Dose Extrapolation Models

Fish Physiologically Based
Toxicokinetic Models

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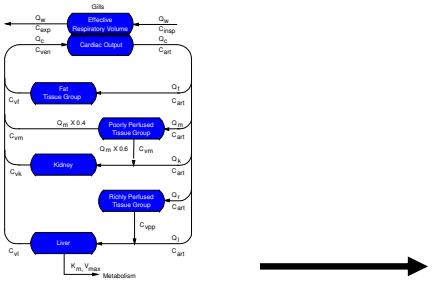
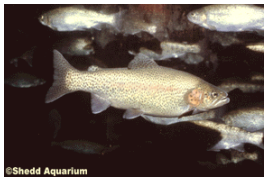
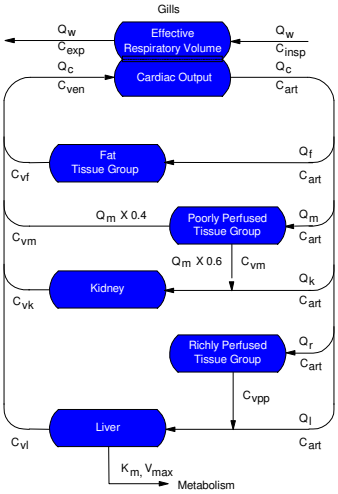
Jim's Question:

"Can fish PBTK models be used to accurately predict uptake, disposition, and elimination of organic chemicals, across routes of uptake and across species? "





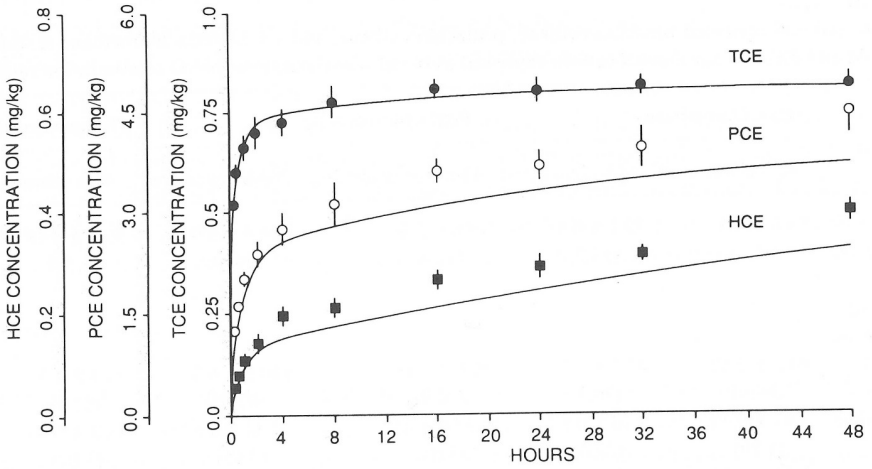


Comparison of Physiological Constants and Chemical Partition Coefficients Used in PB-TK Models for Three Species of Fish.

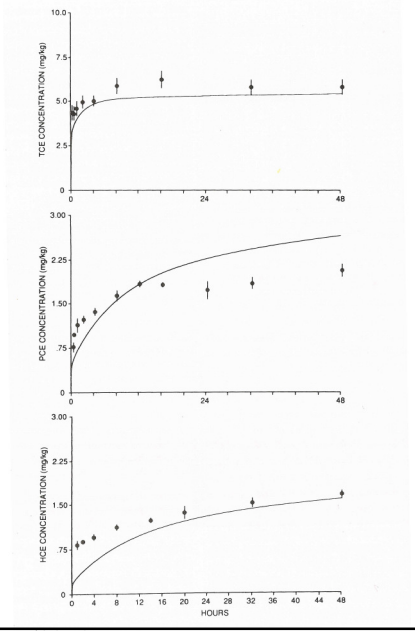
	Channel catfish[a]	Rainbow trout[b]	Lake trout[c]
Ventilation Volume (L/h/kg)	12.8-22.8	10.6	5.8-10.4
Effective Respiratory Volume (L/h/kg)	7.7-13.7	7.2	3.5-6.2
Oxygen Consumption (mg/h/kg)	71.9	63.0	36.0-45.2
Cardiac output (CO) (L/h/kg)	2.5	2.1	0.75
Fat Tissue Volume (% of body wt.)	6.6	9.8	8.1-12.2
Blood Perfusion of Fat (% of CO)	11.2	8.5	8.0-11.2
Blood/Water Partition Coefficient (PCE)	20.8	25.8	5.3-17.8
Fat/Blood Partition Coefficient (PCE)	81.1	85.8	47.2-112.7

[a.] Nichols et al. (1993) [b.] Nichols et al. (1990) [c.] Lien et al. (2001)

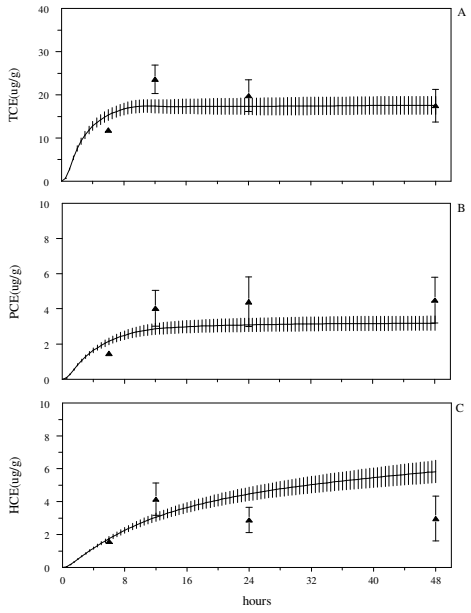
Concentration of three chlorinated ethanes in arterial blood of channel catfish



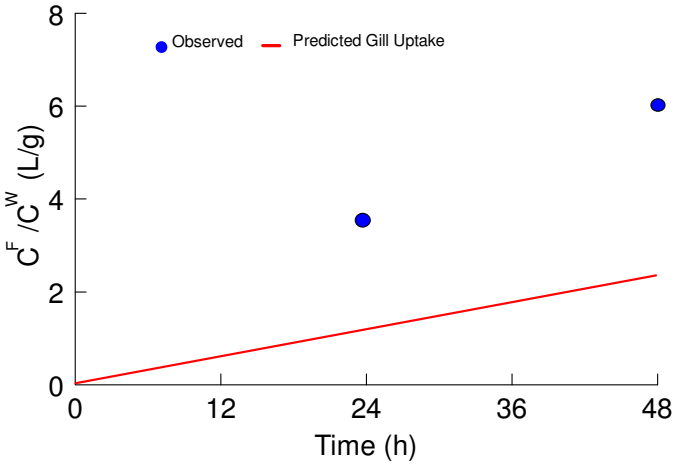
Concentration of three chlorinated ethanes in arterial blood of rainbow trout



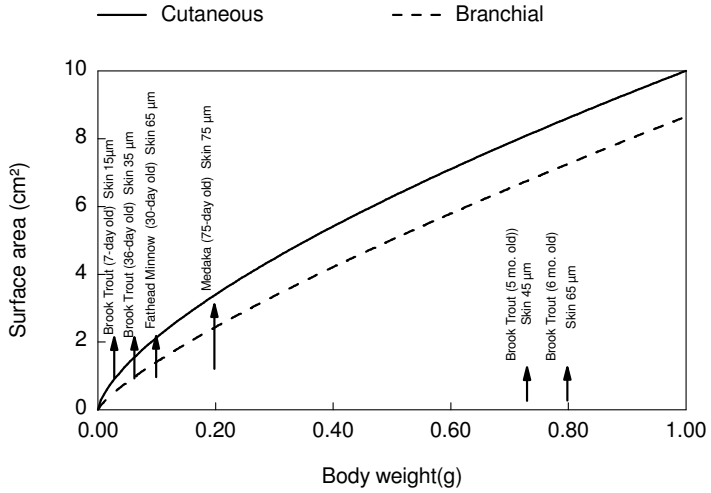
Concentration of three chlorinated ethanes in liver of lake trout



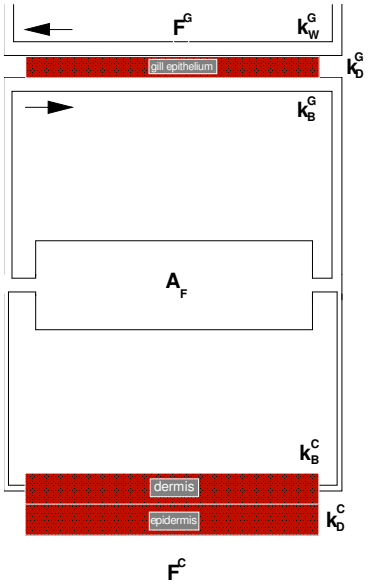
TCB Uptake in Fathead Minnow

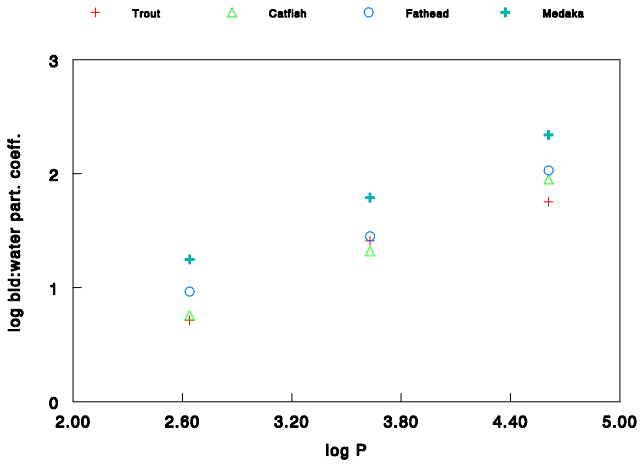


Surface Area as a Function of Body Weight



Bioconcentration model for small fish

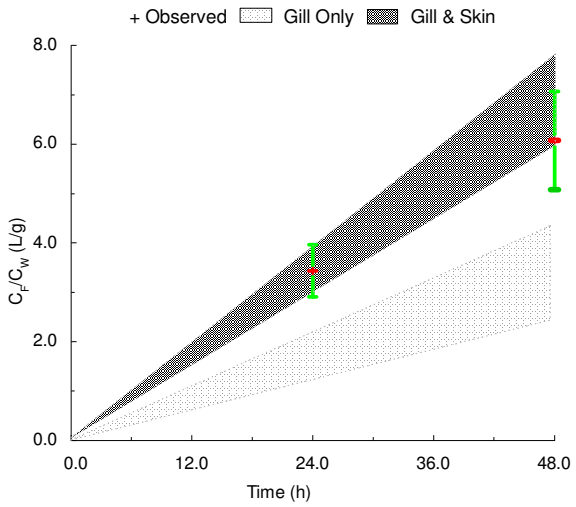


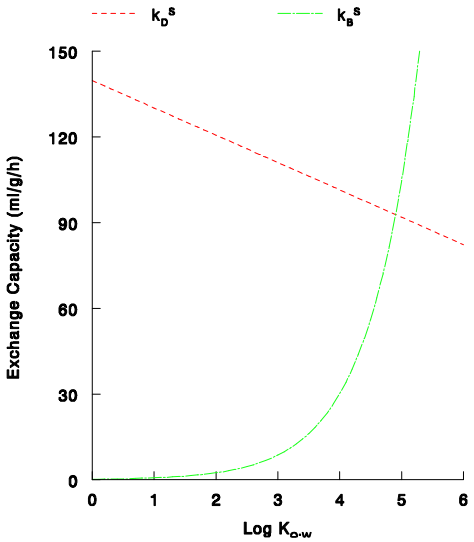


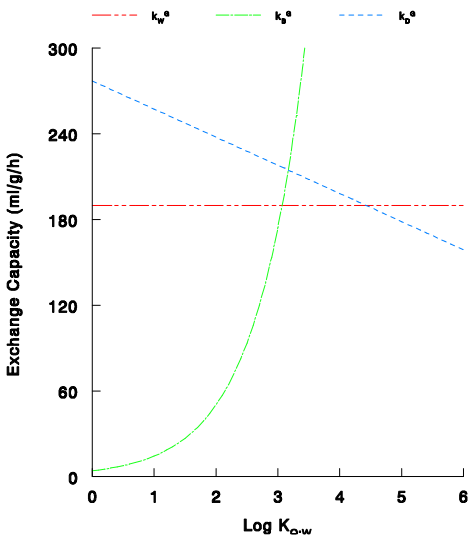
Rate constants (L/h) used to predict branchial and cutaneous uptake of TCB

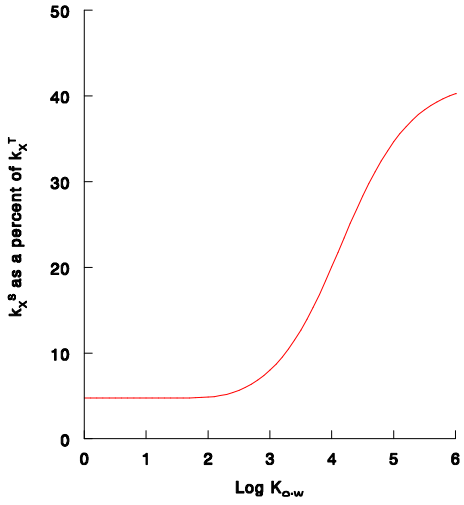
		Fathead minnows	Japanese medaka
Exchange capacity for water to gill	k_W^G	0.007	0.014
Exchange capacity for blood from gill	k_B^G	0.517	2.838
Exchange capacity for blood from skin	k_B^C	0.021	0.114
Exchange capacity for diffusion in gill	k_D^G	0.006[a]–0.026[b]	0.011[a]–0.057[b]
Exchange capacity for diffusion in skin	k_D^C	0.006	0.008
Exchange coefficient for gill uptake	k_X^G	0.004[a]–0.007[b]	0.008[a]–0.013[b]
Exchange coefficient for skin uptake	k_X^C	0.005	0.008
Predicted initial uptake rate constant	k_X^T	0.008[a]–0.011[b]	0.015[a]–0.021[b]

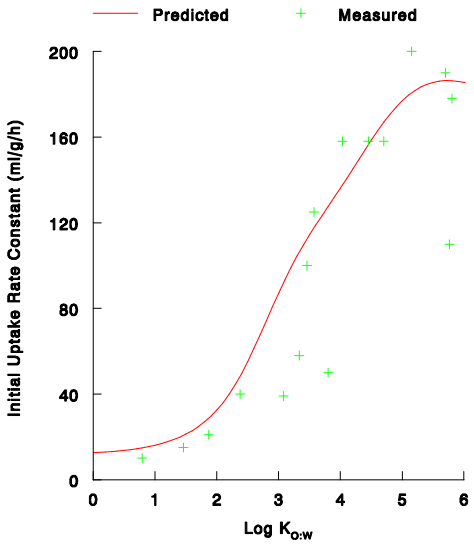
Observed and predicted clearance of TCB by Fathead Minnow



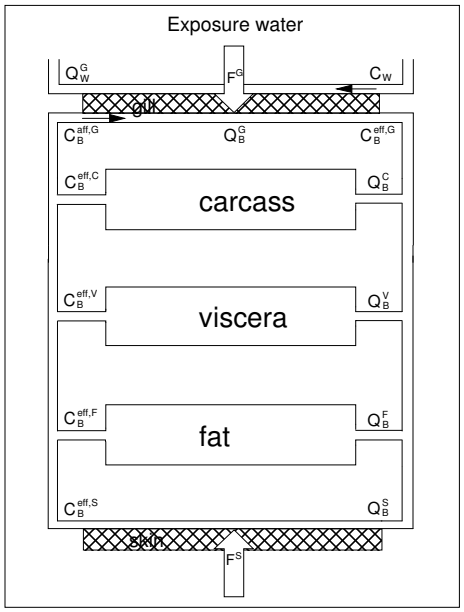



k_w^e
k_s^e
k_b^e
300
240
180
120
60
0
Exchange Capacity (ml/g/h)
0
1
2
3
4
5
6
Log K_{o-w}


50
40
30
20
10
0
k_x^s as a percent of k_x^T
0
1
2
3
4
5
6
Log K_{o-w}



PBTK model for small fish



Physiological Parameters Used to Model the Accumulation of Non-Polar, Non-Metabolized Xenobiotics in Fathead Minnows.

Mean Body Weight (g)	W	0.147
Mean Oxygen Consumption Rate (mg $\cdot h^{-1}$)	VO_2	0.124
Fractional Blood Flow to Carcass Compartment	fQ_B^C	0.400
Fractional Blood Flow to Viscera Compartment	fQ_B^V	0.540
Fractional Blood Flow to Fat Compartment	fQ_B^L	0.010
Fractional Blood Flow to Skin	fQ_B^S	0.050
Fractional Volume of Carcass Compartment	fV^C	0.888
Fractional Volume of Viscera Compartment	fV^V	0.090
Fractional Volume of Fat Compartment	fV^L	0.022

Predicted Rate Constants (mL $\cdot h^{-1}$) for Three Chlorinated Ethanes in 30 day-old Fathead Minnows.

		TCE	PCE	HCE
Exchange Capacity for Water from Gill	k_W^G	21.4	21.4	21.4
Exchange Capacity for Blood from Gill	k_B^G	22.2	71.0	162.3
Exchange Capacity for Diffusion in Gill	k_D^G	24.5	22.6	21.2
Exchange Coefficient for Gill	k_X^G	11.5	13.1	13.1
Exchange Capacity for Blood from Skin	k_B^S	1.1	3.6	8.1
Exchange Capacity for Diffusion in Skin	k_D^S	13.2	12.2	11.4
Exchange Coefficient for Skin	k_X^S	1.1	3.4	6.1
Initial Uptake Rate Constant	k_X^T	12.6	16.5	19.2

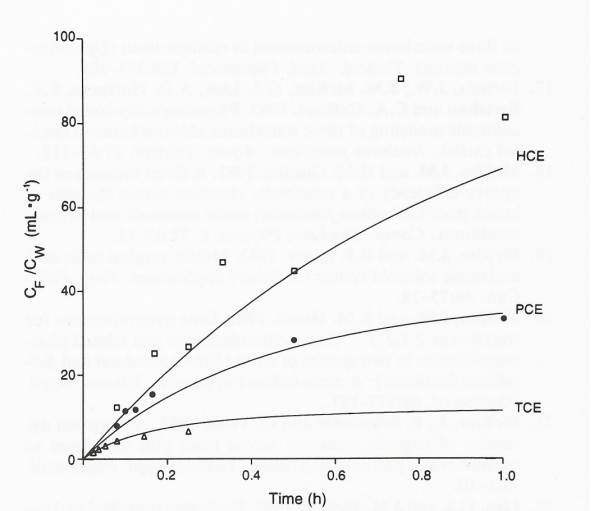
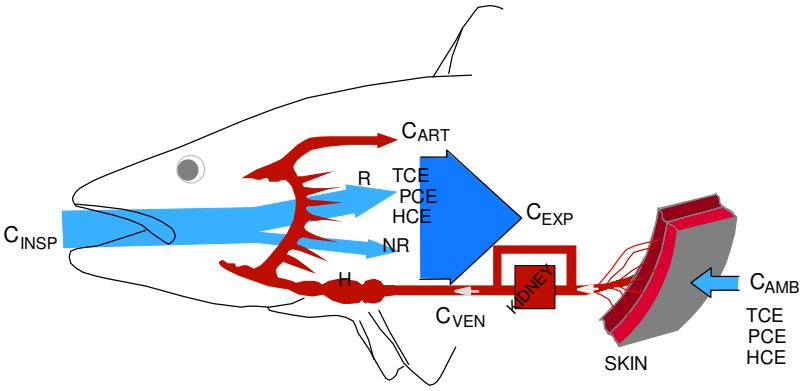
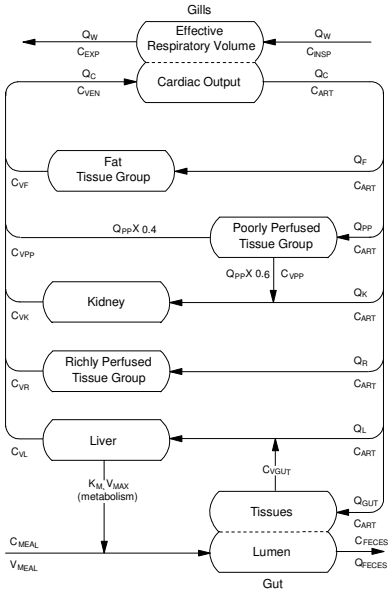
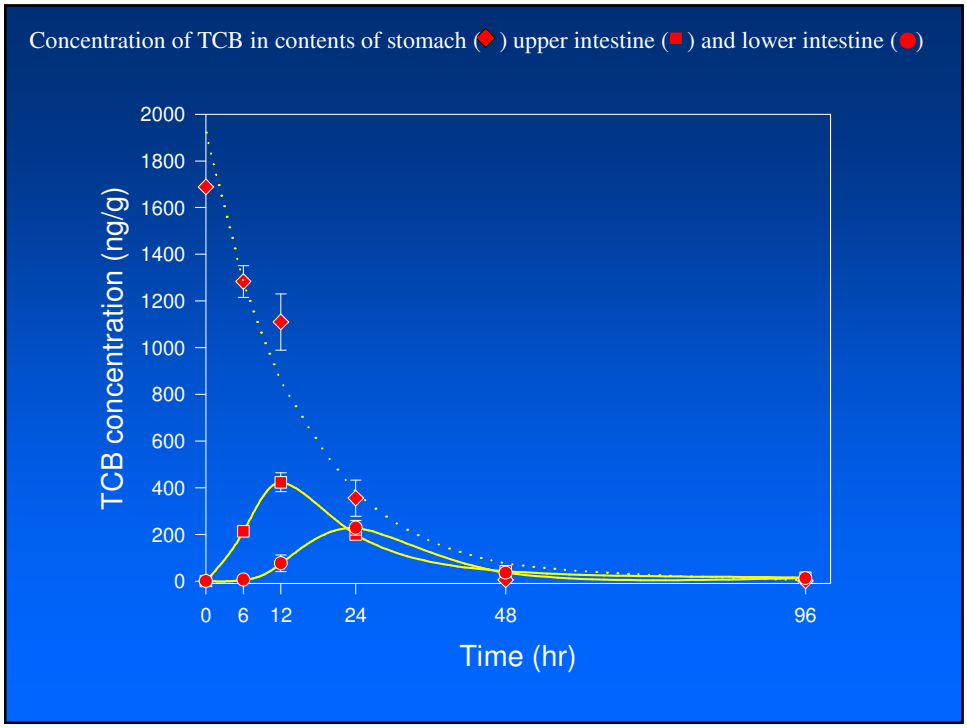


Fig. 4. The observed and predicted accumulations (C_F) of 1,1,2,2-tetrachloroethane (△), pentachloroethane (●), and hexachloroethane (□) normalized for different exposure concentrations (C_w) over time by 30-day-old fathead minnows. Each data point is the mean of duplicate analyses on a composite of 20 fish.



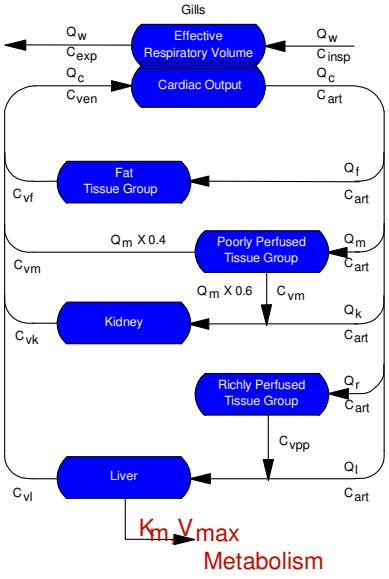
Experiments	$J_S^{0,a}$ μg/hr/kg	$J_{G\,In}^{0,b}$ μg/hr/kg	Dermal flux as % of total
		Rainbow trout	
TCE I	120	9,774	1.2
TCE II	146	11,212	1.3
TCE III	170	10,599	1.6
Mean			1.37
PCE I	37	1,867	1.9
PCE II	343	20,074	1.7
PCE III	291	15,542	1.8
Mean			1.80
HCE I	5.8	390	1.5
HCE II	7.1	572	1.2
HCE III	8.2	565	1.4
Mean			1.37
		Channel catfish	
TCE I	390	13,137	2.9
TCE II	368	13,020	2.7
Mean			2.80
PCE I	87	2,324	3.6
PCE II	100	2,691	3.6
Mean			3.60
HCE I	17.4	485	3.5
HCE II	13.1	424	3.0
Mean			3.25

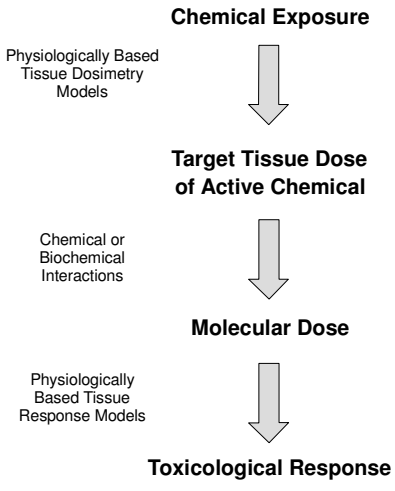


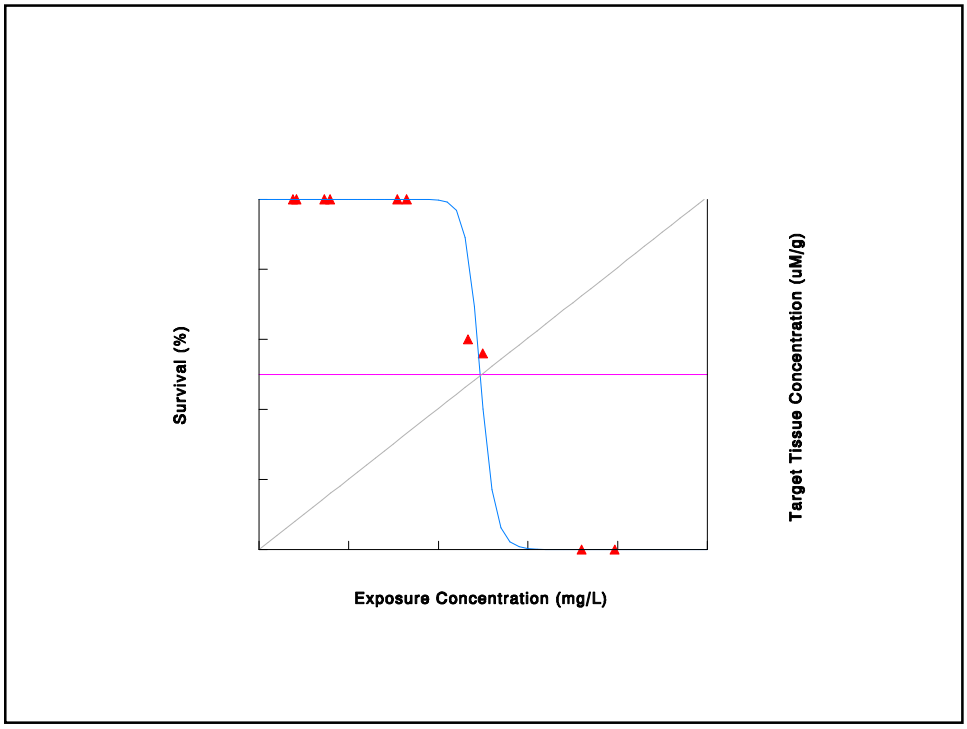


Conclusions:

- PBTK models can be used to accurately predict uptake, elimination, and disposition of organic chemicals in fish.
- PBTK models can be used to accurately predict dose in fish via branchial, cutaneous and gut uptake.
- PBTK models can be used to accurately extrapolate dose across fish species.


Gills
Effective Respiratory Volume
Cardiac Output
Fat Tissue Group
Poorly Perfused Tissue Group
Kidney
Richly Perfused Tissue Group
Liver
Qw
Cexp
Qw
Cinsp
Qc
Cven
Qc
Cart
Qf
Cvf
Cart
Qm X 0.4
Cvm
Qm
Cart
Qm X 0.6
Cvm
Qk
Cvk
Cart
Qr
Cart
Cvpp
Ql
Cvl
Cart
Km Vmax
Metabolism


Chemical Exposure
Physiologically Based Tissue Dosimetry Models
Target Tissue Dose of Active Chemical
Chemical or Biochemical Interactions
Molecular Dose
Physiologically Based Tissue Response Models
Toxicological Response


Survival (%)
Exposure Concentration (mg/L)
Target Tissue Concentration (uM/g)