Optimizing a generic fish PBK model for pharmaceuticals

Level: Master (Biology/Chemistry)
Duration: 21 weeks
Start: March 2022 - onwards
Project form: Literature review, computer modelling, data compilation, validation
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Residues of pharmaceuticals can reach the environment after use or inappropriate disposal of leftovers. Such residues are typically excreted by humans and subsequently transported via the sewerage system to a wastewater treatment plant (WWTP), where part of the residues is removed and the remainder is discharged into the surface water. In the scientific literature, it is often argued that fish species are likely to have the highest risk due to exposure to pharmaceutical residues since concentrations in surface waters are relatively high (compared to other compartments) and the genome of fish is most similar to humans. The latter implies that the human receptors of the pharmaceuticals are most likely to be conserved in fish (compared to, for example, Daphnia and algae). For this reason, environmental risk assessment efforts of pharmaceuticals often focus on fish species.

When a fish is exposed to a pharmaceutical residue, this residue can be absorbed, distributed, metabolized and excreted (ADME). ADME processes determine the ultimate internal exposure level of the fish, i.e. the amount that reaches the site of toxic action. These ADME processes can thus be considered important modulators of potential toxic effects. It is therefore important to account for ADME processes when performing a risk assessment of pharmaceutical residues in fish.

The Environmental Science cluster of Radboud University has developed a generic physiologically-based kinetic model (PBK model) for fish (Wang et al. 2022). This model describes the ADME processes in the fish and can be used to predict internal concentration levels in different fish organs and tissues (e.g., blood and liver). The model uses allometric scaling to account for differences in body size between species/organisms, and includes specific equations to account for ionization of pharmaceuticals. A validation exercise with 5 pharmaceuticals showed that 80-90% of the predictions fall within a factor of 10 of measured internal concentrations. The model has been implemented in Microsoft Excel.

The main aim of the current project is to further optimize the generic fish PBK model by performing the following actions:

- Code the model into the R programming language;
- Critically review and improve the current equations used for modelling (the impact of) ionization;
- Explore the options to (better) account for binding of pharmaceutical residues to blood proteins;
- Extensively validate the model with data sets of measured internal concentrations of pharmaceuticals in fish, extracted from the public literature and obtained from industry.

Wang, J., Nolte, T.M., Owen, S.F., Beaudouin, R., Hendriks, A.J., Ragas, A.M.J., 2022 (*submitted*). A generic physiologically based kinetic model for fish for environmental risk assessment of pharmaceuticals.