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Revisiting elimination half live as an indicator for bioaccumulation in fish and terrestrial mammals

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HIGHLIGHTS

- BCF can be estimated from measured clearance and estimated uptake rate constants.
- Experimental clearance rate constants in fish do not depend on the route of exposure.
- Bioaccumulation in fish or mammals may be estimated from *in vitro* hepatic clearance.

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ABSTRACT

Current bioaccumulation regulation is focused on bioconcentration in fish. An extension to terrestrial mammals, e.g. rat, is urgently needed but will have to use a different metric, most likely the BMF. While both metrics are thermodynamically not equivalent the regulative testing requirements for both might be reduced to the investigation of the respective elimination rate constants k_2 for fish or rat. These k_2 values could be derived from animal tests or from *in vitro - in vivo* extrapolation and could be combined with estimated uptake rate constants to yield either a BCF or a BMF value. The possibility to use *in vitro* methods for k_2 has the advantage that animal tests can be avoided and it bears the chance to experimentally cover species differences which are currently ignored in bioaccumulation regulation. Existing data for BCF and the respective k_2 values for fish - either from feeding studies or from BCF studies themselves-indicate that this approach works. For terrestrial bioaccumulation this approach still needs further experimental support.

1. Introduction

Current regulation on bioaccumulation focuses on the bioconcentration factor (BCF) for fish. However, systematic bioaccumulation assessment should be extended to air-breathing organisms, in particular mammals. The BCF approach itself cannot be extended to terrestrial vertebrates due to the different prevalent uptake pathways and the little value of water as reference phase (Gobas et al., 2009). Instead, the biomagnification factor is often seen as a suitable metric for terrestrial vertebrates. A comprehensive bioaccumulation assessment will need to consider both, the aquatic and terrestrial organisms, which means: a chemical is classified as non-bioaccumulative if bioaccumulation is excluded in both cases. A few years ago, the use of elimination half-life as an indicator for biomagnification in air-breathing organisms was suggested (Goss et al., 2013). A comparable approach is also conceivable for fish and would reduce the regulative testing requirements to the investigation of the elimination rate constant k_2 which is already determined in BCF studies following OECD TG 305 (OECD, 2012a, b).

The BCF is defined as the steady state concentration of a chemical *i* in fish divided by the aqueous concentration in the water that the fish is exposed to (while the fish is feeding uncontaminated food).

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$$BCF_i = \frac{steady\ state\ concentration\ of\ i\ in\ fish\left(\frac{mol_i}{kg\ wet\ weight}\right)}{steady\ state\ concentration\ of\ i\ in\ water\left(\frac{mol_i}{L}\right)} \quad (1)$$

In the OECD TG 305 (OECD, 2012a) this definition of the BCF is complemented by a kinetic definition which can be derived mathematically from the steady-state approach if one assumes the fish to be a single, well-stirred compartment with instantaneous equilibrium partitioning within the fish and with all uptake and elimination processes following first order kinetics. According to the kinetic approach the BCF equals the first order uptake rate constant divided by the first-order elimination rate constant covering all elimination processes for the considered chemical.

$$BCF = \frac{uptake\ rate\ constant,\quad k_1\ \left(\frac{L}{kg\ d}\right)}{elimination\ rate\ constant,\quad k_2\ \left(\frac{1}{d}\right)} \quad (2)$$

Under REACH, a chemical is considered as bioaccumulative if the BCF exceeds a value of 2000 (L/kg) for a standardized fish with 5% lipid content. Both, steady-state measurements as well as kinetic measurements are accepted by the authorities. For fish growing substantially during the duration of the test, a growth correction of the experimental data is needed (Brooke and Crookes, 2012).

It has been suggested that existing kinetic BCF experiments could be simplified by just measuring the elimination rate while the uptake rate is estimated (Brooke and Crookes, 2012; OECD, 2012b; Goss et al., 2013). The reasoning behind this suggestion is that the uptake rate constant, k_1, contains mostly information that we are able to estimate rather reliably and that is not chemical specific (Brooke et al., 2012). In their report Brooke and Crookes (2012) investigated this approach using a dataset from Jon Arnot (http://www.arnotresearch.com) with 169 BCF data points covering 108 chemicals and 14 fish species. They plotted these BCF data versus measured elimination rate constants, k_2, from the same experiments in a double logarithmic plot and found a linear correlation with a slope close to unity. This is what one would expect when the concept of using estimated k_1 works and if all fish had a similar size (which was not the case). But for unknown reasons Brooke and Crookes did not go the next step to really estimate BCF values based on this approach and based on actual fish sizes as required by the allometric formula for estimating k_1. Instead Brooke and Crookes (2012) came to a rather negative conclusion about this approach apparently because of the rather high scatter in their plot. Interestingly, though, the authors did not consider that part of this scatter came from ignoring the size dependence and another part must have come from uncertainties in the experimental BCF values.

The aim of this study was to elucidate whether k_2 values (or elimination half-lives which is equivalent) can be used as an indicator for bioaccumulation in fish. Experimental BCF values from the literature were compared with BCF values calculated for given chemicals using experimental k_2 from the BCF studies and k_1 values estimated according to an allometric scaling formula. Experimental BCF data were further compared with BCF data which were calculated using experimental k_2 from fish feeding studies and estimated k_1 values. Following theory, the uptake path should not matter for the elimination process as long as the well-mixed compartment assumption holds. Therefore, it should be possible to derive BCF values also based on k_2 values from feeding studies. Indeed, this is suggested in the OECD 305 guideline from 2012 (OECD, 2012a) for those chemicals that are so hydrophobic that controlled aqueous exposure is difficult (see also (Gobas and Lo, 2016) (Schlechtriem et al., 2017). Interestingly, a validation of this approach has so far not been available.

Finally we discuss the possibility of also using elimination half-lives for the bioaccumulation assessment of terrestrial organisms.

2. Methods

2.1. Literature search

BCF experiments have been performed for decades and thus many data are available in the published literature. However, in earlier times almost no standardization took place and important experimental parameters were not reported. Hence, there are still data around that are not standardized with respect to lipid content although a standard lipid content of 5% as a reference has been agreed on for a long time. Another important standardization – growth correction-has in fact only become commonly accepted since the latest revision of OECD guideline 305 in 2012. For our first goal, the validation of estimating BCF from a measured k_2 and an estimated k_1, lipid and growth corrected data would have been ideal but this could not be accomplished. The missing lipid correction was less of an issue because both BCF and k_2 had been measured for the same fish but in most cases experimental BCF values from the literature have also been reported without any information on fish weight, Hence, we eventually ended up with rather few data that would allow the calculation of k_1 from the allometric formula based on fish weight (see below). Data collection for our second goal, the comparison of k_2 from BCF experiments and from fish feeding experiments was even more difficult. Our first demand was that both data for a given chemical should have been measured for the same fish species because metabolism is known to be species dependent (Schultz and Hayton, 1999; Bischof et al., 2016). In addition data for similar fish size, normalised to lipid content and corrected for growth would have been desirable. The latter demands could not be fulfilled though.

2.2. BCF calculation with experimental k_2 and estimated k_1

A kinetic BCF can be calculated from an experimental k_2 (taken from the BCF experiment itself) and an estimated k_1. The uptake rate constant, k_1, is a function of the ventilation rate of the fish and the uptake efficiency of the chemical which is defined as the amount of chemical taken up into the circulatory system of the fish divided by the amount of chemical that was dissolved in the ventilated water. Data measured by (McKim et al., 1985) suggest that the uptake efficiency of rather hydrophobic chemicals (i.e. log $K_{ow} > 3.5$) is around 60% without much variance between different chemicals. In a recent physiologically based modelling approach (Larisch et al., 2016) we could confirm this by mechanistic reasoning and show that uptake of these hydrophobic chemicals from ventilated water in the gills is independent of the chemical's properties and only a function of the ventilation rate and the fraction of ventilated water that can equilibrate with well perfused lamellae during the rather short residence time in the gills. This fraction of ventilated water volume is called the respiratory volume and amounts to about 60% of the ventilated water volume as determined in a study on rainbow trout (McKim et al., 1985). For less hydrophobic chemicals uptake efficiency is lower because of blood flow limitation (Larisch et al., 2016). Sijm et al. came to very similar results (Sijm et al., 1994, 1995) in their studies with isolated perfused gills of rainbow trout. These authors suggested an allometric scaling formula with which the uptake rate constants of rather hydrophobic chemicals in fish of various weight can be predicted (Sijm et al., 1995):