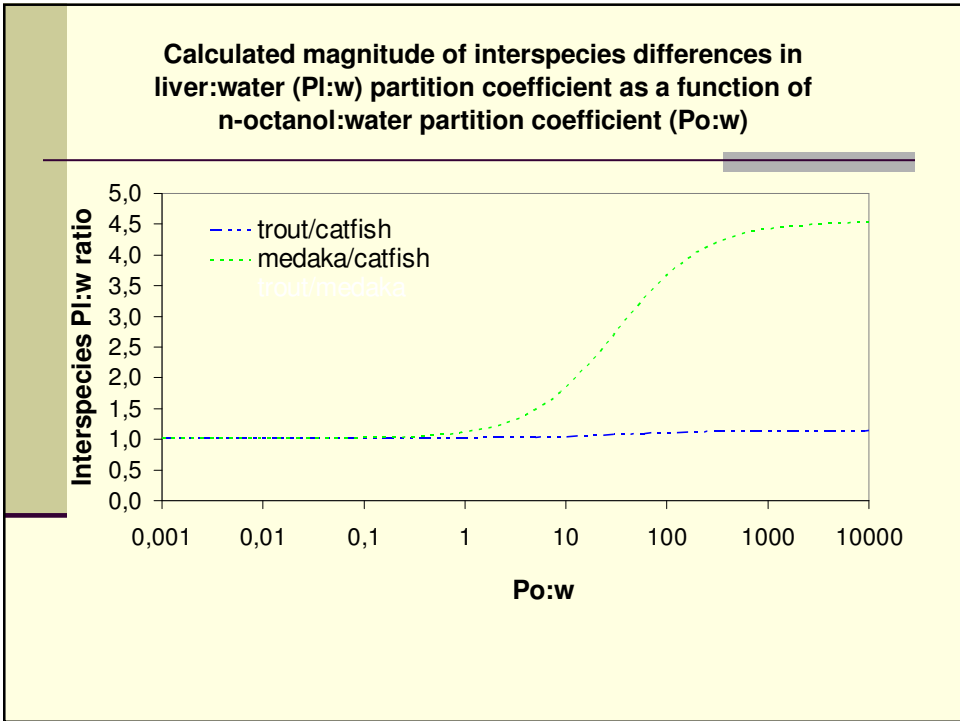
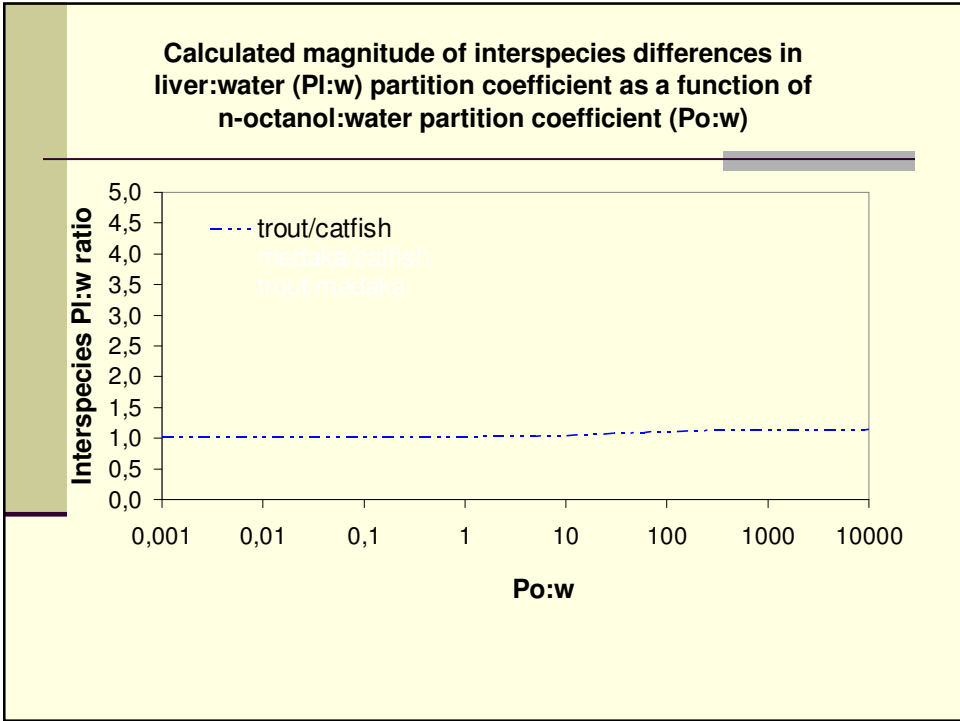
$F_{wt}$  = volume fraction of water in tissue

A & B = two different species

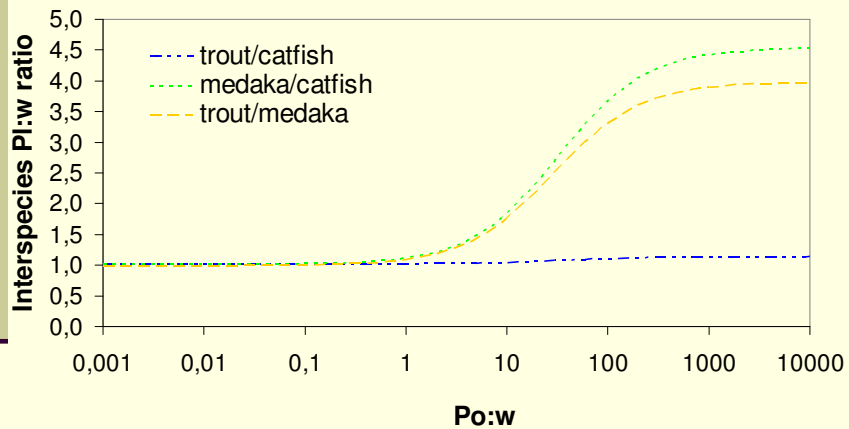








Calculated magnitude of interspecies differences in liver:water (Pl:w) partition coefficient as a function of n-octanol:water partition coefficient (Po:w)



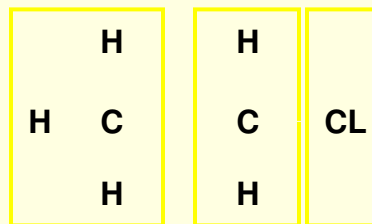
Interspecies extrapolation of metabolism constants

- Vmax in one species
- Allometrically scale to another species
- Assume Km to be species invariant
- Worked well for CYP2E1 substrates

## Structure-Metabolic Constants Relationship Modeling

Structural feature	Log V <sub>maxc</sub>	Log K <sub>m</sub>
AC	.734	.382
CL	.612	.569
BR	.810	.296
H (on C=C)	.453	.584
CH3	.795	7.08E-2
CH2	.269	-.320
CH	-.211	-.845
C	-1.451	-1.544
C=C	-.353	-2.07
R2	0.947	0.752
PRESS/SSY	0.10	0.89

## Application (chloroethane)



$$\text{Log } K_m = 0.071 - 0.32 + 0.569 = 0.26 \text{ vs } 0.19 \mu\text{M}$$

$$\text{Log } V_{maxc} = 0.795 + 0.269 + 0.612 = 1.676 \text{ vs } 1.79$$

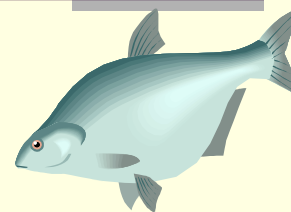
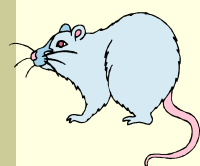
$$10^{1.68} * BW^{0.7} \begin{cases} \rightarrow \text{Human (BW=70 kg)} = 937 \mu\text{mol/hr} \\ \rightarrow \text{Rat (BW=0.25 kg)} = 18.1 \mu\text{mol/hr} \end{cases}$$



## Interspecies extrapolation of metabolism constants

- Turnover rate for one species
- CYP concentration + tissue volume
- Interspecies extrapolation of  $V_{max}$ ...
- Current approach:
  - Classification of substrates (molecular volume, log P)
  - Isozyme-specific substrates ( in vitro QSARs)
  - Species extrapolation based on protein [C] and tissue volume

## Interspecies extrapolation of PK of organic chemicals



### Species SPECIFIC:

- Fluid PCs
- Flows
- Volumes
- Enzyme [C]

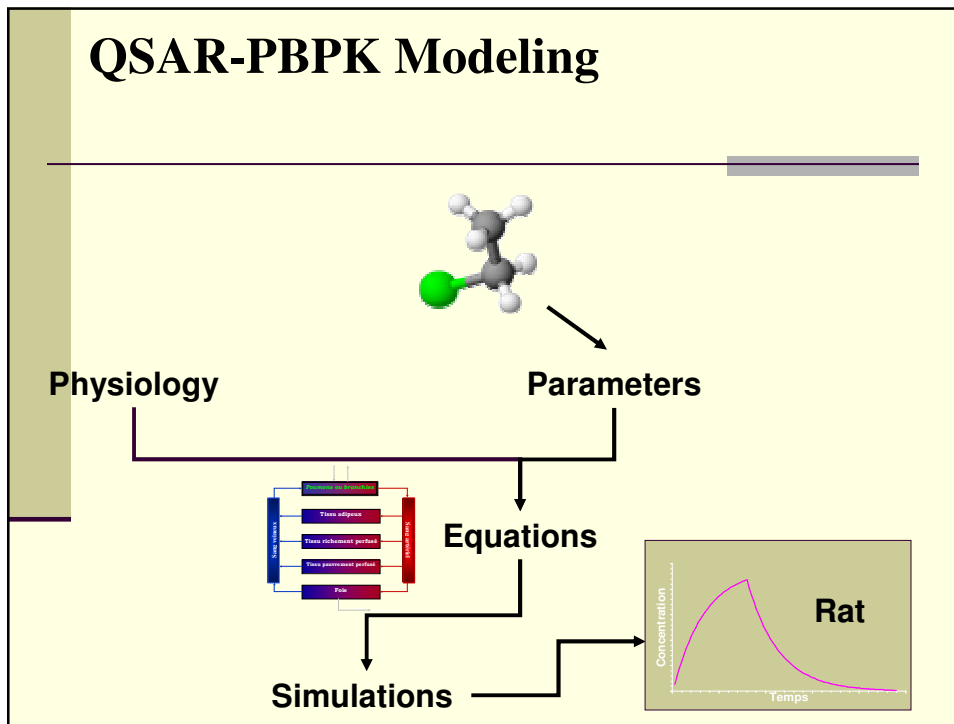
### INVARIANT:

- $V_{max_c}$
- $K_m$

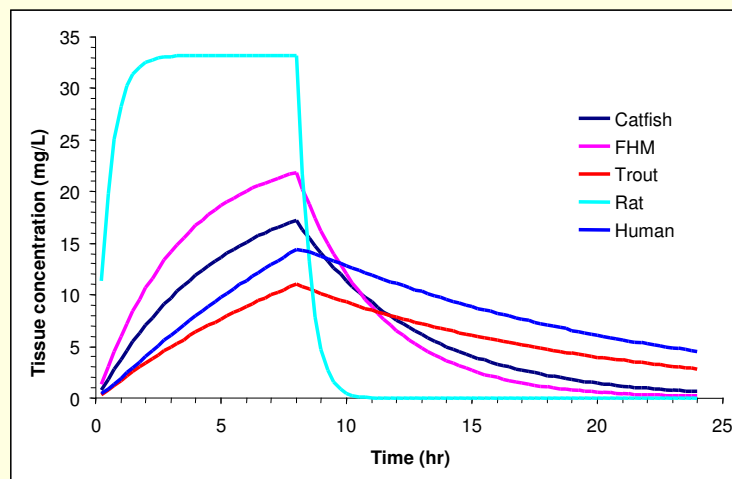
### Species SPECIFIC:

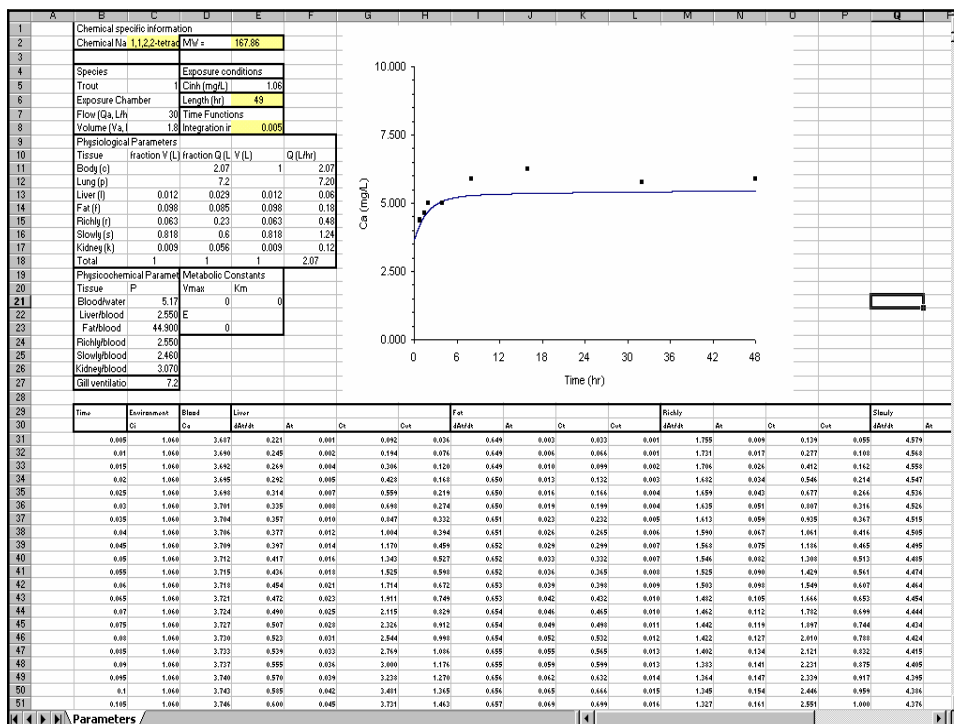
- Blood:air PC
- Flows
- Volumes
- Enzyme [C]

# QSAR-PBPK Modeling

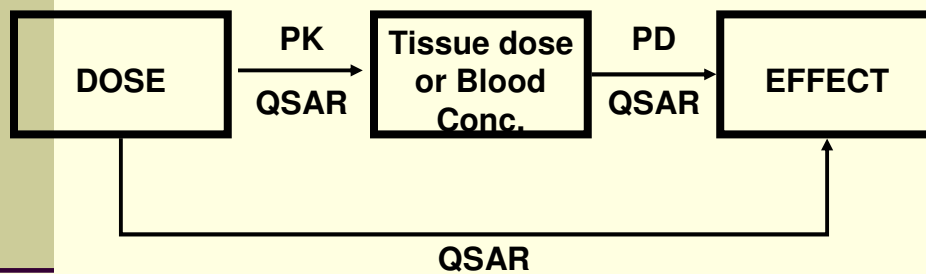


# QSPR-PBPK Modeling: Interspecies extrapolation of tissue concentrations





## QSARs – An alternative paradigm



- Relative contribution of the TK and TD processes
- Extrapolations based on TK determinants

## Conclusions

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- Interspecies differences in metabolic clearance and volume of distribution can be examined using mechanism-based QSARs
- PBPK modeling uniquely allows the integration of such QSARs to simulate interspecies differences in PK profiles
- QSAR-PBPK models facilitate internal dose based risk assessment in multiple species (lethal and non-lethal effects)



Frågor ?