Application brief

Environmental

Out-of-the-box workflow for PFAS quantitation using a full-scan high-resolution approach with the Orbitrap Exploris EFOX Mass Detector

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Keywords

PFAS, drinking water, surface water, groundwater, wastewater, European regulation, FTOH, FTAB, FTS, PFOS, PFOA, PFNA, PFHxS, diPAP, HRMS, high-resolution, Orbitrap Exploris EFOX Mass Detector

Application benefits

- Quantitation of a large panel of 61 PFAS compounds using a full-scan high-resolution acquisition, supporting both targeted and suspect screening, with capabilities for retrospective analyses.
- Designed to comply with current European regulations (0.1 µg/L sum of 20 PFAS; 0.5 µg/L total PFAS) and local ones.
- The sensitivity of our method is compatible with major sample preparation techniques, including solid phase extraction (SPE). Limits of Quantification (LOQs) are achieved in solvent ranges from 50 ng/L for over 80% of targets to 500 ng/L for less than 5% of targets. Corresponding LOQs in matrices range from 0.1 ng/L to 1 ng/L with 500-fold concentration.
- Challenging PFAS such as FTOH and FTAB on the same method with a single HPLC separation.

Goal

To demonstrate the quantitation capabilities of the Thermo Scientific™ Orbitrap Exploris™ EFOX Mass Detector in full scan HRMS mode (high resolution and accurate mass) for the analysis of PFAS in methanolic extracts. The analytical qualification of the method is presented with results on the limit of quantitation, linearity, reproducibility, and robustness. This method is applicable for the analysis of extracted water samples, including drinking water, surface water, groundwater, and wastewater.

Introduction

Per- and polyfluoroalkyl substances (PFAS) are a large group of synthetic chemicals known for their resistance to heat, water, and oil. Due to these properties, PFAS have been widely used in various industrial and consumer products. However, PFAS are often referred to as "forever chemicals" because they do not break down easily and can accumulate in the environment and in human and animal tissues over time. This persistence, along with their widespread use, has led to extensive environmental contamination, particularly in water sources.[1] As a result, analyzing PFAS in different matrices, especially drinking water, has become increasingly important. Analyzing PFAS is critical for understanding their distribution, concentration, and potential risks to human health and the environment.[2] To address these health risks, various governmental regulatory agencies have established validated methods to quantify individual or collective PFAS levels in drinking water.

Regulatory framework in Europe

In Europe, the main regulation governing drinking water quality is the Drinking Water Directive (2020/2184/EU), which sets two thresholds for PFAS:

- 0.1 µg/L for the sum of a group of 20 PFAS
- 0.5 µg/L for the totality of PFAS[3]

Some countries, such as Denmark and Italy, test additional compounds. In the United Kingdom, the testing is based on tiered results with different countermeasures depending on PFAS concentrations (Tier 1: <0.01 µg/L; Tier 2: 0.01 µg/L – 0.1 µg/L; Tier 3: >0.1 µg/L). Additionally, several European countries have established limits for the sum of four PFAS compounds to which the population has been most exposed: PFOA, PFNA, PFHxS, and PFOS.[4]

Regulations for natural waters and wastewater

Natural waters are regulated under directives such as the Water Framework Directive (WFD, 2000/60/EC), the Environmental Quality Standards Directive (EQSD, 2008/105/EC), and the Groundwater Directive (GWD, 2006/118/EC). Though no official European regulation applies to water matrices other than drinking water, proposals for surface water exist, listing compounds to analyze based on relative potency factors. EurEau's research finds that only long-chain PFAS chemicals, which are a minority, find their way into sewage sludge, while the rest enter the aquatic environment.

In October 2022, the Commission proposed quality standards for the sum of 24 PFAS, including PFOS, in surface water and groundwater, with a proposed standard of 4.4 ng/L (as PFOA equivalents). This was based on opinions from the European Food Safety Authority (EFSA) and the Scientific Committee on Health, Environment, and Emerging Risks. Wastewater discharges are regulated under directives mandating PFAS analysis from classified installations, with lists of regulated PFAS varying across Europe. For example, in France, the Order of June 20, 2023 mandates screening for eight additional emerging PFAS compounds in aqueous discharges from classified installations. However, the newly approved Urban Wastewater Treatment Directive (UWWTD) from November 2024 does not set binding limit values for treated wastewater.

Therefore, an exhaustive list of regulations, recommendations, and EPA methods[5] was used to define our list of PFAS included in the method, ensuring a comprehensive and adaptable approach that can evolve with changing legislation.

Analytical approach and methodology

Liquid chromatography coupled with mass spectrometry provides high sensitivity and specificity for detecting a wide range of PFAS compounds. In previous work, we demonstrated the ability to meet regulatory requirements for PFAS analysis using large volume injection and high-end triple quadrupole technology for drinking water analysis.[6] Nevertheless, other types of water need sample preparation, which is often critical, to concentrate PFAS from large volumes and to remove potential interferences.

We have previously demonstrated the capabilities of an automated dispersive liquid-liquid microextraction (DLLME) procedure using a Thermo Scientific™ TriPlus™ RSH SMART autosampler for the extraction and analysis of PFAS in drinking water.[7] The DLLME protocol offers advantages such as automation and the use of small sample and reagent volumes. However the traditional solid phase extraction (SPE) can also be used.[8,9]

Workflow method performance and package

This application brief describes our method for the quantitation of 61 PFAS in organic solvent, including those regulated at the EU level, additional targets monitored by specific EU countries, and emerging PFAS relevant for environmental and food safety. Method performance is presented based on limit of quantitation (LOQ), linear dynamic range, accuracy, precision, and robustness with real sample extracts.

For ease of use and training purposes, our workflow is fully documented and includes:

- A standard operating procedure (SOP) detailing hardware, capillary connections, consumables, and reagents.
- A software package with attached instrument method and processing methods, including view settings for guided, fast, and compliant data review and reporting using the Thermo Scientific™ Chromeleon™ 7.3.2 Chromatography Data System (CDS).
- A data set with examples and performance demonstrations.

Experimental

Instrument configuration and method

The Thermo Scientific™ Vanquish™ Duo Autosampler was used, which consists of two independent flow paths and columns to accelerate analytical throughput. The system comes integrated with two Thermo Scientific™ Vanquish™ Flex Binary UHPL pumps. To leverage HRMS full scan data using the Orbitrap Exploris EFOX and obtain diverse confirmation parameters, the method includes two separate injections onto different chromatographic columns within a single run and a single data file. This provides two retention times (orthogonal confirmation) associated with high-resolution and accurate mass measurement for precursor ions. The two analytical columns have different chemistries and distinct gradients using a combination of water and methanol as the mobile phases. The hardware configuration schematics can be observed in Figure 1 and Table 1. Table 2 recaps the main instrument parameters.

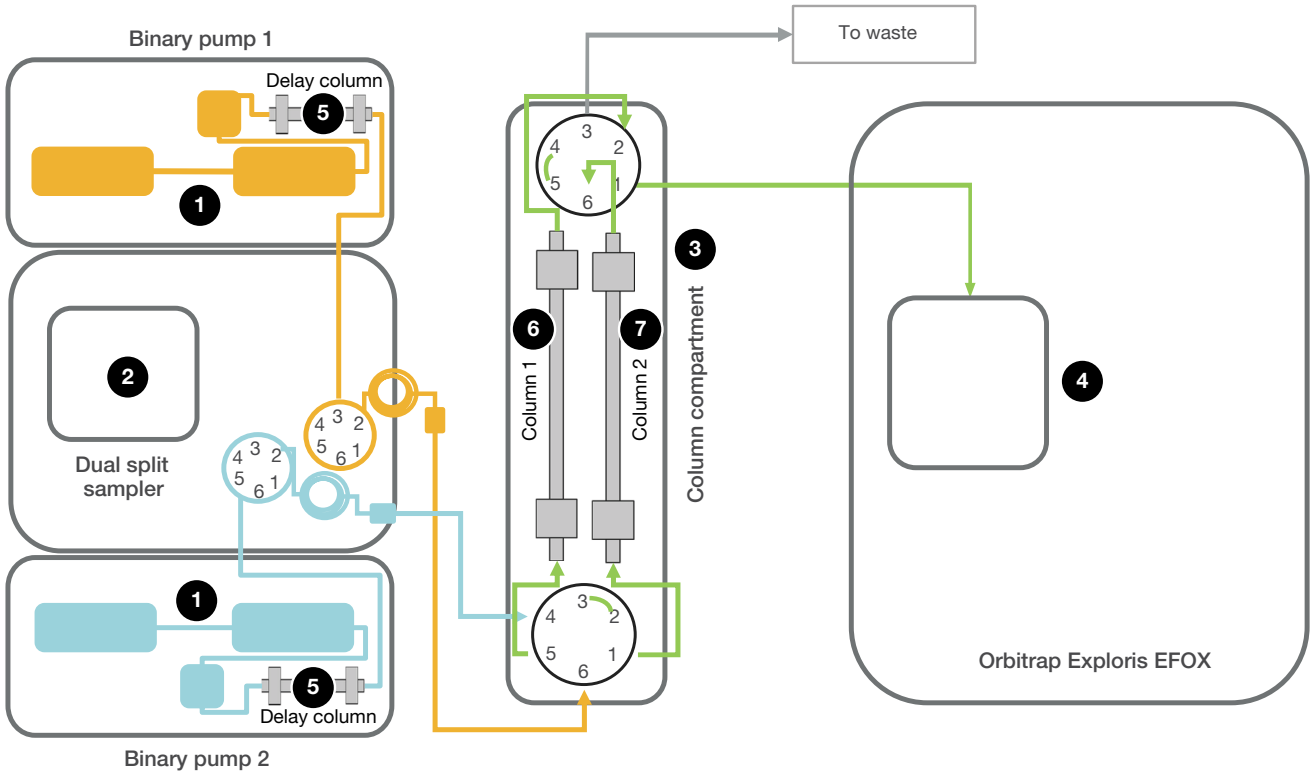

Figure 1. Hardware configuration for the analysis of PFAS in clean water

Table 1. References of configuration utilized for PFAS analysis

Reference	Part number	Instrument
1	VF-P10-A-01	2× Vanquish Flex Binary UHPLC Pump
2	VF-A40-A-02	Vanquish Dual Split Sampler
3	VH-C10-A-03	Vanquish Flex Column Compartment
4	BRE725557	Orbitrap Exploris EFOX MS
5	25002-052130	2× Thermo Scientific™ Hypersil GOLD™ 50 × 2.1 mm, 1.9 µm column
6	25202-102130	Hypersil GOLD C8 100 × 2.1 mm, 1.9 µm column
7	25002-102130	Hypersil GOLD 100 × 2.1 mm, 1.9 µm column

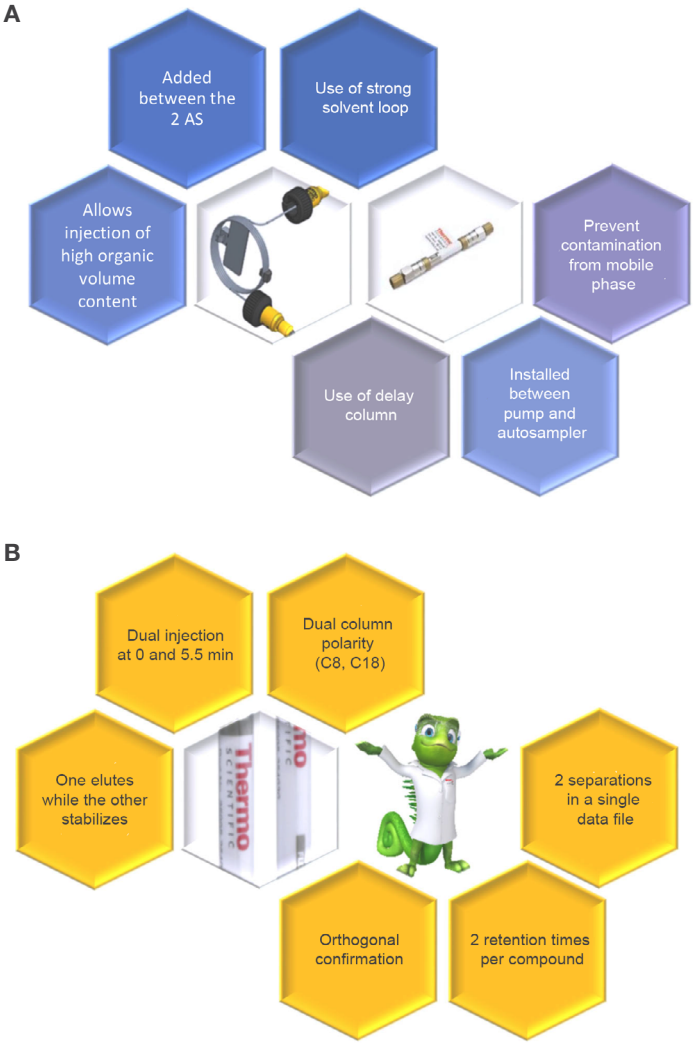

Figure 2. Tips and tricks for PFAS analysis hardware configuration. (A) To prevent contamination and issues with high organic content, use a strong solvent loop between autosampler ports and analytical columns, and add delay columns. (B) To obtain diverse confirmation parameters, the method includes two separate injections in two different chromatographic columns within a single run and a single data file.

Table 2. Instrument parameters

	Parameters
Column 1	Hypersil GOLD C8 100 × 2.1 mm, 1.9 µm
Column 2	Hypersil GOLD 100 × 2.1 mm, 1.9 µm
Mobile phase A	Water at 0.1 mM of ammonium fluoride
Mobile phase B	Methanol at 0.1 mM of ammonium fluoride
Total run time	14.5 min
Injection volume	10 µL
Acquisition type	Full Scan (+2 ion-source fragmentation FS)
Scan range (*m/z*)	70–1,000
Resolution	60,000
Source type	HESI
Polarity mode	Negative

Method qualification results

To ensure that the method is adapted for the analysis of clean and wastewater samples, and to assess its robustness, an analytical qualification of the method was performed.

Sample preparation

Calibration solutions were prepared in methanol with concentrations ranging from 25 ng/L up to 5,000 ng/L, with internal standard concentration at 500 ng/L. Spiking solutions of the 61 studied PFAS compounds were initially prepared in methanol at 1 ng/mL and 10 ng/mL. These solutions were then used for the preparation of calibration standards and a mix of 22 labeled internal standards dissolved in methanol was added to the samples to correct for any possible extraction and matrix effects.

Qualification tests

Linearity assessment, stability testing and method robustness

Linearity was assessed by injecting six calibration sets with varying parameters such as operator, day, and instrument. The limit of detection (LOD) and limit of quantitation (LOQ) were determined by checking for linearity and back-calculated concentrations at each level of concentration. Each LOQ was reproduced and measured for stability with 10 replicate injections. The method robustness was evaluated using quality control (QC) samples studied at LOQ concentrations (50–250 ng/L).

- QCs were injected every 10 injections of matrix samples (including SPE extracts of surface water, DLLME extracts of sewage water, groundwater, and effluent).
- A total of 40 matrix samples, a calibration curve, and 4 replicates of every LOQ were analyzed resulting in 12 QC injected for a period of 17 hours (70 injections)

The different parameters were tested, and their validation criteria are presented in Table 3.

Table 3. Qualification criteria

	Tested	Acceptamce criteria
Calibration and linearity	Calibration curve	≥5 levels, including blank
	Internal standard variation	RSD < 30% compared to the average area for the calibration curve
	Linearity	R^2 ≥ 0.990, back-calculated: ±20%, except LOQ ±40% (solvent calibration curve)
	Qualification	For at least 5 calibration curves validated
Sensitivity	LOQ RSD (%)	<20% for 10 injections
	LOQ bias (%)	<40% for 10 injections
	Two columns	Same LOQ
	Blank injection	Area (LOQ) > 3 x Area (blank)
Robustness	LOQ RSD (%)	<40%
	LOQ bias (%)	<20%

Accuracy and reliability

Aligning with the flexibility allowed by the SANTE guidelines for orthogonal validation methods, it is recommended to verify at least three independent criteria:

- Two exact masses from a single ion, base peak from a full scan HRAM on dual columns, matching within ±5 ppm acceptable tolerance.
- Two retention times within ±0.1 minutes (sample vs. standard) on dual columns with different stationary phases, providing orthogonal confirmation.
- Optionally, for confirmation purposes, fragment ion from a full scan HRAM, exact mass matching within ±5 ppm acceptable tolerance. These fragments are obtained from in-source fragmentation.

Linearity check

The results of the linearity study are consistent across the two analytical columns. Each compound was qualified using at least five different calibration curves, and each curve met the validation criteria (R^2 > 0.990 and a relative amount deviation of less than 40% for the LOQ and less than 20% for other levels).

As shown in Table 4, the limits of quantitation (LOQ) obtained range between 50 ng/L and 250 ng/L for a 10 µL injection. These results comply with current European regulations and require at least a 100-fold concentration factor, which is compatible with standard SPE method extraction protocols.

Table 4 (Part 1). Results of the linearity qualification study

Compound	CAS	Calibration type	Solvent LOQ (ng/L or ppt)	Range (ng/L or ppt)	R^2 (C8 & C18)	Rel. amount dev. (%) (C8 & C18)
10:2FTS	120226-60-0	Quad, WithOffset, 1/A	50	50–5,000	>0.990	<40% at the LOQ <20% for all other levels
11Cl-PF2OUdS	763051-92-9	Quad, WithOffset, 1/A	50	50–5,000		
3,6-OPFHpA	151772-58-6	Quad, WithOffset, 1/A	50	50–5,000		
3:3 FTCA	356-02-5	Quad, WithOffset, 1/A	100	100–5,000		
4:2FTS	757124-72-4	Quad, WithOffset, 1/A	50	50–5,000		
5:3 FTCA	914637-49-3	Quad, WithOffset, 1/A	50	50–5,000		
6:2 FTAB	34455-29-3	Quad, WithOffset, 1/A	100	100–5,000		
6:2 FTOH	647-42-7	Quad, WithOffset, 1/A	250	250–5,000		
6:2/8:2diPAP	943913-15-3	Quad, WithOffset, 1/A	50	50–5,000		
6:2diPAP	57677-95-9	Quad, WithOffset, 1/A	50	50–5,000		
6:2FTS	27619-97-2	Quad, WithOffset, 1/A	50	50–5,000		
7:3 FTCA	812-70-4	Quad, WithOffset, 1/A	50	50–5,000		
7HPFHpA	1546-95-8	Quad, WithOffset, 1/A	50	50–5,000		
8:2 FTOH	678-39-7	Quad, WithOffset, 1/A	235	235–5,000		
8:2 FTUCA	70887-84-2	Quad, WithOffset, 1/A	50	50–5,000		
8:2diPAP	678-41-1	Quad, WithOffset, 1/A	100	100–5,000		
8:2FTS	39108-34-4	Quad, WithOffset, 1/A	50	50–5,000		
8:3FTCA	34598-33-9	Quad, WithOffset, 1/A	50	50–5,000		
9Cl-PF3ONS	756426-58-1	Quad, WithOffset, 1/A	50	50–5,000		
ADONA	919005-14-4	Quad, WithOffset, 1/A	50	50–5,000		
FBSA	30334-69-1	Quad, WithOffset, 1/A	50	50–5,000		
FHxSA	41997-13-1	Quad, WithOffset, 1/A	50	50–5,000		
FOEA	27854-31-5	Quad, WithOffset, 1/A	100	100–5,000		
FOSA	754-91-6	Quad, WithOffset, 1/A	50	50–5,000		
HFPO-DA	13252-13-6	Quad, WithOffset, 1/A	100	100–5,000		
HFPO-TA	13252-14-7	Quad, WithOffset, 1/A	50	50–5,000		
N-EtFOSA	4151-50-2	Quad, WithOffset, 1/A	50	50–5,000		
N-EtFOSAA	2991-50-6	Quad, WithOffset, 1/A	50	50–5,000		

Table 4 (Part 2). Results of the linearity qualification study

Compound	CAS	Calibration type	Solvent LOQ (ng/L or ppt)	Range (ng/L or ppt)	R^2 (C8 & C18)	Rel. amount dev. (%) (C8 & C18)
N-EtFOSE	1691-99-2	Quad, WithOffset, 1/A	50	50–5,000	>0.990	<40% at the LOQ <20% for all other levels
N-MeFBSA	68298-12-4	Quad, WithOffset, 1/A	500	500–5,000		
N-MeFBSAA	159381-10-9	Quad, WithOffset, 1/A	50	50–5,000		
N-MeFOSA	31506-32-8	Quad, WithOffset, 1/A	50	50–5,000		
N-MeFOSAA	2355-31-9	Quad, WithOffset, 1/A	50	50–5,000		
N-MeFOSE	24448-09-7	Quad, WithOffset, 1/A	50	50–5,000		
PF4OPeA	377-73-1	Quad, WithOffset, 1/A	100	100–5,000		
PF5HxA	863090-89-5	Quad, WithOffset, 1/A	50	50–5,000		
PFBA	375-22-4	Quad, WithOffset, 1/A	50	50–5,000		
PFBS	375-73-5	Quad, WithOffset, 1/A	50	50–5,000		
PFDA	335-76-2	Quad, WithOffset, 1/A	50	50–5,000		
PFDoA	307-55-1	Quad, WithOffset, 1/A	50	50–5,000		
PFDoS	79780-39-5	Quad, WithOffset, 1/A	50	50–5,000		
PFDS	335-77-3	Quad, WithOffset, 1/A	50	50–5,000		
PFECHS	646-83-3	Quad, WithOffset, 1/A	50	50–5,000		
PFEESA	113507-82-7	Quad, WithOffset, 1/A	50	50–5,000		
PFHpA	375-85-9	Quad, WithOffset, 1/A	50	50–5,000		
PFHpS	375-92-8	Quad, WithOffset, 1/A	50	50–5,000		
PFHxA	307-24-4	Quad, WithOffset, 1/A	50	50–5,000		
PFHxDA	67905-19-5	Quad, WithOffset, 1/A	100	100–5,000		
PFHxS	355-46-4	Quad, WithOffset, 1/A	50	50–5,000		
PFNA	375-95-1	Quad, WithOffset, 1/A	50	50–5,000		
PFNS	68259-12-1	Quad, WithOffset, 1/A	50	50–5,000		
PFOA	335-67-1	Quad, WithOffset, 1/A	50	50–5,000		
PFOcDA	16517-11-6	Quad, WithOffset, 1/A	50	50–5,000		
PFOS	1763-23-1	Quad, WithOffset, 1/A	50	50–5,000		
PFPeA	2706-90-3	Quad, WithOffset, 1/A	50	50–5,000		
PFPeS	2706-91-4	Quad, WithOffset, 1/A	50	50–5,000		
PFTeDA	376-06-7	Quad, WithOffset, 1/A	50	50–5,000		
PFTrDA	72629-94-8	Quad, WithOffset, 1/A	50	50–5,000		
PFTrDS	791563-89-8	Quad, WithOffset, 1/A	100	100–5,000		
PFUdA	2058-94-8	Quad, WithOffset, 1/A	50	50–5,000		
PFUnDS	749786-16-1	Quad, WithOffset, 1/A	50	50–5,000		

Examples of compound calibration curves are presented in Figure 3. Figure 4 shows the relative amount deviation for each calibration level (green points) across repeated curves on both columns. The white area represents the acceptable deviation limit (%), while the blue area indicates deviations beyond the tolerance limit. The criteria of less than 40% deviation at LOQ and less than 20% for other levels were consistently met in the calibration curves for both columns.

Sensitivity check

The chromatograms below illustrate examples of eight PFAS at the LOQ in solvent, showcasing excellent resolution and peak shape (Figures 5, 6, and 7). The overlays correspond to the base peak plus confirmation with the second most intense ion in the full scan, which can be an adduct ion, a fragment ion, or an isotope ion depending on the specific structural and chemical characteristics of the PFAS. PFHxS and PFOS show the expected resolved peaks for linear and branched isomers.

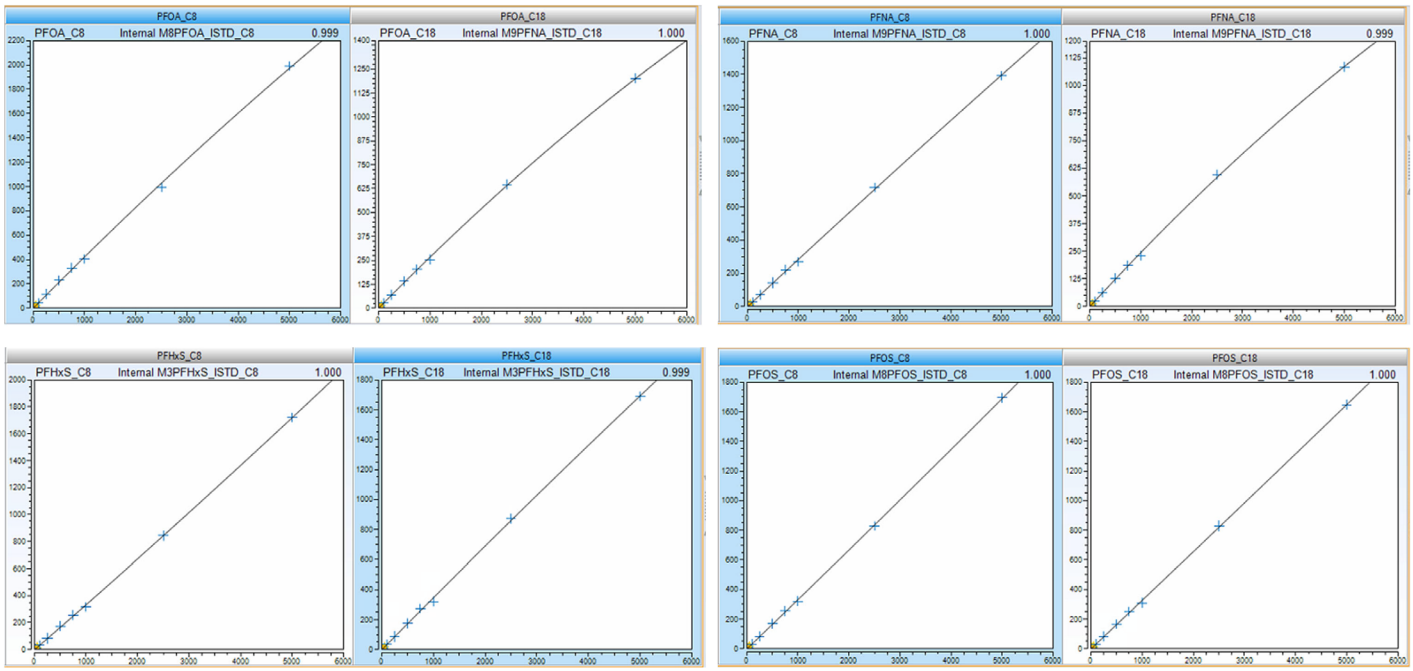

Figure 3. Calibration curves from 25 ppt to 5 ppb for PFOA, PFNA, PFHxS, and PFOS on both C8 and C18 columns

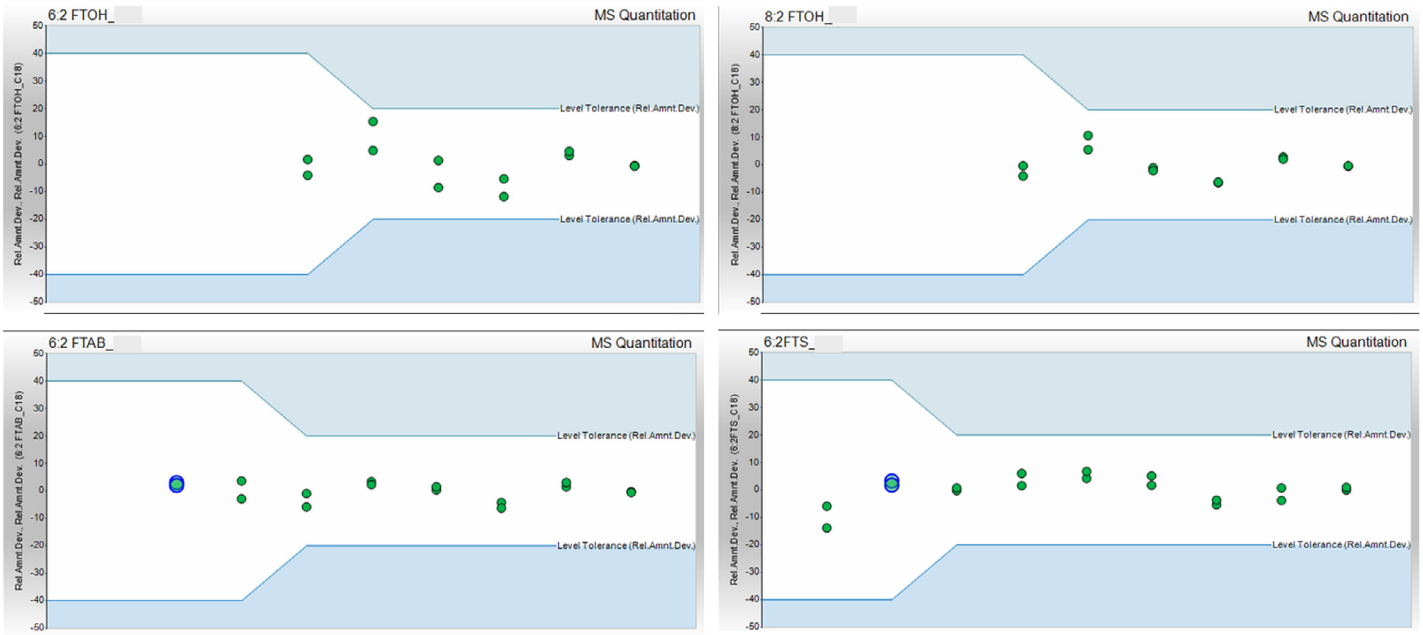

Figure 4. Example of charts to assess the relative amount deviation according to criteria, on both C8 and C18 columns, for 6:2 FTOH, from 250 ppt to 5 ppb; for 8:2 FTOH, from 235 ppt to 4.7 ppb; for 6:2 FTAB, from 50 ppt to 5 ppb; and for 6:2 FTS, from 25 ppt to 5 ppb

While the MS can detect lower LOQs, due to the ubiquitous nature of PFAS in the lab environment, LOQs were limited to the background level of the PFAS in our lab environment. LOQs should be set in accordance to the PFAS level in the end-user laboratory atmosphere. It is acknowledged that some laboratories may experience high levels of air contamination with PFBA. Other background compounds—PFPeA (consumables, pipette tips or reagent contamination), N-MeFBSA (when using acid in sample prep), 6:2FTS (when using SPE as sample extraction protocol)—can also be observed occasionally.

Robustness check

The method robustness was assessed by injecting a QC in solvent at the LOQ every 10 injections of matrix sample (extracts of sewage water, groundwater, and effluent). After 40 consecutive injections, the data presented in Table 5 demonstrated good robustness for injections on both C8 and C18 columns. The amounts were always accurate, and all relative amount deviations (Rel. Amt. Dev.) were clearly below 40%. The stability was very good.

It is important to note that no maintenance or MS tuning was conducted during the evaluation of robustness. For reference, the table also shows the average value and stability of the LOQ when injected 10 times to qualify the limit of quantitation.

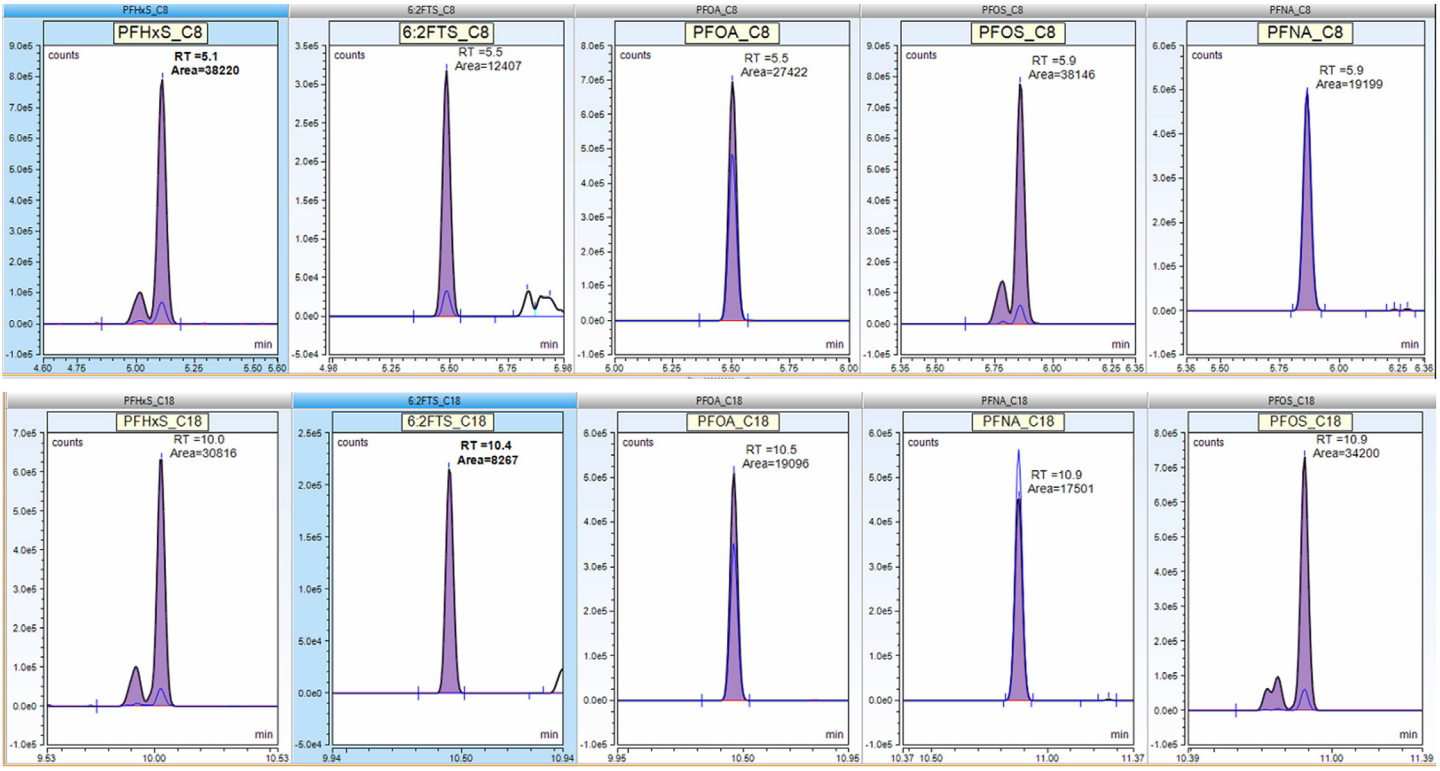

Figure 5. Overlaid full scan at the LOQ (50 ppt) for PFOA, PFNA, PFHx, PFOS, and 6:2 FTS on both C8 and C18 columns

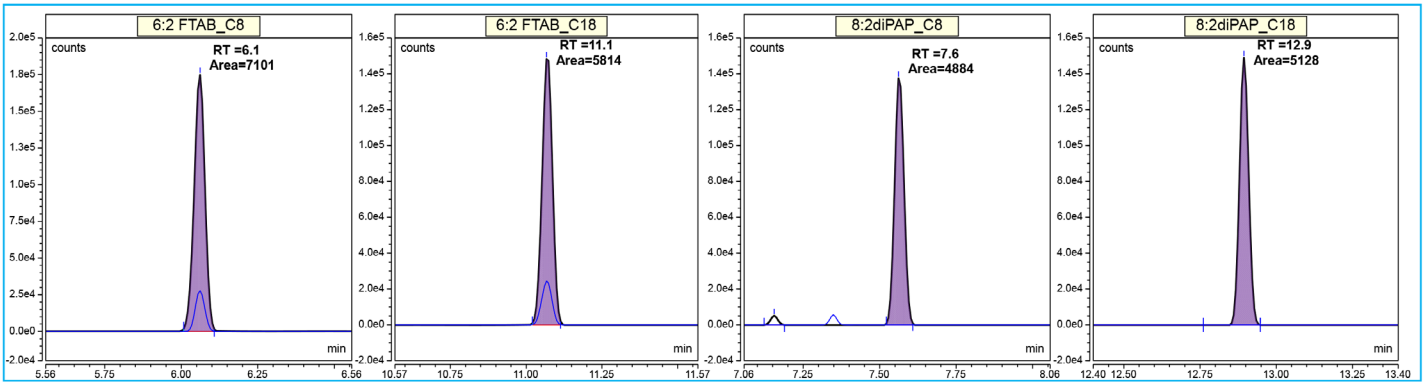

Figure 6. Overlaid full scan at the LOQ (100 ppt) for 6:2 FTAB, and 8:2 di-PAP on both C8 and C18 columns

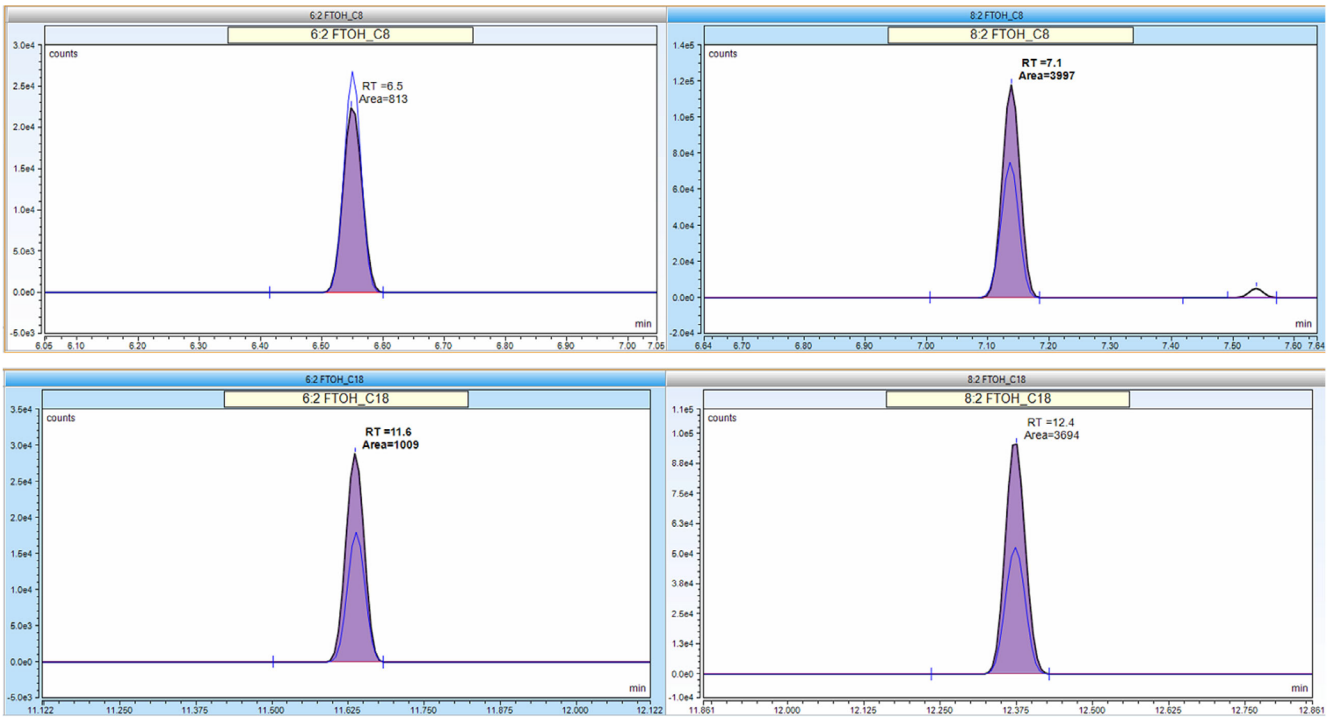

Figure 7. Overlaid full scan at the LOQ (250 ppt) for 6:2 FTOH and 8:2 FTOH on both C8 and C18 columns

Table 5. Stability of LOQ for PFAS for both C8 and C18 columns under stability, repeatability, and robustness tests

PFAS	LoQ	Average R1 to R10	%RSD (n=10)	QC-50-1	QC-50-2	QC-50-3	QC-50-4	Average QC1 to QC4	%RSD (n=4, over 40 matrices extract, over 17 hr)
	ng/L ppt	ng/L ppt	%	Calc amount (% Rel. Amt. Dev.)				ng/L ppt	%
6:2FTS_C18	50	49	5	53 (7%)	50 (1%)	50 (0%)	51 (1%)	51	3
6:2FTS_C8	50	49	4	52 (4%)	56 (12%)	54 (8%)	53 (7%)	54	3
PFHxS_C18	50	49	4	47 (-6%)	56 (11%)	55 (10%)	54 (9%)	53	8
PFHxS_C8	50	49	4	53 (5%)	53 (6%)	53 (6%)	54 (8%)	53	1
PFNA_C18	50	50	3	52 (4%)	51 (2%)	51 (3%)	51 (2%)	51	1
PFNA_C8	50	50	4	50 (1%)	51 (2%)	48 (-3%)	50 (0%)	50	2
PFOA_C18	50	50	5	52 (4%)	52 (4%)	52 (5%)	52 (4%)	52	0
PFOA_C8	50	48	3	50 (0%)	54 (8%)	52 (5%)	52 (3%)	52	3
PFOS_C18	50	49	4	52 (4%)	54 (7%)	55 (9%)	53 (6%)	53	2
PFOS_C8	50	50	3	54 (7%)	54 (8%)	55 (10%)	56 (12%)	55	2
6:2 FTAB_C18	100	100	5	96 (-4%)	99 (-1%)	97 (-3%)	98 (-2%)	97	1
6:2 FTAB_C8	100	96	7	94 (-6%)	109 (9%)	102 (2%)	98 (-2%)	101	6
6:2 FTOH_C18	250	253	10	262 (5%)	310 (24%)	248 (-1%)	276 (10%)	274	10
6:2 FTOH_C8	250	249	8	248 (-1%)	306 (23%)	273 (9%)	233 (-7%)	265	12
8:2 FTOH_C18	235	227	11	233 (-1%)	218 (-7%)	219 (-7%)	240 (2%)	228	5
8:2 FTOH_C8	235	229	9	235 (0%)	256 (9%)	260 (11%)	256 (9%)	252	5

Conclusions

Our method offers significant advantages for PFAS analysis, ensuring accurate, reliable, and compliant results. The major customer benefit is that we provide a ready-to-go solution, already optimized to meet regulatory limits in terms of performance, designed to comply with regulatory criteria, fully tested for robustness, applicable to any environmental sample type, and extremely easy to handle with a user-optimized interface.

- Accurate PFAS quantitation: The method enables the precise quantitation of a broad range of PFAS compounds using full-scan high-resolution acquisition in a targeted approach. Additionally, this configuration opens the door to suspected analysis and provides the capability for retrospective analyses when new PFAS targets enter regulatory lists.
- Regulatory compliance: Designed to comply with current European regulations for PFAS in drinking water (0.1 µg/L sum of 20 PFAS; 0.5 µg/L total PFAS); it can be extended to other regional PFAS lists.
- Robust method: Proven robustness with consistent performance across multiple injections and different matrices (sewage water, groundwater, effluent), maintaining accuracy and stability without the need for maintenance or MS tuning.
- Validated performance: Meets stringent validation criteria, including linearity ($R^2 > 0.990$), accuracy, precision, and robustness, with relative amount deviations well within acceptable limits.
- Orthogonal confirmation: Provides orthogonal confirmation with dual-column analysis and verification of exact masses and retention times, ensuring reliable and accurate PFAS identification.
- Practical application: Applicable for the analysis of extracted water samples, including drinking water, surface water, groundwater, and wastewater, supporting environmental and public health monitoring.

For a conventional approach of this workflow, please refer to its twin application brief, run with the Thermo Scientific™ TSQ Altis™ Plus mass spectrometer.[10]

For further information, contact your local commercial representative.

Acknowledgment

We would like to thank John Quick from ALS Laboratories (UK) for providing us with SPE extracts and for sharing his insights, which significantly contributed to this study.

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