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Critical Perspectives

Research Priorities for the Environmental Risk Assessment of Per- and Polyfluorinated Substances

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Abstract: Per- and polyfluorinated substances (PFAS) are a group of thousands of ubiquitously applied persistent industrial chemicals. The field of PFAS environmental research is developing rapidly, but suffers from substantial biases toward specific compounds, environmental compartments, and organisms. The aim of our study was therefore to highlight current developments and to identify knowledge gaps and subsequent research needs that would contribute to a comprehensive environmental risk assessment for PFAS. To this end, we consulted the open literature and databases and found that knowledge of the environmental fate of PFAS is based on the analysis of <1% of the compounds categorized as PFAS. Moreover, soils and suspended particulate matter remain largely understudied. The bioavailability, bioaccumulation, and food web transfer studies of PFAS also focus on a very limited number of compounds and are biased toward aquatic biota, predominantly fish, and less frequently aquatic invertebrates and macrophytes. The available ecotoxicity data revealed that only a few PFAS have been well studied for their environmental hazards, and that PFAS ecotoxicity data are also strongly biased toward aquatic organisms. Ecotoxicity studies in the terrestrial environment are needed, as well as chronic, multigenerational, and community ecotoxicity research, in light of the persistency and bioaccumulation of PFAS. Finally, we identified an urgent need to unravel the relationships among sorption, bioaccumulation, and ecotoxicity on the one hand and molecular descriptors of PFAS chemical structures and physicochemical properties on the other, to allow predictions of exposure, bioaccumulation, and toxicity. *Environ Toxicol Chem* 2023;00:1–15. © 2023 The Authors. *Environmental Toxicology and Chemistry* published by Wiley Periodicals LLC on behalf of SETAC.

Keywords: Perfluoroalkyl substances; Environmental fate; Ecotoxicology; Risk assessment

INTRODUCTION

Per- and polyfluorinated substances (PFAS) are a group of ubiquitously applied persistent industrial chemicals consisting of >6000 (Glüge et al., 2020) or even 1 million compounds depending on the definition (Sha et al., 2019; Wang et al., 2021). The main feature of PFAS is the C—F bond, which is one of the strongest atomic bonds, and the cause of their great persistence in the environment. Consequently, PFAS are barely degradable and are therefore often labeled "forever chemicals" (Miner et al., 2021). Persistency can be advantageous because it makes chemicals suitable for application in a wide variety of industrial products. Per- and polyfluorinated substances are therefore economically highly desirable, with an increasing number of applications (De Boer & Stapleton, 2019). Of course persistency is also a chemical feature of environmental concern (Cousins et al., 2019). When associated with high lipophilicity, it gives rise to bioaccumulation, food chain transfer, and adverse human and environmental health effects (Fiedler et al., 2019; Guo et al., 2019). Because of this persistency, high production volumes, and broad spectrum of applications, PFAS are ubiquitously present in various abiotic (Ahrens et al., 2010; Campo et al., 2016; Carrasquillo et al., 2008; Esparza et al., 2011; Knight et al., 2021; Kwon et al., 2017; Saito et al., 2003; Scott et al., 2006; Strynar et al., 2012; Washington et al., 2010; Yoo et al., 2010) and biotic (Esparza et al., 2011; Houde et al., 2011; Murakami et al., 2011; Scott et al., 2006; Tittlemier et al., 2007) matrices

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at considerable concentrations (Cousins et al., 2022). Nonetheless, it remains unclear how many of the more than 6000 CAS-registered PFAS are actually present in the various environmental compartments and if so, at what levels (Interstate Technology and Regulatory Council [ITRC], 2022). Although the development of new analytical tools to detect the wide variety of PFAS has shown great progress (Jia et al., 2022), application of these tools to environmental fate studies has been moving slowly, despite the urgent need to study the environmental fate of the different chemical PFAS families.

Most PFAS have a polar head group, and many of them are quite soluble in water (>1000 mg/L; ITRC, 2022), making these compounds mobile in the environment. Based on the amphiphilic properties of many PFAS (suiting their applications as repellant coating, aqueous film-forming agents, etc.), they also tend to accumulate at water–solid and water–air interfaces. This complicates the determination of their bioavailability in complex environmental matrices such as soils and sediments (Reemtsma et al., 2016). Due to their surfactant-like properties, PFAS bioaccumulation is less well predicted by traditional indicators like lipophilicity (log octanol/water partition coefficient [K_{OW}]; Droge, 2019). Consequently, little is known about the bioavailability and bioaccumulation of PFAS (Pietrini et al., 2019), and their potential transfer across food webs (Liu et al., 2018). Research initiatives should therefore focus on appropriate quantification of the bioavailability of PFAS, their bioaccumulation, and their trophic transfer, as well as investigations into which chemical properties of PFAS are able to predict these factors.

Compared with the highly debated and ambiguous information on human health risks based on detailed toxicological and epidemiological information for a limited number of PFAS, less is known about the hazards and risks of PFAS in the environment (Flynn et al., 2019; Society of Environmental Toxicology and Chemistry [SETAC], 2019). We argue that the lack of ecotoxicity data for PFAS could to some extent relate to the scarcity of available standards at affordable prices, in combination with analytical challenges. The effects of PFAS on biota after long-term exposure (SETAC, 2019), and how these are affected by their intrinsic molecular properties and chemical structure, are poorly understood (Ahrens & Bundschuh, 2014; Ding & Peijnenburg, 2013). This means that any established safe limits for PFAS in water, soil, and sediment are preliminary, not based on thorough ecotoxicological considerations and better scientific underpinning (Wintersen et al., 2019). The aim of our study, from this perspective, was therefore to highlight current developments in PFAS environmental research, and to identify knowledge gaps and subsequent research needs, with the aim of developing a comprehensive environmental risk assessment for PFAS. To this end, we consulted the open literature and databases on the environmental occurrence, hazards, and risks of PFAS and integrated our findings into the present critical perspective. We defined PFAS according to the definition proposed by Buck et al. (2011), according to which PFAS are highly fluorinated aliphatic substances that contain one or more carbon (C) atoms on which all the hydrogen (H) substituents (present in the nonfluorinated analogs from which they are notionally derived) have been replaced by fluorine (F) atoms. When we retrieved data from databases, the category PFAS was selected as provided by the database, which did not necessarily stick to the definition proposed by Buck et al. (2011). The way we explored the literature and databases is elaborated in the Supporting Information (Figure S1 and Table S1).

WHICH PFAS ARE DETECTED IN THE ENVIRONMENT?

Per- and polyfluorinated substances include thousands of substances, but it remains unclear how many of these compounds are actually present in the various environmental compartments and if so, at what levels. They have been found in surface and ground waters and even in drinking water (Vughs et al., 2018), as well as in soils (Brusseau et al., 2020) and sediments (Bai & Son, 2021). Exposure pathways and environmental distribution processes of PFAS have been previously described by Panieri et al. (2022) and the ITRC (2022). Nevertheless, a systematic inventory and detailed information on the occurrence and distribution of PFAS in the environment, in terms of both the presence of diverse types of PFAS (profiles) and the concentrations at reference sites and in polluted soils, sediments, and surface waters (levels), are virtually lacking. This becomes explicitly evident during evaluation of the PFAS occurrence data for water and sediment available from the NORMAN database (freshwater 84.7%, brackish water 10.0%, and marine water 5.3%). Such data were available for 41 PFAS, visualized in Figure 1 as the cumulative number of PFAS hits/year (the hits of the previous years were added to each consecutive year). This ranking showed that 50% of the cumulative occurrence data hits involved 8 compounds, and 90% only 21 compounds. Dividing the number of PFAS for which environmental occurrence data were available (41) by the assumed total number of PFAS (6000) revealed that knowledge of their environmental fate is based on analysis of <1% of the compounds that are currently categorized as PFAS. This is quite an alarming observation. Moreover, the data behind Figure 1 revealed a bias toward long-chained carboxylic acids, as defined by the Organisation for Economic Co-operation and Development (OECD, 2018). Hence, PFAS occurrence data are strongly biased toward a limited number of compounds, and for the vast majority of PFAS reliable environmental occurrence data are still lacking. Although most legacy PFAS belong to the commonly studied perfluoroalkyl acid (PFAA) family, the constant production of newly formulated emerging PFAS structures requires us to broaden the spectrum of PFAS analyzed in environmental matrices. This argument is supported by the results of nontarget screening and total oxidizable precursor assay studies, which revealed that the number of quantified PFAS covers only a small fraction of what is actually present in the environment (Hensema et al., 2021; Göckener et al., 2021). As fundamental input for a reliable environmental risk assessment for PFAS, providing this missing information is urgently required.

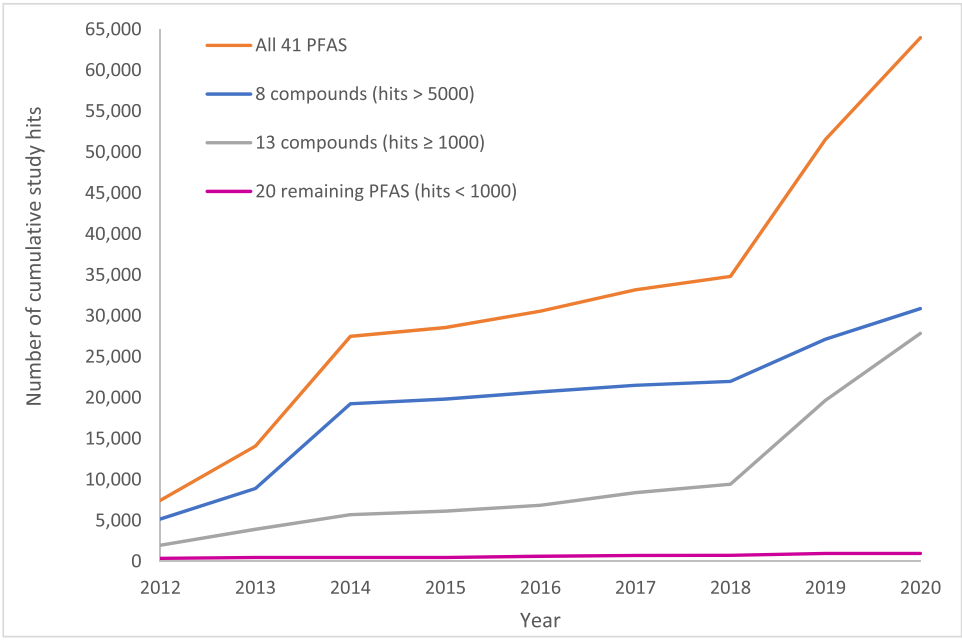

FIGURE 1: Cumulative number of published data on the occurrence of per- and polyfluoroalkyl substances (PFAS) in the aquatic environment (water and sediment), shown for different PFAS, grouped based on the number of cumulative hits. Data were extracted from the NORMAN occurrence data base, which contains information from 2012 to 2020, by filtering for PFAS. See the Supporting Information, Table S2, for a detailed overview of the chemicals that were included in this analysis.

The US Environmental Protection Agency (USEPA) has documented standard methods for PFAS detection in drinking water (2018, 2023) and nonpotable water (2021, 2022a) that can target up to 25 and 40 PFAS, respectively (Lewis et al., 2022; Simon et al., 2019). An International Organization for Standardization guideline (2009) is also available for the determination of perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) in unfiltered samples of drinking water, ground water, and surface water (freshwater and marine water) using high-performance liquid chromatography–tandem mass spectrometry. Within Europe some nations have standardized methods for PFAS analysis, such as the German DIN 38407-42 for water and DIN 38414-14 for sludge, compost, and soil, but to the best of our knowledge there is no European Union–wide unified protocol. Protocols for PFAS detection in other matrices and for additional compounds have been reported, but these concern individual studies, all using slightly different extraction and analytical methods. Because these methods differ from laboratory to laboratory, there is no universal harmonized protocol for detecting a broader spectrum of PFAS. Deploying supplementary types of analysis, like the Total Organic Fluorine method, as well as suspect and nontarget screening, can help to broaden the spectrum of detected PFAS, although the results remain semiquantitative or qualitative in some cases (Helmus et al., 2021).

By employing these diverse analytical methods, the cumulative number of detectable PFAS has increased over the years, up to 446 compounds in 2017 (Xiao, 2017). However, 435 of these could only be tentatively identified, due to the lack of corresponding analytical standards. Although this number is expected to increase over the years, with <80 reference standards available in 2022 (Androulakakis et al., 2022), the number of commercially available reference standards expressed as a percentage of the known PFAS is still below 1.5%. Hence, the first step in enlarging the set of PFAS that can be analyzed would require further standardization of protocols, in combination with the extension of the number of available analytical standards, to increase the efficiency and reliability of suspect and nontarget screening methods.

The available PFAS occurrence data for water and sediment used to construct Figure 1 were obtained from the NORMAN database, which, however, does not contain data for soil, immediately highlighting a bias toward the aqueous environment. Data for PFAS measurements in air are also missing from the NORMAN database, although it is a relevant matrix for some (semi)volatile PFAS structures and comprises an important transport pathway for many PFAS, mainly neutral and volatile precursors (Ahrens et al., 2010; Armitage et al., 2009), along with ocean currents (Zarfl et al., 2012). The bias toward water is further illustrated by compiling the available PFAS occurrence data from the published literature, showing that soils and suspended particulate matter (SPM) remain largely understudied, which we therefore identify as a pressing research priority. In contrast to the lack of air data in the NORMAN database, in the published literature we did find a considerable number of studies on PFAS measurements in air (gas or particle phase). Categorizing the literature data (Supporting Information, Reference Lists S1 and S2) by environmental compartment showed that 62.6% of the studies analyzed PFAS in the water phase and/or sediment and 27.9% measured PFAS in the air, whereas only 5.8% and 3.7% analyzed soil and SPM, respectively. Most of the aquatic studies involved freshwater (69.4%), whereas many fewer studies involved marine (23.5%) and brackish water (7.1%). Historically, water received more attention than soil in

chemical risk assessment, although soil is also an important compartment that should not be neglected. It would therefore be a significant step forward if online databases like NORMAN would expand their PFAS occurrence data to also include the terrestrial environment.

BIOAVAILABILITY, (BIO)DEGRADATION, UPTAKE, AND BIOACCUMULATION OF PFAS

PFAS bioavailability and (bio)degradation

Contaminant bioavailability has been recognized as a critical metric for a proper exposure and effect assessment (Alexander, 2000; Cui et al., 2013). Bioavailability is strongly influenced by the intrinsic chemical properties of the compound, as well as by soil and sediment characteristics (Cui et al., 2013; Milinovic et al., 2015), affecting processes like sorption and diffusion (Reichenberg & Mayer, 2006). The presence of cations and suspended solids can affect the overall sorption of anionic PFAS, consequently affecting the bioavailable fraction (Hammer et al., 2018). The freely dissolved concentration (C_{free}) is considered a useful metric of bioavailability, because it represents the contaminant concentration to which organisms are actually exposed. However, although PFAS are generally rather soluble in water (including those that sorb to solids), C_{free} may not represent all potential uptake routes. Organisms interact with the abiotic environment through complex processes (Van der Meer et al., 2017). Some organisms might be simultaneously exposed to the freely available fraction of PFAS in the porewater, and the accessible fraction sorbed onto solids (Jager, 1998). The surfactant-like properties of PFAS, enabling them to form micelles (Alves et al., 2020; Kancharla et al., 2019) and to stick to interfaces, further complicate the determination of their bioavailability (Reemtsma et al., 2016). Properly assessing PFAS bioavailability, including investigating their interactions with the (a)biotic environment, is thus a prerequisite toward a comprehensive exposure assessment.

The (bio)degradation pathways of PFAS are poorly understood (Zhang et al., 2022). Under ambient environmental conditions, abiotic processes that can transform precursors into nondegradable PFAS include hydrolysis, photolysis, and oxidation (ITRC, 2022). Regarding biotic degradation, the majority of the reported reactions are limited to the removal of the nonfluorinated moieties, whereas complete defluorination seems less plausible (Zhang et al., 2022). Moreover, after the removal of the functional groups, the degraded PFAS were even more persistent in the environment (Li et al., 2020). Certain enzymes, including transition metal-dependent enzymes, might be able to cleave the C—F bond through oxidation or reduction reactions (Shahsavari et al., 2021); however, not all PFAS can be expected to be biodegraded through the same pathway, and a combination of several biodegradation pathways is more probable (Zhang et al., 2022). Identifying these pathways and the resulting breakdown products including their environmental fate and (eco)toxicity is of high relevance for PFAS environmental risk assessment. (Bio)degradation is likely to further affect the composition of the PFAS mixture present in the environment, which can consequently affect the environmental exposure and thereby the ecotoxicity of these compounds.

Uptake and toxicokinetics of PFAS in biota

The accumulation of contaminants from the abiotic environment can take place through uptake from soil/sediment by ingestion, absorption from the water phase, or a combination of these processes. There are, however, doubts about whether existing bioaccumulation metrics are applicable to PFAS (De Silva et al., 2021). One of the main considerations differentiating PFAS from hydrophobic organic compounds is their higher affinity for proteins and phospholipids over storage lipids (Armitage et al., 2017; Dassuncao et al., 2019), a property relevant for both short- and long-chained PFAS. However, the sorption affinity of different PFAAs for proteins varies widely, suggesting site-specific interactions and facilitated transport of some compounds (De Silva et al., 2021; Henneberger et al., 2016). Therefore, it seems worthwhile to consider protein or phospholipid normalization of measured PFAS concentrations (De Silva et al., 2021). For benthic invertebrates, sediment governs PFAS exposure, whereas for pelagic organisms, both water and sediment comprise important sources of PFAS exposure (Liang et al., 2022). For plants, the large root surface can favor the uptake of nutrients, which may potentially also favor the uptake of contaminants (Zhi et al., 2022). Similarly to other biota, the protein and lipid content of the roots may influence PFAS uptake kinetics and bioaccumulation (Wang et al., 2020; Wen et al., 2018; Zhao et al., 2018). Once taken up by the roots, the Casparian strip comprises the main obstacle for PFAS translocation to other parts of the plant (Costello & Lee, 2020), although small and more water-soluble PFAS can easily cross this barrier (Felizeter et al., 2012; Zhang et al., 2019). According to two studies that tried to elucidate active transport mechanisms (Zhang et al., 2019; Zhi et al., 2022), the uptake of PFAAs seems to be an energy-dependent active uptake process, mediated by carrier proteins. Depending on the specific compound and plant species, different channels may be involved in these transport processes (Costello & Lee, 2020; Wang et al., 2020; Zhang et al., 2019). Although knowledge of PFAS bioaccumulation has been steadily increasing, the processes governing the uptake of PFAS by organisms and their partitioning across tissues remain poorly understood, even for commonly studied PFAS (De Silva et al., 2021). Filling this knowledge gap is required for the development of mechanistic models for environmental risk assessment (De Silva et al., 2021).

Although it is assumed that most PFAS cannot be further degraded, certain subclasses can undergo limited metabolism (Kolanczyk et al., 2023; Brase, et al., 2021). Fluorotelomer alcohols and perfluoroalkyl phosphate esters, for instance, can be transformed into perfluoroalkyl carboxylic acids (PFCAs; Butt et al., 2014; D'eon & Mabury, 2011). Other precursors include the perfluoroalkyl sulfonamides (e.g., perfluorobutane

sulfonamide, perfluorooctane sulfonamide), which can result in the formation of perfluorosulfonic acids (PFSAs; Ross et al., 2012). It is important to deepen our understanding of PFAS metabolic pathways and biotransformation products across species because they could play a major role in the toxicity exerted.

Which PFAS are analyzed in biota?

Several studies have reported the accumulation of PFAS in aquatic (in)vertebrates, including amphibians (Abercrombie et al., 2019), zebrafish (Menger et al., 2020), chironomids (Wen et al., 2016), and daphnids (Dai et al., 2013; Xia et al., 2013, 2015), sometimes even reaching high concentrations, as in crabs (Choi et al., 2020). Nonetheless, because bioaccumulation of PFAS is often not considered beforehand, this issue remains largely understudied for the majority of the fluorinated compounds. A list of the compounds analyzed in biota can be found in the Supporting Information.

Most bioaccumulation studies have focused on linear isomers of compounds like PFOS and PFOA and other PFAAs, whereas branched isomers and other PFAS families remain largely understudied, including the compounds that are currently replacing PFOS and PFOA (Karnjanapiboonwong et al., 2018). This is reflected by data from the open literature published from 2012 up to May 2022 (compiled in Figure 2), highlighting a bias toward a limited spectrum of PFAS analyzed in biota. Based on these data, 50% of the studies that included measurements in biota concerned only 8 PFAS, whereas 90% of the studies still concerned only 34 of the 164 PFAS for which bioaccumulation data were available. The most commonly studied PFAS in biota are PFOS and PFOA, accounting for 13% of all studies. Moreover, 14 PFAS were investigated in only two studies (28 hits in total), and 83 PFAS in just one study, pooled together in the orange bars in Figure 2. Taking into consideration the number of PFAS measured in biotic and abiotic matrices according to the open literature and the NORMAN database, this number still remains only a small fraction of the total number of PFAS.

Which organisms are studied for PFAS bioaccumulation?

The PFAS analyses in biota show the same limitations as those in the abiotic environmental compartments, with a strong bias toward aquatic biota, leaving terrestrial organisms largely understudied. This becomes evident when the available literature is consulted, because most of the studies published from 2012 up to May 2022 that quantified PFAS in various biotic matrices focused on aquatic organisms (Table 1). It should be noted that the literature included studies performed under laboratory conditions, as well as measurements in field-collected biota, but did not consider bioaccumulation measurements performed within ecotoxicity studies. Among aquatic organisms, fish were predominantly studied (36% of cases), and aquatic invertebrates and macrophytes less frequently. Considerable research has been performed on terrestrial biota, but most of these data concern agricultural crop species, studied under laboratory conditions, possibly due to their higher

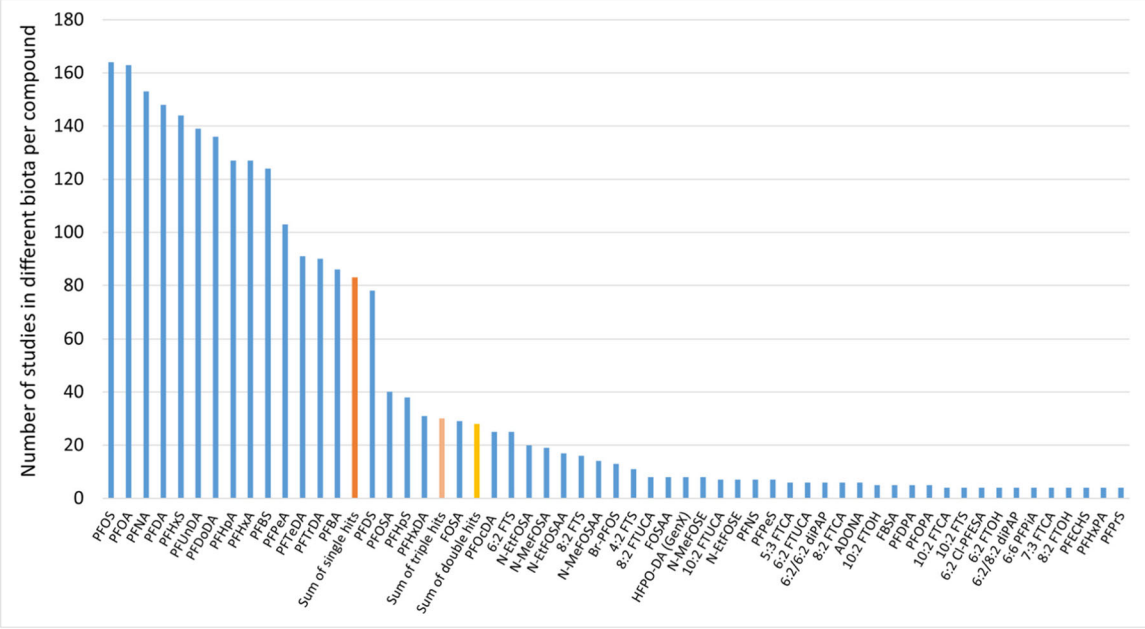

FIGURE 2: Number of studies ("study hits") for different per- and polyfluoroalkyl substances (PFAS) in studies that measured concentrations in biotic matrices, including fish, aquatic and terrestrial invertebrates, mammals, macrophytes, periphytic biofilms, birds, reptiles, amphibians, and eggs. All PFAS with a single hit were grouped together into the orange bar, to facilitate graphical visualization. Studies on PFAS bioaccumulation performed under laboratory conditions were also considered (e.g., mesocosm/mechanistic studies). Data are based on literature published from 2012 up to May 2022. A complete list of the studies included, as well as the PFAS with one hit, can be found in the Supporting Information, Reference List S3 and Table S3, respectively. CAS numbers and full names of PFAS can be found in the glossary, in the Supporting Information.

TABLE 1: Total number of studies on per- and polyfluoroalkyl substances (PFAS) bioaccumulation

	Fish	Aquatic invertebrates and macrophytes	Terrestrial higher plants	Terrestrial invertebrates	Other groups
No. of PFAS studies (laboratory and field)	75	45	24	15	47
Data points on PFAS accumulation from ecotoxicity studies (ECOTOX Knowledgebase)	239	117	581	51	NA

Aquatic and terrestrial biota include both invertebrates and plants. The category "other groups" includes aquatic and terrestrial mammals, birds, reptiles, amphibians, and eggs. Studies on PFAS bioaccumulation under laboratory conditions were also considered (e.g., mesocosm/mechanistic studies). Data in the first row are based on literature published from 2012 up to May 2022. A complete list of the studies included can be found in the Supporting Information, Reference List S4. Data points on PFAS bioaccumulation studied in ecotoxicity studies (second row) were retrieved from the ECOTOX Knowledgebase (USEPA, 2022b).
NA = not applicable; PFAS = per- and polyfluorinated substances.

relevance for human exposure. More information can be found in the Supporting Information (Reference List S4).

In laboratory toxicity tests, sometimes bioaccumulation of PFAS is also measured. Such data are usually calculated from quantified exposure concentrations in media and concentrations within organisms at the end of the toxicity tests. Hence, data on PFAS bioaccumulation in toxicity tests from 2012 to 2022 (latest update: March 15, 2023) were retrieved from the open-access USEPA ECOTOX Knowledgebase, which compiles data from peer-reviewed ecotoxicity studies and is updated quarterly (Olker et al., 2022; Table 1). A data entry requirement is that publications must report biological effects on living organisms (USEPA, 2022b). Thus studies that only focus on bioaccumulation of PFAS into organisms are not part of the ECOTOX Knowledgebase, in our case preventing overlap with the bioaccumulation-only studies just mentioned. We extracted PFAS bioaccumulation data points reported for algae, amphibians, crustaceans, fish, higher plants, fungi, insects, spiders, molluscs, worms, and other invertebrates. Subsequently, these data, listed separately in Table 1, were added as complementary information to the studies that focused on assessing PFAS accumulation in the laboratory and the field, consisting of studies in which no toxicological endpoints were assessed. The available bioaccumulation data retrieved from the ECOTOX Knowledgebase from the past 10 years are strongly biased toward fish and terrestrial higher plants, mainly crops. Because fish are one of the dominant groups used for toxicity testing (as discussed in the section *PFAS ecotoxicity to various organism groups*), the number of accumulation data generated from toxicity tests with fish is also higher compared with the other groups. Because it is argued that PFAS bioaccumulation can be species and compound specific (Johnson et al., 2021; Land et al., 2018), there is a clear need to catch up in assessing the bioaccumulation potential of the wide variety of PFAS structures in a broader range of organisms than have been studied so far.

Trophic transfer of PFAS

Despite the increasing number of recent studies on PFAS transfer along food chains, knowledge on this topic remains limited (Liu et al., 2018). As observed for environmental fate and bioaccumulation, the focus of food web studies is also restricted to a limited number of PFAS, mostly long-chained PFAAs (OECD definition), leaving emerging PFAS families understudied (Figure 3). Based on studies published from 2012 up to May 2022, we found 33 compounds with only a single hit in food web studies. Moreover, 50% of the food web studies concerned 10 PFAS, whereas 90% still concerned only 35 of the 72 PFAS for which we found food web studies. The most studied compound was PFOS; five long-chained perfluoro carboxylic acids (PFOA, perfluorodecanoic acid, perfluorononanoic acid, perfluoroundecanoic acid, perfluorododecanoic acid) and one medium-chained perfluoro sulfonic acid (perfluorohexane sulfonate) shared second place. Strikingly, to the best of our knowledge, only one terrestrial food web study covering more than two distinct trophic levels has been performed (Huang, Li et al., 2022), again showing a bias toward aquatic ecosystems. In terms of specific organism groups, higher plants were included in only 25% of the studies on PFAS food web distribution (Table 2).

ECOTOXICITY OF PFAS

Which PFAS are tested for ecotoxicity?

The need for a comprehensive ecological risk assessment for PFAS calls for an improved understanding of their ecotoxicity. Several studies have concluded, however, that the current information on the ecotoxicity of PFAS is scattered, ambiguous, and strongly biased toward a limited spectrum of compounds and test organisms (ITRC, 2022; Van Keer et al., 2020; Zodrow et al., 2022). To address this knowledge gap, an analysis was conducted using data from studies spanning 2012 to 2022, focusing on algae, higher plants, fungi, amphibians, fish, insects, crustaceans, spiders, molluscs, worms, and other invertebrates. These data were retrieved from the ECOTOX Knowledgebase on May 17, 2023. Prior to analysis, a data filtering process was implemented, excluding studies that failed to report results or relevant endpoints.

This inventory revealed that research on PFAS ecotoxicity has grown drastically over the past 10 years, resulting in an extensive dataset presently containing over 22,000 ecotoxicity data points. However, this dataset covers only a limited selection of 135 PFAS, representing 2.3% of the compounds currently defined as PFAS. The compounds PFOS and PFOA accounted for 45.0% of the entire dataset, and the four following most studied compounds collectively represented 19.6%. The remaining 35.4% of the ecotoxicity data comprised only 129 compounds (Figure 4). All studied compounds were

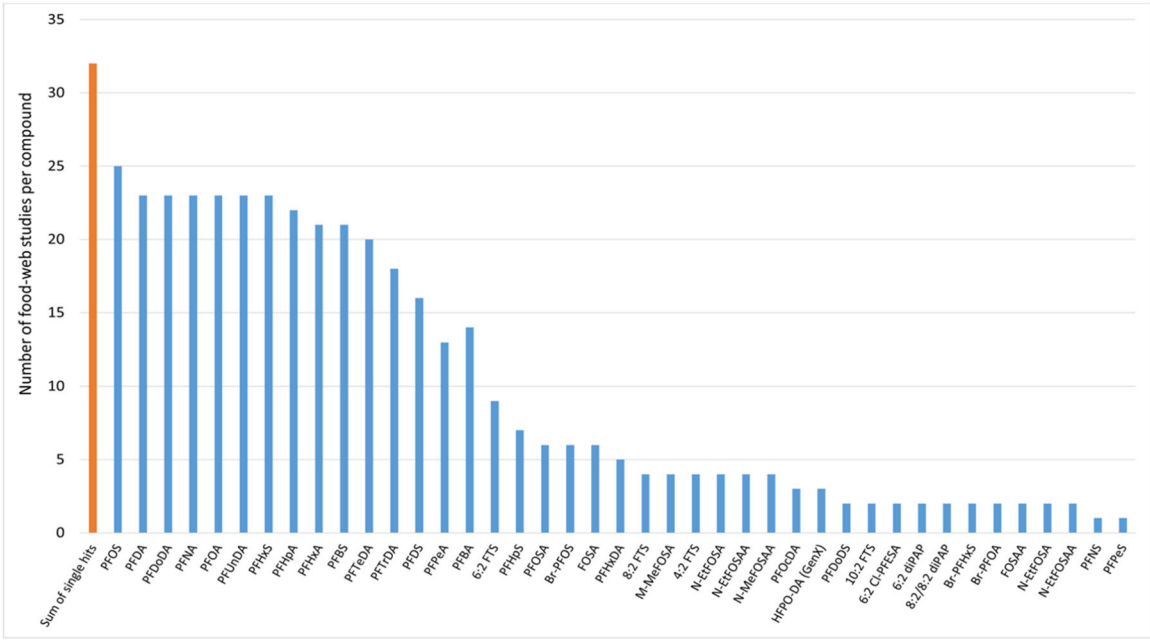

FIGURE 3: Number of study hits for different per- and polyfluoroalkyl substances (PFAS) measured in food web studies. Only studies that covered more than two distinct trophic levels were included. Data are based on studies published until May 2022. All compounds with a single hit were grouped together and summed into the orange bar. A list of these single-hit compounds, as well as the list of publications from which the data were retrieved, is available in the Supporting Information, Table S4 and Reference List S5, respectively. CAS numbers of full names of PFAS can be found in the glossary, in the Supporting Information.

categorized into distinct PFAS families following the OECD risk assessment report No. 39 (OECD, 2018). This report distinguished 134 PFAS categories based on their molecular structures; however, compounds from only 31 PFAS categories have been tested for ecotoxicity. The most studied groups were the PFCAs, with their salts and esters (11 compounds) and the perfluoroalkane sulfonic acids (PFSAs), with their salts and esters (10 compounds). From 29 other PFAS families, less than 5 compounds have been tested for ecotoxicity, and 56 PFAS were not classified into any group. The full list of PFAS and their classification can be found in the Supporting Information (Tables S5 and S6). The present evaluation of the available ecotoxicity data emphasizes that among the thousands of PFAS known to be produced, only a few compounds of a limited number of PFAS categories have been well studied for their environmental hazards. Because there is no clear common mode of action of PFAS (ITRC, 2022), this limited focus impedes a detailed evaluation of PFAS ecotoxicity. Therefore, expanding the compound groups beyond PFSAs and PFCAs and broadening the number of individual PFAS tested in ecotoxicity studies are crucial steps toward a more comprehensive understanding of PFAS ecotoxicity, considering the diversity of molecular structures of PFAS.

TABLE 2: Categorization of food web studies on per- and polyfluoroalkyl substances (PFAS) for each ecosystem type (first row) and inclusion of plants in these studies (second row)

No. of studies	Aquatic	Riparian	Estuary	Terrestrial
No. of studies per ecosystem type	23	2	2	1
No. of studies including higher plants	4	2	1	0

Data are based on literature published up to May 2022. The list of publications is the same as the one from Figure 3 (Supporting Information, Reference List S5).

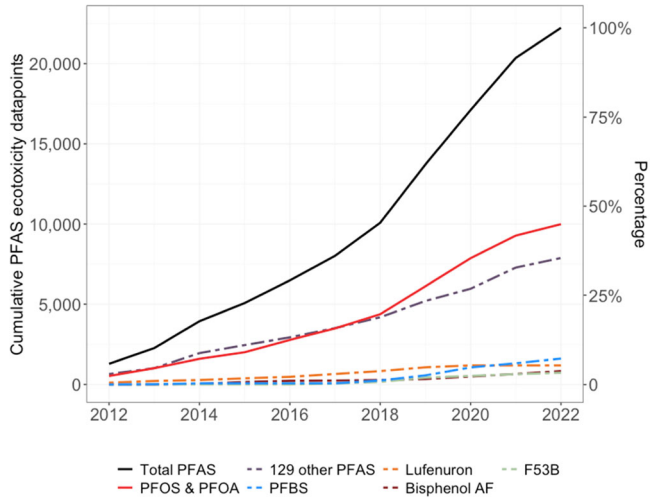

FIGURE 4: Cumulative number of data points for the ecotoxicity study of per- and polyfluoroalkyl substances (PFAS). The total number of ecotoxicity data is shown for all PFAS, along with the number of data points for the most frequently investigated compounds (perfluorooctane sulfonate [PFOS] + perfluorooctanoic aid [PFOA], perfluorobutane sulfonic acid [PFBS], Lufenuron, and F-53B), and for the other PFAS (129 compounds). See the Supporting Information, Tables S5 and S6, for a detailed overview of the PFAS compounds studied.

PFAS ecotoxicity to various organism groups

For both the aquatic and the terrestrial compartment, we categorized the available ecotoxicity data into two species groups, ranking them based on the highest number of available data points. The remaining data were labeled as other species (Figure 5, left). Subsequently, for each environmental compartment, we analyzed the distribution of the available ecotoxicity data over acute and chronic tests, following the criteria summarized by Davey et al. (2022); see the Supporting Information, Table S7. Next we investigated the five most extensively studied endpoints and placed the remaining endpoints within each species group, labeling these as "other effects" in Figure 5 (right).

Our evaluation showed that ecotoxicity studies on PFAS over the past 10 years generated a higher proportion of acute data for aquatic organisms, but in contrast a greater emphasis on chronic ecotoxicity was observed for terrestrial organisms (Figure 5, left). The main conclusion, however, is that the available data are strongly biased toward aquatic biota and a limited number of species groups.

A large number of PFAS ecotoxicity data for aquatic organisms was generated in fish tests, which accounted for 78.0% of the acute data and 60.0% of the chronic data. The acute fish tests were largely restricted to the fish embryo test (FET). This test focuses on developmental effects during the first 5 days post hatch, which is used as an indicator of the modes of action of compounds, and the mechanisms of environment-related diseases in vertebrates, including humans (Hill et al., 2005; Bambino & Chu, 2017). Moreover, over half of the fish tests focused on genetic, biochemical, and morphological endpoints (Figure 5A). Although many valuable data have been obtained by employing these tests, they primarily addressed compound toxicity rather than ecotoxicity, leaving the environmental hazards of PFAS relatively understudied. The second most studied species group in the aqueous environment was crustaceans, although they only comprised 7.0% of the acute data and 9.6% of the chronic data. Among the five most assessed effects, biochemical and genetic endpoints accounted for 34.0% of the data, and population, immobilization, and reproduction tests collectively accounted for 51.0% of the data (Figure 5B). Seven other species groups, including algae, amphibians, molluscs, insects, spiders, worms, and plants, were also studied for PFAS ecotoxicity in the aqueous environment. In these studies, 34.7% of the data concerned genetic, enzymatic, and biochemical endpoints, whereas only 25.0% addressed the effects of PFAS on the population growth of these organisms (Figure 5C). In addition, among the 135 PFAS for which ecotoxicity data were available, fish studies covered 102 compounds, and only 31 compounds were tested on crustaceans; studies on the other seven species groups collectively covered only 56 compounds. Furthermore, 76.8% of the present aquatic toxicity tests were performed in freshwater media, whereas only 10.7% and 12.5% of the tests were performed in saltwater media and other types of culture, respectively.

Ecotoxicity testing for PFAS on terrestrial organisms mainly focused on higher plants and insects/spiders, so that PFAS ecotoxicity to other organisms is comparatively unknown. In addition to significantly fewer data being generated for terrestrial organisms compared with aquatic, the number of PFAS studied for terrestrial ecotoxicity was also severely limited. The ecotoxicity of 34 PFAS was studied in higher plants, with toxicity to insects/spiders investigated for only 17 compounds. Studies on six other terrestrial species groups involved 33 PFAS. It is noteworthy that data on PFOS and PFOA collectively represented 69.0% and 66.0% of the data on higher plants and the six other species groups, respectively. In contrast to the other organism groups, data on the toxicity of 13 compounds, specifically manufactured as pesticides or fungicides, dominated the ecotoxicity dataset for insects/spiders, representing 97.0% of the data. In studies performed on higher plants, 47.7% of the data focused on biochemical, genetic, and enzymatic endpoints, and 28.6% and 15.7% of the data focused on PFAS accumulation and plant growth, respectively (Figure 5D). The endpoints studied for insects/spiders included mortality (38.6%), reproduction and population (33.7%), and

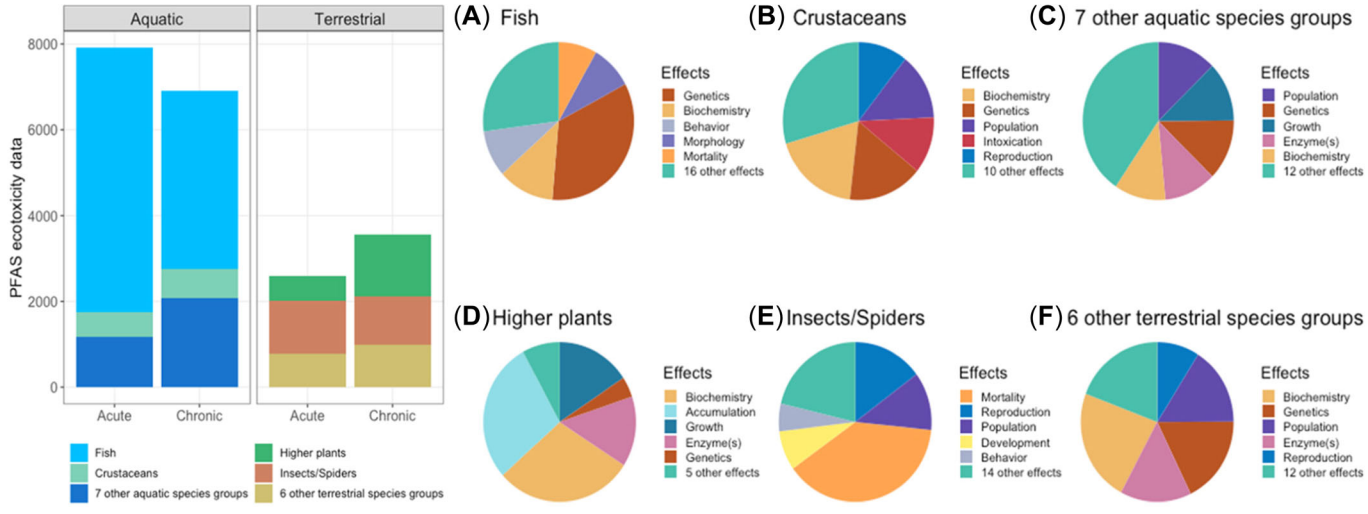

FIGURE 5: Distribution of ecotoxicity data for per- and polyfluoroalkyl substances (PFAS) over acute and chronic tests for aquatic and terrestrial organisms (left), and over the five most studied endpoints in the respective species groups (right; **A–F**).

behavioral and developmental effects (13.6%; Figure 5E). Biochemical, genetic, and enzymatic endpoints collectively represented 55.9% of the data on six other terrestrial species groups, whereas population and reproduction data covered 24.9% of the dataset (Figure 5F).

It has been argued that the concentrations at which PFAS show lethal effects in laboratory toxicity tests are unrealistically high and therefore not very environmentally relevant (Banyoi et al., 2022; Sinclair et al., 2020). However, considering the persistency of PFAS, organisms in PFAS-contaminated areas may be chronically exposed to substantially lower concentrations, potentially causing a wide range of more subtle sublethal effects (ITRC, 2022; Sinclair et al., 2020). Thus, chronic studies focusing on the effects of PFAS on endpoints relevant to the population level, such as growth and reproduction, are considered to be much more important than acute tests with mortality as the only endpoint. However, according to the evaluation in the preceding paragraph, data for such relevant chronic endpoints are virtually lacking. Moreover, given the persistent and bioaccumulative nature of PFAS (Ankley et al., 2021), it is highly likely that organisms are exposed to and accumulate PFAS over multiple generations, which calls for multigenerational studies to obtain a more realistic assessment of the environmental hazards of PFAS (Stefani et al., 2014; Guimarães et al., 2023).

The present inventory of PFAS ecotoxicity data has shown 1) a severe imbalance between the aqueous and terrestrial environments, 2) a severely insufficient knowledge of PFAS ecotoxicity across a broader range of compound families and a broader range of organisms, and 3) a severely insufficient knowledge of PFAS ecotoxicity regarding chronic ecologically relevant endpoints. As a result, current safe limits for PFAS in surface waters, soils, and sediments are preliminary and are primarily derived from human risks instead of ecotoxicological considerations (Smit & Verbruggen, 2022; Wintersen et al., 2019). We therefore identify these knowledge gaps as urgent research priorities for a realistic and reliable environmental risk assessment of PFAS.

THE INFLUENCE OF MOLECULAR PROPERTIES ON PFAS ENVIRONMENTAL FATE AND ADVERSE BIOLOGICAL EFFECTS

For many organic chemicals, relationships have been documented between physicochemical properties and molecular descriptors on the one hand and fate (e.g., sorption, degradation, bioaccumulation; Nguyen et al., 2020) and effects (e.g., ecotoxicity) on the other (Bleeker et al., 1998; Kraak et al., 2009). Such relationships, for instance, predict the potential bioaccumulation of chemicals in aquatic, benthic, and terrestrial organisms from the K_{OW}, or the potential for biodegradation and biotransformation from molecular descriptors (Arnot et al., 2009; Gossett et al., 1983). Promising results have been obtained in predicting PFAS sorption based on such descriptors (Jiang et al., 2022). Nevertheless, currently available tools such as EPI Suite™ do not appear to apply to prediction of the environmental fate of all PFAS, due to their amphiphilic structure, consisting of a polar head and a lipophilic tail. Similarly, predictions of the bioaccumulation of PFAS in aquatic and terrestrial organisms are not reliable, due to a lack of mechanistic understanding of the influence of the physicochemical and molecular properties on sorption behavior in soils and sediments and on the uptake of PFAS in biota. Moreover, recent publications have reported the absence of significant correlations between traditional molecular descriptors, such as chain length, and bioaccumulation or biomagnification of PFAS (Byns et al., 2022; Mazzoni et al., 2020). Phospholipid membrane/water partition coefficients (K_{MW}) could serve as an alternative or complementary predictor of PFAS bioaccumulation potential (Droge, 2019; Ebert et al., 2020). The K_{MW} has been shown to better predict fish BCFs than the K_{OW}, which led to opposite conclusions (Inoue et al., 2012). Nonetheless, the variety of structures, speciation, and biodegradation potential makes generalized predictions on the environmental fate of PFAS almost impossible and requires the screening of a wide diversity of compounds, in combination with mechanistic studies under realistic exposure scenarios and different environmental conditions. Above all, we foresee the need to evaluate the potential of novel molecular descriptors to serve as a better proxy for PFAS environmental fate, like K_{MW} and protein/water ($K_{Albumin\text{-}Water}$) partition coefficients, in addition to traditional parameters like K_{OW} (Allendorf et al., 2019; Droge et al., 2016).

Apart from the intrinsic chemical properties, environmental conditions can also affect the environmental fate of PFAS. Sorption to soils and sediments seems to be related to the organic matter content, but is also highly dependent on other physical (clay content, grain size) and chemical (pH, presence of specific cations) characteristics (Milinovic et al., 2015). For example, pH could change PFAS speciation and soil chemistry, which both affect PFAS mobility (Nguyen et al., 2020). At severely contaminated sites, PFAS environmental fate could also be impacted by the amount initially released into the environment, in combination with their bioavailability, because competitive sorption of PFAS has previously been reported (Huang, Saleem et al., 2022; Maimaiti et al., 2018). This interplay between intrinsic chemical properties and external environmental conditions makes the prediction of PFAS environmental fate challenging.

Few attempts have been made to relate PFAS toxicity to chemical properties, mainly for human health-related endpoints like the acute median lethal dose for rats (see Feinstein et al., 2021). However, no such attempts have been made for sublethal effects or for the ecotoxicity of PFAS to aquatic and terrestrial organisms. There are quantitative structure–activity relationship (QSAR) tools available to predict the median lethal concentration and median effect concentration values of chemicals from their molecular descriptors. Such relationships have been included in tools like the OECD QSAR Toolbox and EPI Suite™, which can be used for predicting the fate and effects of new chemicals submitted within regulatory frameworks like the Toxic Substances Control Act in the United States or the Registration, Evaluation, Authorisation, and Restriction of Chemicals regulation in the European Union. However, QSAR-like modeling requires large quantities of toxicity data, for which the conventional toxicity tests are not

qualified, due to their resource and labor intensity. High-throughput toxicity testing is called for, such as the TTR-TR CALUX test, the FET, the rapid daphnid immobilization tests, and so on. Such tests should be accompanied by exposure and bioavailability assessment, so that the outcome can be translated to relevant environmental conditions. In addition, machine learning techniques have already been incorporated into QSAR modeling to screen 1012 PFAS from the OECD list for 26 toxicity tests, but these were mainly related to human health rather than ecotoxicity (Cheng & Ng, 2019). Hence there is an urgent need to include environmentally relevant ecotoxicity tests in PFAS hazard assessment and to screen a wide diversity of PFAS for fate and effects, to relate these factors to the chemical properties of the compounds.

RESEARCH PRIORITIES FOR AN IMPROVED ENVIRONMENTAL RISK ASSESSMENT OF PFAS

What is hampering PFAS environmental risk assessment?

Environmental risk assessment consists of exposure and hazard assessment. In an attempt to distinguish which of these two pillars comprises the limiting factor for PFAS environmental risk assessment, we investigated the overlap between available occurrence and ecotoxicity data. Data points on aquatic occurrence were obtained from the NORMAN database, which was visited in May 2022. For soil, the publicly available literature was consulted, due to the lack of soil occurrence data in the NORMAN database, and in this case the number of studies ("study hits") was counted. The ECOTOX Knowledgebase was used to gather relevant ecotoxicity datapoints for aquatic organisms and study hits for terrestrial organisms. The datasets were the same as the ones described in sections *Which PFAS are detected in the environment?* and *Which PFAS are tested for ecotoxicity?* Because sediment-inhabiting benthic organisms are not listed as a specific category in the ECOTOX Knowledgebase, we only examined the occurrence-ecotoxicity overlap for the aqueous and soil compartments (Supporting Information, Tables S8 and S9).

A visual representation of the occurrence-ecotoxicity overlap investigation is shown in Figure 6A for water and Figure 6B for soil. For the aqueous environment, there were 29 PFAS with both occurrence and ecotoxicity data available, although several compounds remained seriously understudied, with very few study hits. There were four precursor PFAS for which no ecotoxicity data on aquatic organisms were found, and 91 for which no occurrence data were found. This discrepancy could be attributed to the different PFAS

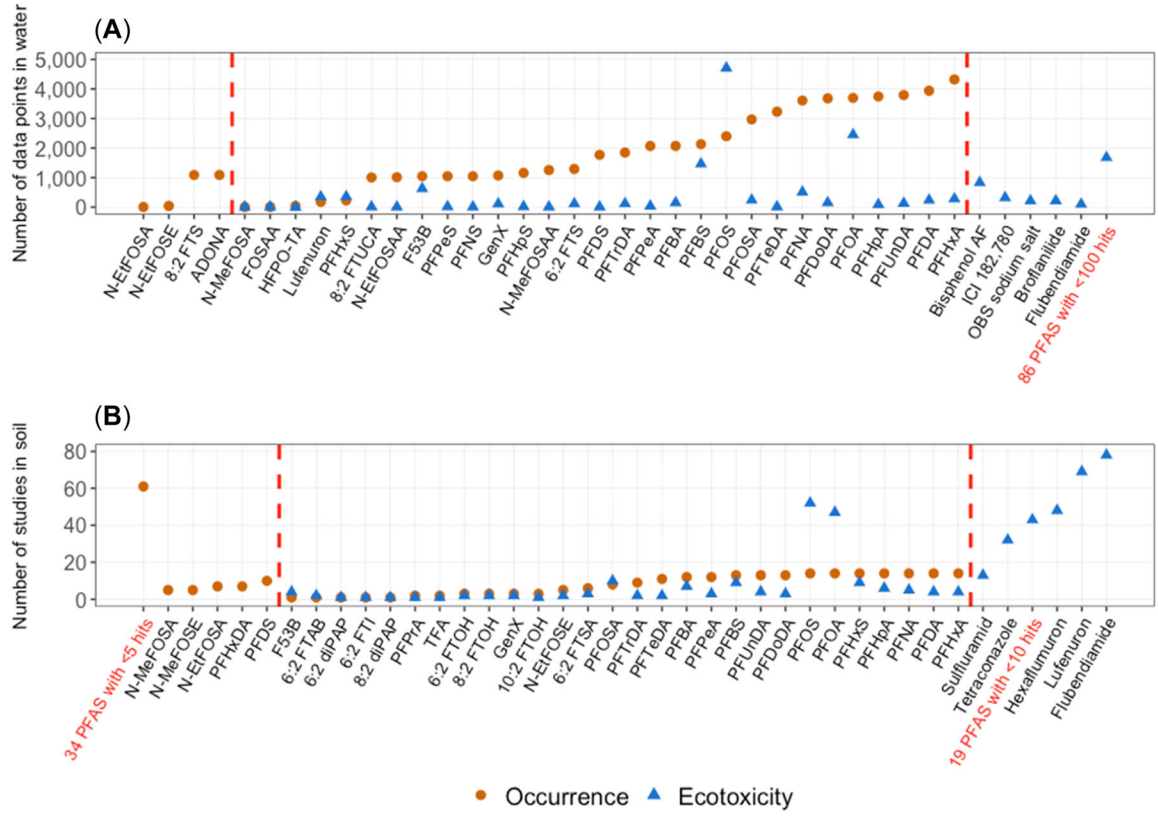

FIGURE 6: Number of data points for the occurrence of per- and polyfluoroalkyl substances (PFAS) and number of studies on the ecotoxicity of PFAS in water (**A**) and soil (**B**). In (**A**), PFAS with less than 100 ecotoxicity data points were grouped together and are highlighted in red. In (**B**), compounds with less than 10 occurrence and ecotoxicity study hits were combined into two different groups and are highlighted in red. See the Supporting Information, Tables S8 and S9, for a detailed overview of the data points and Reference List S6 for the soil study hits/compound. CAS numbers and full names of PFAS can be found in the glossary, in the Supporting Information.

categorization by the NORMAN database and ECOTOX Knowledgebase. For occurrence, most research has been performed on PFAAs, whereas the top compounds studied for ecotoxicity were by far PFOS and PFOA. For soil, both occurrence and ecotoxicity data were available for 28 PFAS and within those all but two (PFOS and PFOA) had <10 ecotoxicity study hits. For a total of 40 PFAS belonging to different families, no ecotoxicity data for terrestrial organisms were found in the ECOTOX Knowledgebase, whereas for 24 compounds (mostly fluorinated pesticides), no soil occurrence data were found in the consulted literature. As just noted, this could also relate to different definitions used for PFAS by the ECOTOX Knowledgebase and the open literature that was consulted. Among the most studied PFAS for soil occurrence were several PFAAs, whereas for ecotoxicity, five pesticides along with PFOS and PFOA were studied far more than the other compounds.

Based on our findings, we identified a bias favoring the aquatic over the soil compartment and a serious knowledge gap for ecotoxicity, with only a very few PFAS having a sufficient number of data points to allow a hazard assessment, especially for terrestrial organisms. For only 29 and 28 PFAS did we find both occurrence and ecotoxicity data for the aquatic and the terrestrial compartments, respectively, and moreover, these compounds were not the same for the two compartments. Only 18 compounds had both occurrence and ecotoxicity data available for both compartments, including PFAAs, GenX, and F-53B. This implies that compounds belonging to other PFAS families are seriously understudied in terms of their aquatic or soil occurrence and ecotoxicity, or both. More importantly, the total numbers of compounds for which we found both occurrence and ecotoxicity data in the two databases and the open literature still represent only a very small fraction (<0.5%) of the compounds that are currently categorized as PFAS. Even if this small fraction were to involve the most abundant and most toxic PFAS, this finding still underscores that the environmental risk assessment knowledge for this group of compounds contains some serious gaps.

Research priorities

To move toward an improved environmental risk assessment of PFAS, the present critical perspectives identified the following research priorities: 1) To increase the efficiency and reliability of target, suspect, and nontarget screening methods for detecting and quantifying PFAS concentrations in different environmental compartments, with an emphasis on understudied PFAS, independent of family and chain length. This calls for further standardization of analytical protocols, in combination with the extension of the available analytical standards. 2) To provide detailed information on the occurrence of PFAS in different environmental compartments, in terms of both chemical composition (profile) and concentrations (total and (bio)available levels). To compensate for the bias toward water and sediment, a special focus on concentrations in soils and SPM is required. 3) To expand the limited spectrum of PFAS analyzed in biota and food web studies, including wild plant species, and to catch up in the terrestrial environment to compensate for the bias toward aquatic organisms and aquatic food webs. 4) To put emphasis on ecotoxicity testing of representatives of the different PFAS families with terrestrial organisms to compensate for the bias toward aquatic organisms, while including chronic and multigenerational ecotoxicity studies on relevant ecological endpoints like growth and reproduction. 5) To relate the environmental fate and ecotoxicological effects of PFAS to their molecular properties to allow for extrapolation to untested compounds. 6) To develop and evaluate methods to translate exposure in complex matrices like soil and sediment versus water-only testing.

Supporting Information—The Supporting Information is available on the Wiley Online Library at https://doi.org/10.1002/etc.5729.

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Data Availability Statement—All data are in the Supporting Information.

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