

## Special Series

# Predicting the Accumulation of Ionizable Pharmaceuticals and Personal Care Products in Aquatic and Terrestrial Organisms

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**Abstract:** The extent to which chemicals bioaccumulate in aquatic and terrestrial organisms represents a fundamental consideration for chemicals management efforts intended to protect public health and the environment from pollution and waste. Many chemicals, including most pharmaceuticals and personal care products (PPCPs), are ionizable across environmentally relevant pH gradients, which can affect their fate in aquatic and terrestrial systems. Existing mathematical models describe the accumulation of neutral organic chemicals and weak acids and bases in both fish and plants. Further model development is hampered, however, by a lack of mechanistic insights for PPCPs that are predominantly or permanently ionized. Targeted experiments across environmentally realistic conditions are needed to address the following questions: (1) What are the partitioning and sorption behaviors of strongly ionizing chemicals among species? (2) How does membrane permeability of ions influence bioaccumulation of PPCPs? (3) To what extent are salts and associated complexes with PPCPs influencing bioaccumulation? (4) How do biotransformation and other elimination processes vary within and among species? (5) Are bioaccumulation modeling efforts currently focused on chemicals and species with key data gaps and risk profiles? Answering these questions promises to address key sources of uncertainty for bioaccumulation modeling of ionizable PPCPs and related contaminants. *Environ Toxicol Chem* 2024;43:502–512. © 2022 The Authors. *Environmental Toxicology and Chemistry* published by Wiley Periodicals LLC on behalf of SETAC.

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## INTRODUCTION

The extent to which chemicals bioaccumulate in aquatic and terrestrial organisms represents a fundamental consideration for chemicals management efforts intended to protect public health and the environment from pollution and waste. Basic and translational research, including professional practice activities, have contributed to the development of bioaccumulation science for inorganic and organic chemicals. Because empirical information for uptake and elimination is unavailable for the vast majority of the approximately 350 000 chemicals and chemical mixtures

registered for global production and use (Wang et al., 2020), it is imperative to understand the processes that result in bioaccumulation and develop predictive computational models that account for these processes. Bioaccumulation models can be used to assess diverse exposure scenarios to quantify environmental risk and prioritize chemicals for control and interventions, including substitution by and design of less hazardous substances.

Most ingredients within pharmaceuticals and personal care products (PPCPs) are introduced to the environment from domestic and industrial wastewater treatment plant discharges and in poorly treated or raw sewage, with additional inputs from veterinary use (aquaculture and livestock production) and the land application of biosolids, effluents, or manure. The PPCPs encompass a diverse group of bioactive ingredients including human and veterinary medicines as well as chemicals in personal care products such as sunscreens, detergents, and

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disinfectants. For the present study, we also included per- and polyfluoroalkyl substances (PFAS), noting that although PFAS are not generally present in PPCPs except as impurities (Brinch et al., 2018; Fujii et al., 2013; Whitehead et al., 2021), their properties (e.g., strong acids, affinity for phospholipids and serum albumin) and known kinetic behaviors in fish can offer significant insights into the bioaccumulation of ionizable PPCPs.

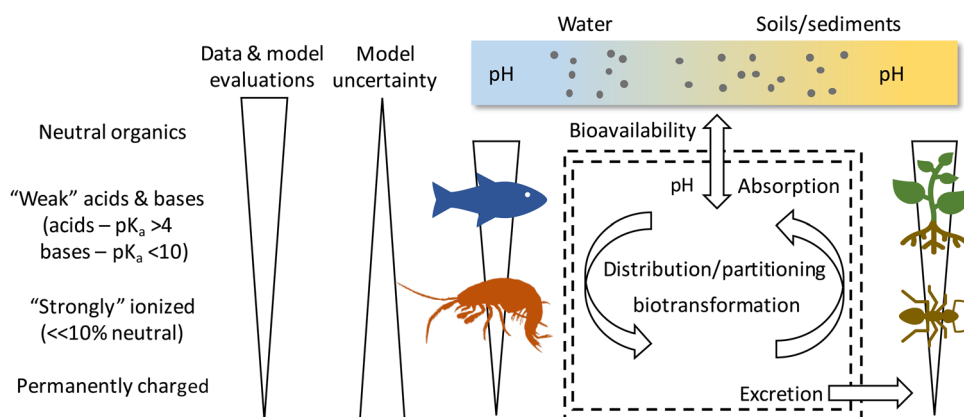
Numerous chemicals in commerce, including the majority of PPCPs, are ionizable across environmentally relevant pH gradients (Franco et al., 2010; Manallack, 2007; Newton & Kluza, 2016). Despite recognition that pH influences bioavailability and toxicity of ionizable contaminants, empirical information for accumulation of ionizable PPCPs in ecological receptors was quite rare a decade ago. Initial observations of bioaccumulation of basic pharmaceuticals by fish in the field (Brooks et al., 2005; Ramirez et al., 2007), along with the development of predictive models for gill uptake of ionizable chemicals (Erickson et al., 2006a, 2006b) stimulated research activities in this area (Daughton & Brooks, 2011). In an earlier review of this topic, Fu et al. (2009) noted the important contribution of ionizable contaminants more broadly to chemicals in commerce. The paucity of attention previously given to ionizable chemicals, coupled with the lack of predictive understanding of the bioaccumulation potential of ionizable PPCPs in aquatic and terrestrial systems led to the identification of this question as a priority research need by Boxall et al. (2012): “How can the uptake of ionizable PPCPs into aquatic and terrestrial organisms and through food chains be predicted?”

In the present study we considered the challenge of predicting the bioaccumulation of ionizable PPCPs, recognizing that this outcome is a function of both uptake and elimination processes. For both aquatic and terrestrial systems, we examined key processes involved in the accumulation of ionizable chemicals by individual species and reflected on research developments over the past decade within a predictive modeling context. We concluded by providing recommendations for future research to improve bioaccumulation predictions of ionizable PPCPs, including identification of priority research questions for the next decade.

Chemical accumulation in living organisms occurs as a net result of absorption, distribution, metabolism (biotransformation), and excretion processes (ADME; Figure 1). Excluding higher vertebrates, current understanding of these processes in ecological receptors is greatest for fish and plants; however, conceptually similar processes can be expected to apply to other taxa including aquatic and terrestrial invertebrates. Common to all ADME processes is a need for chemicals to transit one or more biological membranes. Neutral chemicals bound in the environment (e.g., to dissolved or soil organic material) or within an organism (e.g., to plasma proteins or root tissue protein) cannot diffuse across membranes. For such chemicals, the direction and magnitude of the diffusion gradient is determined by “unbound” (and therefore bioavailable) chemical concentrations on either side of the membrane. For weak acids and bases, the membrane permeability of the neutral form greatly exceeds that of the ionized form. If one assumes that the ionized species does not diffuse across the membrane, the bioavailable fraction is determined by the extent of ionization (based on pH and a chemical's estimated dissociation constant [ $pK_a$ ] value) and binding of the neutral form.

Absorption occurs at exchange surfaces in contact with the environment (e.g., fish gills or the root cuticle in a plant) or an extension thereof (e.g., the gastrointestinal lumen). For aquatic species, chemical uptake is primarily limited to the unbound fraction in water or the contents of the gastrointestinal tract, whereas in terrestrial plants uptake is limited to chemicals that are mobile in soil water or exist in the gas phase. Chemicals absorbed by the organism are distributed internally by bulk transport (e.g., in blood or in xylem and phloem) and may bind to tissue macromolecules such as lipids and proteins. Chemicals that bind noncovalently remain available for transport out of the organism whereas those that bind covalently or with very high affinity are effectively sequestered.

Passive chemical diffusion across an external exchange surface is inherently bidirectional. Net flux due to diffusion at these exchange surfaces is determined, therefore, by competing rates of uptake and elimination. Additional routes of elimination in fish include excretion of a parent chemical in urine and bile, and biotransformation (Kleinow et al., 2008).



**FIGURE 1:** Chemical accumulation in living organisms as net result of absorption, distribution, metabolism (biotransformation), and excretion processes. Knowledge status for different chemical groups.

Membrane transporters, which have evolved to transport polar molecules across biological membranes, may contribute to the elimination of parent chemicals and their metabolites by specific organs such as the liver and kidney (Ferreira et al., 2014; Luckenbach et al., 2014; Popovic et al., 2014). For plants, the only route of elimination apart from loss across the exchange surfaces is biotransformation. Biotransformation and transport by membrane transporters can saturate at high substrate concentrations and may exhibit competitive inhibition when multiple substrates are present. Many chemicals induce the synthesis of biotransformation enzymes and/or membrane transporters, effectively altering an organism's capacity for elimination.

Mathematical models that describe the accumulation of neutral organic chemicals in fish and plants have been developed over several decades and are widely used in chemical regulatory programs to support decision making (Arnot & Gobas, 2003, 2004; Paterson et al., 1994; Trapp, 2007; Trapp & Matthies, 1995). Octanol–water partitioning ( $\log K_{OW}$ ) and proximate composition (i.e., total lipid and water content) are key input parameters required to generate predictions. These models are well supported by empirical data and have been evaluated against data from field sampling efforts and standardized laboratory testing. With simple modifications, models developed for neutral chemicals can be used to predict the bioaccumulation of weak acids and bases if a substantial fraction of total chemical (more than 10%; Armitage et al., 2017) exists internally as the neutral form; in such cases, the contribution of the ionized form to total accumulation is often ignored. Existing data indicate, however, that some highly (more than 99%) ionized chemicals can accumulate in both aquatic and terrestrial biota (Burkhard, 2021; Gredelj et al., 2020; Kierkegaard et al., 2020). In such cases, the simplifying assumption that ionized chemicals do not diffuse across biological membranes is clearly inadequate. In principle, even slow rates of membrane diffusion can support substantial bioaccumulation if exposure is of sufficient duration, elimination is limited, and the chemical has high affinity for tissue constituents. It is imperative, therefore, that predictive models be able to account for these behaviors.

## PROGRESS IN MODELING ACCUMULATION OF IONIZABLE PPCPS IN AQUATIC ORGANISMS

The last decade has seen advances in our ability to predict the accumulation of PPCPs in aquatic invertebrates including the first machine learning approach to predict bioconcentration in *Gammarus pulex* and an approach to characterize pH-dependent uptake by oligochaetes (Karlsson et al., 2017; Miller et al., 2019). It is important to note that whereas the approach by Karlsson et al. (2017) was built on experimental data for PPCPs, the dataset for the machine learning approach by Miller et al. (2019) included a variety of chemicals outside the PPCP domain including pigments, polychlorinated biphenyls, and polyaromatic hydrocarbons, of which

approximately 36% were ionized. Meredith-Williams et al. (2012) observed that the pH-corrected liposome–water partition coefficient was a good predictor of bioconcentration factors (BCFs) for aquatic invertebrates ( $R^2 = 0.83–0.89$ ). A recent study has shown that simple physicochemical parameters related to chemical hydrophobicity (e.g.,  $\log K_{OW}$ ,  $\log D$ ) are insufficient to predict accumulation of PPCPs in aquatic invertebrates because they poorly reflect the underlying behavior of ionizable chemicals (Veseli et al., 2022).

Additional advances have been made in predicting the accumulation of ionizable PPCPs in fish. Specifically, the last 10 years have seen significant developments in the parameterization and application of generic, mechanistic mass balance models for describing bioaccumulation of ionizable PPCPs in fish. Measured and empirically derived bioaccumulation parameters for some PPCPs (e.g., steady-state BCFs, gill uptake rate constants, total elimination rate constants, kinetic BCFs; Chen et al., 2017; Zhao et al., 2017) and regression-based estimation approaches (quantitative structure–activity relationships [QSARs]; Fu et al., 2009) also exist but are not considered in our study. Recent advances in mass-balance modeling include the implementation of a simplified version of the gill exchange model for ionizable organic chemicals proposed by Erickson et al. (2006a) within a generic mass balance bioaccumulation model for fish (Armitage et al., 2013). A key feature of the proposed gill exchange model is that the potential influence of differences between bulk water pH and pH within the gills on uptake and elimination kinetics is considered (Armitage et al., 2017). The BCFs predicted by the model described in Armitage et al. (2013) for 129 acids and 62 bases were reasonably well correlated with the empirical data ( $R^2 = 0.68–0.75$ ) and within a factor of 3 on average. Model evaluations indicated that overall, performance was better for “weakly” ionized chemicals (e.g., acids with  $pK_a$  values of 4 or higher, bases with  $pK_a$  values of 10 or less). However, there was much more uncertainty for “strongly” ionized and permanently charged chemicals.

Biotransformation is a critical determinant of chemical bioaccumulation. Of special interest is the rate of biotransformation, typically expressed as a first-order whole-body rate constant ( $k_B$ ), relative to competing rates of uptake and other elimination processes. Using a model-based approach, Arnot et al. evaluated in vivo BCFs and measured rates of depuration for approximately 700 organic chemicals to obtain a set of estimated  $k_B$  values (Arnot, Mackay, Parkerton, et al., 2008; Arnot, Mackay, & Bonnell, 2008). The resulting  $k_B$  estimates have been used to develop QSARs that predict  $k_B$  from chemical structure/property information (Arnot et al., 2009; Brown et al., 2012; Kuo & Di Toro, 2013; Mansouri et al., 2018; Papa et al., 2014).

An alternative to the QSAR method for  $k_B$  prediction in fish involves the use of in vitro methods (Krause & Goss, 2020; Nichols et al., 2006, 2009; Trowell et al., 2018). The aim in such studies is to extrapolate a measured rate of in vitro intrinsic clearance to an estimate of  $k_B$  (in vitro–in vivo extrapolation [IVIVE]), taking into account differences in chemical binding in vitro and in tissues (blood and/or liver and/or the fish

considered as a whole, depending on the IVIVE approach). With respect to PPCPs, trout live S9 and hepatocyte assays have been used to investigate the biotransformation of pharmaceuticals (Connors et al., 2013; Gomez et al., 2010), fragrance chemicals (Laue et al., 2014), and ionizable surfactants (Chen et al., 2016; Droge et al., 2021). Additional measurements for pharmaceuticals have been obtained using a liver spheroid system (Baron et al., 2017). The utility of in vitro methods for chemicals that undergo slow rates of biotransformation may be limited by the working lifetime of the preparation (Nichols et al., 2021). These methods also fail to account for biotransformation in tissues other than the liver (Saunders et al., 2020).

Lastly, recent observations have stimulated renewed interest in renal clearance as an elimination pathway (Consoer et al., 2014; Ng & Hungerbühler, 2013). Renal clearance is generally ignored in mass balance models for fish because gill elimination is expected to be much greater. However, studies by Consoer et al. (2014) demonstrated the predominance of renal clearance as a mechanism for elimination of perfluorooctanoate (PFOA) in rainbow trout. Modeling studies also suggest that renal clearance plays an important role in elimination of several shorter chain (less than eight perfluorinated carbons) perfluorinated alkyl acids (PFAAs) by fish (Sun et al., 2022). These findings are consistent with earlier research on anionic chemicals such as 2,4-dichlorophenoxyacetic acid (Pritchard & James, 1979) and suggest that active transport to urine mediated by renal organic anion transporters (OATs) plays an important role in the elimination of some anionic substances by fish. Whereas the broader importance of active transport and renal clearance for PPCPs is unclear and relevant empirical data are generally lacking, an approach to model interactions with OATs and renal clearance for PFAAs using in vitro data has been proposed in the literature (Ng & Hungerbühler, 2013) and may be viable for other ionizable PPCPs in the future.

## PROGRESS IN MODELING THE ACCUMULATION OF IONIZABLE PPCPS IN TERRESTRIAL ORGANISMS

In the terrestrial environment, work to date has focused on the accumulation of a select number of ionizable pharmaceuticals by earthworms (Carter et al., 2014, 2016). A first-order one-compartment toxicokinetic model was successfully fitted to the data and allowed the subsequent determination of earthworm BCFs; however, further analysis revealed that previously published QSARs to predict BCFs (see Jager, 1998) performed poorly, which suggested that further model development is required (Carter et al., 2014). In comparison, considerable focus has been on the development, parameterization, and application of models describing bioaccumulation of ionizable PPCPs in plants. The mechanistic description of uptake and redistribution of dissociating electrolytes in plant cells' organelles by Trapp (2000) and further refined and described by Trapp (2004, 2009), forms the basis of a number of approaches that have been

published in the last decade to model the in-plant accumulation of ionizable PPCPs.

Partition coefficients calculated using the cell model are used in several dynamic plant uptake (DPU) models to estimate chemical transport within a plant, accounting for the fact that in typical exposure scenarios, steady-state solutions are not appropriate. For example, the dynamic model for neutral compounds (Trapp, 2015) was modified by González García et al. (2019) to consider additional processes relevant for ionic compounds, such as (1) sorption to proteins, (2) speciation and ion trapping, and (3) phloem transport of weak acids. A similar approach was adopted by Brunetti et al. (2022), who revised their earlier model for neutral compounds (Brunetti et al., 2019), to take into account processes such as chemical dissociation, electrical interaction with plant membranes, and phloem transport to simulate the reactive transport of electrolytes in the soil–plant continuum. The modeling framework connected the cell model to describe processes at a multi-organelle level with a multicompartment DPU model to simulate the reactive transport of electrolytes in the soil and plant (Polesel et al., 2015; Šimůnek et al., 2016; Trapp, 2004). The model outputs confirmed that pH conditions in both the soil and xylem play a crucial role in the uptake and translocation of ionizable chemicals, providing further evidence that we cannot just rely on models developed for neutral compounds.

In an additional level of complexity, integrated models describe chemical fate across different scenarios and compartments (e.g., wastewater/biosolids–soil–crops). For example, Polesel et al. (2015) developed a model to simulate the fate of ionizable PPCPs from human consumption up to the accumulation in the plant following irrigation with wastewater or soil amendment with biosolids. Delli Compagni et al. (2020) have also applied an integrated approach to predict ionizable PPCP fate in different types of wastewater reuse systems. To achieve this, a river water quality model, with extended chemical fate processes accounting for environmental pH on partitioning behavior, was combined with a coupled soil–plant model that described the partitioning of ionizable chemicals between plant tissues and soil, and xylem and phloem flows.

Meanwhile, Prosser et al. (2014) examined the ability of the DPU model and the biosolids-amended Soil Level IV model (BASL4) to predict the concentration of eight PPCPs in plants grown in biosolids-amended soil. In BASL4, ionization of chemicals was accounted for in a number of ways including the replacement of partition coefficients (i.e., organic carbon–water partitioning  $K_{OC}$ ,  $K_{OW}$ ) and water solubility of the neutral PPCP molecules with distribution ratios (i.e.,  $D_{OC}$ ,  $D_{OW}$ ) and adjusted water solubility to address the speciation that occurs at soil pH. It is also important to acknowledge advances in modeling pesticide exposure, and similarities in the ionogenic nature of pesticides offer promise in utilizing these frameworks for modeling the accumulation of ionizable PPCPs. For example, dynamiCROP, which simulates accumulation into multiple crop types (Fantke et al., 2011), has been shown to model uptake of a wide range of pesticides including ionizable compounds such as azoxystrobin in passion fruit with good accuracy (Juraska et al., 2012).



Pharmaceuticals have been extensively studied in laboratory animals and humans. Mechanistic modeling approaches conceptually similar to those used to simulate ionizable PPCPs in fish have recently been implemented to simulate bioaccumulation in air-breathing organisms (Armitage et al., 2021; Arnot et al., 2022). Preliminary model evaluations indicate similar performance for neutral organics and weak acids and bases, but further comparisons are needed. As with aquatic organisms, greater uncertainty is expected for strongly ionized PPCPs due to the challenges in estimating membrane permeation (e.g., gut uptake efficiencies) and sorption to biological macromolecules (i.e., phospholipids, serum albumin, other proteins).

## FUTURE RESEARCH PRIORITIES

As summarized in the previous sections, the last decade has brought significant advances in our ability to model the accumulation of PPCPs. Further model development is hampered, however, by a lack of mechanistic insights for PPCPs that are predominantly or permanently ionized. To improve predictive bioaccumulation models for such chemicals, targeted experiments across environmentally realistic conditions are needed to address the following questions:

### *What are the partitioning and sorption behaviors of strongly ionizing chemicals among species?*

Regression equations that predict steady-state BCFs in fish from  $\log K_{OW}$  have been provided by numerous authors (Mackay, 1982; Veith et al., 1979). Implied by this approach is an assumption that octanol is a good surrogate for the biological phases into which organic chemicals partition. Substantial data indicate, however, that octanol is a poor surrogate phase for ionizable organics and tends to underestimate sorption of ions (Escher & Schwarzenbach, 1996). In recent years, sorption data for ionizable chemicals have been obtained for liposomes (membrane phospholipids), serum albumin, structural proteins, and other biologically relevant phases (Allendorf et al., 2019; Bittermann et al., 2016, 2018; Droge, 2018; Droge et al., 2021; Ebert et al., 2020; Goss et al., 2018; Henneberger & Goss, 2021; Henneberger et al., 2016a, 2016b, 2022; Linden et al., 2017). However, empirical data remain scarce compared with the number of ionizable chemicals requiring assessment. Methods to predict key partitioning coefficients and distribution ratios for strongly ionized chemicals have been developed but are computationally demanding and involve proprietary software (e.g., COSMOmic; Bittermann et al., 2016).

The distributional behavior of a drug in mammals is commonly described by its apparent volume of distribution ( $V_D$ ), which is defined as the sorption capacity of the organism relative to that of blood. The  $V_D$  may be estimated in relatively simple kinetics experiments and, once known, provides an empirical description of internal partitioning regardless of the basis for this behavior. This concept may have special utility for

modeling the accumulation of ionized chemicals in fish (Brooks & Steele, 2018; Nichols et al., 2009). In fact, Zhang et al. (2022) recently found that human  $V_D$  values predicted kinetic-based BCFs of pharmaceuticals in zebrafish to a greater extent than  $D_{OW}$  or  $D_{liposome-water}$ . Presently, there are very few measured  $V_D$  values for nonmammalian species.

Options to replace  $\log K_{OW}$  in plant accumulation modeling have also been proposed. In a recent study, González García et al. (2019) estimated sorption to plant proteins using the human serum albumin–water partition ratio ( $K_{HSA}$ ). Conceptual frameworks for addressing the different sorption behaviors exhibited by ionizable chemicals are therefore well established and have been tested. Nevertheless, significant challenges to reliably predict the partitioning of ions remain. It is also important to recognize that such partition coefficient/distribution ratio approaches are assumed to apply across species, but further evaluations for PPCPs and other ionizable organic contaminants are warranted.

### *How does membrane permeability of ions influence bioaccumulation of PPCPs?*

The membrane permeability of ions is closely related to the previous question of sorption, with the permeability ( $P$ ) of neutral chemicals calculated using the membrane partition coefficient ( $K$ ), the diffusion coefficient ( $D$ ), and the membrane thickness ( $\Delta x$ ; Trapp, 2004). Because the membrane partition coefficient,  $K$ , of neutral compounds is closely related to the  $\log K_{OW}$ , regressions of  $P$  versus the  $\log K_{OW}$  have been proposed (Grayson & Kleier, 1990; Trapp, 2004). New regressions for ions based, for example, on  $K_{lipw}$  (or  $D_{lipw}$ ) are yet to be developed and tested. In any case, due to the strong dipole moment, ions permeate much more slowly (1000–10 000 times; Kleier, 1988) through membranes. Moreover, membranes are electrically charged, and thus membrane permeation of organic ions is correctly described by the Nernst–Planck equation and not by Fick's first law of diffusion (Trapp, 2004). The need to better understand membrane permeability of ionized chemicals is well illustrated by the observed behavior of PFAS in fish. If ionized chemicals did not diffuse across gill membranes, the uptake of such chemicals from water would be negligible. Instead, even though gill uptake efficiencies are low (less than 1% for perfluorooctanesulfonic acid and PFOA in large rainbow trout; Consoer et al., 2016), they are sufficient to support substantial accumulation (Martin et al., 2003).

### *To what extent are salts and associated complexes with PPCPs influencing bioaccumulation?*

To date, modeling approaches have rarely considered that living cells are a “salty” environment (ionic strength [ $I$ ] of cytosol 0.3 M). Ionic strength is a descriptor for the overall concentration of charges in a solution and is therefore important in

determining the activity coefficient ( $\gamma$ ) for neutral molecules and ions. Because partition coefficients for ions increase with ionic strength, changes in chemical activity can lead to chemical enrichment inside the cells and thus alter bioaccumulation predictions (Trapp et al., 2010). For example, an activity coefficient of 0.3 for bivalent ions (when  $I = 0.3$  M, charge ( $z$ ) = 2) suggests chemical enrichment of a factor 3.3 compared with dilute water (Trapp et al., 2010). Moreover, all electrolytes can form salts and complexes involving counter ions, as described by the law of mass action. These complexes are electrically neutral and will behave differently from their ionic form. Few examples have been studied (e.g., tributyl tin; Arnold et al., 1997), and to date it remains undetermined as to the extent that complexation affects the properties of ionizable PPCPs, and therefore related processes such as sorption and membrane permeability. This fundamental knowledge is needed to understand and account for salts and complexes in future bioaccumulation modeling efforts.

### How do biotransformation and other elimination processes vary within and among species?

Biotransformation and other elimination processes are of particular importance when considering the bioaccumulation of strongly ionized chemicals given that the uptake of such chemicals is typically slower than that of neutral molecules. In most cases, biotransformation results in chemical products that possess less potential to accumulate than the parent chemical from which they derive; however, some exceptions are known to exist (Chen et al., 2017; Droge et al., 2021). In some cases, a comprehensive assessment of bioaccumulation potential may require knowledge of both biotransformation rates and the behavior of specific metabolic products.

Fish biotransformation QSARs have been largely trained on  $k_B$  estimates for neutral organic chemicals, obtained by modeling measured bioaccumulation data. Currently, uncertainties relating to uptake and tissue binding of strongly ionized and permanently charged chemicals make it difficult to estimate  $k_B$  values from in vivo data. However, an accurate bioaccumulation model for these chemicals would provide for this possibility. As such models become available, they should be used to generate new  $k_B$  estimates from in vivo data as a means of improving existing biotransformation QSARs. Similarly, the development and use of IVIVE methods for  $k_B$  estimation in fish has focused on neutral, hydrophobic chemicals. Substantial uncertainty exists in the use of such methods for strongly ionized chemicals. Of special concern is a need to accurately predict chemical binding in vitro and in fish tissues. Thus, the research needed to apply IVIVE methods to these chemicals overlaps substantially with that required to estimate in vivo  $k_B$  values. Read-across from mammalian studies offers promise to understand the types of pharmaceutical metabolites that are to be expected in fish and other aquatic organisms, but does not provide quantitative organism-specific biotransformation parameters ( $k_B$  or the whole-body elimination half-life) for model development and improvement. There is a special need to

characterize rates of biotransformation in widely used experimental fish models (e.g., zebrafish) as well as species of commercial importance and those of concern from a conservation perspective.

Additional research should be focused on biotransformation in understudied organisms, such as aquatic invertebrates, which are known to metabolize a range of PPCPs (Chen et al., 2017; Fu et al., 2018; Jeon et al., 2013; Miller et al., 2017; Rösch et al., 2016). There is a clear need to assess biotransformation dynamics across diverse invertebrate taxa, because even closely related species such as *G. pulex* and *Hyallela azteca* may exhibit different rates of biotransformation (Fu et al., 2018) and resulting biotransformation products (Jeon et al., 2013). Models that can be used to estimate in vivo biotransformation rates in invertebrates have been provided (Ashauer et al., 2012; Ratier et al., 2021). Conceptually, therefore, methods used to develop fish biotransformation QSARs for fish could be applied to invertebrates. Given the substantial data requirements for development of a biotransformation QSAR, however, the more useful approach, at least in the short term, may be the development of in vitro biotransformation assays and associated IVIVE procedures.

The “green liver” concept (Sandermann, 1999) has been proposed to relate the metabolic processes of plants and animals. A difference between animals and plants is that the latter excrete complexed metabolites into vacuoles or cell walls, and hence metabolites are not removed from the plant, which may be the reason for the high number of PPCP metabolites identified in plants (Carter et al., 2018; Macherius et al., 2014; Riemenschneider et al., 2017). Analytically, such complexes and bound residues are a challenge, and are thus rarely identified, which limits the availability of empirical data for model development (Kästner et al., 2014; Sandermann, 2004). Moreover, the available data show high variability (Fantke & Juraske, 2013). Focused efforts are therefore required to develop approaches to model biotransformation of ionizable PPCP in plants and the sequestration of metabolites in cell walls and vacuoles.

### Are bioaccumulation modeling efforts currently focused on chemicals and species with key data gaps and risk profiles?

Extensive efforts have aimed to prioritize PPCPs for future study, as noted elsewhere in this special series on priority research questions. Such exercises are pragmatic given the diversity of chemical classes within PPCPs, and the limited availability of information on their environmental fate, effects, and risks. For example, Nendza et al. (2018) screened data sources for aquatic bioaccumulation data. All acids and bases in this evaluation that fulfilled the REACH B criterion (BCF greater than 2000 L/kg; ECHA European Chemical Agency, 2017) were either mostly nonionized under the tested conditions or PFAS. Bioaccumulation test data for mostly or fully ionized chemicals remain relatively scarce, however, in part due to the expectation of low bioaccumulation potential. Furthermore, a low bioaccumulation potential does not negate

potential environmental risk, particularly when biological activities of many PPCPs are more targeted and potent than most industrial chemicals. Ankley et al. (2007) highlighted problems associated with using usage tonnage-based cut-off values to assess and manage PPCPs, and recently published research has demonstrated that low concentrations in aquatic and terrestrial systems can elicit sublethal effects in nontarget organisms (Bertram et al., 2022; Carter et al., 2015; Horký et al., 2021; Martin et al., 2019), with a potential for wider ecosystem effects. It is therefore important that future bioaccumulation models be relevant for chemicals with a broad range of physicochemical properties and not just those expected to accumulate to the greatest extent.

Additional focus needs to be placed on understudied organisms. It is important for future research efforts to consider other nontarget organisms such as aquatic and terrestrial invertebrates (Karlsson et al., 2017; Miller et al., 2015). This is particularly important given the potential for trophic transfer in diverse ecosystems (Du et al., 2014; Haddad et al., 2018) and scenarios, such as nectar and pollen to bees (Carter et al., 2020).

### What are the key sources of uncertainty for PPCP bioaccumulation modeling?

Insufficient process descriptions lead to model uncertainty. For neutral PPCPs, the principal uncertainties relate to biotransformation (rate and behavior of metabolic products) and the behavior of extremely hydrophobic ( $\log K_{OW}$  greater than 9) chemicals. For weak acids and bases ( $pK_a$  4–10), the principal modeling uncertainties relate to binding of the ionized chemical species, the potential role of membrane transporters in chemical elimination, biotransformation, and the impact of pH gradients that are often undescribed or variable. In plants, for example, there can be a large pH gradient between xylem (pH 4.5–5.5) and phloem (pH 8), and between cytosol (pH 7.4) and vacuoles (pH 4.5–5.5). Ion trapping effects may therefore add considerable uncertainty to the prediction of translocation and accumulation (Briggs et al., 1987; Delli Compagni et al., 2020). Similarly, the elimination of metabolically produced acid at fish gills acidifies the microenvironment at the gill surface (Erickson et al., 2006b); however, the generalizability of this phenomena among different fish species, chemicals, and exposure settings is largely unknown. In the design of both experimental studies and field sampling efforts, it is important to consider how such factors could inform model development and to measure and report appropriate parameters. Often, experiments are not described in the necessary detail to simulate observed effects with mathematical models (Doucette et al., 2018; Trapp, 2015).

Ionizable compounds are, by definition, present as more than one molecular species, and the behavior of the neutral and ionized forms can differ substantially. There are thus more processes to consider, and more equations and parameters required for their description than for neutral compounds. This alone leads to an increase in variability and uncertainty in modeled fate predictions. However, it is important to acknowledge that this variation is not limited to the model world: it is also

found in the results of experimental studies in which PPCP accumulation shows wide variance, and a significant challenge remains as to how to account for this (Delli Compagni et al., 2020; Polesel et al., 2015). Additional variability in reported empirical BCF values in plants is introduced by different definitions of the soil concentration when one is deriving BCFs (see Trapp & Eggen, 2013, Supporting Information, Table 6).

For strongly ionized and permanently charged PPCPs, the principal modeling uncertainties relate to diffusion of ionized chemical species across membranes, binding of ionized species to tissue macromolecules, biotransformation, and the potential role of membrane transporters. With respect to these latter elimination processes, existing methods may not provide the sensitivity needed to measure low but “relevant” rates of activity, which are nonetheless important in terms of regulating bioaccumulation. Because uptake rates for ions are relatively slow, short-term laboratory experiments may be insufficient to reliably measure bioaccumulation. It is thus necessary to screen for bioaccumulation of PPCPs in field-collected organisms from both aquatic and terrestrial food webs. As presented, significant progress has been made in the last decade with respect to the development of bioaccumulation models to better account for processes specific to ionizable PPCPs. It is important that research now be tailored toward capitalizing on these developments to address the remaining sources of model uncertainty, which would pave the way for a suite of robust models for a broad spectrum of ionizable PPCPs.

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