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Per- and polyfluoroalkyl substances (PFASs) registered under REACH—What can we learn from the submitted data and how important will mobility be in PFASs hazard assessment?

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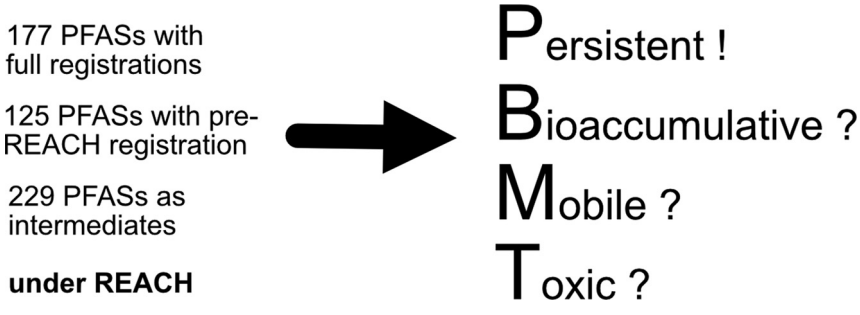
HIGHLIGHTS

- As of September 2021, at least 531 PFASs had been registered under REACH in the EU.
- 177 of these are full registrations, 125 pre-REACH registrations, and 229 intermediates.
- The data currently available for these PFASs are not sufficient to identify PBT substances.
- Including mobility under REACH would make a difference in the hazard assessment of PFASs.

GRAPHICAL ABSTRACT



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ABSTRACT

The EU is planning to restrict the manufacture, placing on the market and use of per- and polyfluoroalkyl substances (PFASs) as a class. For such a broad regulatory approach, a lot of different data are required, including data on the hazardous properties of PFASs. Here, we analyze substances that fulfill the OECD definition of PFASs and that are registered under the regulation on Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) in the EU to obtain a better data basis for PFASs and to elucidate the range of PFASs on the market in the EU. As of September 2021, at least 531 PFASs had been registered under REACH. Our hazard assessment of the PFASs registered under REACH shows that the currently available data are not sufficient to identify those PFASs that are persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB). Using some basic assumptions – which are 1) PFASs or their metabolites do not mineralize, 2) neutral hydrophobic substances bioaccumulate unless they are metabolized and 3) all chemicals exhibit baseline toxicity, and effect concentrations cannot be above effect concentrations for baseline toxicity – shows that at least 17 of the 177 PFASs with full registration are PBT substances, 14 more than currently identified. Moreover, if mobility is considered as a hazard criterion, at least 19 additional substances will need to be considered hazardous. The regulation of persistent, mobile and toxic (PMT) and very persistent and very mobile (vPvM) substances would therefore also affect PFASs. However, many of the substances that have not been identified as PBT, vPvB, PMT or vPvM are either persistent and toxic, persistent and bioaccumulative or persistent and mobile. The planned PFASs restriction will therefore be important for a more effective regulation of these substances.

1. Introduction

Per- and polyfluoroalkyl substances (PFASs) are man-made chemicals which have been produced since the 1940s (Kissa, 2001). PFASs are thermally, biologically, and chemically very stable, which makes them suitable

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for a wide range of applications (Glüge et al., 2020). However, the stability of the carbon-fluorine bond also makes PFASs environmentally persistent (Cousins et al., 2020). Furthermore, some PFASs have been identified as mobile (Arp et al., 2017; Arp and Hale, 2022). While neutral, volatile PFASs are commonly transported via air (D'Ambro et al., 2021; Dreyer et al., 2009), PFASs with acidic functional groups are mobile in water (Joerss et al., 2020; Yamashita et al., 2008). Accordingly, PFASs are found in different environmental media such as rainwater, groundwater, or soil, even in remote regions such as the Arctic (Brusseau et al., 2020; Cousins et al., 2022; RIVM, 2019; Xu et al., 2021). Additionally, some PFASs can bioaccumulate through the food chain. They have been detected in both wildlife and humans (McCarthy et al., 2017; Poothong et al., 2020). Only a small fraction of the whole PFASs class has been tested for their hazardous properties. However, an increasing number of studies show that PFASs can have adverse effects on human health and ecosystems (Cai et al., 2021; Chen et al., 2021; Fenton et al., 2021).

Concerns about the persistence of PFASs in combination with other hazards (such as bioaccumulation) have already led to some regulatory steps. For example, the three perfluoroalkyl acids (PFAAs) perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and perfluorohexane sulfonic acid (PFHxS), as well as their salts and precursors, were added to the Stockholm Convention in 2009, 2019, and 2022, respectively (COP, 2009, 2019, 2022). Furthermore, the use of C_9-C_{14} perfluoroalkyl carboxylic acids was banned in the EU in February 2023 (EC, 2021b). The most inclusive approach of regulating PFASs has been brought forward in the EU by the Netherlands, Denmark, Sweden, Norway, and Germany (BAuA et al., 2023). Their proposal aims to restrict the manufacture, placing on the market and use of PFASs as a class.

In the current study, substances that fulfill the OECD definition of PFASs (OECD, 2021) and that are registered under the regulation on the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) in the EU are analyzed to obtain a better data basis for PFASs and to elucidate the range of PFASs actually on the market in the EU. We also identified those substances that are PFASs according to the OECD definition but are not within the scope of the PFAS restriction proposal submitted to ECHA (BAuA et al., 2023). A first analysis of the REACH data on PFASs already exists in a recent report of the European Environmental Bureau (EEB, 2022). In this report, 67 substances have been identified. However, the definition of PFASs used there is rather narrow, including only substances with a fluorinated carbon chain longer than two, compared to the OECD definition and the one used in the PFAS restriction proposal that includes substances that contain at least one fully fluorinated methyl (–CF_3) or methylene (–CF_2–) carbon atom (OECD, 2021).

In addition to the EEB report, a couple of other studies have been published that analyze the data submitted under REACH. Many of these focus on mobility in the aquatic environment (Arp et al., 2017; Arp and Hale, 2022; Hale et al., 2022; Schulze et al., 2018). No such extensive analyses exist for persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances. However, some studies have analyzed individual endpoints such as bioaccumulation, toxicity or ecotoxicity (Glüge et al., 2022; Luechtefeld et al., 2016; Petoumenou et al., 2015; Pradeep et al., 2021; Sobanska et al., 2014; Teixidó et al., 2020).

The focus of the current study is on a broader analysis of the data for PFASs under REACH. Besides the data availability, the data quality was assessed for different physicochemical and environmental endpoints, such as octanol-water partition coefficient, bioaccumulation, biodegradation, and ecotoxicity. Additionally, a hazard assessment was carried out for the identified substances with a) the data submitted under REACH and b) additional data from COSMO*therm* and models for the bioconcentration factor (BCF) and baseline toxicity in aquatic invertebrates. COSMO*therm* is a program for calculating physicochemical properties based on quantum chemistry and has been found to provide very accurate physicochemical property data (Glüge et al., 2013; Loschen et al., 2020; Stenzel et al., 2014). Based on the available data, an assessment was made on how the introduction of the hazard endpoints persistent, mobile and toxic (PMT) and very persistent and very mobile (vPvM) into REACH would affect the regulation of PFASs. Both the PMT and the vPvM criteria were just recently introduced into the Classification, Labelling and Packaging (CLP) Regulation (EC, 2022) and some substances, e.g., melamine and HFPO-DA, have been identified as Substances of Very High Concern (SVHCs) because of their equivalent level of concern due to the combination of persistence and mobility.

2. Methods

2.1. Data retrieval and management

2.1.1. Study data

The non-confidential information submitted by the registrants to the European Chemicals Agency (ECHA) is available from ECHA's public chemicals database (accessible online via https://echa.europa.eu/de/information-on-chemicals). However, systematic automated data collection of the whole or a substantial part of the ECHA website and the ECHA databases is prohibited. It was therefore not possible to retrieve the registration data directly from the ECHA website. Instead, the data were retrieved as 'REACH study results' from the IUCLID website https://iuclid6.echa.europa.eu/reach-study-results in May 2022, which contained the data as of September 2021. In contrast to the online factsheet, the *REACH study results* only contain a subset of the data available from the REACH registrations. This includes the substance's identity, information on physicochemical properties, environmental fate, ecotoxicity, and also toxicological data. Excluded from the *REACH study results* is, for example, information on classification and labelling or administrative information on e.g., tonnages or the registrant. The *REACH study results* are additionally reduced since free-text fields are not available for download.

The data in the *REACH study results* are organized in 'studies' for all types of data (experimental, calculations or read-across). Information from a study includes in general the endpoint, study type, the methods used and the study results. Sometimes, several results were reported in one study. These can, e.g., be results taken at different point of time of a study or results taken at various temperatures or pH values.

2.1.2. Substance list

The substance list considered here is based on the *Registered Substances Factsheet* list that was downloaded from the ECHA website in June 2022 (https://echa.europa.eu/de/information-on-chemicals/registered-substances). This list contains all important identifiers of the REACH registrations including brief profile ID, factsheet ID, European Community (EC) number, Chemical Abstracts Service Registry Number® (CAS RN) and substance name. Additionally, the substances' tonnages and information on registration types are provided. The Simplified Molecular Input Line Entry Specification (SMILES) for the substances were provided by ECHA in January 2021. Additional SMILES codes were obtained manually from the website in February and May 2022, after which SMILES were available for 94% of all mono-constituent organic substances registered under REACH. The aggregate state, composition (mono-constituent, multi-constituent, etc.) and the substance type (organic, inorganic, organometallic) were retrieved from the general substance information of the *REACH Study results*.

In the *REACH Study Results* the substances are identified by an EC number, CAS RN or a name. Where available the EC number or CAS RN were used to match the REACH Study results and the substance list. The substance name was used where no EC number or CAS RN was available.

2.2. Identification of PFASs

The PFASs in this study were identified via the substance list by searching for SMILES that contain at least two fluorine atoms. For substances where no SMILES was available (6% of substances), the chemical names were searched for the term 'fluoro'. Only organic and mono-constituent substances were considered. Substances with several components (e.g., salts) where one component is fluorinated were also included.

The PFASs were further categorized into substances that contain only one fully fluorinated methyl or methylene carbon atom (C_1-PFASs) and those with at least two consecutive fully fluorinated methylene or methyl carbon atoms (C_2-PFASs). Substances containing a $–CF_2OCF_2–$ or $–CF_2OCFHCF_2–$ moiety were considered as C_2-PFASs. The C_2-PFASs were further divided into subgroups as shown in the Supplementary Material (SM) Table S1. Substances which fulfill several definitions were assigned to the group listed in the highest position in Table S1. Substances that fulfill the OECD definition of PFASs but are not included in the scope of the PFAS restriction proposal are nevertheless included in the analysis in the current study. The implications of not including them in the restriction proposal are discussed in Section 4.1.

For the data analysis, a distinction was made between full registrations, NONS (Notifications of New Substances) and intermediates. Full registrations include all substances which are produced and/or imported to the European Economic Area above 1 t per year. NONS registrations are for substances that were already registered under the previous regulation (Dangerous Substances Directive). These substances were automatically transferred into REACH and are regarded as already registered. Companies were then able to claim the registrations as their own. However, as of January 2022, only around half of all NONS registrations had been claimed (ECHA, 2022a). ECHA ended the possibility of claiming registrations in July 2022 and is planning to set the registration status of non-claimed substances to 'no longer valid' (ECHA, 2022b). Since this was future work at the time of the data processing, it was not possible here to clearly distinguish between claimed and non-claimed NONS registrations.

Compounds which are only produced for the purpose of being transformed into another substance can be registered as intermediates. For intermediates, the data requirements are reduced and, generally, the registrant only needs to provide already available existing information on physicochemical, human-health-related and environmental properties. Intermediates that form part of a synthesis process and are not isolated from the reaction vessel during synthesis do not need to be registered (ECHA, 2023a).

2.3. Evaluation of data availability and quality

Due to the large amount of data, the data availability and quality for most of the study endpoints were analyzed in an automated procedure. For this, two main assessment steps were conducted. During the first step, studies were removed where the automatic data processing would not give meaningful and environmentally relevant results. The specific criteria are shown in Table 1.

The second assessment step was an endpoint-specific quality check. This step was only performed for substances with full registration as the information content in the studies for intermediates and NONS registrations was not sufficient for this purpose. Where possible, the data quality was assessed based on the results of the *REACH Study Results* only. When more information was needed, the factsheets of the registration were accessed online and checked manually. More detailed information on this step is provided in the SM-1 Section S5.

2.4. Calculations with COSMOtherm and MarvinSketch

The log K_{OW} (for neutral and ionic substances) and log K_{OC} (for neutral substances only) were calculated using BIOVIA COSMO*conf* and COSMO*therm* 2020. The pK_a values were calculated using MarvinSketch 22.18 from ChemAxon. More information on both programs and the settings is provided in the SM-1 Section S3.

2.5. Hazard assessment

The conclusions from the registrants were downloaded from https://echa.europa.eu/information-on-chemicals for all PFASs with full registration. As the conclusions on the PBT/vPvB assessment were given per registrant and substance, different conclusions were possible for one substance. In cases where not all registrants provided the same conclusion, conclusions were aggregated as described in the SM-1 Section S8.1. To assess the hazard for P, B and T, the thresholds given in Annex XIII of the REACH regulation were used (SM-1 Section S8.2). Additional screening criteria are available in the Guidance on information requirements and chemical safety assessment, Chapter R.11 (ECHA, 2017). They are shown in SM-1 Section S8.3.

Mobility is currently not regulated under REACH. However, there are efforts to additionally require a mobility assessment as part of the chemical safety assessment (Arp and Hale, 2022; EC, 2021a). Special attention will be paid to chemicals being PMT or vPvM. Both the German Environment Agency and the European Commission suggest using the log K_{OC} as a mobility criterion, and the log D_{OW} (the pH-corrected log K_{OW}) as a screening criterion (Arp and Hale, 2022; EC, 2021a; Neumann and Schliebner, 2019). Neumann and Schliebner (2019) proposed to use the lowest pH-dependent octanol-water distribution coefficient over the pH range of 4–9 as screening criterion. We used here the log K_{OW} at pH 7.4 as screening criterion for mobility to be consistent with the screening for the bioaccumulation potential. The thresholds that were applied in the current study are those from the European Commission (Arp and Hale, 2022; EC, 2021a), which are the same that are now also implemented in the CLP Regulation (EC, 2022) (see also SM-1 Section S8.4).

Table 1
Specific criteria for removing a study during the first assessment step.

Studies/results that were removed during the first assessment step	Endpoints
Studies with data waiver	All
Studies without main result[a]	
Studies labeled as 'not reliable' or that were flagged by the registrants as 'disregarded due to major methodological deficiencies'	All
Studies where the study type was marked as 'not specific'[b]	All
Studies where the field 'purpose flag' was given as 'other information'[b]	All
Studies where the reference substance did not match the registered substance[c]	All
Studies that were not conducted in the pH range 7.4 ± 1.5 or in the temperature range 20 °C ± 5°C[d]	log K_{ow}
Studies that were not conducted in the pH range 5.5 ± 2.5 or in the temperature range 20 °C ± 5°C[d]	log K_{oc}
Results with qualifiers <, ≤, > or ≥ if the hazard could not be clearly identified with the qualifier[e]	All

[a] The main values chosen were the pK_a for the dissociation constant, the log K_{ow} for the octanol-water partition coefficient, the DT_{50} for hydrolysis, and the toxicity values (concentration of chemical in water) for the aquatic toxicity endpoints. For the degradation endpoints, the degradation reported in percent was chosen. Additionally, the biological oxygen demand was chosen for the screening test of degradation in water (ready biodegradability), since this parameter was often used in older ready-biodegradability tests.

[b] Indicates studies with strong deviations from standard procedures.

[c] Was not applied to read-across studies. Substances with non-matching EC numbers were removed.

[d] The pH can influence the chemical speciation and the temperature the partitioning behavior of a substance.

[e] An example are BCF values with a 'smaller than' qualifier and values above 2000.

3. Results

3.1. Identification of PFASs

As of September 2021, at least 531 PFASs had been registered under REACH. 177 of these were full registrations, 125 were NONS and 229 were intermediates. The agreement between SMILES and CAS RN was checked for all full and NONS registrations in a previous study (Glüge et al., 2023). Under this check, 15 substances were removed because their CAS RN and SMILES did not match and it was not possible to identify the exact substances presented in the registration dossiers. A total of 169 full registrations and 118 NONS registrations remained. The identities of the intermediates were checked in the current study according to the workflow

of Glüge et al. (2023) and one substance (CAS RN 139237-90-4) was removed because SMILES and CAS RN did not match.

Of the 515 substances registered that remained, 161 were C_2-PFASs while the others had only one fully fluorinated carbon (C_1-PFASs). Substances with only one fully fluorinated carbon represented therefore 69% of the 515 registered PFASs. The C_2-PFASs were further grouped into subclasses, see Fig. 1A. The most common class was fluorotelomers, followed by fluoroethers, cyclic PFASs and perfluoroalkane sulfonyl fluoride (PASF)-based substances. Only two long-chain perfluoro alkyl acids (PFAAs) have been registered with a full registration (salts of perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA)). The manufacture of both substances has been ceased. With the release of the new substance list in August 2022, 14 additional PFASs were registered. Eleven substances were C_1-PFASs while two were fluorotelomers (CAS RN 1107606-70-1, 153004-31-0) and one a fluoroether (CAS RN 2170099-74-6). Only the fluoroether and four of the C_1-PFASs are full registrations.

Of the 515 substances registered under REACH that are PFASs according to the OECD definition (OECD, 2021), 26 are not included in the scope of the PFAS restriction proposal (see SI-1 Section S4). The reason given in the restriction proposal (BAuA et al., 2023) to exclude them is that they are suspected to mineralize. However, the data on ready biodegradation submitted under REACH for 17 of the 26 substances indicate that these 17 substances are not readily biodegradable. Data are missing for the remaining 9 substances. We decided therefore to include all 26 substances in our analysis, even though they are not within the scope of the restriction proposal.

3.2. Registration quantities

Most of the full registrations were given with a tonnage band (Fig. 1B). Four substances, which were all gaseous, were registered above 10,000 t. These are octafluorocyclobutane (CAS RN 115-25-3), hexafluoropropene (CAS RN 116-15-4), pentafluoroethane (CAS RN 354-33-6) and norflurane (CAS RN 811-97-2). Gaseous PFASs also account for the largest production/import volume overall. Although only 14% of the registered PFASs for which the tonnage is known are gaseous, they account for 87% of the volume. For intermediates registrations, no production and import quantities are reported. Similarly, also for the NONS registrations, no numerical tonnage band is available. Most of the NONS are labeled as 'Tonnage data confidential'; for others, the manufacture has been ceased or the registration is no longer valid (Fig. 1B).

3.3. Data availability

3.3.1. Submitted data

Compared to NONS and intermediate registrations, a higher number of full registrations have data entries (Fig. 2). For example, for the partition coefficient, 100% of all fully registered substances have a data entry, while partition coefficients for NONS and intermediate registrations are only available for 70% and 35% of the substances, respectively. For the NONS registrations, it seems that at least one third of the registrations do not cover the standard information requirements according to REACH. This has been pointed out before and is due to the fact that dossiers for NONS complying with the standard information requirements need to be submitted to ECHA only when the dossiers are updated to increase the tonnage band (Chemsafe-Consulting, 2021; ECHA, 2023b). According to Chemsafe-Consulting (2021) those updates happened in only 8% of the cases until 2021. Otherwise, the dossier does not need to include information that was not required under the previous legislation (i.e. Directive 67/548/EEC) (ECHA, 2023b). For intermediates, on the other hand, only the available existing information must be submitted. It is therefore not surprising that not all intermediates have data entries. For a given registration type, the differences in the percentages between the endpoints are caused by different data requirements (Section S2 in the SM-1).

3.3.2. First assessment step

As described in Section 2.3, two assessment steps were conducted to evaluate the data availability and quality. The first step removed studies that were *inter alia* not environmentally relevant (outside temperature or pH range, wrong chemical species), deviated from standard procedures, had no main results, were not conducted with the registered substance or were labeled by the registrants as 'not reliable' (see Table 1). The most frequent reasons for removal were data waiver and the absence of main results. For substances with full registration, >50% of the studies remained for most of the endpoints (Fig. 3A). Exceptions were biodegradation in soil simulation tests (20%), biodegradation in water simulation test (9.8%), dissociation constant (29%), hydrolysis (29%) and long-term toxicity to fish (44%). For the NONS registrations, far fewer studies remained after the first assessment step (Fig. 3B). Most of the studies were removed because the field 'purpose flag' had been marked as 'other information'. Some random checks showed that in all cases no other information than the main result was given.

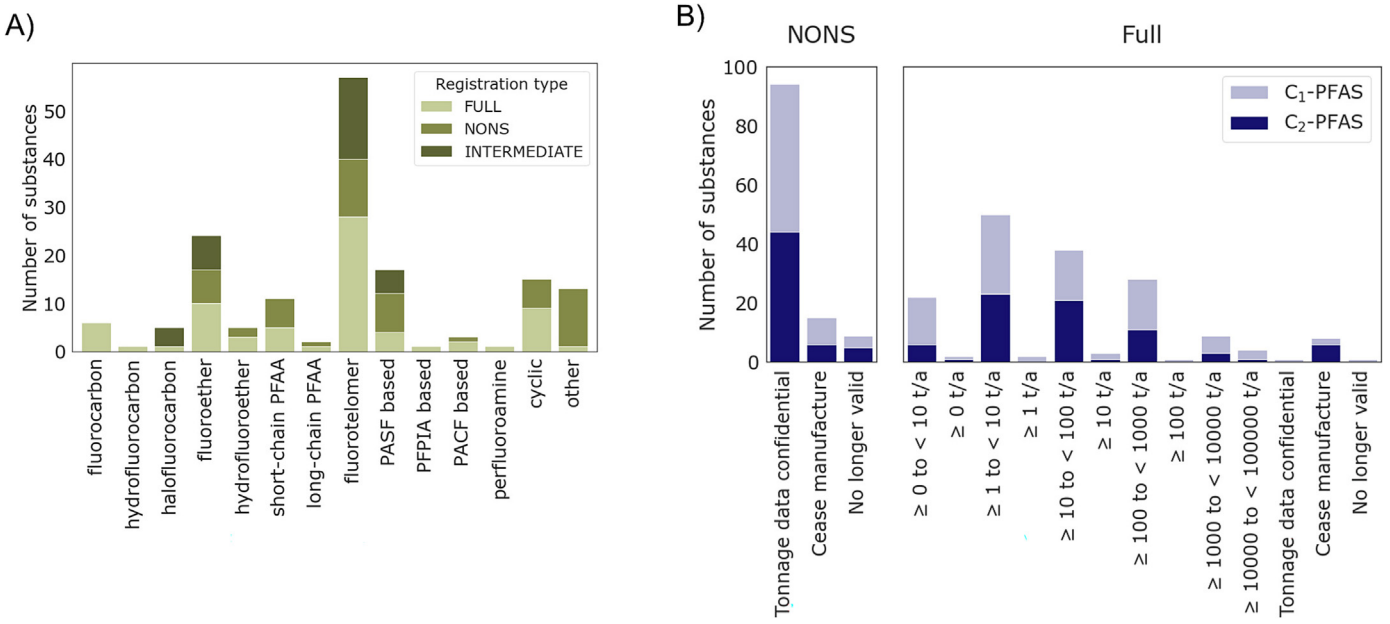


Fig. 1. Classification of C_2-PFASs. B: Tonnage bands registered for NONS and full registrations. The quantities are given as tonnes/year.

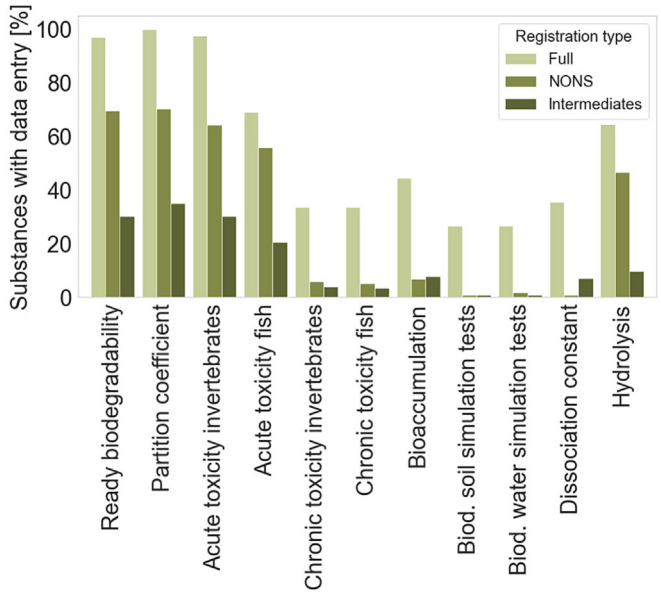


Fig. 2. Percentage of substances with a data entry. 100% would correspond to 169 substances with full registration, 118 substances registered as NONS and 228 substances registered as intermediates, respectively.

3.4. Data quality (second assessment step)

The second assessment step that evaluated the data quality was carried out for each endpoint individually. It was only performed for substances with full registration as the information content for NONS and intermediates was not sufficient for this purpose. In addition to the endpoints described here, data for the short- and long-term toxicity to fish and long-term toxicity to aquatic invertebrates are provided in the SM-1 Section S6.

3.4.1. Octanol-water partition coefficient

Of the 266 initial studies for the octanol-water partition coefficient, 172 studies were available for the second assessment step. Here, the log K_{OW} values from the ECHA database were compared with calculations for the log K_{OW} from COSMO*therm*. A deviation of 1.5 orders of magnitude was chosen as a threshold to detect outliers in the data of the ECHA database. The comparison shows that 10% of the data in the ECHA database are 1.5 orders of magnitude or more below the COSMO*therm* values and 13% are 1.5 orders of magnitude or more above the COSMO*therm* values (Fig. 4). Almost all substances with COSMO*therm* values 1.5 orders of magnitude or more below those from the ECHA database are ionic substances. Some of these have been registered as neutral substances but are actually charged at pH 7.4. The COSMO*therm* values were calculated in these cases for the charged chemical species. All data points for the log K_{OW} in the ECHA database that deviated >1.5 orders of magnitude from the COSMO*therm* values were removed in the second assessment step.

3.4.2. Short-term toxicity to aquatic invertebrates

Of the 273 initial studies for the short-term toxicity to aquatic invertebrates, 199 remained after the first assessment step. The most often reported endpoint was mobility (69% of the 381 results), followed by mortality (14%) and others (9%). For 8% of the studies, no endpoint was reported. Different results were reported for the endpoint mobility. These included effective concentrations but also effective loading rates, e.g., EL_{50}, or immobilization concentrations, e.g., IC_{50}. A manual check of the studies reporting loading rates showed that the reported lethal loading rates were associated with compounds which were poorly soluble in water or compounds which degraded over time. They were thus treated the same as effect concentrations for which nominal concentrations were reported. Six results for the endpoint mobility that were based on lethal concentrations (LC_{50} values) were disregarded as lethal concentrations normally refer to mortality, not mobility.

All datapoints representing EC_{50} values (including EL_{50} and IC_{50}) for immobilization in daphnids were plotted vs. the calculated log K_{OW} values from COSMO*therm* (Fig. 5) for a comparison of the expected baseline toxicity with the measured toxicity. The expected baseline toxicity was calculated from the log K_{OW} based on the QSAR given in EC (1996). Additional QSARs are provided in the SM-3. All values which were more than one order of magnitude higher or lower than the expected baseline toxicity were considered as outliers and checked individually.

Fig. 5A shows that 30 of the 120 EC_{50} values are one order of magnitude or more above the expected baseline toxicity. In most of the cases, this is because the concentration was given as a nominal concentration and the dissolved chemical concentration in water was not actually determined. After removing nominal concentrations (Fig. 5B), a total of 56 results remained, which were all very close to the expected baseline toxicity or had a higher toxicity (lower EC_{50}) than baseline. A discussion of the results with lower EC_{50} values than expected for baseline toxicity is provided in the SM-1

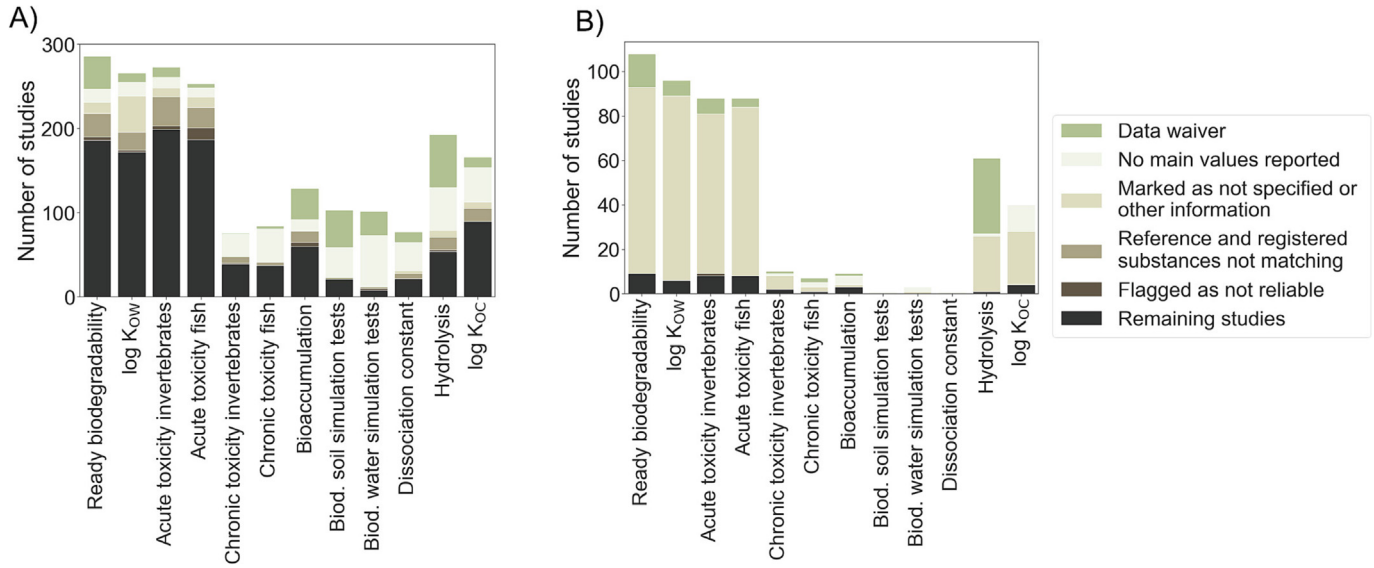


Fig. 3. Analysis of the available data for A) full registrations and B) NONS.

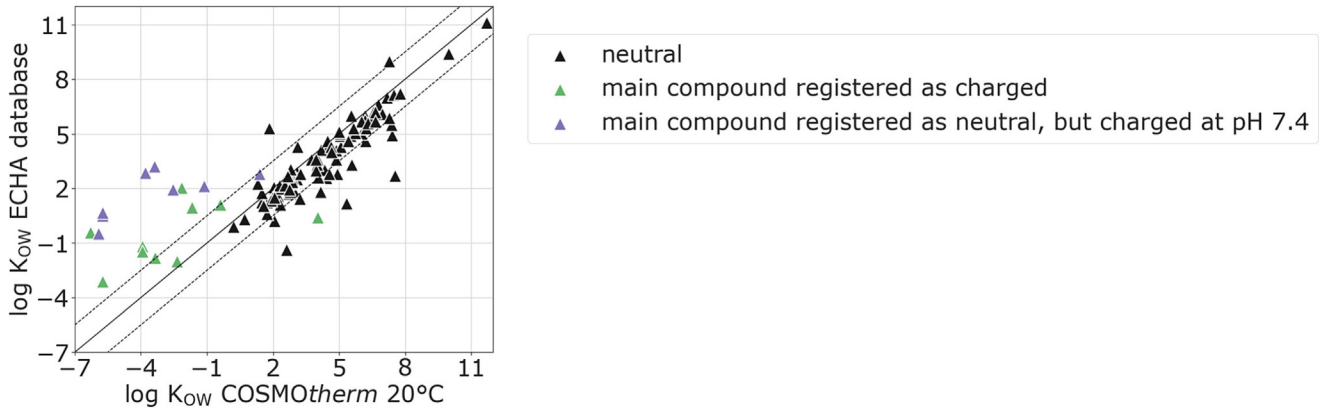


Fig. 4. Comparison between log K_{OW} values available in the ECHA database and values calculated with COSMOtherm. The solid line represents the 1:1 line, the dashed lines a deviation of 1.5 orders of magnitude.

Section S6.1. We also checked how many substances had an $EC_{50} < 1$ mg/L and would therefore need to be considered, according to the classification and labelling requirements, as acutely toxic (EC, 2016; Ecomole, 2022). The identified substances are shown in Table 2.

3.4.3. Bioaccumulation

Of the initial 129 studies that reported bioconcentration factors (BCF), bioaccumulation factors (BAF) or biomagnification factors (BMF), 60 studies remained after the first assessment step. Of these, 19 studies used solvents and were therefore disregarded in this analysis. The remaining studies were manually reviewed in the online factsheets. For 18 of these studies, different quality issues were identified, including again the use of solvents or dispersants, too short study durations, the assessment of the bioaccumulation of metabolites in read-across studies or concentrations in water that were above the solubility of the substances (SM-1 Table S8).

In the initial 60 studies, no reported BMF was above 1. For five substances the BCF was >2000 L/kg. However, for four of these five substances, quality issues with the corresponding studies were observed and two of them were additionally labeled as 'not reliable' by the registrants. An overview of the substances is provided in Table 3.

3.4.4. Ready biodegradability

From the 286 initial studies, 186 remained after the first assessment step. 85% of these studies reported as endpoint ready biodegradability and 11% inherent biodegradability. Six studies reported other endpoints. Of the 114 substances with results for the ready-biodegradability test, two

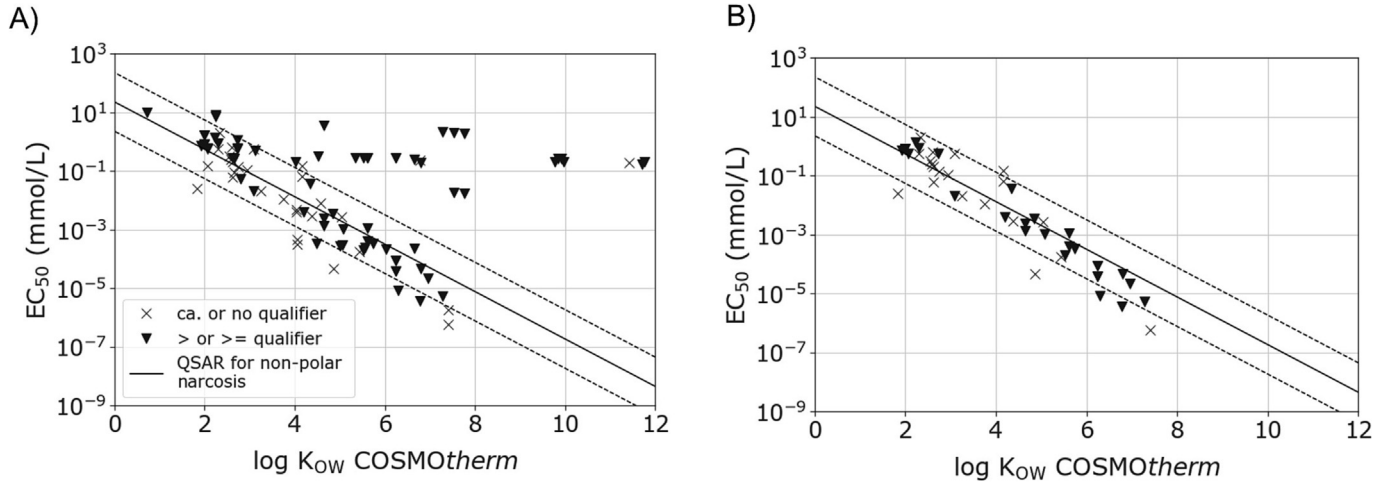
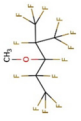


Fig. 5. Comparison between EC_{50} values for immobilization for 48 h exposure of daphnids with log K_{OW} values from COSMOtherm. A) all values, B) nominal concentrations excluded. Solid line: QSAR for non-polar narcosis ($\log EC_{50}$ [mmol/L] $= -0.809 \times \log K_{OW} + 1.36$). QSAR taken from EC (1996).

Table 2
Substances with acute toxicity to daphnids (EC_{50} immobilization <1 mg/L) according to the classification and labelling requirements. *log K_{OW} calculated with COSMO*therm*. **log K_{OW} retrieved from the ECHA database.

CAS RN	Name	Toxicity [mg/L]	log K_{ow}
121451-02-3	3-[3,5-dichloro-2-fluoro-4-(1,1,2,3,3,3-hexafluoropropoxy)phenyl]-1-(2,6-difluorobenzoyl)urea	3.11×10^{-4}	7.40*
3709-71-5	(2E)-1,1,1,2,3,4,5,5,5-nonafluoro-4-(trifluoromethyl)pent-2-ene	1.40×10^{-2}	4.85*
1229654-66-3	1-(3-chloropyridin-2-yl)-N-[4-cyano-2-methyl-6-(methylcarbamoyl)phenyl]-3-{[5-(trifluoromethyl)-2H-tetrazol-2-yl] methyl}-1H-pyrazole-5-carboxamide	1.73×10^{-1}	4.06*
1809816-36-1	(*R*)-2-(2,4-difluorphenyl)-1,1-difluor-3-(tetrazol-1-yl)-1-{5-[4-(2,2,2-trifluorethoxy)-phenyl]-2-pyridyl}-2-propanol-(*R*,*R*)-tartrate	6.84×10^{-1}	1.9**
685563-70-6	4-(difluoro-(3,4,5-trifluoro-phenoxy)-methyl)-3,5-difluoro-benzaldehyde	6.13×10^{-2}	5.4*

Table 3
Substances with a BCF >2000. *log K_{OW} predicted with COSMO*therm*. **log K_{OW} retrieved from the ECHA database.

EC No.	435-790-1	459-520-5	700-684-7	608-209-4	610-623-5
Chemical name	3-ethoxy-1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)-hexane	1,1,1,2,2,3,4,5,5,5-decafluoro-3-methoxy-4-(trifluoromethyl)pentane	1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorooctane	Sorafenib base	5-Brom-2-[(3,4,5-trifluorphenoxy)-difluormethyl]-1,3-difluorbenzene
BCF reported [L/kg]	8530	2900	2600	7300	2678
BCF lipid normalized [L/kg]	10,402	5598	4851	7300	2678
Chemical structure					
log K_{OW}	6.2*	5.1*	5.6*	3.3**	6.6*
Conclusions of registrants on PBT and vPvB	Not PBT, nor vPvB	Not PBT, nor vPvB	No entry	PBT and vPvB	Not PBT, nor vPvB
Study type	Experimental	Experimental	Experimental	Experimental	(QSAR
Remarks on studies	Both studies marked as 'not reliable'	Study marked as 'not reliable'	Solvent used	Solvent used No lipid content provided	No issues observed

had passed the test (EC numbers 2007-028-4 and 700-812-1). Manual inspection showed that these results were caused by artefacts and that actually none of the tested substances is readily biodegradable.

3.5. Hazard assessment

An overview of the data availability for the different endpoints used for the assessment of the P, B, T, and M criteria is provided in the SM-2. The conclusions for the hazard assessment are displayed in two heatmaps. The first heatmap (Fig. 6 left) includes the conclusions on the PBT/vPvB assessment made by the registrants as well as the conclusions for the individual hazard criteria drawn with the data provided in the ECHA database (REACH Study Results and Classification & Labelling Notifications) after our first assessment step. The second heatmap (Fig. 6 right) shows the conclusions for the individual hazard criteria based on the data of the ECHA database after the second assessment step with additional, modeled data. The modeled data include the log K_{OW} and log K_{OC} values from COSMO*therm* for the endpoint mobility, the BCF values provided in Glüge et al. (2022) with the model M14 for the endpoint bioaccumulation, and predictions for the baseline toxicity according to the QSAR provided in Austin and Eadsforth (2014) for the chronic toxicity to fish. More detailed information on the data used in each heatmap is provided in the SM-1 Section S8.5. From the data for P, B, T and M in the second heatmap, conclusions are drawn on PBT/vPvB (column PBT) and PBT/vPvB /PMT/vPvM (column PBMT).

The data in the heatmap show that when additional, modeled data are used, four PFASs instead of one would be identified as PBT or vPvB within those substances registered with a full registration of 10 t and more. Within all PFASs with full registration (see SM-1 Section S9), there would even be 17 PFASs instead of three identified as PBT or vPvB. If mobility is considered as a hazard criterion, 14 PFASs registered above 10 t per year would need to be classified as PMT/vPvM and 19 PFASs from all full registrations. The PBT, vPvB, PMT and vPvM substances are shown again in Table 4.

4. Discussion

4.1. Identified PFASs

In addition to the 531 PFASs mentioned, a few more might have been registered under REACH that could not be identified in the current study because a) no SMILES was provided in the ECHA database and the name did not include 'fluoro' or b) structure, name and CAS RN were kept confidential. We also found that 14 new PFASs have been registered in between September 2021 and August 2022. This shows that the industry continues to rely on PFASs. However, there are also indications of a shift away from PFASs; 3M has announced that it no longer intends to produce and use PFASs from 2025 on (3M, 2022). The entry into force of the PFAS restriction in the EU would also initiate and in some parts force a shift away from PFASs.

Generally, there are few data available for the majority of PFASs, as they are either intermediates (43%) or NONS registrations (23%). Additionally, data for the full registration are not accessible in some cases. This is discussed in more detail in the SM-1 Section S10.

Approximately two-thirds of the registered substances contain only one fully fluorinated methyl or methylene carbon atom (C_1-PFASs) and represent therefore a variety of different substance types. In terms of quantities used, it can be seen for the full registrations that roughly equal quantities of C_1- and C_2-PFASs are used. This shows that besides the C_2-PFASs that have so far been the target of the chemical regulation, attention also needs to be focused on C_1-PFASs and their properties. This is underlined by the fact that all identified vPvB and PBT substances in this study are C_1-PFASs.

Regarding the substances that are PFASs according to the OECD definition but are not included in the scope of the PFAS restriction proposal, it has been shown that a few substances with the $–O–CF_3$ moiety such as

Fig. 6. Hazard maps for PFASs that have been registered with >10 t per year in the EEA. Left: Data from the ECHA database after the assessment step 1. Right: Data from the ECHA database after assessment step 2 combined with modeled data. The column 'PBT' includes PBT and vPvB conclusions, the column 'PBMT' PBT, vPvB, PMT and vPvM conclusions.

trifluoromethoxy-substituted alcohols as well as 10-trifluoromethoxy-decane-1-sulfonate can be mineralized (CropLife, 2022; Frömel and Knepper, 2015; Peschka et al., 2008). However, it is unclear if this can be transferred to –O–CF_3 moieties attached to aromatic groups. The ready biodegradation data suggest that most of them are not mineralizable. Since 11 of the 13 excluded substances with full registration were identified in the current study as vPvB substances, it is of high importance to clarify if these substances should really be excluded from the restriction proposal.

4.2. Data quality

The data quality could only be checked for those studies that had a 'main result' (see Table 1 for specific information on what is a 'main result')

Table 4
Substances identified as vPvB, PBT, vPvM and PMT in the current study.

EC No	PFAS classification	Molecular formula[a]	Substance name
vPvB substances			
848-454-6	C_1-PFAS	$C_{25}H_{21}Cl_2F_4NO_4$	*tert*-butyl 5′-(3-(3,5-dichloro-4-fluorophenyl)-4,4,4-trifluorobut-2-enoyl)-3′*H*-spiro[azetidine-3,1′-isobenzofuran]-1-carboxylate
695-906-1	C_1-PFAS	$C_{27}H_{22}F_8O_3$	*trans*-2-[4′-[difluoro(3,4,5-trifluorophenoxy)methyl]-2,3′,5′-trifluoro[1,1′-biphenyl]-4-yl]-5-butyl-1,3-dioxane
848-455-1	C_1-PFAS	$C_{25}H_{22}Cl_2F_4N_2O_4$	(*S*)-*tert*-butyl 5′-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-3′*H*-spiro [azetidine-3,1′-isobenzofuran]-1-carboxylate
219-154-7	C_1-PFAS	$C_{12}H_{21}F_9O_3Si_3$	2,4,6-trimethyl-2,4,6-tris(3,3,3-trifluoropropyl) cyclotrisiloxane
616-651-4	C_1-PFAS	$C_{26}H_{21}F_7O_2$	2-[4′-[difluoro(3,4,5-trifluorophenoxy)methyl]-3′,5′-difluoro[1,1′-biphenyl]-4-yl]-5-ethyltetrahydro-2*H*-pyran
610-104-3	C_1-PFAS	$C_{39}H_{29}F_3O_2$	5′,5″″-(1,1,1-trifluoropropane-2,2-diyl)bis(1,1′:3′,1″-terphenyl-2′-ol)
606-647-0	C_1-PFAS	$C_{22}H_{29}F_5O$	(*trans*,*trans*)-5-{(4-propyl[1,1-bicyclohexyl]-4-yl)-difluoromethoxy}-1,2,3-trifluorobenzene
603-782-7	C_1-PFAS	$C_{22}H_{31}F_3O$	1-(4-*trans*-propyl-[1,1-bicyclohexyl]-4-*trans*-yl)-4-trifluoromethoxybenzene
610-847-3	C_1-PFAS	$C_{28}H_{26}F_6O$	2′,3,5-trifluoro-4″-(*trans*-4-propylcyclohexyl)-4-trifluoromethoxy-[1,1′;4′,1″]terphenyl
918-322-3	C_1-PFAS	$C_{22}H_{29}F_3O$	1-[4-(*trans*-4-propylcyclohexyl)-1-cyclohexen-1-yl]-4-trifluoromethoxybenzene
608-462-0	C_1-PFAS	$C_{22}H_{15}F_7O$	4-[difluoro(3,4,5-trifluorophenoxy)methyl]-3,5-difluoro-4′-propyl-1,1′-biphenyl
619-490-8	C_1-PFAS	$C_{28}H_{18}F_8O$	4-[difluoro(3,4,5-trifluorophenoxy)methyl]-2′,3,5-trifluoro-4″-propyl-1,1′:4′,1″-terphenyl
610-623-5	C_1-PFAS	$C_{13}H_4BrF_7O$	5-bromo-2-[(3,4,5-trifluorophenoxy)-difluoromethyl]-1,3-difluorobenzene
935-976-5	C_1-PFAS	$C_{29}H_{20}F_8O$	4″-butyl-4-[difluoro(3,4,5-trifluorophenoxy)methyl]-2′,3,5-trifluoro-1,1′:4′,1″-terphenyl
935-977-0	C_1-PFAS	$C_{30}H_{22}F_8O$	4-[difluoro(3,4,5-trifluorophenoxy)methyl]-2′,3,5-trifluoro-4″-pentyl-1,1′:4′,1″-terphenyl
PBT substances			
444-370-5	C_1-PFAS	$C_{28}H_{23}F_3N_6$	4-methyl-2,6-bis[(4-methylphenyl)amino]-5-{[2-(trifluoromethyl)phenyl]azo}pyridine-3-carbonitrile
410-690-9	C_1-PFAS	$C_{17}H_8Cl_2F_8N_2O_3$	*N*-[2,5-dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)-phenyl-aminocarbonyl]-2,6-difluorobenzamide
vPvM substances			
252-046-8	fluorotelomer	$C_{15}H_{19}F_{13}N_2O_4S$	carboxymethyldimethyl-3-[[(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)sulphonyl]amino]propylammonium hydroxide
816-285-7	C_1-PFAS	$C_{20}H_{13}F_3N_4O_2$	1-(pyrimidin-5-ylmethyl)-3-[3-(trifluoromethyl)phen yl]pyrido[1,2-a]pyrimidin-1-ium-3-ide-2,4-dione
700-242-3	fluoroether	$C_6HF_{11}O_3.H_3N$	ammonium 2,3,3,3-tetrafluoro-2-(heptafluoro propoxy)propanoate
695-744-1	C1-PFAS	$C_{13}H_{17}F_3N_4OS$	(1-[2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]-4-heteromonocyclecarbothioamide)
218-500-4	C_1-PFAS	$C_{10}H_{11}F_3N_2O$	fluometuron
603-837-5	C_1-PFAS	$C_{20}H_{18}ClF_3N_2O_6$	1-(allyloxy)-2-methyl-1-oxopropan-2-yl 2-chloro-5-[3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydropyrimidin-1(2*H*)-yl] benzoate
609-256-3	C_1-PFAS	$C_{14}H_{13}F_3N_2O_4S$	(5-hydroxy-1,3-dimethyl-1*H*-pyrazol-4-yl)[2-(methyl sulfonyl)-4-(trifluoromethyl)phenyl]methanone
207-074-5	C_1-PFAS	$C_3H_3F_3O_2$	methyl trifluoroacetate
811-213-0	C_1-PFAS	$C_4H_2F_6$	(2*E*)-1,1,1,4,4,4-hexafluoro-2-butene
468-710-7	C_1-PFAS	$C_3H_2F_4$	2,3,3,3-tetrafluoroprop-1-ene
206-559-9	C_1-PFAS	$C_2H_2F_3NO$	2,2,2-trifluoroacetamide
200-913-6	C_1-PFAS	$C_2H_3F_3O$	2,2,2-trifluoroethanol
261-818-3	fluorotelomer	$C_8H_5F_{13}O_3S.K$	potassium 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonate
415-300-0	C_1-PFAS	$C_2F_6NO_4S_2.Li$	lithium bis(trifluoromethylsulfonyl)imide
688-332-8	C_1-PFAS	$C_{14}H_{14}F_3N_5O_6S.Na$	sodium (4,6-dimethoxypyrimidin-2-yl)({[3-(2,2,2-tri fluoroethoxy)pyridin-2-yl]sulfonyl}carbamoyl)azanide
260-375-3	long-chain PFAA	$C_8HF_{17}O_3S.C_8H_{20}N$	tetraethylammonium heptadecafluorooctanesulphonate
PMT substances			
601-478-9	C_1-PFAS	$C_{18}H_{16}F_3NO_4$	picoxystrobin (*ISO*); methyl (2*E*)-3-methoxy-2-[2-({[6-(trifluoromethyl)pyridin-2-yl]oxy}methyl)phenyl] acrylate
446-630-3	C_1-PFAS	$C_{13}H_9Cl_2F_3N_4OS$	5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(ethylsulfinyl)-1*H*-pyrazole-3-carbonitrile
252-044-7	PASF based	$C_8H_{10}F_9NO_4S$	1,1,2,2,3,3,4,4,4-nonafluoro-*N*,*N*-bis(2-hydroxyethyl)butane-1-sulphonamide

[a] Molecular formula as registered, chemical speciation might be different at pH 7.4.

and whose method did not deviate too much from standard studies. Studies with non-standard methods are difficult to evaluate automatically as the available fields in the ECHA database do not fit well to the parameters describing these non-standard studies. Missing 'main results' and studies with non-standard methods led for some endpoints to the exclusion of over 50% of the studies, which is not ideal but could not be changed with the currently available data.

Quality issues with experimental studies were observed for several endpoints, predominantly for the bioaccumulation potential and the acute toxicity to aquatic invertebrates and to fish. Issues with the bioaccumulation studies included the use of solvents or dispersants, very short test durations, water concentrations above the solubility limit or the reporting of nominal water concentrations only. Nominal concentrations were also the main problem that affected the results of the toxicity testing. It would be very helpful if those issues could be marked by ECHA in order to label a study as unreliable. However, the data are owned by the registrants, and it is currently up to them to rate the reliability of a study.

Fewer quality issues were identified for QSARs and model-based calculations. However, this was mainly because, if information was provided on the applicability domain of the model or on other model details, it was often provided in a free-text field and could thus not be considered in the automated analysis in this study. It is, however, well known that QSARs do not work for all substances equally well and that especially PFASs often fall out of the applicability domain of the models (Chelcea et al., 2020; Lampic and Parnis, 2020). The introduction of an extra field in the ECHA database in which it is mandatory to indicate whether the substance is within the applicability domain of the model would be very important.

4.3. Hazard assessment and the inclusion of mobility

The comparison of the two heatmaps shows that the currently available data under REACH are not sufficient to identify substances that are persistent, bioaccumulative and toxic. Using some basic assumptions – which are 1) PFASs (or at least their metabolites) do not degrade/mineralize (Cousins et al., 2020; ECHA, 2018), 2) hydrophobic (neutral) substances bioaccumulate unless they are metabolized (Glüge et al., 2022; Jonker and van der Heijden, 2007) and 3) all chemicals exhibit baseline toxicity, and effect concentrations cannot be above effect concentrations for baseline toxicity (Austin et al., 2015; Austin and Eadsforth, 2014; EC, 1996; Maeder et al., 2004) – shows that at least 15 of the 177 PFASs are PBT substances,

14 more than currently identified. Moreover, if mobility is considered as a hazard criterion, at least 16 additional substances will need to be considered hazardous.

Many of the substances that have not been identified as PBT/vPvB/PMT/vPvM are either persistent and toxic, persistent and bioaccumulative or persistent and mobile. Even if none of these combinations is regulated under REACH, they are not desired properties and can lead to unwanted effects. The regulation of PMT or vPvM substances would be an important step to limit the use of persistent substances, but we can see from the hazard assessment in this study that this might not be enough to protect humans and the environment from persistent and toxic, persistent and bioaccumulative, or persistent and mobile substances. In our point of view, this will only be achieved if the use of persistent substances is limited in general. The restriction proposal for PFASs will here be a very important step forward and may also influence other regions of the world.

CRediT authorship contribution statement

Elvira Rudin: Methodology, Investigation, Formal analysis, Data curation, Software, Writing – review & editing. **Juliane Glüge:** Conceptualization, Methodology, Software, Validation, Writing – original draft. **Martin Scheringer:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Data availability

The original data are available from the IUCLID website. A summary of the data is provided in the Supplementary Material 2.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.162618.

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