Predicting Aquatic Toxicity of Surfactants Using Simulated Coarse-Grained Membrane-Water Coefficient Derived QSARs

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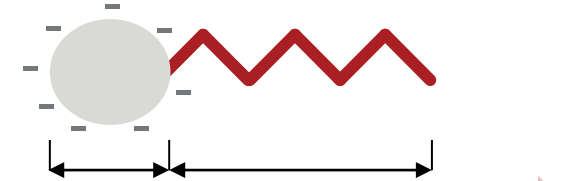
Surfactants – environmental assessments & hydrophobicity (1)

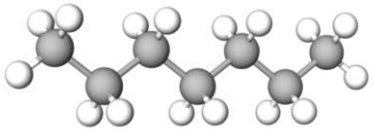
- Amphiphilic structures



Focus on two **case studies** using **anionic** surfactants* for method development

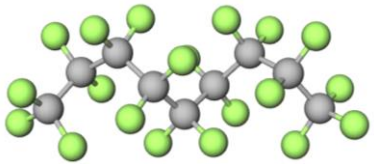
*(-) charge at pH 6-9

Hydrocarbon (HC)



- Anionic HC surfactants are the most widely used surfactants[1]
- > 45 registered under REACH with > 100 t/y [2]
- Mostly readily biodegradable, generally not bioaccumulative in fish due to biotransformation[2]

Perfluorocarbon (FC)



- Per- and polyfluorinated substances (PFAS)
- 1000s of chemicals
- C-F bond is extremely stable – environmental persistence[3,4]
- Many (proven as) toxic and bioaccumulative[3,4]

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[1] Cowan-Ellsberry et al., 2014 [2] Ribbenstedt et al., 2021 [3] Gluge et al., 2020 [4] Ankley et al., 2020

Surfactants – environmental assessments & hydrophobicity (2)

- **Octanol–water partitioning/distribution coefficient (K/D_{ow})** → common hydrophobicity predictor
- Chemical hydrophobicity ~ bioaccumulation & toxicity (baseline/narcosis)

→ common **Quantity – Structure-Activity Relationships (QSARs)**

- 30-40 y of regulatory use, working well for small neutral chemicals, very useful in exposure, hazard, and risk assessment[1]

Octanol – water partition coefficient (K_{ow}) for surfactants/surface active substances

- Experimental determination is unreliable (e.g. surfactants emulsifying octanol & water)[2]
- *In-silico* predictions are often uncertain[2]
- Octanol cannot adequately describe the interactions of polar, charged, or amphiphilic compounds within ordered 3D structures of biological membranes[3]

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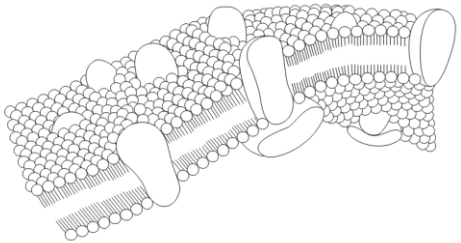
[1]Hermens et al, 2013 [2]Hodges et al, 2019 [3]Klüver et al, 2019

Membrane-water partitioning/distribution coefficient (K_{mw}/D_{mw})



$$\log D_{mw} = \frac{\log[solute]_{membrane}}{\log[solute]_{water}}$$

- **Phospholipid bilayers** used as a model for cell membranes
- **Experimental methods:**
  1) Liposomes (“gold standard”)
  2) SSLM (solid-supported lipid membrane)
  3) HPLC-IAM (High-performance liquid chromatography - Immobilized Artificial Membrane)
- **Computational/predictive methods:** 1) Predictions from K_{ow}, 2) fragment approach, 3) COSMOmic/COSMO-RS

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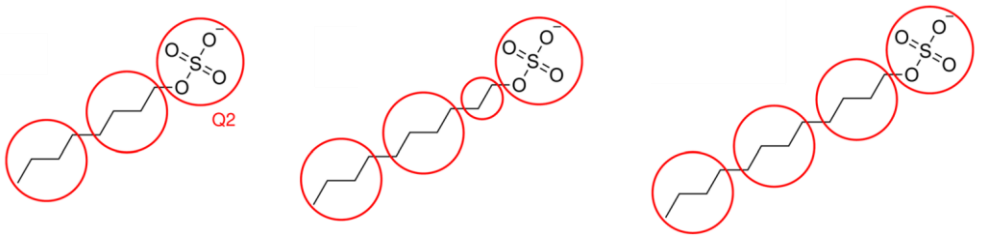
Potter et al, 2023

Coarse-grained simulations for D_{mw}

- **Coarse-grained (CG) simulations** can be used for high-throughput calculations of log D_{mw}
- CG allows for combining groups of atoms into interaction sites known as **'beads'**
- The **Martini force field** is a prominent CG model for biological systems
- Further development of previous work[1,2] and validation for anionic HC and FC surfactants
- Compared with literature and newly generated D_{mw} values (liposomes, SSLM)

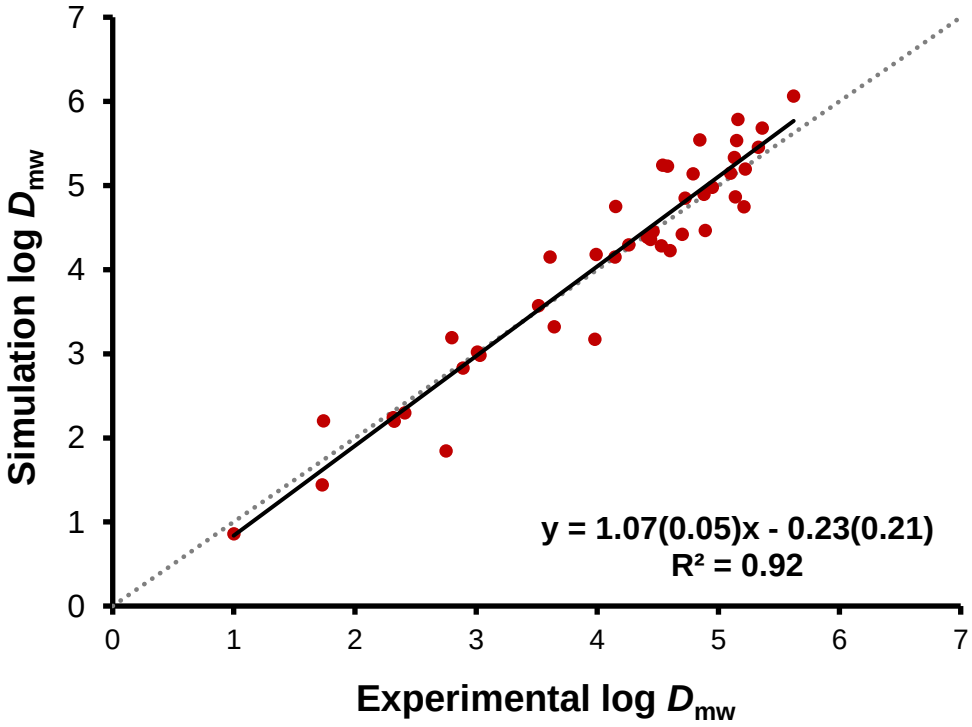


Example of Martini 3 mappings for alkyl sulfates (AS) from Potter et al., 2023

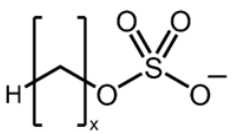
[1] Potter et al., 2021

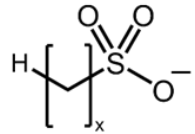
[2] Potter et al., 2023

Comparison of CG simulation against experimental D_{mw}

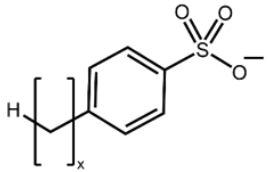


- 43 surfactants with experimental values

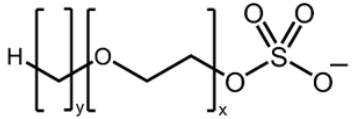




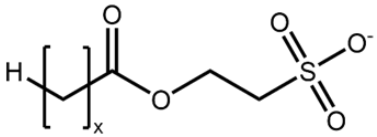
Alkyl sulfates (AS) and sulfonates[1]



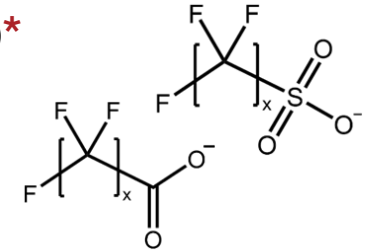
Linear Alkylbenzene Sulphonate (LAS)[2]



Alkyl Ether Sulphates (AES)*



Alkyl isethionates (AI)*



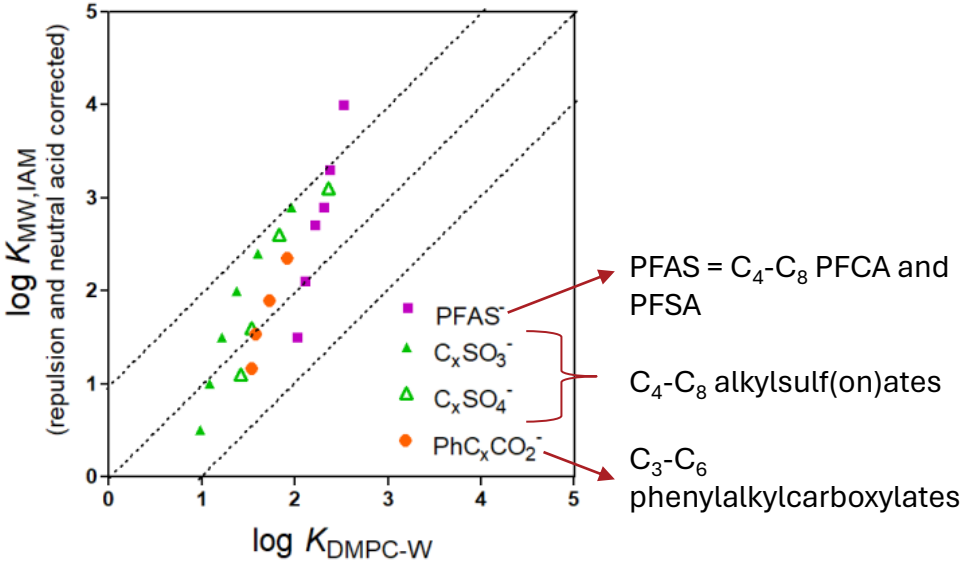
Perfluoro-sulfonic (PFSAs) and -carboxylic (PFCAs) acids[1,3]

[1]Droge, 2019 [2]Droge et al., 2021 [3]Ebert et al., 2020 * New experimental values

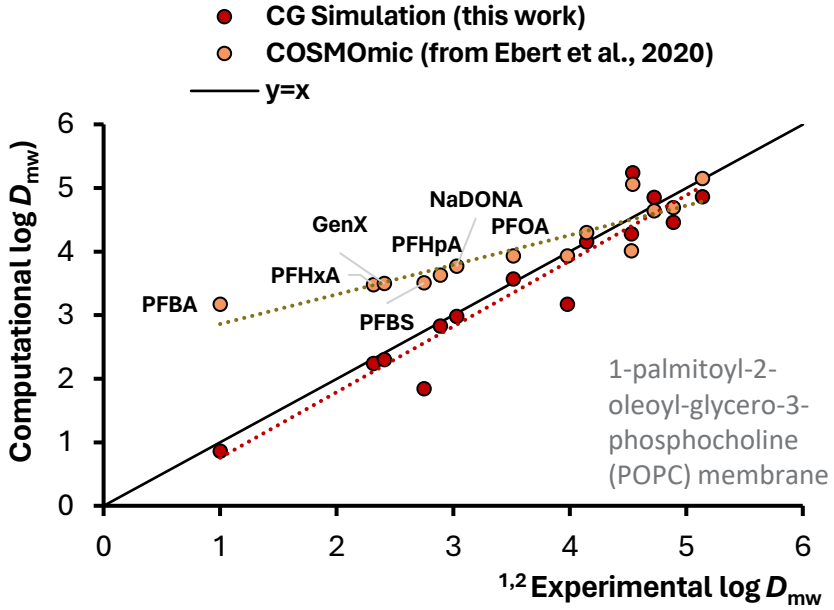
CG simulation method – advantages

- COSMOmic/COSMOtherm tool – applicable for charged compounds

Comparison of COSMOmic generated logK_{mw} and K_{IAM} of different HC and FC surfactants (from Droge, 2019)

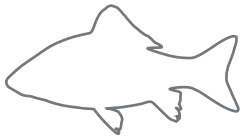


PFCAs/PFSAs and their alternatives

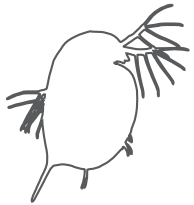


[1]Droge, 2019 [2]Ebert et al., 2020

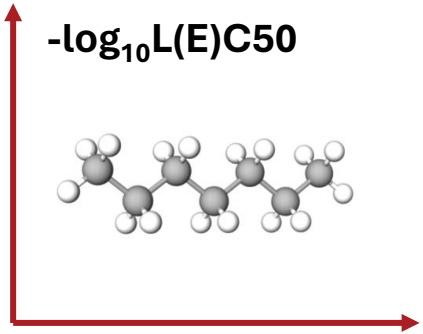
Building (eco)toxicity QSARs with simulated D_{mw} (2)

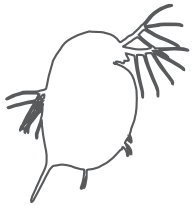


96h LC50s

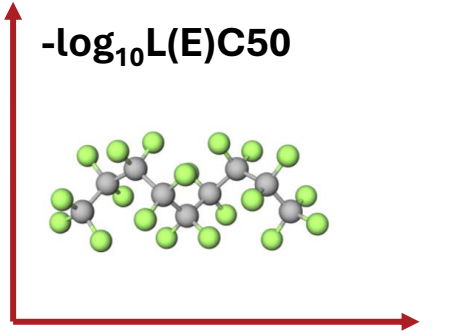


48h L(E)C50s





48h L(E)C50s



- Public ecotoxicity **databases** (USEPA Ecotox, Envirotox), **ECHA dossiers**, **scientific literature**, risk assessment **reports** (e.g. HERA)

- **No restrictions** regarding the choice of fish species, *Daphnia sp.* and *Ceriodaphnia* for daphnids
- Data from experiments with **solubility issues** detected were omitted
- Only **mono-constituent** surfactants
- Geometric means of equivalent endpoints for the same surfactant
- …

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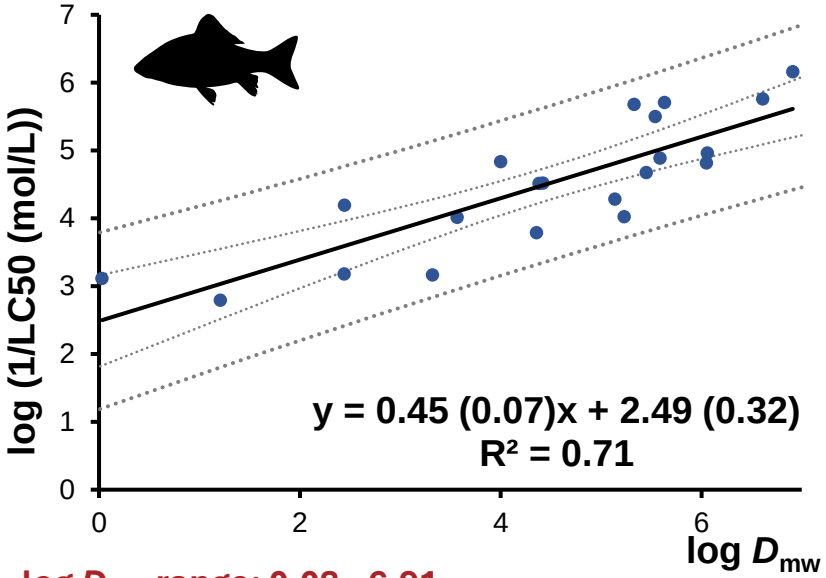
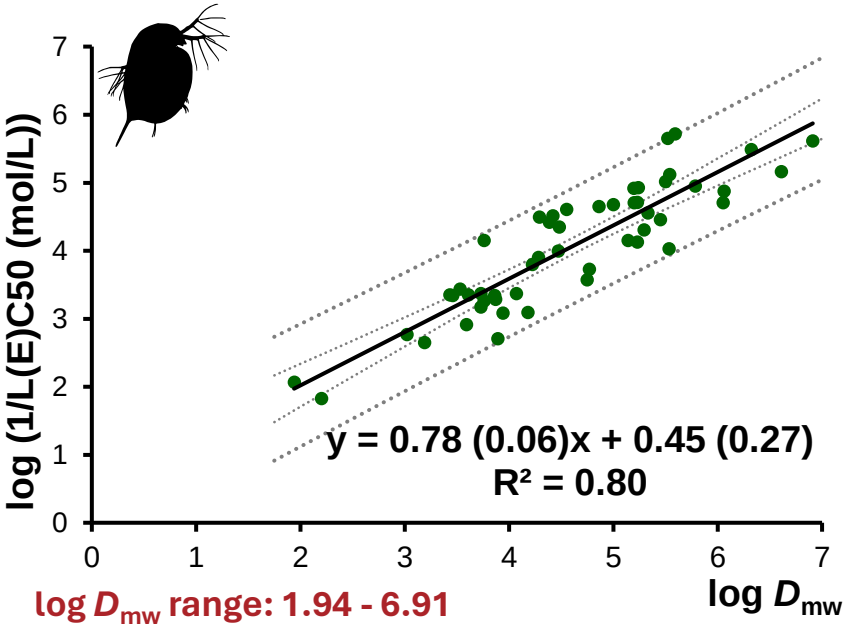
Case study 1- HC surfactant QSARs

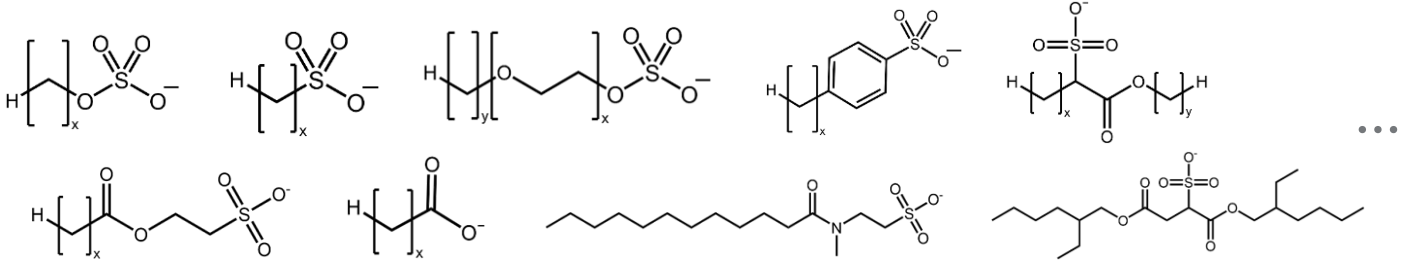


log D_{mw} range: 0.03 - 6.91
MW range: 158 - 566



log D_{mw} range: 1.94 - 6.91
MW range: 216 - 619

Structural domain/subclasses:



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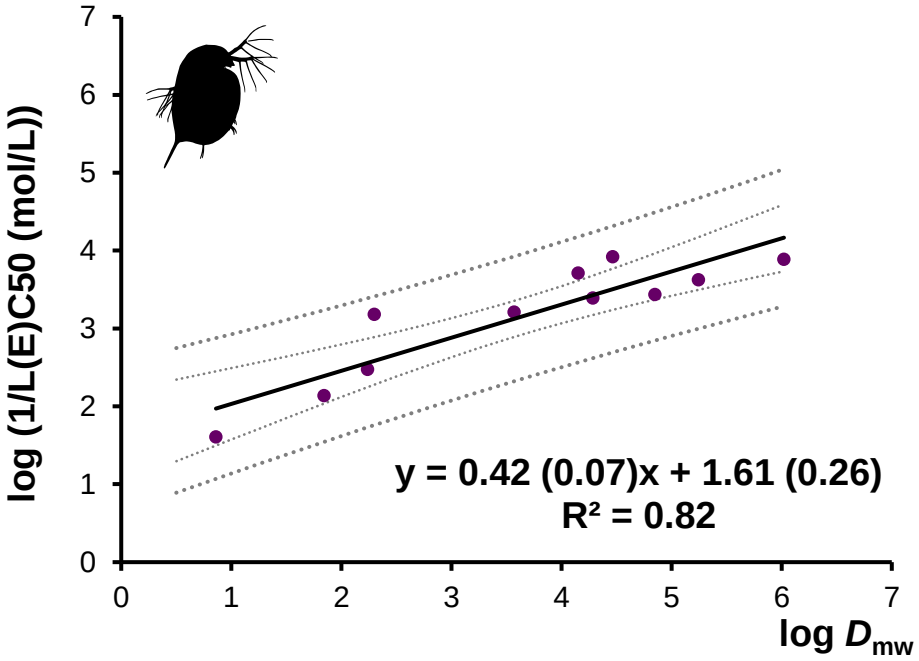
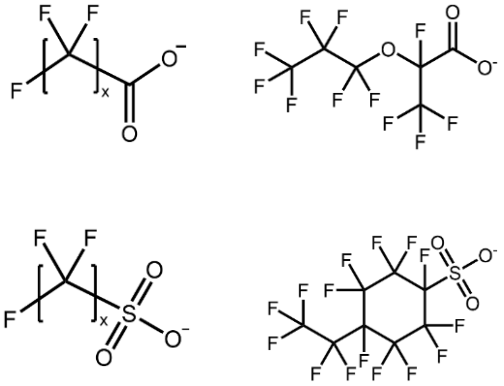
Case Study 2 - FC surfactant QSARs



log D_{mw} range: 0.86 - 6.02
MW range: 213 - 613

Structural domain/subclasses:



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Significance and future work

- Using the CG simulation method for predicting D_{mw} is a **promising approach for charged surfactants**, without depending on their functional groups and backbone types
- D_{mw} can be successfully employed to develop QSARs for fish and daphnid toxicity, that are not species-specific but **inclusive of the whole trophic levels**
- Promising approach **for (eco)toxicity screening of anionic surfactants** and as a part of the weight of evidence approach
- Further work on cationic/zwitterionic surfactants and other ionisable chemicals

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Thank you for your attention!