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Review

A systematic review for non-targeted analysis of per- and polyfluoroalkyl substances (PFAS)

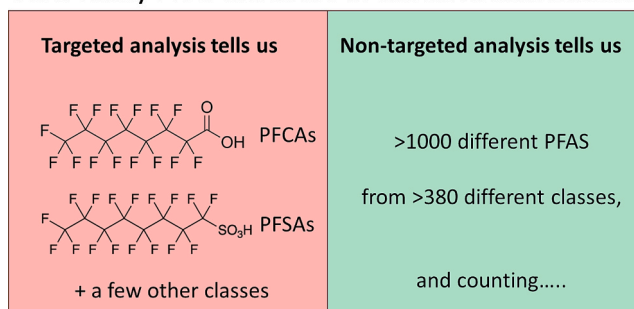
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HIGHLIGHTS

- Systematic review of 115 NTA PFAS manuscripts
- Over 1000 PFAS from 382 classes reported in the literature
- PFCAs and PFSAs are the most commonly reported PFAS.
- More than 95 % of studies conducted in the Northern Hemisphere
- Except for AFFF, commercial and industrial products remain understudied.

GRAPHICAL ABSTRACT

How many PFAS are there in the environment.....?



ARTICLE INFO

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Keywords

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 Suspect screening
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ABSTRACT

This review follows the PRISMA guidelines to provide a systematic review of 115 peer reviewed articles that used non-targeted analysis (NTA) methods to detect per- and polyfluoroalkylated substances (PFAS). This literature highlights the significant positive impact of NTA in understanding PFAS in the environment. Within the literature a geographical bias exists, with most NTA studies (~60 %) conducted in the United States and China. Future studies in other regions (such as South America and Africa) are needed to gain a more global understanding. More research is required in marine environments and the atmosphere, as current studies focus mainly on freshwater, groundwater, soil, and sediments. The majority of studies focus on measuring PFAS in the environment, rather than in commercial products (with the exception of AFFF). Non-lethal blood sampling has been successful for NTA in humans and wildlife, but additional biomonitoring studies are required on exposed cohorts to understand health risks and PFAS biotransformation pathways. NTA methods mostly use liquid chromatography and negative ionisation, which biases the literature towards the detection of specific PFAS. Despite improvements in data reporting and quality assurance and control (QA/QC) procedures, factors such as false

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negative and false positive rates are often overlooked, and many NTA workflows remain highly subjective. Perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulfonic acids (PFASs) are the most detected PFAS classes, identified in over 80 % of NTA studies, and are common in routine monitoring. However, our review identified >1000 PFAS from a total of 382 different PFAS classes, with over 300 classes found in fewer than 5 % of studies. This highlights the variety of different PFAS present in the environment, and the limitations of relying solely on targeted methods. Future monitoring programs and regulations would benefit from considering NTA methods to provide more comprehensive information on PFAS present in the environment.

1. Introduction

Per- and poly-fluoroalkyl substances (PFAS), although beneficial to mankind, have resulted in widespread contamination of the environment and bioaccumulation in humans and wildlife. PFAS have been integrated into industrial and commercial products due to their desirable properties (including chemical and thermal stability, high surfactant properties, and durability) (Z. Wang et al., 2021; Organisation for Economic Co-operation Development, 2021; Buck et al., 2011). PFAS have been used for decades in a variety of different applications including firefighting foams (e.g. aqueous film-forming foams (AFFFs)), insecticides, coolants for electrical and electronic equipment, lubricants, food packaging treatments, and non-stick coatings (Teflon) (1M Company, 1999; Kissa, 1994, 2001; Taylor, 1999). Data is not available for all PFAS, but the numerous kinds that have been tested have shown resistance to natural degradation, can bioaccumulate and can exhibit toxicity. PFAS are considered ubiquitous pollutants because they are observed globally as a result of both direct and indirect environmental releases (De Silva et al., 2021; Houde et al., 2006; Sunderland et al., 2019). Due to numerous reports on the bioaccumulative nature, regulations have been implemented to reduce PFAS prevalence and exposure. PFOS, PFOA, and PFHxS are listed in the Stockholm Convention on Persistent Organic Pollutants (POPs), and “Long-chain perfluoro carboxylic acids” are currently under review. Current regulatory approaches have focused on monitoring a specific number of PFAS using targeted analytical approaches. However, there is little consistency since the list of PFAS monitored changes for different matrices and regulatory bodies. This list of detectable PFAS for routine monitoring appears to be slowly increasing in number, with the United States Environmental Protection Agency (U.S. EPA) recently finalising Method 1633, which assesses 40 PFAS, and the United Kingdom Drinking Water Inspectorate (DWI) using a list of 47 PFAS to assess risks in drinking water (Drinking Water Inspectorate, 2021; USEPA, 2024). Commercial laboratories also continue to increase their testing suites, with some labs now offering targeted analysis for up to 70 different PFAS (Eurofins, 2024). Whilst it is important to prioritise pollutants and streamline analytical methods, there have been objections to methods and regulations that only target a few PFAS. Buck et al. (2021) identified 256 commercially relevant PFAS globally (Buck et al., 2021). However, there are thousands of potential PFAS in the environment, with over 4700 PFAS identified by the OECD (Organisation for Economic Co-operation Development, 2018), and thousands of PFAS included within the U.S. EPA CompTox database (United States Environmental Protection Agency, 2024). It is therefore argued that targeted methods and regulations only monitor the tip of the PFAS iceberg. There are alternatives and complementary methods to supplement targeted PFAS methods. These include total PFAS methods such as extractable organic fluorine (EOF), absorbable organic fluorine (AOF), total oxidisable precursor assay (TOP assay), particle-induced gamma ray emission (PIGE) and fluorine-19 nuclear magnetic resonance spectroscopy (^{19}F NMR) (McDonough et al., 2019). In addition to these total PFAS methods, non-targeted analysis (NTA) is an approach used to identify individual PFAS. NTA methods can be used for targeted analysis, but also allow for detection, discovery and characterization of current and previously unidentified and emerging PFAS (Liu et al., 2019; Schymanski et al., 2021; Strynar et al., 2023). Limitations with NTA include poor inter-lab repeatability (Rostkowski et al., 2019), and issues

communicating findings (Schymanski et al., 2014). This has led to a variety of guidance documents aimed at improving data quality and communication (Hollender et al., 2023a; Schymanski et al., 2014; Peter et al., 2021; Charbonnet et al., 2022). It is important to note that all non-targeted methods have some elements of selection. This results in methods that are well optimised for some PFAS, but may exclude others. One of the most discussed instances of selection is the predominant use of negative ionisation, which can exclude neutral PFAS and PFAS detectable in positive ESI mode (ESI+) (Barzen-Hanson et al., 2017b). However, section processes can also occur during sample collection, extraction, cleanup, chromatography (or direct infusion), mass separation and detection. Once data is obtained, it can then be processed by suspect screening (which targets specific analytes in a database) or true exploratory data analysis which uses a variety of techniques to identify and classify specific compounds. With all these steps, there is some degree of subjectivity, as different research groups have their own methods and preferences (Hernandez et al., 2014; Hernández et al., 2009; Phillips et al., 2018). Numerous reviews on recent advances in the analysis of PFAS have been documented; however, these have been predominantly critical or opinion-based reviews rather than systematic reviews. These have focused on the development of analytical methods for trace levels of PFAS in varied compartments (Al Amin et al., 2020; Jahnke and Berger, 2009; Jiménez-Skrzypek et al., 2023; Strynar et al., 2023), environmental and health impacts of PFAS (Fenton et al., 2021; Panieri et al., 2022; Sunderland et al., 2019), the behaviour, source and fate, and transformation of PFAS in different environmental media (Ahrens and Bundschuh, 2014; De Silva et al., 2021; Domingo and Nadal, 2019; Kurwadkar et al., 2022; Nakayama et al., 2019; Rahman et al., 2014; Xiao, 2017; Young and Mabury, 2010), and humans (Blake and Fenton, 2020; Göckener et al., 2020; Jian et al., 2018; Liu et al., 2019). In 2019, Liu et al. (2019) published a paper on non-target discovery and characterization of PFAS in environmental and human samples. This manuscript did an excellent job of validating the importance of NTA for PFAS analysis by identifying techniques that have been used to discover >750 PFAS from over 130 different classes (Liu et al., 2019). Since the publication of that manuscript, there has been a considerable increase in the number of additional manuscripts on PFAS that have used NTA.

Within this current manuscript, we have completed a systematic review of the scientific literature to identify trends and knowledge gaps for NTA of PFAS. We have assessed publication trends in sample type (including geographical location, and sources of PFAS pollution). We reviewed analytical methods for NTA (including sample preparation, analysis, QA/QC procedures and data analysis). We have compiled results of all studies (including information on the use of confidence levels, total numbers of PFAS reported, different classes of PFAS reported, and the use of complimentary analytical methods). There have been several subtle changes to PFAS definitions throughout the last few decades; throughout this report, we use the OECD definition of PFAS. This includes any chemical containing at least one saturated CF_2 or CF_3 moiety (Organisation for Economic Co-operation Development, 2021).

2. Methodology

2.1. Study selection

This systematic review was undertaken in line with the guidelines set

by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021). Manuscripts were selected from 3 search engines: Web of Science, Scopus, and Google Scholar, using a combination of the following keywords (“PFAS” OR “per- and polyfluoroalkyl substances” OR “PFC”) AND (“non-target analysis” OR “non-target analysis” OR “non-targeted screening” OR “non-target screening” OR “suspect screening”). Google Scholar delivered over 2000 hits; therefore, only the first ten (10) pages (One hundred (100) papers) were screened.

Studies included in the review were based on the following inclusion criteria: studies published in English that performed NTA with a focus on the determination of PFAS. Studies were excluded if they did not focus on PFAS and instead performed non-targeted screening for a wide range of chemicals. In total 376 hits were recorded, 121 from Web of Science, 155 from Scopus and 100 from Google Scholar. Articles from each search engine were combined, and duplicates were removed resulting in a total of 199 articles. Fifty-two (52) articles were then excluded after reviewing the title and abstract. A further thirty-two (32) were excluded following a full review if they contained no primary data, were too broad, did not include NTA or involved NTA on a wide range of pollutants (not PFAS exclusively). This resulted in a total of 115 articles that were reviewed in full to compile the data gathered within this review (SI Fig. 1). The review process did not specifically exclude manuscripts on fluorinated polymers or fluoropolymers; however, none were identified using the final search terms. This manuscript therefore focuses on smaller PFAS molecules, and does not include fluorinated polymers or fluoropolymers.

2.2. Data collection

Data collection was performed in three main areas: 1) sample information, 2) sample analysis, and 3) data reporting. Factors including location of study, type of sample, and targeted sources of potential PFAS were recorded for sample information. Factors including extraction method, analytical method, QA/QC procedures, and data processing method were recorded for sample analysis. Factors including the number of PFAS reported by each study, different classes reported, and complementary analytical methods used were collected under data reporting. All data have been tabulated and reported in the Supplementary information (SI Table 1).

3. Sample information

3.1. Geographical location

In total, sampled media from 25 different geographical locations have been subjected to NTA for PFAS (Fig. 1). Three percent of manuscripts (3/115) did not mention sample locations and in 6 % of studies (7/115) sample location was not appropriate to record as the sample was a reference standard. The majority (59 %) of studies analysed samples obtained from either China (35 studies) or the U.S.A. (33 studies). Twenty-two percent of manuscripts included samples from Europe: Sweden (7 studies) (Haque et al., 2023b; Koch et al., 2021; Miaz et al., 2020; Rehnstam et al., 2023; Söregård et al., 2020, 2021; E. Jiao et al., 2023) and Germany (6 studies) (Joerss et al., 2022; Simon et al., 2023; Ulrich et al., 2024; Vogel et al., 2023; Zweigle et al., 2024, 2023) were the European countries most studied. There is no data for the majority of European countries, but the data gaps are slowly being filled in (e.g. the UK now has one study (Megson et al., 2024), published after our data collection and analysis period). Three percent of studies included samples from Australasia (4 studies from Australia) (Baduel et al., 2017; Dewapriya et al., 2023; Ghorbani Gorji et al., 2024; Gonzalez de Vega et al., 2021), and one study included samples from three different Africa countries (Sudan, Tanzania and Kenya) (Jiang et al., 2023). Some studies were transboundary and included samples obtained from the North Atlantic (Spaan et al., 2020), Baltic Sea (Spaan et al., 2020) and River Danube (Ng et al., 2022). Our review did not identify any studies that analysed samples from South America or Antarctica. The data shows a large bias towards the northern hemisphere (>95 % of studies) with studies from China, North America and Europe dominating. There was relatively little data obtained from developing countries; one study included samples from Africa (Jiang et al., 2023), but no studies were identified with samples from South America.

3.2. Sample type

NTA was performed on over fifty different types of sample media (SI Table 1). This section documents trends in current publications rather than providing a detailed overview of PFAS concentrations reported in different media. This is due to the limitations of reporting concentration data in non-targeted analysis studies which is discussed in detail in

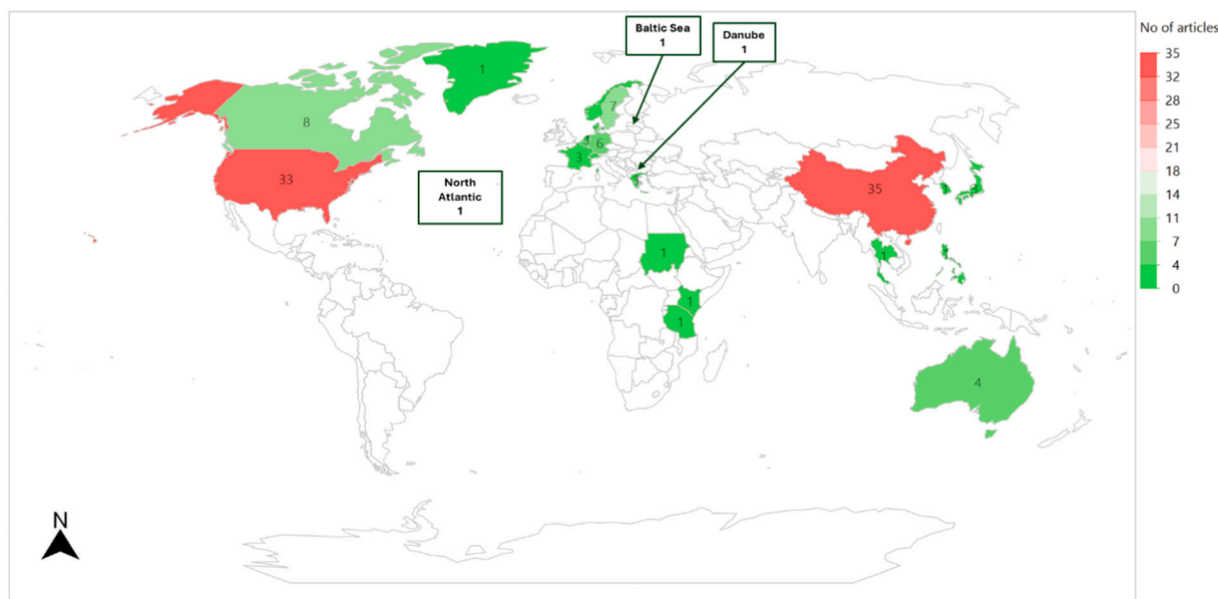


Fig. 1. Geographical distribution of NTA PFAS studies. Coloured shading represents the number of studies in each country, out of the 115 identified, with additional cross boundary studies annotated in green boxes.

Section 5.4 ((Semi)quantitative analysis). Readers requiring information on concentration data are encouraged to use SI Table 1 to locate the relevant primary manuscripts and refer to them directly. Caution is advised when interpreting concentration data as it is likely to be (semi) quantitative due to a lack of reference standards.

Water was the most studied sample type, and was investigated in 52 % (60/115) studies. Terrestrial surface waters (river, lake etc.) were the most widely studied water type (28/60 studies), followed by groundwater (15/60), drinking water (13/60) and seawater (3/60). The focus for NTA water studies has largely been in freshwater systems as opposed to the marine environment. Studies have predominantly focused on establishing inputs to freshwater from firefighting activities, industrial effluents and wastewater treatment plant effluents. There has also been a focus on establishing risks from drinking water resources with 28 studies looking at PFAS in groundwater, as well as tap water and commercial bottled water. Soil (11/115 studies) and sediment (13/115 studies) were fairly widely investigated, with a few studies investigating sewage sludge and compost (7/116). PFAS in the air has not been widely studied, with only 5 studies attempting analysis in air (Ghorbani Gorji et al., 2024; Mok et al., 2023; Qiao et al., 2023; Yu et al., 2018a, 2020a) with tested matrices including particulate matter, indoor dust (Steeves et al., 2023) and rainwater (Kim et al., 2023a). Targeted studies have identified ultra-short (C2 and C3) chain PFAS in rainwater (Yeung et al., 2017), and the increased importance of sea spray aerosols (Casas et al., 2020) which show the importance of the atmosphere as a transport pathway for PFAS. Several publications have shown the benefits of using NTA for indoor and outdoor particulate matter (Kim et al., 2023b; Yu et al., 2018b, 2020b; Steeves et al., 2024), but an increased NTA in the atmosphere and marine environment would help improve our understanding of the global fate and transport of PFAS.

Biomonitoring has been performed on a relatively limited number of plants and animals. Three studies have been performed on plants/crops (Koch et al., 2021; Lasee et al., 2022; Xiao et al., 2023), with 8 studies investigating fish (Crimmins et al., 2014; Z. Jiao et al., 2023; Kaufmann et al., 2022; Ng et al., 2022; Nilsen et al., 2024; Pickard et al., 2022; Ren et al., 2022; Wang et al., 2023). Five studies focused on marine mammals (Barrett et al., 2021; Schultes et al., 2020; Spaan et al., 2020; Wang et al., 2023; Q. Wang et al., 2021), 2 on birds (Chu and Letcher, 2024; Haque et al., 2023a), and 2 on polar bears (Chu and Letcher, 2024; Spaan et al., 2020). Cow (Dewapriya et al., 2023), crustaceans (Wang et al., 2023) and invertebrates (Ren et al., 2022) have all been investigated once. Twelve different tissue types have been investigated, with liver the most studied (9/15 animal studies) (Barrett et al., 2021; Chu and Letcher, 2024; Z. Jiao et al., 2023; Kaufmann et al., 2022; Nilsen et al., 2024; Schultes et al., 2020; Spaan et al., 2020; Wang et al., 2023; Q. Wang et al., 2021), followed by muscle (5/15 studies) (Z. Jiao et al., 2023; Kaufmann et al., 2022; Nilsen et al., 2024; Pickard et al., 2022; Schultes et al., 2020). There were 3 NTA studies that used animal blood as a sample matrix (Dewapriya et al., 2023; Z. Jiao et al., 2023; Schultes et al., 2020), highlighting its applicability to be used as a non-lethal option to perform non-targeted screening of wildlife. PFAS biomonitoring in human populations has been fairly well studied with approximately 10 % (11/115) of NTA studies performed on humans. This literature focused on background exposure and maternal transfer by measuring PFAS in the general population (3/11 studies) (Chen et al., 2024; Li et al., 2022; van Gerwen et al., 2024), and pregnant women (5/11 studies) (Bao et al., 2022; Li et al., 2021, 2020; Miaz et al., 2020; Xia et al., 2022). Only a few studies have investigated groups believed to have increased PFAS exposure including those in proximity to a fluorine chemical plant (1 study) (Bao et al., 2022), and an AFFF-impacted community (1 study) (McDonough et al., 2021). More NTA studies are required on potentially exposed cohorts such as fire fighters to better understand human health risks, biotransformation pathways and the magnitude of PFAS exposure. All 11 studies on human participants used blood (including serum & plasma) as the sample type, with some studies also investigating placenta/umbilical cord (3 studies) (Bao et al., 2022;

Li et al., 2020; Xia et al., 2022).

Commercial products have not been widely studied with majority of studies aimed at determining PFAS in the environment. AFFF was the most investigated product and was identified in over 20 % of studies (25/115). Aside from this, very little non-targeted analytical work has been performed on consumer products. Paper (Mok et al., 2023; Zweigle et al., 2022) and food packaging (Sapozhnikova et al., 2023; Stroski and Sapozhnikova, 2023) have each been the subject of 2 investigations, the following products are the only others to be studied on one occasion: anti-fog products (Steeves et al., 2023), mist suppressants (Cheng et al., 2023), drinking straws (Boisacq et al., 2023) and cosmetic/personal care products (Harris et al., 2022). More research efforts are needed to identify the range of potential PFAS in commercial and industrial products. Human exposure to PFAS from products like cosmetics has recently been identified of concern (Ragnarsdóttir et al., 2024). More NTA studies on commercial products would provide a better understanding on the range of PFAS humans may be exposed to. They would also be of benefit to establish the scale of PFAS pollution to the environment from non-point sources.

3.3. Sources of PFAS

Approximately half (50/115) of the reviewed articles targeted a specific suspected source of PFAS; the remaining 65 articles either performed background measurements or did not clearly state whether a source of PFAS was targeted. AFFFs were the most targeted source of pollution in 50 % (25/50) of studies; this was followed by industrial (fluorochemical plant) emissions- 32 % (16/50), commercial products (excluding AFFF)- 16 % (8/50), and oil/fuel- 6 % (3/50). There was also a geographical bias in the data with studies in North America focusing on AFFF sources- 65 % (15/23). Asian studies focused on industrial emissions- 44 % (7/16) of studies (Fig. 2). The bias towards AFFF in North America is likely associated with the well-funded United States Department of Defense (U.S. DoD) research programmes that have been historically focused on PFAS in AFFF.

4. Sample analysis, QA/QC and data processing

4.1. Sample preparation

Sample preparation is an important step of any NTA study. It is required to isolate analytes of interest from a sample matrix to enhance analyte detection sensitivity and selectivity. The preparation method needs to make the extract clean enough to be injected onto an instrument, but not remove compounds of interest. Impacts of sample preparation on the overall data were not well reported within the literature. Internal standards were used in the majority of studies (88/115) but findings were rarely discussed from a sample preparation optimisation perspective. There are relatively few PFAS standards available (considering the 100 s of PFAS classes that have been reported). Therefore, it is currently challenging for analysts to accurately identify which sample preparation methods are most appropriate for NTA. This has resulted in a vast range of different sample preparation methods being reported in the literature. From reviewing the information in the literature it was not possible to establish which sample preparation methods were most effective. There is therefore a need for studies to investigate the impacts of sample preparation on PFAS NTA. This could be completed through interlab studies, or controlled experiments that test a variety of sample preparation methods on complex PFAS samples covering a wide range of different PFAS classes.

Sample preparation procedures ranged from simple techniques which involved filtration or dilution and direct injection onto an instrument, to more complex methods with several extraction and cleanup steps. An overview of the most commonly used methods is presented as Fig. 3. Solid phase extraction (SPE) was the most used sample preparation method in approximately 75 % (86/115) of studies. There was a

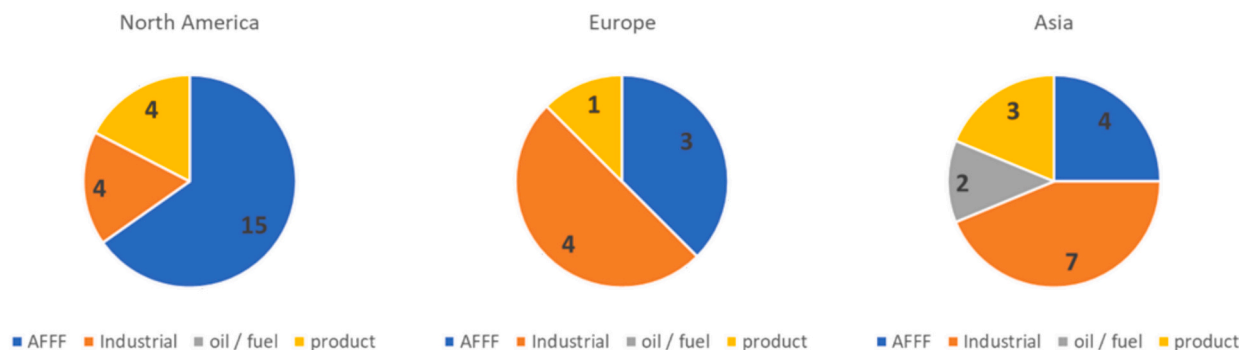


Fig. 2. Sources of PFAS investigated in North America, Europe and Asia. Sources include AFFF, emissions from industrial facilities, oil/fuel, and consumer products (e.g. drinking straws, personal care products, paper and food packaging).

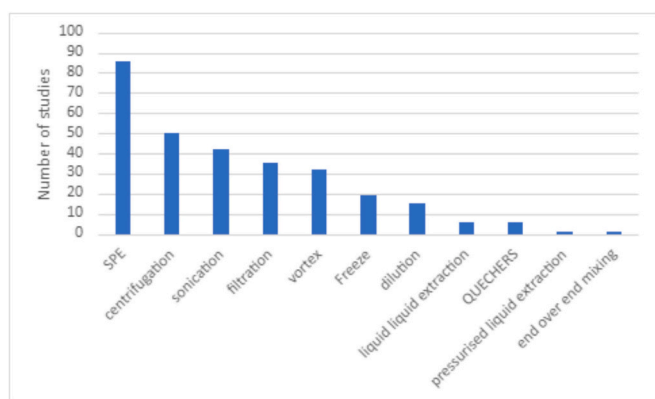


Fig. 3. Overview of sample preparation procedures used.

large variety of sorbents used (over 40 different combinations); sometimes individual sorbents were used, but in many instances, multiple sorbents were combined. Forty-two studies included a sonication step, and 32 studies included vortex mixing. There was a surprising lack of automated extraction methods, with only one study applying pressurised liquid extraction (Simon et al., 2023), and three studies using online SPE (Getzinger and Ferguson, 2021; McDonough et al., 2021; Petrick et al., 2022). Many automated systems can include plastic tubing/pipes that contain PFAS, potentially introducing PFAS contaminants into blanks/samples and thus restricting their use. QuEChERS was first used for pesticide residues in food but has since been adapted for a wide range of applications (Kim et al., 2019; Santana-Mayor et al., 2023; Bruzzoniti et al., 2014). From the review, QuEChERS was used in six different studies (all conducted in China on biological samples) (Bao et al., 2022; Z. Jiao et al., 2023; Li et al., 2023, 2021, 2020; Xia et al., 2022). A large proportion of studies used techniques to remove particulate matter which included centrifugation (50/115 studies) and filtration (35/115 studies). Nine different types of filter paper were used to prepare samples, although in many cases it was not possible to establish how filtration was performed or what type of filter was used.

Methanol was the most widely used solvent and was used in 70 % (82/115) of studies. Methanol was predominantly used in isolation but occasionally combined with water (17 studies), acetonitrile (2 studies) (Chu and Letcher, 2024; Crimmins et al., 2014), or a combination of dichloromethane, acetone and acetonitrile (1 study) (Steeves et al., 2023). Acetonitrile was the next most commonly used solvent and was reported in 17 % (20/115) of studies. The following solvents were only used occasionally; dichloromethane (2 studies, both using gas chromatography) (Steeves et al., 2023; Casey et al., 2023), ethanol (3 studies) (Barzen-Hanson et al., 2017a; Jacob et al., 2021a; Joseph et al., 2023), MTBE (2 studies) (Chen et al., 2024; Li et al., 2023), and ethyl acetate (1

study) (Joseph et al., 2023). We were unable to identify which solvent(s) were used in 4 studies, as the information was not included in the manuscript.

4.2. Sample analysis

Chromatographic separation of PFAS chemical species was predominantly performed by liquid chromatography, with 6 studies using gas chromatography (Casey et al., 2023; Christie et al., 2023; L. Liu et al., 2022; Mok et al., 2023; Qiao et al., 2023; Steeves et al., 2023) and 2 studies skipping chromatography altogether and directly infusing a liquid sample into the mass spectrometer (Yi et al., 2018; Young et al., 2022). The preference for liquid chromatography is understandable as many water-soluble PFAS are amenable to analysis by liquid chromatography. Relatively few studies have been undertaken on atmospheric PFAS where analysis by gas chromatography may be more applicable. Within the literature there was a bias towards PFAS of specific chain lengths. Many studies did not report PFAS below a 3 or 4 carbon chain length. It was not clear if this was because they were not present or because it was not possible for the method to detect them. These PFAS may have been unintentionally removed during sample preparation methods involving SPE, not retained long enough on the HPLC column to be well-defined peaks, or simply ignored and excluded during data processing. Some studies were excellent at acknowledging this bias, but in most cases, it was not mentioned. Ultrashort chain PFAS (C1-C3 PFAS) are an emerging concern but are currently an understudied area (Zheng et al., 2023). Chromatographic separation can be performed using gas chromatography (Zheng et al., 2023), supercritical fluid chromatography methods (Björnsdotter et al., 2019), or carefully optimised liquid chromatography methods (Liang et al., 2023). On the other end of the scale, PFAS with much longer chain lengths (including fluorinated polymers and fluoropolymers) may also have been inadvertently excluded during sample preparation and analysis. Again, within the literature there is little acknowledgment of this bias. Fluorinated polymers and fluoropolymers are often considered to be environmentally stable, and so are considered polymers of low concern; however, they are slowly gaining more attention (Lohmann and Letcher, 2023; Lohmann et al., 2020; Sworen et al., 2024). These are now starting to be considered more widely and have been the subject of at least one NTA method (Sworen et al., 2024), published after we completed our data collection and analysis.

Both high performance liquid chromatography (HPLC) and ultra-high performance liquid chromatography (UPLC) methods were widely used in the literature; however, it was not always clear which technique had been used, with several studies referencing “liquid chromatography”. In LC experiments, electrospray ionisation (ESI) was exclusively used for ionisation. Negative ionisation was the most used method and was reported in 69/115 studies. Both positive and negative ionisation was used in 21/115 studies. Only 2/115 studies used only

positive ionisation (Dubocq et al., 2020; Munoz et al., 2023). PFAS can exist as anions, cations and zwitterions, so NTA methods that use both positive and negative ionisation are likely to provide more comprehensive coverage of PFAS in the environment, compared to methods that focus on either ionisation technique. This trend was observed within the literature (although not at a statistically significant level, ANOVA at 0.05 significance level) as the average number of PFAS detected by studies using positive and negative ionisation was 110 compounds, compared with an average of 76 from negative ionisation experiments and 48 from positive ionisation studies. High resolution mass spectrometric methods were the most common, with nearly 90 % of studies using either a high-resolution quadrupole time of flight mass spectrometer (56/115 studies), or orbitrap (41/115 studies). Eleven (11) studies stated they used high resolution mass spectrometry, and 2 studies mentioned MS/MS, although specific details on the type of instrumentation used were not explicitly stated. Ion mobility was used in 7 studies (Gonzalez de Vega et al., 2021; Kirkwood-Donelson et al., 2023; Mu et al., 2023; Steeves et al., 2023; Yukioka et al., 2021, 2020a, 2020b). This method can resolve compounds based on their shape so it has been especially effective at resolving linear and branched forms of PFAAs, such as PFOS (Dodds et al., 2020; Mu et al., 2023). The ion mobility collision cross section has also been found to be a relatively stable parameter that can be used effectively as an extra line of confidence in NTS methods (Mu et al., 2024). Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS) has an unsurpassed mass resolving power, mass accuracy, and high dynamic range (Huang et al., 2021). This makes it especially effective for the analysis of complex mixtures, and for the identification of unknown compounds (Smith et al., 2018; Megson et al., 2016). Despite this excellent potential, our review only identified 2 manuscripts that used this technique for the NTA of PFAS (Yi et al., 2018; Young et al., 2022). FTICR-MS is regularly operated by direct infusion and so chromatographic parameters are not always obtained. In addition, many FTICR-MS experiments are not commonly set up to collect MS/MS spectra. This makes mapping against existing NTA confidence levels a challenge. However, it is important to note the benefits that this instrument can provide with a mass accuracy of 5 or 6 decimal places allowing for confident detection of PFAS using only the mass of the molecular ions (Young et al., 2022).

4.3. QA/QC

Quality assurance and quality control are an essential part of any analytical method. For targeted methods, analytical standards are used to monitor recovery, precision and accuracy. However, for NTA methods, there is a focus on semi-quantitative or qualitative data to discover which compounds are present in a sample, rather than calculate their concentrations. All but one of the studies in this review used analytical standards as a form of QA/QC. Over 75 % of studies (88/115) used an isotope labelled standard to monitor recovery rates of a set of target analytes during sample preparation. These standards could then also be used for confirmatory analysis and to estimate concentrations of unknown PFAS semi-quantitatively. Blank samples were regularly used within the literature. PFAS are ubiquitous in our environment, and so blanks are essential to check for background contamination. Laboratory or procedural blanks (solvent blanks run on an instrument or carried through a sample preparation method) were used in nearly 90 % of studies (102/115). Field blanks (blanks prepared during sample collection) were also used but in a much lower proportion of studies (19/115 studies). Although most authors were excellent at reporting what blanks were employed, there was little consistency or transparency on what the blanks were used for. Some studies were deemed to be free of contamination while others used blank subtraction. Some studies excluded PFAS found in blanks from the final data set while other studies performed statistical analysis on the blank (e.g. average and standard deviation measurements) to compare levels in the blanks with those in samples to determine what should be excluded from further study.

Although there is widespread use of analytical standards and procedural blanks, there is a lack of QA/QC to establish rates of false positives and false negatives within NTS studies. Manuscripts that propose the use of a workflow do this occasionally, and results show limitations with these methods. False negatives (when the method fails to detect a PFAS present in the sample) are more commonly discussed than false positives (when the method identifies a PFAS that is not present in the sample). Jacob et al. (2021b) proposed the use of sensitivity (Eq. (1)) and selectivity (Eq. (2)) calculations to transparently report rates of false positives and false negatives in PFAS NTA studies. They then performed analysis on a standard solution spiked with 33 known PFAS using three different workflows to better understand these effects (Jacob et al., 2021b).

The equation proposed by Jacob et al. (2021b) uses false negatives to measure the accuracy of a NTA workflow.

$$\text{Sensitivity (accuracy)} = \frac{\text{True positive}}{\text{True positive} + \text{False negative}} \quad (1)$$

The equation proposed by Jacob et al. (2021b) uses false positives to measure precision of a NTA workflow.

$$\text{Selectivity (precision)} = \frac{\text{True positive}}{\text{True positive} + \text{False positive}} \quad (2)$$

The manuscript highlighted benefits of using this relatively simple technique to help optimise workflows. When using default workflow parameters, they only identified approximately one fifth of the PFAS added to a sample. By optimising parameters of the workflow, they were able to considerably improve both accuracy and precision. It will always be challenging to perform this type of assessment on NTA studies, as analysts do not know which analytes to select in optimisation studies. This is even more challenging for PFAS NTA studies where only a small number of PFAS are available as commercial standards. Despite these limitations, more studies would benefit from putting more consideration into rates of false positives and false negatives in their studies. Inter-laboratory trials can also prove a useful mechanism to undertake this type of analysis, and drive forward improvements collaboratively within the community.

Limits of detection were briefly considered within this review, but a detailed analysis was not possible due to reporting discrepancies. Over 50 % of studies reported detection limits, but in many cases, it was not possible to establish if LODs were related to the targeted method or to the NTA method. There was also variability in reporting method detection limits (limit of detection in a sample), and instrument detection limits (limit of detection on an instrument). Some authors reported limits of detection, and others limits of quantification; again, there was variability in the way both parameters were calculated. Where LODs were transparently reported, they were useful to gain information on likely detection levels for PFAS in those samples. However, it is a challenge to then put these values into context for other PFAS that have unknown recovery rates, different ionisation efficiencies and different fragmentation patterns. Standardization of reporting of limits of detection for NTA analysis is imperative to develop in the future so that studies can be compared for detectability.

4.4. Data processing

There are two main ways to undertake non-targeted screening. These involve either the use of a suspect screening approach (where results are compared against a database and so involve a target element) or true exploratory data analysis (which does not use a database and instead attempts to mine and simplify the data to identify features (compounds) of interest) (Hollender et al., 2023b). An example of exploratory data analysis would be using Kendrick mass defect plots to identify groups of compounds containing fluorine (Myers et al., 2014).

There are a variety of different suspect screening lists that have been used for NTA. These lists contain a database of hits which users can compare their data against. There appeared to be little consistency in the database used by different researchers. Some researchers rely on databases supplied by vendors, several have their personal databases and have made them available, and others use open sources such as the NORMAN network suspect list (<https://www.norman-network.com>), the OECD's Comprehensive Global Database for PFAS (<http://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/>), the US EPA CompTox dashboard for PFAS (<https://comptox.epa.gov/dashboard/chemical-lists/PFASDEV>), and the National Institute of Standards and Technology (NIST) suspect list of PFAS (<https://data.nist.gov/od/id/mds2-2387>).

Within articles reviewed, there was no consistency in reporting style or approach. This made it challenging to identify trends and compare studies. Basic instrumental parameters associated with the chromatography were well reported, as were basic mass spectrometer parameters such as positive or negative ionisation and collision energy voltages. However, there was much less consistency in reporting with regards to data acquisition and how features were selected, or how/when MS/MS was triggered. In total, we identified 6 different specific programmes that were used for data processing. However, these did not appear to be widely used with many users instead choosing to use their own workflow using instrument vendor specific software. Sixty nine percent of articles (79/115) used their own specific workflow with 62 % (71/115) citing instrument vendor software as a key part of their data processing method. Fluoromatch was the most widely used non-instrument vendor programme, but was only cited by 4 studies (Koelmel et al., 2020, 2023, 2022; Jacob et al., 2021b). FindPFAS (Zweigle et al., 2022, 2023) and the Norman Digital Samples Freezing Platform (DSFP) (Söregård et al., 2020, 2021) were cited twice and PFAS-IDENT (Ulrich et al., 2024), PFAScreen (Zweigle et al., 2024), MZmine (Bowers et al., 2023) and enviMass (Jacob et al., 2021b) were each cited once. For 9 articles, data processing techniques were not explicitly stated. Only two studies investigated using multiple data processing programmes and demonstrated that different results are obtained from different software packages (Jacob et al., 2021b; Ulrich et al., 2024).

5. Reporting the results of PFAS NTA studies

5.1. Use of confidence levels

Use of confidence levels was first proposed by Schymanski et al. (2014) to improve confidence in the reporting of compounds detected by non-targeted analytical methods. Eighty nine out of the 115 studies reviewed (77 %) used confidence levels to report their findings. Confidence levels presented by Schymanski et al. (2014) were the most used and were cited in 58 % of studies (67/115). In 2022, Charbonnet et al. adapted confidence levels proposed by Schymanski et al. (2014) to develop a set of confidence levels specifically for PFAS. This guidance provided more detailed information on assignments and used detections from PFAS in the same series to boost confidence in an assignment. Charbonnet et al. (2022) confidence levels were cited in 19 % of studies (22/115). Low adoption rate of these confidence levels reflects the large number of studies conducted before this manuscript was published. Forty-five manuscripts were published since 2023 (i.e. post Charbonnet et al.), and Charbonnet et al. was referenced in 49 % of these studies (22/45), with Schymanski et al. referenced in 44 % (20/45). Confidence levels from Fluoromatch were reported in three studies and three studies chose to assign their own confidence levels.

Confidence levels were regularly cited within the literature, but were not always correctly applied. We identified several instances where authors incorrectly assigned confidence levels and provided evidence that did not reflect that level of confidence (e.g. use a library match factor or mass error which is not a condition of that specific confidence level). These Schymanski and Charbonnet papers are excellent

resources, but despite their detailed explanations, it still appears to be a challenge to correctly and consistently apply the rules. Many studies performed analysis by liquid chromatography and mass spectrometry, and the Schymanski and Charbonnet confidence levels align well with data from these instruments. However, there were instances where data gathered from NTS studies did not fit within the Schymanski or Charbonnet confidence levels. To address these limitations, Koelmel et al. (2022) proposed specific confidence levels for GC data, Mu et al. (2024) proposed confidence levels for ion mobility data, and Hensema et al. (2021) proposed additions to align their FIF (fragment ion flagging) workflow with Schymanski confidence levels (Schymanski et al., 2014; Charbonnet et al., 2022; Mu et al., 2024; Koelmel et al., 2022; Hensema et al., 2021). An overview of the different confidence levels produced by each group is provided in the Supplementary information (SI Table 2). These five confidence level scales align well with each other, and each has a broad 5 point scale corresponding to the original Schymanski et al. (2014) confidence levels where: CL1 = Confirmed structure, CL2 = Probable structure, CL3 = Tentative candidate, CL4 = Unequivocal molecular formula, CL5 = Exact mass of interest. These terms are used to describe data in the following Section 5.2, SI Table 1 contains the details of which confidence level was applied for each specific study.

5.2. Total number of PFAS identified by NTA studies

We were unable to clearly ascertain how many PFAS were identified in 18 % of the studies (21/115), as the total number was not clearly reported. This is not a criticism against all papers that did not report a total PFAS number; several of these studies did not aim to use NTA to try and identify a wide range of PFAS. Instead, it was used to answer a different question, such as controlled experiments to identify specific degradation products from a remediation technique. The greatest number of PFAS detected in any study was by Liu et al. (2022) who identified 651 PFAS from 96 different classes. Only 58 % percent of studies (67/115) used reference standards to confirm the presence of a specific PFAS, and therefore report at confidence level 1 (CL1). Reference standards were predominantly sourced from vendors supplying analytical standards, although in two manuscripts authors synthesised their own standards and 1 study used a commercial product bought from a store for confirmatory analysis. There are over 14,000 PFAS, but unfortunately reference standards are only available for <2 % of these (Nason et al., 2021). Therefore, a vast number of PFAS could only be assigned to confidence levels 2–5 (CL2–5). Fig. 4 displays the range and average number of PFAS reported from confidence levels 1–5. On average CL5 contained the highest number of PFAS reported with an average of 52 PFAS, however level 5 confidence was only reported in 16 studies (approximately 10 %). The data suggests a drive towards categorising PFAS at the highest confidence level possible, rather than suggesting the presence of a wide range of PFAS at lower confidence values. However, attempts to reach CL1 are restricted by a lack of commercially available reference materials, with 53 PFAS being the greatest number of PFAS reported by any study at CL1. On average there was a higher number of PFAS identified at CL3 than CL2, this could be partly due to Charbonnet et al. (2022) guidance for CL2 assignment that requires a higher number of diagnostic MS/MS fragments. For some PFAS at low abundances, or those that do not form many fragments, it is therefore a challenge to achieve CL2. An average of 21 PFAS were reported at CL4 in 36 studies. CL4 requires an unequivocal molecular formula assignment but there is no available complementary information from other PFAS within that homologous series and no MS/MS data. As many PFAS occur in a homologous series and most studies use tandem mass spectrometry (105/115 studies), it is not surprising that there was a relatively low number of assignments to this confidence level. Within this confidence level, there could be many important PFAS that are currently not reported as they fragment poorly, and were not detected as part of a series. We would therefore encourage wider reporting and interpretation of PFAS within this confidence level, which

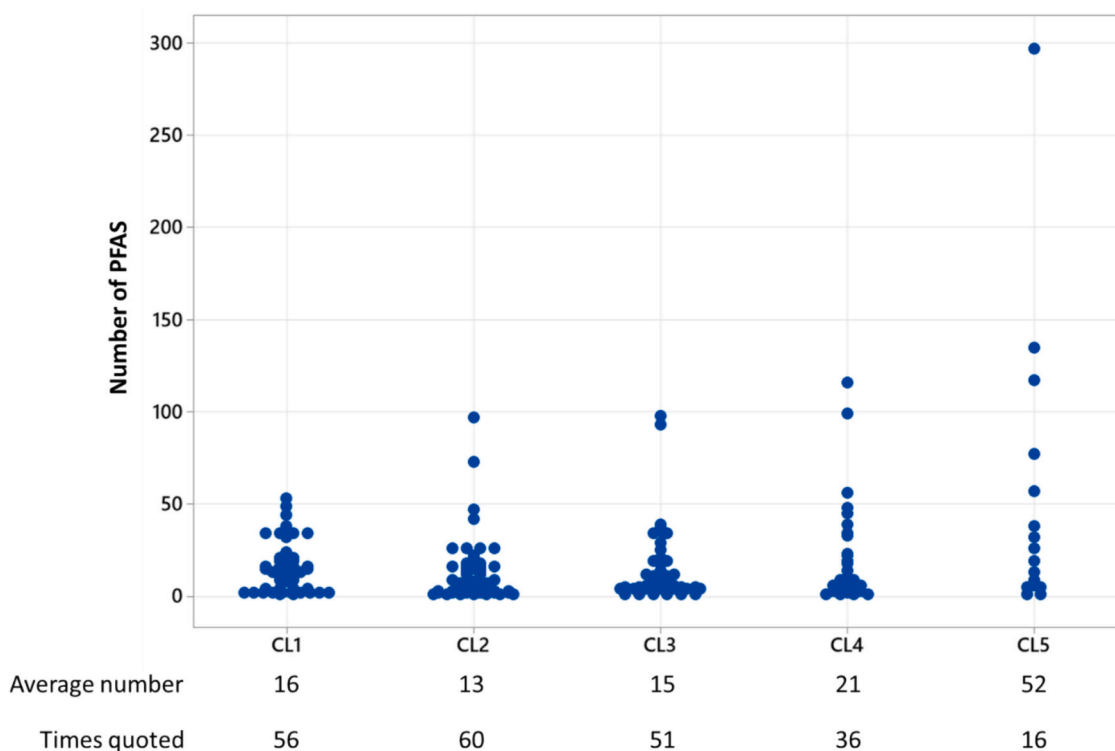


Fig. 4. Comparison of number of PFAS identified at each confidence level. Each dot represents the number of PFAS reported by a specific study.

is often overlooked, as authors tend to focus more on PFAS identified at CL1–3.

5.3. Classes of PFAS reported in the literature

Consistency in terminology is a real issue for PFAS. As a community there has been a struggle to use common acronyms. Even the term PFAS causes confusion, as authors sometimes use PFAS and PFASs interchangeably (rather than to describe PFAS as a group of related chemical substances and use this term throughout). In some studies, PFAS is used to refer to a single substance and PFASs is used to refer to a group of PFAS. In 2011, Buck et al. published a manuscript aimed at unifying terminology on PFAS as a group of related fluorinated chemicals, as they identified inconsistencies that had arisen between various groups of authors. This manuscript has been commonly referred to in the literature, but unfortunately issues with terminology remain, and can lead to some confusion when comparing multiple studies. Many papers refer to PFAS as a class in the introduction, but then within the manuscript they identify different classes of PFAS. A recent report by U.S. EPA classifies PFAS by Family, Class, Subclass, Group and Subgroup (U.S. EPA, 2021), and Buck et al. (2011) refer to families and subfamilies. Some manuscripts refer to “Super classes” (e.g. (Tenorio et al., 2022, T. Liu et al., 2022, Nickerson et al., 2020)), which group together different classes while other manuscripts refer to sub-classes (either as subclasses of the entire class of PFAS, or subclasses of smaller specific classes of PFAS). Some terminology for classes links to the product category or use of the chemical is common in traditional NTA manuscripts which identify chemicals as pharmaceuticals, pesticides etc. Some manuscripts refer to the number of fluoroalkyls e.g. mono-fluoroalkyl carboxylic acids and di-fluoroalkyl carboxylic acids, whereas others report these as one class. Occasionally individual PFAS are referred to as a class, this can be when referring to isomers but also when referring to an individual compound. Harmonisation of a PFAS “family tree” and consistency and clarity in a naming convention is needed, not just for an individual PFAS but for how we group PFAS. We believe this is beyond the scope of this manuscript, and is a task that would benefit from input from a wider

range of experts and stakeholders.

Fifty eight percent ($n = 67$) of manuscripts included in this review attempted to allocate specific PFAS into groups that they defined as a class. We have attempted to summarise this data here. During the review, we only included data for which authors attempted to group PFAS into classes and reported these as an acronym, we did not go through each individual PFAS and allocate them to classes ourselves. This was performed, as the aim of this manuscript was to broadly capture what was presented in the scientific literature and identify general trends. During this process, several issues were noted with nomenclature within the literature for which the same class of PFAS were reported under different names. These included:

- inconsistency of the use of X or n to describe chain length (e.g. X:2 FTSA and n:2 FTSA) between different manuscripts, and sometimes X and n were used interchangeably within the same manuscript
- inconsistency in acronyms stemming from the use of capitalisation, use of “-”, inclusion of “s” at the end of acronyms and inclusion of written text within acronyms (e.g. Keto-PFSA, KPFSAs, K-PFSA)
- Inconsistent splitting or grouping classes (e.g. FTCAs as one class or splitting into n:2 FTCAs and n:3 FTCAs)
- Listing an individual PFAS as a class.

These issues presented challenges in the comparison of PFAS detected in different studies. Some manuscripts were excellent at presenting complementary information to navigate these discrepancies. These manuscripts included details such as: CAS numbers, chemical formulas, structural formulas, SMILES notations, molecular weights, and fully named structures with associated acronyms. But there are several manuscripts where limited information is provided, and so it was not always possible to confidently establish exactly what was detected. NTA of PFAS has been a rapidly emerging field with the discovery of many new PFAS over the last two decades. This has resulted in several different names for the same compound or classes as authors try to get to grips with naming conventions and have their own preferences and reporting styles.

It quickly became apparent that it would be beyond the scope of this manuscript to comprehensively identify every single PFAS ever detected by NTA, nor was it deemed necessary. There are already several resources that are regularly updated to capture this information, and we encourage authors to use those resources to get the most up to date information (listed in Section 4.4). In this review, we attempted to gather information on PFAS classes to identify general trends and understand which classes of PFAS are most detected in NTA studies. In total, 469 different terms were used to describe classes of PFAS in the 67 studies that attempted to allocate PFAS into classes. On average, 14 classes of PFAS were reported. The greatest number of PFAS classes reported in any one study was 92 (96 classes were reported by Liu et al., 2022, but only 18 were named), the fewest reported in any one study was 3 (T. Liu et al., 2022).

We made a conservative attempt to consolidate duplicate entries and

tidy the final dataset (SI Table 3). This involved combining entries with minor typographical differences including; those that use “n” and “x” notations, combining entries that used text (e.g. keto- and k-), combining entries with minor differences in the use of “-” and removing entries that were individual PFAS or general terms (e.g. “Other sulfonate”). This resulted in a total of 382 classes that have been reported using non-targeted approaches. We note that there are several duplicate or overlapping entries (e.g. the same class with different names (FTS and FTSA), or instances where authors subdivide a specific class (FASA to MeFASA and EtFASA)) within this dataset, as well as some classes that may not have been captured and included in the review. However, the aim here was to illustrate the breadth of PFAS that have been reported and to focus on general trends, whilst highlighting the potential for inconsistencies in reporting. We identified 45 different reported classes of PFAS that were detected in over 5 % of NTA studies (SI Table 3), these

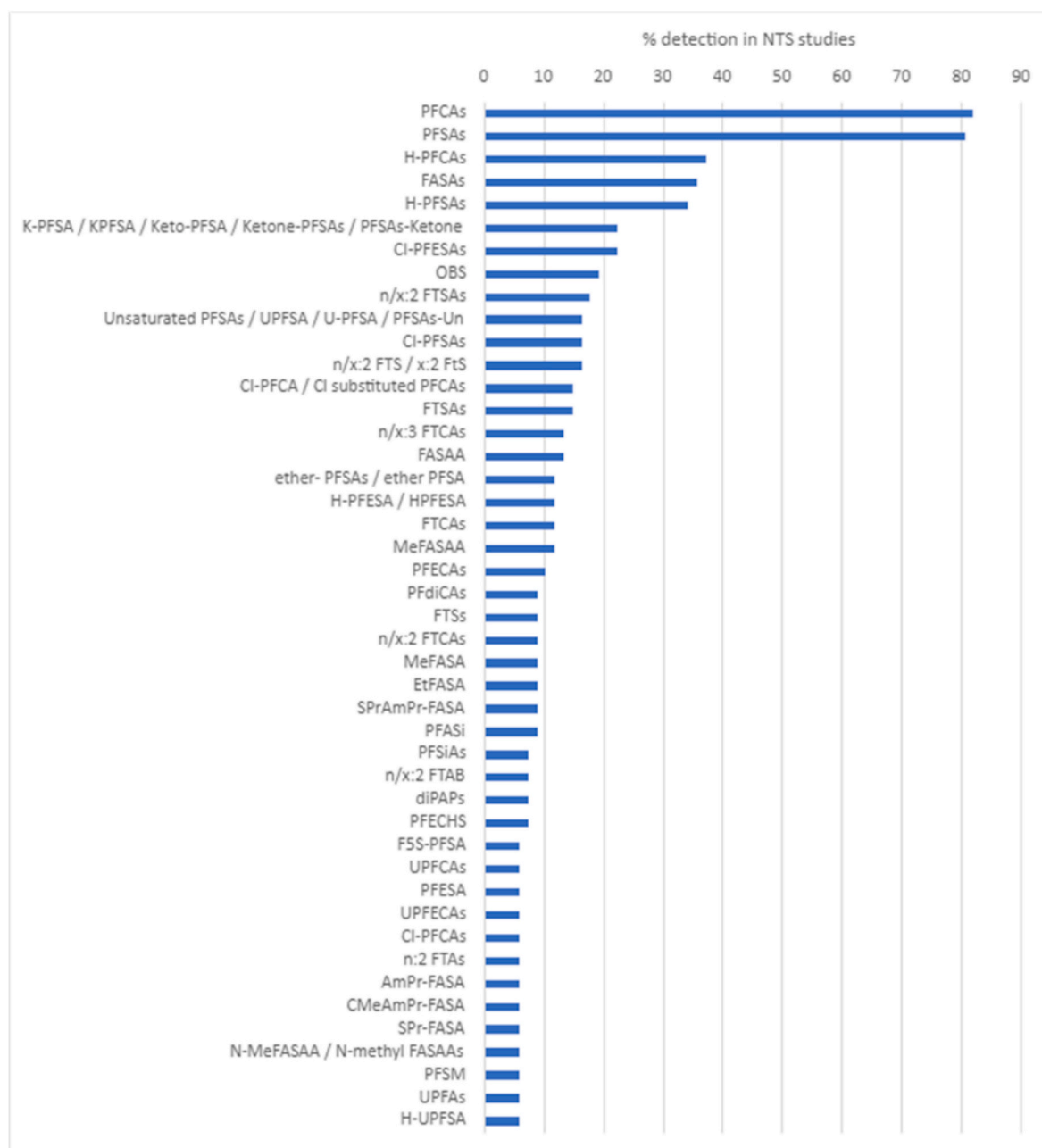


Fig. 5. Ordered list of the most reported classes of PFAS in NTA studies; this list only includes classes reported in >5 % of studies (a full list is provided in the SI Table 3).

classes have been ordered by rates of detection and are presented in Fig. 5. Within this data there may be underreporting of some of the more common PFAS classes as several studies that performed complementary targeted analysis may have only reported the PFAS exclusively detected by non-targeted methods in summary tables.

Results show that the perfluoro alkyl acids (PFAAs) are the most detected PFAS, with PFCAs and PFSA recorded in over 80 % of studies. It is important to note that many classes of PFAA beyond PFCA and PFSA were detected in studies, H-PFCA (37 %), H-PFSA (34 %), K-PFSA (22 %), and Cl substituted PFAAs (16 %) were all regularly detected. Perfluoroalkane sulfonamides (FASAs) were detected in over a third of studies (36 %) and fluorotelomers (e.g. FTSA & n:2 FTSA) were detected in approximately 20 % of studies. The rest of the data was then comprised of many classes of PFAS that were detected in <10 % of studies, these included many electrochemical fluorination based PFAS and degradation products.

Regulations to date have tended to focus on a select few specific PFAS to protect environmental and human health; however, these miss the breadth of PFAS that can be present in the environment. The UK DWI list is one of the most comprehensive lists of PFAS for a regulatory purpose, but only contains PFAS from 10 classes, whereas the U.S. EPA method 533 contains PFAS from 7 different classes (Table 1). These targeted regulations and analytical methods focus on low detection limits and high accuracy, therefore require use of internal standards. Whereas these methods largely capture the most detected PFAS in NTA studies, there are large gaps, and so relying on these targeted methods alone is likely to underestimate human and environmental health risks. It was also interesting to note that FASEs were present on both the UK DWI list and U.S. EPA method 533 but were only reported in 3 % (n = 2) studies. For context, 76 different other classes were reported more often in NTA studies included in this review.

Within the literature, there appeared to be a drive to discover a new class of PFAS in a new matrix. Statements of new discoveries were regularly presented in the abstract and conclusions, in a drive to push the novelty of a specific paper. There were several instances where authors claimed they “believed” they were the first to identify a class of PFAS. However, we identified several instances where this was not the case and that class of PFAS had been previously reported. These are likely honest mistakes where multiple papers were in preparation at the same time (or could indicate the literature was not adequately reviewed), but it also points towards the complexity and lack of consistency of reporting in the literature which makes it challenging to establish what has been previously reported. We hope this manuscript

can help address this issue, and be a useful resource to help authors identify what has been detected by different studies. To help improve the literature, we also recommend that future studies include summary tables that clearly document (as a minimum) PFAS class, individual PFAS detected within the class, acronym, full name, chemical formula, structural formula, CAS number (if available), retention time, accurate mass. MS/MS fragmentation information would also be a valuable addition for new PFAS reported for the first time, and CCS data for ion mobility experiments.

5.4. (Semi)quantitative analysis

Performing accurate quantitative analysis is a challenge for any NTA study. This is not always possible as analysts do not know what chemicals they are going to encounter, and that is the primary reason for choosing NTA over a targeted method. Analytical standards are required to perform accurate quantification, this can be performed by external calibration or internal calibration using isotope dilution. Internal calibration would be preferred but this requires spiking samples with a known amount of an isotope labelled standard prior to extraction and analysis. This is not always possible and the limited number of analytical standards for PFAS means only a few can be quantified in this way. Whilst it is preferable to perform quantification by matching a native PFAS directly with its corresponding isotope labelled PFAS, this is not always possible. It is common practice to use one isotope labelled substance for quantification of a homologous series as these are assumed to have a similar ionisation efficiency and provide a similar response (U.S. EPA method 1668C). This can be expanded to the same class of compound, as similar compounds are assumed to provide a similar response (U.S. EPA method 533). However, for NTA methods, there are so many different PFAS chemistries involved that it is not appropriate to assume a similar response for all. This point was widely acknowledged within many of the articles reviewed. Several studies chose to only report peak areas for all PFAS, rather than estimate a concentration; others provided concentrations but with heavy caveats accepting the limitations and uncertainty of their estimates. However, there were a few articles where these limitations were not fully explained, and semi-quantitative data could easily have been misinterpreted as accurate quantitative data by a casual reader. This is an important point to make as >40 % of articles reviewed (48/115) used NTA data to report a “total PFAS” concentration. The information reported by each study is presented in SI Table 1.

Table 1

Overview of PFAS classes covered in a selection of (inter)national monitoring and regulatory programmes.

PFAS class	% reported in NTA studies	Regulatory/monitoring programme			
		UK DWI (Drinking Water Inspectorate, 2021)	U.S. EPA Method 533 (USEPA, 2021)	(EU) DIRECTIVE 2020/2184 (European Union, 2020)	EEB (European Environmental Bureau, 2023)
PFCA	82	x	x	x	x
PFSA	81	x	x	x	x
PFECA	10	x	x		x
FTCA	12 (FTCA)	x			
	13 (n:3 FTCA)				
PFESA	6	x			
Cl-PFESA	22	x			
FTSA	18 (n:2 FTSA)	x	x		
	16 (n:2 FTS)				
	15 (FTSA)				
FASA	36 (FASA)	x	x		
	9 (MeFASA)				
	9 (EtFASA)				
FASE	3 (FASE)	x	x		
FASAA	13 (FASAA)	x	x		
	12 (MeFASAA)				
	6 (N-MeFASAA)				
	3 (EtFASAA)				

Table 2
Recommended considerations when undertaking a NTA study for PFAS.

Stage	Consideration	Benefits
Sample collection	Include field blanks.	There is a significant possibility of introducing PFAS during sample collection from clothing, cosmetics and equipment. Collection of a field blank will enable users to identify PFAS contamination during the sample collection stage.
Sample preparation	Use analytical standards or reference materials to perform method development and optimisation on a wide range of PFAS chemistries.	PFAS can be present in the environment as positive, negative and neutral species. They also cover a broad range of volatility and polarity. The use of standards or reference materials will allow users to identify limitations of certain sample preparation steps and enable them to optimise NTA sample preparation methods effectively.
Sample analysis	Consider the use of multiple instruments for more comprehensive analysis	Due to the wide range of PFAS chemistries certain PFAS can only be detected by certain techniques. A combination of liquid and gas chromatography with positive and negative ionisation would likely result in a more comprehensive study than if one technique was used in isolation. Again, the use of standards or reference materials would provide data to justify the need for this approach.
Data analysis and interpretation	Use standards/reference materials to perform QA/QC to establish rates of false positives and negatives. Consider the use of multiple tools/software programmes to optimise data processing workflows.	This would allow users to better understand the limitations and biases within data processing methods. It would also provide evidence, and a more valid justification, for many of the subjective parameters used during the data processing stage. Again, the use of standards or reference materials would provide data to justify the need for this approach.

5.5. Complementary analytical methods

Within the literature there were plenty of examples that demonstrated the strength of combining NTA workflows with targeted analytical methods. Nearly 70 % of studies (79/115) performed a complimentary targeted analysis alongside the NTA workflow (SI Table 1). In many instances it was clear to see that this was a separate analytical procedure, sometimes performed by a different sample preparation method with analysis on a different instrument. In some cases, it appeared that the targeted method was ran within the NTA screen by using isotope labelled standards. Although there were plenty of studies that performed complementary targeted analysis, this data was rarely used to check for false negatives within the NTA dataset. In most cases, NTA was used as a tool to identify new PFAS beyond the targeted method. This is a missed opportunity within the literature to evaluate the effectiveness of NTA workflows and transparently comment on their accuracy and applicability. Parameters within a NTA workflow are selected with a high degree of subjectivity and potential bias. This includes which sample preparation steps and sorbents are used, which

chromatography and ionisation source is used for analysis, and how data processing scripts are ran. Using data from a targeted workflow, authors could avoid some of this subjectivity by optimising some elements of the workflow against a targeted list that covers a wide range of PFAS classes (Section 4.3).

In addition to targeted analysis by mass spectrometry, five other complementary analytical methods were recorded within this review (SI Table 1). These included: ion chromatography (IC), extractable organic fluorine (EOF), TOP assay (total oxidisable precursor), ^{19}F NMR (fluorine nuclear magnetic resonance spectroscopy) and fluoride ion selective electrode. These complementary methods were used to try and close the fluorine mass balance and calculate total PFAS concentrations. Each of these complementary methods works in a different way, and has its own limitations which have been well documented in the literature (McDonough et al., 2019; Koch et al., 2020; Shen et al., 2023; Androulakis et al., 2022), and studied as part of our complementary systematic review on total PFAS (Idowu et al., in review). The TOP assay was the technique most paired with NTA and was utilised in 17 of the reviewed studies. It is designed to oxidise PFAS that would not be detected under routine targeted methods, and convert them into PFAS that can be detected (such as PFCAs) (Lange et al., 2024).

The studies reviewed either used TOP assay to compare total PFAS estimates with NTA data or used NTA to establish what had been produced following a TOP assay. EOF was reported in 5 studies (Miaz et al., 2020; Dunn et al., 2024; Schultes et al., 2020; Simon et al., 2023; Vogel et al., 2023), IC in 2 studies (Bowers et al., 2023; Miaz et al., 2020), and ^{19}F NMR (Tenorio et al., 2022) and ion selective electrodes (Soker et al., 2023) used in one study each. These total PFAS methods can provide powerful information to help support NTA studies.

6. Knowledge gaps and recommendations

From reviewing the scientific literature, it is clear to see the strong positive impact that NTA methods have played to help understand the true scale of PFAS in the environment. Total PFAS methods are powerful tools to establish total concentrations of PFAS, and targeted analysis allows for widescale routine monitoring. The combination of these two methods helped to identify that although PFAS pollution is widespread, we are only monitoring a small fraction of PFAS in the environment. NTA methods play an important role in filling in the blanks and identifying the specific PFAS that currently go unmonitored. There was a large geographical bias within the scientific literature, as the majority of NTA studies (~60 %) originated from either the U.S. or China. Remaining studies had largely been conducted within Europe with only 5 studies conducted in the southern hemisphere. Future studies in polar regions, Africa and South America would help provide a better understanding of PFAS on a global scale. More research is also required within the marine environment and atmosphere, with most current studies focused on fresh surface water, groundwater, soils and sediments. Non-lethal sampling techniques that use blood as a sample matrix have been used successfully for NTA in humans and wildlife. However, human biomonitoring studies have predominantly focused on background exposure. More studies are required on potentially exposed cohorts to better understand human health risks and PFAS biotransformation pathways. With the exception of AFFF, commercial products have not been widely studied with majority of studies aimed at determining PFAS in the environment of studies.

Scientific literature is heavily biased towards NTA methods that use liquid chromatography and negative electrospray ionisation. Whilst these are useful to monitor a wide range of PFAS, challenges with ultrashort chain PFAS detection are observed with such methods; resolutely, many NTA studies do not report PFAS that are shorter than C4. There have been some excellent targeted methods for ultrashort PFAS, but currently relatively little NTA work has been performed in this area. Whilst there have been significant improvements and drives to improve confidence in data obtained from NTA studies, there is still some way to

go. Confidence levels (Charbonnet et al., 2022; Schymanski et al., 2014; Koelmel et al., 2022; Mu et al., 2024; Hensema et al., 2021) are now widely reported within the literature which has improved consistency in reporting. However, QA/QC procedures (particularly rates of false negatives and false positives) are rarely considered, and many NTA workflows remain largely subjective with little justification for the parameters chosen. Many manuscripts claim to have performed “comprehensive” analysis but did not assess or acknowledge the biases introduced from sample preparation, analysis and data processing.

PFCA and PFSA were the most widely detected classes of PFAS in NTA studies (82 % & 81 %, respectively), and are commonplace on routine monitoring programmes across the globe. However, our review identified many other classes of PFAS that are currently unmonitored. Only a handful of PFAS classes are routinely monitored, but this review identified 382 classes of PFAS that have been detected in NTA studies. Over 300 of these classes were detected in <5 % of studies. This large diversity of PFAS could be beneficial in environmental forensics studies which could utilise NTA approaches to identify specific sources of PFAS pollution. Overall our review highlights the large variety of PFAS found in the environment, and demonstrates limitations of relying on targeted methods alone. Due to this complexity, large routine PFAS monitoring programmes would benefit from including total PFAS and NTA methods.

There is already lengthy high-quality guidance available to support researchers to perform non-targeted analysis and we would encourage the use of these in future studies (Hollender et al., 2023b; Peter et al., 2021). From reviewing the available literature, we identified several procedures that were not widely used but would benefit future studies undertaking NTA for PFAS (Table 2). Many of these recommendations would be enhanced from an increase in the range of commercially available PFAS standards and reference materials.

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CRedit authorship contribution statement

David Megson: Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Pennante Bruce-Vanderpuije:** Writing – original draft, Investigation, Formal analysis. **Ifeoluwa Grace Idowu:** Writing – review & editing, Visualization. **Okon Dominic Ekpe:** Writing – review & editing. **Courtney D. Sandau:** Writing – review & editing.

Declaration of competing interest

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Data availability

Data is provided in the supplementary information.

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