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Can poly-parameter linear-free energy relationships (pp-LFERs) improve modelling bioaccumulation in fish?

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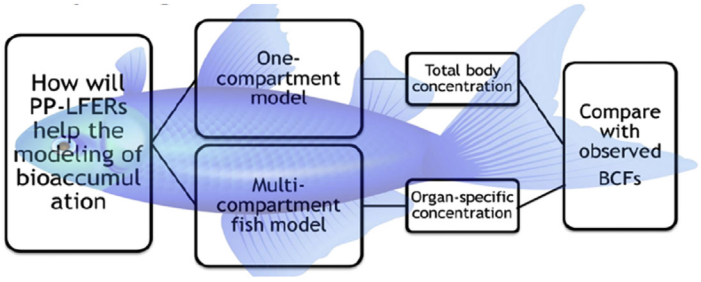
HIGHLIGHTS

- Incorporating pp-LFERs into fish model resulted in greater improvement in PBTK model than that in one-compartment model.
- sp-LFERs overestimated lipid contribution and underestimated protein contribution, which cancelled out each other.
- Large uncertainties are caused by quantification of biotransformation.
- Uncertainties in screening assessments are larger than differences between pp-LFERs and sp-LFERs models.

GRAPHICAL ABSTRACT



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ABSTRACT

A wide range of studies have characterized different types of biosorbent, with regard to their interactions with chemicals. This has resulted in the development of poly-parameter linear free energy relationships (pp-LFERs) for the estimation of partitioning of neutral organic compounds to biological phases (e.g., storage lipids, phospholipids and serum albumins). The aims of this study were to explore and evaluate the influence of implementing pp-LFERs both into a one-compartment fish model and a multi-compartment physiologically based toxicokinetic (PBTK) fish model and the associated implications for chemical risk assessment. For this purpose, fish was used as reference biota, due to their important role in aquatic food chains and dietary exposure to humans. The bioconcentration factor (BCF) was utilized as the evaluation metric. Overall, our results indicated that models incorporating pp-LFERs ($R^2 = 0.75$) slightly outperformed the single parameter (sp) LFERs approach in the one-compartmental fish model ($R^2 = 0.72$). A pronounced enhancement was achieved for compounds with log K_{OW} between 4 and 5 with increased R^2 from 0.52 to 0.71. The minimal improvement was caused by the overestimation of lipid contribution and underestimation of protein contribution by the sp-approach, which cancelled each other out. Meanwhile, a greater improvement was observed for multi-compartmental PBTK models with consideration of metabolism, making all predictions fall within a factor of 10 compared with measured data. For screening purposes, the K_{OW}-based (sp-LFERs) approach should be sufficient to quantify the main partitioning characteristics. Further developments are required for the consideration of ionization and more accurate quantification of biotransformation in biota.

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1. Introduction

Bioaccumulation in aquatic species is a critical endpoint in the regulatory assessment required by authorities, such as the European Chemical Agency (ECHA) and the United States Environmental Protection Agency (Gobas et al., 2009). One widely used assessment metric is the bioconcentration factor (BCF), which assesses the bioaccumulative potential of a chemical to biota through constant aqueous exposure under well-controlled laboratory conditions (Mackay et al., 2013). One principle of the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation is that testing of chemicals on animals should be a last choice (Van der Jagt et al., 2004; Parliament and Union, 2006; Laue et al., 2014). Much effort has been devoted to developing predictive models to estimate BCFs, where no *in vivo* data are available. Typically, chemical is preliminary screened and assessed based on physicochemical properties, like octanol-water partitioning coefficient (K_{OW}). It's widely used as an indicator of hydrophobicity and thus the partitioning of a chemical from water to lipids and other organic phases (e.g., protein) (Debruyn and Gobas, 2007).

Equilibrium partition coefficients for organic chemicals from environmental compartments to a tissue/organism are normally estimated by the total lipid content in combination with the K_{OW} (Mackay, 2001). So chemical concentrations in an organism/tissue are often normalized to the total lipid content, assuming that all lipids have identical sorption properties and the non-lipid fraction has a negligible sorption capacity (Endo et al., 2013). However, the suitability of this simplified approach has been questioned (Hermens et al., 2013; Endo and Goss, 2014a). It has been reported that the sorption capacity varies among different types of lipids (e.g., storage and membrane lipids) (Endo et al., 2011). Furthermore, the non-lipid components (e.g., proteins and serum) could also be a significant accumulation phase for organic compounds, especially for the H-bond donor compounds (Endo et al., 2012). More importantly, correlations with K_{OW} are expected to be valid only for restricted chemical domains (Hermens et al., 2013). As attention on contaminants in the environment with more complex structures, like hormones, pharmaceuticals and surfactants grows, the task to go beyond K_{OW} and explore more refined approaches to mechanistically modelling bioaccumulation is urgently needed.

Much effort has been made for the exploration and development of poly-parameter linear free energy relationships (pp-LFERs), which could account for the contribution of different specific and non-specific inter-molecular interactions (Abraham et al., 1994, 2015). Undeman et al. (2011) estimated the total sorption capacity of the human body directly using the pp-LFERs calibrated for composite tissues/organs, showing limited benefit over the traditional sp-LFERs approach (Undeman et al., 2011). This could be attributed to the unavailability of different pp-LFERs equations in individual biological phases (e.g., neutral lipid, phospholipid and protein) at that time. A single pp-LFER for partitioning to composite tissue/organ (e.g., blood, liver and brain) may only work well for the calibrated chemicals. If a very diverse set of study chemicals out of the calibration domain was applied to pp-LFERs of composite tissue/organ, large errors may occur. For instance, models calibrated by datasets from very polar compounds, which predominately partition into the aqueous phase, may not work well in a biological phase calibrated by compounds mainly partitioning to lipid (Geisler et al., 2011). Thus, if different chemicals have different preferred phases within a composite material (e.g., fat tissue is a composite material mainly made up by water, neutral lipid, phospholipid and protein), a pp-LFERs approach needs to be established for individual biological phases instead of the whole bulk compartment.

Recently, a number of studies have characterized different types of lipids, with regard to their chemical interactions (Endo et al., 2011; Geisler et al., 2012). Meanwhile, pp-LFERs for estimation of partitioning of neutral organic compounds to biological phases have also been calibrated, e.g., storage lipids (Geisler et al., 2012), phospholipids (Endo et al., 2011), serum albumins (Endo and Goss, 2011a) and muscle protein (Endo et al., 2012). In addition, preliminary evaluation has been carried out to directly compare partition coefficients to tissues calculated by pp-LFERs models and K_{OW}-based models, indicating an order-of-magnitude approximation (Endo et al., 2013). Furthermore, another initial evaluation was conducted to examine the effect of pp-LFERs approaches on pharmacokinetic (PBPK) models (Salmina et al., 2016). But they did not incorporate metabolic transformation, which would be a critical issue for rapidly metabolized compounds. Consequently, a comprehensive study to explore their benefit for the prediction of bioaccumulation potential and interpretation of biomonitoring results is desirable.

The main objective of this study was to explore the influence of implementing pp-LFERs on the estimation of bioconcentration factors in different types of fish model. Fish is used as a reference biota due to their important role in human daily diet and the fact that they act as an essential biosorbent for organic chemicals. Additionally, enough data availability exists for fish model evaluation compared to other species. In this study, two types of fish model: a one-compartment fish model (Arnot and Gobas, 2004) and a multi-compartment physiologically based toxicokinetic (PBTK) model (Nichols et al., 1990) were set up with incorporated sp or pp-approaches. Differences between model outputs were evaluated, and predicted BCFs were used to compare with measured BCFs. The implications for research and regulatory practices with regard to chemical risk assessment are also discussed.

2. Methods

2.1. General approach

Two types of mechanistic fish models were selected in this study, the one-compartment fish model (Arnot and Gobas, 2004), which assumes the chemical concentration is the same throughout the organism, and the multi-compartment PBTK model (Nichols et al., 1990), which considers chemical concentration may differ between various organs and tissues. Their selection in the chemical risk assessment depends on the question being addressed and the ease of data collection under different scenarios (Landrum et al., 1992). The one-compartment model is suitable for preliminary risk assessment with simple inputs, while the multi-compartment model is preferred in higher-tier assessments to quantify organ-specific concentration. These two representative models were implemented under both traditional sp-LFERs (traditional K_{OW} -driven) and newly-developed pp-LFERs to explore their performance in term of BCF prediction.

To eliminate difference caused by input parameters, the only distinction between these two approaches of pp-LFERs and sp-LFERs models, is the way of calculating partition coefficients to tissues/organs. All other equations and parameterizations were not modified in these two modelling approaches. Firstly, both models were run using a set of chemicals with the same measured descriptors. Thus, the potential errors in the measurement of chemical descriptors will be eliminated by using the same chemical descriptors for both approaches. Then the compiled dataset with measured BCFs was used as the endpoint to compare with the model predictions. Only chemicals present in neutral form in natural water were considered in this evaluation process.