CEFIC Long-range Research Initiative
Request for Proposals (RfP)

Code and Project Title:
LRI-ECO37: Development and validation of alternative methodologies for predicting bioaccumulation of surfactants

Background

Surfactants, which are comprised of non-ionic, anionic, cationic and zwitterionic structures, are a group of chemicals for which it is difficult to obtain reliable partitioning (log Kow) or bioconcentration factor (BCF) data for inclusion in current models used for performing environmental risk assessments. This issue affects a number of inter-industry organisations such as ERASM, EOSCA and ISOPA. The difficulties revolve largely around the intrinsic properties of surface active substances to adsorb to surfaces and to accumulate at phase interfaces. Despite the limitations of current methods for estimating bioaccumulation potential for a surfactant, submission of log Kow data for surfactants for the purpose of environmental risk assessments is required under REACH, though is not accepted for surfactants under the Harmonised Offshore Chemical Notification (OSPAR HOCNF) guidelines. Reported experimental BCF data for surfactants are limited [1,2], whereas QSARs based on log Kow data for estimating a surfactant BCF are necessarily based on either unreliable or unrepresentative log Kow data, since no surfactant data will be in the training and validation sets.

Most BCF models for organic contaminants take the lipid phase as a single entity and Kow as single parameter to estimate BCF in fish. It has been proposed that, for ionic compounds, distribution coefficients of the neutral and charged form to phospholipids (membranes), neutral lipids (storage lipids) and proteins are needed in BCF models [3]. Distribution coefficients to neutral lipids may still be estimated from Kow, but sorption to membranes include more specific interactions and cannot be modelled via Kow [4-6]. Information about membrane partitioning of organic compounds is even more relevant for interpreting effect concentrations because the cell membrane is the target site for many chemicals. For compounds that elicit their toxicity via narcosis, it has been shown that the internal concentration in the cell membrane of neutral non-polar and polar compounds is relatively constant [7-9]. The development of a model or refinement of an existing model (e.g. BIONIC v2 [10]) is required for use in a tiered approach leading to more refined calculations of BCF values for the different classes of surfactants. The applicability domain of the model should cover a sufficiently wide range and number of surfactants. The surface activity of surfactants is not considered to be a problem when determining Klipw so long as the concentrations are kept below the Critical Micelle Concentration (CMC) [11]. Measurement of Klipw data for typical surfactants using different methods (e.g. liposomes, IAM) and also for neutral lipids and proteins storage lipids with available experimental BCF values data are required which would allow for comparisons of the Klipw properties between the classes of surfactants and possible extrapolations to homologue series and analogue structures. Careful selection of test substances that reflect the range of the surfactant structures available and which are

relatively data rich with respect to hydrophobicity data availability (e.g. log Kow, CMC, BCF, etc.) is required.

Scope

- To review the available current surfactant BCF data and select suitable compounds (non-ionic and ionisable) with high quality BCF data for further Klipw determination (and subsequent comparison of experimental BCF data with BCF predictions using the new/revised model.
- To develop robust methods for measuring partitioning (Klipw) of surfactants structures to liposomes (e.g. phosphatidylcholine; POPC, storage lipids (triglycerides)) and to proteins.
- To assess the relative importance of membranes, storage lipids and proteins for uptake of selected surfactant structures from the aqueous phase into aquatic organism tissues. In particular the potential importance of the different types of phospholipids should be considered, e.g. the use of acidic/negatively charged phospholipids, such as phosphatidylserine, for cationic substances versus neutral phospholipids for zwitterionic substances [12].
- To measure in-vitro biotransformation rates for the selected test compounds using S9 preparations from rainbow trout liver
- Using the data to determine predicted BCF values for the selected surfactants and compare these against experimental BCF data.

Objectives

- Generation of liposome-water partition coefficients for a selection of surfactant structures. This dataset would be used to (a) extend the applicability domain of a Klipw QSAR f to surfactants and (b) once tested be used to derive estimation of BCFs for such compounds in comparison with experimental BCF data.
- Comparison of the experimental Klipw data generated in this work with other Klipw data based on the mechanistic model COSMOmic [13], as well as comparison of Klipw data with other hydrophobicity data available, e.g. Kow, KIAM, Kfw.
- Incorporation of Klipw data and predicted BCF data into a tiered approach which equates with key BCF triggers , ≤500, ≥2000, ≥5000 in an integrated testing strategy (ITS)
- Regular interactions/dialogue with inter-industry contacts in ERASM and EOSCA regarding other ongoing activities as well as with regulatory agencies, such as ECHA and CEFAS, over the acceptability of predicted BCF data for surfactants based on Klipw data.

Deliverables

The project is aimed at generation of experimental data for a selection of surfactant structures with the aim of validation of a suitable QSAR model for prediction of BCF values for a wide range of surfactants.

The final report shall contain an executive summary (2 pages max), a main part (max. 50 pages) and a detailed bibliography. It is expected that the findings will be developed into at least one peer reviewed publication, following poster(s) and presentation(s) at suitable scientific conference(s).

Cost and Timing
Start in early 2017, duration 3 years.
Budget in the order of € 400,000

Partnering/Co-funding
Applicants should provide an indication of additional partners and funding opportunities that can be appropriately leveraged as part of their proposal. Partners can include, but are not limited to, industry, government/regulatory organizations, research institutes, etc. Statements from potential partners should be included in the proposal package.

Fit with LRI objectives/Possible regulatory and policy impact involvements/ Dissemination
Applicants should provide information on how their proposal is aligned with LRI objectives. Furthermore, an indication on how the results could influence regulatory and policy areas should be provided.
Dissemination plans should also be laid down.

Cited references

1 European Oilfield Speciality Chemicals Association (EOSCA). Bioaccumulation Potential of Surfactants: A Review, 2000.
2 Krop, H., de Voogt, P. Bioconcentration factors of surfactants in seawater. IVAM, Amsterdam, 2007
3 Armitage, J.M., Arnot, J.A., Wania, F., Mackay, D. Development and evaluation of a mechanistic bioconcentration model for ionogenic organic chemicals in fish. Environ. Toxicol. Chem. 2013, 32, 115-128.
4 Endo, S., Brown, T.N., Goss, K.U. General model for estimating partition coefficients to organisms and their tissues using the biological compositions and polyparameter Linear Free Energy Relationships. Environ. Sci. Technol. 2013, 47, 6630-6639.
5. Endo, S.; Escher, B.I.; Goss, K.U. Capacities of membrane lipids to accumulate neutral organic chemicals. Environ. Sci. Technol. 2011, 45, 5912-5921.
6. Vaes, W.H.J.; Urrestarazu Ramos, W.; Verhaar, H.J.M.; Cramer, C.J.; Hermens, J.L.M. Understanding and estimating membrane/water partition coefficients: approaches to derive quantitative structure property relationships (QSPR). Chem. Res. Toxicol. 1998, 11, 847-854.
7. Escher, B.; Schwarzenbach, R.P. Partitioning of substituted phenols in liposome-water, biomembrane-water, and octanol-water systems. Environ. Sci. Technol. 1996, 30, 260-270.

8. Vaes, W.H.J.; Ramos, E.U.; Verhaar, H.J.M.; Hermens, J.L.M. Acute toxicity of nonpolar versus polar narcosis: Is there a difference? Environ. Toxicol. Chem. 1998, 17, 1380-1384.
9. van Wezel, A.P.; Punte, S.S.; Opperhuizen, A. Lethal body burdens of polar narcotics: chlorophenols. Environ. Toxicol. Chem. 1995, 14, 1579-1585.
10 Armitage, J.M., Brown, T.N., Wania, F., Mackay, D, Arnot, J.A. Introducing BIONIC v2: A mechanistic mass balance model for predicting bioconcentration factors (BCFs) of ionizable organic chemicals in fish. In SETAC North America 36th Annual Meeting. Salt Lake City, 2015
11. Müller, M.T., Zehnder, A., Escher B.I. Liposome-water and octanol-water partitioning of alcohol ethoxylates. Environ. Toxicol. Chem. 1999, 18, 2191-2198.
12 Schmitt, W. General approach for the calculation of tissue to plasma partition coefficients. Toxicology in Vitro, 2008, 22, 457-467.
13 Bitterman, K., Spycher, S., Endo, S., Pohler, L., Huniar,U., Goss, K-U., Klamt, A. Prediction of phospholipid-water partition coefficients of ionic organic chemicals using the mechanistic model COSMOmic. J.Phys.Chem.B.,2014, 118,14833-14842.

DEADLINE FOR SUBMISSIONS: 31 August 2016

Please see www.cefic-lri.org for general LRI objectives information, project proposal form and further guidance for grant applications.