A New BCF in silico Model Based on the Critical Body Burden (CBB) Principle

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INTRODUCTION

Bioconcentration studies are chronic studies with high cost and vertebrate animal use. While a **Bioconcentration Factor (BCF)** is used in regulatory ecotoxicology, alternatives to the aqueous testing method are needed for hydrophobics, notably the fish dietary accumulation test. This study includes the substance in food and measures depuration rate from the fish. This results in a BMF factor with limited regulatory relevance and can only be transformed with uncertainty into a BCF by estimating uptake (K1) via hypothetical uptake equations. NAMs that can replace the BCF and BMF studies are therefore desirable.

Historically, fish BCF has been linked to fish toxicity by the critical body burden (CBB) concept which states: **BCF (L/Kg) = CBB (Mol/Kg) / EC10 (Mol/L)** (McCarty *et al.,* 1992)

The aim of this model is to provide a quantitative BCF linking iSafeRat® fish toxicity HA-QSARs to their BCF using a CBB value and relating this to the concentration of the chemical in the medium at steady state up to a maximum hydrophobicity where BCF will not exceed 1.

METHODS

The model is based on a calculation method using CBB principles and hydrophobicity. Simple Linear Regressions or fixed values are selected on the basis of an initial evaluation of chemical class. The **Subcooled Liquid Water Solubility (SLWS)** is used as the descriptor rather than the log K_{OW} which is used in most other BCF models.

The calculation of BCF was developed from the chronic toxicity model for fish for MechoA 1.1 (non-polar narcotics) compounds following Bauer *et al.* (2018) using the iSafeRat® fish EC10 QSAR model with an R^2/Q^2 at *Ca*. 0.9. This model is based on experimental data from 32-day fish embryos/larvae studies. The relationship between the toxicity and the SLWS can be mathematically described using a simple linear regression until solubility of the substance is so low than no chronic toxic effects are observed. The model is separated into three phases using SLWS as the descriptor: a linear regression phase; a plateau phase and finally a phase where there is no toxicity beyond a solubility cut-off limit (Thomas *et al.,* 2019). Toxicity data are transposed to BCF values using the equation above as a "mirror image" of the toxicity data and a CBB value.

THE BIOCONCENTRATION FACTOR IS MODELLED BY COMBINING 3 CONCEPTS, BUILDING CONFIDENCE IN THE OUTCOME:

Ecotoxicity

Chemical activity

Critical Body Burden (CBB)

RESULTS

The results are graphically depicted below for MechoA 1.1 (non-polar narcotics) using log mol/L SLWS on the X-axis versus the fish EC10 data on the Y axis (graph a) with the corresponding regression and plateau (blue dotted lines) and finally toxicity cut-off point at the solubility (solid black) line. In graph b, the mirror image of this regression line is used (via the predicted CBB value, from the ecotoxicity regression where log solubility = 0, where equilibrium is expected between fish tissue and external medium). Thus as hydrophobicity increases, a corresponding plateau for BCF is expected at the same solubility values as the fish toxicity. Finally, for very hydrophobic substances, when the solubility cut-off level is reached, the solubility dictates the bioavailability of the test substance with increasing hydrophobicity and the BCF is expected to decrease following this solubility line.

No BCF data were used to create the regression lines in graph b as the ecotoxicity data were used as a surrogate training set. Thus experimental BCF data (e.g. coloured dots in graph b) were taken as the BCF validation set. As seen from the graph, the model remains slightly conservative for highly hydrophobic substances.

According to the data used in iSafeRat® acute and chronic fish toxicity QSARs, at a certain level of hydrophobicity, a plateau is reached where toxicity lies between the regression line and the solubility cut-off. After reaching the solubility line, acute and chronic toxicity are no longer observed.
It is hypothesised that corresponding mirror image plateaus are observed for BCF

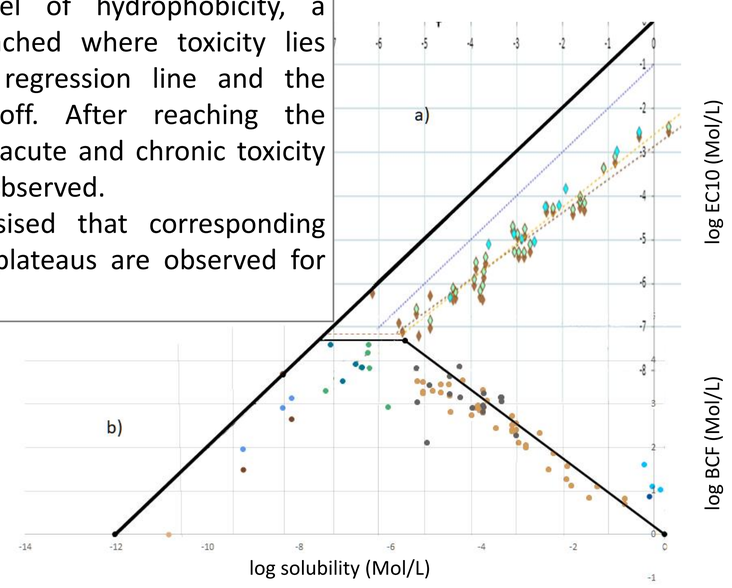

Figure 1: a) graph of chronic fish ecotoxicity vs hydrophobicity in log mol/L b) mirror image using fish BCF vs hydrophobicity in log mol/L

CONCLUSIONS

The poster describes a new methodology for QSAR production deviating from the routine QSAR « Training set => validation set » creation method generally prescribed. We postulate this actually strengthens the quality of the the prediction compared to standard QSAR methods for the following reasons:

1) It relies on a recognised, but until now poorly quantified, relationship between 3 ecotoxicogical properties;
2) The relationship between these properties increases the pertinence of the result as it explains a direct causal relationship between them (i.e. a mechanistic relationship);
3) It allows all valid data to be included in the validation set without a need to include them in the training set.

Initial results of this BCF QSAR are encouraging and QMRFs and QPRFs with statistical justification of the reliability of the results are available. The method has been particularly useful in cases where the test substance is highly hydrophobic as the model has distinct advantages over BCF/BMF tests (notably, the large number of vertebrate animals required and uncertainty in the estimation of the uptake (K1) parameter in the BMF study).

REFERENCES

1) McCarty LS, Mackay D, Smith AD Ozburn GW et al., (1992) Residue based Interpretation of Toxicity and Bioconcentration QSARs from Aquatic Bioassays: Neutral Narcotic Organics. Environmental Toxicology & Chemistry 11. 917-930.
2) Bauer F, Thomas PC, Fouchard S, Neunlist S (2018) High-accuracy prediction of Mechanisms of Action using structural alerts. Computational Toxicology, 7, 36-45.
3) Thomas PC, Bicherel P, Bauer P (2019). How in silico and QSAR approaches can increase confidence in environmental hazard and risk assessment. Integrated Environmental Assessment and Management 15, 1, 40–50.

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