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# A liquid chromatography tandem mass spectrometry method for determining 18 per- and polyfluoroalkyl substances in source and treated drinking water

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ABSTRACT

Per- and polyfluoroalkyl substances (PFASs) have been determined in waters intended for human consumption, causing concern due to their potential toxic effects in humans and the environment. Drinking water is acknowledged to be one of the major routes of exposure to PFASs, which has led to the implementation of regulatory guidelines for PFASs in drinking water. In this study a fast, simple, sensitive and cost-effective method is developed for the determination of 18 PFASs in river and drinking water. The proposed method consists of directly injecting 900 µL of sample into a liquid chromatograph coupled to a triple quadrupole mass analyser, which involves minimal sample treatment as the sample only needs to be filtered. The method was validated in influent and effluent water from a drinking water treatment plant. Strong matrix effects were found for some of the target PFASs, and matrix-matched calibration curves were performed to enable accurate (87–114%) and precise (%RSD between 3 and 18%) quantification ($n$ = 5, at 5 and 75 ng·L$^{-1}$) with very good sensitivity (method quantitation limits between 0.1 and 2.0 ng·L$^{-1}$). The method was applied to water samples from the influent and effluent of a drinking water treatment plant located in Catalonia (Spain), as well as in tap water and bottled water. The most abundant PFAS in all the types of water was PFBA, which represents 48%, 49%, 66% and 69% of total PFASs found in influent, effluent, tap and bottled water respectively. Relative mean abundances and the sum of mean concentrations in influent and effluent water suggests poor removal of PFASs during drinking water treatment. The concentrations of PFASs in bottled waters were generally lower than those in tap waters.



## 1. Introduction

Per- and polyfluoroalkyl substances (PFASs) are a family of anthropogenic chemicals that are characterized by containing one or more C atoms in which all the H substituents (present in the non-fluorinated analogues from which they are notionally derived) have been replaced by F atoms, so they contain at least one perfluoroalkyl moiety ($C_nF_{2n+1}$–) [1]. PFASs form a large group of over 4000 chemicals [2] that have been used worldwide in a great variety of industrial and consumer applications since the late 1940s. Their molecular structures confer useful properties such as chemical inertness, extreme resistance to hydrolysis, photolysis, microbial degradation and surfactant activity [3]. Their widespread use together with their high stability make these compounds extremely persistent [4], and their ionic nature and great solubility make them highly mobile in the aqueous system [5]. Consequently, PFASs have been extensively reported in aquatic environments including surface waters, ground waters, wastewaters and drinking waters [5–13]. Due to transport over long distances and diffuse sources related to domestic applications [14,15], PFASs can be detected in drinking water sources from non-industrial areas in the lower ng·L$^{-1}$ range, with waste streams from both industrial and municipal wastewaters being the main source of PFASs entering environmental waters [9,16,17].

One of the primary routes of human exposure to PFASs is dietary intake including food, drinking water, and indoor and outdoor air inhalation [18]. Human exposure to PFASs from drinking water is of serious concern because they are recalcitrant to conventional drinking water treatment processes [8,19,20], leading to permanent exposure of the general population. Studies of exposed populations show that concentrations of PFASs in the low ng·L$^{-1}$ level in drinking water can lead to high exposure levels [21–23],

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and human exposure to PFASs has been linked to cancer [24], high cholesterol [25], obesity [26], immune suppression [27], endocrine disruption [28], and prenatal and neonatal toxicity [29].

Of the PFASs, the two most-studied substances are perfluorooctanesulphonic acid (PFOS) and perfluorooctanoic acid (PFOA) as they were the most used in industry until 2006, when stringent restrictions to their production and use were introduced in Europe and the United States [30,31]. In response to this, the EU introduced an annual average environmental quality standard (AA-EQS) of 0.65 $ng{\cdot}L^{-1}$ for ΣPFOS (sum of linear and branched isomers) in inland surface water [32], and PFOA has been included on the list of substances of very high concern (SVHC) by the European Chemicals Agency [33]. Although most current guidelines focus only on PFOS and PFOA, the restrictions to their production have led to the increasing use of new fluorinated alternatives, shifting human exposure patterns to shorter-chain homologues of these compounds [14,34]. Monitoring programmes are needed for a better understanding of PFAS levels in the aquatic environment – particularly in drinking water source areas – and their presence in finished drinking waters in order to help the regulatory process and establish better protection of the ecosystem and human health [35–37]. A recently published proposal for a Directive of the European Parliament and of the Council on the quality of water intended for human consumption included 20 PFASs with a parametric value of 0.1 $\mu g{\cdot}L^{-1}$ $\Sigma_{20}$PFASs [38]. In accordance with this the Commission has a period of three years after the Directive comes into effect to update the technical guidelines covering the analytical methods whereby detection limits, parametric values and sampling frequencies must be established.

So far most of the analytical methods to determine PFASs in aqueous matrices have been based on liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) employing solid-phase extraction (SPE) [39,40]. Trace-level extraction and analysis of PFASs in environmental matrices is very challenging as their quantitation in low nanogram-per-liter concentrations in drinking water typically requires large volumes of sample to be extracted (50–500 mL). Depending on the chain length and functional group present in the molecules, their physicochemical properties can vary greatly, hindering the recovery of all PFASs during the extraction and clean-up processes due to incomplete elution, breakthrough and/or volatilization during solvent exchange. Moreover, due to the presence of fluorinated polymers in materials and equipment commonly used in laboratories, sample manipulation and treatment increase the risk of sample contamination. On-line SPE-LC-MS/MS methods have been developed for determining PFASs in water samples as their full automation reduces the labor involved in off-line SPE while minimizing sample manipulation and treatment, thus increasing analytical throughput [41-45]. This methodology also reduces the sample volume, since in a typical on-line SPE the preconcentrated volumes required are much lower (1–10 ml) than in an off-line SPE. In addition, analyte loss is reduced as desorption of the analytes is performed with the mobile phases and the gradient elution used to perform the chromatographic separation, so the whole eluate goes into the analytical column with no need for extract evaporation.

Large-volume direct injection of samples (LVDI) is an alternative approach that allows an increase in sample throughput when compared with both off-line and on-line SPE without the need for extra equipment and materials. The LVDI technique involves the injection of sample volumes greater than 10% of the analytical column void volume (typically from 100 to 1800 µL) [46,47]. With this methodology the whole sample is transferred directly to the analytical column, avoiding the use of SPE cartridges and solvents and eliminating the analyte loss intrinsic to extraction procedures. This methodology also minimizes sample contamination due to its minimal sample manipulation and treatment and has been applied in several studies reported in the literature for the determination of different types of micropollutant in aqueous samples, including PFASs [48–50]. Matrix effects (ME), which can affect the sensitivity, selectivity and reproducibility of an analytical method, are reported for both LVDI and SPE methodologies [51], and despite the absence of extraction and clean-up steps when using the LVDI approach, there are studies that demonstrate that SPE does not reduce matrix effects more than direct analysis by LVDI [52].

Given this context, the aim of the present study is to develop and validate a rapid, simple analytical method based on the LVDI approach for determining the dissolved fraction of 18 PFASs in aqueous samples that makes it possible to monitor PFASs in water intended for human consumption at low and sub $ng{\cdot}L^{-1}$ levels. To this end the compounds selected for the study were 10 perfluorocarboxylic acids and 6 perfluorosulfonic acids that are included in the new proposal for a Directive of the European Parliament and of the Council on the quality of water intended for human consumption [37], along with 1 fluorotelomer sulfonic acid and 1 perfluoroether carboxylic acid, since these are commonly used as PFOS alternatives in various applications [53,54]. The method was then applied using water samples collected from the influent and effluent of a drinking water treatment plant (DWTP) to determine the presence of the target PFASs in both the drinking water source and the resulting drinking water. The method was also applied to tap water samples collected from houses that receive water from the DWTP and to the bottled water of five different commercial brands. The results were then compared.

## 2. Materials and methods

### 2.1. Reagents and standards

Methanol (MeOH), water, ammonium acetate and formic acid, all of LC-MS grade, were purchased from Chem-Lab (Zedelgem, Belgium). Stock standards of perfluoro-2-propoxipropanoic acid (PFPrOPrA), perfluorobutanoic acid (PFBA), perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorohexane sulfonic acid (PFHxS), perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) were purchased from Dr. Ehrenstorfer (Augsburg, Germany). Stock standards of nonafluoro-1-butanesulfonic acid (PFBS[a]), 2-(perfluorohexyl) ethane-1-sulfonic acid (6:2 FTSA), perfluorotridecanoic acid (PFTrDA) and perfluorododecanoic acid (PFDoA) were purchased from Lab Mix 24 (Hamminkeln, Germany). Stock standards of perfluoroundecanoic acid (PFUnDA), perfluorodecane sulfonic acid (PFDS), pefluoropentane sulfonic acid (PFPS) and perfluorononane sulfonic acid (PFNS) were purchased from Cambridge Isotope Laboratories (Andover, USA). All compounds had a chemical purity of 95.0% or higher. Spiking solutions were prepared at a concentration of 100 $\mu g{\cdot}L^{-1}$ in MeOH and stored in glass vials with screw tops with aluminum lining at −21 °C. Working mixtures of all PFASs were prepared daily in MeOH or water at an appropriate concentration to prepare the standards and spike the samples.

### 2.2. Sample collection

Water samples from the DWTP were collected at their influent and effluent between January and April 2020. The DWTP is located in L'Ampolla, in southern Catalonia (Spain), and collects water from the River Ebro in Campredó. It can process up to 4 $m^3\ s^{-1}$ with the conventional treatment, including pH adjustment with $CO_2$, pre-oxidation with ozone, coagulation, flocculation, decantation, sand filtration, post-oxidation with ozone, granular-activated carbon filtration (GAC) and final chlorination with NaClO.

Tap water was collected from seven different houses that receive water from the DWTP. Grab samples were collected in 250 mL amber glass bottles equipped with screw top with aluminum lining. Before sample collection, the bottles were pre-rinsed with sample three times. 250 µL of sodium thiosulfate 0.1 M was added to the samples collected at the effluent of the DWTP and the tap water to prevent further reaction with sodium hypochlorite. If samples could not be analysed the same day they were collected, they were stored at 3 ± 2 °C until analysis. Bottled water from five commercial companies, whose spring water comes from different sources, were purchased from a supermarket. To prevent particles from interfering with the analysis and causing damage to sensitive instrumentation, the samples were filtered with regenerated cellulose (RC) syringe filters 0.45 µm (Chromafil, USA). This filter was selected as it has been reported that the loss of most of the PFASs included in this study are low or negligible in this type of filter material [55]. As the filtration step removes suspended particulate matter from the sample, it is important to mention that only the dissolved fraction of the PFASs has been determined. In this regard, it has been reported that the compounds evaluated in this study are almost completely partitioned in the dissolved phase [56], so the analysis of the dissolved fraction provides a realistic picture of their presence in the aquatic environment.

### 2.3. Equipment and chromatographic conditions

#### 2.3.1. Large volume direct injection (LVDI)

LVDI liquid chromatography analyses were performed using an Agilent chromatographic system (Agilent Technologies, Waldbronn, Germany) equipped with a 1260 HiP degassing unit, 1260 binary pump, 1260 multisampler (equipped with a 900-µL syringe, a 900-µL sample loop, a 100-µL analytical head and an injection valve) and a 1260 thermostatted column compartment. An analytical LC column (Poroshell 120 EC–C18, 4.6 × 100 mm × 2.7 µm) was used as a delay column and installed between the mobile phase mixing chamber and the sample injector, to separate the background contamination from the target PFASs present in the sample.

The analytes were chromatographically separated with a Poroshell 120 EC–C18 (3 × 100 mm × 2.7 µm) equipped with a Poroshell 120 EC–C18 (3 × 5 mm × 2.7 µm) guard cartridge kept at 40 °C. The mobile phase consisted of (A) water with 5 mM ammonium acetate and (B) MeOH. The elution gradient conditions were as follows: 2% B maintained for 4 min, increased to 40% over 2 min, increased to 90% over 9 min, after which 100% B was maintained for 5 min and returned to initial conditions over 0.5 min and held for 3 min in order to start the re-equilibration of the analytical column. The re-equilibration of the column was finished while the next sample was being loaded into the sample loop. During the first 10 min, the flow from the analytical column was diverted to waste through a divert valve located between the analytical column and the ESI source. The total run time for each injection was 25 min. The flow rate was kept at 0.350 ml·min$^{-1}$ throughout the run, and the sample volume injected was 900 µL.

#### 2.3.2. MS/MS determination

The chromatographic system was coupled to an Agilent 6470 triple quadrupole mass spectrometer (Agilent Technologies) equipped with an electrospray ionization source (ESI). The ESI operated in negative ionization mode using the deprotonated molecules $[M\text{-}H]^-$ as the precursor ions. The optimized source conditions were: drying gas ($N_2$) temperature at 250 °C, drying gas flow at 10 L·min$^{-1}$, sheath gas ($N_2$) temperature 400 °C, sheath gas flow 12 L·min$^{-1}$, capillary at 2000 V, nebulizer at 15 psi and nozzle voltage at 0 V. MS/MS analysis was carried out using dynamic multiple reaction monitoring (dMRM). The two most intense transitions for each compound were selected (except for PFBA and PFPeA, in which only one transition could be used); the most intense one was used for quantification (Q) and the other as a qualifier (q) for confirmation purposes. A summary of the optimized compound-dependent MS parameters is given in **Table S1** in the supplementary information.

### 2.4. Analytical batch QC and reporting criteria

Eight-point matrix-matched calibration curves were performed for each matrix (influent, effluent and bottled water) at the beginning of the sample batch, from the MQL of each analyte covering two orders of magnitude (tap water was quantified using calibration curves performed with effluent water). Accuracy criterion for continuous calibration points was ±20%. Quality controls (QCs) consisting of influent and effluent water spiked at the second calibration level (0.2, 0.5, 1 and 2.5 ng·L$^{-1}$ depending on the analyte) were analysed every ten sample injections, and recoveries in the range 70–120% were considered satisfactory. In order to rule out any possible system contamination, instrumental blanks (the gradient program with no injection) were included in each injection batch. In addition, two blanks consisting of LC grade water were injected after each QC injection to control and prevent sample contamination.

Commission decision 2002/657/EC criteria were followed to confirm the presence of the target analytes in the water samples. The tolerance within the retention time of an analyte present in a water sample compared to that of a reference standard was therefore set at ±2.5%, and the relative abundance of the two selected transitions (q/Q ratio) set at ±20% [57]. Possible false positives due to contamination were mitigated by censoring analyte signal in samples which were not four times greater than the signals measured in corresponding blanks.

## 3. Results and discussion

### 3.1. Background elimination

Background contamination is a major challenge in the trace analysis of PFASs. Sources of instrumental and procedural blank contamination have already been described, as well as the techniques for reducing it [58,59]. In the present study, in order to reduce procedural blank contamination, the septum of the vials was removed, the use of fluoropolymer materials was avoided during all preparations and storage, and all the material used was rinsed three times with methanol before use and dried in an oven at 100 °C. To reduce instrumental background contamination, an analytical HPLC column (Agilent Poroshell 120 EC–C18, 4.6 × 100 mm × 2.7 µm) was installed after the mixing valve of the binary pump and before the autosampler to reduce interferences from the solvent delivery system. This is common practice in the determination of PFASs, flame retardants and plasticizers [50,60,61].

### 3.2. LVDI optimization

Based on the literature, methanol and water with ammonium acetate 5 mM were selected as the organic and aqueous mobile phase respectively [62]. A Poroshell 120 EC–C18 (3 × 100 mm × 2.7 µm) analytical column was used for the chromatographic separation of the target analytes. The gradient profile used was based on a published HPLC method [60] that reported an improvement in the peak shape of short-chain PFASs when compared with a linear gradient.

Three different injection volumes (500 µL, 750 µL and 900 µL) were tested in LC grade water and influent and effluent water from a DWTP to evaluate the effect of directly injecting an increasing

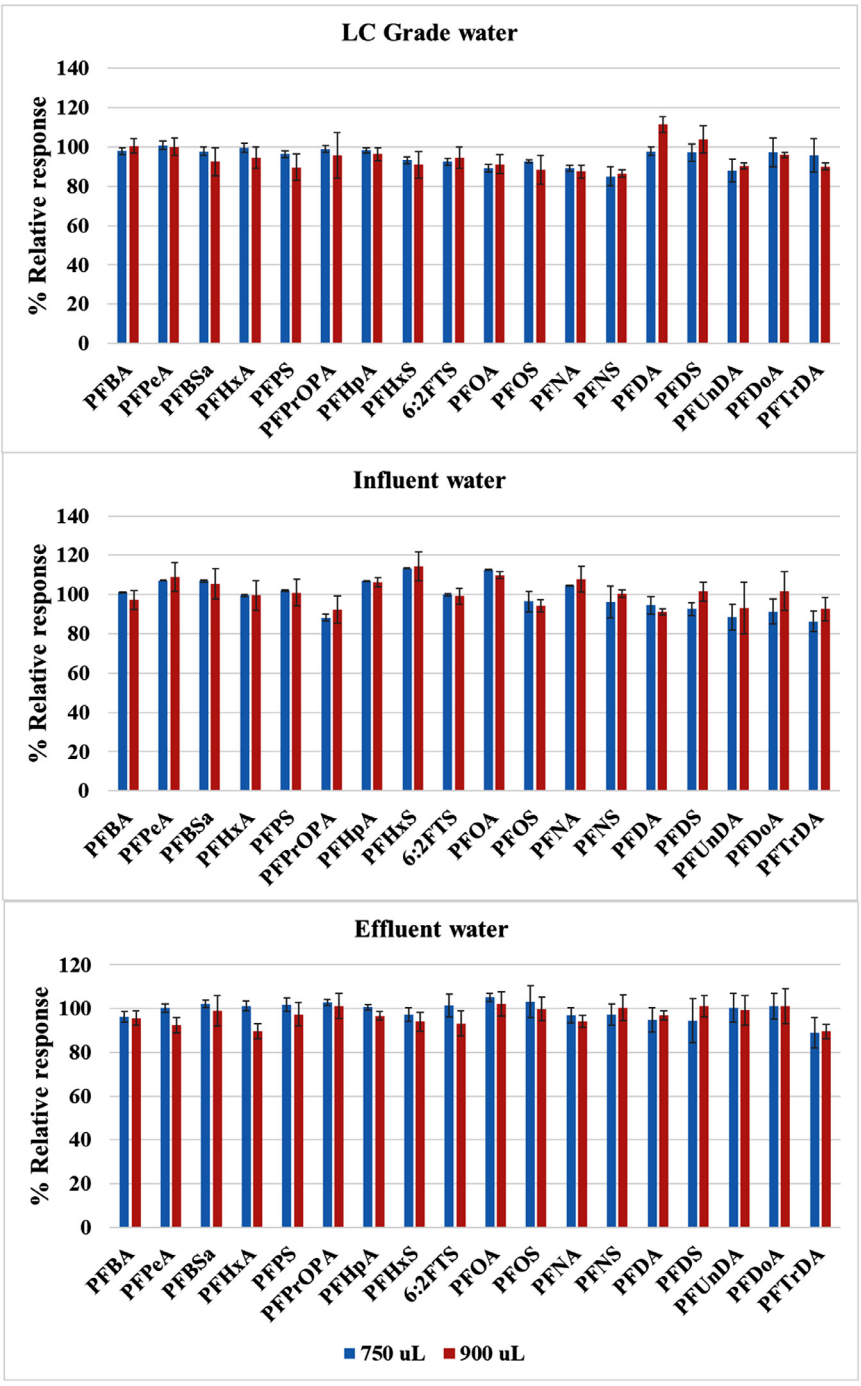


**Fig. 1.** Relative responses of target analytes with different injection volumes in the different studied matrices. Injections performed in triplicate. Error bars correspond to standard deviation.

volume on the response of the target analytes in the different matrices. To this end, standards and influent and effluent water spiked at 50 ng·L$^{-1}$ were injected at the three injection volumes evaluated, and as can be expected, increasing the injection volume increased the response of all target analytes in the matrices studied. Nevertheless, suppression of signal was observed for some compounds in influent and effluent water when compared with the injection of standards (see **Fig. S1** in the supporting information). In order to evaluate the effect of increasing the injection volume on signal suppression, another set of experiments were performed and the responses obtained with the injection of 750 µL (spiked at 60 ng·L$^{-1}$) and 900 µL (spiked at 50 ng·L$^{-1}$) were compared with that obtained with the injection of 500 µL (spiked at 90 ng·L$^{-1}$) in each different matrix and the results presented as relative responses. As can be observed in Fig. 1, relative responses in the three evaluated matrices were in the range 85–112% for the injection of 750 µL and between 86 and 115% for the injection of 900 µL, indicating that the increase in injection volume in the evaluated range did not significantly affect suppression of the analyte responses within the same matrix. Considering these results, 900 µL was selected as the most suitable injection volume as it gives the highest response for all analytes, without increasing signal suppression.

Another important factor that determines the maximum volume that can be directly injected is the analyte peak dispersion,

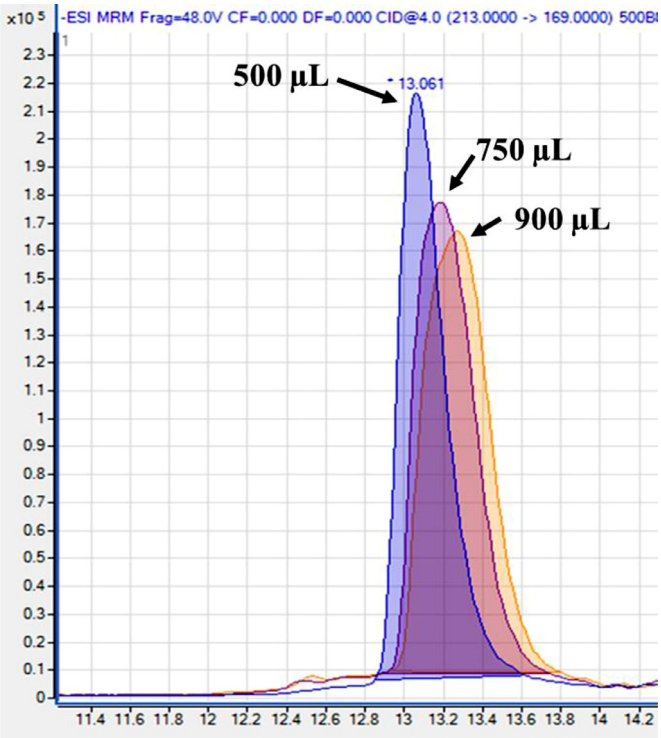


**Fig. 2.** Peak shape of PFBA with different injection volumes (50 ng·L$^{-1}$ standard).

since this affects the selectivity and sensitivity of separation methods. Deterioration of the peak shape of analytes caused by the injection of high volumes is dependent on many parameters, such as the volume injected, the analyte's physicochemical properties and the sample's pH [63]. The LVDI method developed in this study revealed an absence of peak broadening for all compounds in the three evaluated matrices, even with the direct injection of 900 µL, except for the PFBA compound. It is known that band-spreading effects are more pronounced in early-eluting analytes, since they are poorly retained in the analytical columns and this hinders their focalization. For PFBA, a slight deterioration in the peak shape was observed with the increase in the sample injection volume (Fig. 2).

The draw speed was set at 500 µL min$^{-1}$ with a post-time of 20 s after each draw to prevent vacuum build-up in the vials. Although 3 min were enough to transfer the sample from the 900 µL sample loop to the analytical column, the injection valve was kept in the main pass position for the first 4 min to wash the injection system to prevent carry-over. To minimize the total run time, the valve was then switched to the bypass position because this decreases the time required for the gradient to reach the analytical column. To protect the ionization source from the polar and salt components present in the sample, the first 10 min were sent to waste through a two-position six-port valve installed before the ionization source.

### 3.3. LVDI quality parameters

In this study the matrix effect on ionization efficiency was quantified using calibration curves prepared with standard solutions, influent water and effluent water ($n = 5$). Seven spiking levels were used: 1, 2.5, 5, 10, 25, 50 and 100 ng·L$^{-1}$. The extent of ME was calculated in accordance with the following equation:

$$ME\% = \frac{m_{sample}}{m_{standard}} \cdot 100$$

where $m_{sample}$ is the slope of the calibration curve obtained in matrix, and $m_{standard}$ is the slope of the calibration curve prepared with standards. Thus ME% values near to 100% indicated there is no ME or its insignificant, and values outside the range from 80% to 120% were considered as significant ME% [64] (Table 1).

Fig. 3 shows matrix/solvent slope ratios for each analyte in influent and effluent water. Signal suppression or enhancement was considered negligible if the value was between 0.8 and 1.2, which corresponds to a ME% < 20%. Values between 0.6 and 0.8, which corresponds to a signal suppression between 20 and 40%, indicate moderate signal suppression and values <0.6 (signal suppression > 40%) indicate strong signal suppression [65,66]. It can be observed that for PFPS, PFProPrA, PFHpA, PFHxS, 6:2 FTS and PFTrDA the matrix effects are negligible in both influent and effluent water. However, PFOS, PFNA, PFNS, PFDA, PFDS and PFUnDA underwent strong signal suppression in the two matrices. PFBA and PFDoA experienced strong and moderate signal suppression in influent and effluent water respectively, and for the compounds PFPeA, PFBS[a], PFHxA and PFOA moderate signal suppression was observed in influent water while negligible matrix effects were obtained in

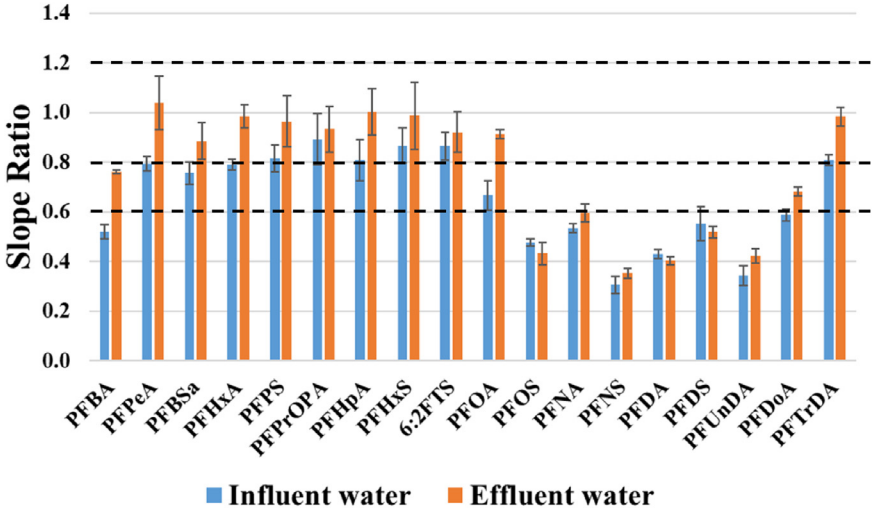


**Fig. 3.** Slope ratios between matrix-matched and solvent calibration of the target PFASs in influent and effluent water samples ($n = 5$). Error bars represent standard deviation.

**Table 1**
Quality parameters of the method. IDL, IQL, MDL and MQL in ng·L$^{-1}$.

| | Influent water | | | | | | | | Effluent water | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IDL ($n$ = 5) | IQL ($n$ = 5) | MDL | MQL | %Accuracy 5 ng·L$^{-1}$ ($n$ = 5) | %RSD 5 ng·L$^{-1}$ ($n$ = 5) | Accuracy 75 ng·L$^{-1}$ ($n$ = 5) | %RSD 75 ng·L$^{-1}$ ($n$ = 5) | ME% | MDL | MQL | %Accuracy 5 ng·L$^{-1}$ ($n$ = 5) | %RSD 5 ng·L$^{-1}$ ($n$ = 5) | Accuracy 75 ng·L$^{-1}$ ($n$ = 5) | %RSD 75 ng·L$^{-1}$ ($n$ = 5) | ME% |
| PFBA | 0.25 | 0.5 | 0.5 | 1.0 | 91 | 4 | 97 | 7 | 52 | 0.3 | 0.6 | 103 | 4 | 106 | 5 | 76 |
| PFPeA | 0.1 | 0.25 | 0.1 | 0.3 | 90 | 10 | 90 | 9 | 79 | 0.1 | 0.25 | 98 | 10 | 99 | 9 | 104 |
| PFBS[a] | 0.05 | 0.1 | 0.1 | 0.2 | 91 | 8 | 93 | 11 | 76 | 0.05 | 0.1 | 95 | 9 | 95 | 10 | 88 |
| PFHxA | 0.1 | 0.25 | 0.1 | 0.3 | 92 | 7 | 88 | 11 | 79 | 0.1 | 0.25 | 96 | 9 | 91 | 6 | 99 |
| PFPS | 0.25 | 0.5 | 0.30 | 0.6 | 89 | 8 | 97 | 12 | 82 | 0.25 | 0.5 | 96 | 12 | 95 | 10 | 96 |
| PFPrOPrA | 0.1 | 0.25 | 0.1 | 0.3 | 99 | 13 | 95 | 8 | 89 | 0.1 | 0.25 | 94 | 13 | 90 | 9 | 93 |
| PFHpA | 0.05 | 0.1 | 0.05 | 0.1 | 100 | 15 | 96 | 17 | 81 | 0.05 | 0.1 | 96 | 10 | 92 | 11 | 100 |
| PFHxS | 0.25 | 0.5 | 0.3 | 0.6 | 91 | 8 | 96 | 9 | 87 | 0.25 | 0.5 | 92 | 11 | 96 | 11 | 99 |
| 6:2 FTS | 0.1 | 0.25 | 0.1 | 0.3 | 89 | 7 | 106 | 5 | 86 | 0.1 | 0.3 | 99 | 10 | 114 | 17 | 92 |
| PFOA | 0.1 | 0.25 | 0.2 | 0.4 | 91 | 6 | 98 | 10 | 67 | 0.1 | 0.3 | 92 | 9 | 95 | 13 | 91 |
| PFOS | 0.1 | 0.25 | 0.2 | 0.5 | 93 | 7 | 101 | 4 | 48 | 0.25 | 0.6 | 95 | 14 | 101 | 8 | 43 |
| PFNA | 0.05 | 0.1 | 0.1 | 0.2 | 87 | 4 | 95 | 13 | 53 | 0.1 | 0.2 | 93 | 10 | 101 | 5 | 60 |
| PFNS | 0.1 | 0.25 | 0.3 | 0.8 | 103 | 16 | 111 | 11 | 31 | 0.3 | 0.7 | 94 | 9 | 104 | 4 | 35 |
| PFDA | 0.1 | 0.25 | 0.2 | 0.6 | 95 | 9 | 105 | 10 | 43 | 0.25 | 0.6 | 95 | 13 | 107 | 7 | 40 |
| PFDS | 0.5 | 1 | 1.0 | 2.0 | 103 | 10 | 103 | 6 | 55 | 1.0 | 2.0 | 96 | 12 | 107 | 9 | 52 |
| PFUnDA | 0.25 | 0.5 | 0.7 | 1.5 | 100 | 17 | 112 | 3 | 34 | 0.6 | 1.2 | 93 | 7 | 101 | 3 | 42 |
| PFDoA | 0.1 | 0.25 | 0.2 | 0.4 | 96 | 18 | 109 | 5 | 59 | 0.15 | 0.4 | 95 | 12 | 110 | 7 | 68 |
| PFTrDA | 0.25 | 0.5 | 0.3 | 0.6 | 94 | 10 | 106 | 7 | 80 | 0.25 | 0.5 | 113 | 5 | 100 | 6 | 98 |

IDL: instrumental detection limit; IQL: instrumental quantitation limit; MDL: method quantitation limit; MQL: method detection limit;%RSD;%relative standard deviation; ME%;%matrix effect.

effluent water. To compensate for this effect, matrix-matched calibration curves were performed in influent and effluent water and used for quantification in the present study. The linearity of the response was studied at seven different concentrations, covering two magnitude orders (1 to 100 ng·L$^{-1}$), with a coefficient of regression $\geq$ 0.997 and residuals < 20%.

Instrumental detection limits (IDLs) and instrumental quantitation limits (IQLs) were established as the concentration giving a signal-to-noise ratio (S/N) $\geq$ 3 and 10 respectively, in standard solution by replicated ($n$ = 5) (Table 1). Method detection limits (MDLs) and method quantitation limits (MQLs) were calculated in accordance with the following equations to incorporate the effect of the matrix to method sensitivity [50]:

$$MDLs = \frac{IDLs \cdot 100}{ME\%};\ MQLs = \frac{IQLs \cdot 100}{ME\%}$$

Good sensitivities were achieved for all the investigated compounds, with MQLs in the range 0.1 – 2.0 ng·L$^{-1}$ in both influent and effluent water. The MQL obtained for PFOS in influent water (0.5 ng·L$^{-1}$) was lower than the European EQS stipulated for inland waters (0.65 ng·L$^{-1}$), which is considered a challenging limit for every LC-MS analytical method [43,44,50].

The accuracy and precision of the method were evaluated in influent and effluent water at two concentrations (5 and 75 ng·L$^{-1}$; $n$ = 5). The results obtained were satisfactory for all compounds at the two concentration levels, with accuracies between 87 and 112% in influent water and 91–114% in effluent water. Precision, expressed as relative standard deviation (%RSDs), was in the range 3 - 18% in both influent and effluent water (Table 1).

### 3.4. Method comparison

Various LC-MS/MS methods for the determination of PFASs in aqueous samples have been reported in the literature. The comparison of these methods regarding sensitivity, precision and analytical throughput is complicated because of the number of analytes included, different injection volumes and the different sample preparation approaches used (i.e. off-line SPE, on-line SPE, LVDI …). In this section, the main characteristics of the analytical method herein proposed is compared with previously published high-throughput methods using the same approach (LVDI-LC-MS/MS) or on-line SPE-LC-MS/MS (Table 2). Off-line SPE methods were excluded as they cannot be considered high-throughput methods, due to that the pre-concentration step is performed manually.

Regarding sensitivity, our method represented a general improvement in comparison with previously published on-line SPE methods for determining PFASs in aqueous matrices [43,45] despite the fact that only 0.9 mL were injected instead of the 5 mL required in those methods. The difference in sensitivity was especially remarkable when the method proposed herein was compared with that of Llorca et al. [42], who reported MQLs in the range 0.90–50 ng·L$^{-1}$. Regarding precision, inter-day and intra-day variations higher than >20%were frequently reported for on-line SPE methodologies. For instance, Llorca et al. [42] reported inter-day RSD% >20% for 17 out of the 21 studied PFASs and Mazzoni et al. [43] reported inter-day RSD% as high as 65% for PFDoA. Total run times of those methods are comparable to the obtained for our method, with the exception of the method developed by Barreca et al. [45] with a total run time of only 12 min, probably due to that elution was performed with a flow rate of 1.6 mL·min$^{-1}$.

The LVDI approach was employed by Ciofi et al. [50] for the determination of nine PFASs in different aqueous matrices. Despite the fact that the volume injected was only 0.1 mL, the MQLs obtained were similar to those obtained with our method, with intra-day and inter-day precision <5.7%. In general, higher RSDs% were

**Table 2**
Comparison of main characteristics of the method herein proposed with previously published high-throughput methods for determination of PFASs.

| Technique | Sample Volume | Analysis time | MQL ($ng \cdot L^{-1}$) | | | | | | | | | | | | | [Reference] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (mL) | (min) | PFBA | PFPeA | PFBsA | PFHxA | PFHpA | PFHxS | 6:2 FTS | PFOA | PFOS | PFNA | PFDA | PFDS | PFUnDA | PFDoA | |
| LVDI-LC-MS/MS | 0.9 mL | 25.0 | 1.0 | 0.3 | 0.2 | 0.3 | 0.1 | 0.6 | 0.3 | 0.4 | 0.5 | 0.2 | 0.6 | 2.0 | 1.5 | 0.4 | This study |
| LVDI-LC-MS/MS | 0.5 mL | 20.0 | n.i. | n.i. | 0.7 | 0.5 | 0.5 | 0.8 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | n.i. | n.i. | [48] |
| LVDI-UHPLC-MS/MS | 0.1 mL | 20.0 | n.i. | 0.38 | 0.033 | 1.0 | 0.42 | 0.03 | n.i. | 0.3 | 0.17 | 0.61 | 0.13 | n.i. | n.i. | n.i. | [50] |
| On-line SPE LC-MS/MS | 5.0 mL | 16.25 | 26 | 38 | 8.2 | 50 | 17 | 0.90 | n.i. | 2.8 | 1.3 | 6.3 | 8.0 | 1.2 | 3.9 | 12 | [42] |
| On-line SPE LC-MS/MS | 5.0 mL | 16.5 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | n.i. | 2.0 | 2.0 | 2.0 | 2.0 | n.i. | 1.0 | 1.0 | [43] |
| On-line SPE LC-MS/MS | 5.0 mL | 12.0 | 5.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | n.i. | 1.0 | 0.2 | 1.0 | 5.0 | n.i. | 5.0 | 5.0 | [45] |

n.i. = not included in the study.

**Table 3**
Summary of PFASs occurrence in water samples collected at the influent and the effluent of a DWTP, tap water and bottled water.

| | Influent water ($n = 23^{*}$; $n = 5^{**}$) | | | | | Effluent water ($n = 23^{*}$; $n = 5^{**}$) | | | | | Tap water ($n = 7$) | | | | | Bottled water ($n = 5$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | DF % | QF % | Abundance $\%\Sigma_{18}$PFASs | Max $ng \cdot L^{-1}$ | Mean $ng \cdot L^{-1}$ | DF % | QF % | Abundance $\%\Sigma_{18}$PFASs | Max $ng \cdot L^{-1}$ | Mean $ng \cdot L^{-1}$ | DF % | QF % | Abundance $\%\Sigma_{18}$PFASs | Max $ng \cdot L^{-1}$ | Mean $ng \cdot L^{-1}$ | DF % | QF % | Abundance $\%\Sigma_{18}$PFASs | Max ng $L^{-1}$ | Mean ng $L^{-1}$ |
| PFBA* | 100 | 100 | 48 | 23.8 | 4.1 | 100 | 100 | 49 | 20.4 | 4.2 | 100 | 100 | 66 | 7.4 | 4.5 | 100 | 100 | 69 | 3.9 | 2.4 |
| PFPeA* | 100 | 91 | 9 | 2.5 | 0.86 | 100 | 96 | 10 | 2.3 | 0.89 | 42 | 26 | 7 | 1.1 | 0.52 | 100 | 20 | 4 | 0.26 | <MQL |
| PFBS[a]* | 100 | 91 | 3 | 0.57 | 0.32 | 100 | 100 | 5 | 3.2 | 0.54 | 57 | 14 | 2 | 0.33 | 0.13 | 60 | 20 | 1 | 0.13 | <MQL |
| PFHxA* | 91 | 57 | 6 | 3.1 | 0.54 | 100 | 87 | 8 | 2.2 | 0.72 | 100 | 100 | 9 | 2.6 | 0.63 | 100 | 60 | 7 | 0.36 | 0.25 |
| PFPS** | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0.0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d |
| PFProPrA** | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0.0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d |
| PFHpA* | 61 | 35 | 4 | 2.6 | 0.44 | 100 | 70 | 3 | 1.9 | 0.28 | 29 | 14 | 1 | 0.12 | <MQL | 40 | 0 | <1 | <MQL | n.d |
| PFHxS* | 65 | 39 | 8 | 1.7 | 0.73 | 35 | 30 | 7 | 2.5 | 0.63 | 57 | 0 | 4 | <MQL | <MQL | 40 | 0 | 3 | <MQL | n.d |
| 6:2 FTS* | 100 | 48 | 3 | 0.9 | 0.32 | 0 | 0 | 0.0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d | 60 | 0 | 5 | <MQL | <MQL |
| PFOA* | 96 | 48 | 6 | 2.6 | 0.51 | 91 | 43 | 4 | 0.77 | 0.34 | 100 | 57 | 4 | 0.38 | <MQL | 100 | 60 | 7 | 0.32 | <MQL |
| PFOS* | 87 | 22 | 7 | 4.3 | 0.69 | 65 | 13 | 7 | 3.9 | 0.62 | 86 | 57 | 6 | 0.70 | <MQL | 40 | 0 | 3 | <MQL | n.d |
| PFNA* | 43 | 26 | 3 | 0.58 | 0.33 | 39 | 22 | 3 | 0.54 | 0.24 | 29 | 0 | 1 | <MQL | <MQL | 40 | 0 | 1 | <MQL | n.d |
| PFNS** | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0.0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d |
| PFDA* | 35 | 13 | 3 | 0.73 | <MQL | 43 | 13 | 5 | 1.0 | <MQL | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d |
| PFDS** | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0.0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d |
| PFUnDA** | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0.0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d |
| PFDoA** | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0.0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d |
| PFTrDA** | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0.0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d | 0 | 0 | 0 | n.d | n.d |

* Compounds determined in 23 samples;.

** Compounds determined in 5 samples;DF: detection frequency (% of samples ≥MDL); QF: quantification frequency (% of samples ≥MQL); Abundance mean relative abundance ($\%\Sigma_{18}$P5FASs); Min: minimum concentration observed ($ng \cdot L^{-1}$); Max: maximum concentration observed ($ng \cdot L^{-1}$); Mean: average concentration; n.d: non detected; <MQL: concentration between the MDL and the MQL.

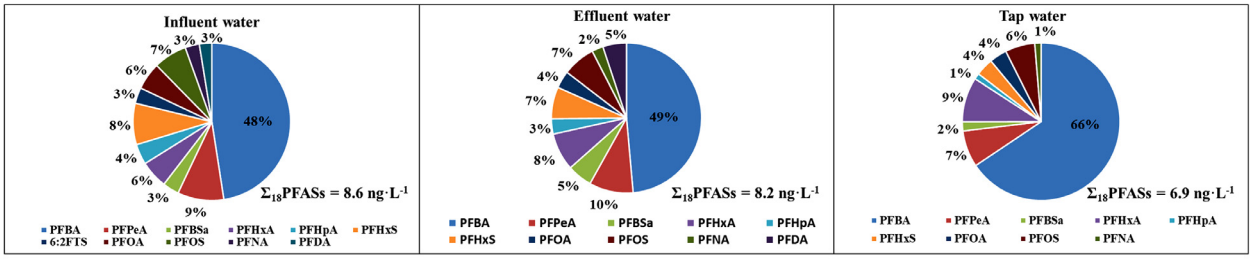


**Fig. 4.** Relative mean abundance of detected PFASs and sum of mean concentrations in influent, effluent and tap water.

observed in our method, which could be attributed to the injector precision due to the high injection volume used. Schultz et al. [48] also employed the LVDI approach for the analysis of selected PFASs in wastewaters, with sensitivity and analysis time comparable to those achieved in our method.

### 3.5. Analysis of water samples

The LVDI method developed was used to evaluate the presence of PFASs in 23 influent and 23 effluent water samples collected from a DWTP between January and April 2020. The method was also applied to 8 tap water samples and 5 bottled waters. Matrix-matched calibration curves were performed at the beginning of each sample batch, with residuals between ±20% between adjacent calibration points. The overall QCs recoveries in the spiked samples for most of the analytes were in the range 70–120% for all QCs injected. Background signals were not observed in instrumental blanks. Although no peaks corresponding to target analytes were observed in most of the LC-grade blank injections, in some cases slight contamination for short-chain PFASs was observed, but in all cases with signals below the MDLs.

#### 3.5.1. Occurrence of selected PFASs in influent water

From the 18 analytes included in this study, 11 were detected in effluent water samples at frequencies between 35 and 100% (Table 3). PFBA, PFPeA, PFBS[a] and 6:2 FTS were detected in all the samples. PFOA, PFHxA, PFOS, PFHxS and PFHpA were the next most frequently found chemicals, with detection rates of 96%, 91%, 87%, 65% and 61% respectively. PFNA and PFDA had a lower detection frequency (43% and 35% respectively). PFBA and PFPeA were also the compounds most frequently observed in another study performed on the River Ebro [67]. The maximum concentrations measured in samples were for PFBA (23.8 ng·L$^{-1}$), followed by PFOS (4.3 ng·L$^{-1}$), PFHxA (3.1 ng·L$^{-1}$), PFHpA (2.6 ng·L$^{-1}$), PFOA (2.6 ng·L$^{-1}$) and PFPeA (2.5 ng·L$^{-1}$). In agreement with our results, Lorenzo et al. [67] reported PFBA as the PFAS found at the highest concentration in the River Ebro. The mean relative abundance of each individual compound was calculated as a percentage of $\Sigma_{18}$PFASs. The most abundant perfluorinated chemical was by far PFBA (48%), followed by PFPeA (9%), PFHxS (8%), PFOS (7%), PFOA (6%) and PFHxA (6%). The highest $\Sigma_{18}$PFASs level found in a sample was 32.0 ng·L$^{-1}$, which is beyond the parametric value of 0.1 µg·L$^{-1}$ $\Sigma_{20}$PFASs included in the proposal for a Directive of the European Parliament and of the Council on the quality of water intended for human consumption [38]. The fact that all the PFASs measured in this study are in the low or sub ng·L$^{-1}$ level indicates that there is no large point source contamination in this part of the Ebro. These low levels may result from diffuse sources, such as the long-range atmospheric transport and deposition of PFSAs, PFCAs and their precursors (i.e. fluorotelomer alcohols or carboxylic acids or fluorotelomer unsaturated carboxylic acids) [68-71]. Although 6:2 FTS cannot be considered volatile, long-range atmospheric transport cannot be discarded and needs to be further investigated. Short-chain compounds PFBA, PFPeA, PFBS[a], PFHxA and PFHpA were observed among the most abundant PFASs, pointing to the gradual replacement of long-chain substances with shorter-chain substitutes in industrial manufacturing [10].

#### 3.5.2. Occurrence of selected PFASs in effluent water

The presence of PFASs in the effluent water of the DWTP is similar to that obtained in the influent water (Fig. 4). The sum of the mean concentrations of the target PFASs determined in the influent (8.6 ng·L$^{-1}$) and the effluent (8.2 ng·L$^{-1}$) are very close, indicating that these compounds are either not removed or poorly removed during drinking water treatment. The literature reports a positive correlation between PFAS concentrations in the influent and effluent water from DWTPs, with levels in the raw water sometimes being identical to those in the drinking water produced [19], which is in agreement with the results obtained in this study. Our results reveal that only 6:2 FTS was effectively removed in the DWTP, since this compound, which was detected in all the influent samples, was not detected in any of the effluent samples. Xiaoling et al. [72] reported that 6:2 FTS can be degraded into PFHpA or PFHxA through advanced oxidation processes (AOP) like ozonation, so the ozonation treatment applied in the DWTP involved in this study was probably responsible for eliminating this compound.

#### 3.5.3. Occurrence of selected PFASs in tap and bottled water

It is generally accepted that the contamination of tap water is related to contamination in the source. The tap water samples evaluated in this study were collected from houses that receive water from the effluent of the DWTP discussed in the previous paragraph. As can be observed in Fig. 4, the relative abundance profiles of PFASs found in tap waters are similar to those found in the effluent of the DWTP. All the perfluorochemicals detected in the effluent of the DWTP were detected in tap waters, with the exception of PFDA. In this study PFBA was the most abundant PFAS, followed by PFHxA and PFOS. In agreement with our results, Enderlick et al. [73] reported PFBA and PFOS as being the most abundant compounds in Turkish tap waters, followed by PFBS[a], PFHpA and PFHxA. Kaboré et al. [12] also reported PFBA and PFOS as being the most abundant compounds in tap water samples from Canada and other countries.

As regards bottled waters, the concentrations and detection frequencies of PFASs are shown in Table 3. The most frequently detected PFASs in bottled waters were PFBA, PFPeA, PFHxA and PFOS. As for abundancy, PFBA was the dominant compound (69%), followed by PFHxA (7%) and PFOA (7%). PFAS detection frequencies and concentration levels in bottled waters were lower than in tap waters, and similar results have been obtained in other studies conducted in Spain, Canada, France and Turkey [12,73–75].

## 4. Conclusions

The method proposed in this study for determining PFASs in source and drinking water is fast, simple and easy, since it is based on the direct injection of large-volume water samples with very simple pre-treatment because the river and drinking waters only need to be filtered before injection. The main advantage of this method is the high sensitivity obtained with no need for a pre-concentration step due to the injection of a large volume of sample. Despite some of the compounds experiencing strong signal suppression, the use of matrix-matched calibration curves allowed accurate, precise quantification. Applying the method to waters from the influent of a DWTP that collects water from the River Ebro revealed the presence of short-chain PFASs, with PFBA being the compound found at the highest frequencies and concentrations. Similar concentrations were found in waters collected from the effluent of the DWTP, indicating poor removal of these compounds during the drinking water treatment processes. PFASs were also determined in tap and bottled waters, indicating a widespread presence of these compounds in aquatic compartments.

## Declaration of competing interest

The authors declare that they have no conflict of interest.

## CRediT authorship contribution statement

**Josep Borrull:** Conceptualization, Methodology, Validation, Investigation, Data curation, Writing - original draft, Visualization. **Agustí Colom:** Conceptualization, Resources, Supervision, Project administration, Funding acquisition. **Josepa Fabregas:** Resources, Supervision, Project administration, Funding acquisition. **Eva Pocurull:** Conceptualization, Methodology, Writing - original draft, Visualization, Supervision, Project administration, Funding acquisition. **Francesc Borrull:** Conceptualization, Methodology, Writing - original draft, Visualization, Supervision, Project administration, Funding acquisition.

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## Supplementary materials

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