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# Uptake, distribution and elimination of chemicals in fish – Which physiological parameters are the most relevant for toxicokinetics?

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## HIGHLIGHTS

- Physiological differences lead to different toxicokinetics in different fish species and individuals.
- The most important parameters are lipid content, ventilation rate and metobolization
- Variability in up-take via food are the least understood.

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## ABSTRACT

Bioconcentration and toxicity studies are regularly conducted for the risk assessment of chemicals. If such tests yield different results for different fish species, this can either be due to differences in toxicokinetics or to differences in toxicodynamics. Here we investigate which physiological parameters could cause major differences in the toxicokinetics in fish. To this end it is important to distinguish physiological parameters that affect the sorption capacity of the fish from those that affect kinetic processes. Variability in the lipid content of a fish is the most influential parameter for the sorption capacity of fish and therefore most relevant for the total concentration in fish under steady-state conditions when metabolism is not relevant. In terms of kinetics, ventilation rate, uptake efficiency from food and metabolism are the most influential factors. While ventilation rate can roughly be estimated from allometric scaling equations, little general information is available on the uptake efficiency from food. The metabolism rate constant appears to be the single most influential toxicokinetic factor. This information cannot be estimated but must be determined experimentally, preferably from in vitro experiments.



## 1. Introduction

Bioaccumulation or toxic effects as a response to chemical exposure may be quite different among multiple individuals but also among species. Bioaccumulation studies according to OECD 305 can be performed with any one out of the recommended 9 fish species with defined size ranges (OECD, 2012a). However, physiological differences among divers fish species or between young and older fish may lead to different results and thus complicate data interpretation (OECD, 2012a; Test No, 2012). Similarly, diverging results in a toxicity test may either be due to different toxicokinetics driven by differences in physiology but they might also be due to different toxicodynamics. Hence, a good understanding of the physiological factors that influence internal concentration of chemicals is required. This work tries to give an overview on the most important physiological parameters for toxicokinetics in fish.

Our approach is to analyse the major resistances for uptake, distribution and elimination, a concept that has be used long before already (e.g. in Gobas et al. (Clark et al., 1990; Gobas and Mackay, 1987)). The major difference lies in the details of the approach: Our knowledge on important physiological parameters and toxicokinetic processes is much more accurate than it had been 30 years ago: e.g. the understanding of how membrane permeability of chemicals depends on molecular structure of the chemicals has made huge progress over the last decades and the importance of micelles for facilitating the uptake of super hydrophobic chemicals in the gut is also better understood nowadays (Westergaard and Dietschy, 1976; Larisch and Goss, 2018) than it was years ago.

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Classical model approaches considered lipids as the only sorbing tissue which were approximated by octanol in order to estimate the relevant partition constant. In contrast our model considers two different sorts of lipids (storage lipids and membrane lipids) and three different sorts of proteins (albumin, muscle protein and collagen) and estimated the respective partition constants based on the pp-LFER approach (Endo et al., 2013; Stenzel et al., 2013). The novelty of our work therefore lies in the higher level of detail and in the advanced process understanding that underlies our model calculations.

## 2. Method

In order to analyse the major resistances in up-take and distribution we use our previously validated physiology-based model for fish (Larisch et al., 2017), TK-fish, in order to identify those physiological parameters that are most influential for the toxicokinetics in fish and to analyse how big their influence may be. The model gives a detailed account of the relationship between fish physiology and the processes that govern uptake, distribution and elimination of chemicals (Larisch and Goss, 2018; Larisch et al., 2017). In fact, with respect to the used physiological information and process understanding it is the most detailed model that we are aware of. It does not utilize any calibrated parameters. Instead, all parameters have a clear physiological meaning and are determined by independent methods. Therefore, it should be a suitable tool for the goal of this work.

## 3. Results

In principal the internal concentration of a chemical depends on the exposure concentration, the equilibrium partitioning of this chemical to the various tissues of the fish and various kinetic processes. In the simplest exposure scenario, a constant long term exposure, the concentration in fish and all its tissues will attain a steady-state concentration. If no metabolism occurs and exposure is only via water and not via food then this steady-state concentration in fish is merely a result of equilibrium partitioning. In this case information on the composition of the fish in terms of various lipids and proteins is the only relevant physiological information needed. However, as soon as metabolism, up-take via food or short term variations in the exposure concentration come into play, a variety of kinetics must be considered that are affected by physiological parameters such as, blood flow rate, ventilation rate, residence time and assimilation efficiency of food in the gastro-intestinal-tract (GIT). The focus of this work is on these kinetic processes. Equilibrium partitioning is only shortly reviewed in the beginning because this information is well known already. We note that this work only deals with processes that are relevant for neutral organic chemicals. Our mechanistic process understanding for ionic chemicals is still too limited for an analysis like the one intended here.

### *3.1. Equilibrium partitioning*

Equilibrium concentration of chemicals in fish depends on the exposure concentration, the equilibrium partition coefficients and the composition of the fish in terms of the main sorbing matrices (Endo et al., 2013). The relevant sorbing compartments are storage lipids (triglycerides), membrane lipids (phospholipids), structural proteins and plasma proteins (Endo et al., 2013). Among these, storage lipids are often the most relevant and their relative contribution to the total body mass shows the highest variability between species but also between individuals. The whole body lipid content varies among species (Lien and McKim, 1993) to age (Bertelsen et al., 1998) to feeding procedure (Yamamoto et al., 2002). It can even vary between season and location and can range from around 0.5%–20% w/w or more in the wild (Schlechtriem et al., 2012). Due to this variability we do not expect allometric scaling to be applicable to the lipid content of fish. Therefore, measuring lipid content of the individuals is inevitable. Examples for the lipid content for different species and its variability are shown in Figs. S1 and S2. Variation within a species can reach up to a factor of 20. Even within a few weeks lipid content may change substantially (OECD, 2012b) (See Fig. S2). Chemicals exert no known toxic effect when sorbed to storage lipids so the relevance of this sorbing matrix lies mostly in the transfer of chemicals within the food chain and in its buffer effect on the internal concentration in the fish: any elimination process that acts on the unbound concentration in the organism (e.g., metabolism, ventilation etc.) is retarded because chemical that is eliminated from the unbound concentration pool in the organism is partly replaced by desorption of the sorbed chemical from the storage lipids.

### *3.2. Uptake rate constant from water*

Uptake of chemicals in fish via gills is typically described as a first order rate process. The uptake rate constant (in units of time$^{-1}$ *wet weight$^{-1}$) depends on the ventilation rate or better respiratory rate and the up-take efficiency. The ventilation rate is the amount of water ventilated through the gills per time. The respiratory rate is that fraction of the ventilated water volume that has sufficient contact to the gill surface to allow for efficient oxygen uptake and therefore, also for chemical exchange. It is expressed as volume per time and wet weight. The respiratory rate is smaller than the ventilation rate because not all water entering the gills gets into close enough contact with perfused lamellae to enable the transfer of oxygen/chemicals. This difference between the respiratory and the ventilation rate has been studied by various researchers in terms of the oxygen up-take efficiency Erickson and McKim (1990). It may vary for different species and their activity. For more active fish like rainbow trout respiratory rate is found to be around 70% (Erickson and McKim, 1990; Gehrke, 1987; Hughes, 1966) of the ventilation rate but can be less (60%) for smaller or sluggish fish like guppies (Erickson and McKim, 1990; Hughes, 1966). Gehrke et al. (Gehrke, 1987) estimated that for resting trout the respiration rate can even drop down to 36% of the ventilation rate. The respiratory rate multiplied with the water concentration of the chemical quantifies the amount of chemical that is delivered to the gills per time and per wet weight. The up-take efficiency quantifies how much of this amount is taken up into the organism. In principal the up-take efficiency is a complex function of physiological and physico-chemical parameters such as blood flow rate, membrane permeability and partition coefficients of the chemical. For hydrophobic organic chemicals (log Kow >3), however, experimental evidence as well as mechanistic modelling suggest that the up-take efficiency is close to 100% (Larisch et al., 2017; McKim et al., 1985). In principle both, the ventilation rate and the respiration rate can be used to describe the uptake process, if one considers the different meaning and how to use them correctly. As ventilation rate is the most commonly used in literature and to avoid confusion it will be used in the following text. The amount of chemical taken up from ventilated water in the gills depends on the processes: i) the ventilation of water through the gills, ii) the permeability of chemicals through the gill cell layers that separate the water from the blood capillaries and III) the transport capacity of blood for that chemical. The cellular permeability depends on two major transport resistances in series: various unstirred aqueous phases (aqueous boundary layers (ABL)