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Hidden PFAS and other undefined organic fluorine



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Bridging Science to Practice Classificatie: Intern

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Hidden PFAS and other undefined organic fluorine

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Managementsamenvatting

Om (nog) onbekende PFAS te identificeren is een uitgebreide benadering nodig

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Veel bekende maar ook nog onbekende PFAS-verbindingen bedreigen gezondheid en milieu. Zo worden fluorverbindingen in geneesmiddelen en pesticiden gebruikt, die CF_2 - of CF_3 -groepen bevatten, en daarom worden geclassificeerd als PFAS. Daarnaast is steeds meer duidelijk dat atmosferische depositie en elektronisch afval ook PFAS-bronnen vormen voor emissies naar het milieu.

Dit onderzoek leverde een inventarisatie op van 14 PFAS die relevant zijn voor de drinkwatersector en waarvoor monitoring wenselijk is. Het rapport beschrijft ook verschillende analysetechnieken om monitoring en detectie van PFAS uit te breiden, die elk specifieke voordelen en beperkingen hebben. Om het gebruik van de beschikbare technieken te optimaliseren, is een leidraad ontwikkeld die helpt bij de keuzes tussen de verschillende analysetechnieken met als doel een uitgebreide monitoringstrategie op PFAS.



Conceptuele weergave van de chemische PFAS-ruimte die door verschillende analysetechnieken wordt afgedekt

Belang: onbekende PFAS bedreigen menselijke gezondheid en ontsnappen aan huidige monitoring

PFAS zijn een zeer brede en diverse groep gefluoreerde chemicaliën die een risico vormen voor de menselijke gezondheid en het milieu. Van de duizenden PFAS worden momenteel slechts een zeer klein deel van de PFAS gemonitord en gereguleerd. Veel bronnen van PFAS zijn nog niet goed in beeld, zoals geneesmiddelen, gewasbeschermingsmiddelen, atmosferische depositie en lithium-ion batterijen, een potentiële opkomende bron voor fluorpolymeren en gefluoreerde zijketenpolymeren. De aanwezigheid van aanzienlijke hoeveelheden ongedefinieerd organisch fluor in oppervlaktewater en afvalwater, gevonden in een eerder onderzoek in Nederland, benadrukt de noodzaak van uitgebreidere methoden om PFAS te detecteren en te beoordelen. Dat wordt bemoeilijkt door de uiteenlopende fysisch-chemische eigenschappen van PFAS, die verschillende analysemethoden vereisen voor detectie en kwantificering.

Aanpak: literatuuronderzoek, inventaris van analysetechnieken en kandidaat verbindingen

Voor dit onderzoek zijn relevante wetenschappelijke literatuur en rapporten bekeken om over het hoofd geziene bronnen van PFAS te identificeren, te inventariseren welke analytische benaderingen mogelijk zijn om PFAS met verschillende fysischchemische eigenschappen breder te detecteren en nieuwe stoffen voor te stellen voor opname in de routinematige monitoring.

Resultaten: nog onbekende PFAS en een geïntegreerde monitoringbeoordeling

Gebruik en aanwezigheid van PFAS

Fluorverbindingen worden op grote schaal gebruikt in producten zoals geneesmiddelen en pesticiden omdat ze specifieke eigenschappen hebben: ze verhogen bijvoorbeeld de houdbaarheid of dringen verder in cellen in. Sommige van deze verbindingen bevatten CF₂- of CF₃-groepen en kunnen worden geclassificeerd als PFAS. In sommige gevallen worden PFAS biotische of abiotische afgebroken tot stabielere PFAS zoals trifluorazijnzuur (TFA). Het verbeterde beeld van de productie en het gebruik van fluorpolymeren (een aparte groep van PFAS stoffen) laat zien dat de ze worden gebruikt in kunststoffen, rubbers en elektronische apparaten. Fluorpolymeren worden als laag risico beschouwd vanwege hun lage biologische beschikbaarheid, maar tijdens hun levenscyclus (productie, gebruik en verwijdering) kunnen uitloogbare PFAScomponenten vrijkomen. Dit is aanleiding voor bezorgdheid over langetermijneffecten op milieu en gezondheid. Elektronisch afval kan ook bijdragen aan het vrijkomen van PFAS door onjuiste verwijdering of een gebrek aan recyclingfaciliteiten. Een andere nog relatief onbekende bron is de atmosferische depositie die zorgt voor diffuse PFAS verontreinigingen in de bodem en het water en potentieel grondwater en drinkwaterbronnen bedreigt. Tijdens de inventarisatie zijn 14 PFAS

geprioriteerd die van bijzonder belang worden geacht voor de drinkwatersector.

Beschikbare analysetechnieken

Door de verschillende fysisch-chemische eigenschappen van PFAS zijn verschillende analysetechnieken nodig om deze verbindingen uitgebreid te monitoren, omdat elke analysetechniek een eigen beperkt analysevenster heeft. Daarom is steeds een combinatie van verschillende analysetechnieken nodig, die ook rekening houden met de gevoeligheid die nodig is voor verschillende soorten water (d.w.z. drinkwater vs. afvalwater) (zie ook de figuur).

Toepassing: uitbreiding van analytische mogelijkheden voor PFAS-detectie

Om het gebruik van de beschikbare technieken te optimaliseren, stellen we een kader voor dat een leidraad biedt voor het gebruik van de verschillende analysetechnieken die nodig zijn voor een uitgebreide monitoringstrategie. Dit kader houdt rekening met de verschillende fysisch-chemische eigenschappen van PFAS, met de vereisten voor verschillende soorten water (inclusief drinkwater) en met de beschikbaarheid en gereedheid van bestaande technieken.

Met het hier voorgestelde beoordelingskader is het mogelijk PFAS uitgebreid te monitoren en strategieën te ontwikkelen om veilige niveaus in drinkwater te garanderen. Het kader biedt betere mogelijkheden om de afweging te maken welke PFAS moeten worden opgenomen in routinematige monitoring.

The Report

Dit onderzoek is beschreven in het rapport *Hidden PFAS and other undefined organic fluorine* (KWRW 2025.035).

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1 Introduction

1.1 PFAS – a diverse group

Per- and polyfluoroalkyl substances (PFAS) are a large group of synthetic chemicals with varying physicochemical properties (Buck et al., 2011; Wang et al., 2021). The vast diversity of this chemical group hampers its comprehensive monitoring and assessment. According to the latest definition provided by the Organization for Economic Cooperation and Development (OECD), a chemical containing a perfluorinated methylene (CF₂) or perfluorinated methyl (CF₃) group can be classified as PFAS (unless the methylene and methyl groups are bound to H, Cl, Br or I) (Wang et al., 2021) (Figure 1). This includes a large variety of compounds, which are subdivided in many distinct categories based on their chemical structures. The most reported and investigated PFAS are the perfluoroalkyl acids (PFAA), which include, among others, perfluoroalkyl carboxylic acids (PFCA) such as perfluoroctanoic acid (PFOA), and perfluoroalkyl sulfonic acids (PFSA) such as perfluoroctanesulfonic acid (PFOS).

PFAA can be used to illustrate the vast diversity of PFAS. These compounds contain perfluorinated alkyl chains of varying length (typically < 15-20 carbon atoms (C)) and an acid moiety, typically a carboxylic or sulfonic group. The length of the alkyl chain influences the polarity of the molecule, and thereby its behavior (e.g., partitioning between the aqueous and solid phases) and bioavailability (i.e., its chemical speciation, exposure pathways and interactions with biological systems) in the environment. The shorter the chain the higher the mobility, which in turn results in lower removal efficiency from water (Hofman-Caris, 2024; Hofman-Caris et al., 2024; Scheurer et al., 2017), but also potentially lower toxicity (de Baat et al., 2023; Hoondert et al., 2023). The C-F bond provides these chemicals with enhanced chemical stability, which makes these compounds very resistant to environmental degradation, while the acid group provides high solubility and mobility in water.

PFAA are just a relatively small subclass among the many existing subclasses of PFAS. Based on the OECD definition of PFAS, hydrofluorocarbons, pesticides, pharmaceuticals, polymers, and more, can be considered PFAS. Over 7 million PFAS are reported in PubChem, although the database includes also PFAS that are produced in negligible amounts or not produced at all (Schymanski et al., 2023).

Tracing PFAS sources is also particularly challenging due to their many commercial and industrial applications and uses, emissions pathways, and different transport and mobility in the environment. Furthermore, some PFAS may undergo biotic or abiotic transformation, resulting in the formation of more stable and recalcitrant PFAS (i.e., legacy PFAS), which hinders their traceability. These less chemically stable compounds are generically referred to as 'precursors. Known precursors include compounds such as hydrofluorocarbons, which degrade in the atmosphere to form trifluoroacetic acid (TFA) (Russell et al., 2012; Wang et al., 2023), and fluorotelomers, which convert to PFCA (Hamid et al., 2020; Liu et al., 2021). Emissions from degradation of precursors are still expected to be a significant source of PFOS in the coming years (Wang et al., 2017). In addition, release from environmental compartments where these compounds have accumulated over time, such as soil, sediment, and seawater, may contribute to additional emissions (Amato et al., 2023a; Balgooyen and Remucal, 2022; Sha et al., 2022).





Figure 1. General classification of PFAS (adapted from Bokkers et al. (2019)).

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1.2 PFAS regulations and monitoring in water

Due to the very broad OECD definition of PFAS, steps have been taken to provide a more comprehensive assessment of PFAS in water. In the European Union, the Drinking Water Directive (DWD) has recently introduced monitoring requirements for at least one of two additional parameters, i.e., PFAS total' and 'Sum of PFAS'.

Note that 'PFAS total' refers to the "totality of per- and polyfluoroalkyl substances" while 'Sum of PFAS' to the sum of 20 PFAS (Table 1). This approach aims to provide a more comprehensive assessment of PFAS; however, it still overlooks several substances. For instance, 'Sum of PFAS' only focuses on 20 compounds, and the assessment of 'PFAS total' is hampered by several analytical challenges (European Union, 2024) (which will be further discussed in this report). As a result, several substances are often neglected and their occurrence in drinking water (and its sources) remains unknown.

Table 1. PFAS currently regulated in the DWD.

Perfluorobutanoic acid (PFBA)	Perfluorobutane sulfonic acid (PFBS)
Perfluoropentanoic acid (PFPA)	Perfluoropentane sulfonic acid (PFPS)
Perfluorohexanoic acid (PFHxA)	Perfluorohexane sulfonic acid (PFHxS)
Perfluoroheptanoic acid (PFHpA)	Perfluoroheptane sulfonic acid (PFHpS)
Perfluorooctanoic acid (PFOA)	Perfluorooctane sulfonic acid (PFOS)
Perfluorononanoic acid (PFNA)	Perfluorononane sulfonic acid (PFNS)
Perfluorodecanoic acid (PFDA)	Perfluorodecane sulfonic acid (PFDS)
Perfluoroundecanoic acid (PFUnDA)	Perfluoroundecane sulfonic acid
Perfluorododecanoic acid (PFDoDA)	Perfluorododecane sulfonic acid
Perfluorotridecanoic acid (PFTrDA)	Perfluorotridecane sulfonic acid

1.3 Motivation for research, questions and objectives

Recently, "all PFAS" have been classified as substances of very high concern in the Netherlands (IenW, 2024). Drinking water companies have developed a strong track record in research on PFAS as they have identified a wide share of PFAS in several matrices including drinking water (Sadia *et al.*, 2023). Moreover, previous and current Waterwijs/BTO projects focus on several aspects of PFAS such as their occurrence, environmental behavior and treatment options (website KWR, January 2023).

The proposed PFAS restriction (see text box) triggered numerous responses from a wide range of producers and users, and it became clearer that PFAS may also include pharmaceuticals and pesticides as described in the literature (Glüge et al., 2020). These compounds are already on the radar as they are known to end up in all drinking water sources, not only surface but also groundwater. In all, this raised concerns among drinking water companies over the actual extent of PFAS contamination and how to monitor it. A concise overview of PFAS and potentially overlooked PFAS is currently lacking in the Dutch context. Next, concerns were raised by water companies regarding the (upcoming) stringent regulation of PFAS in drinking water (van der Aa *et al.*, 2022), the impact of including the assessment of 'PFAS total' in water monitoring, and the analytical challenges associated with evaluating this parameter.

This report provides insights into PFAS that may be potentially overlooked, and how to effectively detect and quantify them. Implications for monitoring strategies, including 'PFAS total' measurements, will be discussed to provide a more robust assessment of PFAS in water.

The objectives of this study are:

- 1. identifying potentially overlooked PFAS (chapter 2).
- providing an inventory of analytical approaches useful for detecting and identifying a broad range of PFAS (chapter 3).
- 3. developing a framework for the comprehensive assessment of PFAS in water (chapter 4).
- 4. providing recommendations for new substances to be considered for routine monitoring (chapter 5).

Restriction proposal for use of PFAS in the EU

Restricting the use of PFAS has been proposed by Denmark, Germany, the Netherlands, Norway and Sweden (ECHA, 2024) and is supported by EurEau/Vewin on a European level. Here, a broad definition has been used to define which PFAS should be restricted: "Any substance that contains at least one fully fluorinated methyl (CF3-) or methylene (-CF2-) carbon atom (without any H/Cl/Br/I attached to it). A substance that only contains the following structural elements is excluded from the scope of the proposed restriction: CF3-X or X-CF2-X', where X = -OR or -NRR' and X' = methyl (-CH3), methylene (-CH2-), an aromatic group, a carbonyl group (-C(O)-), -OR'', -SR'' or -NR''R''', and where R/R'/R''' is a hydrogen (-H), methyl (-CH3), methylene (-CH2-), an aromatic group or a carbonyl group (-C(O)-)."

The reason for this broad restriction is described in the text of the proposal: "PFASs are, or ultimately transform into, persistent substances, leading to irreversible environmental exposure and accumulation. Due to their water solubility and mobility, contamination of surface, ground- and drinking water and soil has occurred in the EU as well as globally and will continue. It has been proven very difficult and extremely costly to remove PFASs when released to the environment. In addition, some PFASs have been documented as toxic and/or bioaccumulative substances, both with respect to human health as well as the environment. Without taking action, their concentrations will continue to increase, and their toxic and polluting effects will be difficult to reverse."

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2 Overlooked PFAS

PFAS use categories and applications have been extensively investigated to improve our understanding of PFAS emissions and their occurrence in the environment. However, new uses and sources continue to emerge. In this chapter, we report the most up-to-date use categories and potentially overlooked PFAS compounds and sources of PFAS, with a focus on their potential impact on the (drinking) water sector.

2.1 Potentially overlooked PFAS compounds

2.1.1 Up-to-date use categories

PFAS are used in a wide range of industry branches and commercial products. Some of these uses have been largely reported in the scientific literature, such as fire-fighting foam, textile impregnation, and electroplating, while others are less known, for instance in ammunition, artificial turf, and musical instruments.

Previous studies focusing on PFAS life cycles have shown that field concentrations can be estimated by combining emission inventories with global multimedia mass-balance models (e.g., CliMoChem) (Boucher et al., 2019; Wang et al., 2017, 2014). This suggests that, for some PFAS, a good understanding of PFAS emissions sources exists. However, lack of reported data and inconsistent monitoring may lead to underestimated environmental concentrations, as observed, for instance, in the southern hemisphere. Furthermore, there are potentially many new PFAS produced and introduced on the market that are currently not monitored, highlighting the need of approaches that include a wider range of compounds.

Upon review of assigned used from North European and the US databases, Glüge et al. (2020) identified 16 PFAS that are in more than 10 use categories (Figure 2). These included commonly known PFAS such as PFOA and PFOS (in their salt form) and PFAA precursors (e.g., perfulorosulfonamides and perfluoroalkyl ethers), but also hydrofluorocarbons (pentafluoroethane and decafluoropentane) and monomers (e.g., tetrafluoroethylene). While some of these compounds are volatile and unlikely to be found in water (e.g., pentafluoroethane, decafluoropentane and tetrafluoroethylene), fluorad FC 170C (CAS No. 29117-08-6), 1-propanaminium, 3- [[(heptadecafluorooctyl)sulfonyl]amino]-N,N,N-trimethyl-, iodide (CAS No. 1652-63-7), and 1-propanaminium, 3- [[(heptadecafluorooctyl)sulfonyl]amino]-N,N,N-trimethyl-, chloride (38006-74-5) may be considered for monitoring due to their solubility in water, and widespread applications reported.

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Figure 2: PFAS used in more than 10 use categories (Glüge et al., 2020).

A recent data set covering a broad range of uses (and relative compounds) was compiled by Glüge et al. (2020). This dataset includes a comprehensive list of use categories and industry branches and identifies more than 200 use categories and subcategories for more than 1400 individual PFAS. The compounds assigned to each category and estimated emissions for some sectors and uses are reported as well. For instance, in 2016, the highest uses were identified for "Electrical equipment, appliance, and component manufacturing" and "Machinery manufacturing" (2180 tons). This dataset was compiled using data from the US Toxic Substances Control Act (TSCA) and the Substances in Preparations in Nordic Countries (SPIN) database (including Denmark, Finland, Norway and Sweden), and thus, it may not be exhaustive. Furthermore, the dataset focuses on polymeric PFAS containing the -CF₂-moiety and non-polymeric PFAS containing the -CF₂-CF₂-moiety, whereas non-polymeric substances that only contain a -CF₃- or -CF₂- moiety are not included (with a few exceptions). This results in the omission of compounds such as trifluoroacetic acid (TFA) and some pesticides and pharmaceuticals (see sections 2.2.1 and 2.2.2). A similar list of use categories has been compiled by Gaines (2023). The two lists largely overlap, although the names of the use categories may vary and we have been compiling them into one table (Table 2). Both databases include patents as a source to identify PFAS uses, although it is not known whether the use indicated in the patent actually occurred. The use of inventories, in combination with environmental fate modelling, has proven useful for estimating environmental concentrations, and thus, understand the global impact of pollutants on the environment (see Figure 3). This requires the identification of emission pathways throughout the life cycle of a synthetic product, which includes emission deriving from its production, use, and disposal.



Figure 3. Schematic workflow combining emission inventories and fate modelling approaches for estimating environmental concentrations (Wang et al., 2017).

Table 2. Industry branches and use categories where PFAS are or were utilized (adapted from Glüge et al. (2020) and Gaines (2023)).

Industry branches	
Aerospace	Mining
Biotechnology	Nuclear industry
Building and construction	Oil & gas industry
Chemical industry	Pharmaceutical industry
Electroless plating	Photography and lithography industries
Electronic industry	Production of plastic and rubber
Electroplating	Semiconductor industry
Energy sector	Textile production
Food production industry	Watchmaking industry
Machinery and equipment	Wood industry
Manufacture of metal products	
Other use categories	
Aerosol propellants	Lubricants and greases
Adhesives	Medical utensils
Air conditioning	Metallic and ceramic surfaces
Ammunition	Music instruments
Antifoaming agent	Optical devices
Apparel	Paper and packaging

Automotive	Particle physics
Ceramics and nanostructures synthesis	Personal care products
Cleaning compositions	Pesticides
Coatings, wax, paint, varnish, and inks	Pharmaceuticals
Conservation of books and manuscripts	Pipes, pumps, fittings and liners
Cook- and baking ware	Plastic, rubber and resins
Dispersions Printing	Recycling and material recovery
Dry cleaning	Refrigerant systems
Electronic devices	Scientific, general use
Etching	Sealants and adhesives
Explosives	Soil remediation
Fingerprint development	Soldering
Fire-fighting foam	Sport article
Flame retardants	Stone, concrete and tile
Floor covering including carpets and floor polish	Textile and upholstery
Glass	Tracing and tagging
Household applications	Water and effluent treatment
Laboratory supplies, equipment and instrumentation	Wire and cable insulation, gaskets and hoses
Leather	

2.1.2 Pharmaceuticals

Fluorine is largely employed in the pharmaceutical industry due to its unique properties that allow to modulate the biochemical behaviour of molecules (Meanwell, 2011; Purser et al., 2008). For instance, replacing a hydrogen atom with a fluorine atom typically increases lipophilicity, modulate basicity, and modify metabolic stability. Among the many drug design applications that rely on the use of fluorine, some may result in the synthesis of fluorinated compounds that can be classified as PFAS (Table 3). Some examples include substituting CF₃ for a CH₃, or O-CH₂-O with O-CF₂-O, to increase metabolic stability and improve cellular permeability. Due to fluorine's strong electronegativity, CF₂H is a more lipophilic H-bond donor than either OH or NH, offering the potential for improved membrane permeability. Modulating metabolic stability is also useful for investigating the metabolism of drugs of abuse such as methylenedioxymethamphetamine (MDMA) (Meanwell, 2011). Some examples of pharmaceuticals that can be classified as PFAS are shown Table 4. Based on the review of previous studies, these compounds often contain one or two CF₃ groups, and less frequently a CF₂. This also indicates that pharmaceuticals may be potential source of trifluoroacetic acid (TFA) (UBA, 2022), a PFAS that is frequently detected in the environment (Amato et al., in preparation; (Amato et al., 2023b).

A list fluorinated pharmaceuticals was compiled by Inoue et al. (2020) using the publicly available KEGG drug database (KEGG, 2021). These authors listed 340 organofluorine pharmaceuticals as being registered between 1954 and 2019 in Japan. A similar list was prepared by Hammel et al. (2022), consisting of 363 organofluorine pharmaceuticals that are approved in the U.S., Japan, and Europe. Further, these authors noted that 50% of these organofluorine pharmaceuticals contain a single fluorine; 35% contain a single aromatic fluorine; 10% contain more than three fluorine atoms. Four pharmaceuticals were fully or nearly fully fluorinated aliphatic compounds. There were 88 compounds containing at least one trifluoromethyl moiety (R-CF3) where R is not hydrogen, 15 of which contained two trifluoromethyl moieties. In the article, authors elaborate on the importance of using a clear definition of PFAS and addressing its regulatory implications, particularly as the use of some of these compounds may be considered essential.

Table 3. Examples of fluorine applications for drug design uses (from Meanwell (2011)).

Fluorine as an isostere of hydrogen

Fluorine for hydrogen exchange to modulate metabolism

Fluorine to modulate basicity in KSP inhibitors

Substitution of hydrogen by fluorine to influence conformation

Fluorine/hydrogen exchange to influence membrane permeability

Fluorine/hydrogen exchange to modulate potency

Fluorine/hydrogen exchange to influence membrane permeability

2,6-Difluorophenol as a CO₂H mimetic.

Fluorine as a C=O isostere in factor VIIa and thrombin inhibitors

Fluorine as a C=O isostere in FKBP12 mimetics

We also noted that several fluorinated pharmaceuticals have been approved by the US Food and Drug Administration (US-FDA) over the last couple of years (Shabir et al., 2023; Wang et al., 2024), and fluorinated drugs *"played a very crucial role to control the COVID pandemic and saved many lives"* as stated in a recent review paper (Chandra et al., 2023). These authors surveyed all ten fluorinated drugs approved by the US-FDA in 2021, including *pylarify*, a radioactive diagnostic agent for cancer, and emphasised that the use of fluorinated pharmaceuticals is expected to increase due to their unique properties. Note that these articles were written without the focus on the EU restriction proposal that is using a broad definition, which means that a lot of these pharmaceuticals may be included or excluded depending on the exact definition.

In light of the restriction proposal submitted by Denmark, Germany, the Netherlands, Norway and Sweden, the Dutch parliament raised attention on this topic (Tweede Kamer Motie 35-334 35-334). As a follow-up, the Dutch Ministry of Health, Welfare and Sport requested the RIVM to draw up an overview of medical products containing substances that are classified as PFAS in June 2023. RIVM focused on the use of PFAS substances in products in the Netherlands that are specifically applied for medical care, so not limited to pharmaceuticals only (RIVM, 2023). Similar PFAS-containing products are likely to be used in Belgium as well, although such a study has not been conducted yet, drawing attention from the public media (Artsenkrant, 2024). The RIVM first described information on the fully authorised medicinal products, i.e., their active ingredient, excipients and the packaging. Next, it described the use of PFAS in medical devices and *in vitro* diagnostics (IVDs), although details on the composition of these devices are not publicly available, and their chemical structures cannot be investigated. However, it is known that PFAS polymers are commonly used in medical devices (Table 2), and some information may be found in public factsheets and the EU restriction proposal (ECHA, 2024).

The most comprehensive information is available for active substances in medicines, as these are centrally registered in databases that can be searched on the basis of structural elements. RIVM mentions the use of the KEGG COMPOUND Database (KEGG, 2023) and KEGG DRUG Database (KEGG, 2024) similar to the previous article by Hammel et al. (2022). The RIVM overview resulted in 66 different active substances that are present in 734 different products (Table 4). We have repeated the compounds that RIVM identified in (Table 4), although this table should be used with caution as a comprehensive overview of the composition of medical products is not always publicly available or searchable for chemical structures.

PFAS can also be present in excipients – inactive substances that serve as vehicles or media for drugs or other active substances. However, the Dutch database on registered pharmaceuticals (Geneesmiddeleninformatiebank, 2025) mentions only two fluorinated pharmaceutical excipients, norflurane and heptafluoropropane, which are used as spray propellants for medicines used in respiratory diseases. Norflurane (1,1,1,2-Tetrafluoroethane) is present in 132 different products, while heptafluoropropane (1,1,1,2,3,3,3-Heptafluoropropane, also known as HFC-227ea) is present in 12 different products. Note that the use of these compounds is not only limited to pharmaceuticals, as norflurane is commonly used as refrigerant in cars' air conditioners and heptafluoropropane is used in fire suppression systems. Information on PFAS in packaging is very limited. While it is generally known that PFAS polymers (e.g., PTFE and PTCFE) can be used in the packaging of medicines to enhance repellence of moisture, the composition of this packaging is not publicly available. These fluorinated polymers can also be applied in ampoules, single and multi-dose containers, bottles (including caps and actuators), pressurized containers, syringes and vials. The RIVM also noted that inhalers for the administration of asthma medication may be coated with a PFAS plastic (fluoropolymers) that falls under the PFAS definition. Although these products are formally seen as a medical aid, the main effect of the product is that of a medicine.

While the RIVM study on PFAS in pharmaceuticals is one of the most detailed studies in the Netherlands, it does not specify the extent of use of these compounds nor quantifies the potential emissions to the environment. Yet, we are unable to perform such calculation as we have limited access to usage data of pharmaceuticals. This should be addressed in future studies to quantify the poll of the 'hidden PFAS' associated with the use of pharmaceuticals. Also, the study may be complemented with veterinary pharmaceuticals and other sources of PFAS such as pesticides.

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Table 4. List of medicines registered in the Netherlands (in May 2023) whose API (active ingredient) falls under the PFAS definition in the restriction proposal, the corresponding Anatomical Therapeutic Chemical (ATC) code and the number of products(s) containing that active substance listed on the CBG-MEB website (n) (Geneesmiddeleninformatiebank, 2025), see more details in text of this report and the RIVM memo from which this table is copied (RIVM, 2023).

Active ingredient	ATC code	n	Active ingredient	ATC code	n
Alpelisib	L01EM03	3	Letermovir	J05AX18	4
Apalutamide	L02BB05	1	Lomitapide	C10AX12	6
Aprepitant	A04AD12	34	Lumacaftor	R07AX30	4
Asciminib	L01EA06	2	Maraviroc	J05AX09	5
Avacopan	L04AA59	1	Mefloquine	P01BC02	4
Bivalirudin	B01AE06	3	Methoxyflurane	N02BG09	1
Berotralstat	B06AC06	1	Nilotinib	L01EA03	3
Bicalutamide	L02BB03	17	Nilutamide	L02BB02	2
Cangrelor	B01AC25	1	Nitisinone	A16AX04	14
Celecoxib	M01AH01	25	Pantoprazole	A02BC02	49
Cinacalcet	H05BX01	71	Paxlovid	J05AE30	1
Corticorelin	V04CD04	1	Perflutren	V08DA01	2
Delamanid	J04AK06	2	Ponatinib	L01EA05	3
Desflurane	N01AB07	2	Pretomanid	J04AK08	1
Doravirin	J05AG06	2	Regorafenib	L01EX05	1
Dutasteride	G04CB02	20	Riluzole	N07XX02	10
Efavirenz	J05AG03	31	Roflumilast	R03DX07	2
Eflornithine	D11AX16	1	Sevoflurane	N01AB08	4
Elexacaftor	R07AX32	2	Silodosin	G04CA04	14
Enzalutamide	L02BB04	5	Siponimod	L04AA42	3
Etofenamate	M02AA06	1	Sitagliptin	A10BH01	170
Flecainide	C01BC04	32	Sonidegib	L01XJ02	1
Fluoxetine	N06AB03	8	Sorafenib	L01EX02	15
Flupentixol	N05AF01	10	Tafluprost	S01EE05	11
Fosaprepitant	A04AD12	2	Telotristat	A16AX15	1
Fluvoxamine	N06AB08	12	Teriflunomide	L04AA31	6
Fulvestrant	L02BA03	19	Tezacaftor	R07AX31/R07AX32	4
Gemcitabine	L01BC05	24	Tipranavir	J05AE09	2
Glecaprevir	J05AP57	2	Trifluridine	L01BC59	2
Isoflurane	N01AB06	2	Travoprost	S01EE04	20
Lansoprazole	A02BC03	6	Upadacitinib	L04AA44	3
Ledipasvir	J05AP51	4	Vinflunine	L01CA05	1
Leflunomide	L04AA13	22	Voxilaprevir	J05AP56	2

2.1.3 Plant protection products

The introduction of halogen atoms into an active ingredient is an important tool to modulate the properties of new plant protection products. Between 2010 and 2016, around 96% of the these products (herbicides, fungicides, insecticides/acaricides and nematicides) contained halogens, of which approximately half included fluorine (Jeschke, 2017).

As for pharmaceuticals, the focus on fluorinated plant protection products has also been growing. In 2020, Ogawa et al. reported that approximately 16% of the 1,261 investigated pesticides (including organic and inorganic compounds, acids and their salts) contained fluorine. Authors also reported that 127 agrochemical compounds out of 238 registered between 1998 and 2020 contained fluorine (Figure 4). According to Joerss et al. (2024), a total of 202 of 1934 entries in the Pesticide Properties DataBase (UH, 2024) met the revised definition of the OECD (Wang et al., 2021). Some examples of crop protection compounds that can be considered PFAS are listed in Table 5.

Similarly to pharmaceuticals, also crop protection compounds are bioactive and include fluorine atoms to module their biochemical activity, and thus, PFAS that belong to these categories typically share similar fluorine moieties (i.e., CF₂ or CF₃). In addition, the production of TFA from the degradation of these compounds may be expected (UBA, 2022). Joerss et al. (2024) estimated TFA formation potentials from plant protection products across Europe, the United States of America and China. A total of 143 of these entries contained a –CF₃ group linked to a carbon atom that is not fully fluorinated, making these potential parent compounds (i.e., precursors) of TFA. For instance, direct and indirect photolytic processes for pesticides – one containing a benzylic CF₃ group (penoxsulam) and another containing a CF₃-substituted heteroaromatic group (sulfoxaflor) – can result in the TFA formation (Bhat et al., 2022).



Figure 4. Prevalence of fluoro/non-fluoro-agrochemicals that have been assigned new ISO common names between 1998 and 2020 (Ogawa et al., 2020).

The study further reported that from the 143 substances that had the potential to degrade to TFA, a total of 39 substances are currently approved in the European Union, while 48 are registered in the USA, and 68 are registered in China. Based on their use, potential TFA emissions were estimated to range from 0 to 83 kg/km² per year. The authors further stated that the importance of plant protection products as a major TFA source is supported by field data from a region in Germany, which revealed a significant increase in TFA groundwater concentrations in areas with a proportion of agriculture use > 50% (median = $1.1 \, \mu$ g/L, n = 411) compared to land with agricultural use < 50% (median = $0.61 \, \mu$ g/L, n = 1187).

In light of these recent findings, concern arose in the Dutch drinking water sector over the possible threat to groundwater posed by TFA following degradation of plant protection products. In a previous study commissioned by VEWIN, the consultancy firm CLM carried out an initial exploration (CLM, 2024). First, they stated that especially reports published by the Pesticide Action Network and Générations Futures in November 2023 were of special interest. These reports list 37 PFAS pesticides that have been authorised in Europe. As a result of the above-mentioned publication, questions have been asked in the House of Representatives regarding the authorisation of PFAS pesticides in the Netherlands, similar to those previously asked about pharmaceuticals, considering the risks to soil, water and human health. In the answers to the parliament, the Ministry stated that 25 PFAS pesticides have been authorised in the Netherlands. These are active substances that are used in 105 authorised plant protection products and 3 authorised biocides. In addition, PFAS are also added as an adjuvant to plant protection products to improve their effectiveness. In the Netherlands, 5 authorised plant protection products and 1 authorised biocide contain PFAS as an adjuvant. Of all plant protection products, approximately 10% contains PFAS (as an active ingredient and/or as an adjuvant), for biocides it is less than 1%, according to the Ministry of Agriculture, Nature and Food Quality in the Answering questions about PFAS in pesticides dated 16 February 2024 (CLM, 2024).

CLM performed a search on the use of PFAS pesticides by focusing on sales data. Here, they found that over the period 2010-2022, sales of PFAS pesticides grew between 2014-2016, followed by a decline. However, in recent years, sales of PFAS pesticides have sharply increased by 83.2% in the years 2020-2022. The largest sales and strongest increase of PFAS pesticides concerned the group of fungicides. The three most commonly sold fungicides - fluazinam, fluopyram and fluopicolide – are extensively used across various crops.

In their analyses, CLM focused on the potential for leaching to soil as it may pose a threat to drinking water production, and for that they defined so-called environmental impact points in the Netherlands (In Dutch: Milieumeetlat, see https://www.milieumeetlat.nl/). By using this method, CLM showed that PFAS pesticides are not all equally sensitive to leaching into the groundwater. Next, this methods shows that over the period 2010-2022, the impact on the soil of PFAS pesticides increased sharply. Five PFAS pesticides, two fungicides and three herbicides, amount to more than 1,000 environmental impact points in groundwater as CLM summarized in their report (CLM, 2024). Three of these five drugs also show high sales figures. The PFAS pesticide with the highest value for environmental impact points 'groundwater x sales' is *fluopyram*. This substance is the most decisive for the risk of leaching. As described by CLM, the Dutch so-called groundwater atlas gives a first indication. There are significant variations in the measurement frequency of substances, and a several PFAS pesticides do not appear in the groundwater atlas, suggesting they are not being monitored.

Table 5. Examples of pharmaceuticals and pesticides that can be classified as PFAS.

Pharmaceuticals			
Camptothecin derivate		Ledipasvir	NHCO2Me I-Pr' FO N FF N O NHCO2Me NHCO2Me
Oxoazepane derivate		Fluoxetine (Prozac)	
Plant protection	products		
Sulfoxaflor		Flutianil	H_3C^{-0}
Pyflubumide		Fluopyram	CF ₃ O H H CF ₃ O CF ₃ CF ₃
Fipronil	F_3C Cl CN $S=0$ CI H_2N CF_3	Oxathiapiprolin	$ \begin{array}{c} & & \\ & & $
Fluensulfone		Trifluralin	$\begin{array}{c} H_3C & CH_3 \\ O_2N & H_3C_2 \\ CF_3 \end{array}$
Fluopyram	CF ₃ O H H		

2.1.4 Emerging PFAS (from scientific literature)

In this paragraph, we focus on PFAS in drinking water and its sources as derived from scientific literature. A recent monitoring study conducted in the US, focusing on 70 PFAS in drinking water samples from 44 locations in 16 states, revealed the presence of 26 PFAS, of which 12 are typically not monitored in the US (US EPA Methods 537.1 or 533) (Table 6). These compounds included, among others, (i) ultrashort-chain PFAS (C < 4) such as perfluoropropionic acid (PFPrA), perfluoro-2-methoxyacetic acid (PFMOAA), perfluoropropanesulfonic acid (PFPrS), perfluoro-2-methoxypropionic acid (PFMOAA), perfluoropropionic acid (MTP), (ii) small (C = 4) ethers (e.g., perfluoro-3,5-dioxahexanoic acid (PFO2HxA)), (iii) larger (C > 4) ethers (e.g., 2,2,3,3,4,5,5,5-octafluoro-4-(1,1,2,2-tetrafluoro-2-sulfoethoxy)-pentanoic acid (R-PSDA)) and (iv) sulfonamides (perfluorooctanesulfonamide (FOSA)). PFPrA was the most frequently detected (ultrashort-chain) PFAS (24 times), followed by R-PSDA and PFMOAA, which were much less frequently found (5 and 4 times, respectively). Given their challenging removal from water, short and ultrashort-chain PFAS identified in this study may warrant additional monitoring in drinking water and its sources.

Table 6. PFAS detected in drinki	ng water in the US usin	g a method including	70 targeted substances	(Pelch et al., 2023)
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PFAS	Chemical name	CASRN	Frequency \geq MRL	Concentration range (ng/L)	Coverage by US EPA methods
PFPrA	Perfluoropropionic acid	422-64-0	24	2.5-140	-
PFOS	Perfluorooctanesulfonic acid	1763-23-1	18	1.9-1700	537.1 & 533
PFOA	Perfluorooctanoic acid	335-67-1	17	2.0-2100	537.1 & 533
PFHxA	Perfluorohexanoic acid	307-24-4	17	2.1-610	537.1 & 533
PFPeA	Perfluoropentanoic acid	2706-90-3	17	1.8-570	533
PFHxS	Perfluorohexanesulfonic acid	355-46-4	15	1.8-390	537.1 & 533
PFBS	Perfluorobutanesulfonic acid	375-73-5	15	2.1-95	537.1 & 533
PFBA	Perfluorobutanoic acid	375-22-4	10	5.3-140	533
PFHpA	Perfluoroheptanoic acid	375-85-9	9	2.1-1100	537.1 & 533
R-PSDA	2,2,3,3,4,5,5,5-octafluoro-4-(1,1,2,2-tetrafluoro-2-sulfoethoxy)-Pentanoic acid	2416366-18-0	5	2.3-27	-
PFMOAA	Perfluoro-2-methoxyacetic acid	674-13-5	4	2.1-15	-
PFPeS	Perfluoropentanesulfonic acid	2706-91-4	3	6.6-100	533
PFPrS	Perfluoropropanesulfonic acid	423-41-6	3	3.6-31	-
PFO2HxA	Perfluoro-3,5-dioxahexanoic acid	39492-88-1	3	3.8-8.8	-
PFNA	Perfluorononanoic acid	375-95-1	2	19-400	537.1 & 533
PFHpS	Perfluoroheptanesulfonic acid	375-92-8	2	5.5-67	533
R-EVE	4-(2-carboxy-1,1,2,2-tetrafluoroethoxy)-2,2,3,3,4,5,5,5-octafluoro-Pentanoic acid	2416366-22-6	2	7.0-7.6	-
PMPA	Perfluoro-2-methoxypropionic acid	13140-29-9	2	5.1-6.8	-
Hydrolyzed PSDA	2-fluoro-2-[1,1,2,3,3,3-hexafluoro-2-(1,1,2,2-tetrafluoro-2-sulfoethoxy) propoxy]-Acetic acid	2416366-19-1	2	5.4–5.8	-
FOSA	Perfluorooctanesulfonamide	754-91-6	2	2.7-3.1	-
PFDA	Perfluorodecanoic acid	335-76-2	1	59	537.1 & 533
MTP	3-(Methoxy)tetrafluoropropionic acid	93449-21-9	1	19	-
6:2 FTSA	6:2 Fluorotelomer sulfonic acid	27619-97-2	1	8.0	533
HFPO-DA (GenX)	Hexafluoropropylene oxide dimer acid	13252-13-6	1	6.1	537.1 & 533
PFECHS	Cyclohexanesulfonic acid, decafluoro(1,1,2,2,2-pentafluoroethyl)-	133201-07-7	1	2.2	-
PFO3OA	Perfluoro-3,5,7-trioxaoctanoic acid	39492-89-2	1	2.2	-

Neutral PFAS are challenging to measure using conventional LC-MS analysis (see section 3.1.2) and are therefore often overlooked. Despite being more volatile than the charged PFAS, some of these compounds are sufficiently polar to be present in water samples. For instance, FTOH have been detected in influents and effluents of WWTP (Chen et al., 2017; Habib et al., 2023; Ma et al., 2022), indicating a potential risk of contamination of surface water. These compounds are also suspected to contribute to the formation of PFCA after release and degradation in the atmosphere (Ellis et al., 2004).

Ultrashort-chain PFAS were detected in drinking water from Flanders (Belgium), both in tap (perfluoroethanesulfonic acid (PFEtS) and perfluoropropanesulfonic acid (PFPrS)) and bottled water (trifluoromethanesulfonic acid (TFMS)) (Cappelli et al., 2024). TFMS was also detected in drinking water samples in the US and in surface water in Sweden (Björnsdotter et al., 2019). PFPrA and PFPrS were reported in bottled water from the US, with PFPrA occurring at median concentrations (0.92 ng/L) twice as high as those of other PFAS, including PFOA and PFOS (0.23–0.55 ng/L) (Chow et al., 2021). In Germany, TFA, TFMS, and PFPrA were frequently detected in drinking water sources at levels approximately 1 (TFMS and PFPrA) to 3 (TFA) orders of magnitude higher than other PFAS (Neuwald et al., 2022). Hexafluoroisopropanol (HFIP), used polymer chemistry organic in and synthesis, and bis(trifluoromethylsulfonyl)imide (NTf2), used in lithium batteries, were among the more novel ultrashort-chain PFAS detected.

Polyfluoroalkyl phosphates (PAP) are also among the less investigated PFAS that have been previously detected in drinking water (Ding et al., 2012) and groundwater (Liu et al., 2020), and shown to be poorly removed by drinking water treatments (Zhang et al., 2024). While the di-substituted form of these compounds is expected to be more hydrophobic and less mobile, the mono-substituted molecules may represent a greater risk for drinking water due to higher mobility and hydrophilicity.

2.1.5 Emerging PFAS (from BTO reports)

In this paragraph, we focus on PFAS in drinking water and its sources as derived from the joint research programme BTO (now called: Waterwijs). Methods for measuring ultrashort-chain PFAS developed at KWR have enabled the monitoring of these compounds in drinking water and its sources (Vughs et al., 2023). Recent reports indicated that these compounds do occur in drinking water sources such as surface water, dune and river bank infiltrated water, groundwater, and in drinking water as well (Amato et al., 2023b; Vughs et al., 2023)(Amato et al., in prep.). While these compounds are not regulated in the EU, and their toxicity is still largely unknown (except for TFA), TFMS and PFPrA are consistently detected in Dutch surface water (Amato et al., 2023b), and to a lesser extent, also in groundwater (Amato TFA in preparation). Furthermore, TFMS was also detected in deposition samples at levels comparable to TFA (Amato et al. in prep).

Suspect and non-targeted screening (SNTS) analyses using LC-HRMS have been increasingly used to tentatively identify unknown PFAS in water. At KWR, a few studies have focused on SNTS analyses of groundwater (Been TKI in prep), surface water (Amato et al., 2023b) and coastal aerosol samples near drinking water production sites (Amato and Béen, 2023). While former identification with analytical standards has not been performed, often due to lack of analytical standards, a number of substances have been tentatively identified with high confidence. These included polyfluorinated analogous of PFOA and PFOS, which are characterized by a fluorine atom being replaced by a hydrogen atom (H-PFOA and H-PFOS), N-methylperfluorobutane sulfonamido acetic acid (MeFBSAA), and 6:2 fluorotelomer sulfonamide betaine (6:2 FTAB). Among these, MeFBSAA and 6:2 FTAB seem to be particularly relevant due to occurrence in drinking water and multiple drinking water sources. Despite being less frequently detected, polyfluorinated compounds such as H-PFOS and H-PFOA may also be prioritized due to the almost identical chemical structures to PFOA and PFOS, and their potential similar toxicity.

2.2 Potentially overlooked PFAS sources

2.2.1 Fluoropolymers and side-chain fluorinated polymers

Fluoropolymers are used in the production of plastics and rubbers. Their use includes applications as mould release agents, foam blowing agents, foam regulators, polymer processing aids, in the etching of plastic, as anti-blocking agents for rubber, and as curatives in the production of plastic and rubber (Glüge et al., 2020). The (past or present) disposal of plastics and rubbers in landfills may potentially contribute to the release of PFAS from these materials in the environment. Although fluoropolymers are known to be chemically stable, their degradation during use and after disposal may still represent a source of PFAS. Degradation of fluoropolymers may be induced under specific conditions, such as the disposal of ammunition via open burns, where fluoropolymers may thermally degrade to non-polymeric PFAS or hydrofluorocarbons (Triumph and Vyas, 2023). Thermal degradation of fluoropolymers is expected to occur in waste incinerators, where incomplete mineralization of PFAS may lead to the formation and release of fluorinated organic compounds in the atmosphere (Seay et al., 2023; Weitz et al., 2024; Winchell et al., 2024). For instance, thermal degradation studies indicated that fluoropolymers may be converted into TFA and other PFCA following exposure to high temperature (Figure 5). Similarly, (bio)degradation of side-chain fluorinated polymers in the environment and landfills may lead to the release of PFAS precursors and represent a substantial source of PFAS in the long term (Wang et al., 2017, 2014).

Electronic devices can also contain fluoropolymer-insulated wiring and fluoropolymers as coating for fingerprintresistant screens. Disposal of e-waste in Europe is regulated by the Waste Electrical and Electronic Equipment Directive to reduce the environmental impact of electronic devices, however, insufficient availability of recycling facilities and improper disposal may still result in e-waste ending up in landfills.

Fluoropolymers are considered polymers of low concern due to their low bioavailability and toxicity (Henry et al., 2018; Korzeniowski et al., 2023), however, concerns remain on the impact of leachable components (e.g., monomers, oligomers and PFAS) released during the fluoropolymer life cycle (i.e., production, use and disposal) on human health and the environmental (Lohmann et al., 2020).

In general, due to thermal, abiotic and biotic degradation, and the large amounts produced, fluoropolymers and sidechain fluorinated polymers can be considered a relevant source of non-polymeric PFAS (Ellis et al., 2001; Lohmann and Letcher, 2023; Russell et al., 2012; Schellenberger et al., 2019; Sun et al., 2020; Washington et al., 2009) (Figure 5).



Figure 5. Potential mechanisms of degradation of A) side-chain fluorinated polymers (Lohmann and Letcher, 2023), B) fluoropolymers (Ellis et al., 2001), C) non-polymeric PFAS (Wang et al., 2022), and D) perfluorocarbons (Russell et al., 2012; Wang et al., 2022).

2.2.2 Hydrofluorocarbons

The use of hydrofluorocarbons has been reported in electronic devices such as panel displays or liquid crystal displays, and for testing of electronic devices and equipment, as heat transfer fluids/cooling agents, in cleaning solutions, and to deposit lubricants (Glüge et al., 2020). Hydrofluorocarbons, in particular hydrofluoroolefines, are known to undergo atmospheric degradation and produce TFA (Russell et al., 2012; Wang et al., 2023), which in turn becomes a source of contamination for water and soil via atmospheric deposition (Amato et al., 2024c; Amato and van der Grift, 2024).

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2.2.3 Lithium-ion batteries

An emerging PFAS in this industry is lithium bis(trifluoromethanesulfonyl)imide (LiTFSI), which is commonly used as an electrolyte salt in lithium-ion batteries (Figure 6). This compound is of particular interest due to its high solubility in water and its similar chemical structure to ultrashort-chain PFAS. Toxicological data on LiTFSI is lacking, although preliminary investigations have been performed by ECHA and EPA, indicating potential effects on rats and mice (Sands et al., 2024; USEPA, 2023). More PFAS have been reported in lithium-ion batteries, including polymeric and non-polymeric PFAS (Figure 6). Emissions of PFAS from lithium-ion battery may occur during recycling processes that do not operate at temperature sufficient to mineralized PFAS, such as hydrometallurgical processes (Rensmo et al., 2023). Given the rapid surge in lithium-ion batteries applications in the recent years, emissions from disposal and recycling processes after their use should be monitored and may be a potential source of PFAS.



Figure 6. Fluorinated substances reported in lithium-ion batteries (from Rensmo et al. (2023)). Shaded areas indicated substances that can be classified as PFAS (according to the OECD).

2.2.4 Atmospheric deposition

PFAS emitted in the atmosphere are reintroduced into waterways and soil via atmospheric deposition (Galloway et al., 2020; Shimizu et al., 2021). Dry deposition involves the settling of particles due to gravity or direct uptake of gases by vegetation, soil, and surface water, whereas wet deposition occurs with precipitation such as rainfall or snowfall. Atmospheric deposition has been linked to contamination of soil and groundwater and may thus pose a risk to drinking water sources (Schroeder et al., 2021).

PFAS found in topsoil samples collected in coastal dunes in North Holland were consistent with those detected in sea-spray aerosols (SSA), suggesting that deposition of SSA may be a major process contributing to soil contamination in or near the coastal dune area of The Netherlands (Amato and van der Grift, 2024). This raise concerns over the potential risk of contamination in groundwater and dune-infiltrated water in coastal dunes.

PFAS contamination in rain-fed heathland pools in the Brabantse Wal (south of the Netherlands) was also linked to atmospheric deposition (Figure 7) (Amato et al., 2024c). PFAS deposition fluxes at this location were overall consistent with those measured in a site located in the province of Gelderland, more than 100 km north-east of the

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Brabantse Wal, indicating that, for most PFAS, diffuse contamination (likely not restricted to the Dutch borders) contributed to PFAS deposition rather than localized point sources (except for a few exceptions such as HFPO-DA, also referred to as GenX). This suggests a potential risk of widespread contamination of soil and surface water in the Netherlands. The direct impact of atmospheric deposition on drinking water sources has not been quantified yet, however, this contamination source should be further investigated.

TFA contamination is also known to be linked to atmospheric deposition due to the degradation of hydrofluorocarbons (HFC) (Henne et al., 2012; UBA, 2022). Some of these halogenated gases, such as 1,1,1,2-tetrafluoroethane (HFC-134a), have been shown to degrade in the atmosphere to form TFA, which, due to its very high solubility in water, is then transported into soils and waters through precipitation (Franklin, 1993). An even less stable TFA precursor, such as HFC-1234yf, has been used as a replacement for HFC-134a (Henne et al., 2012). These processes contribute to diffuse contamination of TFA, as opposed to localised inputs such as discharge from wastewater treatment plants (WWTP) or landfills. TFA levels have been consistently increasing in several environmental media, raising concerns over their potential impact on the environment and human health (Arp et al., 2024).



Figure 7. Relationship between PFAS concentrations measured heathland pools (means, n = 2 or 4) and deposition fluxes (from Amato et al. (2024c)

3 Inventory of analytical techniques for monitoring PFAS in water

This chapter focuses on chemical analytical techniques that are suitable for measuring PFAS and generic organic fluorine in water samples. This list is not exhaustive, and focuses on analytical techniques that are commonly used or have been documented for chemical analysis of PFAS and organic fluorine in water. Note that besides chemical analyses, effect-based monitoring techniques are also available (e.g. bioassays described by de Schepper et al., (2024) and Behnisch et al., (2021).

3.1 Targeted screening methods

3.1.1 Liquid chromatography

3.1.1.1 Reversed-phase

The most common analytical approach used for measuring PFAS in water samples relies on reversed-phase (RP) liquid chromatography coupled to mass spectrometry (LC-MS). Commercial laboratories typically measure approximately 20-40 compounds (mainly PFAA and precursors), although additional PFAS can be measured when alternative chromatographic techniques are used (e.g., ultrashort-chain PFAS such as TFA). This approach is suitable for compliance with regulatory requirements, which, in the EU, include 20 PFAA (Table 1). However, this is only a small fraction of the PFAS that have been reported or documented in field studies, and amounts to a much smaller portion of the substances that have been listed as (or match the definition of) PFAS (Schymanski et al., 2023; Wang et al., 2021). It is currently unclear whether the portion of PFAS measured by conventional LC-MS methods offers a reasonable estimation of PFAS contamination, however, this is likely dependent on the type of sample analysed: for instance, measuring PFAA is likely to be poorly representative of heavily contaminated matrixes such as WWTP influents and effluents or aqueous film-fighting foam (AFFF) contaminated sites, where a complex mixture of PFAS may be present. This approach is limited by poor retention of very polar PFAS, such as TFA, and poor ionization efficiency of neutral PFAS (using electrospray ionization (ESI), such us fluorotelomer alcohols (FTOH). Despite the low ionization efficiency, analysis of FTOH in water using ultra performance liquid chromatography-electrospray ionization-tandem mass spectrometry (UPLC-ESI-MS/MS) has been reported, with limits of detection in the range 0.01-0.1 ng/L (Chen et al., 2017; Ma et al., 2022).

3.1.1.2 Mixed-mode chromatography

A major limitation of LC-MS methods based on RP chromatography is the lack of retention of ultrashort-chain PFAS, which may represent a substantial fraction of PFAS in some water samples (Amato et al., 2023b). Alternative separation techniques such as mixed-mode (MM) chromatography can be utilized to detect these compounds (Amato et al., 2023b; Vughs et al., 2023).

3.1.2 Gas chromatography

Gas chromatography can be used to determine PFAS that are poorly ionized by ESI (e.g., fluorotelomer olefins (FTOS), FTOH, perfluorosulfonamides and perfluorosulfonamido-ethanols). This technique uses different ionization sources such as electron ionization (EI) (Ayala-Cabrera et al., 2021; Bach et al., 2016) and atmospheric pressure chemical ionization (APCI) (Portolés et al., 2015) that are suitable for neutral PFAS, enabling detection in the low ng/L range and even in the pg/L range for APCI. FTOH have been detected in influents as well as effluents of WWTP (Chen et al., 2017; Habib et al., 2023; Ma et al., 2022), suggesting that these compounds may be released in surface water and pose a risk to drinking water sources.

3.2 Suspect and non-targeted screening analysis (LC-HRMS)

Targeted screening methods are important tools for assessing PFAS concentrations in environmental samples, however, these typically focus on a selection of compounds (typically 20-40) that may represent a (small) fraction of the total burden of PFAS in samples. Suspect and non-targeted screening (SNTS) analyses using liquid chromatography coupled to high-resolution mass spectrometry (LC-HRMS) offer the opportunity to investigate a broader range of PFAS. This approach is very promising and versatile, and can be applied in multiple ways. For instance, libraries containing thousands of substances can be used to search for a large set of PFAS in a sample. This is achieved using automated workflows that enable rapid selection of relevant features followed by comparison with mass spectral libraries. Furthermore, SNTS can be used to potentially identify PFAS that have not been reported yet, however, this requires time-consuming data processing which increases the overall cost of the analysis. Workflows developed at KWR and data analysis tools specifically designed for PFAS assessment such as FluoroMatch (Koelmel et al., 2022) or the MD/C-m/C approach (Zweigle et al., 2023), can be used for this purpose. A more detailed assessment of SNTS advantages and challenges, with a focus on BTO research, is provided elsewhere (Amato et al., 2024a).

3.3 PFAA precursors

The Total Oxidizable Precursors (TOP) assay uses oxidative conversion to transform PFAS precursors into stable perfluoroalkyl carboxylic acids (PFCAs) that are commonly included in routine monitoring. This process employs hydroxyl radicals produced through the thermolysis of persulfate under basic conditions (pH >12). The change in PFCA concentrations before and after oxidation can be used to infer the presence of PFAS precursors in the sample. The amount of precursors can vary significantly among samples, and in some cases, precursors may constitute a dominant fraction compared to the PFAS typically measured by conventional methods (Jia et al., 2023; Schaefer et al., 2023). This technique is inherently more selective than other methods that measure generic organic fluorine, such as extractable organic fluorine (EOF), adsorbable organic fluorine (AOF), and particle-induced gamma-ray emission (PIGE). However, some samples may contain PFAS precursors that do not convert into the PFAA typically included in the targeted method, such as PFAS ethers (Zhang et al., 2019) or polyfluorinated precursors, which convert into polyfluoroalkyl acids instead of perfluoroalkyl acids. As a result, the overall PFAS burden in a sample might be underestimated. Nevertheless, this method is compatible with instruments commonly found in analytical laboratories (i.e., LC-MS), and is more sensitive than standard methods relying on generic total organic fluorine determination, which makes it suitable for analysis of drinking water and relatively less contaminated water samples. It should be noted that oxidation of PFAA precursors may result in the formation of ultrashort-chain PFAA that are not detectable by convention RP chromatography. Thus, the combination of RP with additional chromatographic techniques suitable for ultrashort-chain PFAS (e.g., MM) is recommended.

3.4 Combustion ion chromatography

Combustion ion chromatography (CIC) involves the conversion of organic fluorine into hydrofluoric acid obtained by combustion at 900-1000 °C, followed by absorption of hydrofluoric acid in a solution of hydroxide and quantification of fluoride ion by means of ion chromatography (IC). This procedure can be used in combination with techniques such as adsorbable organic fluorine (AOF) and extractable organic fluorine (EOF), which isolate organic fluorine from its matrix (although a step to separate inorganic from organic fluorine is needed for AOF). In general, these approaches can be used to determine the total organic fluorine (TOF) content in a sample.

3.4.1 Adsorbable organic fluorine

Adsorbable organic fluorine (AOF) relies on the extraction of PFAS from aqueous media by means of activated carbon. A clean-up step to remove the inorganic fluorine that may have adsorbed on the activated carbon during the extraction phase may be included prior to CIC analysis. This clean-up typically involves washing the activated carbon with a NaNO₃ or KNO₃ solution.

AOF procedures have been standardized in Germany (DIN 38409-59:2022-10. Part 59) and are under development by the US Environmental Protection Agency (Draft Method 1621) and ISO (ISO/CD 18127). These methods are based on an adaptation of the adsorbable organic halogens (AOX) method, which is designed to measure halogens but it is not suitable for fluorine (Wagner et al., 2013). AOF is commonly used for the analysis of water samples, and no application in other matrixes has been reported in the scientific literature. One limitation of this method is the relatively high LOQ (~1 μ g/L), which may not be suitable for samples that are typically less contaminated, such as surface water and drinking water. Han et al. (2021) improved LOQs by minimizing fluoride interferences and increasing sample volumes (i.e., 300 mL instead of 100 mL).

3.4.2 Extractable organic fluorine

Extractable organic fluorine (EOF) is a procedure similar to AOF, where ion-paring methods (for instance weak anion exchange (WAX)) are used instead of activated carbon for the extraction of PFAS (D'Agostino and Mabury, 2017). Han et al. (2021) offered a comparison between different methods for measuring 'total' PFAS indicating decreasing concentrations in the order EOF > AOF > TOP, for aqueous film forming foam (AFFF) concentrates, and EOF > TOP > AOF, for impacted surface water samples, respectively. The better performance of the EOF method in two out of four surface water samples was attributed to the higher recovery of short-chain PFAS (C3 and C4). It should be noted that TFA and other ultrashort-chain PFAS may not be efficiently measured by AOF (or PIGE) due to poor adsorption on activated carbon. In contrast, EOF is suitable for charged PFAS, including ultrashort-chain compounds. However, this method lacks of selectivity for neutral PFAS and may result in the underestimation of the total organic fluorine content if very polar molecules are present.

3.5 Fluorine-19 nuclear magnetic resonance

Nuclear magnetic resonance (NMR) spectroscopy using the fluorine-19 isotope can be used to provide quantitative and structural information of PFAS in environmental samples and quantify total organic fluorine by integrating peaks associated with compounds containing a carbon–fluorine bond. This technique has been used to measure PFAS in lake water (Gauthier and Mabury, 2023), surface water (Moody et al., 2001), groundwater (Anderson et al., 2018), rainwater (Ellis et al., 2000), wastewater (Camdzic et al., 2023), and drinking water (Gauthier and Mabury, 2022). Some studies have reported LOQs suitable for analysis in drinking water (i.e., in the ng/L range) (Ellis et al., 2000; Gauthier and Mabury, 2022).

3.6 Particle induced gamma ray emission spectroscopy

Particle induced gamma ray emission (PIGE) spectroscopy uses a proton beam directed onto the sample to excite fluorine nuclei from PFAS molecules and produce gamma-rays that are measured by a detector. The obtained spectrum includes a fluorine peak from which the fluorine concentration can be determined. Tighe et al. (2021) applied this technique to measure total fluorine in water samples. The procedure involved extraction of fluorine by gravity filtration of the sample through an activated carbon felt, followed by analysis of total fluorine by means of PIGE spectroscopy. After analysis, the carbon felt was washed with HNO₃ to remove potential inorganic fluorine interferences, and analysed again to provide a measure of total organic fluorine. However, this procedure is expected to results in the removal of short-chain PFAS (C < 4) as well. Authors reported LOQ of 50 ng of F/L (equivalent to approximately ~70 ng/L of PFOA), but declared that levels of 10 ng of F/L (~15 ng/L of PFOA) may be achieved by filtering larger volumes of sample.

Technique	Advantages	Limitations
TOF	Inclusive	Poor selectivity
	Quantitative	Poor sensitivity
		Requires dedicated instrumentation
		No structural information
TOP assay	Selective	Less inclusive
	Sensitive	Requires multiple chromatographic
	Quantitative	approaches
	Compatible with common instrumentation	No structural information
SNTS	Enables structural elucidation	Time consuming data analysis
	Selective	Requires different ionization sources
	Inclusive	Requires multiple chromatographic
	Sensitive	approaches
		Requires dedicated instrumentation
		Semi-quantitative
NMR	Enables structural elucidation	Requires dedicated instrumentation that
	Inclusive	is typically not available in commercial
	Sensitive	laboratories
	Quantitative	
PIGE	Inclusive	Requires dedicated instrumentation that
	Sensitive	is typically not available in commercial
	Quantitative	laboratories
		No structural information

Table 7. Advantages and limitations of analytical techniques used for PFAS analysis (see legend below with explanations of terms).

Legend:

Inclusive: enables to include as many PFAS as possible.

Selective: enables to selectively target PFAS (and not generic organic fluorine).

Sensitive: provides detection limits suitable for analysis of relatively uncontaminated samples (e.g., drinking water). Quantitative: enables to accurately determine the analyte concentration (fluorine or individual PFAS compounds).

4 Comprehensive assessment of PFAS in water

4.1 Fluorine mass balance

In this chapter, we describe a framework that aims to close the fluorine mass balance and provide a comprehensive assessment of PFAS contamination in water samples. Our approach is based on the assumption that all the organic fluorine measured in the sample originates from PFAS. A tiered assessment framework, relying on different analytical techniques, determines whether the organic fluorine detected can be explained by PFAS measurements using a mass balance approach. In case the fluorine content deduced by PFAS measurements does not explain the total organic fluorine content, more in-depth investigations are suggested.

Due to the broad diversity of PFAS, a one-fit-all approach for determining the overall content of PFAS in a sample does not currently exist. As a result, a combination of different analytical techniques that allow to comprehensively cover the PFAS 'chemical space' is needed. This is relevant not only for environmental quality assessment, but also in the growing sector of remediation and destruction techniques, where the assessment of PFAS destruction/mineralization is hampered by the various (unknown) transformation products that result from such destruction processes, which require the use of different analytical techniques to be determined (Smith et al., 2024).

4.2 Combining multiple analytical techniques

The need for combining multiple analytical techniques was demonstrated in a recent study conducted on wastewater and surface water samples collected in the Netherlands (Amato and Vughs, 2024). The study compared targeted analysis with the TOP assay and AOF to assess the added value of including additional analytical methods to assess the occurrence of PFAS. A considerable increase in PFCA concentrations (> 60%) was observed after TOP assay in 30% and 40% of wastewater and surface water samples, respectively. This increase could not be explained by the precursors already included in the targeted method, indicating the presence of additional precursors in the samples. Organic fluorine concentrations measured by AOF were often higher than those estimated by targeted analysis, including TOP assay, suggesting that PFAS may be potentially overlooked by these analyses. In 27% of the samples, targeted analysis measured higher levels of organic fluorine than AOF, but exclusively when TFA (and in one case also TFMS) was included in the targeted method. This confirmed that AOF does not detect TFA, and similarly, neither other ultrashort-chain PFAS. In addition, AOF measurements were below the detection limit in 12% of the samples, highlighting the relatively poor sensitivity of this technique. A study focusing on municipal wastewater found that PFAS with perfluoroalkyl chain lengths ranging from approximately 5 to 14 carbon atoms accounted for a fraction $(\sim 2\%)$ of the organic fluorine measured using EOF (Spaan et al., 2023). Following suspect screening analysis using HRMS, a substantial portion of this fraction was ascribed to pharmaceuticals and pesticides – including ticagrelor transformation products (4.0%), ezetimibe (3.9%), and bicalutamide (3.5%) – which were annotated with high level of confidence. However, of the 31 detected targets and suspects, 8 compounds did not meet the OECD definition of PFAS, indicating that a relevant portions of organic fluorine may not be PFAS.

This approach is inherently conservative and aims at detecting the largest portion of PFAS possible. However, methods for the assessment of total organic fluorine may not be adequate in case samples are characterised by relatively low contamination levels, and other more sensitive (yet less inclusive) approaches, such as the TOP assay, are a better alternative to expand the assessment of PFAS. Thus, we suggest two different assessment methods based on the type of sample: 'Assessment A' for samples expected to contain relatively high contamination levels, and 'Assessment B' for samples expected to contain lower levels of contamination (Figure 8).

An additional distinction is made for ultrashort-chain PFAS, which require specific analytical methods due to their unique physicochemical properties (Section 3.1.1.2). For these compounds, a separate but similar framework is recommended, using EOF instead of AOF and MM chromatography instead of RP chromatography (Figure 8). It should also be noted that the method proposed here is primarily focused on negatively charged species. As a result, neutral and positively-charged molecules, which are not ionized by ESI or extracted by WAX, will be missed (see section 3.1.2). To prevent this, the use of GC-MS has been included in the last tier of the assessment. In general, monitoring data on neutral and positively-charged PFAS, including pharmaceuticals, is currently limited and requires further investigation.



Figure 8. Overview of analytical approaches recommended for different matrixes and PFAS with more or fewer than 4 carbon atoms.

The development of techniques that can separate compounds with largely varying polarities may enable the simultaneous assessment of PFAS and ultrashort-chain PFAS. For instance, two-dimensional LC combining RP and hydrophilic interaction liquid chromatography (HILIC) or supercritical fluid chromatography coupled with hydrophilic interaction liquid chromatography (SFC-HILIC) may be useful for such application (Amato et al., 2024b; Neuwald et al., 2021).

4.3 Assessment A: surface water, WWTP influents and effluents

4.3.1 PFAS (C ≥ 4)

<u>Tier 1. Σ PFAS + AOF</u>. This tier focuses on the comparison between the sum of targeted PFAS (Σ PFAS) and AOF (upon conversion of Σ PFAS into equivalent fluorine concentrations) (Figure 9). The comparison allows to perform an initial fluorine mass balance which can be used to assess the extent to which the targeted analysis is approaching the AOF content in the sample. For instance, in case the targeted analysis explains > 80% of the AOF content, no further investigations are required. In contrast, if > 20% of the AOF content is unexplained, more investigations are needed. We suggest a threshold of 80%, however, this should be adjusted based on the level of contamination in the water (i.e., 20% may still correspond to potentially harmful levels of organic fluorine) and its intended use (e.g., drinking water, agricultural irrigation, etc.).

<u>Tier 2. TOP assay.</u> In case the targeted analysis does not explain the total organic fluorine detected in the sample, the TOP assay is performed. This analysis aims to detect the presence of PFAA precursors that may account for the remaining organic fluorine. If the presence of precursors explains the missing fraction of total organic fluorine in the sample, the mass balance is closed. However, the identity of these precursors remains unknown. In case the cumulative fluorine content estimated using targeted analysis and the TOP assay is still lower than 80% of the fluorine content measured by AOF, more analyses are needed.

<u>Tier 3. Suspect and non-targeted screening with LC-HRMS.</u> This tier relies on the use of SNTS analysis to (i) (tentatively) identify precursors detected in Tier 2, and/or (ii) further characterize the missing fraction of organic fluorine that was not explained in the previous tier. Using tentative annotation followed by semi-quantitative analysis of suspect and unknown PFAS, this approach provides a means to understand what other fluorinated compounds might be present in the sample. However, semi-quantification for PFAS is very approximative and based on reporting concentrations as equivalents of standard compound. If the precursors have very different structures/ionisation efficiencies compared to the standard compound (typically a legacy PFAS) large uncertainties can be expected.

This method allows to investigate the chemical structure and thereby the 'identity' of the compounds that contribute to the observed difference in fluorine mass balance. Because HRMS provides an exact mass from which a unique chemical formula can be inferred, compounds containing C-F bonds can be detected and quantified for comparison with AOF-derived fluorine levels, provided that reference standards for these compounds are available or can be synthesised. Semi-quantification based on HRMS results is also possible, however this provides indicative results at best, given that more advanced methods specifically developed to estimate concentration of fluorinated compounds detected with SNTS are currently still lacking.

Tier 4. Suspect and non-targeted screening with GC-HRMS (or different ionization sources). The lack of agreement between LC-MS-based approaches and total organic fluorine measurements may be due to the presence of compounds that are not efficiently ionized by electrospray ionization (ESI), such as neutral or positively-charged PFAS. Volatile and neutral PFAS can be analysed and ionised more efficiently by GC coupled with electron ionisation and mass spectrometry. If the cumulative fluorine estimated thus far using varying analytical techniques does not contribute to at least 80% of the organic fluorine content, the use of ¹⁹F-NMR or alternative ionization sources (e.g., APCI or soft ionization by chemical reaction in transfer (SICRIT®)) may be considered.



Figure 9. Decision tree suggested in Assessment A. Note that SNTS-derived fluorine concentrations are rough estimates, and the comparison with AOF should be viewed as indicative. A 20% difference between AOF and F equivalents estimated by other techniques could be used as trigger for further investigations (i.e., to move to the following tier level), although this threshold should be adjusted based on the level of contamination in the water (i.e., 20% may still correspond to potentially harmful levels of organic fluorine) and its intended use (e.g., drinking water, agricultural irrigation, etc.).

4.3.1 PFAS (C < 4)

The assessment for PFAS with fewer than 4 carbon atoms follows the same procedure used for PFAS with 4 or more carbon atoms, except that AOF is replaced by EOF. Because EOF is not selective for neutral compounds, Tier 4 should be excluded from the assessment. However, neutral ultrashort-chain PFAS (or organic fluorine) are expected to be highly volatile and thus scarcely present in water.

4.4 Assessment B: surface water, groundwater and drinking water

Assessment B is identical to Assessment A, expect that AOF and EOF are replaced by the TOP assay (Figure 10). This is due to the high LOQ of the CIC used for AOF and EOF analyses, which is not adequate for relatively uncontaminated samples such as drinking water and groundwater (and in some cases also surface water). Pelch et al. (2023) applied the TOP assay to drinking water and detected more PFAS in 3 out of 11 samples. The authors also reported increased reporting limits for the TOP assay (due to matrix effects), suggesting that this approach may be more suitable for more contaminated samples. Inconsistencies were also observed by Amato and Vughs (2024), who found lower concentrations after the TOP assay compared to before, but only in 4 out of 33 samples of surface water and wastewater. While the TOP assay proved useful for surface water and wastewater, further research is needed to better assess the benefits of the TOP assay for drinking water. Until more evidence are available, we recommend to perform both TOP assay and SNTS as initial tier of assessment for a better understanding of drinking water contamination.

Tier 1

Tier 2

Tier 3

HRMS (C \ge 4)

Mass balance

(SNTS and TOP)



Most

precursors are

identified

amenable PFAS

A substantial portion of

precursors is not amenable by

the LC/GC-MS used; other

Figure 10. Decision tree suggested in Assessment B. Note that SNTS-derived fluorine concentrations are rough estimates, and the comparison with AOF should be viewed as indicative. A 20% difference between AOF and F equivalents estimated by other techniques could be used as trigger for further investigations (i.e., to move to the following tier level), although this threshold should be adjusted based on the level of contamination in the water (i.e., 20% may still correspond to potentially harmful levels of organic fluorine) and its intended use (e.g., drinking water, agricultural irrigation, etc.).

 $SNTS \simeq TOP$

5 Conclusions and recommendations

5.1 Conclusions

The investigation of 'hidden PFAS', via the review of use categories and potentially overlooked sources of PFAS, indicated that several classes of contaminants, such as pesticides, pharmaceuticals, fluoropolymers and hydrofluorocarbons, may be currently overlooked as potential contributors to the total PFAS loads in the environment. Atmospheric deposition also appeared to be a mechanism that is potentially underestimated, which may contribute to significant levels in surface water and groundwater, even in areas where contamination is not expected due to the absence of localized sources.

Due to their diversity, the comprehensive assessment of PFAS in water requires the use of additional analytical methods other than conventional targeted analysis. The TOP assay is a suitable candidate as it enables to selectively target PFAS precursors and relies on procedures that can be rapidly implemented in routine laboratories. However, the fraction of organic fluorine measured by AOF may exceed that of the TOP assay. This was recently supported by a study conducted in the Netherlands, which identified the AOF fraction as the most abundant in surface water and wastewater. While the TOP assay and AOF provide a broader picture of PFAS contamination, both methods do not provide information on the individual components that contribute to this fraction, which requires further analysis by suspect and non-targeted screening. Furthermore, these methods result in the loss of compound-specific information such as persistence, mobility and toxicity (PMT). Furthermore, substantial amounts of ultrashort-chain PFAS (mainly TFA, TFMS and PFPrA), as well as neutral and positively-charged compounds, are also neglected by conventional methods that are not able to detect these compounds (e.g., RP-LC-ESI-MS) and require warrant research.

To assist with the development of a comprehensive monitoring strategy for the assessment of PFAS, we provided a tiered-assessment framework that accounts for several types of matrixes, molecules, and detection limits. This assessment is based on a fluorine mass balance analysis and can be used to reduce the exposure to unknown PFAS and ensure safe levels in drinking water. This requires a combination of multiple analytical techniques.

The review of BTO reports and the scientific literature identified 14 unmonitored PFAS that may potentially occur in drinking water sources. These compounds – measurable using methods available at drinking water laboratories and/or KWR – may be selected for preliminary screening and future inclusion in routine monitoring programmes in the Netherlands (Table 8). Some of these substances are already known and others have been selected using screening methods and still require formal identification.

5.2 Recommendations

Based on the results of this study, we recommend all use categories to be investigated for overlooked sources, assess mass transfer across different environmental compartments, and evaluate environmental risks to underpin restriction policy. Among the PFAS sources identified, atmospheric deposition may be potentially underestimated and should be further investigated. The list of potentially overlooked PFAS compounds may also be further improved by adding compounds listed in discharge permits of known emitters, such as PFAS manufacturers. In the Netherlands (Drinkwaterbesluit), the parameter 'sum of PFAS' is adopted for monitoring PFAS in drinking water; however, for a more comprehensive assessment, additional investigations are needed. In Chapter 4, we proposed a tiered-assessment framework which prioritizes analytical techniques based on their analytical window and sensitivity, using the exceedance of trigger values to prompt more in-depth investigations. These investigations are intended to complement routine monitoring (for drinking water and its sources) and help assess its effectiveness. Based on this evaluation, recommendations can be made to improve monitoring where needed. It should be noted that effect-based monitoring was not discussed in more detail in this report. However, we do recommend that effect-based approaches that include a mixture effect and relate to a toxicity driven assessment.

Our advice to improve future monitoring comprises the following:

- Include ultrashort-chain PFAS in monitoring programmes due to high levels detected in both surface water and groundwater. This analysis requires the use of alternative chromatographic techniques, and should also be performed after the TOP assay to verify the presence of precursors that may be converted to targeted ultrashort-chain PFAS;
- Include a preliminary assessment of unknown PFAS using additional analytical techniques such as TOP assay, AOF and EOF to ensure adequate coverage of PFAS contamination, and explore how effect-based methods contribute. This is crucial for assessing the full extent of PFAS contamination and mitigate risks to drinking water. Organic fluorine or PFAS precursors that are excluded from conventional targeted methods are expected to occur in most drinking water sources;
- When unknown PFAS are detected, these should be formally identified using SNTS, and potentially included in routine monitoring programmes (note that identification at the highest confidential level requires availability of standard). After identification, sources and toxicity of these substances should be also assessed;
- Identify and integrate national and regional projects focusing on emission sources (of PFAS) to maximise impact. Effective source identification requires extensive information; digital technologies combined with relevant water knowledge can elucidate PFAS emission patterns and sources. We noted that considerable PFAS measurements are performed by several parties, including the Inspectorate ILT. Drinking water companies could play an active role in advocating to collate measurement data from these projects. This not only enables a more concise overview of emission and occurrence patterns, but may also feed refined assessments of potentially overlooked PFAS;
- Evaluate the impact of potentially overlooked PFAS, such as pharmaceutical and pesticides, by performing a preliminary fluorine mass balance based on the comparison between existing routine monitoring data of F-containing organic compounds and total organic fluorine measurements
- Perform a preliminary screening of the PFAS prioritized in this study (Table 8).

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Name	CAS	Structure	Analytical technique	Matrix	Source	Motivation
Perfluorooctanesulfonamid o ammonium	70225-25-1		RP-LC-MS	na	Glüge et al., 2020)	Presence in more than 10 use categories
Fluorad FC 170C	29117-08-6		RP-LC-MS	na	Glüge et al., 2020)	Presence in more than 10 use categories
Perfluoropropionic acid (PFPrA)*	422-64-0		MM-LC-MS/ RP-LC-MS	Drinking water, surface water	Amato et al., 2023b; Pelch et al., 2023 Been TKI in prep (Amato TFA)	Found in drinking water / very polar / high detection frequency in US (moderate in NL)
Perfluoro-2-methoxyacetic acid (PFMOAA)	674-13-5		RP-LC-MS	Drinking water	Pelch et al., 2023	Found in drinking water (US) / very polar
Perfluoropropanesulfonic acid (PFPrS)*	423-41-6	F F F O F F O F F O	RP-LC-MS	Drinking water	Pelch et al., 2023	Found in drinking water (US) / very polar
Perfluoro-2- methoxypropionic acid (PMPA)	13140-29-9		RP-LC-MS	Drinking water	Pelch et al., 2023	Found in drinking water (US) / very polar
3- (methoxy)tetrafluoropropi onic acid (MTP)	93449-21-9		RP-LC-MS	Drinking water	Pelch et al., 2023	Found in drinking water (US) / very polar

 Table 8. Selection of compounds to be considered for future monitoring (based on review of the scientific literature and BTO projects).

Hidden PFAS and other undefined organic fluorine

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Perfluoro-3,5- dioxahexanoic acid (PFO ₂ HxA)	39492-88-1		RP-LC-MS	Drinking water	Pelch et al., 2023	Found in drinking water (US) / polar
2,3,3,3- tetrafluoropropanoic Acid* [∆]	359-49-9	F F F F H OH	MM-LC-MS	Surface water	ILT, 2024	Included in a discharge permit application of Chemours (NL)
Trifluoromethanesulfonic acid (TFMS)*	1493-13-6	F F S O	MM-LC-MS	Drinking water, groundwater, surface water, dune-infiltrated water, river bank infiltrated water	Vughs et al., 2023(Amato et al. TFA)	Found in drinking water and multiple drinking water sources / very polar / high detection frequency (NL)
Polyfluoroctanoic acid (H- PFOA)**	na		RP-LC-MS	Surface water, (AFFF- contaminated) groundwater	Been TKI	Found in groundwater (NL)
H-PFOS**	na	F F F F F F F F F F F F F F F F F F F	RP-LC-MS	(AFFF-contaminated) groundwater, aerosols	Been TKI; Amato and Béen, 2023	Found in groundwater and coastal aerosols (NL)
2-[dimethyl-[3- (3,3,4,4,5,5,6,6,7,7,8,8,8- tridecafluorooctylsulfonyla mino)propyl]azaniumyl]ace tate (6:2 FTAB)	34455-29-3		RP-LC-MS	Raw water, groundwater, surface water, dune- infiltrated water, drinking water, aerosols	Been TKI, Amato et al., 2023b; Amato and Béen, 2023	Raw water and multiple drinking water sources (NL)
N-methylperfluorobutane sulfonamido acetic acid (MeFBSAA)	159381-10-9		RP-LC-MS	Aerosols, drinking water, groundwater, surface water	Been TKI (but what sample?); Amato et al., 2023b	Found in drinking water and multiple drinking water sources (NL)

na = not available.

Hidden PFAS and other undefined organic fluorine

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* Recently added in the method of KWR for ultrashort-chain PFAS.

** Indicative structure.

^A Also occurs as distinct isomer (2,2,3,3-TFPA, CAS: 756-09-2) which should be added to the analytical method.

References

Amato, E.D., Béen, F., 2023. Non-targeted screening of PFAS in sea-spray aerosols. KWR Water Research Institute.

- Amato, E.D., Béen, F., van Leerdam, T., Vughs, D., 2024a. Implementation of screening and NTS methods (No. BTO 2024.067). KWR Water Research Institute.
- Amato, E.D., Béen, F., Vughs, D., 2023a. PFAS in sea-spray aerosols, BTO 2023.47. KWR Water Research Institute.
- Amato, E.D., Emke, E., Meekel, N., 2024b. Inventarisatie toegevoegde waarde van SFC, BTO 2024.040. KWR Water Research Institute.
- Amato, E.D., Hockin, A., Van Leeuwen, J., 2024c. Assessment of PFAS deposition in two drinking water production sites, BTO 2024.085. KWR Water Research Institute.
- Amato, E.D., van der Grift, B., 2024. Fate of PFAS during dune infiltration, KWR 2024.044. KWR Water Research Institute.
- Amato, E.D., Vughs, D., 2024. Assessing the added value of the TOP assay and AOF in water management (No. KWR 2024.112). KWR Water Research Institute.
- Amato, E.D., Vughs, D., Kooij, P., Béen, F., 2023b. PFAS Bedreiging voor de waterketen, BTO 2023.056. KWR Water Research Institute.
- Anderson, R.H., Long, G.C., Porter, R.C., Anderson, J.K., 2018. Occurrence of Select Perfluoroalkyl Substances at US Air Force Aqueous Film-Forming Foam Release Sites Other than Fire Training Areas: Field Validation of Critical Fate and Transport Properties, in: Perfluoroalkyl Substances in the Environment. CRC Press.
- Arp, H.P.H., Gredelj, A., Glüge, J., Scheringer, M., Cousins, I.T., 2024. The Global Threat from the Irreversible Accumulation of Trifluoroacetic Acid (TFA). Environ. Sci. Technol. https://doi.org/10.1021/acs.est.4c06189
- Artsenkrant (2024) Nederland wil PFAS uit medische producten, België wacht af. Online, website accessed April 2025 link
- Ayala-Cabrera, J.F., Santos, F.J., Moyano, E., 2021. Recent advances in analytical methodologies based on mass spectrometry for the environmental analysis of halogenated organic contaminants. Trends Environ. Anal. Chem. 30, e00122. https://doi.org/10.1016/j.teac.2021.e00122
- Bach, C., Boiteux, V., Hemard, J., Colin, A., Rosin, C., Munoz, J.-F., Dauchy, X., 2016. Simultaneous determination of perfluoroalkyl iodides, perfluoroalkane sulfonamides, fluorotelomer alcohols, fluorotelomer iodides and fluorotelomer acrylates and methacrylates in water and sediments using solid-phase microextraction-gas chromatography/mass spectrometry. J. Chromatogr. A 1448, 98–106. https://doi.org/10.1016/j.chroma.2016.04.025Balgooyen, S., Remucal, C.K., 2022. Tributary Loading and Sediment Desorption as Sources of PFAS to Receiving Waters. ACS EST Water. https://doi.org/10.1021/acsestwater.1c00348
- Behnisch, P. A., Besselink, H., Weber, R., Willand, W., Huang, J., & Brouwer, A. (2021). Developing potency factors for thyroid hormone disruption by PFASs using TTR-TRβ CALUX® bioassay and assessment of PFASs mixtures in technical products. *Environment International, 157*, 106791. doi:https://doi.org/10.1016/j.envint.2021.106791Bhat, A.P., Pomerantz, W.C.K., Arnold, W.A., 2022. Finding Fluorine: Photoproduct Formation during the Photolysis of Fluorinated Pesticides. Environ. Sci. Technol. 56, 12336–12346. https://doi.org/10.1021/acs.est.2c04242
- Björnsdotter, M.K., Yeung, L.W.Y., Kärrman, A., Jogsten, I.E., 2019. Ultra-Short-Chain Perfluoroalkyl Acids Including Trifluoromethane Sulfonic Acid in Water Connected to Known and Suspected Point Sources in Sweden. Environ. Sci. Technol. 53, 11093–11101. https://doi.org/10.1021/acs.est.9b02211
- Bokkers, B., van de Ven, B., Janssen, P., 2019. Per- and polyfluoroalkyl substances (PFASs) in food contact materials. Rijksinstituut voor Volksgezondheid en Milieu RIVM. https://doi.org/10.21945/RIVM-2018-0181
- Boucher, J.M., Cousins, I.T., Scheringer, M., Hungerbühler, K., Wang, Z., 2019. Toward a Comprehensive Global Emission Inventory of C4–C10 Perfluoroalkanesulfonic Acids (PFSAs) and Related Precursors: Focus on the Life Cycle of C6- and C10-Based Products. Environ. Sci. Technol. Lett. 6, 1–7. https://doi.org/10.1021/acs.estlett.8b00531
- Buck, R.C., Franklin, J., Berger, U., Conder, J.M., Cousins, I.T., de Voogt, P., Jensen, A.A., Kannan, K., Mabury, S.A., van Leeuwen, S.P., 2011. Perfluoroalkyl and polyfluoroalkyl substances in the environment: Terminology, classification, and origins. Integr. Environ. Assess. Manag. 7, 513–541. https://doi.org/10.1002/ieam.258
- Camdzic, D., Dickman, R.A., Joyce, A.S., Wallace, J.S., Ferguson, P.L., Aga, D.S., 2023. Quantitation of Total PFAS Including Trifluoroacetic Acid with Fluorine Nuclear Magnetic Resonance Spectroscopy. Anal. Chem. 95, 5484–5488. https://doi.org/10.1021/acs.analchem.2c05354

- Cappelli, F., Ait Bamai, Y., Van Hoey, K., Kim, D.-H., Covaci, A., 2024. Occurrence of short- and ultra-short chain PFAS in drinking water from Flanders (Belgium) and implications for human exposure. Environ. Res. 260, 119753. https://doi.org/10.1016/j.envres.2024.119753
- Chandra, G., Singh, D.V., Mahato, G.K., Patel, S., 2023. Fluorine-a small magic bullet atom in the drug development: perspective to FDA approved and COVID-19 recommended drugs. Chem. Pap. 77, 4085–4106. https://doi.org/10.1007/s11696-023-02804-5
- Chen, H., Peng, H., Yang, M., Hu, J., Zhang, Y., 2017. Detection, Occurrence, and Fate of Fluorotelomer Alcohols in Municipal Wastewater Treatment Plants. Environ. Sci. Technol. 51, 8953–8961. https://doi.org/10.1021/acs.est.7b00315
- Chow, S.J., Ojeda, N., Jacangelo, J.G., Schwab, K.J., 2021. Detection of ultrashort-chain and other per- and polyfluoroalkyl substances (PFAS) in U.S. bottled water. Water Res. 201, 117292. https://doi.org/10.1016/j.watres.2021.117292
- CLM, 2024. PFAS-pesticiden en grondwater (No. CLM-publicatie: 1193).
- D'Agostino, L.A., Mabury, S.A., 2017. Certain Perfluoroalkyl and Polyfluoroalkyl Substances Associated with Aqueous Film Forming Foam Are Widespread in Canadian Surface Waters. Environ. Sci. Technol. 51, 13603–13613. https://doi.org/10.1021/acs.est.7b03994
- de Baat, M., Hoondert, R.P.J., Pronk, T.E., Ter Laak, T.L., 2023. Zijn persistente mobiele stoffen minder giftig?, BTO 2023.060. KWR Water Research Institute
- de Schepper, J. K. H., van Oorschot, Y., Jaspers, R. J., Hamers, T., Lamoree, M. H., Behnisch, P., Besselink, H., & Houtman, C. J. (2023). The contribution of PFAS to thyroid hormone-displacing activity in Dutch waters: A comparison between two in vitro bioassays with chemical analysis. *Environment International, 181*. doi:10.1016/j.envint.2023.108256
- Ding, H., Peng, H., Yang, M., Hu, J., 2012. Simultaneous determination of mono- and disubstituted polyfluoroalkyl phosphates in drinking water by liquid chromatography–electrospray tandem mass spectrometry. J. Chromatogr. A 1227, 245–252. https://doi.org/10.1016/j.chroma.2012.01.004
- Ellis, D.A., Mabury, S.A., Martin, J.W., Muir, D.C.G., 2001. Thermolysis of fluoropolymers as a potential source of halogenated organic acids in the environment. Nature 412, 321–324. https://doi.org/10.1038/35085548
- Ellis, D.A., Martin, J.W., De Silva, A.O., Mabury, S.A., Hurley, M.D., Sulbaek Andersen, M.P., Wallington, T.J., 2004. Degradation of Fluorotelomer Alcohols: A Likely Atmospheric Source of Perfluorinated Carboxylic Acids. Environ. Sci. Technol. 38, 3316–3321. https://doi.org/10.1021/es049860w
- Ellis, D.A., Martin, J.W., Muir, D.C.G., Mabury, S.A., 2000. Development of an 19F NMR Method for the Analysis of Fluorinated Acids in Environmental Water Samples. Anal. Chem. 72, 726–731. https://doi.org/10.1021/ac9910280
- European Union, 2024. Commission Notice Technical guidelines regarding methods of analysis for monitoring of per- and polyfluoroalkyl substances (PFAS) in water intended for human consumption.
- Franklin, J., 1993. The atmospheric degradation and impact of 1,1,1,2-tetrafluoroethane (hydrofluorocarbon 134a). Chemosphere 27, 1565–1601. https://doi.org/10.1016/0045-6535(93)90251-Y
- Gaines, L.G.T., 2023. Historical and current usage of per- and polyfluoroalkyl substances (PFAS): A literature review. Am. J. Ind. Med. 66, 353–378. https://doi.org/10.1002/ajim.23362
- Galloway, J.E., Moreno, A.V.P., Lindstrom, A.B., Strynar, M.J., Newton, S., May, A.A., Weavers, L.K., 2020. Evidence of Air Dispersion: HFPO–DA and PFOA in Ohio and West Virginia Surface Water and Soil near a Fluoropolymer Production Facility. Environ. Sci. Technol. 54, 7175–7184. https://doi.org/10.1021/acs.est.9b07384
- Gauthier, J.R., Mabury, S.A., 2023. Identifying Unknown Fluorine-Containing Compounds in Environmental Samples Using 19F NMR and Spectral Database Matching. Environ. Sci. Technol. 57, 8760–8767. https://doi.org/10.1021/acs.est.3c01220
- Gauthier, J.R., Mabury, S.A., 2022. Noise-Reduced Quantitative Fluorine NMR Spectroscopy Reveals the Presence of Additional Per- and Polyfluorinated Alkyl Substances in Environmental and Biological Samples When Compared with Routine Mass Spectrometry Methods. Anal. Chem. 94, 3278–3286. https://doi.org/10.1021/acs.analchem.1c05107
- Geneesmiddeleninformatiebank, 2025. Geneesmiddeleninformatiebank van de Nederlandse Medicijnautoriteit CBG. https://www.geneesmiddeleninformatiebank.nl/ords/f?p=111:1:0::NO:1:P0_DOMAIN,P0_LANG:H,NL
- Glüge, J., Scheringer, M., Cousins, I.T., DeWitt, J.C., Goldenman, G., Herzke, D., Lohmann, R., Ng, C.A., Trier, X.,
 Wang, Z., 2020. An overview of the uses of per- and polyfluoroalkyl substances (PFAS). Environ. Sci.
 Process. Impacts 22, 2345–2373. https://doi.org/10.1039/D0EM00291G

Habib, A., Landa, E.N., Holbrook, K.L., Walker, W.S., Lee, W.-Y., 2023. Rapid, efficient, and green analytical technique for determination of fluorotelomer alcohol in water by stir bar sorptive extraction. Chemosphere 338, 139439. https://doi.org/10.1016/j.chemosphere.2023.139439

- Hamid, H., Li, L.Y., Grace, J.R., 2020. Formation of perfluorocarboxylic acids from 6:2 fluorotelomer sulfonate (6:2 FTS) in landfill leachate: Role of microbial communities. Environ. Pollut. 259, 113835. https://doi.org/10.1016/j.envpol.2019.113835
- Hammel, E., Webster, T.F., Gurney, R., Heiger-Bernays, W., 2022. Implications of PFAS definitions using fluorinated pharmaceuticals. iScience 25, 104020. https://doi.org/10.1016/j.isci.2022.104020
- Han, Y., Pulikkal, V.F., Sun, M., 2021. Comprehensive Validation of the Adsorbable Organic Fluorine Analysis and Performance Comparison of Current Methods for Total Per- and Polyfluoroalkyl Substances in Water Samples. ACS EST Water 1, 1474–1482. https://doi.org/10.1021/acsestwater.1c00047
- Henne, S., Shallcross, D.E., Reimann, S., Xiao, P., Brunner, D., O'Doherty, S., Buchmann, B., 2012. Future Emissions and Atmospheric Fate of HFC-1234yf from Mobile Air Conditioners in Europe. Environ. Sci. Technol. 46, 1650–1658. https://doi.org/10.1021/es2034608
- Henry, B.J., Carlin, J.P., Hammerschmidt, J.A., Buck, R.C., Buxton, L.W., Fiedler, H., Seed, J., Hernandez, O., 2018. A critical review of the application of polymer of low concern and regulatory criteria to fluoropolymers. Integr. Environ. Assess. Manag. 14, 316–334. https://doi.org/10.1002/ieam.4035
- Hofman-Caris, R., 2024. PFAS-verwijdering uit drinkwater; overzicht van literatuur en kooldata uit de praktijk (No. BTO 2024.037). KWR Water Research Institute.
- Hofman-Caris, R., Harmsen, D., Siegers, W., 2024. Geavanceerde reductie en anodische oxidatie voor de verwijdering van PFAS uit concentraatstromen (No. BTO 2024.002). KWR Water Research Institute.
- Hoondert, R.P.J., de Baat, M., Yanagihara, M., Ter Laak, T., 2023. A deeper understanding of PMOC toxicity, BTO 2023.086. KWR Water Research Institute.
- IenW, 2024. Enkele moties en ontwikkelingen ten aanzien van PFAS.
- ILT, 2024. Aanvraag Chemours omgevingsvergunning lozingseisen DFA, PFPrA en TFPrA, OLO nummer: 8294501, DCMR zaaknummer: 2408853.
- Inoue, M., Sumii, Y., Shibata, N., 2020. Contribution of Organofluorine Compounds to Pharmaceuticals. ACS Omega. https://doi.org/10.1021/acsomega.0c00830
- Jeschke, P., 2017. Latest generation of halogen-containing pesticides. Pest Manag. Sci. 73, 1053–1066. https://doi.org/10.1002/ps.4540
- Jia, Y., Shan, C., Fu, W., Wei, S., Pan, B., 2023. Occurrences and fates of per- and polyfluoralkyl substances in textile dyeing wastewater along full-scale treatment processes. Water Res. 242, 120289. https://doi.org/10.1016/j.watres.2023.120289
- Joerss, H., Freeling, F., van Leeuwen, S., Hollender, J., Liu, X., Nödler, K., Wang, Z., Yu, B., Zahn, D., Sigmund, G., 2024. Pesticides can be a substantial source of trifluoroacetate (TFA) to water resources. Environ. Int. 193, 109061. https://doi.org/10.1016/j.envint.2024.109061
- KEGG, 2024. KEGG DRUG Database. https://www.genome.jp/kegg/drug/
- KEGG, 2023. KEGG COMPOUND Database. https://www.genome.jp/kegg/compound/
- Korzeniowski, S.H., Buck, R.C., Newkold, R.M., Kassmi, A.E., Laganis, E., Matsuoka, Y., Dinelli, B., Beauchet, S., Adamsky, F., Weilandt, K., Soni, V.K., Kapoor, D., Gunasekar, P., Malvasi, M., Brinati, G., Musio, S., 2023. A critical review of the application of polymer of low concern regulatory criteria to fluoropolymers II: Fluoroplastics and fluoroelastomers. Integr. Environ. Assess. Manag. 19, 326–354. https://doi.org/10.1002/ieam.4646
- Liu, S., Junaid, M., Zhong, W., Zhu, Y., Xu, N., 2020. A sensitive method for simultaneous determination of 12 classes of per- and polyfluoroalkyl substances (PFASs) in groundwater by ultrahigh performance liquid chromatography coupled with quadrupole orbitrap high resolution mass spectrometry. Chemosphere 251, 126327. https://doi.org/10.1016/j.chemosphere.2020.126327
- Liu, Y., Robey, N.M., Bowden, J.A., Tolaymat, T.M., da Silva, B.F., Solo-Gabriele, H.M., Townsend, T.G., 2021. From Waste Collection Vehicles to Landfills: Indication of Per- and Polyfluoroalkyl Substance (PFAS) Transformation. Environ. Sci. Technol. Lett. 8, 66–72. https://doi.org/10.1021/acs.estlett.0c00819
- Lohmann, R., Cousins, I.T., DeWitt, J.C., Glüge, J., Goldenman, G., Herzke, D., Lindstrom, A.B., Miller, M.F., Ng, C.A., Patton, S., Scheringer, M., Trier, X., Wang, Z., 2020. Are Fluoropolymers Really of Low Concern for Human and Environmental Health and Separate from Other PFAS? Environ. Sci. Technol. 54, 12820–12828. https://doi.org/10.1021/acs.est.0c03244

- Lohmann, R., Letcher, R.J., 2023. The universe of fluorinated polymers and polymeric substances and potential environmental impacts and concerns. Curr. Opin. Green Sustain. Chem. 41, 100795. https://doi.org/10.1016/j.cogsc.2023.100795
- Ma, C., Peng, H., Chen, H., Shang, W., Zheng, X., Yang, M., Zhang, Y., 2022. Long-term trends of fluorotelomer alcohols in a wastewater treatment plant impacted by textile manufacturing industry. Chemosphere 299, 134442. https://doi.org/10.1016/j.chemosphere.2022.134442
- Meanwell, N.A., 2011. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. J. Med. Chem. 54, 2529–2591. https://doi.org/10.1021/jm1013693
- Moody, C.A., Kwan, W.C., Martin, J.W., Muir, D.C.G., Mabury, S.A., 2001. Determination of Perfluorinated Surfactants in Surface Water Samples by Two Independent Analytical Techniques: Liquid Chromatography/Tandem Mass Spectrometry and 19F NMR. Anal. Chem. 73, 2200–2206. https://doi.org/10.1021/ac0100648
- Neuwald, I., Muschket, M., Zahn, D., Berger, U., Seiwert, B., Meier, T., Kuckelkorn, J., Strobel, C., Knepper, T.P., Reemtsma, T., 2021. Filling the knowledge gap: A suspect screening study for 1310 potentially persistent and mobile chemicals with SFC- and HILIC-HRMS in two German river systems. Water Res. 204, 117645. https://doi.org/10.1016/j.watres.2021.117645
- Neuwald, I.J., Hübner, D., Wiegand, H.L., Valkov, V., Borchers, U., Nödler, K., Scheurer, M., Hale, S.E., Arp, H.P.H., Zahn, D., 2022. Ultra-Short-Chain PFASs in the Sources of German Drinking Water: Prevalent, Overlooked, Difficult to Remove, and Unregulated. Environ. Sci. Technol. 56, 6380–6390. https://doi.org/10.1021/acs.est.1c07949
- Ogawa, Y., Tokunaga, E., Kobayashi, O., Hirai, K., Shibata, N., 2020. Current Contributions of Organofluorine Compounds to the Agrochemical Industry. iScience 23, 101467. https://doi.org/10.1016/j.isci.2020.101467
- Pelch, K.E., McKnight, T., Reade, A., 2023. 70 analyte PFAS test method highlights need for expanded testing of PFAS in drinking water. Sci. Total Environ. 876, 162978. https://doi.org/10.1016/j.scitotenv.2023.162978
- Portolés, T., Rosales, L.E., Sancho, J.V., Santos, F.J., Moyano, E., 2015. Gas chromatography–tandem mass spectrometry with atmospheric pressure chemical ionization for fluorotelomer alcohols and perfluorinated sulfonamides determination. J. Chromatogr. A 1413, 107–116. https://doi.org/10.1016/j.chroma.2015.08.016
- Purser, S., Moore, P.R., Swallow, S., Gouverneur, V., 2008. Fluorine in medicinal chemistry. Chem. Soc. Rev. 37, 320–330. https://doi.org/10.1039/B610213C
- Rensmo, A., K. Savvidou, E., T. Cousins, I., Hu, X., Schellenberger, S., P. Benskin, J., 2023. Lithium-ion battery recycling: a source of per- and polyfluoroalkyl substances (PFAS) to the environment? Environ. Sci. Process. Impacts 25, 1015–1030. https://doi.org/10.1039/D2EM00511E
- RIVM, 2023. PFAS in medische producten (No. Memo GZB 2023-0026).
- Russell, M.H., Hoogeweg, G., Webster, E.M., Ellis, D.A., Waterland, R.L., Hoke, R.A., 2012. TFA from HFO-1234yf: Accumulation and aquatic risk in terminal water bodies. Environ. Toxicol. Chem. 31, 1957–1965. https://doi.org/10.1002/etc.1925
- Sands, M., Zhang, X., gal, A., Laws, M., Spinella, M., Erdogan, Z.-M., Irudayaraj, J., 2024. Comparative hepatotoxicity of novel lithium bis(trifluoromethanesulfonyl)imide (LiTFSI, ie. HQ-115) and legacy Perfluorooctanoic acid (PFOA) in male mice: Insights into epigenetic mechanisms and pathway-specific responses. Environ. Int. 185, 108556. https://doi.org/10.1016/j.envint.2024.108556
- Schaefer, C.E., Hooper, J.L., Strom, L.E., Abusallout, I., Dickenson, E.R.V., Thompson, K.A., Mohan, G.R., Drennan, D., Wu, K., Guelfo, J.L., 2023. Occurrence of quantifiable and semi-quantifiable poly- and perfluoroalkyl substances in united states wastewater treatment plants. Water Res. 233, 119724. https://doi.org/10.1016/j.watres.2023.119724
- Schellenberger, S., Jönsson, C., Mellin, P., Levenstam, O.A., Liagkouridis, I., Ribbenstedt, A., Hanning, A.-C., Schultes,
 L., Plassmann, M.M., Persson, C., Cousins, I.T., Benskin, J.P., 2019. Release of Side-Chain Fluorinated
 Polymer-Containing Microplastic Fibers from Functional Textiles During Washing and First Estimates of
 Perfluoroalkyl Acid Emissions. Environ. Sci. Technol. 53, 14329–14338.
 https://doi.org/10.1021/acs.est.9b04165
- Scheurer, M., Nödler, K., Freeling, F., Janda, J., Happel, O., Riegel, M., Müller, U., Storck, F.R., Fleig, M., Lange, F.T., Brunsch, A., Brauch, H.-J., 2017. Small, mobile, persistent: Trifluoroacetate in the water cycle – Overlooked sources, pathways, and consequences for drinking water supply. Water Res. 126, 460–471. https://doi.org/10.1016/j.watres.2017.09.045

- Schroeder, T., Bond, D., Foley, J., 2021. PFAS soil and groundwater contamination via industrial airborne emission and land deposition in SW Vermont and Eastern New York State, USA. Environ. Sci. Process. Impacts 23, 291–301. https://doi.org/10.1039/D0EM00427H
- Schymanski, E., Zhang, J., Thiessen, P., Chirsir, P., Kondic, T., Bolton, E., 2023. Per- and polyfluoroalkyl substances (PFAS) in PubChem: 7 million and growing (preprint). Chemistry. https://doi.org/10.26434/chemrxiv-2023j823z
- Seay, B.A., Dasu, K., MacGregor, I.C., Austin, M.P., Krile, R.T., Frank, A.J., Fenton, G.A., Heiss, D.R., Williamson, R.J., Buehler, S., 2023. Per- and polyfluoroalkyl substances fate and transport at a wastewater treatment plant with a collocated sewage sludge incinerator. Sci. Total Environ. 874, 162357. https://doi.org/10.1016/j.scitotenv.2023.162357
- Sha, B., Johansson, J.H., Tunved, P., Bohlin-Nizzetto, P., Cousins, I.T., Salter, M.E., 2022. Sea Spray Aerosol (SSA) as a Source of Perfluoroalkyl Acids (PFAAs) to the Atmosphere: Field Evidence from Long-Term Air Monitoring. Environ. Sci. Technol. 56, 228–238. https://doi.org/10.1021/acs.est.1c04277
- Shabir, G., Saeed, A., Zahid, W., Naseer, F., Riaz, Z., Khalil, N., Muneeba, null, Albericio, F., 2023. Chemistry and Pharmacology of Fluorinated Drugs Approved by the FDA (2016-2022). Pharm. Basel Switz. 16, 1162. https://doi.org/10.3390/ph16081162
- Shimizu, M.S., Mott, R., Potter, A., Zhou, J., Baumann, K., Surratt, J.D., Turpin, B., Avery, G.B., Harfmann, J., Kieber, R.J., Mead, R.N., Skrabal, S.A., Willey, J.D., 2021. Atmospheric Deposition and Annual Flux of Legacy Perfluoroalkyl Substances and Replacement Perfluoroalkyl Ether Carboxylic Acids in Wilmington, NC, USA. Environ. Sci. Technol. Lett. 8, 366–372. https://doi.org/10.1021/acs.estlett.1c00251
- Smith, S.J., Lauria, M., Higgins, C.P., Pennell, K.D., Blotevogel, J., Arp, H.P.H., 2024. The Need to Include a Fluorine Mass Balance in the Development of Effective Technologies for PFAS Destruction. Environ. Sci. Technol. 58, 2587–2590. https://doi.org/10.1021/acs.est.3c10617
- Spaan, K.M., Seilitz, F., Plassmann, M.M., de Wit, C.A., Benskin, J.P., 2023. Pharmaceuticals Account for a Significant Proportion of the Extractable Organic Fluorine in Municipal Wastewater Treatment Plant Sludge. Environ. Sci. Technol. Lett. 10, 328–336. https://doi.org/10.1021/acs.estlett.3c00108
- Sun, M., Cui, J., Guo, J., Zhai, Z., Zuo, P., Zhang, J., 2020. Fluorochemicals biodegradation as a potential source of trifluoroacetic acid (TFA) to the environment. Chemosphere 254, 126894. https://doi.org/10.1016/j.chemosphere.2020.126894
- Tighe, M., Jin, Y., Whitehead, H.D., Hayes, K., Lieberman, M., Pannu, M., Plumlee, M.H., Peaslee, G.F., 2021. Screening for Per- and Polyfluoroalkyl Substances in Water with Particle Induced Gamma-Ray Emission Spectroscopy. ACS EST Water 1, 2477–2484. https://doi.org/10.1021/acsestwater.1c00215
- Triumph, Z., Vyas, S., 2023. Chemical bonding in potential PFAS products from the thermal degradation of energetic devices, a DFT analysis. Chemosphere 345, 140363. https://doi.org/10.1016/j.chemosphere.2023.140363
- UBA, 2022. Reducing the input of chemicals into waters: trifluoroacetate (TFA) as a persistent and mobile substance with many sources. Umweltbundesamt.
- UH, 2024. Pesticide Properties Database. University of Hertfordshire. https://sitem.herts.ac.uk/aeru/ppdb/en/index.htm
- USEPA, 2023. ORD Human Health Toxicity Value for Lithium bis [(trifluoromethyl)sulfonyl]azanide (HQ-115) (CASRN 90076-65-6 | DTXSID8044468). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-22/195F, 2023.
- Vughs, D., Meekel, N., Reus, A., Hoondert, R., 2023. Zeer polaire stoffen II: Analyse van zeer polaire stoffen in de waterketen, BTO 2023.084. KWR Water Research Institute.
- Wagner, A., Raue, B., Brauch, H.-J., Worch, E., Lange, F.T., 2013. Determination of adsorbable organic fluorine from aqueous environmental samples by adsorption to polystyrene-divinylbenzene based activated carbon and combustion ion chromatography. J. Chromatogr. A 1295, 82–89. https://doi.org/10.1016/j.chroma.2013.04.051
- Wang, J., Lin, Z., He, X., Song, M., Westerhoff, P., Doudrick, K., Hanigan, D., 2022. Critical Review of Thermal Decomposition of Per- and Polyfluoroalkyl Substances: Mechanisms and Implications for Thermal Treatment Processes. Environ. Sci. Technol. 56, 5355–5370. https://doi.org/10.1021/acs.est.2c02251
- Wang, Q., Bian, Y., Dhawan, G., Zhang, W., Sorochinsky, A.E., Makarem, A., Soloshonok, V.A., Han, J., 2024. FDA approved fluorine-containing drugs in 2023. Chin. Chem. Lett. 35, 109780. https://doi.org/10.1016/j.cclet.2024.109780
- Wang, Y., Liu, L., Qiao, X., Sun, M., Guo, J., Zhang, J., Zhao, B., 2023. Projections of National-Gridded Emissions of Hydrofluoroolefins (HFOs) in China. Environ. Sci. Technol. 57, 8650–8659. https://doi.org/10.1021/acs.est.2c09263

Classificatie: Intern

- Wang, Z., Boucher, J.M., Scheringer, M., Cousins, I.T., Hungerbühler, K., 2017. Toward a Comprehensive Global Emission Inventory of C4–C10 Perfluoroalkanesulfonic Acids (PFSAs) and Related Precursors: Focus on the Life Cycle of C8-Based Products and Ongoing Industrial Transition. Environ. Sci. Technol. 51, 4482–4493. https://doi.org/10.1021/acs.est.6b06191
- Wang, Z., Buser, A.M., Cousins, I.T., Demattio, S., Drost, W., Johansson, O., Ohno, K., Patlewicz, G., Richard, A.M., Walker, G.W., White, G.S., Leinala, E., 2021. A New OECD Definition for Per- and Polyfluoroalkyl Substances. Environ. Sci. Technol. 55, 15575–15578. https://doi.org/10.1021/acs.est.1c06896
- Wang, Z., Cousins, I.T., Scheringer, M., Buck, R.C., Hungerbühler, K., 2014. Global emission inventories for C4–C14 perfluoroalkyl carboxylic acid (PFCA) homologues from 1951 to 2030, part II: The remaining pieces of the puzzle. Environ. Int. 69, 166–176. https://doi.org/10.1016/j.envint.2014.04.006
- Washington, J.W., Ellington, J.J., Jenkins, T.M., Evans, J.J., Yoo, H., Hafner, S.C., 2009. Degradability of an Acrylate-Linked, Fluorotelomer Polymer in Soil. Environ. Sci. Technol. 43, 6617–6623. https://doi.org/10.1021/es9002668
- Weitz, K., Kantner, D., Kessler, A., Key, H., Larson, J., Bodnar, W., Parvathikar, S., Davis, L., Robey, N., Taylor, P., De la Cruz, F., Tolaymat, T., Weber, N., Linak, W., Krug, J., Phelps, L., 2024. Review of per- and poly-fluoroalkyl treatment in combustion-based thermal waste systems in the United States. Sci. Total Environ. 932, 172658. https://doi.org/10.1016/j.scitotenv.2024.172658
- Winchell, L.J., Wells, M.J.M., Ross, J.J., Kakar, F., Teymouri, A., Gonzalez, D.J., Dangtran, K., Bessler, S.M., Carlson, S., Almansa, X.F., Norton Jr, J.W., Bell, K.Y., 2024. Fate of perfluoroalkyl and polyfluoroalkyl substances (PFAS) through two full-scale wastewater sludge incinerators. Water Environ. Res. 96, e11009. https://doi.org/10.1002/wer.11009
- Zhang, C., Hopkins, Z.R., McCord, J., Strynar, M.J., Knappe, D.R.U., 2019. Fate of Per- and Polyfluoroalkyl Ether Acids in the Total Oxidizable Precursor Assay and Implications for the Analysis of Impacted Water. Environ. Sci. Technol. Lett. 6, 662–668. https://doi.org/10.1021/acs.estlett.9b00525
- Zhang, Y., Meng, J., Zhou, Y., Song, N., Zhao, Y., Hong, M., Yu, J., Cao, L., Dou, Y., Kong, D., 2024. Transport and health risk of legacy and emerging *per*-and polyfluoroalkyl substances in the water cycle in an urban area, China: Polyfluoroalkyl phosphate esters are of concern. Sci. Total Environ. 920, 171010. https://doi.org/10.1016/j.scitotenv.2024.171010