**Comparison of three different models for predicting the phospholipid membrane-water partition coefficients of ionic organic chemicals and investigation of the toxicity of organic ions**

Kai Bittermann1, Kai-Uwe Goss 1, 2

1 UFZ - Helmholtz Centre for Environmental Research, Analytical Environmental Chemistry, Permoserstraße 15, 04318 Leipzig, Germany, kai.bittermann@ufz.de

2 Department of Physical and Theoretical Chemistry, University of Regensburg, 93040 Regensburg, Germany

The sorption of ions to phospholipid membranes is a very important process for various fields like biophysics and drug design; but also for environmental science, because it is a main key for understanding baseline toxicity of ions. While different models already describe the sorption of neutral compounds reasonably well, the sorption behavior of ions is not yet well understood. Adequate models are necessary because roughly half of the preregistered chemicals under REACH are ionogenic.

In this work, we investigated liposome-water partition coefficients (*K*lipw) of 24 cationic, 51 anionic compounds, two zwitterions and two divalent cations; which is to our knowledge the biggest dataset of ionic compounds available. We compared three different modelling approaches with increasing complexity: 1) an empirical correlation with log *K*ow, 2) an extension of the polyparameter linear free energy relationship (pp-LFER) for ionic compounds and 3) COSMO*mic*, which is based on quantum chemistry and fluid phase thermodynamics.[1] We subsequently used the best model, COSMO*mic*, to question the toxic mode of action of organic ions.

The empirical correlation approach with log *K*ow, though lacking a strict mechanistic reasoning, is the easiest-to-use and is thus the widely used model. The prediction of anionic compounds was reasonably well (root-mean-square error (RMSE) = 0.79), but cationic compounds exhibit a RMSE bigger than one log unit. The pp-LFER approach turned out to be unsuited for the prediction of *K*lipw of ions, although it performed best among all three models in predicting *K*lipw of neutral compounds. Apparently one pp-LFER equation cannot capture the heterogeneous structure of the membrane and the resulting different physicochemical environments which are responsible for the partitioning. COSMO*mic* is based upon a mechanistic concept and can calculate *K*lipw without restrictions in charge or chemical classes.[2] Not only did it give the best predictions for anions (RMSE = 0.66) and cations (RMSE = 0.71), it also was the only one of the three models that could handle zwitterions and divalent ions. With COSMO*mic* we present a model that predicts the sorption of new pollutants to membranes outside the chemical space of the current fitting data.

We next investigated the toxicity of compounds that are fully charged under environmental conditions: glyphosate, a widely used broad spectrum herbicide, and 35 naphthenic acids that arise in large quantities from oil sand processing. The *K*lipw values predicted with COSMO*mic* explain how the different speciations of glyphosate additively act together as baseline toxicants. In the case of naphthenic acids it was shown that bicyclic acids have an excess toxicity revealing a different mode of action than baseline toxicity.

[1] Bittermann, K.; Spycher, S.; Goss, K.-U.; submitted

[2] Bittermann, 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, 110, 5132–5138.