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Assessing the toxicity of ionic liquids – Application of the critical membrane concentration approach

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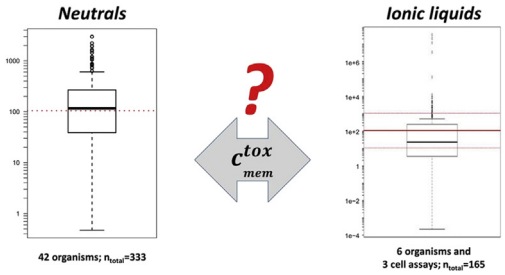
HIGHLIGHTS

- Toxic membrane concentration of neutrals confirmed (333 chemicals, 42 organisms).
- Concentration of ~100 mmol/kg (membrane lipid) causes toxic effect.
- $K_{mem/w}$ values of ionic liquids (ILs) predicted with COSMO*mic*.
- ILs exhibit critical membrane concentrations in the range of neutrals.
- Critical discussion of artefacts that hamper definite conclusions.

GRAPHICAL ABSTRACT



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ABSTRACT

Charged organic chemicals are a prevailing challenge for toxicity modelling. In this contribution we strive to recapitulate the lessons learned from the well-known modelling of narcosis (or baseline toxicity) of neutral chemicals and apply the concept to charged chemicals. First we reevaluate the organism- and chemical independent critical membrane concentration causing 50% mortality,c^{tox}_{mem}, based on a critical revision of a previously published toxicity dataset for neutral chemicals. In accordance to values reported in the literature we find a mean value for c^{tox}_{mem} of roughly 100 mmol/kg (membrane lipid) for a broad variety of 42 aquatic organisms (333 different chemicals), albeit with a considerable scatter. Then we apply this concept to permanently charged ionic liquids (ILs). Using COSMO*mic*, a quantum mechanically based mechanistic model that makes use of the COSMO-RS theory, we predict membrane-water partition coefficients ($K_{mem/w}$) of the anionic and cationic IL components. Doing so, $c^{tox}_{mem}(total)$ for permanently charged ILs can be estimated assuming independent, concentration additive contributions of the cationic and its respective anionic species. The resulting values for some of the toxicity data for ionic liquids are consistent with the expected range for baseline toxicity for neutral chemicals while other values are consistently greater or smaller. Based on the calculation of toxic ratios we identify ILs that exert a specific mode of toxic action. Limitations of the modelling approach especially but not exclusively due to the use of nominal concentrations instead of freely-dissolved concentrations in the published literature are critically discussed.

1. Introduction

The high number of ionizable or even permanently charged organic chemicals potentially released into the environment is a

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Nomenclature

c_{mem}^{tox}	critical membrane threshold concentration causing a toxic effect
$K_{mem/w}$	(biological) membrane-water partition coefficient
$K_{lip/w}$	liposome-water partition coefficient
K_{ow}	octanol-water partition coefficient
pp-LFER	polyparameter linear free energy relationship
COSMO-RS	Conductor-like Screening Model for Real Solvents
COSMO*mic*	COSMO-RS for MICells
IL	ionic liquid
TR	toxic ratio

challenge for ecotoxicology (Franco et al., 2010). For neutral chemicals the minimal level of nonspecific toxicity is referred to as narcosis or, in the field of environmental science, baseline toxicity (Escher and Schwarzenbach, 2002; Wezel and Opperhuizen, 1995). The baseline toxicity concept states that nonspecific toxicity occurs at a consistent range of membrane concentrations, independent of both the chemical as well as the (aquatic) organism, although the exact mechanisms is not yet fully clarified. Underlining the non-specificity, baseline toxicity was found to act via concentration addition for mixtures (Deneer et al., 1988). It is likely that the chemicals sorbing to the membrane change its properties, e.g., its fluidity and permeability, to such a degree that its (biological) function is disturbed (Wezel and Opperhuizen, 1995). A different theory explains baseline toxicity via specific interactions of molecules with sensitive proteins in the central nervous system (Franks and Lieb, 1990). However, it was also demonstrated that baseline toxicants accelerate the decay of the membrane potential after a very short pulse of light that induced a certain membrane potential in an isolated photosynthetic membrane vesicle originating from a photosynthetic bacterium (Escher et al., 2002), which rather supports the explanation of baseline toxicity by non-specific disturbance of the membrane structure and functioning.

Vaes et al. showed that there is no difference in the baseline toxicity between polar and apolar neutral organic chemicals, when the liposome-water partition coefficient ($K_{lip/w}$) is used as a descriptor instead of the octanol-water partition coefficient (K_{ow}). This finding has been corroborated later (Escher and Hermens, 2002; Escher and Schwarzenbach, 2002), albeit with a relatively limited set of chemicals. The $K_{lip/w}$ acts as a surrogate for the (biological) membrane-water partition coefficient $K_{mem/w}$. More recent studies substantiate these earlier findings (Endo, 2016; Escher et al., 2017; McCarty et al., 2013). Along the same line of thoughts are also earlier concepts like the critical body residue concept (Endo, 2016; McCarty and Mackay, 1993), or the target lipid model (TLM), based on a critical body burden (Kipka and Di Toro, 2009). Just recently COSMO*mic* predicted $K_{lip/w}$ values have been used successfully to calibrate a baseline toxicity QSAR for neutral and ionizable chemicals and their mixtures for the bioluminescence inhibition assay with *Aliivibrio fischeri* (Baumer et al., 2017; Escher et al., 2017). In these studies, three permanently charged cations, namely the ionic liquids hexadecyltrimethylammonium, hexadecylpyridinium and didecyldimethylammonium, could be classified as baseline toxicants as well as most of the ionizable drugs investigated (the latter had to be modeled via the use of an ion trapping model). A different access to explain non-specific toxicity has been put forward recently with the activity approach (Thomas et al., 2015), which has been criticized (Goss and Endo, 2016) – partly because it is intrinsically not applicable to ionic chemicals. Moreover, the assumption of a critical membrane threshold concentration is principally not consistent with a critical membrane activity. Both concepts cannot be correct at the same time (Vaes et al., 1998).

In this work we want to address the question whether the baseline toxicity concept based on a threshold concentration in the membrane can also be applied for ionic chemicals. Further we want to investigate which ILs have to be classified as specifically acting toxicants. While the partitioning of neutral chemicals to membranes can easily and reliably be predicted with a pp-LFER ($n = 131$, $SD = 0.3$, $R^2 = 0.98$ (Endo et al., 2011)), it has only recently been shown (Bittermann et al., 2016, 2014) that the partitioning of organic ions to membranes can reliably be predicted with COSMO*mic* ($n = 36$ cations, $RMSE = 0.71$, $R^2 = 0.62$ and $n = 56$ anions, $RMSE = 0.66$, $R^2 = 0.66$), albeit with a smaller accuracy. COSMO*mic* (i.e., COSMO-RS for MICells) is based on COSMO-RS (i.e., COnductor like Screening MOdel for Real Solvents), which describes fluid-phase thermodynamic properties using quantum chemical calculations of all chemical species involved in the partitioning process (Klamt, 2005).

The critical membrane concentration of roughly 100 mmol/kg (membrane lipid) is well known in the literature but tested only for a limited number of organisms (see e.g., (Escher and Schwarzenbach, 2002) and literature cited above). Therefore we start out by resuming the investigation of baseline toxicity for neutral chemicals, because we want to ensure the broad applicability domain of the concept before applying it to charged chemicals. We investigated the concept for more organisms (42) and different chemicals (333) than any previous study we know of by reevaluating a big data set from the literature. This exercise should help to assess the uncertainties within the baseline toxicity concept and to interpret the results when the concept is expanded to ionic chemicals, which are the main target of this work. In order to prevent additional complexity in the modelling of toxicity for ions such as ion trapping (further discussed below) we focused on permanently charged ionic liquids (ILs). In the literature a multitude of quantitative structure property relationship (QSPR) models can be found that describe IL toxicity for different species (Thuy Pham et al., 2010), but, to the best of our knowledge, none of these QSPRs is strictly examining whether the experimental toxicity data of ILs can be described as baseline toxicity. This might well be due to the fact that the partitioning of organic ions to membranes could not be reliable predicted until recently (Bittermann et al., 2016, 2014).

2. Materials and methods

2.1. Basic assumptions and considerations

A principal assumption within the baseline toxicity concept is that baseline toxicity can be described independently of the organism with only one partition coefficient, i.e., that the membranes in different organisms exhibit similar sorption characteristics. It is important to keep in mind that the $K_{lip/w}$ is based on a pure phospholipid membrane whereas the $K_{mem/w}$ describes the sorption to a real (and complex) biological membrane, including other components such as cholesterol, different kinds of phospholipids and proteins. Here, we take the $K_{lip/w}$ as surrogate for the $K_{mem/w}$, irrespective of the kind of organism or cell culture, which is generally a well-accepted assumption (Endo et al., 2011). For phenols it has been shown that liposomes composed of zwitterionic phosphatidylcholine mimick the sorption behavior of isolated membranes from *Rhodobacter sphaeroides* well (Escher and Schwarzenbach, 1996). The second crucial assumption of the