**Reliable QSAR Predictions of Fish Acute Toxicity: Classification of Toxicants by Mode of Action (MOA)**

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Alternative methods to assess the (eco)toxicity of chemicals are required in different regulatory contexts (e.g. REACH). Prior to testing, all available *in vitro* data, *in vivo* data, historical human data, data from valid QSARs (quantitative structure-activity relationships) and data from structurally related substances (read-across) shall be assessed. The aim is to use existing knowledge and to reduce animal testing. Our work contributes building blocks towards high quality QSAR predictions that meet the requirements for regulatory acceptance. Our objective is to develop user guidance to select appropriate baseline QSARs for query compounds. We suggest to replace *in vivo* fish acute toxicity tests for baseline toxicants with valid QSAR predictions based on classification methods to discriminate between baseline and excess toxicants.

Reliable QSAR predictions consider (eco)toxicological modes of action (MOA). Compounds belonging to different MOA classes are toxic in different ways and different QSARs are needed to predict their ecotoxic effects. MOA is, however, not a constant property of a compound but it may vary between species and change with concentration and duration of exposure. The concept of functional similarity of chemicals combines (eco)toxicological knowledge (which toxicity pathways are stimulated in which species under which exposure conditions) with chemical expertise (which chemical (sub)structures and physicochemical properties are involved in which interactions) to discriminate between baseline and excess toxicants. Only for baseline toxicants, it is possible to predict the fish acute toxicity with sufficient accuracy from log *K*ow and, hence, valid QSARs can replace *in vivo* testing. In contrast, excess toxicants, and chemicals not reliably classified as baseline toxicants, require further *in silico*, *in vitro* or *in vivo* assessments. We present a stepwise approach to identify more than 50 % baseline toxicants in a precautionary way, not ignoring possible excess toxicants. At the same time, we tolerate a certain fraction of false positives, i.e. baseline toxicants without specific effects that may be directed to testing instead of QSAR predictions.

The next step is a classification scheme to discriminate specific MOA classes. A promising hierarchical approach is based on Weight-of-Evidence (WoE) from multiple criteria like structural features related to receptor binding affinities, physico-chemical descriptors describing bioavailabilities at target sites and sophisticated profiler like the OECD Toolbox. Fall-back loops are needed to account for multiple MOAs. An important aspect is to include ionisable substances. Fine-tuning the system in an iterative process will optimize its performance.