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The Use of Toxicokinetic Models to Improve the Understanding of Internal Concentration for Ionisable Organic Chemicals in Fish

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Introduction

Currently, there are several thousands of chemicals in use globally covering a broad chemical space. Many of these chemicals ionise at environmentally relevant pH levels as acids, bases, and zwitterionics.

Whilst there is evidence that zwitterionic membrane lipids have a significant impact on uptake of ionised chemicals, the aim of this work is to investigate a simple approach considering $D_{o/w}$ to improve an existing simple one compartment model's prediction of fish internal concentrations as part of a tiered approach [1, 5], so that the impact of physicochemical properties (**pKa**) and environmental conditions (**pH**) on the ionised chemical uptake by fish can be incorporated.

Triclosan is used as a case study chemical to demonstrate the improvement of the prediction of fish internal concentration using the method proposed.

Triclosan Example

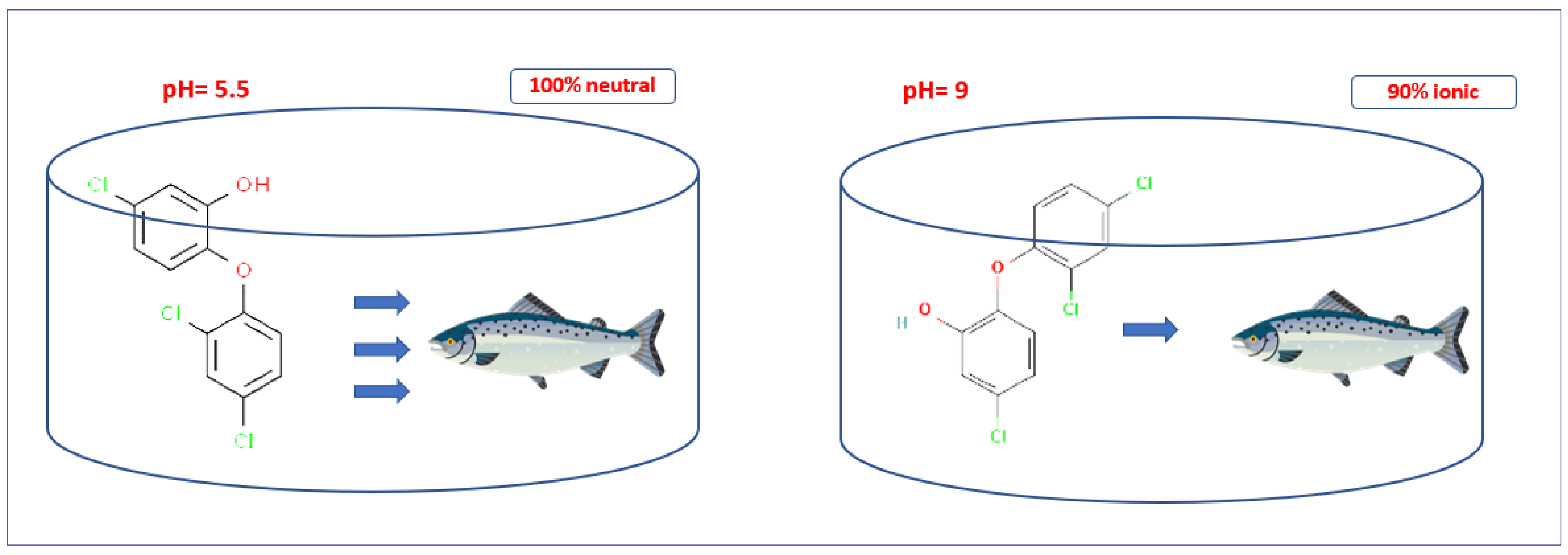

Figure 1: Illustrative example showing the difference in uptake of the same chemical

Objectives

1) Integrate ionisation into a one-compartment model for predicting the internal concentration of chemicals in fish species;
2) Estimate and compare the predictions of internal chemical concentration for ionic chemicals with and without the integration of ionisation

Methodology

Steady-state compartmental models [2, 3] predict internal concentration, y_∞, as the product of the octanol-water partition coefficient ($K_{o/w}$), the organism lipid fraction, v, and the external water concentration, y_e

$$y_\infty = y_e \cdot v \cdot K_{o/w} \quad (1)$$

However, many chemicals, including pesticides and pharmaceuticals can be ionised at environmentally relevant pH values. Therefore, to account for the potential impact of ionisable chemicals the distribution ratio ($D_{o/w}$) combined with the pH can be calculated potentially improving internal concentration predictions.

Summary and flow chart of the method (assuming chemical has a single ionisation site) is below. For multiple ionisation sites, chemical is regarded as an acid or a base while calculating the $D_{o/w}$ according to the ion that is most likely to be formed.

Establish chemical ionisation behaviour — 1. The SMILES string of a chemical is used as input for an ensemble of *in silico* tools (e.g. ACDLabs) to compute its pKa(s).

Choose a single pKa value — 2. To obtain a single pKa value the weighted average from multiple *in silico* predictions is calculated, by keeping the prediction uncertainty of each *in silico* tool into account.

Estimate log Dow values — 3. The so obtained pKa can be used to calculate the $D_{o/w}$, which can be used in place of the $K_{o/w}$:

$$log\ D_{o/w} = log\ K_{o/w} - \log(1 + 10^{A(pH - pka)})$$

Where $A = 1$ if the chemical is an acid, otherwise $A = -1$.

Results

A univocal pKa value for the chemical is calculated from the different pKa values provided by the different software used. In this poster, a realistic approach is to compute the average pKa value across different models, weighing each prediction by the inverse of their model standard deviation: in this way, the more robust predictions will have a stronger influence on the final pKa value.

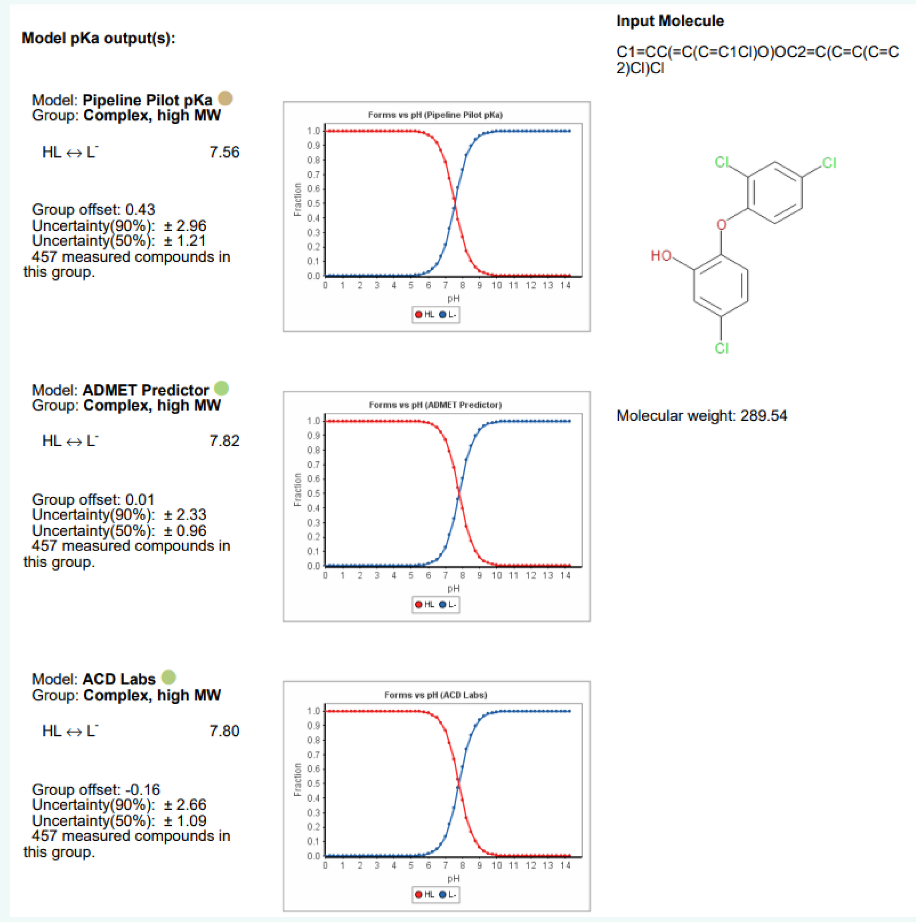

Figure 2: pKa values for triclosan generated by different in silico tools

The plot below shows how the $D_{o/w}$ could be a better choice to approximate the internal concentration of Triclosan ($K_{o/w}$ = 4.76) in zebrafish using an exposure scenario [4] where environmental concentration of triclosan is equal to 30 µg/kg (hence $y_e = 30$ in equation (1)). Next to the plot, a table showing how $D_{o/w}$ changes over the environmental related pH range (4-9) is displayed. We also assume the total lipid fraction of the fish is 0.067 as per literature [2].

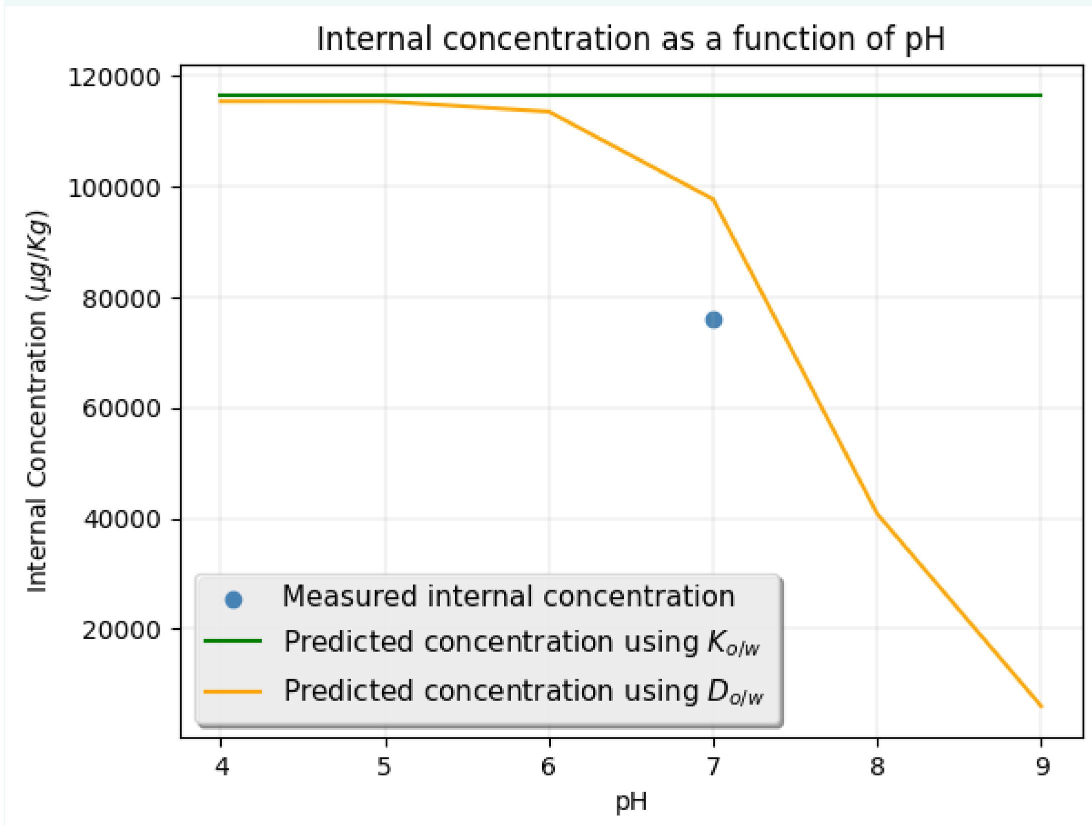

Figure 3: Using the $D_{o/w}$ instead of $K_{o/w}$ allows a more accurate estimate of the internal concentration, which was experimentally determined under neutral pH conditions by Orvos et al. [4].

pH	$logK_{o/w}$	$logD_{o/w}$
4	4.760	4.760
5	4.760	4.759
6	4.760	4.752
7	4.760	4.687
8	4.760	4.308
9	4.760	3.473

Table 1: The table shows $logD_{o/w}$ changing over different pH values. $logK_{o/w}$ remains unchanged.

Discussion

1. The use of $D_{o/w}$ *instead of* $K_{o/w}$ *for triclosan, an ionisable chemical, corrects its lipophilicity (and thus its permeability) for a certain pH.*
2. *The method provides a better estimate of the internal concentration of triclosan in zebrafish (in steady-state conditions),*
3. *As the method only considers the impact of environmental pH and chemical pKa among other factors that influencing fish update of ionised chemicals, further efforts can include consideration/inclusion of other models/parameters (such as* K_{MW}*) to better model ionisable chemicals.*

References

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