Environmental and fate ecotoxicity models

BCF Base-Line Model

Laboratory of Mathematical Chemistry, Bulgaria

Biodegradation CATALOGIC 301C model

Modeled phenomenon

Bioconcentration of chemicals in fish driven by their lipophilicity.

Modeled endpoint

Bioconcentration (BCF) - the ratio at equilibrium of the concentration of a chemical in the tissues of the fish to the concentration of the chemical in solution in the water:

$$BCF = \frac{C_{tissues}}{C_{water}}$$

Mechanistic background

1. Nonpolar organic chemicals partition in tissue lipids until an equilibrium is reached.

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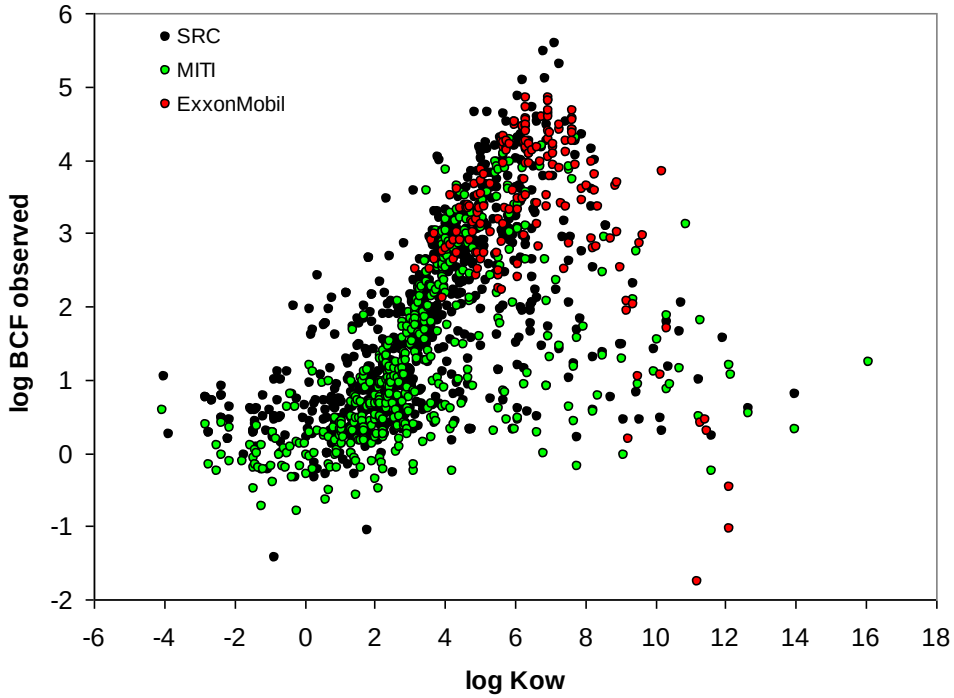
2. This equilibrium is proportional to octanol/water partitioning coefficient (log K_{OW}) - BCF is expected to be proportional to log K_{OW}.

Empirical Knowledge



Why this is not true?

SRC + MITI (NITE Japan) + ExxonMobil

Totally:

1433 observed BCF values
Different fish
Different laboratories
Different methodologies

Mechanistic background

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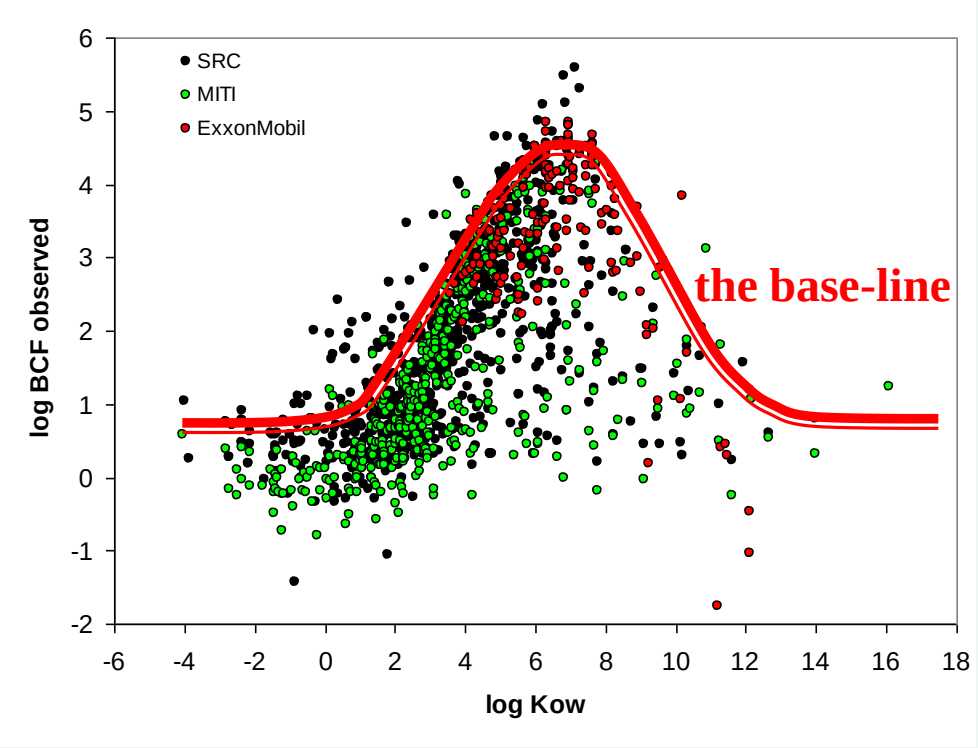
5. Ionized chemicals has lower affinity for the lipid phase compared to non-ionized chemicals with the same log K_{OW}.

6. Bioaccumulation of metals is based on formation of metal-ligand complexes, carrier mediated transport, diffusion through ion channels, endocytosis, etc.

LMC modeling approach – The concept

1. Maximum possible bioconcentration (the base-line)

It is conditioned by the chemical lipophilicity.



LMC modeling approach – The concept

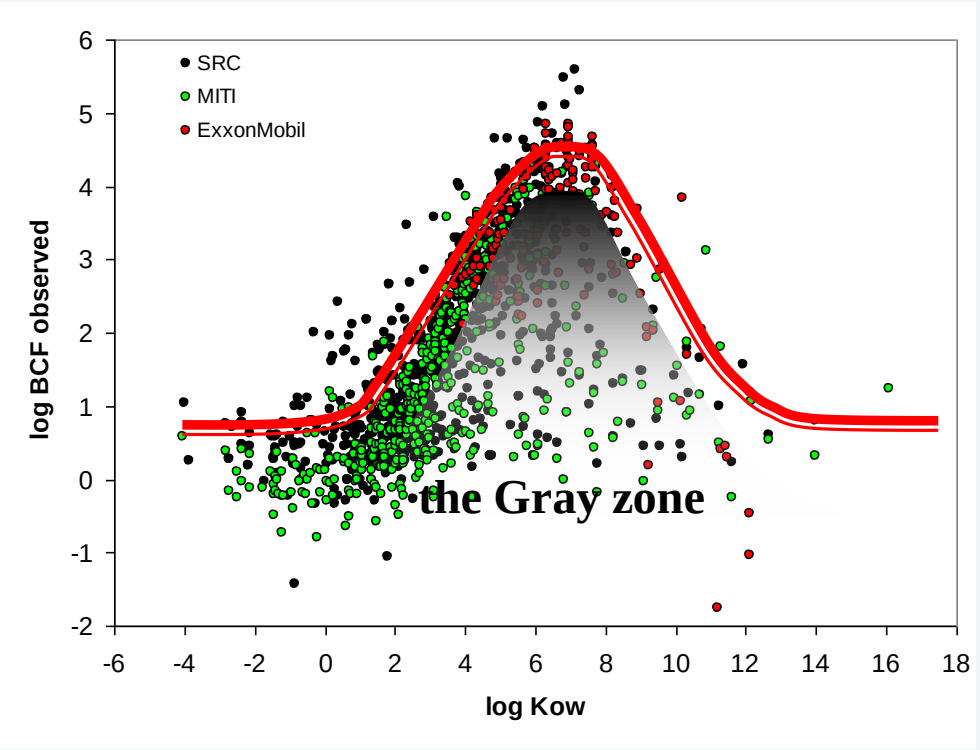
1. Maximum possible bioconcentration (the base-line)

It is conditioned by the chemical lipophilicity.

2. Mitigating factors

A gray zone where BCF is below the base-line as a result of:

- Metabolism,
- Ionization,
- Molecular size,
- Etc.

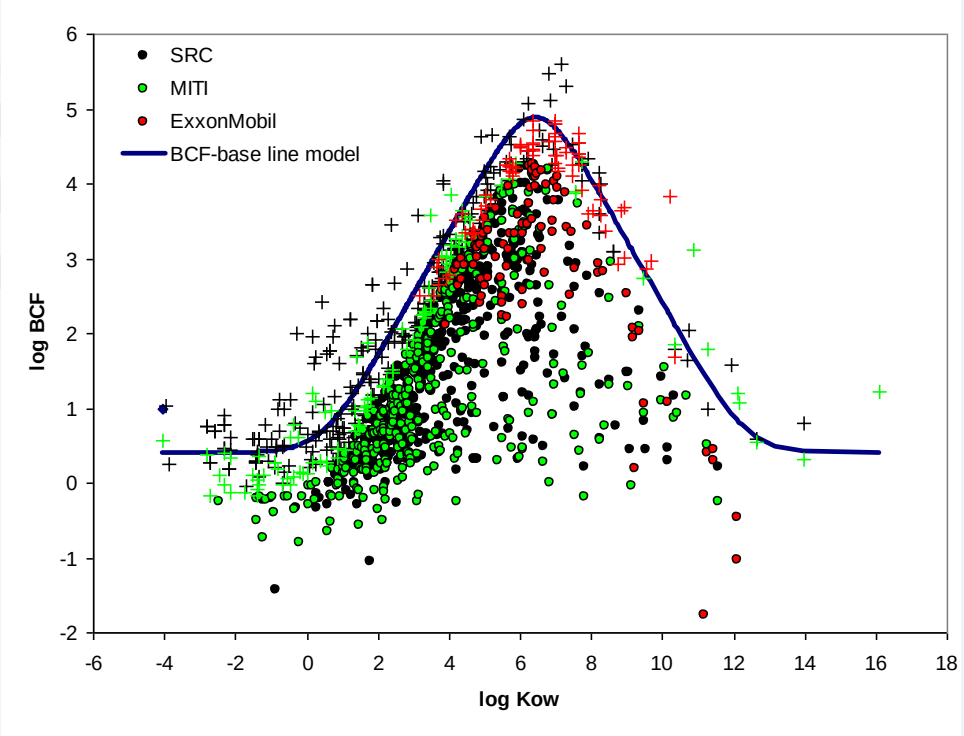


BCF Base-line model

1. Maximum possible bioconcentration (the base-line)

$$\log BCF_{MAX} = \log\left(\frac{K_{OW}{}^{n}}{(aK_{OW}+1)^{2n}} + F_W\right)$$

Modeled by the multicompartment model (Bintein et al., 1993)



BCF Base-line model

2. Mitigating factors – implemented in the multicompartment model

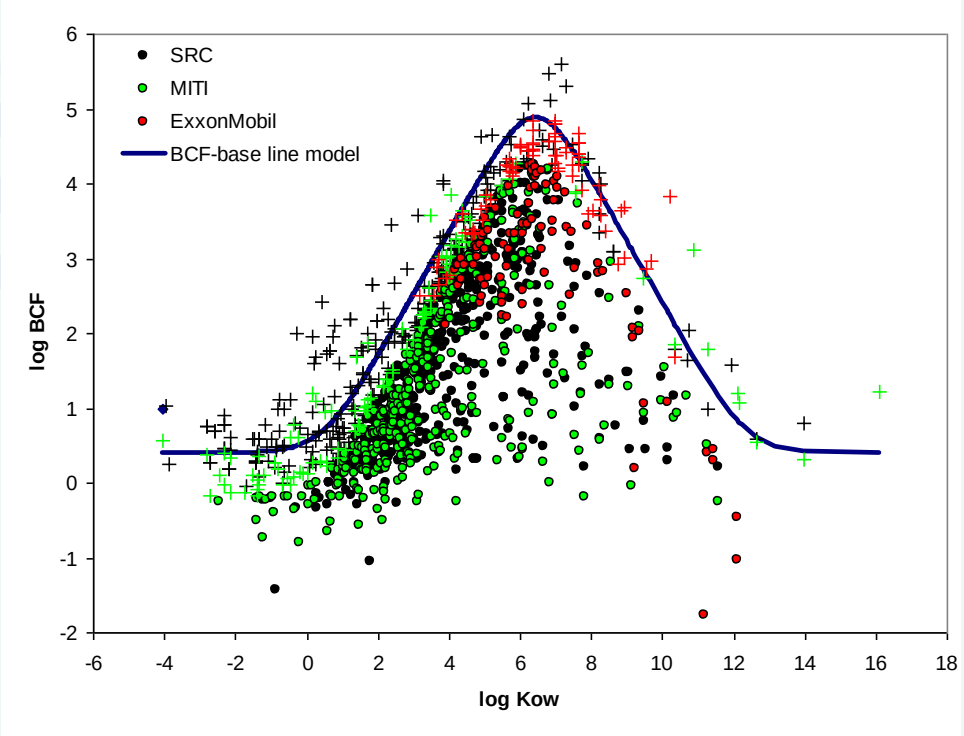
$$\log BCF = \log\left(\prod_i F_i \frac{K_{OW}{}^{n}}{\left(aK_{OW}+1\right)^{2n}} + F_W F_{WS} \right)$$

Chemical dependent factors

- Molecular size
- Absorptions
- Volatilization
- Ionization

Organism dependent factors

- Permeability
- Metabolism



BCF Base-line model

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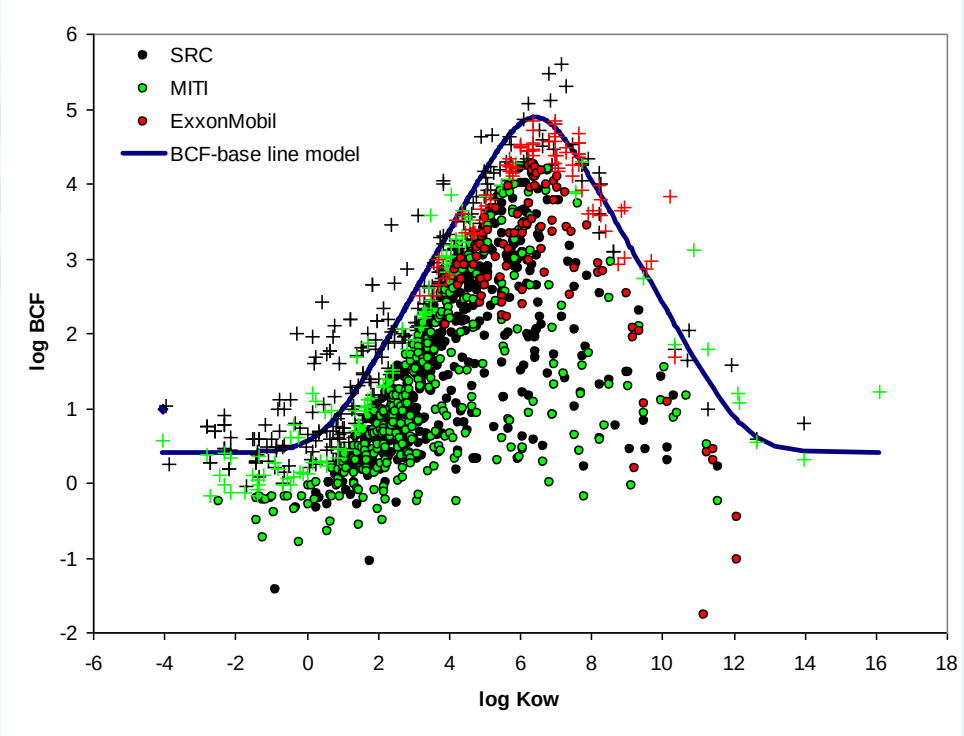
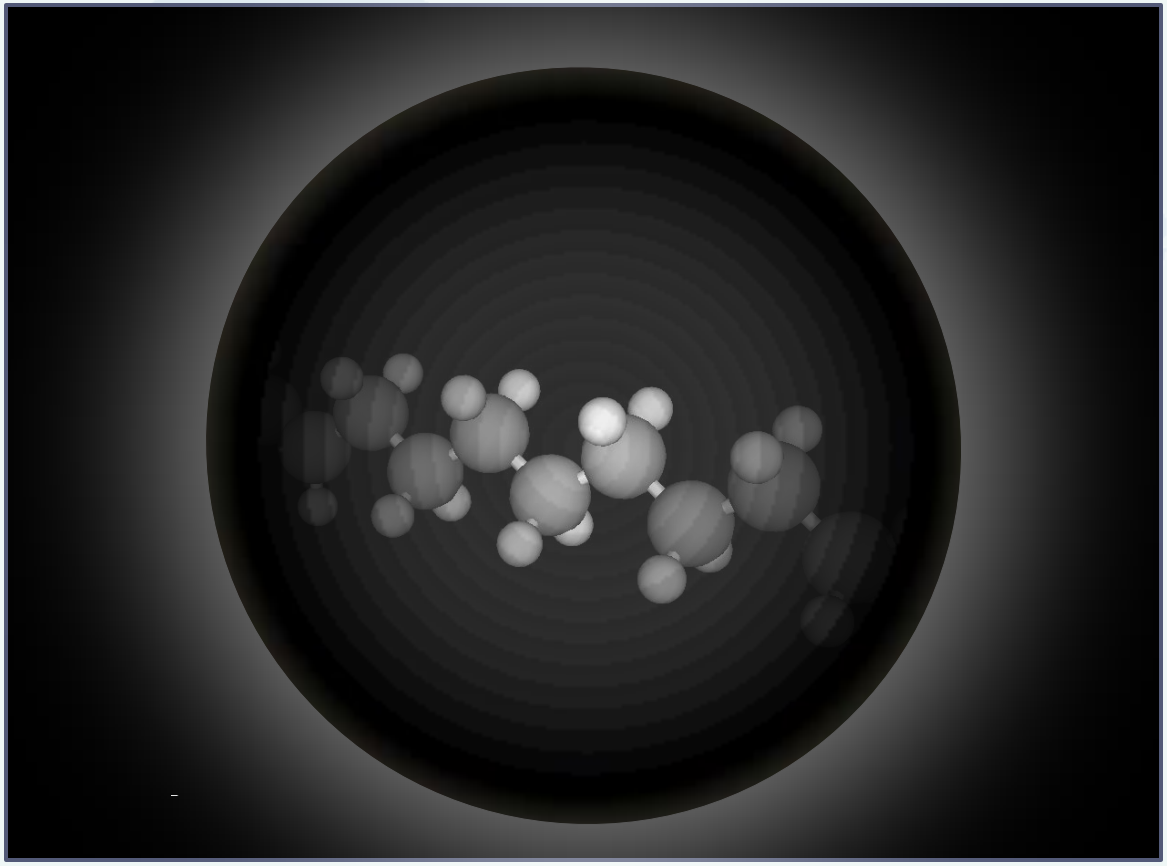


BCF Base-line model - Mitigating factors

Measures of molecular size

Maximum diameter, D_{Max}

the sphere with minimum diameter within which the molecule could be inscribed

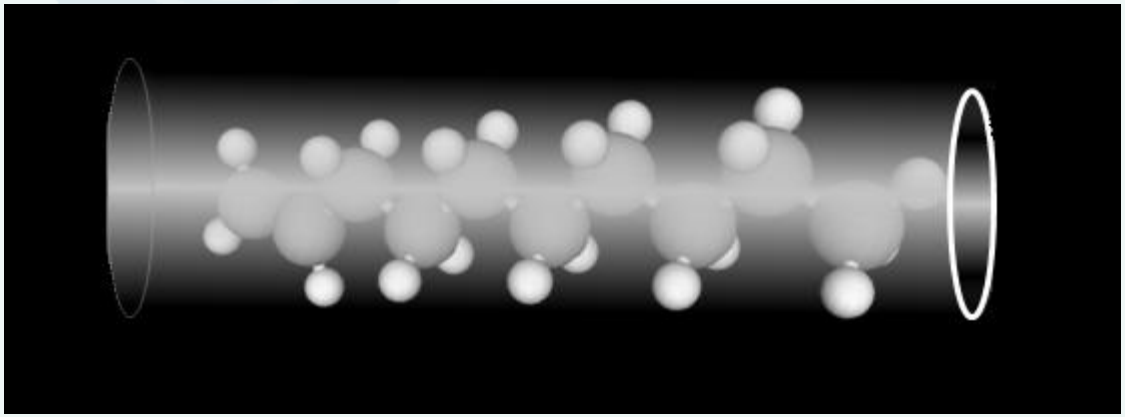


BCF Base-line model - Mitigating factors

Measures of molecular size

Effective diameter, D_{Eff}

the cylinder with minimum diameter within which the molecule could be inscribed

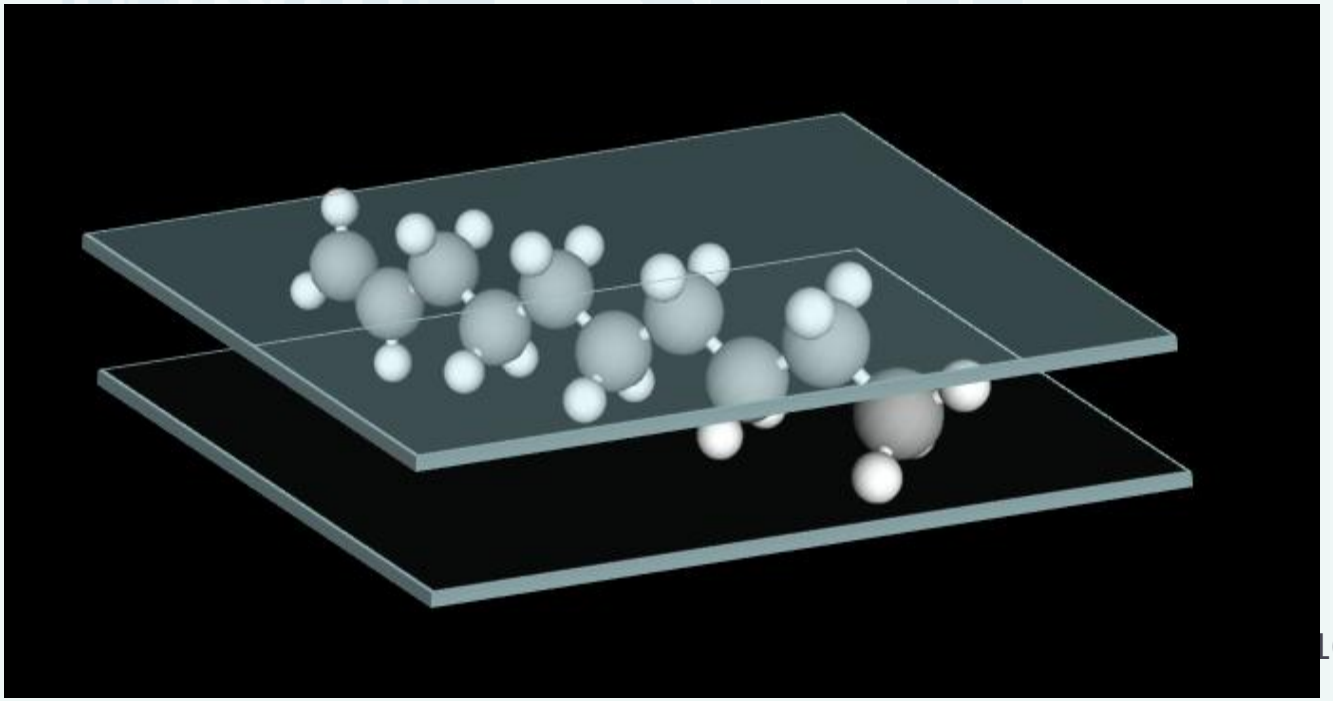


BCF Base-line model - Mitigating factors

Measures of molecular size

Minimum diameter, D_{Min}

the minimum distance between two parallel surfaces where the molecule could be inscribed



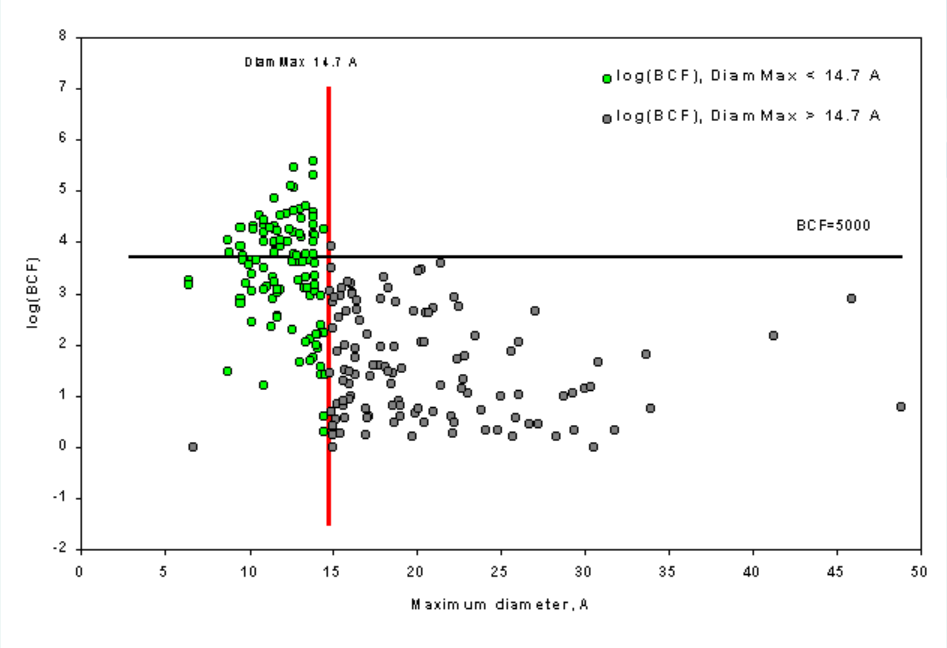
BCF Base-line model - Mitigating factors

Effect of molecular size

Problem – what to flexible molecules? ΔH^{o}_{Min}

log BCF versus D_{Max}

Lipophilic chemicals (log(Kow) > 5), Meylan et al., 1999)



D_{Max} ≈ 15 Å cutoff?

BCF Base-line model - Mitigating factors

Effect of molecular size

Problem – what to flexible molecules? **All conformers**

log BCF versus D_{Max}

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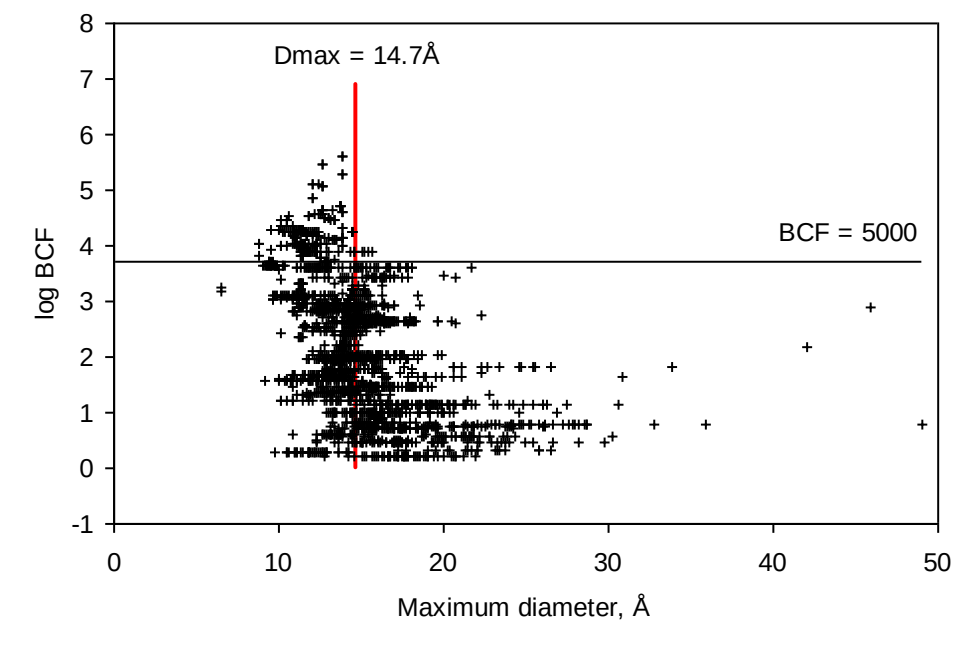


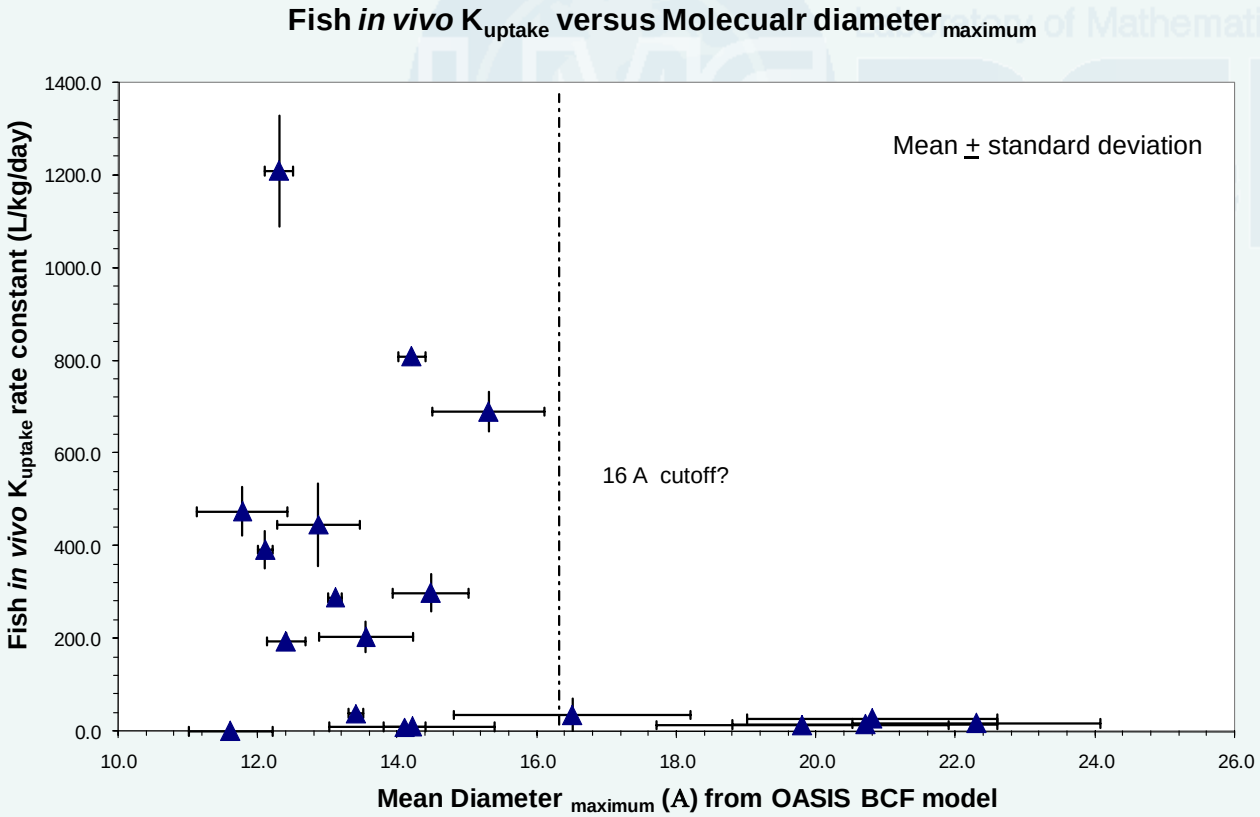
D_{Max} ≈ 15 Å cutoff?

BCF Base-line model - Mitigating factors

Effect of molecular size

K_1 (uptake) versus D_{Max}

Beyond lipophilicity: The influence of other physico-chemical parameters on water/gill uptake rates in fish. K.B. Woodburn, A.V. Weisbrod, B. Versonnen, N. Jeliazkova, **SETAC North America 28th Annual Meeting**, 2007



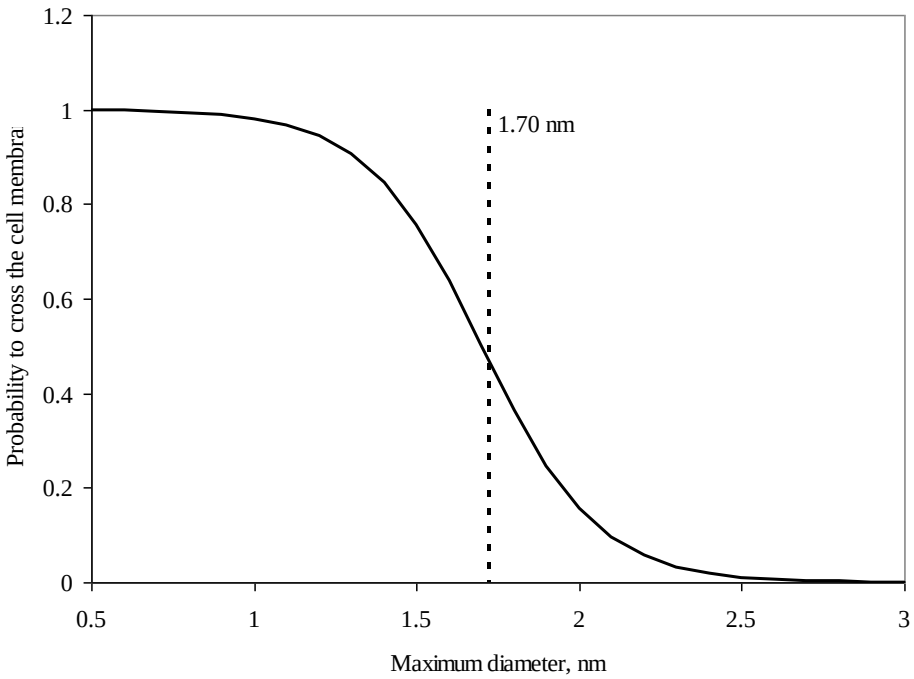
D_{Max} ≈ 16 Å cutoff?

BCF Base-line model - Mitigating factors

Molecular size

Mitigating factor of molecular size = Probability of a chemical to cross the cell membrane

$$F_{MS} = 1 - \frac{1}{1 + e^{-c(D_{\text{Max aver}} - D_{\text{Max thr}})}}$$



$D_{\text{Max aver}}$ is the averaged D_{Max} across conformers

$D_{\text{Max thr}}$ is the threshold for molecular size

BCF Base-line model - Mitigating factors

Effect of ionization

- **Ionizing molecular fragments**
- **Distribution coefficient**

BCF Base-line model - Mitigating factors

Effect of ionization

- **Ionizing molecular fragments**
- Distribution coefficient

- Carboxylic acids and their alkaline salts
- Sulphonic acids and their alkaline salts
- Phosphoric acids and their alkaline salts
- Phenols with four or five halogen atoms

$$F_{Ionic} = 1 - b_{Ionic}.A$$

A = 1 for ionizing chemicals
A = 0 for other chemicals

BCF Base-line model - Mitigating factors

Effect of ionization

- Ionizing molecular fragments
- **Distribution coefficient**

$$D = \frac{[neutral\ species + ionized\ species]_{octanol}}{[neutral\ species + ionized\ species]_{water}}$$

The distribution coefficient is the ratio of the sum of the concentrations of all forms of the compound (ionized plus un-ionized) in water and 1-octanol.

$$F_{Ionization} = \left(\frac{D}{P}\right)^{b}$$

b – adjustable parameter

$\frac{D}{P}$ – relative reduction of lipophilicity as a result of ionization

The partition coefficient: $P = K_{OW} = \frac{[neutral\ species]_{octanol}}{[neutral\ species]_{water}}$

BCF Base-line model - Mitigating factors

Effect of metabolism

- Metabolism is the major weapon of organisms against xenobiotiks.
- Evolutionary developed to transform lipophilic chemicals into hydrophilic metabolites.
- Most of the metabolic studies are focused on mammalian metabolism.
- Only the first level of metabolism affects the bioconcentration.

BCF Base-line model - Mitigating factors

Effect of metabolism

Data used to simulate fish metabolism

433 documented biotransformation maps for rat and fish liver metabolism have been used to extract:

- 450 Phase I metabolic transformations
- 50 Phase II metabolic transformations

The transformation probabilities were fitted by fish BCF data

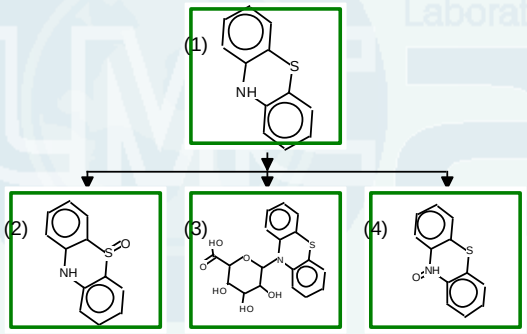
BCF Base-line model - Mitigating factors

Effect of metabolism

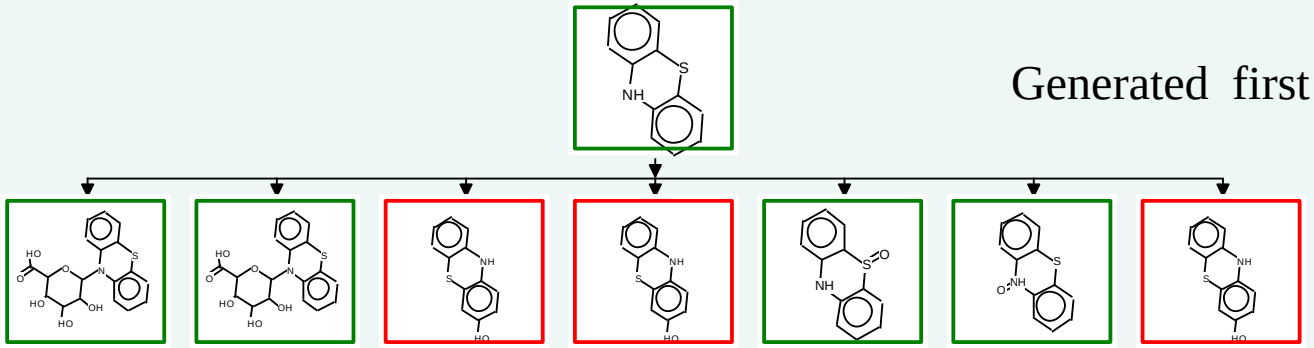
Metabolism mitigating factor = probability of parent chemical to be metabolized

$$F_{\mathrm{M}} = 1 - P \qquad P = 1 - \prod_i \left(1 - P_i\right)$$

P_i – probabilities of competing transformations



Observed first level metabolites



Generated first level metabolites

Model parameterization

BCF base-line model

$$\log BCF = \log\left(\prod_i F_i \frac{{K_{OW}}^n}{\left(aK_{OW}+1\right)^{2n}} + F_W.F_{WS} \right)$$

Training set - Fish *log BCF* data – 873 values
(MITI database, NITE, ExxonMobil**)**

Parameter Estimation

$$\min_{a,n,F_W,b,c,D_{MaxThr},S_{WTrh},P_i} SSR = \sum_j \left(\log BCF_j^{Obs} - \log BCF_j^{Calc}\right)^2$$

Statistics

- $R^2 = 0.92$
- For 87% of training set chemicals differences between observed and calculated log BCF values are within 0.75 l. u.

Applicability domain

Consists of the following sub-domain levels:

- **General parametric requirements** - includes ranges of variation of log K_{OW} and *MW*,
- **Structural domain** - based on fragmentation of correctly predicted chemicals into fragments (atom-centered fragments ACFs),
- **Mechanistic domain** – based on mode of bioaccumulation chemicals
  - ***In domain*** – bioaccumulation driven by the lipophilicity of chemicals
  - ***Out of domain*** – formation of metal-ligand complexes, carrier mediated transport, diffusion through ion channels, etc.

Conclusions

CATALOGIC BCF Base-line model has

1. Strong mechanistic background ,

2. Clear algorithm and transparent predictions,

3. Defined applicability domain,

4. Appropriate measures of goodness-of-fit, robustness and predictivity.

5. Explicitly accounts the effect of metabolism, molecular size and ionization.