**Modeling frameworks for the prediction of the ecotoxicity of ionizable organic chemicals**

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The ecotoxicological effects of ionizable organic chemicals (IOCs), i.e., compounds that can exist in neutral and charged form in the environment, depend very much on their speciation because toxicokinetics, toxicodynamics and even mode of action of IOCs can be strongly influenced by the pH and speciation. For example, the important mechanism of toxicity of uncoupling oxidative photophosphorylation entirely depends on the interplay between the neutral and charged species of weak lipophilic acids. Studies with aquatic organisms have also demonstrated pH-dependent potency, which were attributed to differences in ionization state that influenced uptake, and ultimately effects. The substantial difference in potency among neutral and charged forms of some IOCs suggest that ecotoxicity of IOCs could be modelled as a mixture effect of all species involved. The ecotoxicological effects of IOCs were the focus of one of the work groups assembled as part of the “Experts Workshop on the Ecotoxicological Risk Assessment of Ionizable Organic Chemicals: Towards a Science-Based Framework for Chemical Assessment” (November 5th-7th, 2014). The main objective of the work group was to discuss how speciation of IOCs may influence their ecotoxicity. The purpose of this presentation is to communicate the main findings of the workshop related to predictive models for describing the ecotoxicity of IOCs.

Existing ecotoxicological prediction models can be adapted for IOCs. Three main classes of modes of action that are affected by the speciation are baseline toxicity, receptor binding and uncoupling of oxidative phosphorylation. For baseline toxicity we assume that all species of IOCs contribute with equal internal potency to the overall effect. The Target Lipid Model (TLM) for baseline toxicity can then be adapted to IOCs by accounting for differences in the partitioning of neutral and charged species to the target lipids. Weak phenolic acids are typically more potent than baseline toxicants because they can act as uncouplers of oxidative phosphorylation. The mechanism underlying uncoupling is a protonophoric shuttle mechanism, where the neutral species carries protons across the membrane and releases them on the opposite side, thereby destroying the electrochemical proton gradient that is needed to drive ATP synthesis in the mitochondria. Models are presented to predict the highly pH dependent activity of uncouplers. If the target of an IOC is a protein, e.g., a nuclear receptor or an enzyme, one can invoke a binding model with species-dependent binding affinities of IOCs. Target-specific toxicity predictions of ecotoxicological effects, including endocrine disruptions, can be made with a growing panel of detailed three dimensional models of the binding pockets of hormone receptors and/or the co-crystal structures of the ligands bound to them built and tested for aquatic species. If neutral and charged species are present in parallel, a binary mixture toxicity model is useful to explain the different contribution of neutral and charged species to the mixture effect. These and other models are presented and their applicability and limitations as well as research needs are discussed.

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