Species extrapolation with PBPK models

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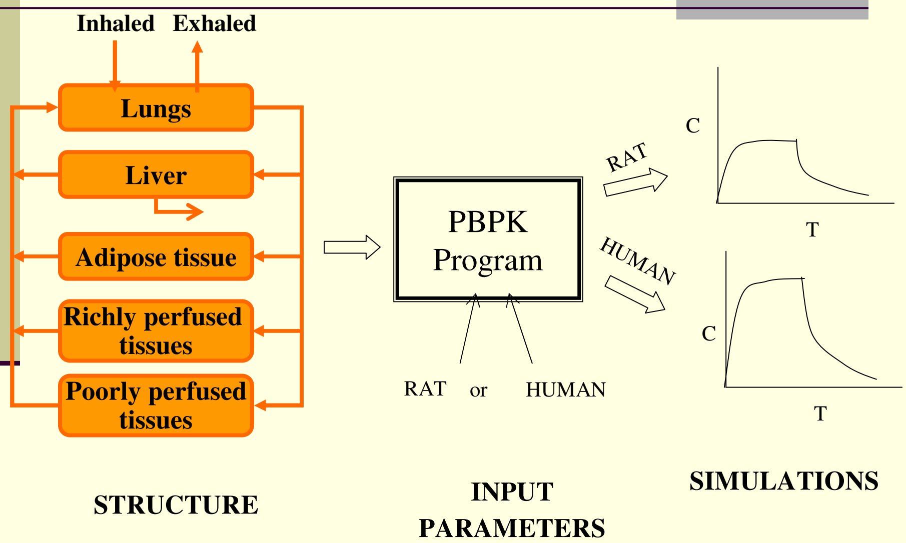
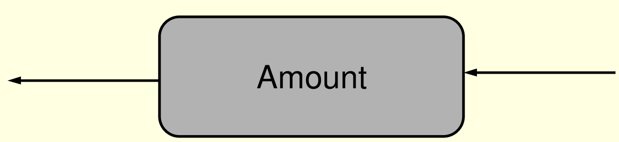
Outline

- 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

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

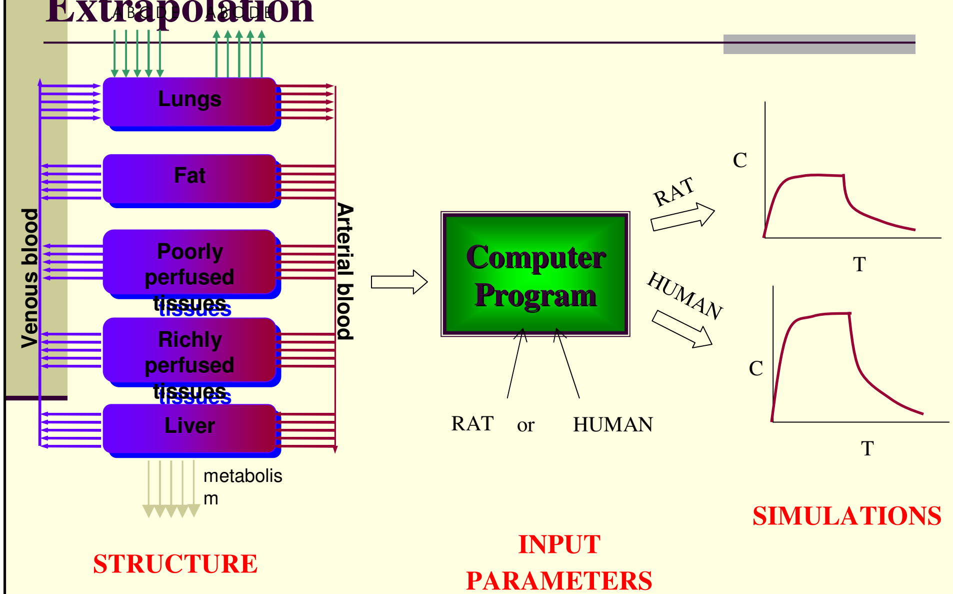
V_{max} = maximum velocity of metabolism
K_m = Michaelis-Menten constant
C = concentration of chemical

Metabolizing enzyme, its levels, tissue volume

Interspecies extrapolation of PK of chemicals

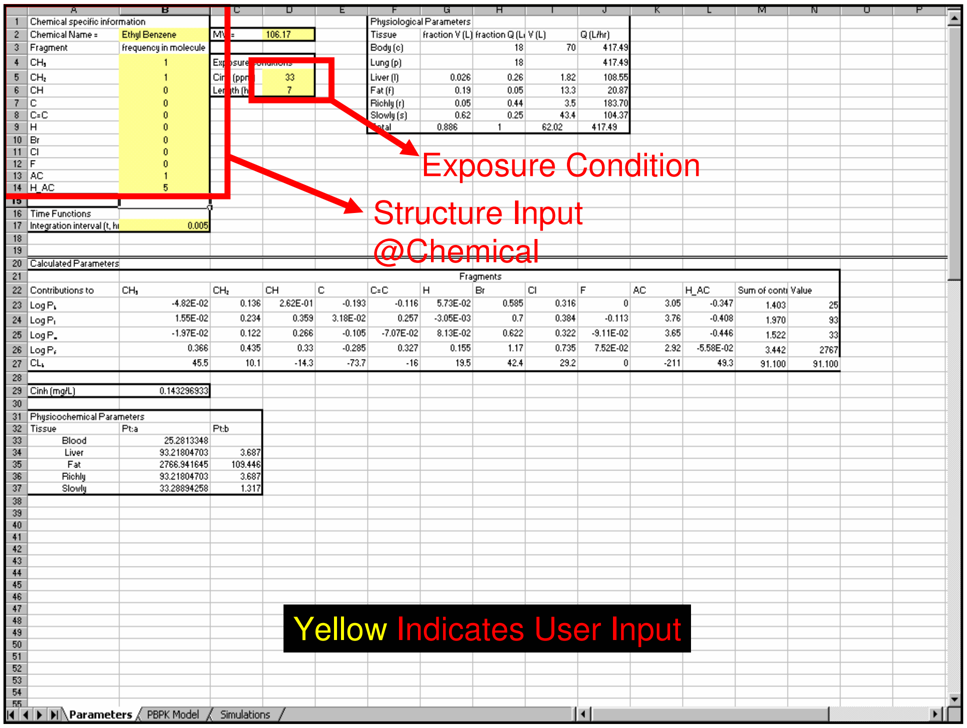
Species SPECIFIC:	INVARIANT:	Species SPECIFIC:
➢Blood:air PC	➢$Vmax_c$	➢Blood:air PC
➢Flows	➢Km	➢Flows
➢Volumes	➢Tissue:air PC	➢Volumes
➢[P-450]		➢[P-450]

Mixture PBPK Models and Interspecies Extrapolation

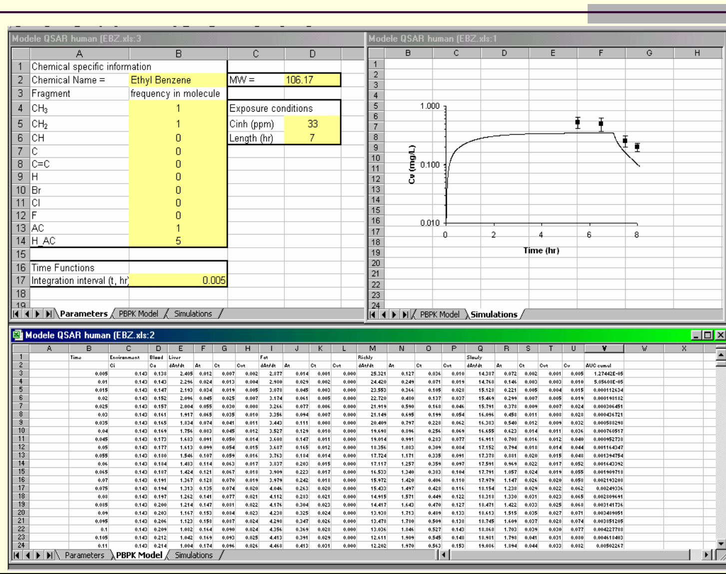


QSARs for PBPK Parameters

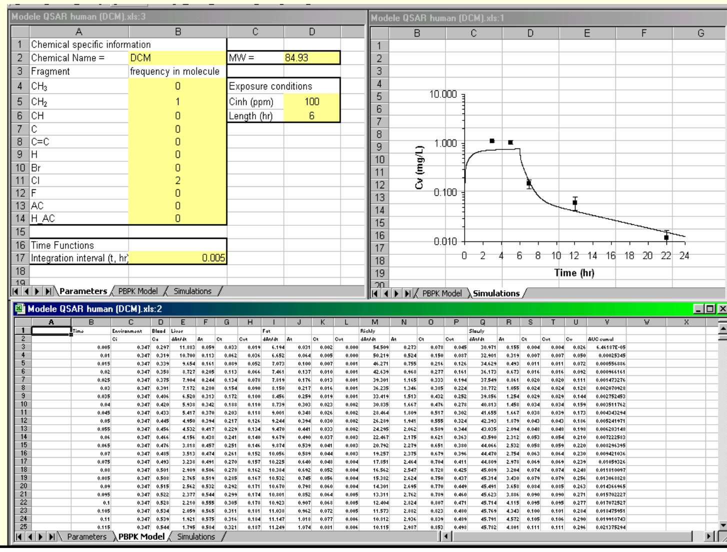
- Fragment constant approach
  - $P_{pbpk} = \Sigma n_f \cdot C_f$
- Multilinear regression (SPSS®)
- 46 VOCs, Fragments: CH_3, CH_2, CH, C, C=C, H, Cl, Br, F, B-ring, 2 E1 substrates
- Cross-validation, external validation



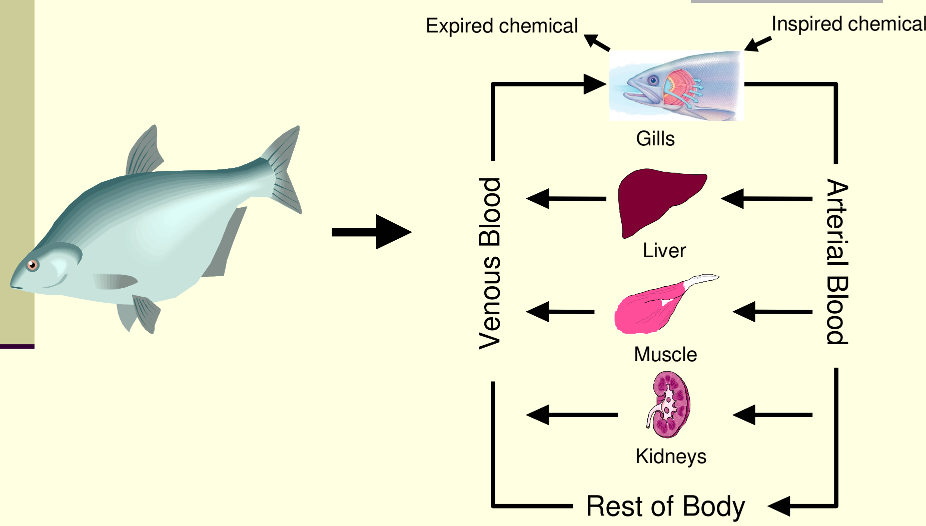
QSAR/PBPK model – Ethyl benzene

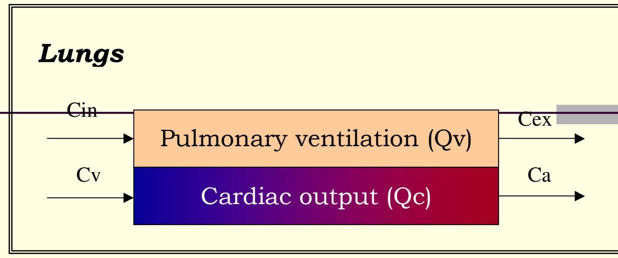


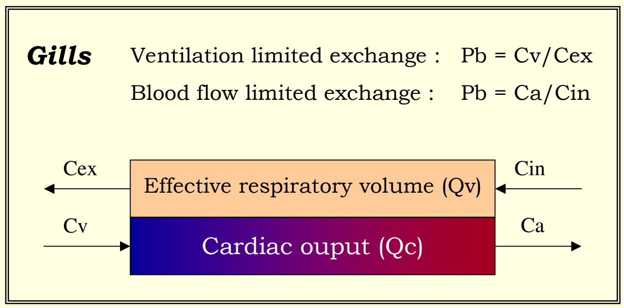
QSAR/PBPK model:Dichloromethane



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

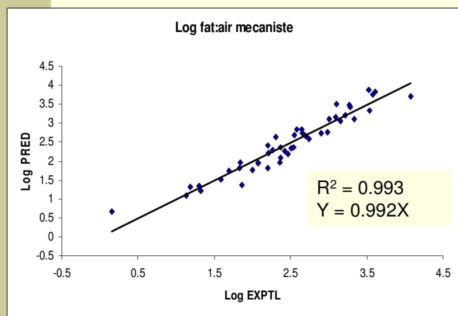
$$P_{t:e} = P_{o:e}\left(F_{nt} + 0.3\,F_{pt}\right) + \left(F_{wt} + 0.7\,F_{pt}\right)$$

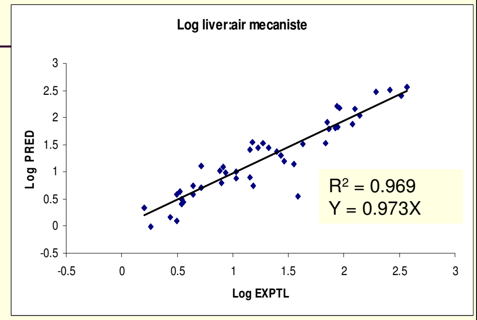
Po:e = *n*-octanol:env partition coefficient
Pt:e = tissue:env partition coefficient
Fnt = volume fraction of neutral lipids in tissue
Fpt = volume fraction of phospholipids in tissue
Fwt = volume fraction of water in tissue

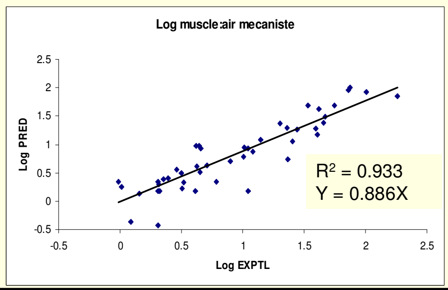
Interspecies differences in mechanistic determinants (PCs)

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

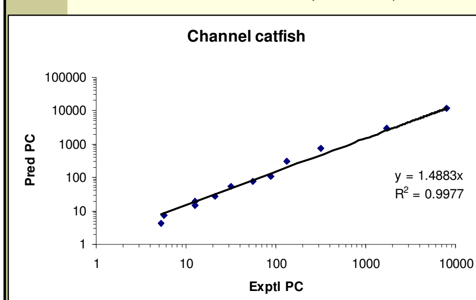
Interspecies extrapolation of tissue:air partition coefficients (Humans)

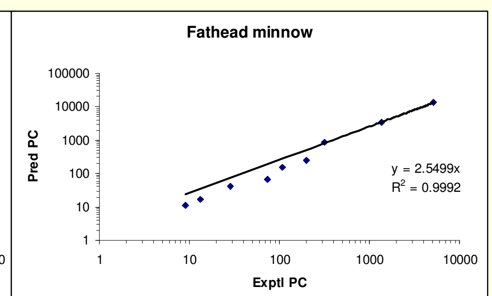


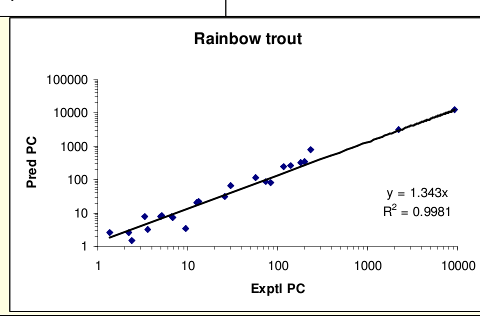




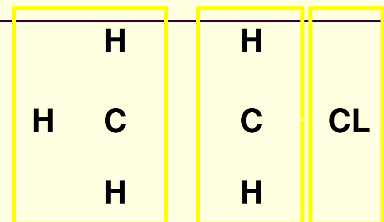
Interspecies extrapolation of tissue:air partition coefficients (Fish)







Application (chloroethane)



Log Poa = 0.373+0.433 +0.785 = 1.6
Log Pwa = -0.031 -0.225 +0.471 = 0.215

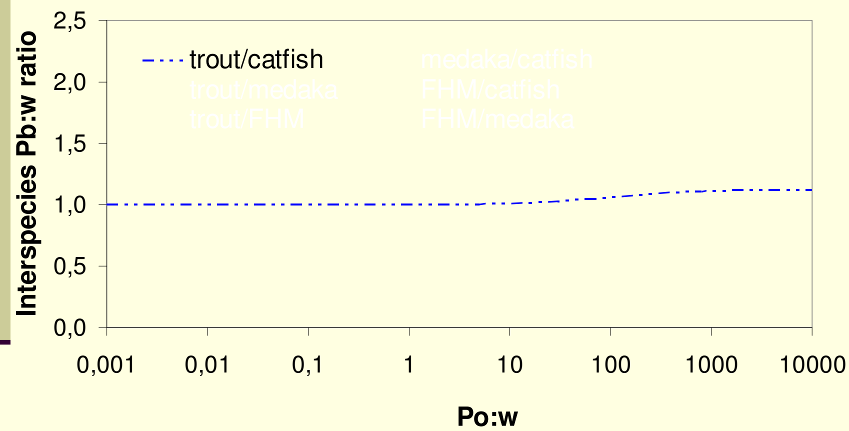
Rat Pla	**0.0425**	**$*10^{1.6}$**	**+**	**0.7176 $*10^{0.215}$**	**= 2.87**
Trout Pla	**0.0261**	**$*10^{1.6}$**	**+**	**0.7649 $*10^{0.215}$**	**= 2.29**

Magnitude of Interspecies Differences in Tissue:Water PCs

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

Po :w = *n*-octanol:water partition coefficient
Pt :a = tissue:water partition coefficient
Fnt = volume fraction of neutral lipids in tissue
Fpt = volume fraction of phospholipids in tissue
Fwt = volume fraction of water in tissue
A & B = two differents species

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



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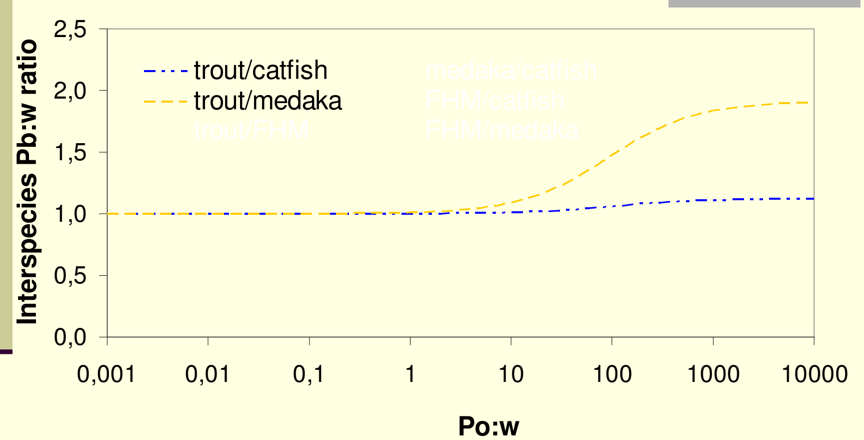

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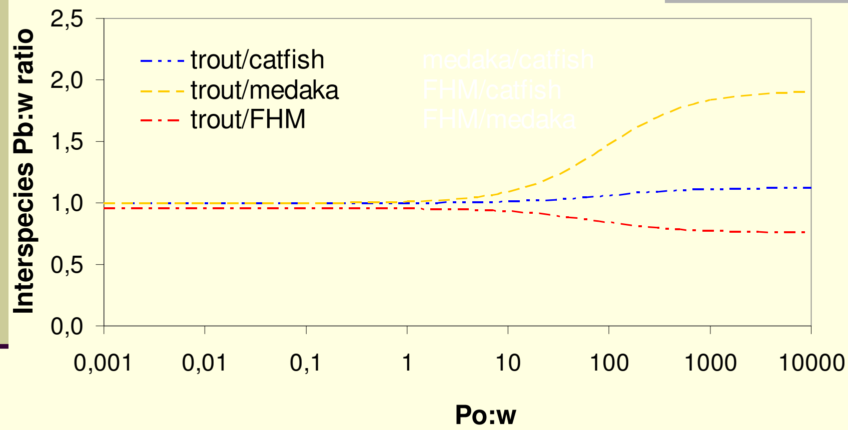

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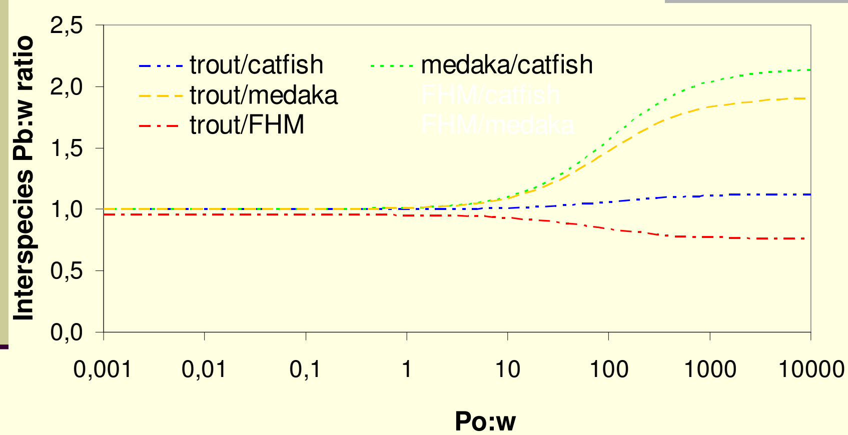

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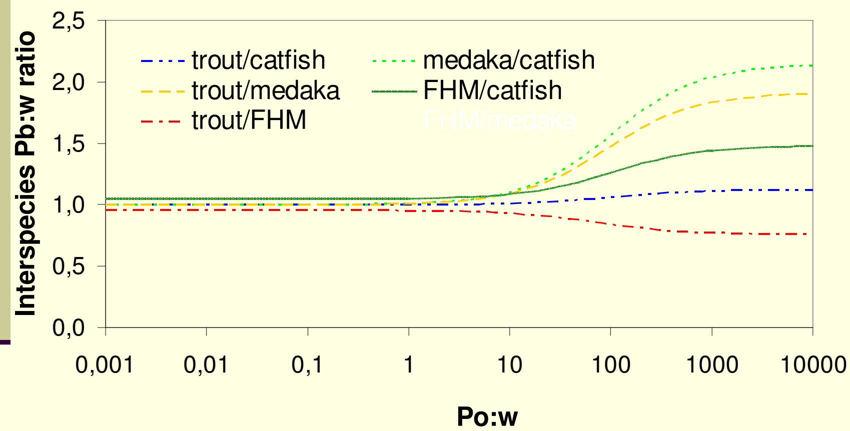

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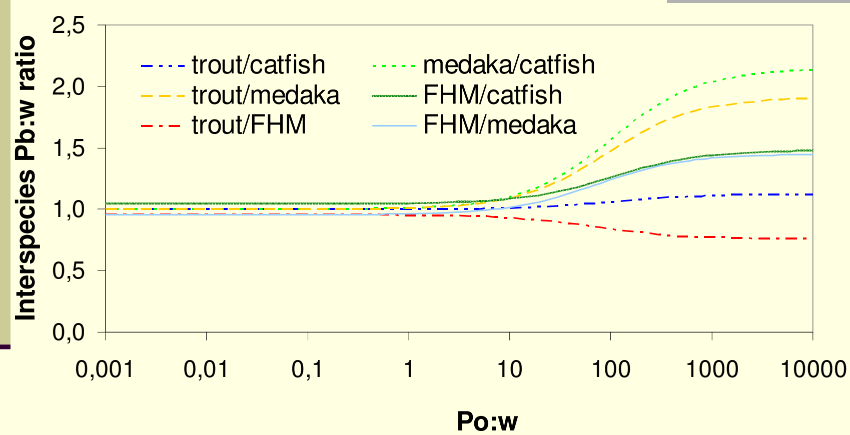
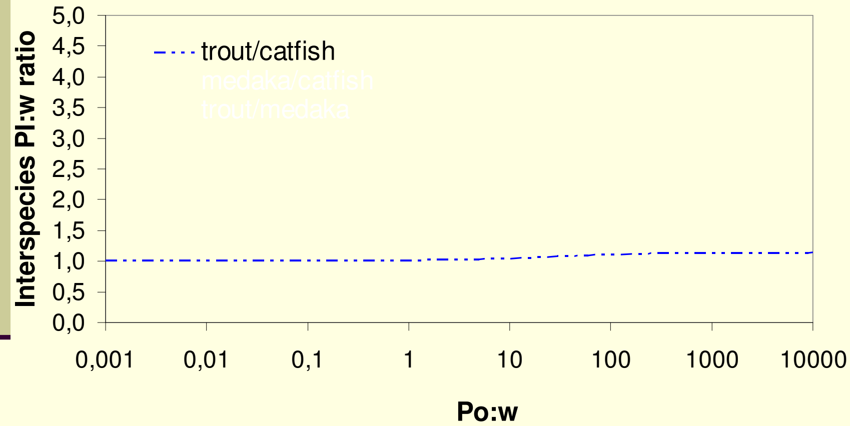
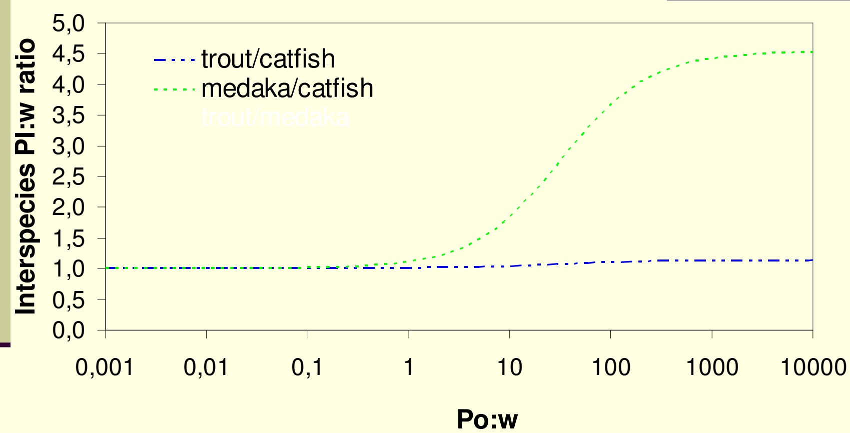


Calculated magnitude of interspecies differences in liver:water (Pl:w) partition coefficient as a function of n-octanol:water partition coefficient (Po:w)



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



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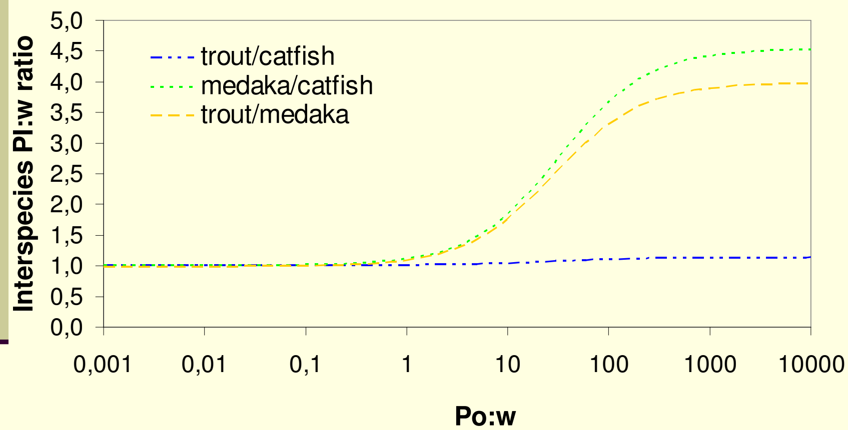


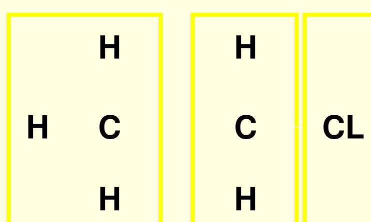
Interspecies extrapolation of metabolism constants

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

Structure-Metabolic Constants Relationship Modeling

Structural feature	Log V_{maxc}	Log K_m
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)



Log Km = 0.071 - 0.32 + 0.569 = 0.26 vs 0.19 µM

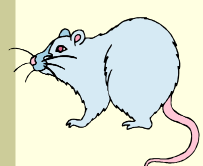
Log Vmaxc = 0.795 + 0.269 + 0.612 = 1.676 vs 1.79

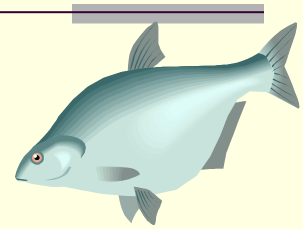
$10^{1.68}$ * $BW^{0.7}$ →
- **Human (BW=70 kg) = 937 µmol/hr**
- **Rat (BW=0.25 kg) = 18.1 µmol/hr**

Interspecies extrapolation of metabolism constants

- Turnover rate for one species
- CYP concentration + tissue volume
- Interspecies extrapolation of Vmax…
- 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]**

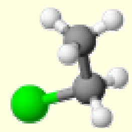
INVARIANT:

- **$Vmax_c$**
- **Km**

Species SPECIFIC:

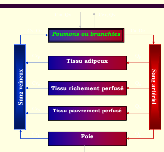
- **Blood:air PC**
- **Flows**
- **Volumes**
- **Enzyme [C]**

QSAR-PBPK Modeling



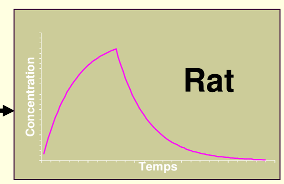
Physiology

Parameters

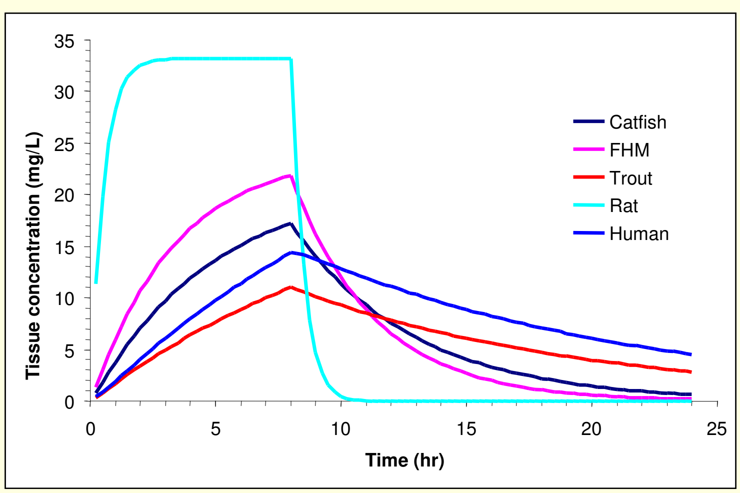


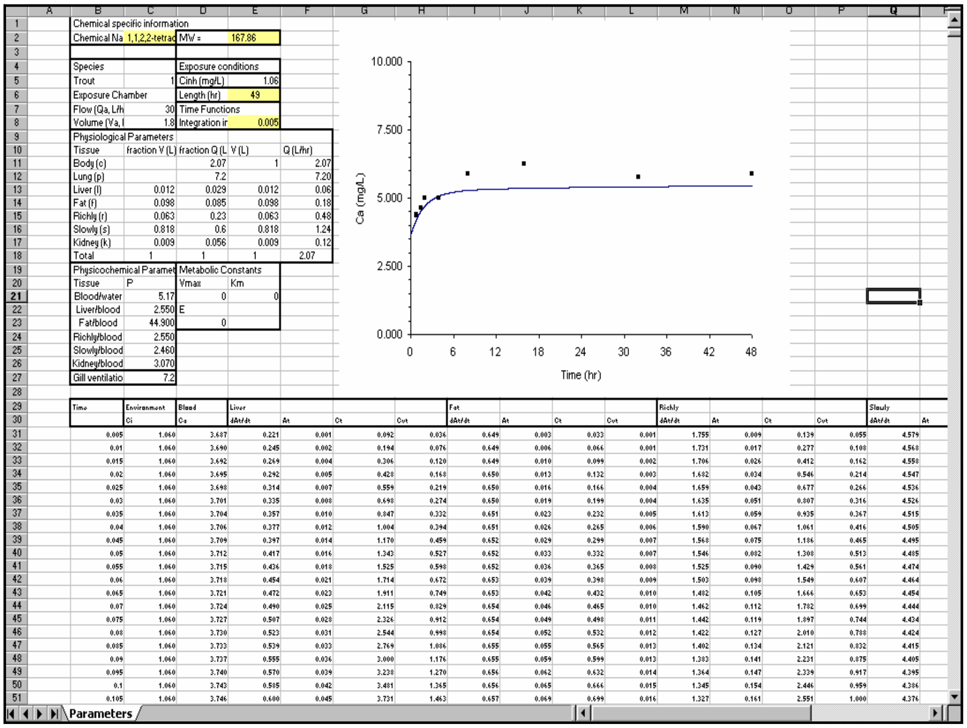
Equations

Simulations

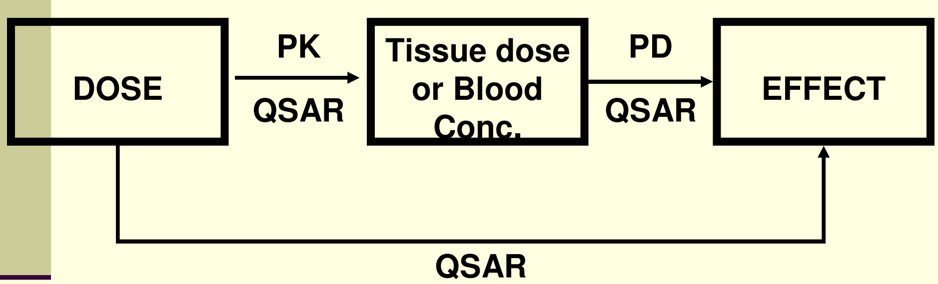


QSPR-PBPK Modeling: Interspecies extrapolation of tissue concentrations





QSARs – An alternative paradigm



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

Conclusions

- 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)