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Deriving fish and *Daphnia* toxicity QSARs for anionic surfactants by using experimental and computational membrane-water partition coefficients

Andrea Gredelj[1], Elin L. Barrett[1], Jayne Roberts[1], Eoin Kearney[2], Alexandre Teixeira[1], Nicola Haywood[1], Geoff Hodges[1], Mark A. Miller[2]
[1] Safety and Environmental Assurance Centre, Unilever, Bedford, MK44 1LQ, UK [2] Department of Chemistry, Durham University, South Road, Durham DH1 3LE, UK

1. INTRODUCTION

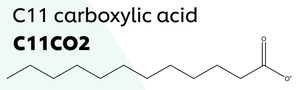
- **Quantitative Structure Activity Relationships (QSARs)** are a viable alternative to *in-vivo* toxicity testing of chemicals.
- Many (eco)toxicity QSARs are hydrophobicity-based relationships using the **octanol-water partition coefficient, logK_{OW}** as a common descriptor for chemicals' toxicity.
- Determination of logK_{OW} for ionisable chemicals 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.
- **Membrane-water partition/distribution coefficient (logK_{MW}/D_{MW})** provides a more biologically realistic approach for these compound types.
- As experimental determination of logK_{MW} /D_{MW} can also be complex and time consuming, we have calculated logK_{MW} /D_{MW} using the regression method developed by Droge *et al.* [2] and coarse-grained simulations [3] to develop **fish and *Daphnia* toxicity QSARs for anionic surfactants**.

2. METHODOLOGY

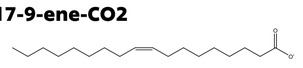
- Previously, we have shown good correlation of simulated logD_{MW} against experimental values of chemicals, and presented several QSARs with homologue series of anionic surfactants successfully using logD_{MW} as an (eco)toxicity proxy [4,5].
- Here, database of **fish and *Daphnia*** literature toxicity data [6-8] containing **mono constituent anionic surfactants** (Table 1) was compiled and used to develop new QSARs.
- To address logD_{MW} experimental data gaps regarding the chemical space coverage (limited surfactant groups) we are also using two computational methods for logD_{MW} (Droge *et al.* [2] & coarse-rained simulation [3]), with the advantages and disadvantages of various methods for deriving logD_{MW} being discussed.
- Finally, we have used QSARs based on the same chemical space to make preliminary comparisons of species sensitivity for fish and *Daphnia*.

Table 1. List of used anionic surfactants (with chemical structures and **abbreviations**)

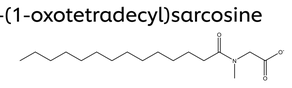
C11 carboxylic acid **C11CO2**



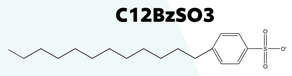
C17-9-ene carboxylate **C17-9-ene-CO2**



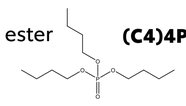
N-(1-oxotetradecyl)sarcosine **C14-SAR**



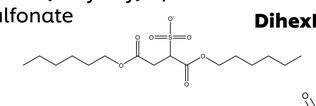
Dodecylbenzenesulphonate **C12BzSO3**



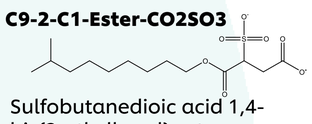
Phosphate ester **(C4)4PO4**



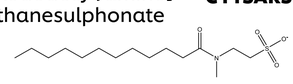
1,4-Bis(hexyloxy)-1,4-dioxobutane-2-sulfonate **DihexDiEsterSO3**



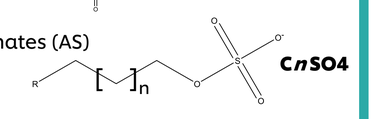
Disodium C-isodecyl sulphonatosuccinate **C9-2-C1-Ester-CO2SO3**



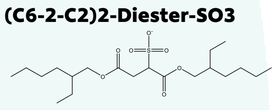
Sodium 2-[methyl(1-oxododecyl)amino] ethanesulphonate **C11SARSO3**



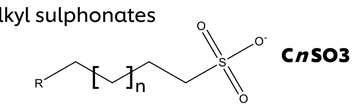
Alkyl sulphates (AS) **C*n*SO4**



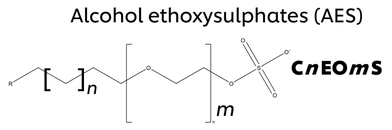
Sulfobutanedioic acid 1,4-bis(2-ethylhexyl) ester **(C6-2-C2)2-Diester-SO3**



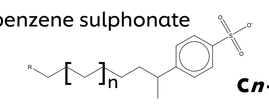
Alkyl sulphonates **C*n*SO3**



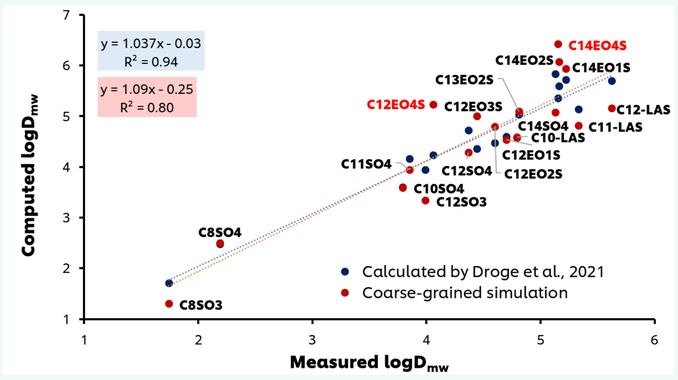
Alcohol ethoxysulphates (AES) **C*n*EO*m*S**



Linear Alkylbenzene sulphonate (LAS) **C*n*-LAS**



3. LogD_{MW} METHODS EVALUATION



Comparison of experimentally determined logD_{MW} with computational data indicates good correlation between the two.

Figure 1. Comparison of calculated logD_{MW} with measured logDmw (SSLM method from Droge, 2019 [9] & Droge et al., 2021 [3] & liposome internal data from SEAC, Unilever)

- The Droge *et al.* method is a multiple regression based equation with limitations in surfactant group coverage (e.g. sarcosinates, phosphate esters), whereas simulation method is not restricted to certain surfactant groups.
- However, we have identified a limitation in simulation method for chemicals containing ethoxylate units (EO > 4).

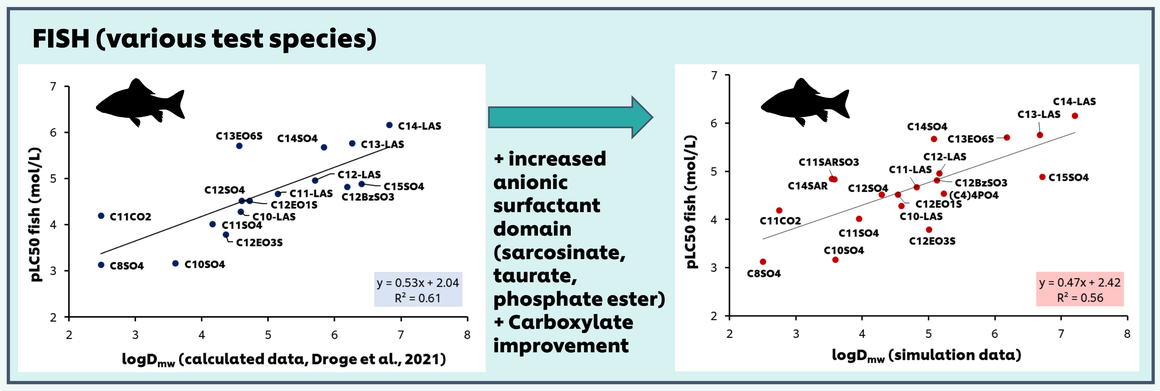


Figure 2. Comparison of fish QSARs based on calculated logD_{MW} by the Droge *et al.* regression and coarse-grained simulations

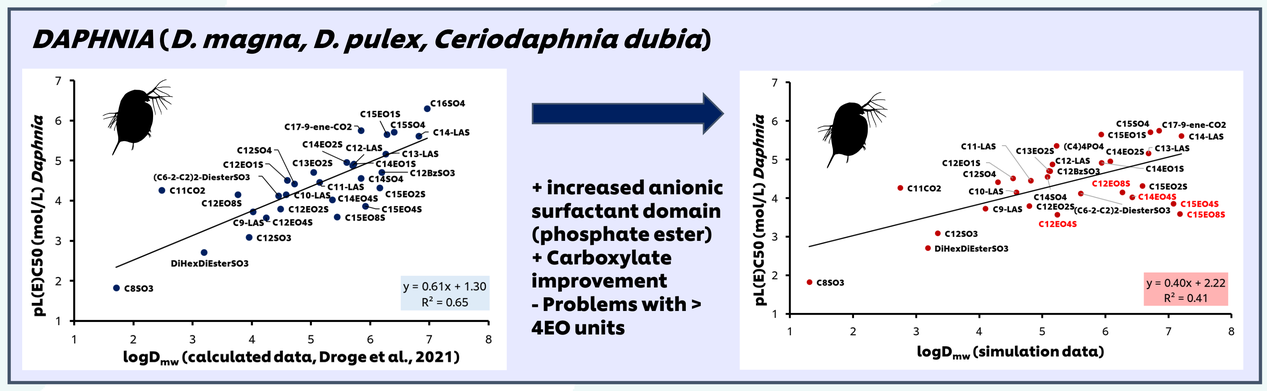


Figure 3. Comparison of *Daphnia* QSARs based on calculated logD_{MW} by the Droge *et al.* regression and coarse-grained simulations

4. FISH & *DAPHNIA* logD_{MW} QSARs

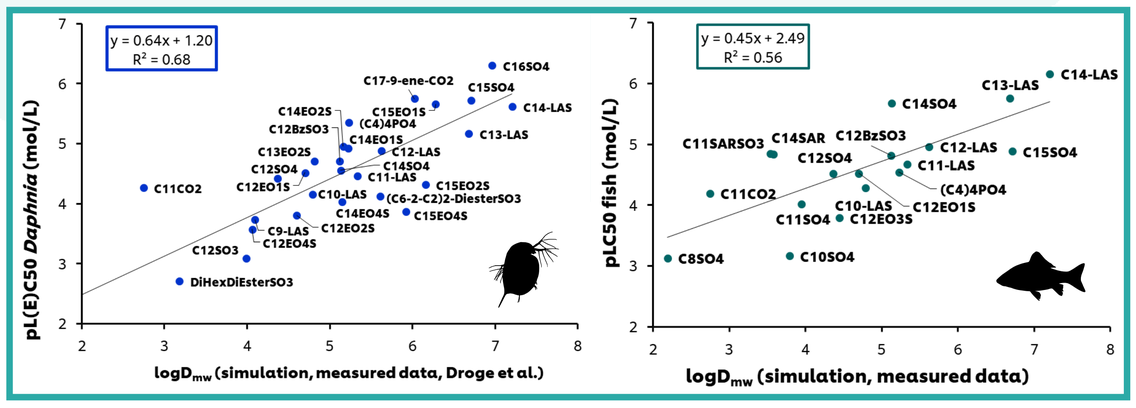


Figure 4. Anionic surfactants fish and *Daphnia* QSARs

- This work represents the first step towards generating logD_{MW} based QSARs for anionic surfactants with potential to be used in **environmental risk assessment** and/or **regulatory submissions** avoiding the need for unnecessary fish testing

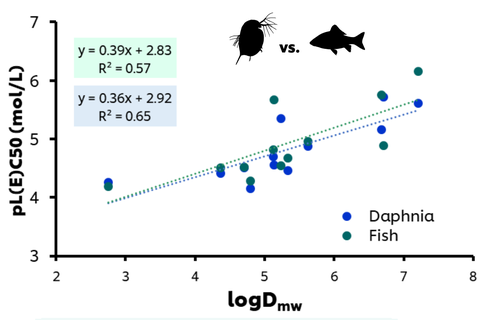


Figure 5. Fish and *Daphnia* QSARs comparison

- QSARs were compared for chemicals where both *Daphnia* and fish toxicity data are available (including LAS, AS, AES, phosphate esters).
- Statistically significant differences were not observed between slopes and intercepts, indicating there is **potentially no difference between sensitivity** of these trophic levels to anionic surfactants.

5. CONCLUSIONS AND FUTURE WORK

- Using literature (eco)toxicity data for a variety of mono constituent anionic surfactants we have shown it possible to generate **general anionic surfactant – based QSAR** using logD_{MW} for the prediction of aquatic toxicity to fish and *Daphnia*.
- **Species sensitivity** between fish and *Daphnia* based on the same chemical dataset suggests that there is no difference between the two. This could provide the opportunity to waive the need for acute fish toxicity testing for anionic surfactants. However, further work would be required to expand the data set to provide a more robust analysis.

Development of a reliable computational logD_{MW} method which covers a wide chemical space is required. Further work has been identified to **refine the approach for chemicals with EO > 4.**

To improve the QSAR regression, consideration could be given to **include additional (eco)toxicity data from multi-constituent surfactants**, however this requires previous knowledge of the chain length distribution in order to predict a representative logD_{MW}.

6. REFERENCES

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