Membrane-water partition coefficients to aid ionogenic surfactant risk assessment

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ISSUE

- Surfactants are bulk volume down-the-drain chemicals
- Chemical fate & toxicokinetic models rely heavily on K_{OW} values
- K_{OW} guidelines 107/117 are not suitable for surfactants
- K_{OW} QSARs are highly uncertain for most surfactants
- ionic/permanently charged surfactants outside applicability dom.

SOLUTION

- Partitioning of surfactants into phospholipid membranes (K_{MW}) can be directly measured with small experimental error [1,2,5]
- Partitioning of **ionic surfactants** into phospholipid can be predicted using quantum-chemistry based calculations [2,3]
- K_{MW} likely dominates bioconcentration in organic tissue,[4] and thus likely relates to baseline toxicity

INNOVATIVE APPROACH

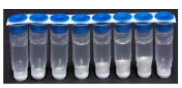
1. Calculate K_{MW} with COSMOmic DMPC[3] for relevant species
2. Evaluate experimental feasibility[2] ($1.5 < \log K_{DMPCW} < 6$), look for smaller chain surfactant homologues for extrapolation
3. Evaluate need for experimental validation ($\log K_{DMPCW} > 3$?)
4. Select experimental methodology: dialysis[1,6], solid supported lipid membranes (SSLM)[2,5], IAM-HPLC[2,7])

consider: narcotic LBB (~100 mmol/kg lipid) / $K_{MW} \approx LC_{50}$ …

consider: K_{MW} does not replace soil sorption coefficients …

K_{MW} DATA AVAILABILITY

- 9 **alcohol ethoxylates** + QSAR[1] (e.g. $\log K_{MW}$ $C_{12}EO_8$ = 3.4)
- 18 **cationic** surfactants + COSMOmic validation[2] (e.g. $\log K_{MW}$ C_{10}benzalkonium = 4.0, dioctylamine = 4.6)
- 16 **ionic liquid** salt cations[5] (e.g. $\log K_{MW}$ $C_{12/1}$imidazolium = 3.8)
- 15-20 **anionic** surfactants (in prep.) (e.g. $\log K_{MW}$ $C_{12}SO_3^-$ = 4.0)
- 5-10 **zwitterionic** surfactants (in prep.) (e.g. $\log K_{MW}$ $C_{12}N^+O^-$ = 3.5)
- fluorinated surfactants (in prep.)

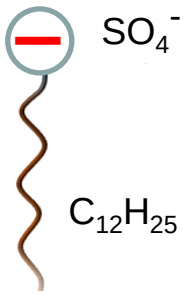


needed: OECD protocol ? K_{MW} QSARs + COSMOmic validation for all surfactant types

"SLS" example

https://echa.europa.eu/information-on-chemicals

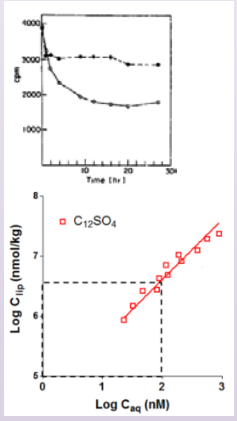
- **K_{OW} is highly uncertain**



"logK_{OW}"	source
1.6	Leo & Hansch
0.8	OECD 123 (slow stirring)
1.7	EPISuite
-2.0	max. $sol_{oct.}$ /CMC (*recommended*)

$\log K_{OW}$ range -2 to 1.7: factor 5000

- **K_{OW} also strongly underestimates K_{MW}**

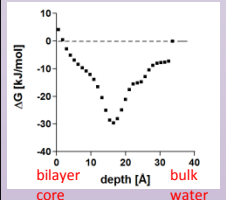


Kalmanzon *et al.* 1997[6]
^{35}S-SLS & liposome dialysis measured near CMC:
$\log K_{MW}$ = 3.5

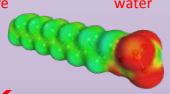
Droge 2018 (in preparation)
SLS & solid supported lipid membanes <<CMC:
$\log K_{MW}$ = 4.6

K_{MW} factor 3.000.000 > $K_{OW,recommended}$

- **K_{MW} can be accurately predicted**



COSMOtherm's COSMOmic module
TZVP level for all 3D conformers.
3D hydrated DMPC input.[3]
perform calculations in 33 steps:
bulk water → membrane core.



weighted $\log K_{DMPC-W}$ = 4.4

$K_{DMPC-W,calculated}$ factor ~2 < $K_{MW,measured}$

K_{MW} + LBB approach: good toxicity predictor

fish (sheepshead minnow) experimental 96h-LC_{50}
14 µM

LBB predicted LC_{50}
2.5 µM

ref 1: Muller et al ET&C 1999, p. 2191
ref 2: Timmer & Droge ES&T 2017, p. 2890
ref 3: Bittermann et al. J. Phys Chem. B 2014, p. 14833
ref 4: Armitage et al. ET&C 2013, p. 115
ref 5: Dolzonek et al Environ. Poll. 2017, p. 378
ref 6: Kalmanzon et al. Bioch. Bioph. Acta 1997, p.148
ref 7: Droge Anal. Chem. 2016, p. 960