Safety & Environmental Assurance Centre

Unilever

Use of Simulation Methods to Predict Membrane-Water Partitioning and its Application within Environmental Risk Assessment

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1. Introduction

- In risk assessment, $logK_{OW}$ is used to predict hydrophobic properties in environmental systems.
- Determination of $logK_{OW}$ for ionisables and surfactants is empirically difficult due to their tendency to accumulate at the octanol-water interface. Predictive methods are also often unreliable [1]
- Octanol cannot adequately describe the interactions of polar, charged, or amphiphilic compounds within ordered 3D structures of biological membranes.
- $LogK_{MW}$ provides a more biologically realistic approach for these compound types.
- Experimental determination of $logK_{MW}$ can be complex and time consuming, therefore we have used coarse-grained simulation to predict $logK_{MW}$.
- The simulation approach is compared to other experimental and computational methods for predicting toxicity of narcotics, and applied to perfluoroalkyl acids (PFCAs) as a case study.

2. Methods

- As non-specific toxicity (narcosis) is driven by critical accumulation in the phospholipid membranes, only chemicals with narcotic mode of action were used in this work, including experimental ecotoxicity data (LC50s) from the Fathead Minnow (FHM) database [2]

Experimental $logK_{MW}$ data

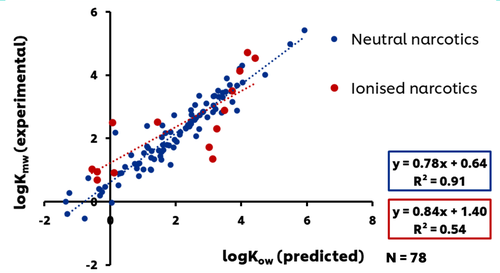
- Liposome and Immobilised Artificial Membrane (IAM) are internal and literature data [3], [4]

Predictive $logK_{MW}$ data

- COSMOmic (developed by COSMOlogic [5]) was used to predict $logK_{MW}$. Calculations were carried out using conformers generated from COSMOconf and micelle models from [6], using COSMOtherm 2021
- Simulation data were predicted using coarse-grained simulations, following the mapping and parametrisation scheme described in [7].

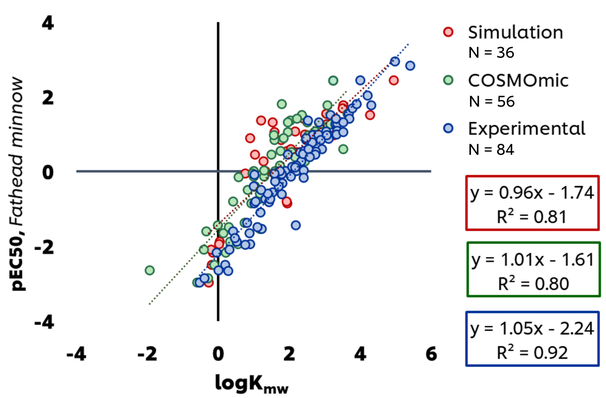
3. $logK_{MW}$ vs. $logK_{OW}$

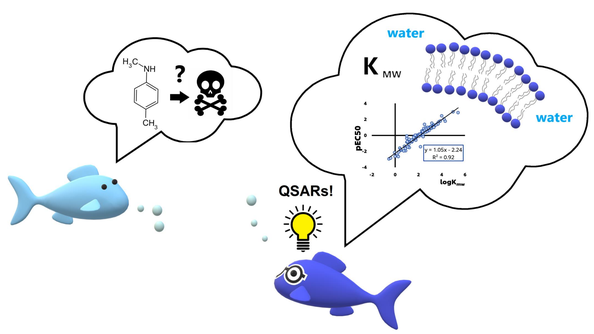
- $LogK_{OW}$ was predicted using ClogP (BioLoom v 1.7)
- A chemical was considered neutral if it was >85% neutral at pH where $logK_{MW}$ was derived
- $LogK_{OW}$ and $logK_{MW}$ are well correlated for the neutral narcotics, being in agreement with the previous findings [3].
- Although the data are limited the results also illustrate the differences between $logK_{OW}$ and $logK_{MW}$ for ionised chemicals



4. Using $logK_{MW}$ for predicting aquatic toxicity

- COSMOmic data, experimental data from [8],[9] and results from coarse-grained simulations for neutral narcotics are plotted against pEC50 values for Fathead Minnow [10]
- The results suggest a good agreement between predicted and experimental values and a potential for the use of simulated $logK_{MW}$ in developing QSARs for neutral narcotics.

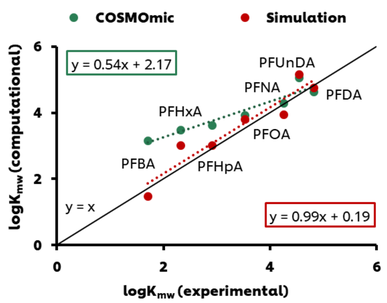


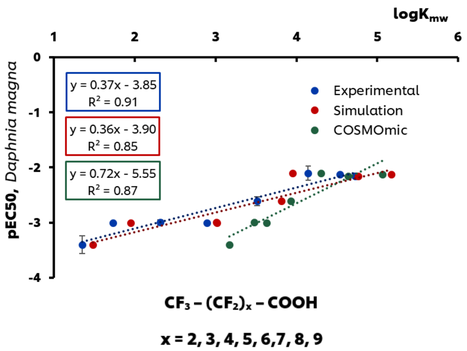


5. Case Study – PFCAs

A homologous series of PFCAs were used as a case study for predicting toxicity of ionisable surfactants as "hard to predict" chemicals, being both ionised and surfactants

- *Daphnia magna* ecotoxicity data were obtained from [10]
- Data from COSMOmic [8], experiments [8],[9] and coarse-grained simulations are compared
- Simulation method provides the significant improvement for prediction of $logK_{MW}$ for PFCAs, when compared to COSMOmic
- This suggests simulation method better captures interactions between PFCAs and biological membranes than COSMOmic





6. Conclusions/Future Work

- Whilst $logK_{OW}$ can be considered an adequate descriptor of neutral narcotic chemicals, $logK_{MW}$ provides a more realistic alternative for predicting aquatic toxicity for ionisable compounds due to its ability to account for more biologically relevant interactions with membrane phospholipids
- Experimental methods, COSMOmic and coarse-grained simulation could all be used to create QSARs for predicting aquatic toxicity of neutral narcotics
- Considering similarity between COSMOmic and simulation data, simulation is an attractive alternative for large or flexible molecules for which running COSMOconf can be prohibitively slow
- Future work includes extension of simulations to more hard-to-test substances such as surfactants and charged molecules

References

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