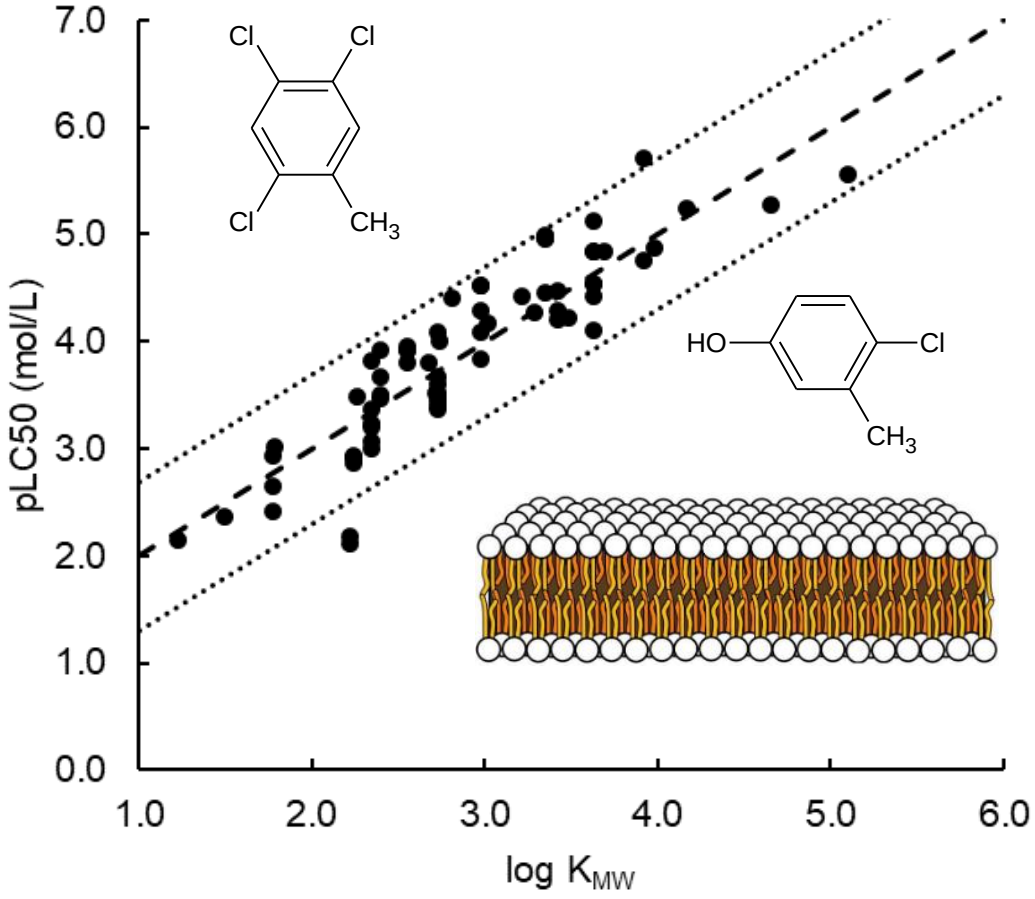
Exploring an Underlying Assumption of Baseline Toxicity QSARs for Fish Using a Mechanistic Bioaccumulation Model



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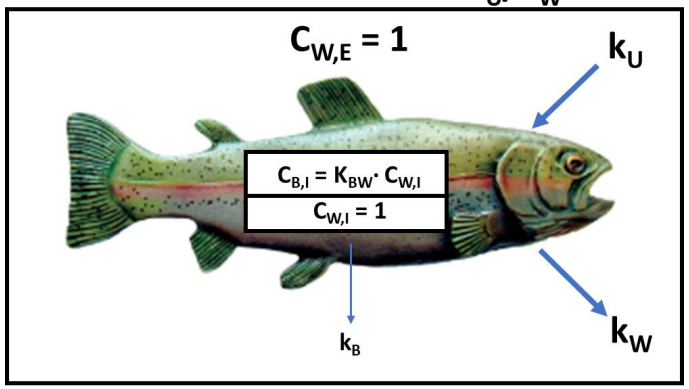
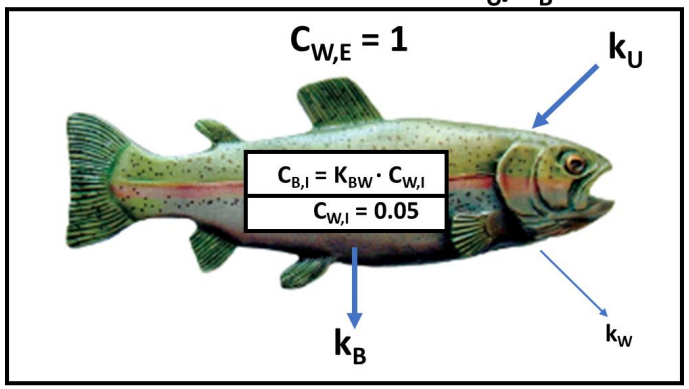
Scenario 1 – BCF ~ k_U/k_W



Steady-state & Equilibrium

Scenario 2 – BCF ~ k_U/k_B



Steady-state & Non-Equilibrium

JM Armitage, JA Arnot, R Van-Egmond

SETAC Europe 32nd Annual Meeting, May 15-19th 2022

Baseline Toxicity QSARs for Fish (Empirical)

Baseline toxicity QSARs to estimate acute toxicity in fish (LC50s) are well-established

$$pLC50 = \log(1/LC50) = a\ logK_{OW} + \mathrm{b}$$

Examples

US EPA ECOSAR v1.11

$pLC50 = 0.8981\ logK_{OW} + 1.2892$

Könemann 1981

$pLC50 = 0.87\ logK_{OW} + 1.13$

Klüver et al. 2016

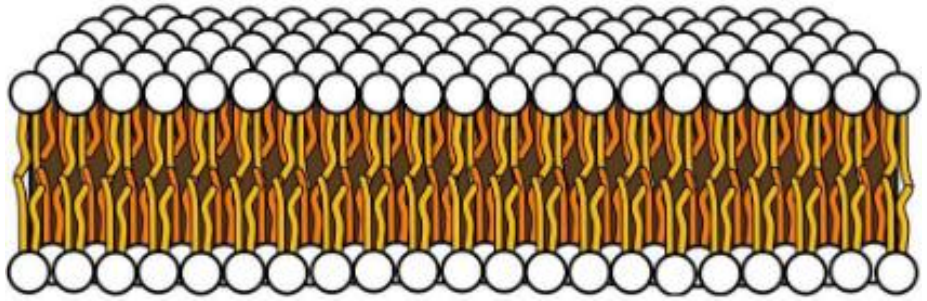
$pLC50 = 0.99\ logK_{OW} + 0.98$

Fish embryo test (FET)

NO EXPLICIT CONSIDERATION OF BIOTRANSFORMATION

Baseline Toxicity QSARs for Fish (Theoretical)

1. Assume baseline toxicity occurs for all chemicals when the membrane concentration = 100 mmol/kg



2. Assume the concentration of chemical inside the organism is at equilibrium with water

$$LC50 = \frac{100\,mmol/kg}{K_{MW}}$$

K_{MW} = Membrane-water partition coefficient

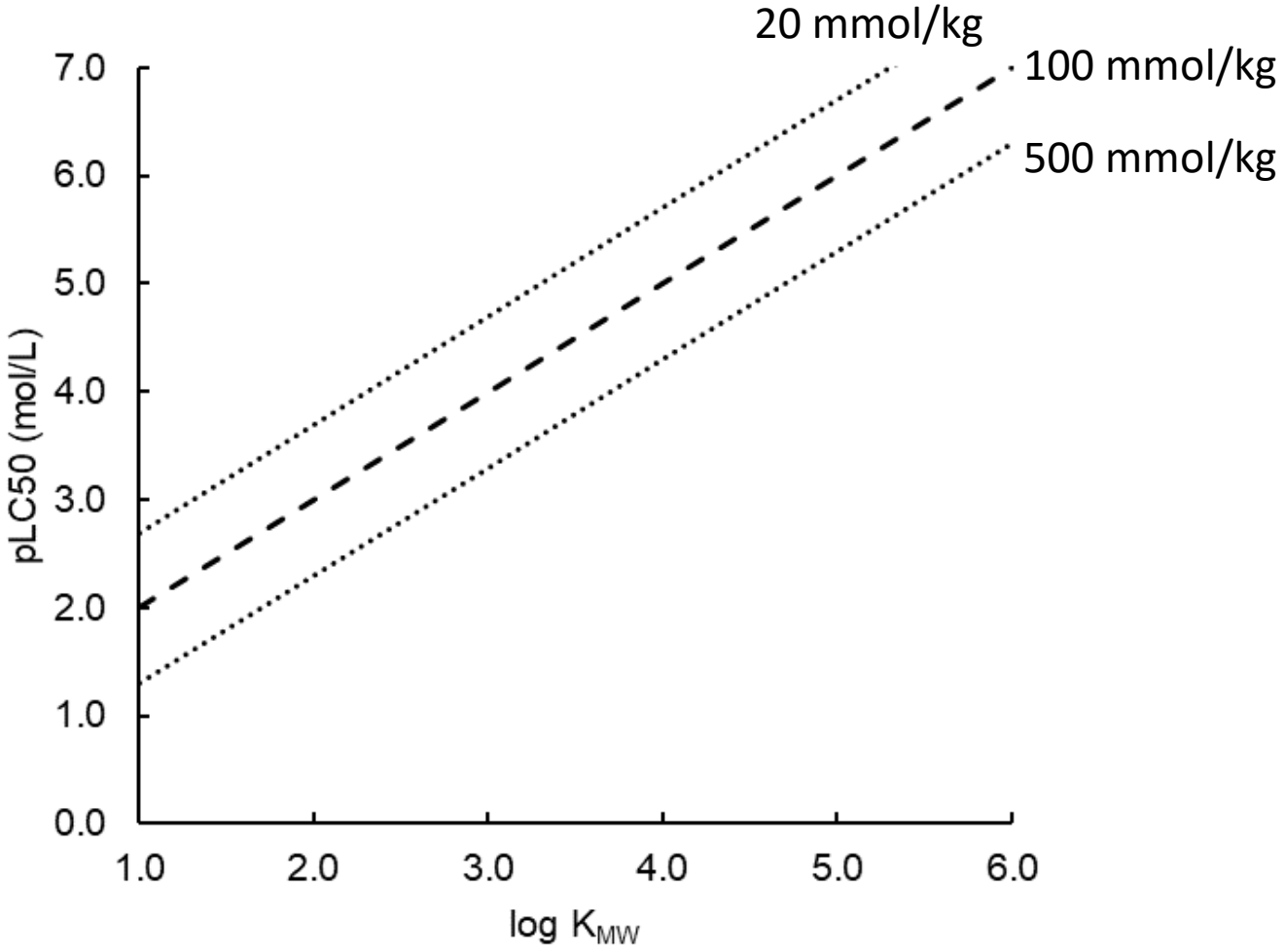
Note: Could use D_{MW} (membrane-water distribution ratio for ionizable organics)

$$pLC50 = \log(1/LC50) = logK_{MW} + 1$$

where LC50 is in units of mol/L

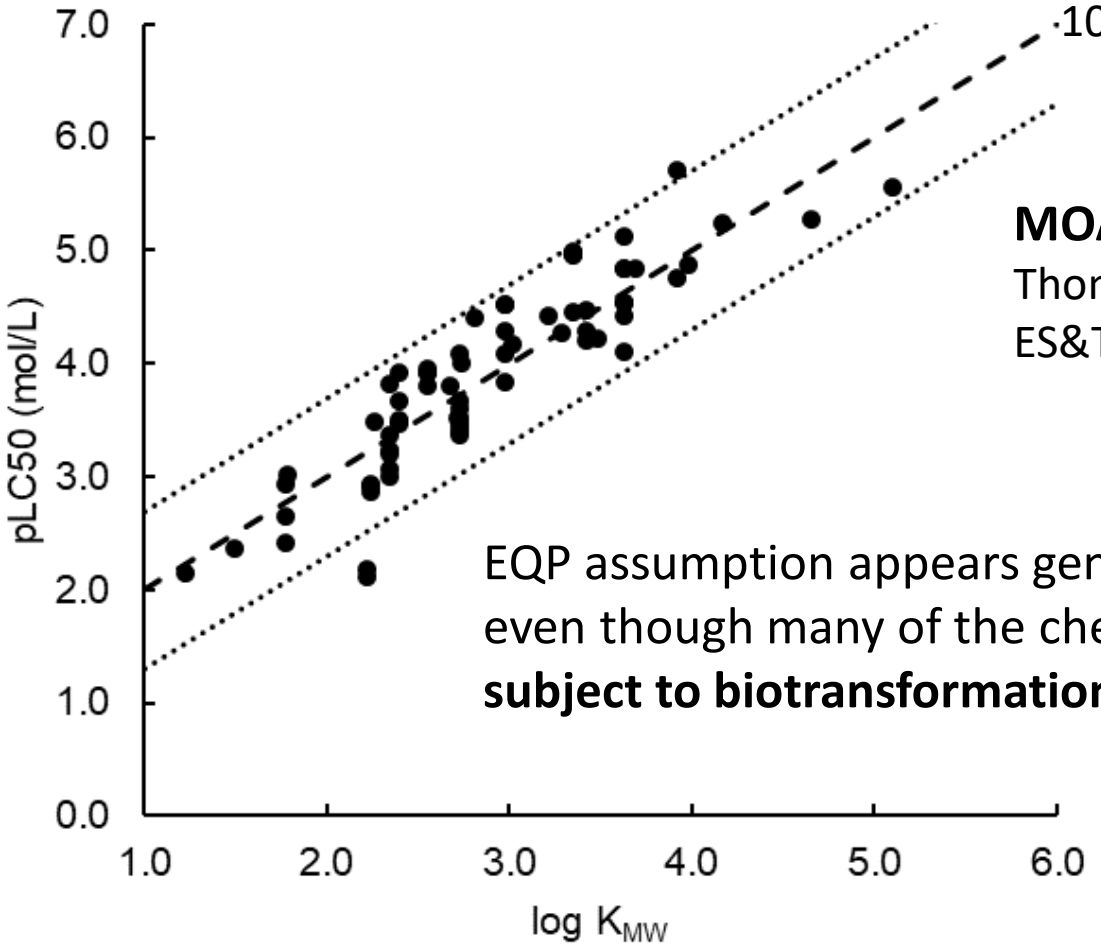
Baseline Toxicity QSARs for Fish (Theoretical)

$$pLC50 = \log(1/LC50) = logK_{MW} + 1$$



Baseline Toxicity QSARs for Fish (Theoretical)

$$pLC50 = \log(1/LC50) = logK_{MW} + 1$$



MOA1 "Narcotic" Chemicals
Thomas et al. 2015
ES&T 49(20):12289

EQP assumption appears generally **valid** even though many of the chemicals are **subject to biotransformation**

https://pubs.acs.org/doi/10.1021/acs.est.5b02873

Application of BIONIC v3.0 (Bioaccumulation model)

CASE STUDY: Nonpolar and polar "narcotics" from Vaes et al. 1998

INPUTS

Partitioning Properties
Biotransformation (k_B QSARs)

LC50

BIONIC v3.0

OUTPUTS

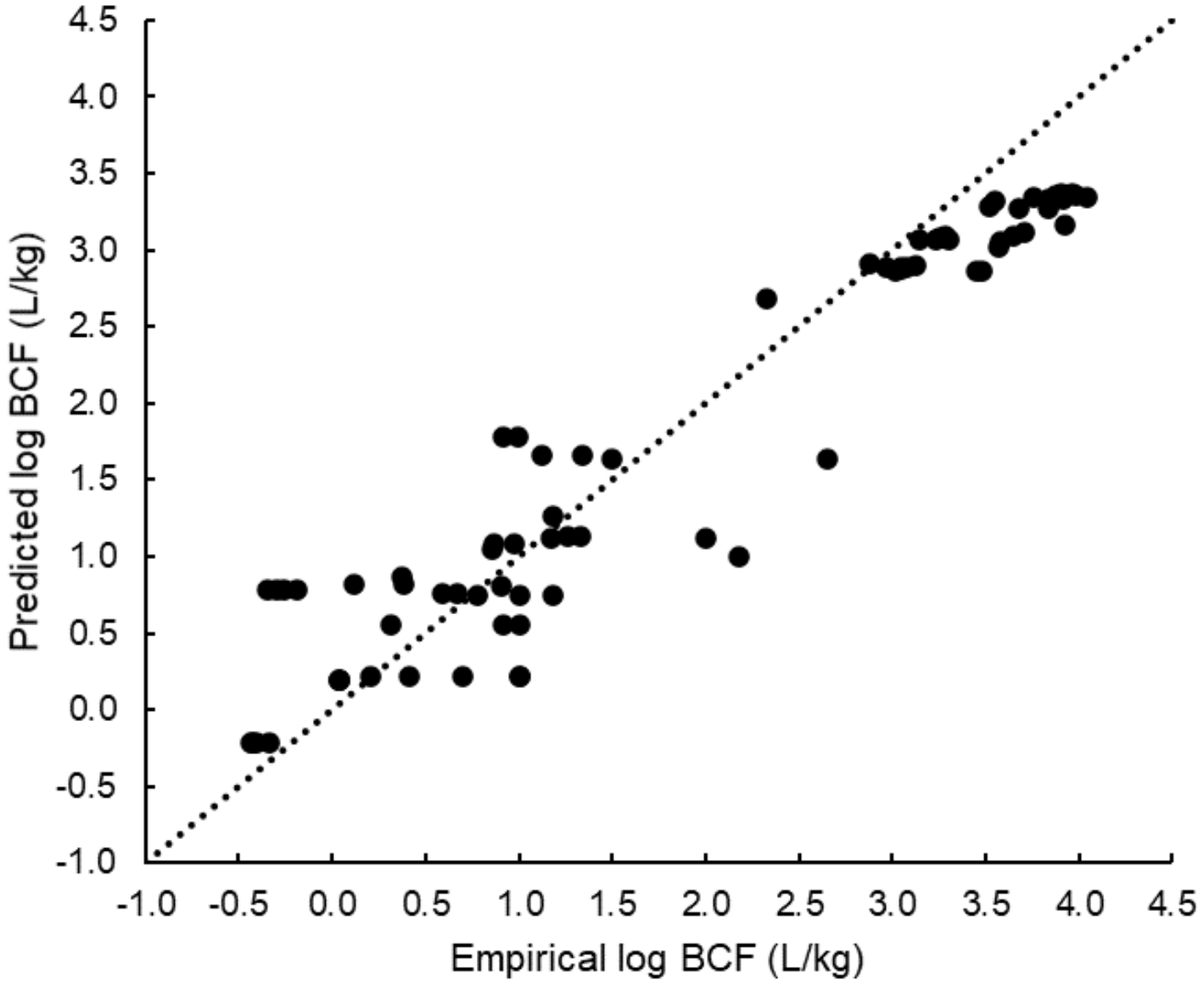
Whole body BCF (L/kg)
Elimination rate constants

Membrane concentration (CMC_{50},mmol/kg)

To what extent is equilibrium achieved?
What influence does biotransformation have on body burden?

https://setac.onlinelibrary.wiley.com/doi/abs/10.1002/etc.5620170723

Application of BIONIC v3.0 (Empirical vs Predicted BCFs)

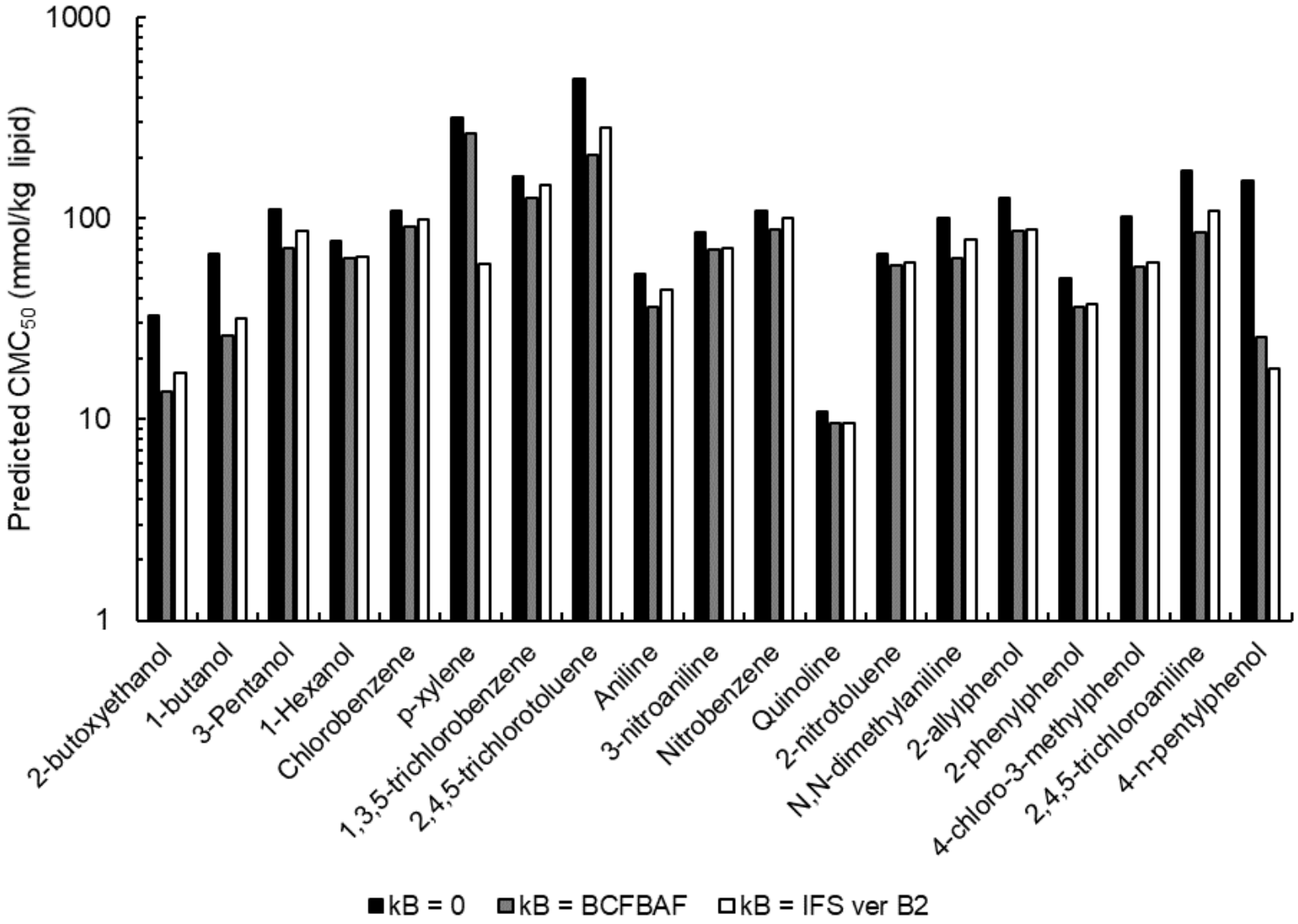


n = 76

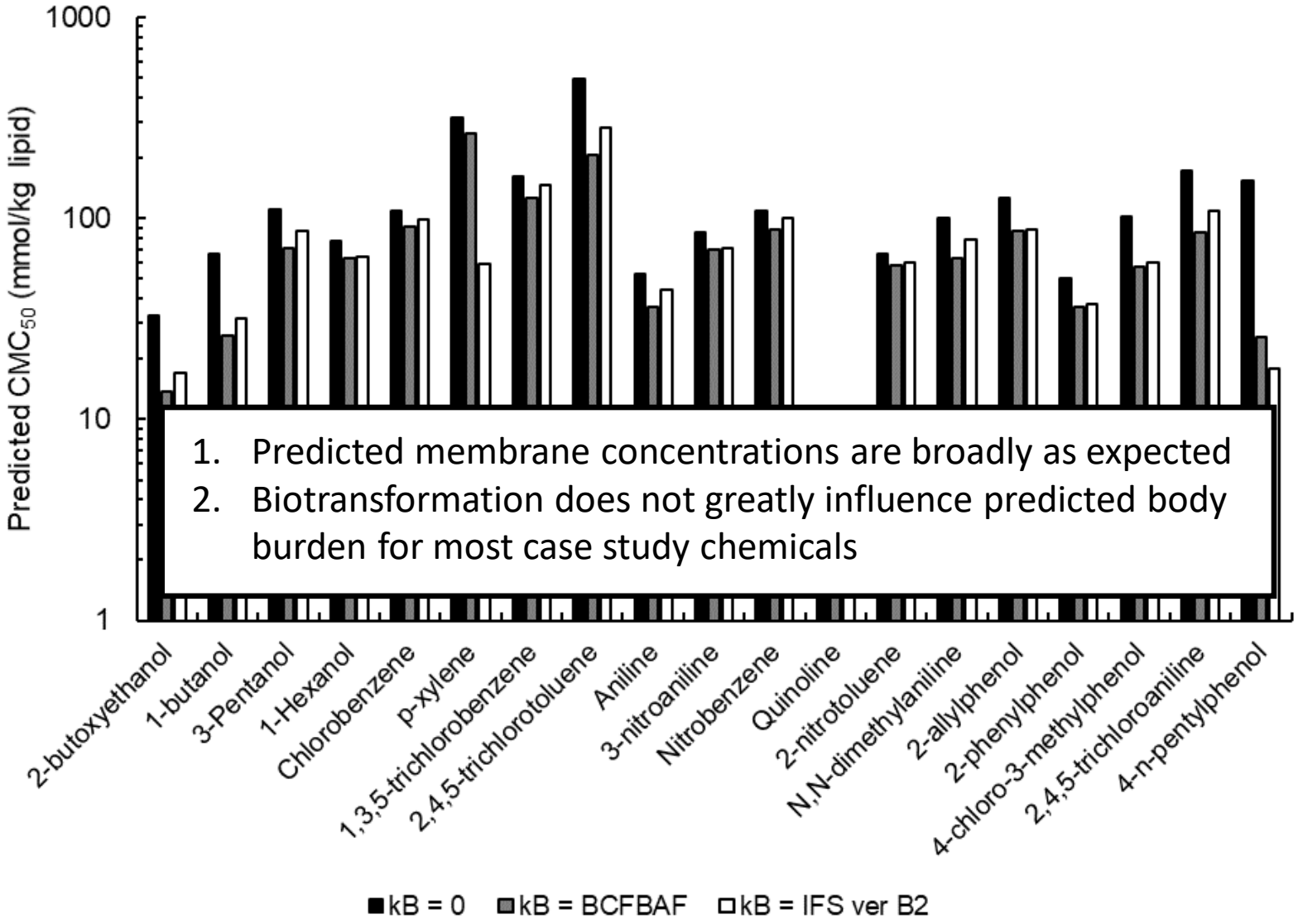
r^2 = 0.91

Average FoA
2.5

Application of BIONIC v3.0 (Predicted CMC_{50}s)



Application of BIONIC v3.0 (Predicted CMC_{50}s)



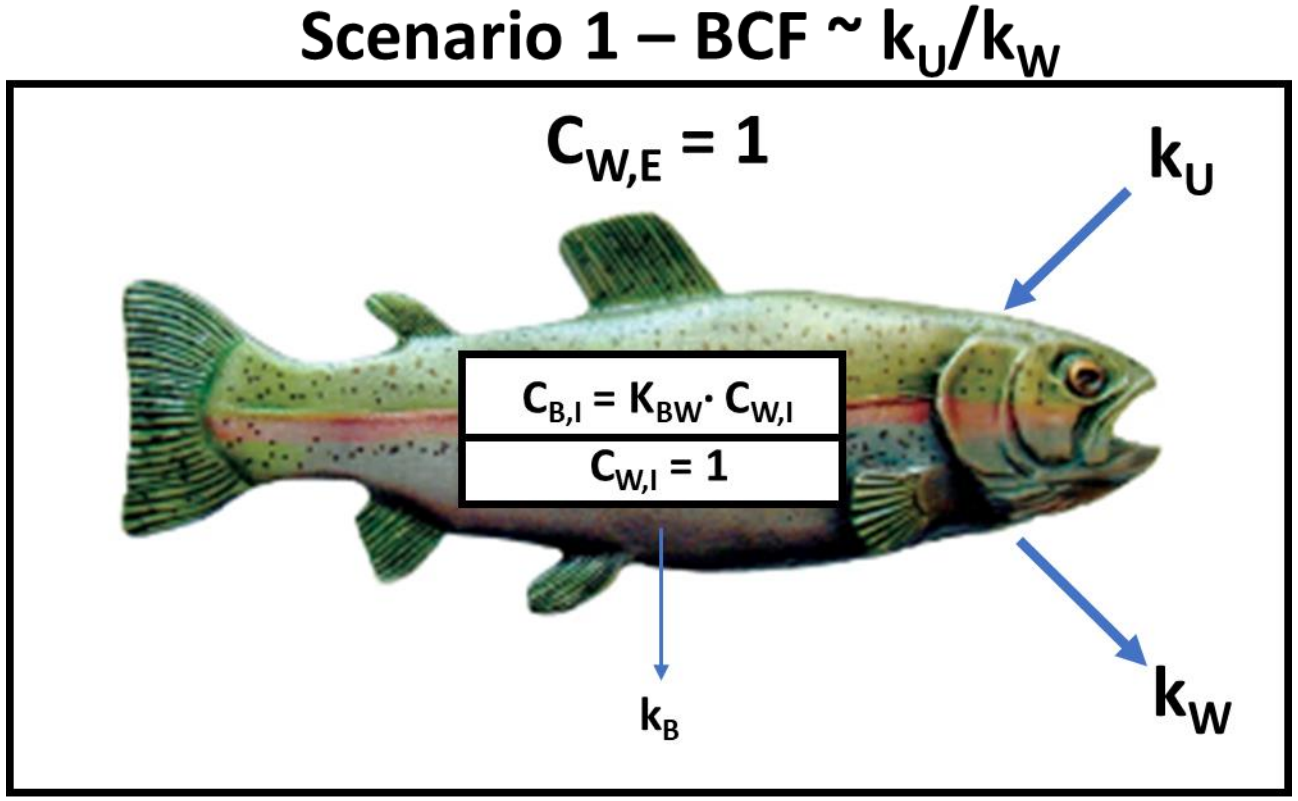
1. Predicted membrane concentrations are broadly as expected
2. Biotransformation does not greatly influence predicted body burden for most case study chemicals

Application of BIONIC v3.0 (Gill elimination k_W vs k_B)

Name	log K_{OW}	log K_{MW}	Gill elimination k_W (1/d)	Biotransformation k_B 1/d)
MOA1				
2-butoxyethanol	0.83	0.60	14.3	8.7
1-butanol	0.88	0.45	10.2	7.2
3-Pentanol	1.21	1.00	24.2	4.4
1-Hexanol	2.03	1.91	31.5	4.3
Chlorobenzene	2.90	2.81	9.3	0.6
p-xylene	3.15	2.98	5.8	16.5
1,3,5-trichlorobenzene	4.19	3.95	0.6	0.04
2,4,5-trichlorotoluene	4.78	4.77	0.2	0.1

For most chemicals (not all shown), the **gill elimination** rate constant **is greater** than the biotransformation rate constant

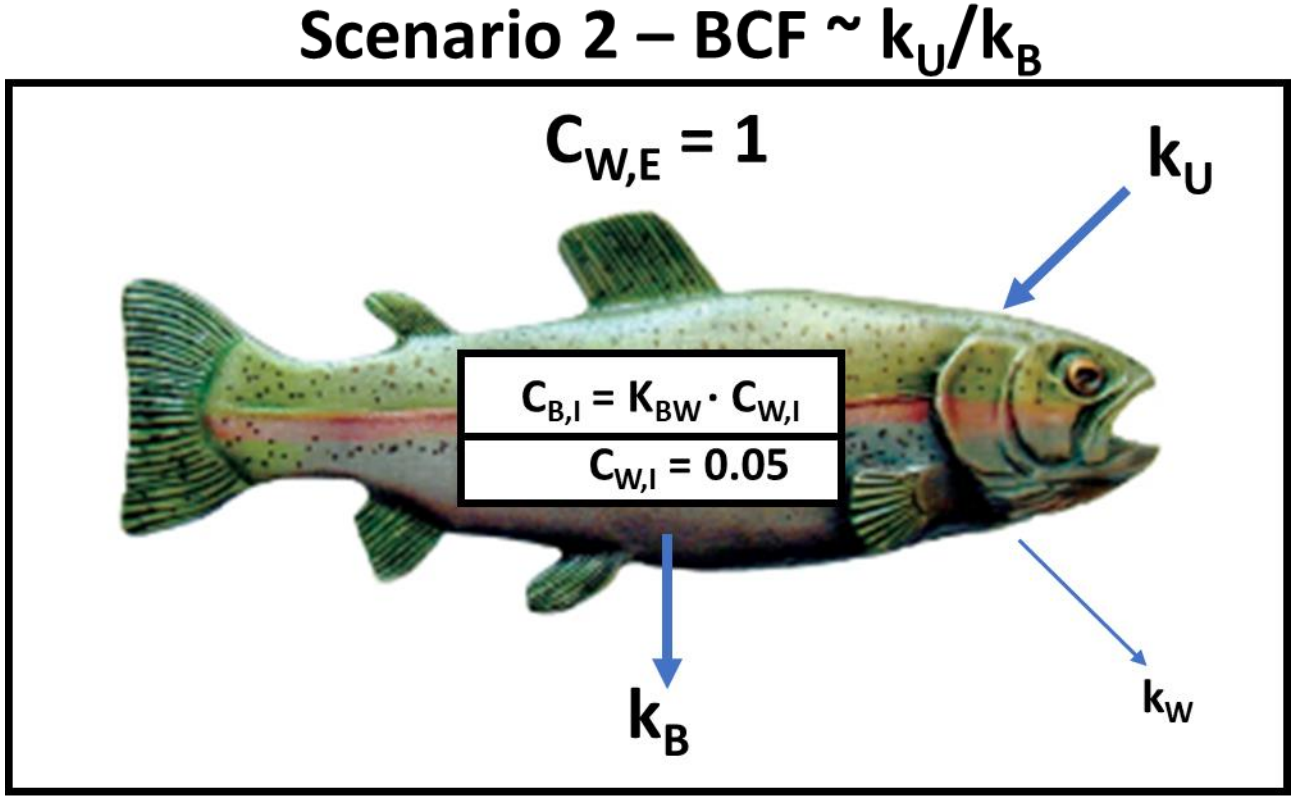
Implications (Toxicokinetic paradigms)



Steady-state & Equilibrium

Equilibrium is approached
Existing Baseline toxicity QSARs are likely valid

Implications (Toxicokinetic paradigms)



Steady-state & Non-Equilibrium

Equilibrium is NOT approached
Existing baseline toxicity QSARs are not reliable

Implications (Toxicokinetic paradigms)

How to quickly assess which toxicokinetic paradigm applies

Option 1 – Empirical BCF data available

Step 1 – Estimate equilibrium biota-water partitioning (K_{BW})

$$K_{BW} = f_{SL}K_{SLW} + f_{ML}K_{MLW} + f_{SP}K_{SPW} + \cdots + f_W$$

Storage Lipid (SL)
Membrane Lipid (ML)
Structural Protein (SP)
….
Water

Step 2 – Compare empirical BCF to K_{BW}

If BCF ~ K_{BW}
Scenario 1 applies – Existing baseline toxicity QSARs should be valid

If BCF << K_{BW}
Scenario 2 applies – Existing baseline toxicity QSARs not expected to be reliable

Implications (Toxicokinetic paradigms)

How to quickly assess which toxicokinetic paradigm applies

Option 2 – Empirical BCF data NOT available

Step 1 – Estimate the whole body biotransformation rate constant (k_B)

kB-QSARs* IVIVE of hepatic clearance rates

Step 2 – Parameterize a mechanistic bioaccumulation model (e.g., BIONIC v3)
Step 3 – Compare gill elimination (k_W) to biotransformation (k_B)

If $k_W >> k_B$
Scenario 1 applies – Existing baseline toxicity QSARs should be valid

If $k_B >> k_W$
Scenario 2 applies – Existing baseline toxicity QSARs not expected to be reliable

*Try a few out at https://beta-reg.eas-e-suite.com/

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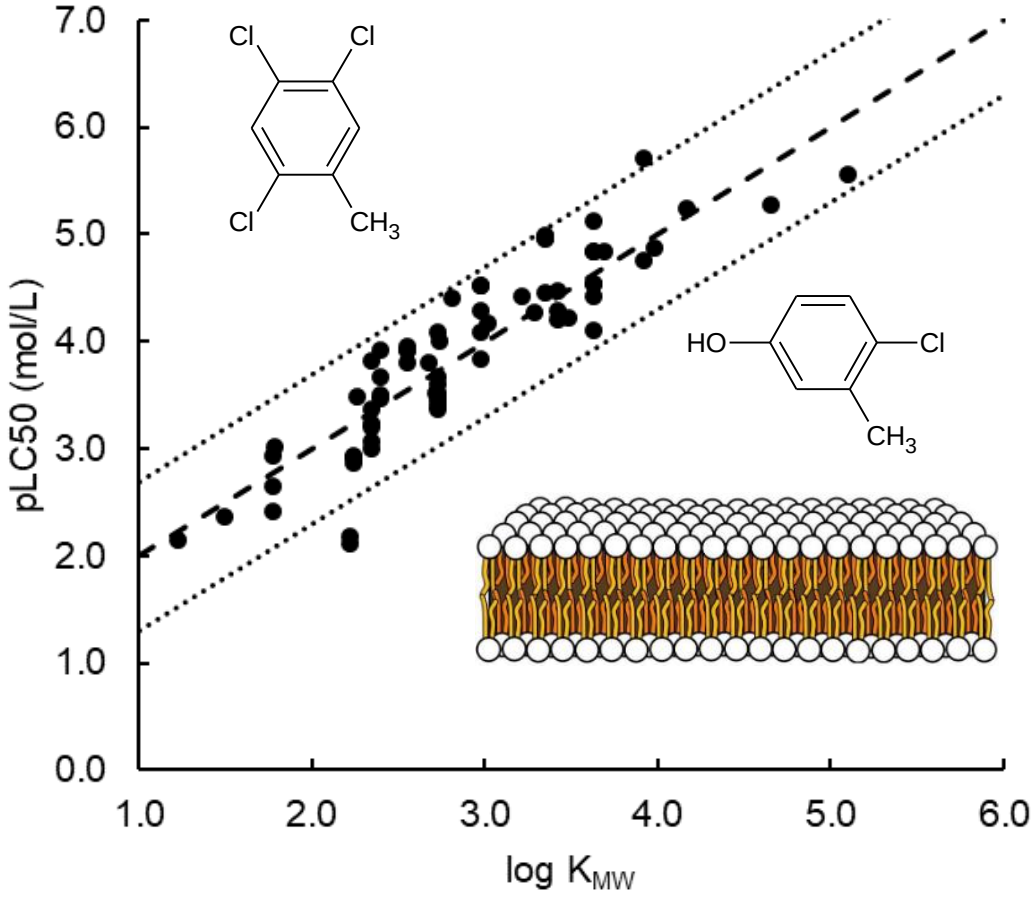

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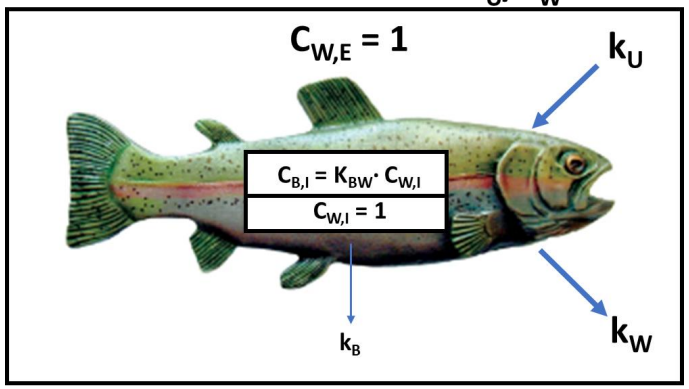
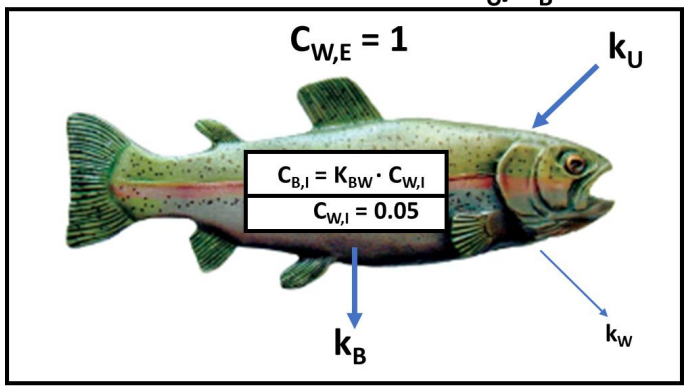


Steady-state & Equilibrium

Scenario 2 – BCF ~ k_U/k_B



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