Environmental Pollution 329 (2023) 121705

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Review

Analytical approaches for screening of per- and poly fluoroalkyl substances in food items: A review of recent advances and improvements[☆]

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ARTICLE INFO

Keywords:
PFAS
Processed food
LC-MS/MS
Non-targeted analysis
HRMS

ABSTRACT

Per and polyfluoroalkyl substances (PFAS) are a group of man-made chemicals characterized by their ubiquitous nature in all environmental compartments which makes them of increasing concern due to their persistence, bioaccumulation, and toxicity (PBT). Several instrumental methodologies and separation techniques have been identified in the literature for the detection and quantification of PFAS in environmental samples. In this review, we have identified and compared common separation techniques adopted for the extraction of PFAS in food items, and analytical methodologies for identification and quantification of PFAS in food items of plant and animal origin, highlighting recent advances in tandem techniques for the high selectivity and separation of PFAS related compounds as well as knowledge gaps and research needs on current analytical methodologies.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a group of manmade chemicals used for both industrial and domestic purposes such as fire-fighting foams (FFFs), paint, carpets, cosmetics, and food packaging materials (Feng et al., 2019). Their desired use is related to the unique chemical characteristics of the compound with hydrophilic head groups and hydrophobic fluorocarbon chains which makes them ubiquitous in all environmental compartments. Although persistent organic pollutants (POPs) analogues tend to fractionate into the fat content of food items due to their lipophilic nature, certain PFAS have been reported to exhibit bioaccumulation and biomagnification potentials in the protein content of aquatic organisms due to their proteinophilic characteristics, especially from legacy PFAS such as perfluorooctanoic acid (PFOA) and perfluorooctane sulphonic acid (PFOS), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA) and expressing high toxicity to human and animal health at lower concentration levels ((Blake and Fenton, 2020); Burkhard, 2021). Furthermore, adverse effect on both human and aquatic health becomes significant due to long range environmental transport of PFOA, PFOS, perfluorohexane sulfonic acid (PFHxS), salts of these compounds, and other related compounds (such as perfluorooctane sulfonyl fluoride: PFOS-F), hence, they are included in the Annexes of Stockholm Convention (Ruan and Jiang, 2017; UNEP, 2011). The strength of the C–F bond confers resistance to environmental degradation which makes them a persistent, toxic, and bioaccumulative (PBT) group of compounds (Gar Alalm & Boffito, 2022). Although some PFAS have been phased out, replacement PFAS compounds are in use, including the short chain ($C < 8$) compounds, which are more easily transported in the environment and may be equally toxic (Brendel et al., 2018). Some of the most common classes of PFAS being currently monitored and ubiquitously distributed in the food web includes: perfluoroalkyl sulphonic acids (PFSAs), perfluoroalkyl carboxylic acids (PFCAs) especially those with C_4–C_{11} chain lengths, fluorotelomers with carboxylic and hydroxyl end groups (FTCAs and FTOHs) and perfluorinated sulfonamides (Fig. 1) (Capriotti et al., 2013). These compounds are reported in literature as precursors to cancer (Eriksen et al.,

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[☆] This paper has been recommended for acceptance by Charles Wong.

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https://doi.org/10.1016/j.envpol.2023.121705
Received 27 February 2023; Received in revised form 18 April 2023; Accepted 21 April 2023

2009; Gilliland & Mandel, 1993; Klaunig et al., 2015; Vieira et al., 2013), immunological and reproductive disorders (Grandjean et al., 2012; Klaunig et al., 2015; Rickard et al., 2022) and neurodevelopmental effects (Liew et al., 2018; Sunderland et al., 2019; Wang et al., 2011) in humans. One important exposure pathways for PFAS is through diet with potential treats to human health (Cakmak et al., 2022; Wielsøe et al., 2022). Possible potential sources of PFAS contamination in food items includes contact with food packaging materials, contaminated water used for irrigation of farm produces, and use of soil and application of biosolids containing PFAS for fertilization of crops. Additionally, seafood, cattle, and poultry consumed by humans may accumulate PFAS (through water consumption and the food chain) and contribute to dietary exposure (Vorst et al., 2021). Several studies have reported the presence of PFAS in meat and fast foods (Tittlemier et al., 2007); seafoods and vegetables (Lin et al., 2020), and packaged food items (Seshasayee et al., 2021).

Recent advances and improvements in the analytical methods for the efficient extraction and quantitation of PFAS especially from seafood and plant derived foods have been noteworthy (Genualdi et al., 2022; Kannan et al., 2005; Powley et al., 2008; Sadia et al., 2020; Stahl et al., 2014). Various extraction techniques utilized includes sonication ((Rawn et al., 2022) Tang et al., 2014), liquid-liquid extraction (LLE) (Tang et al., 2014; Vela-Soria et al., 2021), microwave-assisted extraction (MAE) (Beser et al., 2011), solid liquid extraction (SLE) ((Rawn et al., 2022); Vorst et al., 2021), solid phase extraction (SPE) (Hassan et al., 2023; Kuklenyik et al., 2004) and more recently, the use of QuEChERS (Genualdi et al., 2021a; Krepich, 2019). A combination of extraction methods, such as sonication and SLE have been also used in tandem for PFAS extraction (Raw et al., 2022; Tang et al., 2014). QuEChERS stands for quick, easy, cheap, effective, rugged, and safe technique frequently used for extraction of organic compounds in food items, that has demonstrated to be robust and reliable for PFAS. This procedure utilizes acetonitrile and acidified inorganic salts for salting out analytes of interest into the organic phase which ensures high efficiency and trace level determination of PFAS (Hlouskova et al., 2013). Although, some methods require the use of small amount of solvent than others, matrix effects due to the complex nature of biological samples remains a recurrent issue during extraction (Valsecchi et al., 2013a). Most common phenomenon is the coextraction of lipids and other interferent matrix constituents which can cause ion suppression or enhancement of targeted analytes (Llorca et al., 2009; Nania et al., 2009; Valsecchi et al., 2013a). Hence the need to develop a robust cleanup method to eliminate issues associated with matrix effect. Most QuEChERS based extraction are often used in conjunction with dispersive solid phase (dSPE) as a cleanup step. dSPE is useful for removal of co-extracting matrix after extraction from samples, whereas typically used reagents consists of graphitized carbon black (GCB), primary and secondary amine (PSA), C_{18} and $MgSO_4$ which are applied in various proportions. GCB functions to remove nonfluorinated compounds especially aromatic compounds (responsible for color in biological matrixes) since they are strongly adsorbed due to interactions with π electrons of GCB while PSA (a weak anion exchanger) is used for the removal of various polar organic acids and sugars that might act as instrument interference thus ensuring efficient purification process of extracts (Powley et al., 2005; Valsecchi et al., 2013a; Zheng et al., 2015).

The development of selective and sensitive instrumental methods for separation and quantification of PFAS is deemed essential for the variety of PFAS classes having different physical chemical properties. In the case of semi-volatile and nonvolatile PFAS, liquid chromatography (LC) in tandem with mass spectrometry (MS/MS) is often used as a preferred chromatographic technique for the separation of PFAS congeners. Although some PFAS including PFCAs are amenable to gas chromatographic separations after derivatization using diazomethane, benzyl bromide, 2,4-difluoroaniline, methanol, butanol and methyliodide (Trojanowicz & Koc, 2013), volatile PFAS such as fluorotelomer alcohols (FTOHs) can be directly analyzed using gas chromatographic-mass spectrometry (GC-MS) with chemical ionization (CI) techniques (Berger et al., 2004; Moody et al., 2002; Stock et al., 2004). Reverse phase (RP) chromatography consisting of a polar mobile phase (ammonium formate/acetate buffer and methanol) and a non-polar stationary phase (C_{18}) is commonly used for the separation of most PFAS congeners. For most anionic PFAS congeners such PFSAs and PFCAs, LC-MS/MS with a negative electrospray ionization (ESI) interface is often the preferred method of analysis via deprotonation of the functional groups, providing high sensitivity and wide dynamic range (Jahnke and Berger, 2009; Weiss et al., 2013). Although high selectivity and sensitivity have been achieved through traditional target method (LC-MS/MS) based on available standards, there is still a good number of PFAS, to which no reference standards are available, and many unknown PFAS, considering that the knowledge of their transformation and degradation is rather limited. Hence, there arises the need for high-resolution mass spectrometry (HRMS) applications, combining suspect screening and non-targeted analysis of PFAS, especially in food items (Krauss et al., 2010; Panieri et al., 2022; Ruan and Jiang, 2017; Taylor and Sapozhnikova, 2022).

This review provides an overview of common approaches and recent advancements in terms of sample processing and analysis of food samples, especially those from plant and animal origin. Gas and liquid

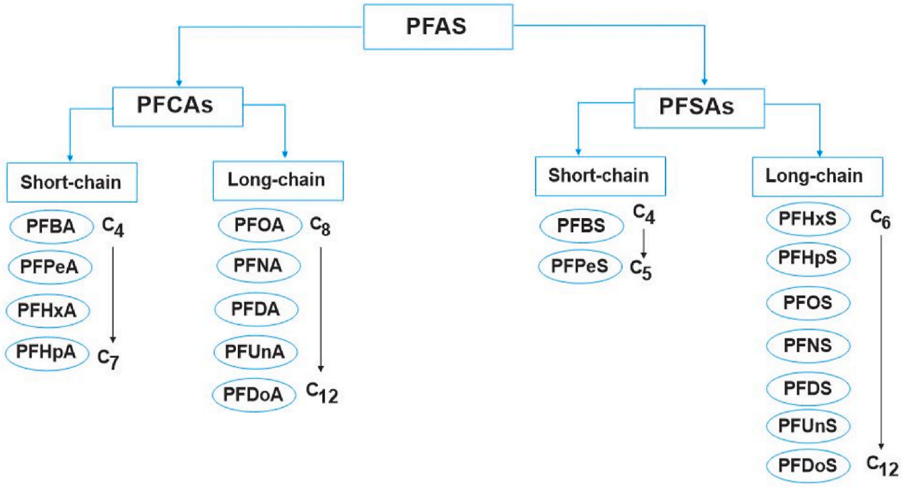

Fig. 1. PFAS classification based on the terminology for PFAS proposed by Buck et al. (2011), showing commonly reported compounds in food items of plant and animal origin.

chromatographic techniques used in tandem with different mass spectrometer such as QqQ MS/MS, qTOF-HRMS, Orbitrap MS/MS are compared in order to improve understanding on advantages and disadvantages of each instrument related to PFAS separation, detection and quantification in food and plant derived samples. In addition, we also identified potential knowledge gaps on analytical methodologies, discussed alternative approaches and research needs. The scientific materials referenced in this review article were sourced from several online databases of peer-reviewed journals with the phrases "analytical methodologies of PFAS, extraction of PFAS in food items, and non-targeted analysis of PFAS and ionization of PFAS". The online database employed includes Google, Google scholar, Science Direct, PubMed and others. Complementary searches were also made using the Scopus database to get recent publications and identify research gaps related to our review article. Lastly, rigorous, and extensive search was conducted on all published journals between 1975 till 2023 as shown in the reference section of this review paper.

2. Comparative studies of sample preparation methods for extraction of PFAS in food items

This section focuses on the various sample steps adopted for the extraction of PFAS in food items of plant and animal origin including figures of merits, such as % recoveries, method detection limits, and potential limitations of each method. The majority of sample preparation methods that focuses of the extraction of PFAS from food matrices from plant and animal origin involves: Ion-pair extraction (IPE) (Lacina et al., 2011; Schiavone et al., 2009), Solid-Liquid extraction (SLE) (Gosetti et al., 2010; Powley et al., 2005), Solid phase extraction (SPE) (Pignotti et al., 2017; Wang et al., 2010) and QuEChERS (Baduel et al., 2015; Genualdi et al., 2021b; Organtini et al., 2021.; Santana-Mayor et al., 2019). Achieving good sensitivity and selectivity is one of the prioritized aims in every analytical practice. The aforementioned extraction methods have been utilized in literature for extracting environmental contaminants including PFAS from wide spectrum of complex food matrices such as dairy products, seafood items, vegetables, and processed foods. Guidelines for laboratory use of these methods are itemized in the ASTM (D7979-17 and D7968-17a), and U.S. EPA (537 and 537.1) handbook.

Ion pairing extraction (IPE) was one of the earliest and initial method for extracting legacy PFAS (Pan et al., 2020; 2017). This extraction method basically utilizes a counter ion of opposite charge to aid the distribution of ionic compounds into an organic phase (Persson and Karger, 1986). The solid samples are usually introduced to acid (e.g formic acid) or alkaline (e.g KOH/NaOH) digestion prior to ion pairing using tetra-n-butylammonium hydrogen (TBA) as the pairing agent with anionic PFAS. This helps in reducing the polarity of PFAS in the matrix. However, one major setback of this method is that during the extraction of the ion-pair, the matrix is co-extracted alongside with the non-polar solvent-methyl-tert-butyl ether (MTBE) leading to poor recovery (30–80%) as a result of high lipid content in food matrices, which can potentially affect the sensitivity of PFAS especially when trace levels are present in the sample (Sadia et al., 2020). To improve the quality of extracts, alkaline-based-IPE coupled with solid phase extraction (SPE) techniques has been utilized in literature (Farahin Mohd Ali et al., 2022; Sadia, 2018; ten Dam et al., 2020). Although acid digestion has been utilized for food and biological samples (Kärrman et al., 2005; Lacina et al., 2011; Wang et al., 2010; 2010c; Yeung et al., 2009), this could potentially lead to partial oxidation of PFAS precursors and impurities in the analysis of PFAS (Abafe et al., 2021; Young et al., 2012). Alkaline digestion has been the most preferred method for extraction of PFAS congeners in food matrices because it minimizes interferences and matrix effects, improve sensitivity and selectivity (Lacina et al., 2011; Powley et al., 2005). However, it has been identified new co-extracted compounds that could suppress or interfere the detection of some short chain PFAS. For example, Lacina et al. applied alkaline digestion using NaOH followed by lipid hydrolysis on fish samples and results obtained showed an intense co-eluting interference especially for short chain PFAS – PFPeA and PFBA due to the presence of glycerol and fatty acids released during alkaline digestion (Lacina et al., 2011). Methanol and acetonitrile are regarded as good and common solvent preferably used for the extraction of PFAS since they have medium polarity functionalities (Sadia, 2018; ten Dam et al., 2020). Sadia et al. compared the use of methanol and acetone using solid-liquid extraction followed by solid phase extraction (SPE) as a clean-up step, suggesting that acetonitrile showed better recoveries than methanol for extraction of milk, beef, fish butter, egg, and chicken samples (Sadia, 2018). However, a more recent study carried out by Zhang et al. investigated the stability of commonly used solvents such as water, isopropyl alcohol (IPA), methanol, acetonitrile (ACN) and dimethyl sulfoxide (DMSO) in environmental and toxicological studies, showing that none of the PFAS homologues had measurable degradation products in deionized water, IPA, and methanol in the span of 30 days. However, about nine polyfluoroalkyl ether acids (PFEAs) and hexafluoropropylene oxide (HFPO) homologues were degraded after 30 days in polar aprotic solvents namely: acetone, ACN and DMSO (Zhang et al., 2021) indicating that solvent choices should be greatly considered when performing IPE, LLE and SPE on food items as they can significantly affect analytical performance and results of analysis.

SLE is aimed at removing soluble components from solid matrices using a suitable solvent. SLE was initially applied for the extraction of PFAS from soil and sediment samples (Pan et al., 2020; Yu et al., 2018). Extraction of analyte from solid matrices with SLE is always coupled with sonication. Polar solvents such as methanol and acetonitrile are often used for these extraction procedures. Protein precipitation using ACN has been reported for tissue and blood analysis of aquatic food due to good recovery and easy handling. However, the limitation of SLE is the inefficient extraction of wide range of PFAS such as non-polar long chain and hydrophilic short-chain PFAS homologues (e.g $PFSA_{C4\text{-}C8}$ and $PFCA_{C4\text{-}C14}$) that potentially accumulates in aquatic organisms (Valsecchi et al., 2013b). In response to this, an optimized micro-extraction version of SLE was developed by adjusting solvent polarities using Tetrahydrofuran (THF): water (H_2O) (75:25, v/v) mixture for the extraction of PFAS homologues from the muscle and liver samples of wide spectrum of marine animals. Luque et al. (2010) obtained good recovery >85% for $PFAS_{C4\text{-}C14}$. Solid phase extraction (SPE) techniques are often used for dual purposes (extraction and clean-up step) in the preparation steps of food items. It is regarded as a less laborious and faster alternatives than other traditional methods for the isolation and preconcentration of PFAS from both biotic and abiotic samples (Lacina et al., 2011) and it is often reported as a popular method in literature for the direct extraction of PFAS in liquid samples (e.g., milk) and fish (mixed with water followed by SPE) due to the double-fold advantages of extraction and clean-up, all in one step (Abafe et al., 2021; Guerranti et al., 2013). Considering the timeframe involved in the solid phase extraction step, a fast-screening and high throughput technique such as an on-line SPE method was developed for the analysis of PFAS compounds in aquatic organisms. It is essentially an automated method requiring a small amount of the sample, little analyst interference and less extraction time than the offline SPE process. For example, Gosetti et al. (2010) extracted fish fillet using methanol as extraction solvent, followed by dilution and acidification of the clean supernatant with 20/80 (v/v) mixture of 0.1% formic acid in CH_3OH and 0.1% formic acid in ultrapure H_2O and analysis by online-SPE-LC-MS-MS. This technique produced recoveries of >83% of PFAS irrespective of the concentration of the analyte in the 10-1000 ngL^{-1} range (Gosetti et al., 2010). The online SPE procedure (Fig. 2) simply follows through injection of sample into the sample loop, loading the sample into the SPE column with the aid of an LC pump followed by a short wash step to eliminate interferences from matrices. Targeted analytes are expected to be retained on the SPE column, while unwanted matrix/solvent are removed into the waste while equilibration of the analytical column

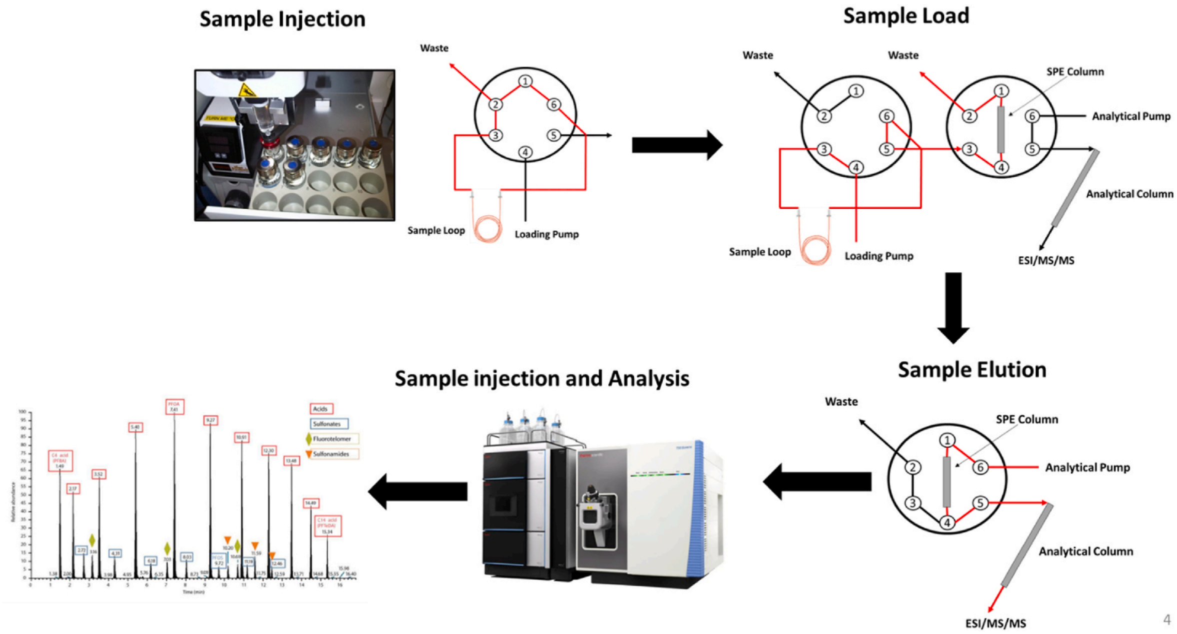

Fig. 2. Schematic workflow of an online-SPE-LC-MS-MS system.

happens concomitantly. After some time interval, the valve is switched and the retained analytes are backflushed from the SPE column into the analytical column for separation and analysis by LC-MS/MS (Quinete et al., 2013). Amongst the 11 analytes analyzed by Gosetti et al., PFHxS (92.6 ± 2.7%) and PFTeDA (82.9 ± 5.8%) compounds recorded the highest and lowest percent recoveries respectively, and this may be due to differences in their carbon chain length (Gosetti et al., 2010). Furthermore, it should be noted that clogging of the SPE column due to matrix build up could be a potential limitation of this method. This necessitates the application of solvent mixtures with a wide range of polarities for flushing and keeping the system clean of matrices trap.

QuEChERS method is generally considered a highly productive and accurate method for extraction of emerging contaminants at ultra-trace level (ten Dam et al., 2020; Valsecchi et al., 2013b). It was initially designed and utilized for the extraction of multiresidue pesticide contaminants in vegetable and fruits (Santana-Mayor et al., 2019b). Since it has capabilities of extracting wide spectrum of organic contaminants, it is now adopted for the extraction of PFAS compounds coupled with cleanup step using dSPE(Envicarb) in seafoods (Álvarez-Ruiz et al., 2021; Lacina et al., 2011), meats (Hlouskova et al., 2013), dairy (Abafe et al., 2021; Lacina et al., 2011), fruits and vegetables (Meng et al., 2022; Scordo et al., 2020; Zhou et al., 2019) and processed foods (Genualdi et al., 2021a; Sznajder-Katarzyńska et al., 2020). Non-ionic and ionic PFAS such as perfluorooctane amides (FOSAs) and perfluoroalkane sulfonic acids (PFSAs), perfluoroalkyl carboxylic acids (PFCAs), perfluorophosphonic acids (PFPAs) were extracted from fish and milk samples using QuEChERS coupled with dSPE using C18 and ENVI-carb to produce high recoveries of 70–120%. Recently, Meng et al. (2022) adopted a modified U.S. EPA extraction method using basic MeOH for extraction and SPE-Oasis (WAX) for the cleanup step of PFAS compounds in vegetables and fruits. High recoveries were obtained for PFCAs, PFSAs and FTSs ranging from 79 to 133%. However, based on this method, long chain PFAS such as PFTrDA and PFDS had poor recoveries. It was hypothesized that these compounds have less potential in bioaccumulating in vegetables and fruits due to their low mobility (Meng et al., 2022) and impeded membrane passage into the different parts of plant with increase in chain length ((Lesmeister et al., 2021)). The loss of PFAS classes during SPE cleanup step coupled with contamination during the procedural steps are some of the limitations of this method. Hence an efficient and comprehensive method that can eliminate unwanted matrix interferences and also capture wide expanding list of PFAS with diverse physico-chemical properties is required. More recently, Taylor and Sapozhnikova (2022), developed and compared a QuEChERS mega-method (also known as QuEChERSER) with broader range of polarities than the already established QuEChERS method for the analysis of food items (Fig. 3) and validated the QuEChERSER method for six food items (chicken, powdered egg, pork, catfish, liquid eggs, and beef) using high-resolution mass spectrometer, resulting in recoveries of 70–120% for 33 targeted PFAS compounds (Taylor and Sapozhnikova, 2022a). In summary alkaline based extraction is commonly used for the extraction of PFAS compounds in fish tissues compared to IPE due to less matrix interference. However, the co-elution of compounds with similar chemistry to PFPeA and PFBA (e.g., fatty acids) could be a potential setback of this method in some food samples. Solid phase extraction offers a dual-purpose application for extraction and cleanup step of food items. Although it is a fast and less laborious alternative to traditional methods, cartridges used are commercially expensive, especially when a large number of samples is involved. On-line SPE on the other hand requires a small sample size, less labor intensive and offers faster extraction time compared to manually operated SPE method. Major challenges encountered in the automation process involve clogging of the SPE column and carry-over effects, therefore requiring washing steps with solvents of wide range of polarities. QuEChERS methods are currently being used for routine extraction due to its lower cost (even though QuEChERS kits could be equally expensive as SPE, salts and sorbents can be purchased separately for cheaper price) and comprehensive removal of wide spectrum of organic contaminants from environmental matrices. Different extraction methods and Instrumental techniques including the advantages and limitation of each extraction method utilized for analysis of PFAS in food items are summarized in Tables S1 and S2 respectively.

3. Clean up methods for elimination of matrix in food samples

Removal of endogenous substances from the extraction step is a crucial factor for the total elimination of matrix interference. Different procedural steps have their merits and demerits depending on the type of targeted analyte and the composition of the matrix (Valsecchi et al., 2013a). SPE which can be categorized into retentive and non-retentive modes have been utilized for the cleanup of matrices in food items

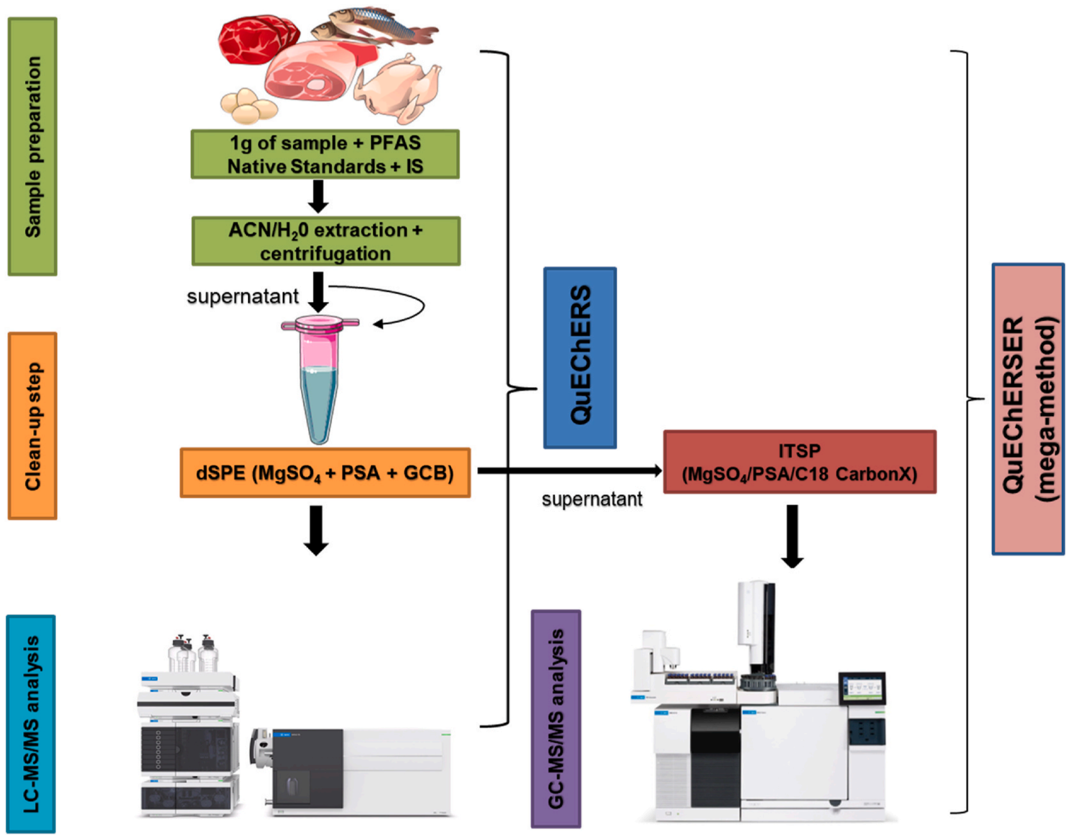

Fig. 3. Workflow showing the comparative analysis of QuEChERSER and QuEChERS method for the extraction of PFAS in food items.

after extraction (ten Dam et al., 2020). In the retentive modes, different forms of SPE used for cleanup includes weak anion exchangers (WAX) such as Strata- XAW (*Phenomenex, Torrance, CA, USA*) and Oasis WAX (*Waters, Milford, MA, USA*), and hydrophilic-lipophilic sorbents also known as polymeric reversed phases such as Strata-X and Oasis HLB (Lorenzo et al., 2018; Pan et al., 2020). HLB cartridges are utilized for the cleanup of extracts, but recovery of short chain PFAS homologues could be low due to the poor retention of hydrophilic compounds on the sorbent (Lin et al., 2016). Furthermore, So et al. (2006) posited that the use of HLB sorbents is not suitable for the extraction of short chain PFCAs such as PFBA, PFHxA and PFPeA as the recoveries obtained are <30% in oysters samples (So et al., 2006; ten Dam et al., 2020). However, WAX polymeric cartridges have been reported to show better recoveries of those short chain homologues through electrostatic interactions (Pan et al., 2020). Basically, the WAX sorbent was protonated to enhance the adsorption of PFAS homologues on the secondary amine (stationary phase) at a pH = 4 (So et al., 2006; ten Dam et al., 2020; Vierke et al., 2013). Since the PFAS compounds are in the anionic form, they can bind with the protonated amine group through electrostatic interactions. The pH is kept at 4 during the washing step to maintain the ionic states of the participating charged groups (i.e., the anionic analytes and the cationic WAX sorbent). Subsequent upon the elution step, the polarity of the WAX sorbent is deactivated through increase in pH which essentially neutralize the secondary amines in the sorbent/stationary phase, leading to the release of the PFAS analytes from the sorbent using basic MeOH (i.e., NH_4OH in MeOH) as a suitable eluting solvent (ten Dam et al., 2020). Cationic, zwitterionic and neutral PFAS homologues can be extracted and fractionated using mixed-mode WAX sorbents (Munoz et al., 2018). These classes of PFAS compounds can be eluted using MeOH while the anionic PFAS are retained in the column. The anionic PFAS homologues can be dislodged from the sorbent using basic MeOH as previously mentioned. WAX based sorbents have been utilized for the satisfactory recoveries of emerging PFAS families such as Cl-PFESAs (Pan et al., 2020; Xu et al., 2017), FTABs (Hansen et al., 2001; Pan et al., 2020), Sodium *p*-perfluorous nonenoxybenzensulfonate (OBS) (Hansen et al., 2001; Pan et al., 2020) and PFECAs (Pan et al., 2020; Song et al., 2018).

Non-retentive mode of SPE using dSPE with Envi-Carb (graphitized carbon) has been previously used for the removal of co-extracts from matrix after SLE. dSPE has been applied with other purification techniques for methanol, acetonitrile (Powley et al., 2008) and THF:$H_2$0 (Swiegelaar et al., 2015) extracts. It should also be noted that PFCAs enriched with π electrons do not effectively interact with graphitized carbon even in the presence of weak eluants such as MeOH, suggesting that these compounds will not be adsorbed and retained on it (Powley et al., 2005). This is attributed to the presence of highly electronegative fluorine atoms in the structure. In contrast, most non-perfluorinated compounds with aromatic properties will tend to be adsorbed strongly through dispersive reactions with π electrons of graphitized carbon, thus ensuring effective removal of these compounds from the extracts. Published results in literature proposed that the utilization of graphitized carbon black could help in complete elimination of matrix interferences due to high recoveries obtained for spiked extracts before LC-MS/MS analysis (Powley et al., 2008; Valsecchi et al., 2013). However, a more recent study by Organtini et al. (2021) demonstrated that the use of GCB as a clean-up step after QuEChERS extraction resulted in incomplete elimination of the interferences, therefore causing ion suppression of PFOA (−24%) and PFTreDA (−47%) in cranberry (Organtini et al., 2021). Nevertheless, Envi-Carb was previously reported for the purification of SPE eluates from IPE and alkaline digestion extracts (Labadie and Chevreuil, 2011). Considering protein and fat-based food items, efficient and more rigorous clean-up steps are required to eliminate all matrix interferences that could potentially affect ionization efficiency. More recently, Sadia (2018) used Envi-Carb as cleanup for SPE extract of high-fatty food contents (milk and egg), however gelatinous appearance in the eluate suggested that Envi-Carb might not be effective enough for the cleanup of high fatty contents in food and milk. This was attributed to the presence of the endogenous compound taurodeoxycholic acid (TDC) - an isomer of cholic acid found in proteinous food items such as chicken eggs, causing ion suppression of PFAS homologues with similar retention time. Huge ion suppression (85% for PFOS) was reported in egg samples. However, with the application of additional cleanup step such as WAX-SPE, better signal response was obtained showing that multiple clean-up steps might be necessary depending on the nature of matrix involved (Sadia, 2018). The use of C_{18} sorbents have been reported for their exceptional ability in producing good peak shapes and high recovery specifically for legacy PFAS such as PFOA and PFOS (Abafe et al., 2021; Schiessel, 2017). It has also been used for the elimination of lipophilic components as well as removal of non-polar co-extracts such as triacylglycerols (Valsecchi et al., 2013). However, reports from other researchers suggested that it could contain trace level of PFAS (Macheka-Tendenguwo et al., 2018; Sun et al., 2017; Wang et al., 2014). The summary of different types of cleanup procedures previously published in the literature is shown in Table S3.

4. Advances in extraction of PFAS from food items

4.1. Use of magnetic solid phase extraction techniques (MSPE)

Although MSPE has been implemented for the extraction of traditional contaminants, there is very limited information on the adoption of this method for extraction of PFAS in food items. This technique basically works by introducing magnetic adsorbents to sample solutions in order to adsorb analytes followed by the collection of the analytes using an external magnetic field (Farahin Mohd Ali et al., 2022; Safarikova et al., 2005). One pronounced advantage of this method is that centrifugation or filtration is not required since the analyte is desorbed/dislodged from the sorbent surface using a suitable solvent. Furthermore, it is a simple extraction technique that requires a small volume of sample and solvent for the extraction and desorption of targeted analytes. Hence, this ensures effective analyte concentration, high recovery of analytes coupled with short extraction time. These sorbents can also be recycled for further use making it eco-friendly (Vasconcelos and Fernandes, 2017). The general workflow of MSPE is shown in Fig. 4 below. Magnetic particles (MPs) with superparamagnetic and ferromagnetic capabilities such as nickel, iron, cobalt, and their respective oxides have been previously utilized as potential sorbents for MSPE (Farahin Mohd Ali et al., 2022; Giakisikli and Anthemidis, 2013). They are also reported to have high adsorption capacity for sorption of metals due to their high surface-to-volume ratio (Farahin Mohd Ali et al., 2022). Functionalized iron-oxide MPs have been used for the extraction of polar and moderately non-polar organic contaminants in water samples (Ye et al., 2016; Farahin Mohd Ali et al., 2022; Gong et al., 2017; Wu et al., 2016).

More recently, the use of MSPE (in dispersive mode) is currently on the rise since it offers a rapid and easy way of separating extracts from sample solution with small amount of solvent after SPE using an externally applied magnet. A typical MSPE known as Cucurbit(n)uril (CB(n)) composed of a supramolecular cage structure (a hydrophobic inner cavity) has been provided good selective extraction of salvianolic acids (Zhang et al., 2019), uranium ions (Shao et al., 2016), and cytokinin (Zhang et al., 2016). It is usually composed of glycosyl subunits, where n represents the number of subunits present in the molecule. The CB(n) molecules contain cavities that are coated with ureido carbonyl functional groups making them suitable for dipole-dipole and electrostatic interactions. Hence, these functionalities make them suitable for molecular recognition, macromolecular assembly interactions, supramolecular self-assembly and more importantly environmental pollution control (Huang et al., 2022). Although this material has been successfully implemented in the analytical and separation science research space, application of this sorbent is still new and is currently attracting attention for the extraction of emerging contaminants such as PFAS in environmental matrices. This would be a promising extractive material in the sense that the OH^-, COO^- and SO_3^- hydrophilic groups in PFAS homologues can undergo H-bonding or electrostatic interactions with the carbonyl functional groups of CB(n) molecule. Furthermore, the formation of an "host-guest" relationship between the hydrophobic C–F chain length of PFAS and the inner hydrophobic cavity of CB(n) molecule qualifies this material as a promising sorbent for the extraction and separation of PFAS from environmental and food samples. Huang et al. (2022) synthesized a modified CB(n) sorbent functionalized with magnetic iron (III) oxide (Fe_3O_4@CB(n)) for the extraction of short and long

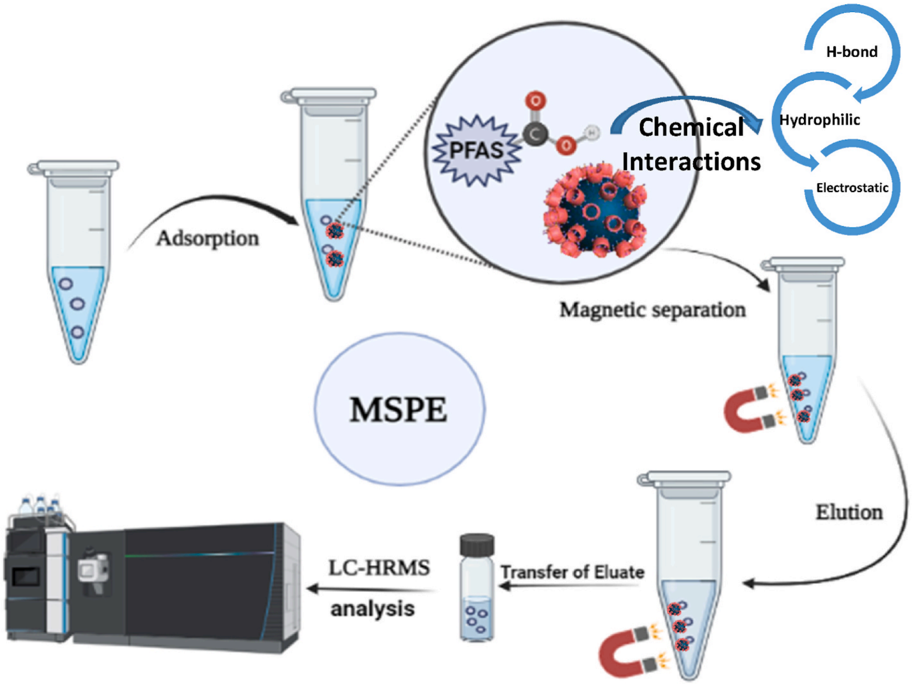

Fig. 4. Workflow of the magnetic solid phase extraction (MSPE) for extracting PFAS from sample matrices.

chain PFAS compounds from fish muscle samples. After the extraction and dilution step, Fe_3O_4@CB(n) was used as a dispersive phase to extract PFAS as shown in Fig. 4 below. Good recoveries (73–124%), low LOD (0.004–0.04 μg/L) and LOQ (0.005–0.1 μg/L) (Huang et al., 2022) suggests that Fe_3O_4@CB(n) is a promising MSPE for extracting PFAS from food items and should be further explored for other food class.

4.2. Use of molecularly imprinted polymers (MIPs)

Molecularly imprinted polymers (MIPs) are characterized with high selectivity and affinity for targeted molecules and are widely used across the field of separation science. Herein, promising and emerging materials are synthesized in the presence of a template molecule followed by subsequent removal of the template to produce a "memory site" that can selectively recognize and bind targeted compound in matrix solution (Cantarella et al., 2019; Zare et al., 2022). MIPs are advantageous considering the ease of preparation coupled with high tendency of creating a tailor-made binding site to the target molecule (as template) during the polymerization process. These materials have been successfully utilized and reported as an excellent sorbent for removal of pharmaceutical contaminants from wastewater (Augusto et al., 2012; Cantarella et al., 2019; Li and Row, 2019; Zare et al., 2022). Even though adsorption is a common method for the removal of both organic and inorganic contaminants in environmental matrices, several adsorbents such as clays, activated carbon and chitosan can't selectively remove organic contaminants in trace levels (Cantarella et al., 2019). Furthermore, other modes of SPE such as stir bar sorption extraction (SBSE) and solid phase microextraction (SPME) takes longer extraction time, while QuEChERS and other commercial SPE sorbents are expensive and/or often large quantities of sorbents beds are required. In addition, commercial adsorbents such as WAX-SPE are expensive and as earlier discussed and some of the SPE modes are unsuitable for extraction of short chain PFAS with <8 carbon atoms. Hence, there is the need to synthesize a low-cost adsorbent that ensures a rapid mass transfer of PFAS from environmental and food matrices to the sorbent. As a further criterion, the adsorbent must be selectively compatible for simple extraction of PFAS from complex matrices in a short period of time. In a recent research, Zou et al. (2022) synthesized a hydrophilic based MIP with synthetic phenolic resin (MIP-PR) (Fig. 5) in dispersive mode for the selective extraction of long chain PFAS in pork samples. Low LODs (0.011–0.08 ng/g), excellent recoveries (89.3–116.3%) coupled with short extraction time (6–8 min) and small amount of adsorbent (2 mg) were obtained for long chain PFAS (Zou et al., 2022). These findings suggest that MIP could be an efficient and excellent competitor to other commercial modes of SPE used for recovering trace levels of PFAS from high fatty food matrices. Although this study was successful for the selective extraction of long-chain PFAS, there is need to develop structurally modified MIPs that can adsorb both short chain and other novel PFAS classes in environmental and food matrices.

5. LC-MS/MS and ionization sources for targeted analysis of PFAS in food items

Liquid chromatography has been frequently used for the analysis of PFAS compounds in environmental and food matrices since they are amenable for semi-volatile and non-volatile, polar, higher molecular weight and thermally unstable compounds (Wang et al., 2022). Electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) and atmospheric pressure photoionization (APPI) are the commonly used ion sources for the ionization of organic contaminants (Jessome and Volmer, 2006). However, LC-ESI-QqQ (QqQ-triple quadrupole) is most often used ionization source to quantify legacy and emerging PFAS since most of the identified PFAS congeners ranges from ionic to semi-volatile compounds (Krauss et al., 2010; Pan et al., 2020). Moreso, (−) ESI ion source is effective for ionizing polar compounds such as PFAS. Zacs and Bartkevics investigated the ionization efficiency of different ion sources for PFOA and PFOS compounds. Results obtained in order of decreasing sensitivity is ESI > APPI > APCI indicating that ESI showed the highest instrumental sensitivity (Zacs and Bartkevics, 2016).

However, it is important to clarify that one major limitation of ESI is the higher susceptibility to matrix effects compared to other ionization sources (Lorenzo et al., 2018; Zacs and Bartkevics, 2016), this means that ion enhancement or suppression could occur depending on the nature of the co-eluting compounds in the matrix. TDC have been reported to co-elute with PFOS using a C_{18} column under LC separation conditions. Since TDC (m/z 498.2968) has similar mass to PFOS (m/z 498.92) and same observed transition 499 > 80, the presence of this co-eluting compound could potentially cause ion-enhancement of signals, causing an increase in the method detection limit (MDL) and over estimation of PFOS concentration in the sample due to increased instrument response related to TDC concentrations (Genualdi et al., 2021b; Sadia, 2018). Hence, efficient, and multiple clean-up steps are necessary to eliminate this bias. Signal suppression can also occur in ESI mode; as shown by Matuszewski et al. (2003), the increase in surface tension and viscosity in droplets as a result of high concentration of matrix interference is a major contributor (Matuszewski et al., 2003). To remediate these effects, Sadia (2018) used 250 mg ENVI-Carb SPE to efficiently eliminate TDC from chicken egg extract, thus eliminating the suppressed signal for PFOS analyte (Sadia, 2018).

Furthermore, it was suggested by most authors to apply matrix calibration matches and isotopically labelled C-13 or deuterated analogues as internal standards to account for matrix effect when quantifying PFAS in food samples (Macheka-Tendenguwo et al., 2018; SUN et al., 2017; van Leeuwen et al., 2009; Villagrasa et al., 2006). Negative ESI is mostly used for the analysis of PFAS due to high sensitivity, wide dynamic range, good linearity, and the fact that anionic PFAS easily loses a proton. Taylor and Sapozhnikova reported better linearity using (−) ESI-QqQ ($R^2 > 0.99$) for 98% of the analytes compared to only 96%

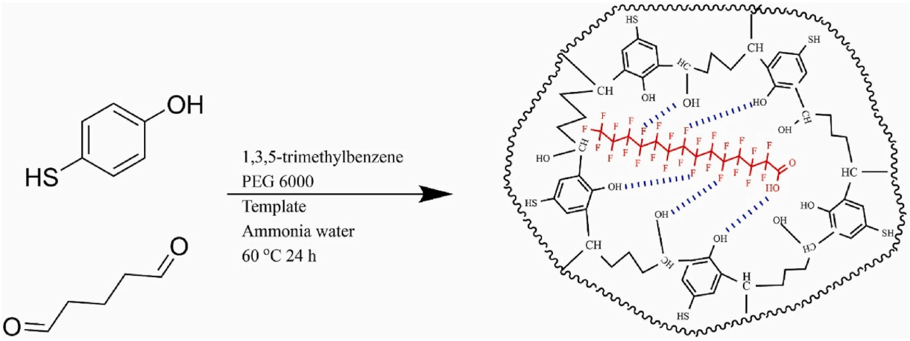

Fig. 5. Synthesis of MIP-PR used for the selective extraction of PFAS compounds from food samples. Reprinted from (Zou et al., 2022). Copyright (2022), with permission from Elsevier.

for high-resolution mass spectrometry (HRMS) in food safety inspection services (FSIS) regulated foods. Furthermore, QqQ offers broader linear ranges especially for longer chain PFCAs, sulfonamides and novel PFAS (FOSAAs, HFPODA and NFDHA) at trace level of 0.05 ng/mL (Taylor and Sapozhnikova, 2022b).

Different types of columns have been used for separation of PFAS in food items (Macheka-Tendenguwo et al., 2018; Valsecchi et al., 2013), with reverse phase (RP) chromatography being preferably used for the separation of PFAS compounds in LC analysis. C18 shorter columns coupled with small size particles are of growing interest since small internal diameter reduces the separation time thereby reducing the time of analysis and increasing resolution of PFAS peaks at trace levels. Methanol, acetonitrile, and buffer in water are common mobile phases used in RP-LC analysis, due to capabilities of achieving good selectivity and better peak shape. Koronaiou et al., (2022), investigated two commercially available stationary phases for the separation of PFAS compounds (Thermo Hypersil GOLD aQ column and Restek Raptor ARC-18). Thermo Hypersil GOLD aQ column (50 × 2.1 mm, 1.9 μm) had better instrumental performance in terms of analysis rate, separation, and sharp peaks than Restek Raptor ARC-18 (150 mm × 2.1 mm, 2.7 μm) although both columns produced acceptable results (Koronaiou et al., 2022). The presence of water molecules can act as a modifier to the hydrophobic stationary phases by aiding interactions such as ion exchange, dipole-dipole and π-π. PFSAs (≥C8) compounds tend to elute later than the PFCAs since they are less polar hence, proper elution time must be programmed in order to prevent carry over. In situations where shorter chain PFAS elutes too early, tetrabutylammonium hydrogensulfate (TBAS) is added as an ion-pairing reagents to the vial before analysis although this issue wasn't reported for the Hypersil GOLD aQ column (Awchi et al., 2022). Since most of the PFAS analysis are performed in (−) ESI modes, ammonium acetate or ammonium formate buffer (5 mM) is often added to improve the efficiency of ionization (Macheka-Tendenguwo et al., 2018).

6. High resolution mass spectrometers (HRMS) for non-targeted analysis of PFAS in food items

Targeted analysis using LC-MS/MS instrumental techniques offers high sensitivity for PFAS analytes with available standards. However, there are novel compounds without available standards that point out the limitations of targeted MS/MS methods. Hence, HRMS offers higher selectivity and resolving power for both targeted and novel PFAS in environmental and food samples, while providing information on accurate mass and empirical formula for the reliable interpretations of unknown compounds. Common HRMS used in environmental analysis includes quadrupole-time-of-flight (Q-TOF) and quadrupole-Orbitrap (Q-Exactive) (Liu et al., 2019; Valsecchi et al., 2013). Different approaches are performed in literature for the identification of novel PFAS, however, they all follow similar workflow including: (a) peak detection by mass filtering, (b) molecular assignment (annotation) to the exact mass of interest, and (c) database search for possible structure match (Fig. 6). Among the commonly available software packages used for PFAS identification, are the commercially available Compound Discoverer (Thermo), Mass Profiler (Agilent) and MetaboScape (Bruker) and the open-source software FluoroMatch, EPA's CompTox Chemicals Dashboard, Chemspider, among other. Regarding the different acquisition modes, data independent acquisition (DIA) and data dependent acquisition (DDA) are majorly utilized in non-targeted screening of analytes. In DIA mode, all the selected ions in the m/z range are fragmented and ionized in the MS second stage (tandem arrangement) for the detection of numerous unknown chemical compounds, i.e., MS and MS/MS data of the unidentified compounds are acquired in one chromatographic run simultaneously. This is advantageous in the sense that it ensures comprehensive screening and detection of all peaks and MS/MS data acquisition without the establishment of any mass filter or threshold before injection (Martínez-Bueno et al., 2019; Schulze et al., 2020). On the contrary, in DDA mode, data is acquired by selecting the most intense precursor ion of highest abundance in full scan mode (MS^1) and subjecting it to further fragmentation in the MS^2 mode (Martínez-Bueno et al., 2019; Schulze et al., 2020). Considering the choice of HRMS for accurate molecular formula assignment and identification of novel PFAS in complex matrices especially in food samples is crucial. HRMS with high resolving power (RP > 30,000) have been recommended for this purpose, thus making Q-orbitrap preferentially preferred compared to q-TOF (RP ~8000) (Liu et al., 2019, 2018; Ren et al., 2022). Non-targeted analysis (NTA) attempts to screen and detect vast number of contaminants with chemical characteristics amenable by mass spectrometry analysis, being a promising tool for developing contaminant profiles of specific aquatic species as well as discovery of new contaminants in various geographical locations (Alonso et al., 2017; Miaz et al., 2020). Barrett et al. (2021) reported for the first time the use of LC-(−) ESI-DIA-Orbitrap MS in full MS scan (RP = 70,000) and seven DIA MS/MS (RP = 3500) for suspect screening and non-targeted analysis of novel and legacy PFAS in beluga whales. A total of 54 PFAS grouped into nine classes (PFCAs, PFSAs, fluorotelomer carboxylic acids: FTCAs, single-hydrogenated perfluoroalkyl carboxylates: H–PFCAs, perfluoroalkyl sulfonamides derived acids: PFSAAs, single-hydrogenated perfluoroalkyl sulfonates: H–PFSAs, ether perfluoroalkyl sulfonates: Ether-PFSAs, single-hydrogenated perfluoroalkyl sulfonamides: H-Sulfonamides, and Sulfonamides) were identified (Barrett et al., 2021).

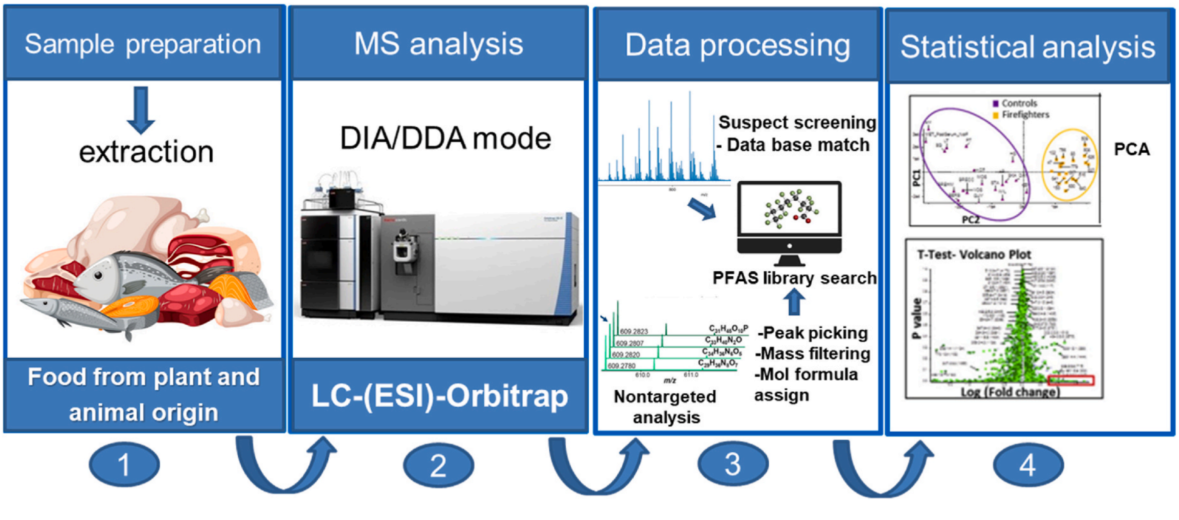

Fig. 6. Sample workflow for Suspect screening analysis (SSA) and non-targeted analysis (NTAs) of Legacy and novel PFAS in food samples.

Furthermore, in more recent applications, researchers are adopting NTA and suspect screening analysis (SSA) to understand both legacy and especially, novel PFAS accumulation in the food web since there are numerous precursors and metabolites that are present in the aquatic food web and are reported to be more deleterious than the parent PFAS compound (Kourtchev et al., 2022; Valsecchi et al., 2013a; Xiao et al., 2017). Ren et al. (2022)) recently applied LC- (−)-ESI-DDA-Q-TOF for NTA and SSA to understand the profiles of PFAS precursors and their metabolites in Lake Ontario aquatic food web. It was reported that 14 PFAAs (C5 – C14), legacy PFAS with already known precursors (n = 15) and novel PFAS (n = 400) biomagnified in the food web. Furthermore, benthic organisms from Lake Ontario were reported to contain more precursors than other aquatic species in the food web, suggesting that they constitute a large reservoir of these PFAS groups (Ren et al., 2022). Distribution patterns of PFAS and their precursors vary in the aquatic system depending on the influence of anthropogenic activities into the locations. Liu et al. discovered over 330 novel PFAS using Q-orbitrap-HRMS categorized into 10 classes: N-heterocycle (n = 1), carboxylate (n = 1), amine (n = 2), and sulfonate (n = 6) classes in fish samples collected from Yangtze River and Tangxum lake, with four of the PFAS classes being reported for the first time (Liu et al., 2018). Most research involving food matrices are recently implementing NTA and SSA as a complementary and confirmatory approach in addition to the results obtained from targeted analysis. SSA employs a complied lists of potential candidates/suspects from a defined database containing information on the accurate mass, molecular formula, and isotopic patterns of potential PFAS candidates (Miaz et al., 2020; Ren et al., 2022).

One of the unique advantages of NTA using HRMS is the elimination of co-eluting interferences (at least to the minimal) that could potentially underestimate or overestimate the PFAS levels in food items (Macheka-Tendenguwo et al., 2018). As previously established, ion enhancement/suppression is commonly associated with LC-(ESI)-MS/MS analysis, however, application of HRMS would help to discriminate between the difference in accurate masses of these co-eluting compounds and the analyte, therefore decreasing the chances of false positive (Macheka-Tendenguwo et al., 2018; Taylor and Sapozhnikova, 2022b).

7. Ion mobility mass spectrometry as emerging techniques for PFAS detection in food items

The term ion mobility spectrometry (IMS), initially called plasma chromatography is a technique that measures gas phase ions drifting through a region filled with a buffer gas in the presence of an electric field (Ellis et al., 1976; Revercomb and Mason, 1975)Revercomb and Mason 1975; Ellis, Pai et al.). The process measures mobility (K), an intrinsic property of an ion, and is similar to retention time in gas and liquid chromatography analyses ((Gabelica et al., 2019)). By calculating collisional cross sections (CCS) values based on mobility data, one can increase the reliability of identification of compounds in complex mixtures ((Celma et al., 2021)).

In 2019, the first application of IMS for separation of linear and branched PFAS isomers was reported ((Ahmed et al., 2019)). In this study, the advantage of differential mobility spectrometry-mass spectrometry (DMS-MS) over conventional liquid chromatography-mass spectrometry (LC-MS) technique was described. One of the advantages includes increasing throughput and achieving separations of PFAS isomers within a shorter analysis time, i.e., milliseconds timescale compared to conventional LC-MS methods that may take >30 min. In this particular study, the use of 1:1 He: N2 as bath gas increases resolution of isomers by 200% and 500% for PFOA and PFOS, respectively. As a result, linear, secondary-branched, and tertiary-branched isomers of PFOA and PFOS as well as those that differ by the position of a single perfluoro methyl group were resolved by DMS-MS. In another approach, IMS incorporated into existing LC-MS workflow was reported for PFAS analysis. This work showcased the use of LC- drift tube ion mobility spectrometry (DTIMS-MS) for characterization of PFAS species and isomeric content in both standards and environmental samples. The use of IMS separation provided a link between m/z and collision cross section (CCS) for some PFAS families and can be related to compositional differences in molecular structure ((Foster et al., 2022); Dodds et al., 2020) (Fig. 7). In addition, the use of CCS with retention time and accurate mass were beneficial in characterizing branching positions and identification of emerging PFAS species (Dodds et al., 2020). Furthermore, IMS have been successfully implemented for separation of co-eluting compounds with branched and long-chain PFAS compounds in ground water (Yukioka et al., 2021). However, there is limited information on the application of IMS for resolving isomeric PFAS compounds in food items.

8. Conclusion

Several methods have been previously developed and applied for the extraction of PFAS from environmental and food matrices. Those commonly reported in literature include ion pairing (alkaline and acid-based) extraction, solid-liquid extraction, SPE and QuEChERS extraction methods. In terms of matrices interference elimination, alkaline based extraction is preferentially utilized compared to IPE which is prone to co-elution of competing compounds with PFAS analytes during LC-MS/MS analysis. SPE offers a fast and less labor-intensive approach although high cost of commercially sold sorbents can be a limitation. QuEChERS method can alternatively be used since materials are easily sourced, less costly and promising for comprehensive extraction of wide range of organic pollutants in food items. There are different stationary phases (SPE) used for both PFAS extraction and clean-up process for elimination of matrices interferences in food sample extract. Depending on the chemistry of interaction between the different commercially available sorbents and their preferential selectivity to some PFAS classes, potential limitations in their extraction/clean-up capabilities can be observed, affecting recoveries, limit of detection and overall method performance. For example, ionic PFAS compounds are generally extracted using weak anion exchange SPE cartridges (e.g., WAX-SPE and Oasis-WAX) whereas neutral PFAS compounds are extracted using neutral sorbents such as Strata-X or Oasis HLB SPE cartridges. As a result, to date, a holistic and unified approach to PFAS sample preparation considering the wide range of PFAS physico-chemical properties is still missing. Having this in perspective, the implementation of highly selective sorbents for PFAS extraction from food items (such as MIPs and MSPE) to compensate for the deficiencies of the commercially sold SPEs is noteworthy and should be considered in further studies, especially for complex matrices such as food. These emerging sorbents are reported to be rapid and efficient, producing high recoveries for PFAS congeners, being cost-effective and

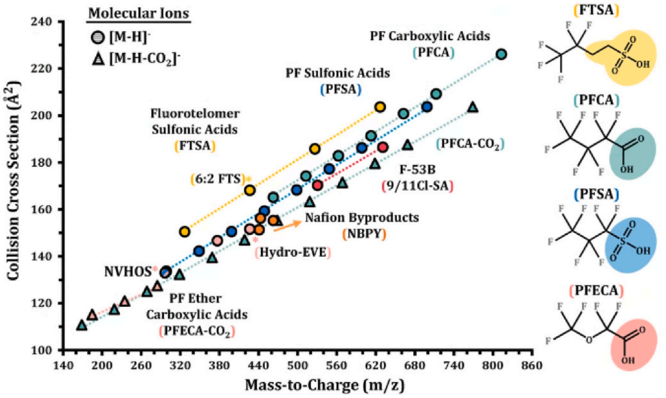

Fig. 7. Typical m/z vs CCS plot for specific PFAS subclasses showing a unique trendlines relating molecular classes based on their differences in gas phase packing efficiency. Reprinted with permission from (Dodds et al., 2020) Copyright 2023, American Chemical Society.

environment-friendly, since they can be reusable after each extraction step, thus having the potential to streamline current PFAS sample preparation processes for downstream chromatographic separation and analysis.

Undoubtedly, targeted analysis using (−) ESI LC-MS/MS is encouraged for use in the analysis of PFAS congeners however, issues emanating from peak interference due to co-eluting peaks have been commonly reported in literature. We suggest the application of HRMS and non-targeted analysis as a complementary technique to targeted analysis for PFAS assessment in complex food matrices, which has the potential to reduce interferences (false positives) while screening for a wide variety of PFAS without the need for reference standards. Although only few studies have explored the application of HRMS for analysis of PFAS in food items, recent studies showed promising results in the screening of legacy and novel PFAS-specie-specific profiles in the aquatic food web, which can give researchers insights into other toxic class of the family that could possess deleterious threats to both human and aquatic life. Finally, the application of ion mobility spectrometry techniques is growing exponentially in food science analysis especially in the aspect of isomeric resolution of proteins, carbohydrates, micronutrients, and even environmental contaminants. However, we identified research gaps in the application of this burgeoning technique for PFAS analysis in food items although, recent findings have proven its uses in water samples. We further encourage its application as a confirmatory technique in addition to HRMS for isomeric resolution as well as separation of co-eluting interferences with PFAS, especially in the case of < 5 ppm accurate mass difference.

Credit author statement

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Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

Acknowledgments

This material is based upon work supported by the National Science Foundation under Grant No. HRD-1547798 and Grant No. HRD-2111661. These NSF Grants were awarded to Florida International University as part of the Centers of Research Excellence in Science and Technology (CREST) Program. This is contribution number #1568 from the Institute of Environment, a Preeminent Program at Florida International University.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2023.121705.

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