Session: Benefits of BiER: How Biotransformation and Elimination Rate Related Science Can Improve the Regulation and the Sustainable Use of Chemicals
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Biotransformation Leading to Increased Toxic Metabolites: an Overlooked Risk in Aquatic Organisms?

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Numerous micropollutants have been detected concurrently in aquatic systems. Biotransformation plays a critical role in the bioaccumulation and toxicity of these chemicals by altering their hydrophobicity and toxic potency to certain species. This study aimed to elucidate how biotransformation change the toxicokinetics and toxicity of parent compounds and to gain a better comprehensive understanding of the risk for the aquatic environment. Therefore, we first investigated bioaccumulation and biotransformation of the widely used nonsteroidal anti-inflammatory drug diclofenac in two representative aquatic invertebrates, i.e. *Gammarus pulex* and *Hyalella azteca*. Second, we compared acute toxicities and toxicokinetics of parent compound diclofenac and its major metabolites in *G. pulex* and *H. azteca*. Furthermore, we validated its widespread occurrence in other chemicals and other aquatic organism (fish in vitro) at environmental relevant level.

Diclofenac methyl ester was the primary metabolite in all three species. The methylation was also observed for triclosan and bezafibrate with distinct structures and was further determined in organisms exposed to environmentally relevant levels of chemicals, suggesting that methylation might be a general process in aquatic organisms.
Bioaccumulation factors (BAFs) of diclofenac methyl ester were 229 $L*kg_{ww}^{-1}$ and 84 $L*kg_{ww}^{-1}$ in *H. azteca* and *G. pulex*, which were 168-458 times higher than the parent compound diclofenac in these two species. This can be explained by the higher hydrophobicity (log D_{ow} = 0.9 for diclofenac; log D_{ow} = 4.4 for diclofenac methyl ester at pH 7.9). The LC_{50}s of diclofenac methyl ester was decreased by 3 order of magnitude (432 times) to 0.53 $L*mg^{-1}$ in *H. azteca* in agreement with the higher bioaccumulation. Toxicokinetic modelling in *H. azteca* suggests that the secondary major BTP diclofenac taurine continuously accumulated in the organisms and resulting in prolonged half-life. This could be explained by ion trapping of the ionized diclofenac taurine.

Our results show that methylation of diclofenac forms diclofenac methyl ester, which leads to higher bioaccumulation potential and exerts higher toxicity to aquatic invertebrates. In addition, diclofenac taurine is highly accumulated in *H. azteca*. The findings suggest that biotransformation leads to more hydrophobic compounds which should be taken into consideration for future risk assessment.