A novel methodology for the determination of neutral perfluoroalkyl and polyfluoroalkyl substances in water by gas chromatography-atmospheric pressure photoionisation-high resolution mass spectrometry

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Abstract

Here, we developed and validated a new gas chromatography-atmospheric pressure photoionisation-high-resolution mass spectrometry (GC−APPI−HRMS) method combined with headspace–solid-phase microextraction (HS−SPME) for the determination of neutral perfluoroalkyl and polyfluoroalkyl substances (PFASs) in water samples. The method includes fluorotelomer olefins (FTOs), fluorotelomer alcohols (FTOHs), fluoroctanesulfonamides (FOSAs) and sulfonamido-ethanols (FOSEs). The feasibility of the GC-APPI interface for the ionisation of the target compounds was evaluated, achieving the best results using negative-ion dopant-assisted ionisation with acetone and a source and capillary temperatures of 225 °C and 175 °C, respectively. Under optimal conditions, FTOs and FTOHs mass spectra showed intense in-source CID fragment ions from the fluoroalkyl chain but also the superoxide $[M+O_2]^{-\bullet}$ adduct ion. For FOSAs, $[M–H]^{-}$ was the main ion generated, while FOSEs mass spectra showed fragment ions corresponding to the different cleavages of the functional group. The high ionisation efficiency achieved with the GC-APPI interface provided limits of the detection lower than those obtained using traditional GC-MS ionisation techniques, with a high sensitivity, selectivity and precision. For water analysis, a fast and simple HS-SPME procedure was developed, avoiding evaporation steps, which could lead to the loss of the most volatile compounds. The developed HS-SPME GC-APPI-HRMS method showed a good analytical performance for the analysis of river water samples, providing very low limits of detection (0.02–15 ng L^{-1}), good repeatability (RSD < 11%) and trueness (relative error < 12%).

***Keywords*:** Gas chromatography · Atmospheric pressure photoionization · High resolution mass spectrometry · Neutral per- and polyfluoroalkyl substances · Headspace-Solid-phase microextraction

1. Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFASs) consist on a functional group attached to a fully or partially fluorinated alkyl chain. Since 1950, PFASs have been produced in high volumes due to their high chemical and thermal stability, their ability to repel both water and oil, and their stain resistance. These unique properties have made them useful in numerous industrial and domestic applications, including polymer manufacture, food-contact paper coatings, fire-fighting foams, textile, and carpet and leather treatments [1–5]. Among them, fluorotelomer olefins (FTOs), fluorotelomer alcohols (FTOHs), fluorooctane sulfonamides (FOSAs), and sulfonamido-ethanols (FOSEs), have been used as precursors and/or intermediates in the telomerisation process to manufacture other PFASs and fluorotelomer-based polymers [2]. However, these neutral PFASs are easily biodegraded and/or oxidised in the environment leading to persistent and more toxic PFASs, such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), that can be easily bioaccumulated and biomagnified by living organisms [5–7] and are subjected to international regulations (i.e., PFOS) or under evaluation process (i.e., PFOA) [8,9]. Until now, most of the targeted and non-targeted strategies have been focused on the analysis of other ionic and non-ionic precursors and toxics PFASs [10–12]. However, the determination of FTOs, FTOHs, FOSAs and FOSEs has still a long way to go to facilitate accurate measurements of their environmental levels and estimate their real relevance in the environment. In fact, there are still a limited number of studies conducted to determine the presence of these compounds in environmental samples, especially in water, and therefore, there is a great need for reliable data about their occurrence and distribution in the aquatic media.

Neutral PFASs have been currently determined by gas chromatography coupled to mass spectrometry (GC-MS) using electron ionisation (EI) and chemical ionisation (CI) of positive ions [13–18], while negative ion chemical ionisation (NICI) has been applied for confirmation purposes [14,18]. Although these ionisation techniques have proven useful in detecting neutral PFASs, relatively high instrumental limits of detection are usually achieved, ranging from 0.06 to 429 μg L^{-1} [19, 20]. In the last years, GC-MS applications are moving from conventional ionisation techniques (e.g., EI and CI) to the atmospheric pressure chemical ionisation (APCI) and photoionisation (APPI) technologies [21,22]. Thus, the GC-APCI and GC-APPI interfaces are being introduced progressively in the analytical laboratories, opening new fields of applications due to their capabilities to ionise a great range of compounds. In addition, these sources are soft ionisation techniques that decrease the fragmentation of the molecular ion and improve the sensitivity of the instrumental methods [23]. GC-APCI has been the most used interface because it was firstly commercialised, but methods based on GC-APPI have also been developed, although to a lesser extent. Thus, GC-APPI interface has been applied to the analysis of steroids [24], polycyclic aromatic hydrocarbons (PAHs) [24,25], polychlorinated biphenyls (PCBs) [26], polibrominated diphenyls ethers (PBDEs) [27], some environmental priority pollutants [28], and light crude oil fraction [29], among others. However, the GC-APPI interface has not yet been evaluated for the determination of the neutral PFASs, although the effectiveness of the APPI source has been demonstrated in the analysis of these compounds by liquid chromatography-tandem mass spectrometry (LC–MS/MS) [20]. Recently, an efficient GC-APPI interface based on a vortex design for GC-Orbitrap mass analyser has been commercialised [30], and it could be an excellent alternative to traditional GC-MS ionisation methods for the analysis of neutral PFASs.

Currently, the extraction methods most commonly used for the determination of neutral PFASs in water samples are based on liquid-liquid extraction or solid-phase extraction [31–33]. These extraction techniques require the use of large sample volumes and several preconcentration steps to achieve limits of detection low enough for water analysis. Nevertheless, the use of these methods resulted in losses of the analytes during the evaporation step , especially for FTOs (from 75 to 85%) and FTOHs (from 23 to 72%), and a significant matrix effect (15-60%) that caused an important decrease in the LC-MS/MS responses [34]. In this way, headspace-solid-phase microextraction (HS-SPME) could be an excellent alternative for the determination of neutral PFASs. SPME is a rapid, inexpensive and solvent-free extraction technique that allows an *in-situ* preconcentration of the analytes. This technique offers a reliable and essay method for the determination of volatile organic compounds [35–37], avoiding the evaporation steps currently required in solid-phase extraction, which could cause losses of volatile analytes.

The aim of the present work is to evaluate the potential of the atmospheric pressure photoionisation source in GC-HRMS using an Orbitrap mass analyser for a selective and sensitive determination of neutral PFASs in water samples. For this purpose, several parameters that affect the ionisation behaviour of the target compounds, such as source and capillary temperatures, and the use of dopants, were optimised. In addition, the feasibility of headspace-solid-phase microextraction (HS-SPME) for a rapid and reliable extraction of the target compounds from water samples was also examined. The developed HS-SPME GC-APPI-HRMS method was validated and its applicability to the analysis of river water samples was investigated to propose a new analytical method for the accurate determination of neutral PFAS at low concentration levels.

2. Materials and Methods

2.1. Reagents and standards

Twelve neutral semi-volatile PFASs were selected from the families of FTOs, FTOHs, FOSAs and FOSEs as target compounds (Table 1). Individual standards of FTOs (4:2 FTO, 6:2 FTO and 8:2 FTO) and FTOHs (4:2 FTOH, 6:2 FTOH, 7-Me-6:2 FTOH) were obtained from Fluorochem Ltd. (Derbyshire, UK), while 8:2 FTOH and 10:2 FTOH were supplied by Alfa Aesar GmbH & Co KG (Karlsruhe, Germany) at a purity higher than 96%. Individual stock standard solutions of FTOs and FTOHs (1000 µg mL^{-1}) were prepared in methanol (LiChrosolv® grade, Merck, Darmstadt, Germany) from the respective pure standards. Standard solutions (50 µg mL^{-1}) of *N*-MeFOSA, *N*-MeFOSE and *N*-EtFOSE in methanol were purchased from Wellington Laboratories Inc. (Guelph, Ontario, Canada), while a stock standard solution (1000 µg mL^{-1}) of *N*-EtFOSA was prepared in methanol from a solid standard (purity > 99%) supplied by Dr. Ehrenstorfer GmbH (Ausburg, Germany). Individual standards of 1H, 1H-pentadecafluoro-1-octanol (7:1 FA), 1H, 1H-perfluoro-1-nonanol (8:1 FA), 1H, 1H-perfluoro-1-decanol (9:1 FA) and 1H, 1H-perfluoro-1-dodecanol (11:1 FA), supplied by Fluorochem Ltd., were used as internal standards for FTOs and FTOHs, while N-ethyl-$^{2}H_5$-perfluoro-1-octanesulfonamide (d_5-*N*-EtFOSA) and 2-(N-Ethyl-$^{2}H_5$-perfluoro-1-octane-sulfonamido)-ethan-$^{2}H_4$-ol) (d_9-*N*-EtFOSE) from Wellington Laboratories Inc. were employed for FOSAs and FOSEs, respectively. All the internal standards were at a purity higher than 95%. For optimising the GC-APPI-HRMS method, a standard mixture of all the target compounds were prepared in methanol at 1 µg mL^{-1}. For validation purposes, a set of seven calibration solutions ranging from 0.1 ng mL^{-1} to 100 ng mL^{-1} (FTOs between 1 ng mL^{-1} and 500 ng mL^{-1}) were prepared by successive dilution of stock standard solutions. All these standard solutions contained appropriate amounts of the internal standards to give concentrations of 10 ng mL^{-1} for 7:1 FA and d_5-*N*-EtFOSA, 5 ng mL^{-1} for 8:1 FA and 9:1 FA, and 2 ng mL^{-1} for 11:1 FA and d_5-*N*-

EtFOSE. All these solutions were stored at 4 ºC until their analysis (1 µL) by GC-APCI-HRMS.

Anisole anhydrous (purity 99.7%), toluene and chlorobenzene for HPLC (Chromasolv^{TM} Plus, purity ≥ 99%) were supplied by Sigma-Aldrich (Merck, Darmstadt, Germany). Tetrahydrofuran (Photrex^{TM} reagent, purity of 99%) was purchased from J. T. Baker (Deventer, The Netherland) and acetone (LiChrosolv®, purity ≥ 99.8%) was obtained from Merck. Vapours of all these solvents were used as dopants for the optimisation of APPI source conditions. Moreover, a Milli-Q system coupled to an Elix 3 (Millipore, Bedfore, MA, USA) was used to obtain ultra-pure water. All glassware was cleaned with chromo-sulphuric acid and rinsed with Milli-Q water and acetone before use. Helium Alphagaz^{TM} 1 (purity ≥ 99.9993%), supplied by Air Liquide (Madrid, Spain), was employed as GC carrier gas while nitrogen (purity > 99.9995%), purchased from Linde (Barcelona, Spain), was used as make-up gas for the GC-APPI interface.

2.2. Water samples

River water samples were collected from the lower section of Llobregat River (Barcelona, Spain). This river runs through a highly densely and industrialised area before flowing into the Mediterranean Sea, receiving extensive urban and industrial wastewater discharges coming from different factories and populations inhabiting its surroundings. The water samples were taken upstream and downstream of an industrial area located at the towns of Sant Boi de Llobregat and Cornellà, dedicated to textile, clothing and footwear manufacturing. In addition, tap water samples were also taken from the supply of the city of Barcelona to assess the possible contribution of the pipeline network. All these samples were collected using 1,000 mL glass bottles filled without leaving headspace, to prevent possible losses, and stored in the refrigerator at 4

^{o}C before being analysed. Field blanks consisting of 100 ml of natural mineral water (Font Vella, San Hilari Sacalm, Spain) were prepared at the same sampling points and analysed along with the river and tap water samples.

2.3. Sample treatment

Target compounds were extracted from water samples by headspace-solid-phase microextraction (HS-SPME) using a manual fibre holder supplied by Supelco (Bellefonte, PA, USA). Five SPME fibres, purchased from Supelco, were tested: 100-µm polydimethylsiloxane (PDMS), 85-µm polydimethylsiloxane/carboxen (PDMS/CAR), 65-µm polydimethylsiloxane/divinylbenzene (PDMS/DVB), 85-µm polyacrylate (PA) and 50/30-µm divinylbenzene/carboxen/polydimethylsiloxane (DVB/CAR/PDMS). These fibres cover different polarities, which could interact with different parts of the molecules, to improve the extraction of the different families of compounds from non-polar FTOs to relatively polar FOSAs). Before use, each fibre was conditioned in the GC injection port under helium flow according to the manufacturer's recommendation. After conditioning, fibre blanks were periodically analysed to ensure there were no contaminants or carryover present.

After optimisation, the HS-SPME procedure was carried out as follows: 10 mL of water were placed in a 20 mL screw-cap glass vial fitted with rubber septa containing a 10 mm x 5 mm stir bar and an appropriate amount of the internal standards was added through the sample vial septum. The internal standard concentrations in the final vial were 20 ng L^{-1} for 7:1 FA, 10 ng L^{-1} for 8:1 FA and 9:1 FA, 30 ng L^{-1} for d_5-*N*-EtFOSA, and 4 ng L^{-1} for 11:1 FA and d_9-*N*-EtFOSE. Polytetrafluoroethylene (PTFE) coating of stir bar was removed before use. Before HS-SPME analysis, the sample vial was conditioned for 15 minutes in a thermostatic water bath at the extraction temperature. Then, water samples and calibration solutions were extracted from the headspace with a DVB/CAR/PDMS fibre at 60 ºC for 30 min using a constant agitation rate of 750 rpm. Finally, thermal desorption of the target compounds was carried out by exposing the fibre into a GC injection port at 250 ^{o}C for 3 min in splitless injection mode. After desorption, the fibre was kept in the GC injector for an additional time of 20 min in split mode (purge on) for cleaning the fibre and preventing possible carryover between samples. For quantification of neutral PFASs, seven calibration water standard solutions were prepared by adding adequate amounts of standard mixtures into a 20 mL screw-cap glass vial containing 10 ml of Milli-Q water to give concentrations ranging from 0.2 and 2000 ng L^{-1}. In addition, appropriate amounts of internal standard were added to each calibration solution to obtain similar concentrations than those used for water samples. Further details about the optimisation of the HS-SPME procedure are given in section 3.3.

2.4. Instrumentation

Neutral PFASs were determined on a Trace 1300 gas chromatograph coupled to a Q-Exactive Orbitrap mass spectrometer (Thermo Fisher Scientific, San Jose, CA, USA), using an atmospheric pressure photoionisation source for GC-MS analysis (GC-APPI) (MasCom Technologies GmbH, Bremen, Germany). For the chromatographic separation, a DB-624 (6% cyanopropylphenyl 94% dimethyl polysiloxane) GC fused-capillary column of 60 m of length, 0.25 mm I.D. and 1.40 µm of film thickness (Agilent Technologies, Santa Clara, CA, USA) was employed. The injector was operated at 250 ^{o}C in the splitless injection mode (3 min) using a glass inlet liner (I.D., 0.75 mm, Agilent Technologies) for the HS-SPME experiments. Helium was used as carrier gas at a constant flow rate of 1.3 mL min^{-1} held by electronic flow control. The oven temperature program was as follow: from 50 ^{o}C (held for 3 min) to 120 ^{o}C at 10 ^{o}C min^{-1} and then to 250 ^{o}C at 25 ^{o}C min^{-1} (held for 10 min). The transfer line, source and capillary temperatures were set at 250 ^{o}C, 225 ^{o}C and 175 ^{o}C, respectively. The GC-APPI source was equipped with a 10.6 eV krypton lamp (Syagen, Santa Ana, CA, USA) and it worked in the negative-ion mode using nitrogen as make-up gas (gas pressure of 5 a.u.) and acetone vapours (70 µL min^{-1}) as dopant. Data acquisition was performed in full-scan mode from *m/z* 100 to *m/z* 800 at a resolution of 35,000 (FWHM, at 200 *m/z*), using a maximum injection time of 200 ms for good peak reconstruction with at least 12 data points per peak and an automatic gain control (AGC) of $3 \cdot 10^{6}$ to achieve the highest sensitivity. With identification and quantification purposes, extracted ion chromatograms (EICs) were obtained using ±5 ppm precision extraction windows. Xcalibur *υ 3.1* software was used to control the instrument setup and process the data acquisition. ACD/Labs Percepta software (Advanced Chemistry Development Inc., Toronto, Canada) was used to estimate the vapour pressure values of the target compounds.

2.5. Quality control and method validation

Quality control standard solutions and procedural blanks were introduced among the analysis of standards and samples for ensuring the quality of the results and for checking the GC separation, the sensitivity of the GC-APPI-HRMS system and the validity of the calibration. The accurate mass calibration in the Orbitrap was performed every 72 h using an electrospray source with a calibration solution containing caffeine, MRFA peptide, Ultramark 1621 and butylamine in acetonitrile/methanol/water (2:1:1, *v/v*) with 1% (*v/v*) formic acid. Procedural blanks covering both the instrumental and HS-SPME procedure were periodically analysed to evaluate the potential contribution of interfering compounds on the neutral PFASs measurements and the possible carryover between samples. Instrumental (ILODs) and method limits of detection (MLODs) were estimated as the smallest analyte concentration that provides a well-defined chromatographic peak with a good peak shape and a mass error on the HRMS mass spectrum lower than 5 ppm for the characteristic ions. These criteria were used because almost no baseline noise was recorded in the extracted ion chromatograms due to the narrow mass error threshold (< 5 ppm) and the high resolution used (FWHM 35,000 at *m/z* 200) on the Orbitrap mass analyser. Instrumental (ILOQs) and method limits of quantification (MLOQs) were experimentally established by analysing standards and spiked blank water samples at low concentration levels according with the respective limits of detection and linearity. Intra-day precision (n=3) was routinely tested by analysing blank river water samples spiked with the target compounds at low ng L^{-1} levels.

3. Results and Discussion

3.1. Determination of neutral PFASs by GC-APPI-HRMS

Since FTOHs, FTOs, FOSAs and FOSEs cannot be directly photoionised using APPI, the ionisation was assisted by a dopant which was introduced into the source as a gas-phase. In addition, positive-ion APPI mode did not allow the ionisation of the target compounds, may be due to their high electronegativity. Therefore, the ionisation behaviour of these compounds in negative-ion mode was investigated using different solvents, such as toluene, acetone, chlorobenzene, tetrahydrofuran and anisole, as potential APPI dopants. All these experiments were carried out using a source and capillary temperatures of 250 ^{o}C and 200 ^{o}C, respectively. Generally, the mass spectra obtained using these solvents showed ions that did not depend of the dopant used, although differences in their ion intensities were observed (see Table S1). As an example, Fig. 1 shows the GC-APPI-HRMS mass spectra obtained for 8:2 FTOH, 8:2 FTO, *N*-MeFOSA and *N*-EtFOSE using acetone as dopant. The mass spectra for most of FTOHs using acetone as dopant showed the presence of the superoxide $[M+O_2]^{-\bullet}$ ion as base peak and some in-source CID fragments corresponding to different cleavages of the fluorinated alkyl chain (Fig. 1a). For FTOs, mass spectra were characterised by the odd-electron fragment ions generated from the unstable $[M+O_2]^{-\bullet}$ adduct (i.e., $[M+O_2–HF_2O]^{-}$, $[M+O_2–HF_2]^{-}$ or $[C_9OF_{15}]^{-}$) and some ions coming from the fragmentation of the fluorinated alkyl chain, being the $[M–CH_3F_2]^{-}$ the base peak in all the spectra (i.e., $[C_9F_{15}]^{-}$ for 8:2 FTO, Fig. 1b). The presence in the mass spectra of superoxide-related fragment ions could be attributed to the entry of air mixed with the dopant into the APPI source, which promote the formation of a non-stable superoxide adduct ion that yield characteristic fragment ions. These superoxide adduct-related ions were not observed in LC-APPI-MS [29,32] because the dopant is introduced in the APPI source in liquid-phase. Concerning FOSEs, they were ionised by the formation of a superoxide adduct ion but also generating fragment ions corresponding to the loss of the ethanol chain $[M–C_2H_4OH]^-$ (base peak of the spectra) or even the functional group $[M–NRC_2H_4OH]^-$ (R: $–CH_3$, C_2H_5) (Figure 1c for *N*-EtFOSE). Otherwise, FOSAs showed the deprotonated molecule as the base peak of the mass spectrum, although some low abundant in-source CID fragment ions generated by the loss of the sulfonamide group from deprotonated molecule were also observed (Figure 1d). The presence of these characteristic fragment ions in the mass spectra provided valuable structural information for confirming the identification of the analytes and detecting related unknown compounds. To select the most suitable dopant for the efficient ionisation of the target compounds the responses of the most abundant ions were compared. Among the dopants studied, acetone provided the best result for most of the compounds, especially for FTOHs (Fig. 2). This fact could be related with the high vapour pressure of acetone that may allow a higher generation of $O_2^{-\bullet}$ in the gas-phase and, consequently, a more efficient ionisation of superoxide adduct ions. In the case of 4:2 FTO, tetrahydrofuran showed the highest response, although acetone also provided an adequate ionisation efficiency (Fig. 2). Therefore, acetone was selected as APPI dopant for the subsequent experiments. To maximise the response of the target compounds the acetone vapours flow-rate was then optimised from 30 to 70 µL min^{-1}, obtaining the best results at 70 µL min^{-1} (Fig. S1), which is close to the recommended maximum value for avoiding turbulent flow. Moreover, APPI source (from 200 ^{o}C to 250 ^{o}C) and capillary temperatures (from 175 ^{o}C to 225 ^{o}C) were also evaluated to maximise the ionisation efficiency by reducing the in-source CID fragmentation. Since no significant differences in the response were observed at the temperatures tested, a source temperature of 225 ^{o}C and a capillary temperature of 175 ^{o}C were chosen. Table 2 summarises the two most intense ions selected from each high-resolution full-scan mass spectrum for the GC-APPI-HRMS determination of neutral PFASs. Concerning *N*-EtFOSA, the $[M–NFC_2H_5]^−$ fragment ion (*m/z* 464.9447) was chosen as qualifier ion because the second most intense ion, $[M–NHC_2H_5]^−$ (*m/z* 482.9353, $[C_8F_{17}O_2S]^−$), was interfered by the same fragment ion from d_5-*N*-EtFOSA internal standard.

The performance of the developed GC-APPI-HRMS method was evaluated by determining the linearity, instrumental limits of detection and quantification, sensitivity, precision and trueness (Table S2). Linearity was tested by injecting seven calibration solutions at concentrations ranging from 0.1 ng $mL^{−1}$ to 100 ng $mL^{−1}$ (FTOs in the range 1-500 ng $mL^{−1}$). Internal standard calibration curves were established by least-squares regression analysis obtaining correlation coefficients (*r*) for all the compounds higher than 0.999. The sensitivity of instrumental method was determined from the slope of the calibration curves and were from 10 to 500 times higher than those obtained in a previous work with LC-APCI-MS/MS [34], demonstrating the good performance of the method. Instrumental limits of detection (ILODs) ranged from 0.03 to 0.3 ng $mL^{−1}$ for most of the target compounds, although for 4:2 FTO and 6:2 FTO the ILOD values were 1 and 8 ng $mL^{−1}$, respectively (Table S2). To improve the ILODs of FTOs an increase of the source temperature is required, since the ionisation efficiency of these compounds in APCI and APPI sources is favoured at high temperatures (around 400 ºC) [20], but the GC-APPI source does not allow to operate at temperatures higher than 250 ºC. In general, GC-APPI-HRMS provided ILODs lower than those obtained with both LC-APCI-MS/MS and GC-MS using chemical ionisation (CI) [34,38,39]. In addition, the ILOD values were around 50 times better than those obtained with LC-APPI-MS/MS [34], with an important improvement for FTOs of about three to four order of magnitude. The intra-day precision on the determination of the target compounds was examined by analysing in triplicate of two standard solutions at concentrations very close (low level) and around ten times higher (medium level) than the limits of quantification (Table S2), achieving relative standard deviations (RSD %) lower than 10%. Moreover, the trueness in the determination of the target compounds showed relative errors lower than 10%. These results demonstrated the performance and validity of the developed GC-APPI-HRMS for the determination of the neutral PFASs.

3.3. Optimization of HS-SPME procedure

The feasibility of headspace-solid-phase microextraction to the determination of neutral PFASs in water samples at low concentration levels (ng L^{-1}) was investigated. The first step in the optimisation of the SPME procedure was the selection of the appropriate fibre. To obtain the best sensitivity and selectivity, the following five SPME fibres were tested: DVB/CAR/PDMS, PDMS/CAR, PDMS/DVB, PDMS and PA (section 2.3.). For this purpose, the fibres were evaluated using 10 mL of water samples spiked at 500 ng L^{-1} and the analytes were extracted from the headspace by exposing the fibre during 15 min at 60 ^{o}C using constant stirring (750 rpm). The desorption temperature was 250ºC for all fibres, which is within the recommended operating temperature range. Among the studied fibres, the PDMS and PA showed the worst results with a very low extraction efficiency of FOSAs, FOSEs and FTOs. Fig. 3 shows the extraction efficiency of the DVB/CAR/PDMS, PDMS/CAR and PDMS/DVB fibres for the determination of all the compounds. As can be seen in Fig. 3a, FTOHs showed a similar behaviour on the three fibres, while FOSAs and FOSEs achieved the best extraction yields with the DVB/CAR/PDMS fibre. In contrast, for FTOs the highest responses were achieved using the PDMS/CAR fibre, although the DVB/CAR/PDMS fibre also provided a high extraction efficiency. As a compromise, the DVB/CAR/PDMS was selected for all subsequent experiments.

Extraction temperature was then evaluated (from 30 ^{o}C to 70 ^{o}C) to improve the extraction of the analytes. As can be seen in Fig. 3b, the responses of FOSAs and FOSEs increased with the temperature, while a high extraction efficiency for FTOs and FTOHs were observed at temperatures ranging between 30 and 50 ^{o}C (Fig. 3b). This may be due to a decrease in the distribution constants between the headspace and the fibre coating of the FTOs and FTOHs when the temperature increases, since they have a higher vapour pressure than FOSAs and FOSEs (Table 1). Therefore, an extraction temperature of 60 ^{o}C was selected as optimum value for the extraction of all the compounds. In addition, the extraction time was evaluated from 1 to 40 min. As shown in Fig. 3c, an extraction time of 30 min was enough to reach the equilibrium and it was chosen as the optimal value for subsequent experiments. Finally, the effect of salt addition (0-30% NaCl) and pH adjustment (2-10) on extraction yield were investigated and, as expected, no significant differences in response were observed for any of the compounds.

3.4. Performance of the HS-SPME GC-APPI-HRMS method for river water analysis

In order to study the applicability of the proposed HS-SPME GC-APPI-HRMS method for the determination of neutral PFASs at low concentration levels, several river water samples were analysed in triplicate. As none of the analysed samples showed detectable concentrations of the target compounds for quantification, they were considered suitable for determining the figures of merit of the developed method and demonstrate its feasibility for achieving an accurate determination. For this purpose, quality parameters of the HS-SPME GC-APPI-HRMS method were established and the results are summarised in Table 2. Linearity was estimated by analysing seven calibration water solutions using HS-SPME over the range of 0.2 to 2000 ng L^{-1} and high correlation coefficients were obtained (r > 0.998) for all the compounds. Method limits of detection (MLODs) were stablished and ranged from 0.02 to 0.24 ng L^{-1} for most of the analytes, except for 4:2 FTO which was 15 ng L^{-1}, while method limits of quantification (MLOQs) were comprised between 0.08 and 50 ng L^{-1}. These values were about 40–200 times lower than those previously reported for some FTOHs and FOSAs (20 to 100 ng L^{-1}) using HS-SPME GC-MS with electron ionisation [40]. For LC-MS/MS with electrospray ionisation, the proposed method also provided lower MLOQs values of at least 500 times for FTOHs (60-90 ng L^{-1}) [41], 2-4 times for FOSAs (0.29 to 0.62 ng L^{-1}) [32,42] and around 30 times for FOSEs (2.2 ng L^{-1}) [43]. In addition, the reported MLOQs for the analysis of the target compounds using LC-MS/MS methods with APPI or APCI sources were 2-100 times higher for FTOHs, FOSAs and FOSEs (0.3 to 6 ng L^{-1}) [34] and at least 400 times higher for FTOs (0.07-6 µg L^{-1}) [20]. These results confirm the good detectability of the HS-SPME GC-APPI-HRMS method. The repeatability (intra-day precision) of the developed method was determined using a blank river water sample spiked at two concentration levels (low: 0.4–200 ng L^{-1}; medium: 5–2500 ng L^{-1}). Good repeatability was achieved with a relative standard deviation (RSD, %) values ranged from 2 to 11% (n=3). Moreover, trueness, expressed as the relative error (RE, %), was also examined at the two same concentration levels, and the results were always lower than 12% (n=3) (Table 2). Fig. 4 shows as an example of the GC-APPI-HRMS extracted high resolution full-scan chromatograms obtained by spiking 10 mL of a blank river water sample (from 0.4 ng L^{-1} to 4 ng L^{-1}, except for 4:2 FTO which was 200 ng L^{-1}). Under these conditions, it was possible to separate all the analytes in less than 22 min with a good sensitivity and selectivity. On base of these finding, the validity of the HS-SPME GC-APPI-HRMS method has been demonstrated and can be propose for the reliable determination of FTOs, FTOHs, FOSAs and FOSEs in water samples at low concentration levels.

4. Conclusions

The feasibility of a new analytical method based on HS-SPME combined with GC-APPI-HRMS for the determination of neutral PFASs in water samples has been demonstrated. The use of dopant-assisted APPI in the negative-ion mode with vapours of acetone as dopant allowed a high ionisation efficiency for all the compounds, providing characteristic in-source CID fragment ions to ensure the proper quantification and confirmation of the target compounds. In addition, the information provided by the high resolution mass spectra makes it possible to ensure unequivocal identification of the analytes and detect possible related compounds. The HS-SPME using a DVB/CAR/PDMS fibre has proven to be a fast and effective technique for the extraction of the target compounds from water samples, simplifying the sample treatment and avoiding possible losses of the analytes. The developed HS-SPME GC-APPI-HRMS method provided low limits of detection (0.02 to 15 ng L^{-1}) a good repeatability (RSD% < 11) and trueness (RE% < 12), demonstrating the good performance of the method for the analysis river water at low concentration levels (ng L^{-1}). As far as we know, this article reports for the first time the excellent performance of the GC-APPI interface coupled to HRMS (Q-Orbitrap) for the analysis of neutral PFAS, providing significant advantages over existing methods in terms of sensitivity and selectivity.

Declaration of interests

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

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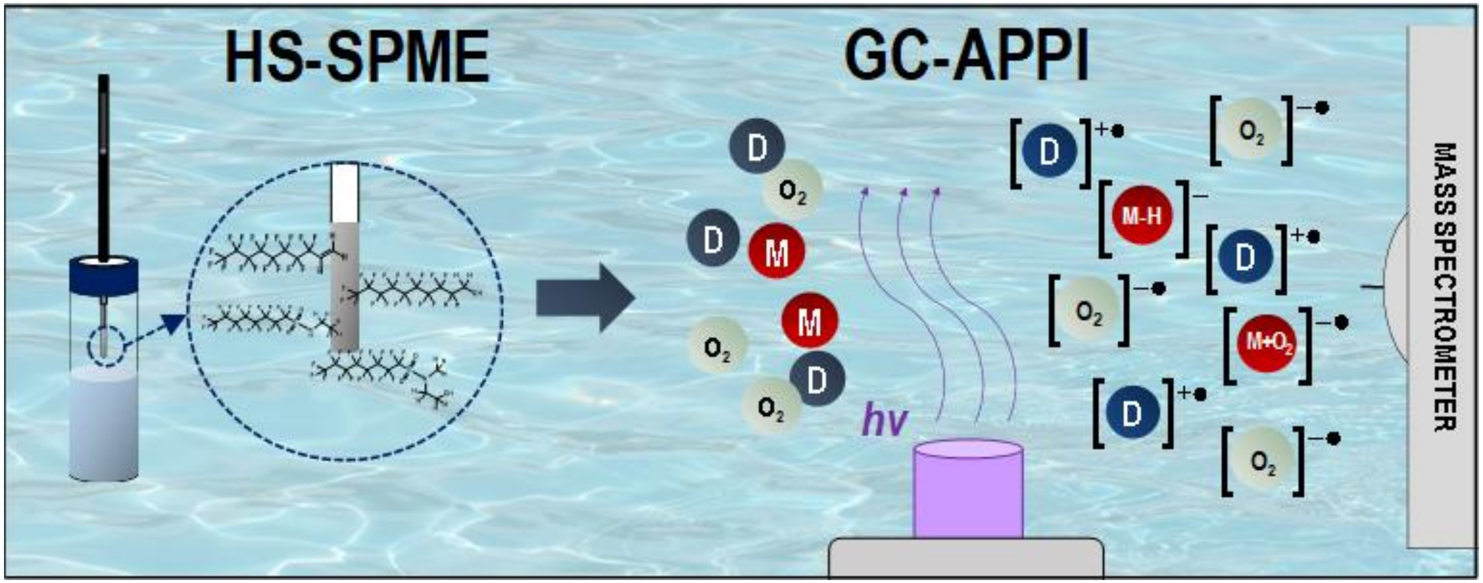
***Graphical Abstract**



Highlights (*from 3 to 5- max. 85 characters per highlight*)

- GC-APPI-HRMS was applied for the first time to determine neutral PFASs in water.
- GC-APPI(-) with acetone as dopant allowed an efficient ionization of neutral PFASs.
- GC-APPI-HRMS method significantly improved in the detectability of the analytes.
- HS-SPME allowed a fast and effective extraction of neutral PFASs from water.
- The new method allowed a sensitive determination of neutral PFASs in river water.

Table 2

Selected ions from GC-APPI-HRMS high-resolution full-scan for the quantification of target compounds.

Compound	Quantification Ion		Confirmation Ion	
	m/z	Assignation	*m/z*	Assignation
4:2 FTO	192.9894	$[C_5F_7]^-$	208.9843	$[C_5OF_7]^-$
6:2 FTO	292.9830	$[C_7F_{11}]^-$	308.9779	$[C_7OF_{11}]^-$
8:2 FTO	392.9766	$[C_9F_{15}]^-$	408.9715	$[C_9OF_{15}]^-$
4:2 FTOH	192.9894	$[C_5F_7]^-$	296.0101	$[M+O_2]^{-\bullet}$
6:2 FTOH	396.0037	$[M+O_2]^{-\bullet}$	292.9830	$[C_7F_{11}]^-$
7-Me-6:2 FTOH	305.9908	$[C_8HF_{11}]^{-\bullet}$	446.0005	$[M+O_2]^{-\bullet}$
8:2 FTOH	495.9973	$[M+O_2]^{-\bullet}$	392.9766	$[C_9F_{15}]^-$
10:2 FTOH	595.9909	$[M+O_2]^{-\bullet}$	492.9702	$[C_{11}F_{19}]^-$
N-MeFOSA	511.9612	$[M-H]^-$	482.9353	$[M-NHCH_3]^-$
N-EtFOSA	525.9775	$[M-H]^-$	464.9447	$[M-NFC_2H_5]^-$
N-MeFOSE	511.9619	$[M-C_2H_5O]^-$	588.9857	$[M+O_2]^{-\bullet}$
N-EtFOSE	525.9775	$[M-C_2H_5O]^-$	603.0014	$[M+O_2]^{-\bullet}$
Internal Standards				
7:1 FA	398.9872	$[M-H]^-$	431.9848	$[M+O_2]^{-\bullet}$
8:1 FA	448.9840	$[M-H]^-$	481.9817	$[M+O_2]^{-\bullet}$
9:1 FA	498.9808	$[M-H]^-$	531.9784	$[M+O_2]^{-\bullet}$
11:1 FA	598.9748	$[M-H]^-$	631.9720	$[M+O_2]^{-\bullet}$
d_5-*N*-EtFOSA	531.0089	$[M-H]^-$	465.9510	$[M-NFC_2HD_4]^-$
d_9-*N*-EtFOSE	531.0089	$[M-C_2H^2H_4O]^-$	612.0579	$[M+O_2]^{-\bullet}$

Table 3

Table 3

Quality parameters of the developed HS-SPME GC-APPI-HRMS method.

Parameter		4:2 FTO	6:2 FTO	8:2 FTO	4:2 FTOH	6:2 FTOH	7-Me-6:2 FTOH
MLOD (ng L^{-1})		15	0.24	0.09	0.12	0.06	0.06
MLOQ (ng L^{-1})		50	0.80	0.30	0.40	0.20	0.20
Spiked conc. (ng L^{-1})	Low level	200	4.0	1.6	2.0	1.0	1.0
	Medium level	2500	50	20	25	12.5	12.5
Found conc. ± SD[a] (ng L^{-1})	Low level	210 ± 14	3.5 ± 0.4	1.5 ± 0.1	2.1 ± 0.1	0.99 ± 0.09	1.02 ± 0.06
	Medium level	2342 ± 167	52 ± 4	19 ± 2	24 ± 1	12.1 ± 0.9	12 ± 1
Repeatability (RSD, %)[a]	Low level	6	11	9	6	9	11
	Medium level	7	8	9	3	8	6
Trueness (Rel. Error, %)[a]	Low level	5	–12	–3	5	–1	2
	Medium level	–3	4	–3	5	–3	–8

Parameter		8:2 FTOH	10:2 FTOH	*N*-MeFOSA	*N*-EtFOSA	*N*-MeFOSE	*N*-EtFOSE
MLOD (ng L^{-1})		0.06	0.02	0.15	0.15	0.02	0.02
MLOQ (ng L^{-1})		0.20	0.08	0.50	0.50	0.08	0.08
Spiked conc. (ng L^{-1})	Low level	1.0	0.4	3.0	3.0	0.4	0.4
	Medium level	12.5	5.0	37.5	37.5	5.0	5.0
Found conc. ± SD[a] (ng L^{-1})	Low level	0.9 ± 0.1	0.39 ± 0.01	3.3 ± 0.2	3.2 ± 0.2	0.44 ± 0.03	0.39 ± 0.04
	Medium level	11.6 ± 0.8	5.0 ± 0.6	40.6 ± 0.4	39.5 ± 0.5	4.7 ± 0.1	4.9 ± 0.4
Repeatability (RSD, %)[a]	Low level	11	11	6	6	8	11
	Medium level	7	6	2	2	2	8
Trueness (Rel. Error, %)[a]	Low level	–5	–3	12	7	10	–3
	Medium level	–7	1	8	5	7	–2

[a] $n = 3$

Figure Captions

Figure 1. Negative-ion APPI mass spectra of (a) 8:2 FTOH, (b) 8:2 FTO, (c) *N*-EtFOSE and (d) *N*-MeFOSA using acetone as APPI-dopant.

Figure 2. Effect of APPI-dopants on the response of neutral PFASs using negative-ion GC-APPI-HRMS. (THF: tetrahydrofuran)

Figure 3. (a) Extraction efficiency of the SPME fibres on the response of neutral PFASs. (b) Effect of extraction temperature and (c) extraction time on the absorption of 8:2 FTO, 10:2 FTOH, *N*-MeFOSA, and *N*-EtFOSE, using a DVB/CAR/PDMS fibre.

Figure 4. GC-APPI-HRMS extracted ion chromatograms of a blank river water sample spiked at concentrations ranging from 0.4 ng L^{-1} to 4 ng L^{-1} for all the compounds, except for 4:2 FTO which was 200 ng L^{-1}.

Figure 1

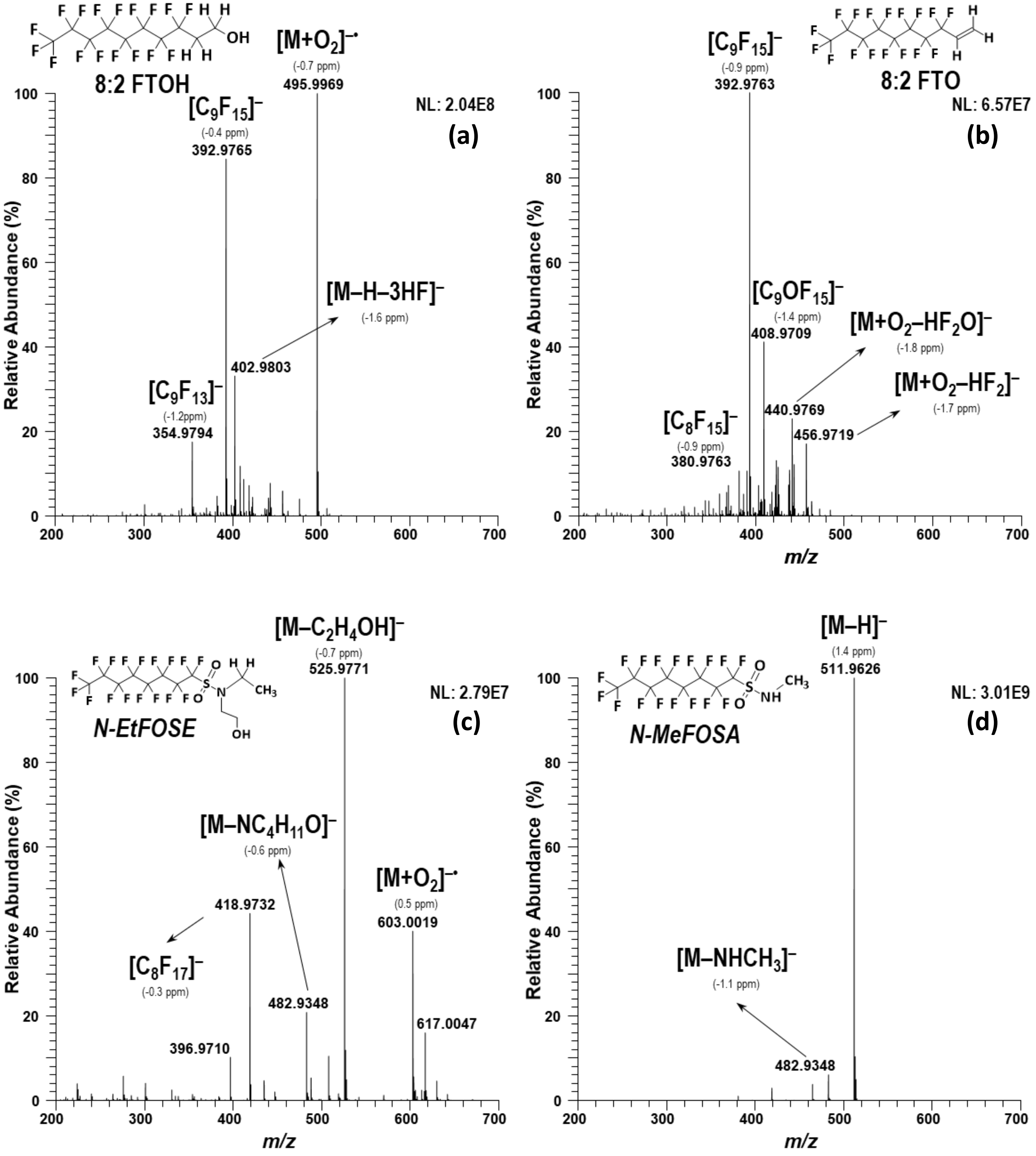

8:2 FTOH
OH
[M+O2]–•
(-0.7 ppm)
495.9969
[C9F15]–
(-0.4 ppm)
392.9765
NL: 2.04E8
(a)
[M–H–3HF]–
(-1.6 ppm)
402.9803
[C9F13]–
(-1.2ppm)
354.9794
Relative Abundance (%)
100
80
60
40
20
0
200
300
400
500
600
700
[C9F15]–
(-0.9 ppm)
392.9763
8:2 FTO
NL: 6.57E7
(b)
[C9OF15]–
(-1.4 ppm)
408.9709
[M+O2–HF2O]–
(-1.8 ppm)
440.9769
[M+O2–HF2]–
(-1.7 ppm)
456.9719
[C8F15]–
(-0.9 ppm)
380.9763
m/z
[M–C2H4OH]–
(-0.7 ppm)
525.9771
N-EtFOSE
CH3
OH
NL: 2.79E7
(c)
[M–NC4H11O]–
(-0.6 ppm)
[M+O2]–•
(0.5 ppm)
603.0019
418.9732
[C8F17]–
(-0.3 ppm)
482.9348
617.0047
396.9710
[M–H]–
(1.4 ppm)
511.9626
N-MeFOSA
CH3
NH
NL: 3.01E9
(d)
[M–NHCH3]–
(-1.1 ppm)
482.9348

Figure 2

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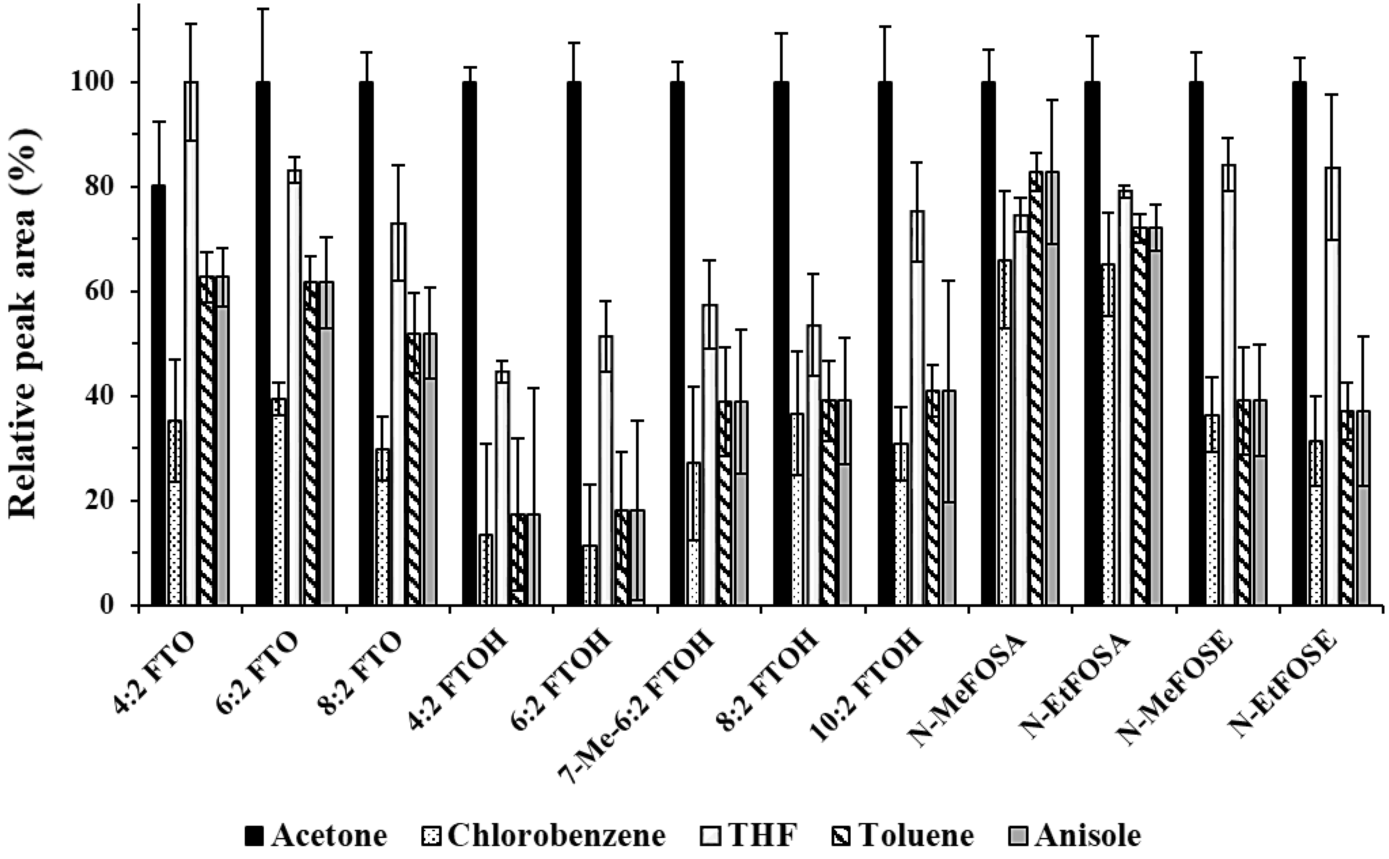

Figure 3

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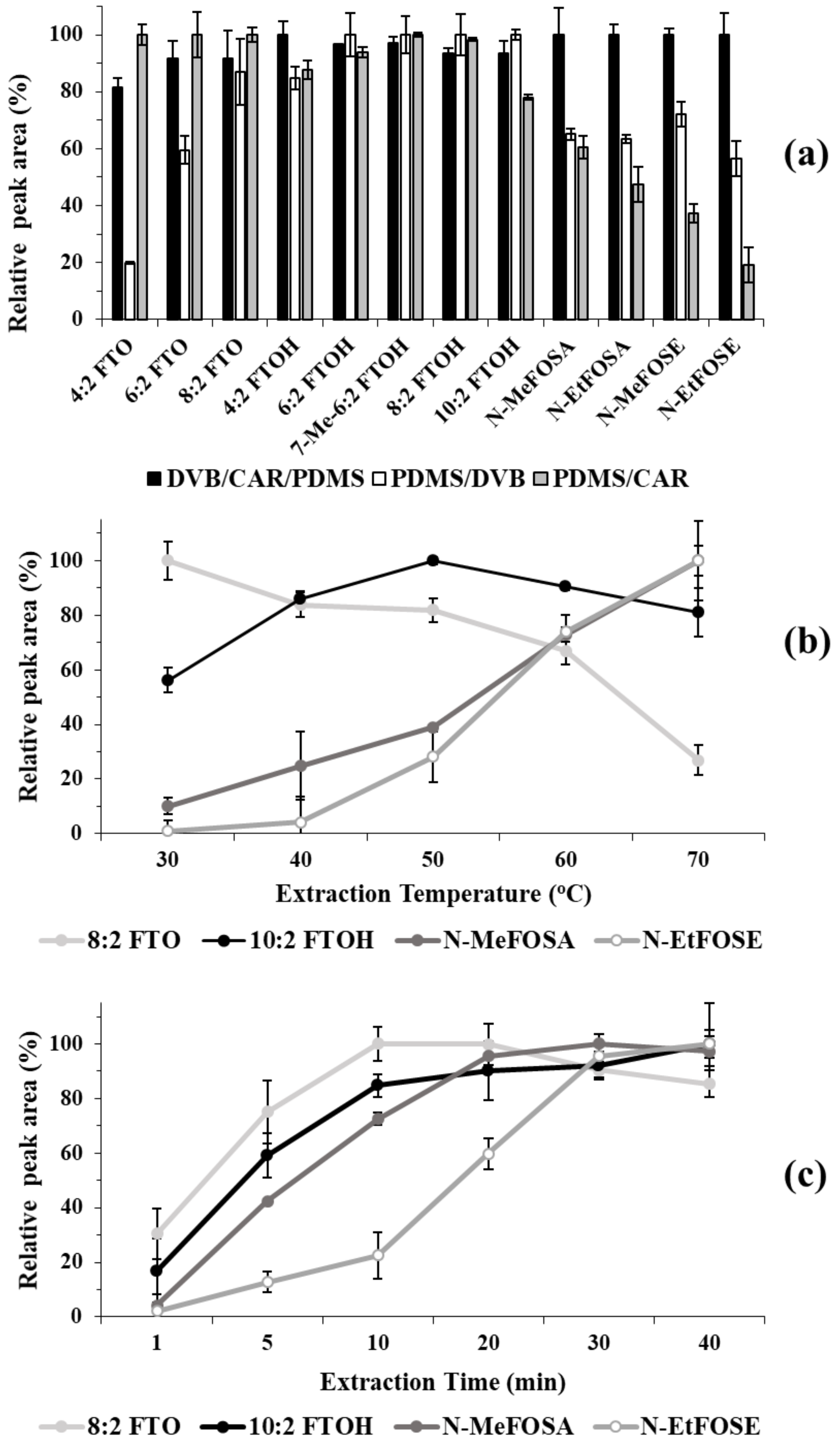

Figure 4

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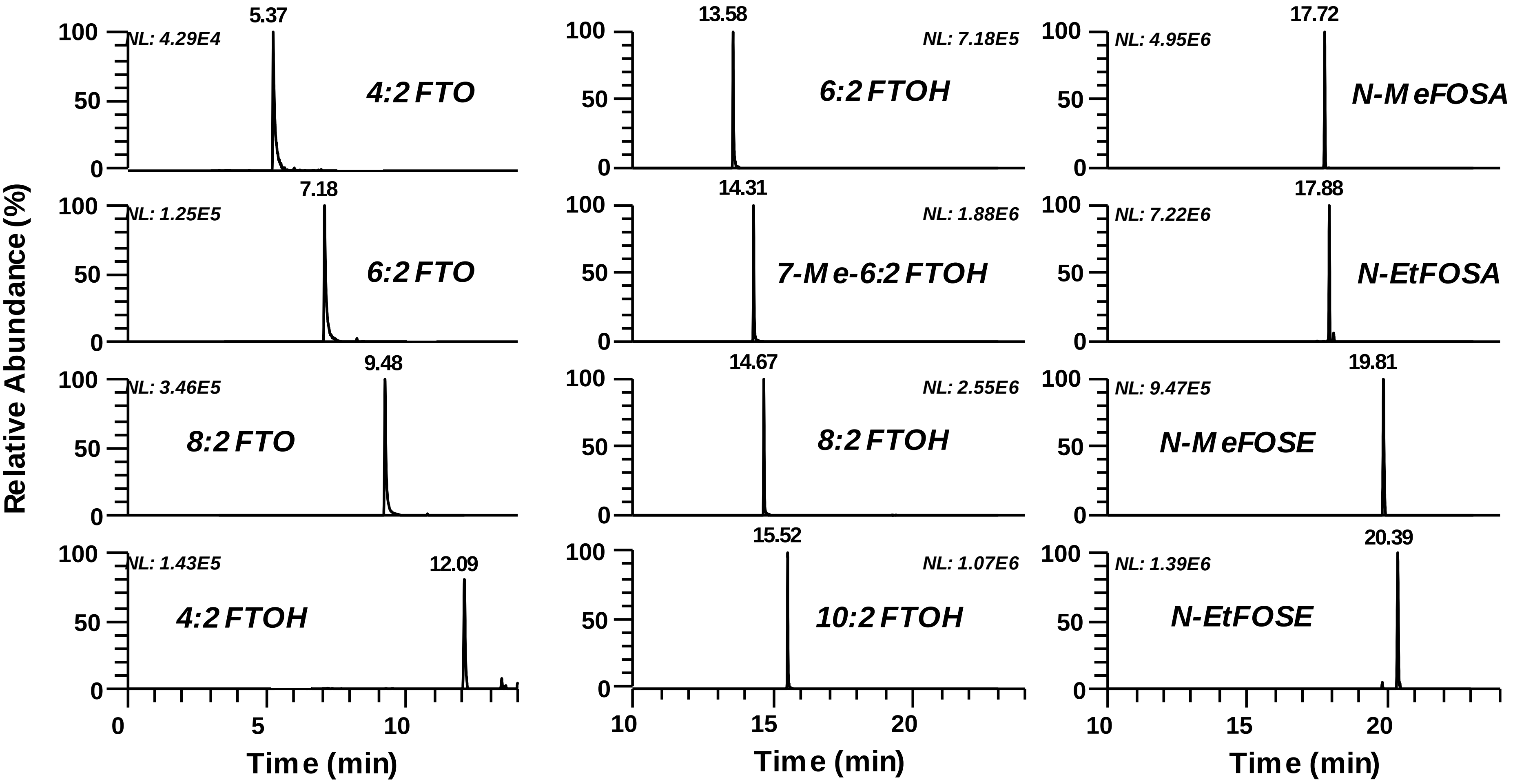

CRediT author statement

A novel methodology for the determination of neutral perfluoroalkyl and polyfluoroalkyl substances in water by gas chromatography-atmospheric pressure photoionisation-high resolution mass spectrometry.

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A. Contreras-Llin: Methodology, Investigation, Validation, Formal analysis.

E. Moyano: Conceptualization, Methodology, Supervision, Project administration, Writing-Reviewing and Editing.

F. J. Santos: Conceptualization, Methodology, Supervision, Project administration, Writing-Reviewing and Editing.