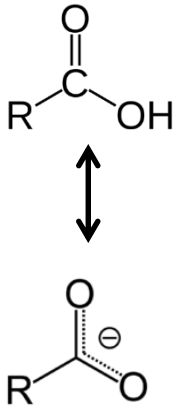
LRI-ECO21

Mechanistic bioaccumulation model(s) for ionogenic organic substances in fish

Cefic-LRI Annual workshop

Brussels, Nov. 2015



Partner 1

Partner 2

Partner 3

Partner 4

Partner 5

Rationale

1. Bioaccumulation data required for **PBT & RISK** assessment
2. Scarce empirical **B** data for ionogenic organic compounds (IOCs)
3. Majority of **B** models trained/developed for neutral organic chemicals
4. Modeling **B** for IOCs needs **new input data** + include **pH dependency**

IOCs:

Cationic surfactants

Pharmaceuticals & veterinary drugs

Anionic surfactants

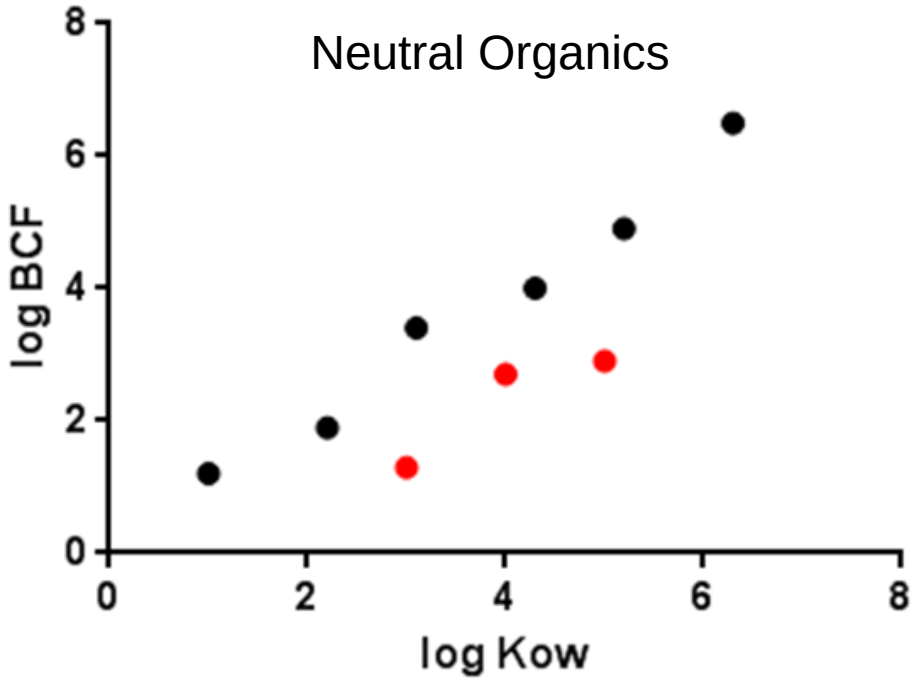
Halogenated phenolics

Resin acids

Biocides

Naphthenic acids

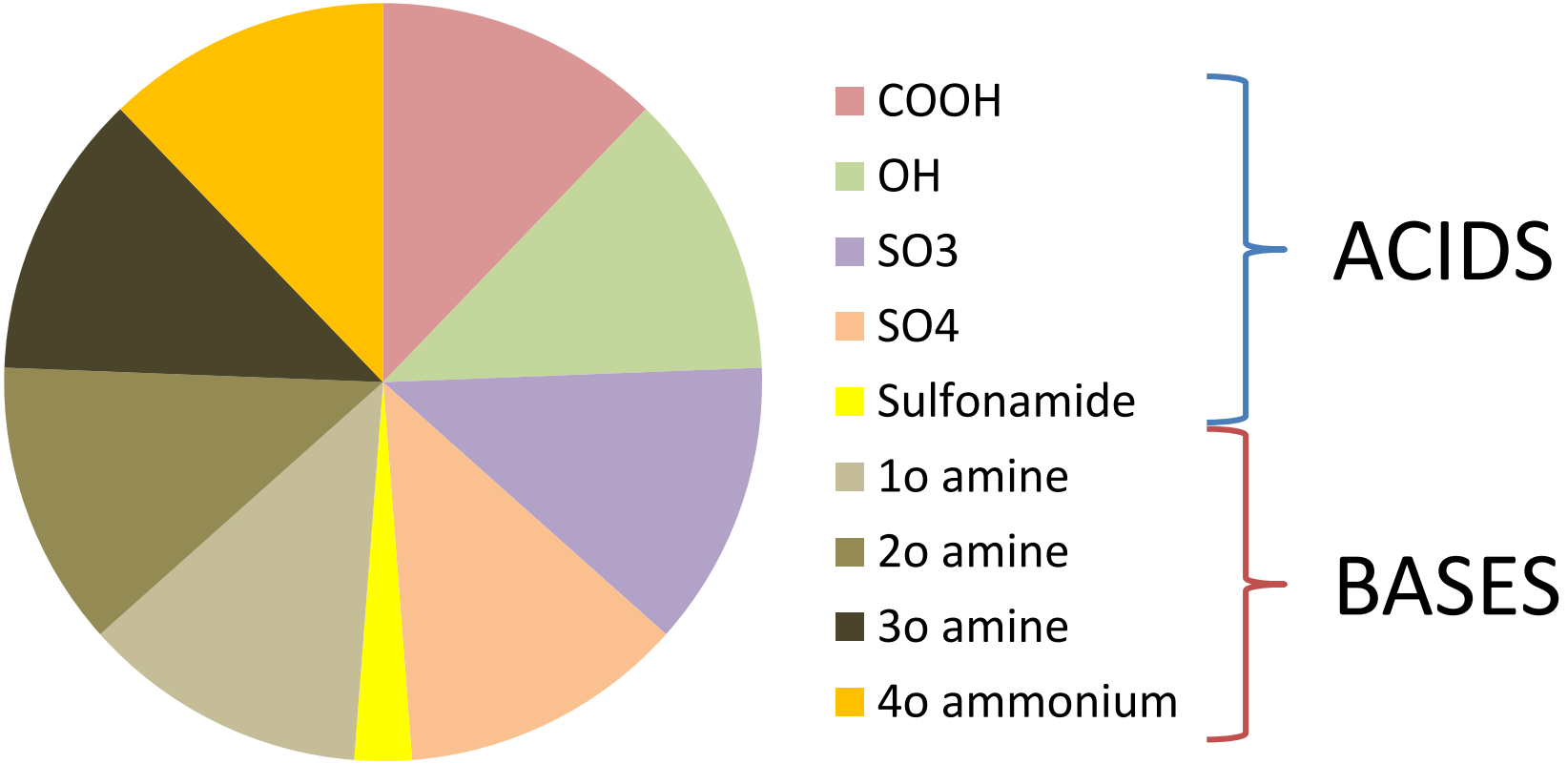
Influence of Hydrophobicity on Bioconcentration



Bioconcentration factor (BCF) can be predicted from K_{OW}

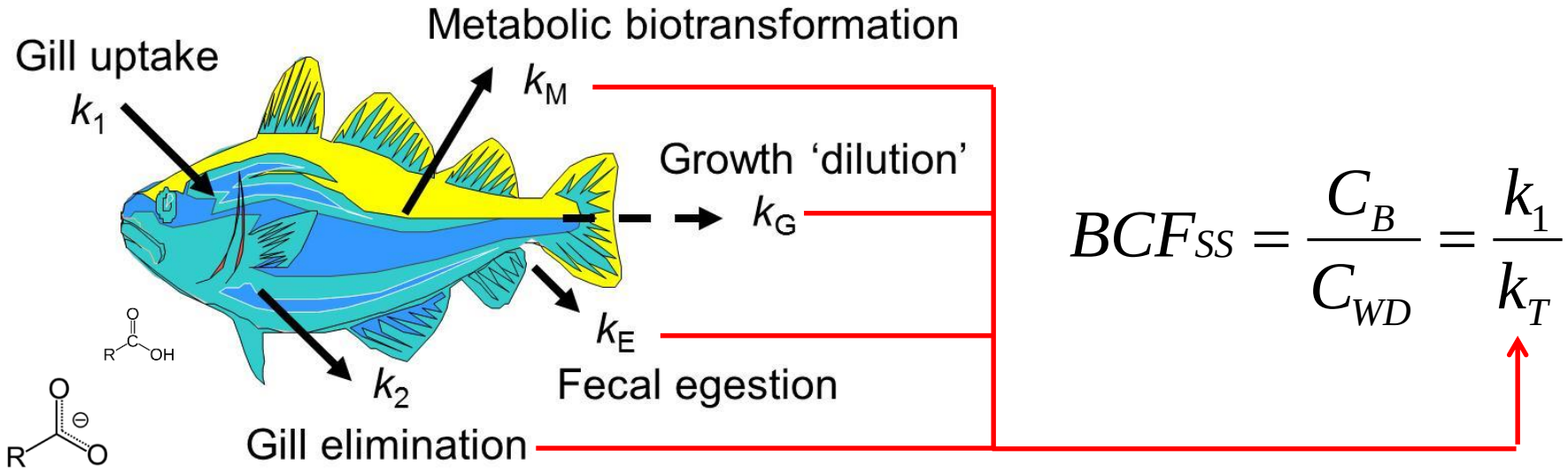
Rapid biotransformation reduces the BCF in comparison to K_{OW}

IONOGENIC compounds



- *NEED: hydrophobicity and metabolization rates*
- K_{OW} – BCF relation <u>inadequate</u> if IOC >95% ionized
- Susceptibility of IOCs to biotransformation?

BIONIC model (Armitage et al. 2013)

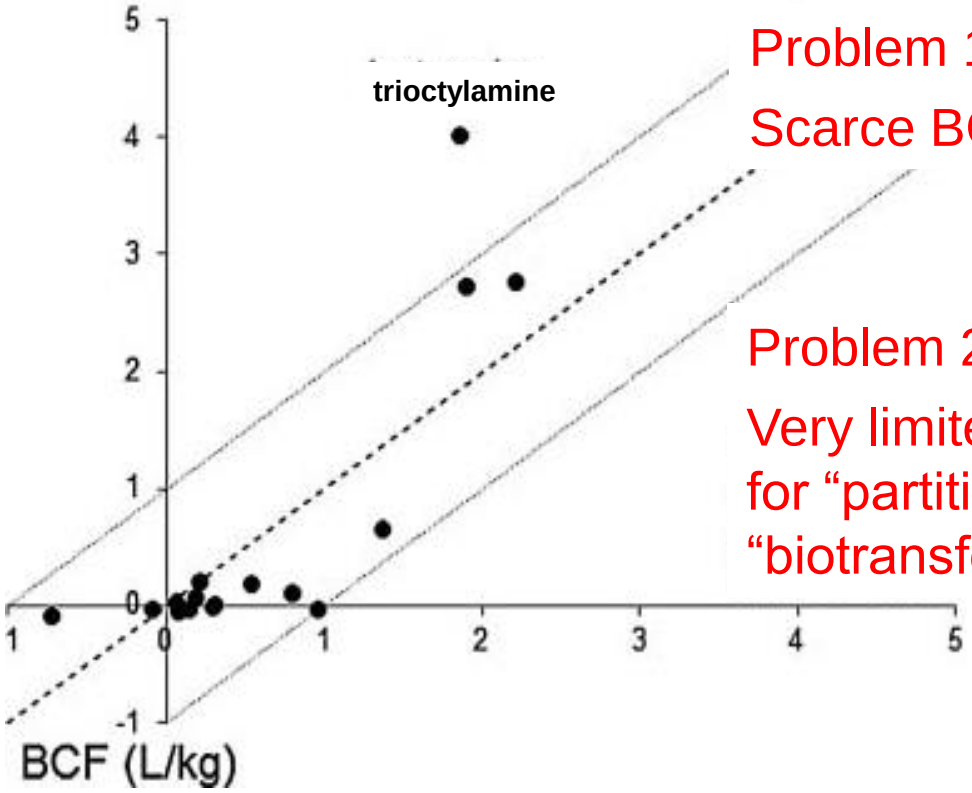


$$BCF_{SS} = \frac{C_B}{C_{WD}} = \frac{k_1}{k_T}$$

- Can address pH-dependence of BCFs
  - at gill: diffusive transport dominated by neutral form
  - in tissue: ions mainly sorb to membrane (*phospholipids*)
  - in liver: fish drug biotransformation rates ≠ human

IOC - BCF model* performance

78 BCF values for **IONIZED** acids
16 BCF values for **IONIZED** bases



Problem 1:

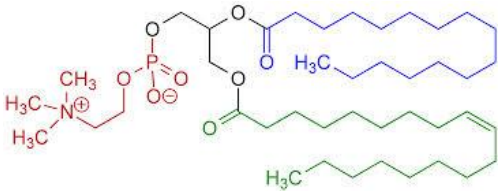
Scarce BCF data for >95% ionized IOCs

Problem 2:

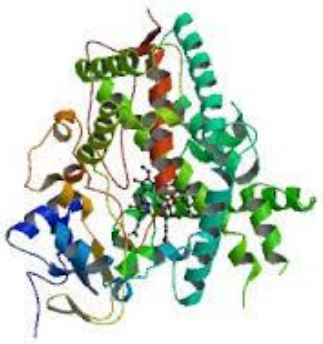
Very limited applicability domain for QSARs for “partitioning” (membrane) and “biotransformation rate” due to few data

* Armitage et al. 2013. Environ. Toxicol. Chem. 32, 115 - 128

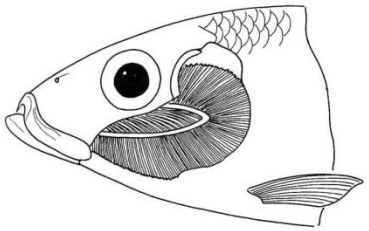
Objectives



1. Develop *new experimental data;*
   - Membrane-water partition coefficient (K_{MW})
   - Intrinsic fish hepatic clearance rate (*in vitro* S9 test)



2. Explore *development of new QSARs* to parameterize B models for IOCs;
   - Gill uptake rate: pH at gill surface
   - Improve/adapt QSAR for K_{MW} and k_M for IOCs



3. *Facilitate adaptation into existing screening tools*;
   - e.g., EPISuite - BCFBAF

Key IOCs tested

- ~50 IOCs >99% charged

1º amines	sulfates
2º amines	sulfonates
3º amines	carboxylic acids
4º amines	phenolic acids

- ~20 IOCs with BCF data available (ECO21 goal)

  direct comparison of accuracy of BCF-model
  BUT, non-ideal chemicals to improve QSARs

- ~30 model IOC structures (ECO21 extension)

  understand influence of specific molecular features
  active filling of knowledge gaps → systematic approach to expand applicability domains

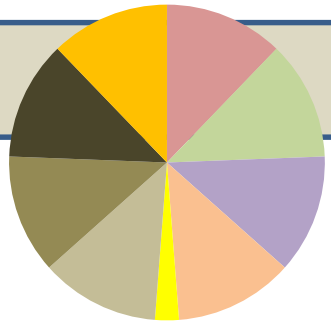
Membrane-water partitioning

K_{MW} for ion = ?

K_{OW} works for neutral compounds

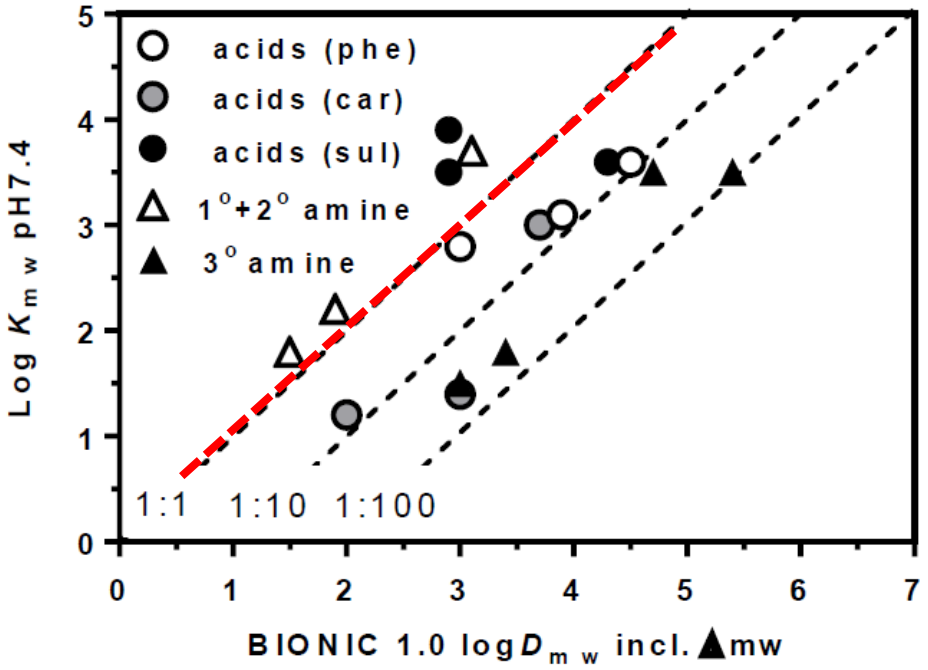
K_{OW} is a poor predictor for IOCs

K_{MW} data



<2012	25 Cations	50 Anions	QSAR
ECO21	20	14	
>2016	+150 IAM-HPLC	?	

Membrane-water partitioning



With 2013 " BIONIC v1 " K_{MW}-QSAR/assumptions:

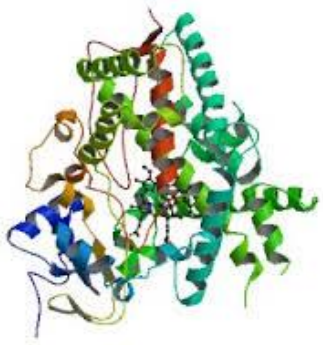
- 12 IOCs predicted within ± 10 x
- 5 IOCs over-predicted 10 - 100 x

New QSARs in development

Biotransformation (k_M)

- Current *in vivo* k_M QSARs includes 10 ionized IOCs
- may get more *in vivo* k_M IOC estimates with new BIONIC model

Rainbow trout liver homogenate (S9): *in vitro* clearance



- Phase I & Phase II enzymes active
- extrapolate to *in vivo* k_M
- intra- /inter- study consistency
- compare *in vitro* k_M with *in vivo* k_M

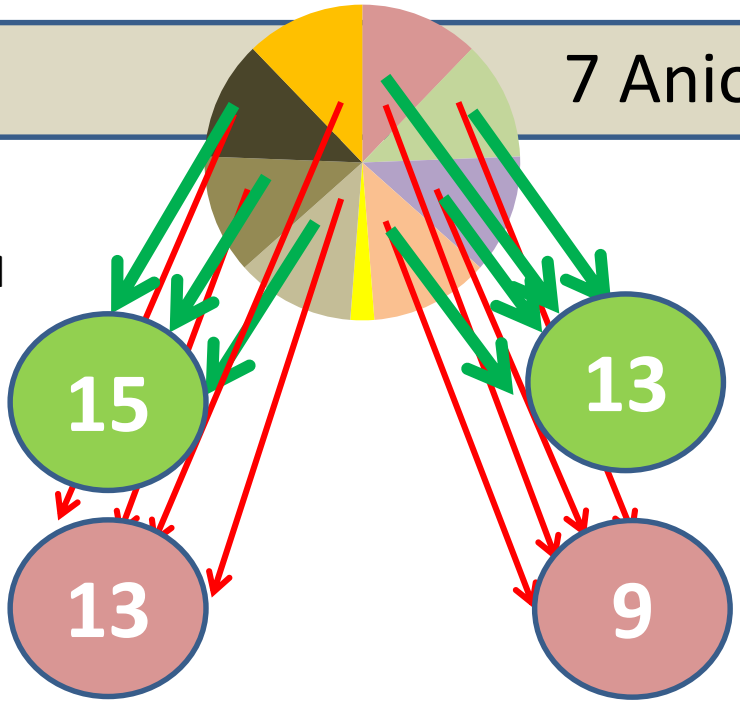
Biotransformation (k_M)

in vivo QSAR

IOCs >70% charged

***empirical* data**

in vivo 3 Cations 7 Anions QSAR



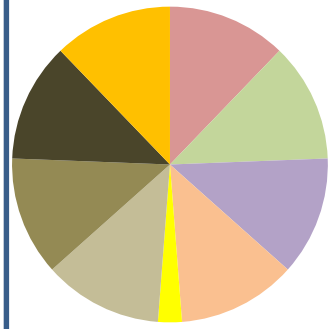
ECO21 : 50 *in vitro* k_M

significant k_M

insignificant k_M

Intrinsic hepatic clearance ($CL_{intr,in\ vitro}$)

In vitro data



- C_8-(NH_3^+)
- C_8-(NH_2^+C)
- C_8-($NH^+(C)C$)
- C_8-($N^+(C)(C)C$)
- C_8-SO_4^-
- C_8-SO_3^-
- C_8-CO_2^-

- C_{10}-(NH_3^+)
- C_{10}-($NH^+(C)C$)
- C_{10}-CO_2^-

- C_{12}-(NH_3^+)
- C_{12}-(NH_2^+C)
- C_{12}-($NH^+(C)C$)
- C_{12}-($N^+(C)(C)C$)
- C_{12}-SO_4^-
- C_{12}-SO_3^-
- C_{12}-CO_2^-

- does the …ionic group influence k_M ?
- …hydrophobicity ? (Only tested up to C_{12}…)
- …position of the ionic group ?
- …branching (steric effects) ?
- …additional functional groups ?

Gill uptake rate constant (k_1)

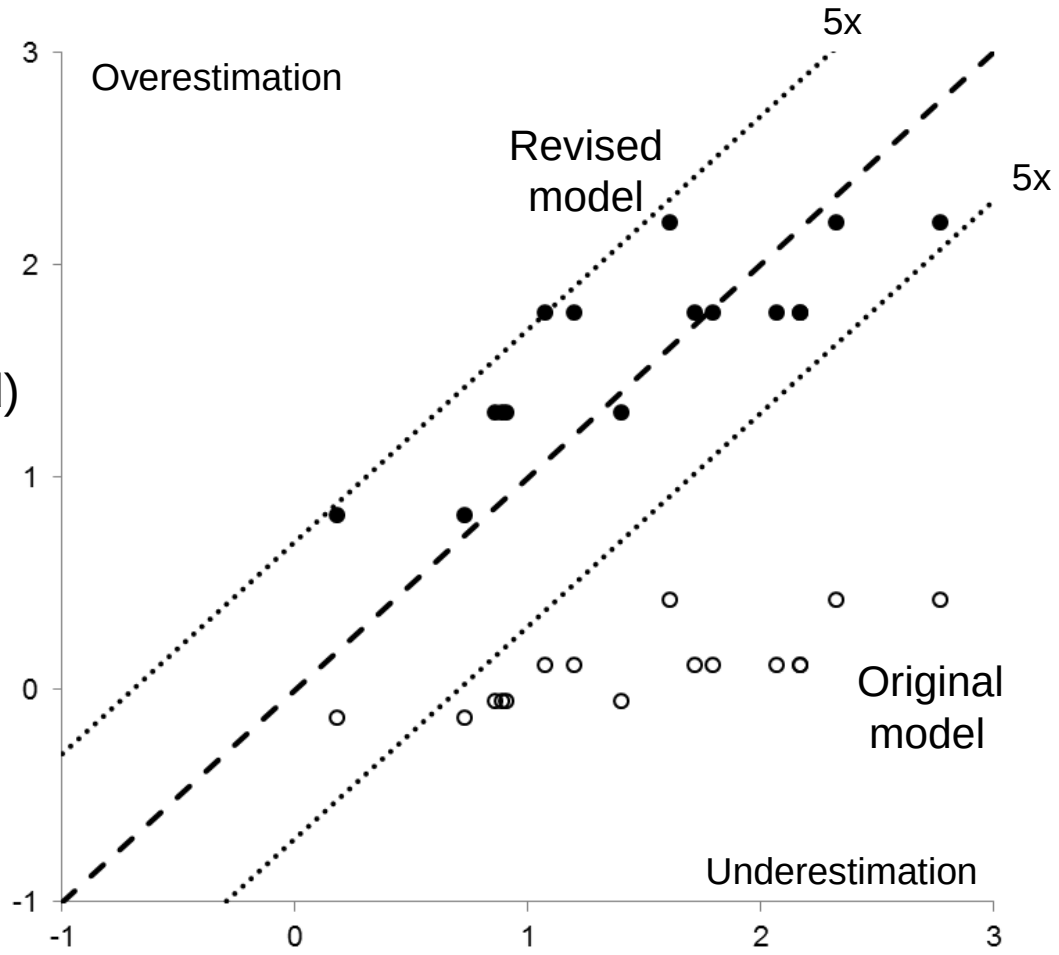
$$k_1 = \frac{E_W G_V}{W} \longrightarrow \begin{array}{l} E_W = f\,(\mathrm{p}K_a, K_{OW,N}) \\ G_V = f\,(\mathrm{size}, O_2, \mathrm{T}) \end{array}$$

k_1 database for IOCs

- Paucity of empirical data (*n* ~ 100)
- Modeled k_1 typically within a factor of 3-5 for most IOCs (3 case studies)
- Poor performance for highly dissociated IOCs (e.g., LAS, pK_a < 1) using *original* (2013) *model*
- Uptake of “charged form” explicitly considered (*implemented in BIONIC V2.0*)

ECO21

LAS: Revised vs. original k_1 model



LAS
C10-2
C11-2
C11-5
C12-2
C12-3
C12-5
C13-2
C13-5

* Tolls et al. 1997

Planned activity for Final Report:

Improved k_1 + empirical (k_M + K_{MW}) → BCFs

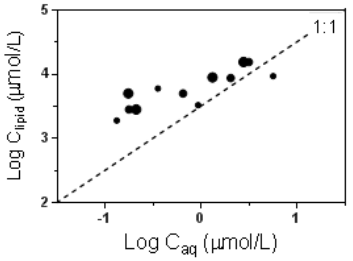
Original Model (Armitage et al. 2013)

Estimated model input parameters
(K_{OW}-based K_{MW}, k_M-QSAR)

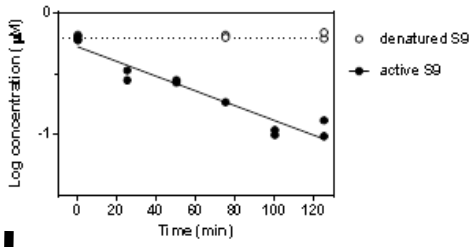
Predicted BCFs (L/kg)

BIONIC v2

Empirical model input parameters



K_{MW}



S9-based k_M

Predicted BCFs (L/kg)

Measured BCFs (L/kg)

ECO21 'continuation'

Can in vitro measurements improve BCF predictions ?

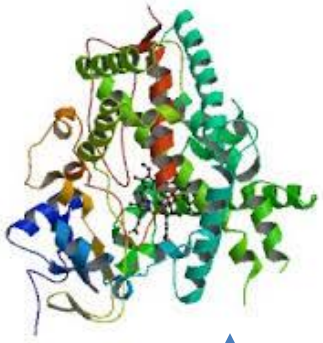
- *in progress*

Additional data gaps

- Full tissue data (phospholipids, plasma & structural proteins)
- specific factors (hydrophobicity) on IOC biotransformation rates

High tier needs:

- measured K_{PLIPW}, "K_{plasma}" & in vivo k_M (+ metabolites)



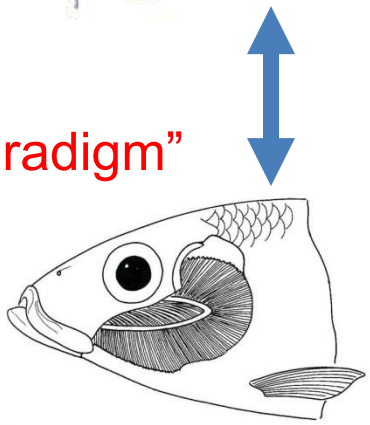
Lower tier needs: improved QSARs + IVIVE

- expand the chemical domain for **S9 – QSAR:**

  intrinsic clearance of IOCs, "part of k_M screening paradigm"
  shortcutting uptake uncertainties

- expand chemical domain for **$K_{MW,ion}$-QSAR:**

  move away from K_{OW} dependent extrapolation



Thanks

Questions?