Processes related to ADME (absorption, distribution, metabolism, excretion) as determinants of chemical uptake and toxicity in zebrafish embryos

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Uptake, distribution and excretion processes of chemicals in biological tissues are usually not purely based on passive diffusion but also principally governed by activities of cellular transporters. These can actively translocate compounds against a concentration gradient and metabolizing enzymes which may modify the chemical structure and thus change the physico-chemical properties such as water solubility. In pharmacology, these processes are taken into account for pharmacokinetic assessments of the delivery of a drug to its therapeutic target site. However, in ecotoxicology, toxicokinetic assessments of compounds are usually only based on their physico-chemical properties; biological processes are mostly not considered. Biologically active compounds, such as drugs and pesticides, that also interfere with cellular ADME processes are often charged suggesting that ADME enzymes may commonly act on toxicokinetics of ionic chemicals, also ones not intended to be used on biological targets. One reason why these chemical – enzyme interactions are only marginally considered may be that there is still relatively little specific knowledge about these processes in ecotoxicologically relevant organisms such as fish. For the zebrafish (*Danio rerio*), an important ecotoxicological test species, the availability of its genome provides the basis for identifying important components of its cellular ADME system. Recently, relevant transporter and metabolic enzymes were identified and functionally characterized. Thus, the cellular ABC (ATP binding cassette) efflux transporter Abcb4 was shown to antagonize accumulation of ionic model compounds rhodamine B, a fluorescent dye, and vinblastine, a cytotoxic compound, in zebrafish embryos: Disruption of Abcb4 function resulted in two to three-fold increased accumulation and raised toxicity of test compounds. Ionic chemicals, such as for instance the model inhibitor verapamil, can also disrupt transporter function. The results, thus, point to two aspects of ADME-enzyme interaction of chemicals: 1) Interaction of a chemical with the enzyme influences its toxico-kinetics; 2) Chemicals can interfere with enzyme function, thus affecting toxicokinetics of other chemicals. We will present current knowledge on ADME processes in zebrafish embryos and show current results providing evidence for the importance of these processes for toxicokinetics of chemicals.