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REVIEW ARTICLE

# Recent developments in methods for analysis of perfluorinated persistent pollutants

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**Abstract** Perfluoroalkyl substances (PFASs) are proliferated into the environment on a global scale and present in the organisms of animals and humans even in remote locations. Persistent organic pollutants of that kind therefore have stimulated substantial improvement in analytical methods. The aim of this review is to present recent achievements in PFASs determination in various matrices with different methods and its comparison to measurements of Total Organic Fluorine (TOF). Analytical methods used for PFASs determinations are dominated by chromatography, mostly in combination with mass spectrometric detection. However, HPLC may be also hyphenated with conductivity or fluorimetric detection, and gas chromatography may be combined with flame ionization or electron capture detection. The presence of a large number of PFASs species in environmental and biological samples necessitates parallel attempts to develop a total PFASs index that reflects the total content of PFASs in various matrices. Increasing attention is currently paid to the determination of branched isomers of PFASs, and their determination in food.

**Keywords** Perfluoroalkyl substances · Persistent organic pollutants · PFOS · PFOA · Liquid chromatography · Gas chromatography · Mass spectrometry

## Introduction

The progress in chemical technology is very fruitful for various areas of modern life, but since many decades also affects strongly natural environment. In order to reduce all unwanted consequences there is a strong parallel trend to develop new technologies, which allow the minimization of the emission of anthropogenic pollutants into the environment, or their decomposition in environment, but from the other side there is permanent increase of number of new discovered chemical substances which find different applications.

A special class of anthropogenic compounds, which focuses in last two decades a particular interest, is focused on perfluoroalkyl substances (PFASs) with long alkyl chains from 4 to 18 carbon atoms, where all or almost all hydrogen atoms are substituted with fluorine atoms. Although this class of organic compounds contains thousands of chemical species, the compounds, which are especially common in environment and are widely examined, are perfluoroalkyl carboxylic acids (PFCAs), perfluoroalkane sulfonates with most commonly detected perfluorooctane sulfonate (PFOS), and fluorotelomer alcohols [1]. Due to their unique physical and chemical properties and stability, they found numerous applications e.g. for impregnation of paper or textiles, as lubricants, or as components of a fire fighting foams. The main industrial application of PFCAs is production of fluorinated polymers. Those properties resulted also in including them into the list of persistent organic pollutants (POPs) [2]. This is class of anthropogenic pollutants, which are especially stable in natural environment, can be transported for long distances, they are not significantly degraded in environment, but can be accumulated by living organisms, and they create a risk for animals and human health.

Although some of them are produced for several decades, since 1990-ties only it is realized their presence on a global scale in environment and living organisms. The turning point, which initiated a wide interest in those compounds, and resulted in undertaking intense studies, including also the development of analytical methods, was the publication of several crucial observations. They included the finding a high level of PFOS in blood of workers involved in production of PFASs [3], and contaminated ground water [4], but first of all their presence, especially also PFOS, in wildlife around the world [5]. It has to be admitted, however, that also

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in earlier literature one can find information about finding perfluorooctanoic acid (PFOA) in pooled blood, or in drinking water. Generally, as the real beginning of history of PFASs one can indicate the discovery of the fluoropolymer Teflon in 1935, and developing of its manufacturing in 1949 [1].

Among various PFASs, especially large attention is focused on long-chain PFCAs, their sources, global fate and transport pathways [6, 7]. The global emission of PFCAs, estimated as thousands tons together in North America, Europe and Asia [6], has its direct and indirect sources. The direct one includes the direct emission from the manufacturing processes, and applications, but indirectly they are produced as result of degradation in environment of precursor compounds such as fluorotelomer alcohols [8, 9]. Based on modeling studies it was concluded, that transport of perfluoroalkyl carboxylates from direct sources to remote regions is more efficient via oceanic pathways in comparison to atmospheric transport [10]. Besides perfluoroalkyl substances, mostly PFCAs, produced in processes of electrochemical fluorination or telomerization, which are mostly used as emulsifiers in production of fluoropolymers, thousands of other PFASs are produced and applied in industry, e.g. polyfluoroalkyl phosphate esters and perfluorinated phosphonic acids [11].

A wide occurrence of those compounds in environment and human organisms, and also animals, is a basic cause of intense toxicological studies on their effects [12–15]. Investigations of chronic exposure of rats and monkeys to PFOS demonstrated effects on lowering the body mass, interferences in liver functions, and also affected the mortality. The PFOA in rodents caused the liver enlargement, changes in lipids metabolism, and also resulted in some carcinogenicity. Those data cannot be directly transposed to human organism, and although one can find some works suggesting the carcinogenicity for humans, those data are generally considered as inconclusive [16].

Parallel wide studies are focused on occurrence of PFASs in the aquatic environment [17], including river waters [18, 19], oceans [20], and also drinking water [21]. Those are only selected examples of such determinations reported in hundreds papers published in environmental and analytical journals. The level of PFASs detected in surface waters is in the range of 1 to 1,000 $ng \cdot L^{-1}$, and is strongly affected e.g. by proximity localization of point sources of industrial emission. In sea and oceanic waters that level is usually 1–2 orders of magnitude lower. An increasing attention is also focused on the determination of PFASs in consumer articles, especially in foods, which is considered as a significant source of those compounds in humans [22]. Similarly intense studies are carried out on PFASs content in human blood, as it is commonly accepted that whole population in the industrialized world contain them on the level of $ng \cdot mL^{-1}$ [23], although some effects of geographical differences, and also life style and possibly genetic factors are discussed [24].

That presented above environmental importance and health hazard by PFASs is the obvious reason of intensive development of analytical methods for their monitoring in various types of samples. This increase of interest in PFASs can be well illustrated by data taken from ISI Web of Knowledge data-base, showing fast increase of number of published papers in recent years (Fig. 1). It was also reported that total number of research papers published about perfluoroalkyl substances in recent decade exceeded 2,500 [25]. Although numerous methods have been developed, still many challenges and uncertainties remain. Because of wide spread of PFASs of great importance is especially instrumental simplification of those methods, which could allow using them more easily in routine monitoring of environment, as well as easier in control of food and analysis of biological samples. The ultra-trace determination of large number of PFASs in complex natural matrices is a great challenge for analysts, but reliable data are essential for the understanding of the fate and toxicity of PFASs.

The progress in development of analytical methods can be followed based on published original papers, as well as on increasing numbers of reviews devoted to particular type of analytes, e.g. emerging contaminants in waters analysis [26], or numerous competent reviews on development of analytical methods for determination of PFASs in various matrices [27–29]. The main intention of preparing this review was presentation in condensed format, the progress in the area of application of high-performance separation methods, which without doubt are main and widely accepted methods for determination of PFASs. Although they are important aspects in trace determination, there will be separate discussion about problems specifically attributed to analysis of particular matrices and also preconcentration and sample clean-up methods. Also some rather rarely used methods in routine laboratories will not be presented in details such as $^{17}F$ NMR [30], which offers a very low sensitivity, but also some possibilities of determination branched PFASs, as well as Fourier transform infrared spectroscopy [31], or radiochemical methods [32].

## Liquid chromatography methods

The liquid chromatography methods are the most commonly used analytical methods for determination of PFASs. They can be employed with different detection methods, but determinations with mass spectrometry (MS) detections, with different configurations of MS analyzers, are commonly considered as the reference methods. They are widely employed for different analyzed samples, such as biological ones, aqueous and mineral solid matrices, air, foods and various consumer products [28]. Sporadically, the application of mass spectrometry was also reported for direct injection measurements, where due to

complex matrices, and usually large number of different analytes, it is difficult to reach satisfactory resolution without chromatographic separation [33, 34].

The main advantage of the use of LC/MS methods is the possibility of both the identification of analytes, as well as sensitive quantitative determination, although both those factors depend significantly on instrumental configuration of the setup determinations with MS detections, with different configurations of MS analyzers. Practically, in almost all reported measuring setups the electrospray ionization (ESI) is used, and very rarely other methods as e.g. atmospheric pressure photoionization (APPI), which was reported for the determination of PFASs in waters in LC/MS system with on-line extraction [35]. It is rather difficult task to compare the functional parameters of different measuring systems, employed separately in different works. Especially, that they can be essentially affected by various individual experimental factors, e.g. different methods of preconcentration and samples clean-up employed different purity of used reagents, or the contamination from the ambient conditions. Basically, such parameters of the determination as resolution or limits of detection depend first of all on the efficiency of the separation in chromatographic system, and employed MS analyzer. Recently, in determinations of PFASs in waters the LC/MS setups were compared employing triple quadrupol MS/MS with three generations of HPLC systems [19]. They included the conventional HPLC system with C18 column 150 mm×2 mm, 3 μm, the ultra-high-performance liquid chromatography system (UHPLC) with 50 mm×2.1 mm, 1.8 μm, and also the capillary liquid chromatography system (CLC) with column 150 mm×0.5 mm, 3.5 μm. The results of a very thorough comparison are shown schematically on the histogram in Fig. 2, where a score 5 is the best option. Briefly, the conventional HPLC provides worst linearity of response, precision and sensitivity, and also the longest analysis time. The UHPLC system provides the shortest analysis time and the best LOD for most of the analytes. The CLC system exhibits the best precision and sensitivity.

Another crucial element of the LC/MS setup is the mass analyzer. Also in this case one can find in the literature numerous examples of configurations with quadrupol, ion-trap, and time-of-flight (ToF) analyzers, and even combinations of ToF with high resolution MS, used for determination of PFASs in different biological samples [36]. The simplest LC/MS systems with a single quadrupol can provide also sufficient detectability, e.g. limits of quantitation (LOQs) reported in the range 0.28–0.58 $ng \cdot L^{-1}$ in determination of PFASs in surface waters [37], but due to limited selectivity they require more thorough clean-up of the samples. In the study comparing LC/MS systems with different mass analyzers (ion-trap, triple quadrupol, and high resolution ToF-MS HRMS), as the most satisfactory system was considered LC-ToF-HRMS setup, combining high selectivity with optimal sensitivity [38]. The best sensitivity in determinations of PFASs in waters was reported in the LC/MS/MS system at LOD level 0.4–5.2 $pg \cdot L^{-1}$ in analysis of seawaters [39]. The example of results of the determination of PFASs in river water samples showing a large variety of determined analytes is illustrated by the histogram shown in Fig. 3 [18]. An interesting example of application of LC/MS/MS system is the investigation of transplacental exposure of neonates in order to examine whether infants are exposed to PFOS and PFOA via their mothers' blood [40]. It was found that PFOS decreased from maternal to cord plasma concentration by a factor of 0.4 to 0.8, while PFOA crossed the placental barrier unhindered.

The LC-MS/MS method was also applied for determination of polyfluoroalkyl phosphates (PAPs). Polyfluoroalkyl phosphoric acid diesters (diPAPs) were predominant in all of 102 residential dust samples [41]. 6:2/8:2 diPAP was found in all measured samples with median concentration 614 $ng \cdot g^{-1}$, LOD and LOQ for this compound were 1.5 and 9.0 $ng \cdot g^{-1}$ respectively. The median sum of diPAPs concentration, 2,214 $ng \cdot g^{-1}$, was 30 and 67 times higher than median 75 $ng \cdot g^{-1}$ for PFOS and 33 $ng \cdot g^{-1}$ for PFOA levels and 16 times higher than median

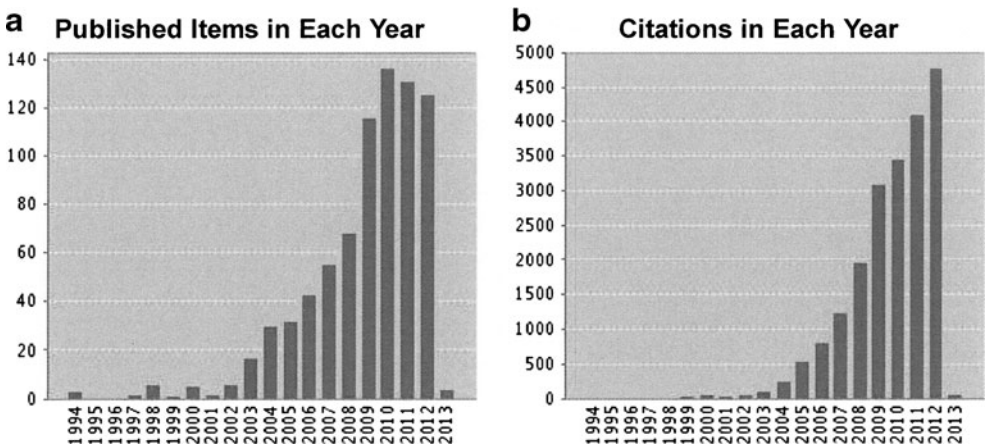


**Fig. 1** Number of papers published (**a**) and number of citations (**b**) in years 1994–2013 on environmental aspects of perfluoroalkyl substances according to Web of Knowledge, February 2013

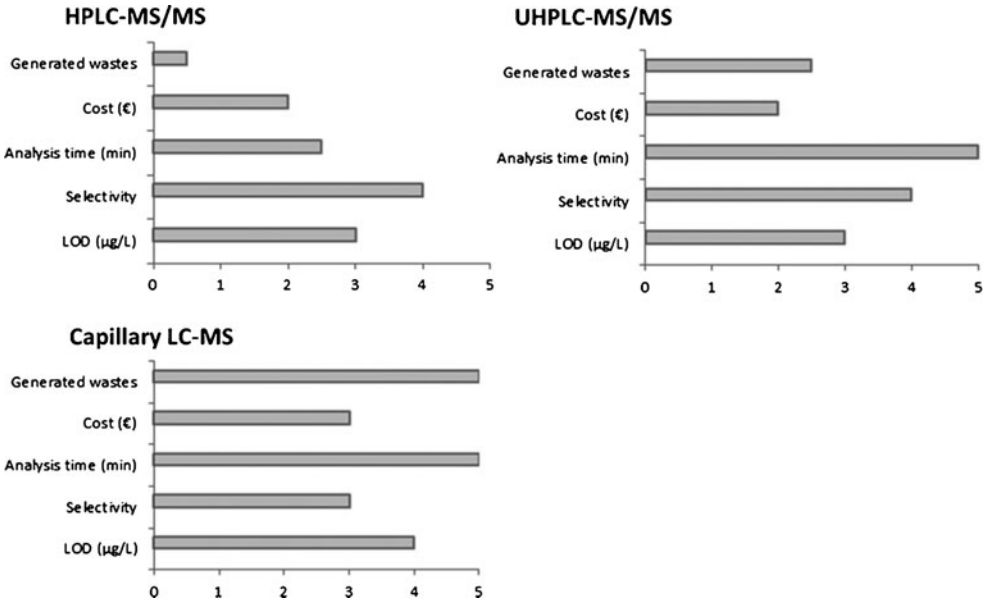


**Fig. 2** Comparison of the functional characteristics of different HPLC systems with MS detection in determination of PFASs in river waters [19]. Score 5 corresponds to the least generated wastes and costs, the most rapidity, the best selectivity and the lowest LOD values

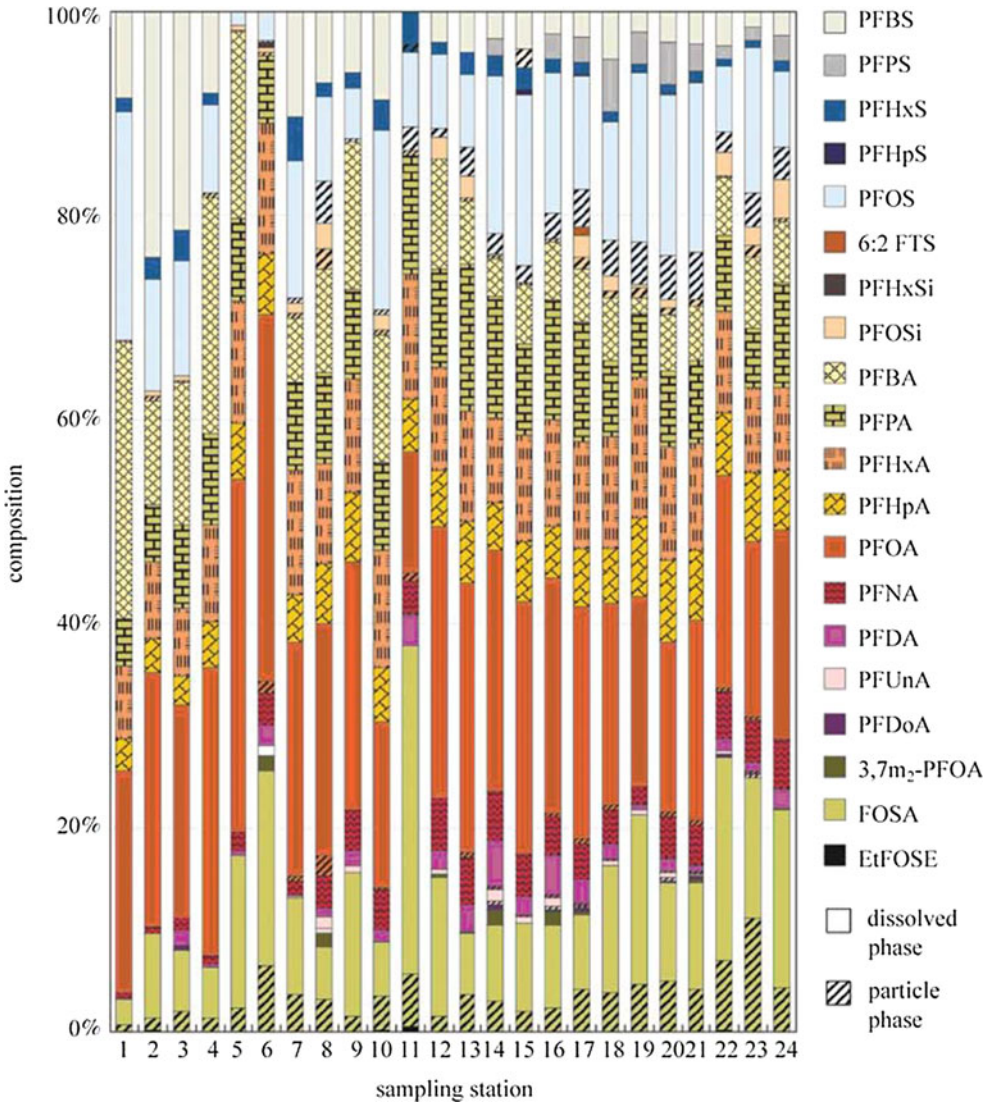


**Fig. 3** Relative composition of individual PFASs determined by LC/MS/MS for the dissolved and particulate phases in the river Elbe and the North Sea [18]

sum of PFCAs measured before in the same dust samples [42]. Considering the high concentration level, PAPs may represent important indirect source of PFCA exposure, because they are present in human food contact paper product [11] and PAPs have recently been identified as potential precursors to PFCAs, including PFOA [43].

Although one can observe evident increase of the use of LC/MS systems in organic trace analysis in recent decade, including determination of PFASs, this instrumentation still belongs to rather expensive ones, requiring highly trained personnel, and their common routine applications for environmental monitoring, analysis of food or medical diagnostics still cannot be considered as common. It seems to be necessary, therefore, to develop also new methods based on widely available instrumentation, which might fulfill analytical requirements, and might be authentically employed for routine monitoring of commonly occurring PFASs. The HPLC instruments with simpler detections than MS are commonly employed in routine analytical laboratories nowadays, hence search for developments of methods of their use for PFASs determination.

As perfluoroalkyl carboxylic acids in neutral and alkaline conditions occur in ionized form, there are attempts to determine them using high-performance ion-chromatography with suppressed conductivity detection. In the method developed for determination of C3 to C8 PFCAs in waters the LODs obtained were at the level of 50 $\mu g \cdot L^{-1}$ [44]. The same suppressed conductivity detection was employed recently using reversed-phase columns for determination of PFOA and PFOS in water matrices [45], and in determination of C4-C8 PFCAs in studies of PFCAs' decomposition using microwave-induced persulfate [46]. In the first of mentioned works, with the use of on-line matrix elimination and preconcentration, the LOD values were reported as 0.37 to 0.38 $\mu g \cdot L^{-1}$ for PFOA and PFOS, respectively (LOQ 1.1 and 4.0). Then in the latter one, the LOD values were evaluated in the range from 0.11 to 0.18 $mg \cdot L^{-1}$ for C4-C8 PFCAs [46]. In the same work short chain PFCAs (trifluoroacetic and pentafluoropropionic acids) were determined with the use of ion-exchange column at level 0.05 to 0.08 $mg \cdot L^{-1}$.

Besides mass spectrometry, one of the most sensitive detection in HPLC is considered fluorimetric detection. Its application in the determination of PFASs requires the derivatization of analytes with appropriate fluorophore prior to the detection. First such attempt for determination of PFASs was reported using laboratory-synthesized 3-bromoacetyl-7-methoxycoumarin for derivatization [47]. The developed method was employed for determination of PFCAs in rats' liver, and in later works of the same research group in the investigation of renal transport of PFOA and toxicokinetic studies. In recent work of our research group, the HPLC method with fluorimetric detection for determination of PFCAs was developed using off-line derivatization with 3-bromoacetyl coumarin, and in optimized conditions the base-line separation of PFCAs from C3 to C12 was obtained in 30 min run (Fig. 4a) [48]. In order to apply the developed method for PFCAs determination in natural water samples, the preconcentration based on solid-phase extraction (SPE) was optimized using various commercially available sorbents. In the optimized conditions, using C18 Sep-PAK (Waters) sorbent and using sample volume 100 mL, the developed method was employed in the analysis of river waters (Fig. 4b), and its LOD values were evaluated as 43 to 75 $ng \cdot L^{-1}$ for examined PFCAs. Those LOD values are similar to those reported earlier in the application of LC/MS/MS method for the determination of PFCAs in river water [49], or the determination of fluorotelomer alcohols in surface water and artificial sea waters [50]. It seems then, that reported method may find some routine applications in environmental analysis.

In recent years an increasing attention is also focused on the determination of isomers of PFASs, which can be helpful in tracing the origin of those anthropogenic pollutants. The example of the separation of several branched isomers of PFOA using HPLC with fluorescence detection is shown in Fig. 5a [51]. Especially large attention is devoted to the investigation of isomers of PFOS. Their determination in LC/MS system with ion trap MS/MS allowed to identify ten isomers of PFOS in technical preparation (see example recording in Fig. 5b) [52]. Similar analytical studies were reported for human serum and human plasma, where in addition to linear PFOS a total of eight signals were detected [53].

The determination of PFASs in human hair and urine samples was also reported with the use of turbulent flow chromatography (TFC), coupled to tandem mass spectrometry [54]. Generally, it enables the eliminating a time-consuming sample clean-up, and increases productivity with good sensitivity. With LOD values ranging from 0.01 to 2.68 $\mu g \cdot L^{-1}$ in urine (LOQ 0.1 to 9), it was employed for the determination of 18 PFASs in urine, and 21 PFASs in human hair. The TFC method was earlier reported for selective determination of PFOS in river water, where no off-line sample preparation was needed [35]. In that method an on-line extraction was carried out by the injection of sample onto a column under TFC conditions, and then PFOS was back-flushed onto a reversed-phase column via on-line column switching, and resolved chromatographically at a laminar flow. The LOD was evaluated as 5.35 $ng \cdot L^{-1}$.

PFASs analysis for several years has been very difficult. In the 1st interlaboratory study (ILS) coefficients of variation between laboratories amounted up to 95 % for PFOS in water and 125 % in fish sample [55]. Identified problems were: the limited availability of standards and mass-labelled standards, severe matrix effects and interferences, the occurrence of branched isomers and blank problems due to contamination from labware and instrumentation. In the next ILS reported

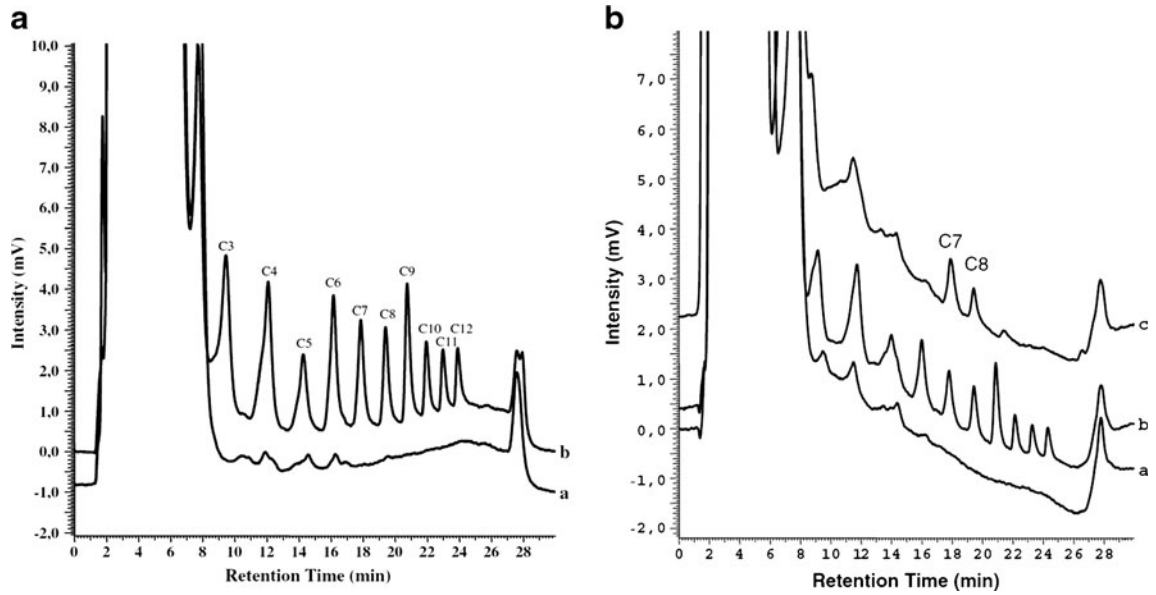


**Fig. 4** HPLC chromatograms obtained with fluorescence detection using derivatization with 3-BAC. **a** blank (a) and mixture of PFCAs 0.5 mg·L$^{-1}$ each (b); **b** blank (a), mixture of PFCAs 0.1 mg·L$^{-1}$ each without preconcentration (b), river water sample after SPE preconcentration (c) [48]

results matched much better than in the first study, due to a large range of isotope-labelled IS that were distributed with the samples to the laboratories [56]. Those measurements highlight the importance of labelled IS for accurate PFASs measurements.

## Gas chromatography methods

Less commonly than LC methods, but also widely applied in determination of PFASs in various matrices is gas chromatography (GC). Basically, GC offers much larger efficiency of chromatographic separations, but its practical limitation is the volatility of analytes to be determined. It can be employed in direct determination of neutral, volatile PFASs such as fluorotelomer alcohols or sulfonamides, and perfluorinated acrylates. Numerous such methods were developed for analysis of indoor and outdoor air, e.g. the GC/MS determination with particularly low values of the Method Detection Limit (MDL) 0.001 to 3.5 pg·m$^{-3}$, was reported for the determination of a large group of volatile perfluorinated compounds in outdoor air with the use of high volume samples and efficient enrichment step [57]. It allowed a very sensitive determination of fluorotelomer alcohols and perfluoroalkyl ethanols in various locations of the North Atlantic and Canadian Archipelago (Fig. 6). The obtained results confirmed the efficient long-range atmospheric transport of volatile PFASs and widespread distribution in the Arctic region. The GC determination of polar PFCAs, or PFOS requires the derivatization, which can be carried out with benzyl bromide, 2,4-difluoroaniline, diazomethane, methyliodide, butanol, or methanol. The additional difficulty of such methods can be also a limited stability of derivatives formed.

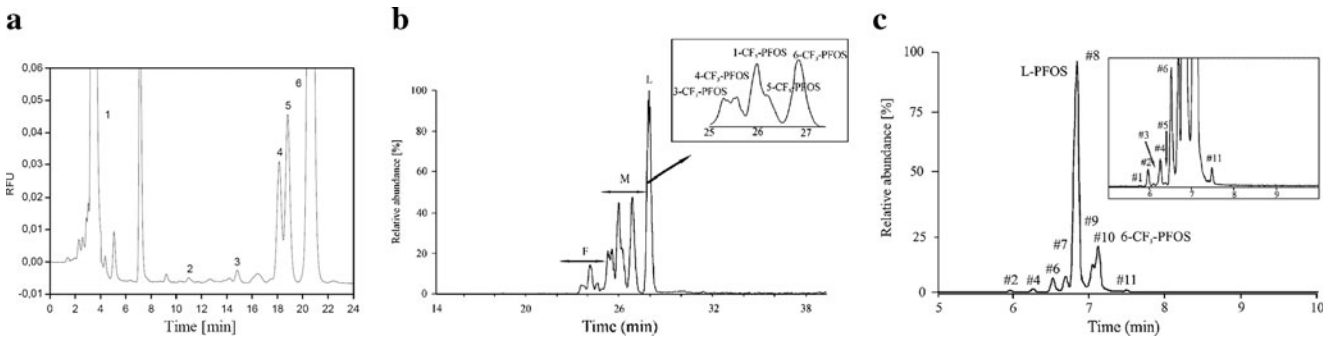


**Fig. 5** Comparison of chromatographic determination of PFASs' isomers in different measuring systems. **a** HPLC separation of structural isomers of PFOA obtained for technical preparation using fluorescence detection with 3-BAC for derivatization, and isocratic conditions [51]. Peak identification: 1 – excess of 3-BAC, 2 – C6 PFCA, 3 – C7 PFCA, 4 – 4-(trifluoromethyl) perfluoroheptanoic acid, 5 – 3-(tri-fluoromethyl) perfluoro-heptanoic acid and 6-(trifluoromethyl) perfluoro-heptanoic acid, 6 – linear PFOA. **b** ESI(−)-IT-MS$^2$ base peak chromatogram of technical PFOS separated on a PFP phase and assignment of identified isomers [52]. Molecular anions were fragmented with 40 % collision energy. **c** High-resolution GC/MS mass chromatogram (m/z 463) of a derivatized PFOS technical mixture with numbered isomers [58]

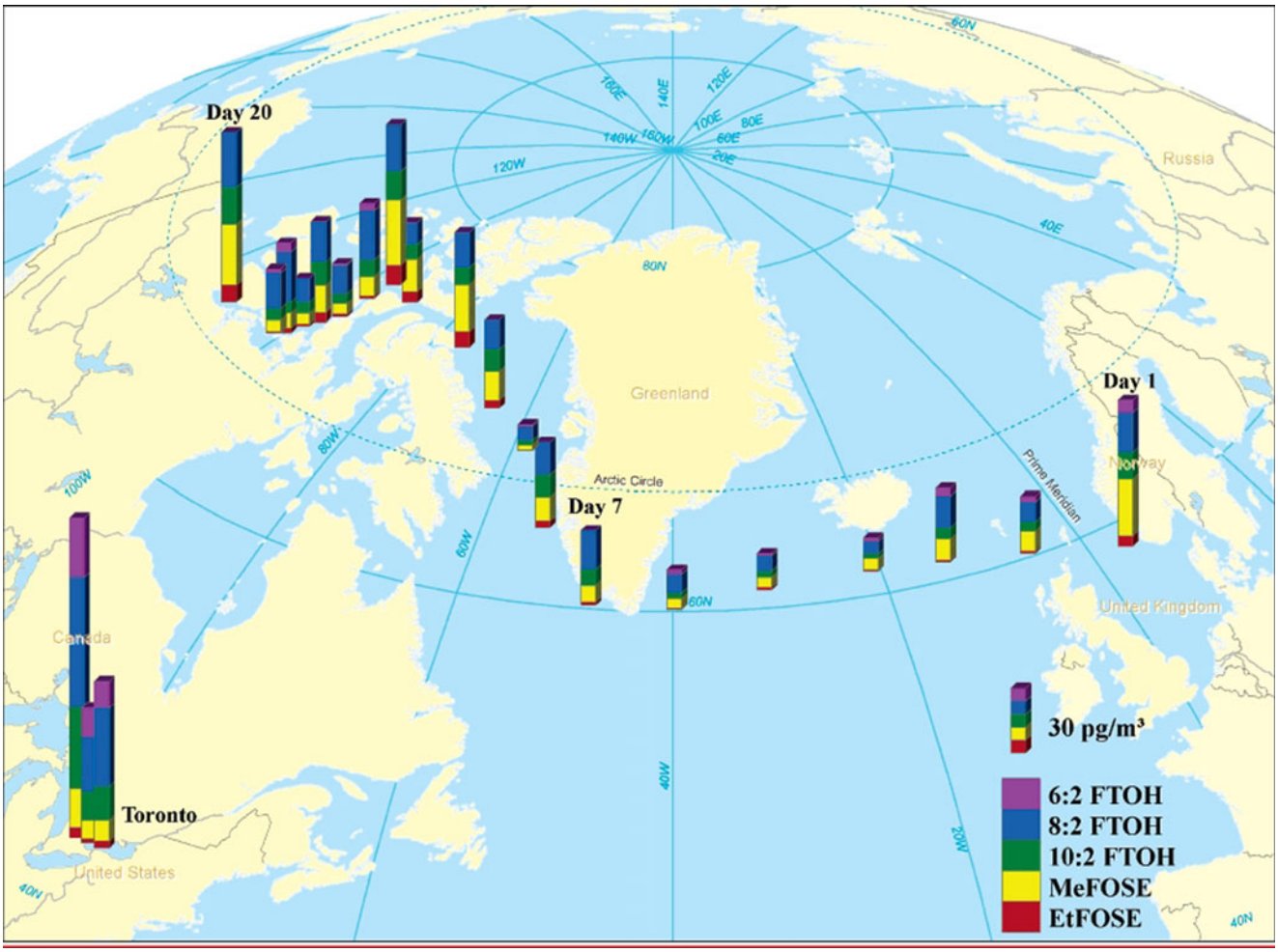


**Fig. 6** Total air concentrations (sum of gas phase and particle phase) for fluorotelomer alcohols FTOHs) and perfluoroalkyl sulfonamide ethanols (PFASs) determined by GC/MS across the North Atlantic Ocean, Canadian Archipelago and in Toronto [57]

The resolution of GC chromatographic separations can be very advantageous for the determination of branched isomers, which was reported for PFOS (Fig. 5c) [58]. GC/MS with chemical ionization was also employed for studies of isomer distribution of perfluoroalkyl carboxylates in human blood [59]. From the obtained isomer profiles it was concluded, that a direct exposure to PFOA from electrochemical fluorination process is a source of the branched PFOA isomer in humans.

In reported GC methods for the determination of PFASs, mostly mass spectrometry detection is employed, which is carried out with electron impact or chemical ionization, and with single quadruple mass analyzer. Rarely for this purpose is used a flame-ionization detection (FID), reported e.g. for determination of PFOA derivatized with benzyl bromide in plasma, and urine with LOD 0.1–1.0 $\mu g \cdot mL^{-1}$ [60]. This is about 2–3 orders of magnitude poorer compared to MS detection. A similar level of detection limit was reported for determinations of PFCAs in cell growth media using the derivatization with 2.4-difluoroaniline and dicyclohexylcarbodiimide as catalyst [61].

Due to a high content of halogen in PFASs molecules, one can expect that application of the electron capture detection (ECD) might be advantageous, and it was reported in several works [62–64], and also the element specific microwave plasma detector [65]. In comparison of PFCAs determination after derivatization with isobutyl chloroformate, it was shown that much better values of the LOD can be obtained for the MS detection with the electron impact ionization, than with the ECD [63]. The comparison of GC chromatograms recorded in the systems with different detections is shown in Fig. 7. GC methods with those detections were employed for analysis of biological materials [62, 64, 65].

The determinations of volatile PFASs are most commonly carried out with the use of GC/MS without derivatization. In mentioned already determinations of PFASs in the Arctic atmosphere the GC/MS setup with positive chemical ionization was reported, and for the confirmation for perfluoroalkyl sulfonamide ethanol the electron impact ionization was employed [57]. Determinations of perfluoroalkane sulfonamides in outdoor and indoor air were carried out in GC/MS system with the electron impact ionization [66], and the same analytes together with fluorinated telomer alcohols and sulfonamide ethanols in the system with positive chemical ionization [67]. The latter method was later optimized to

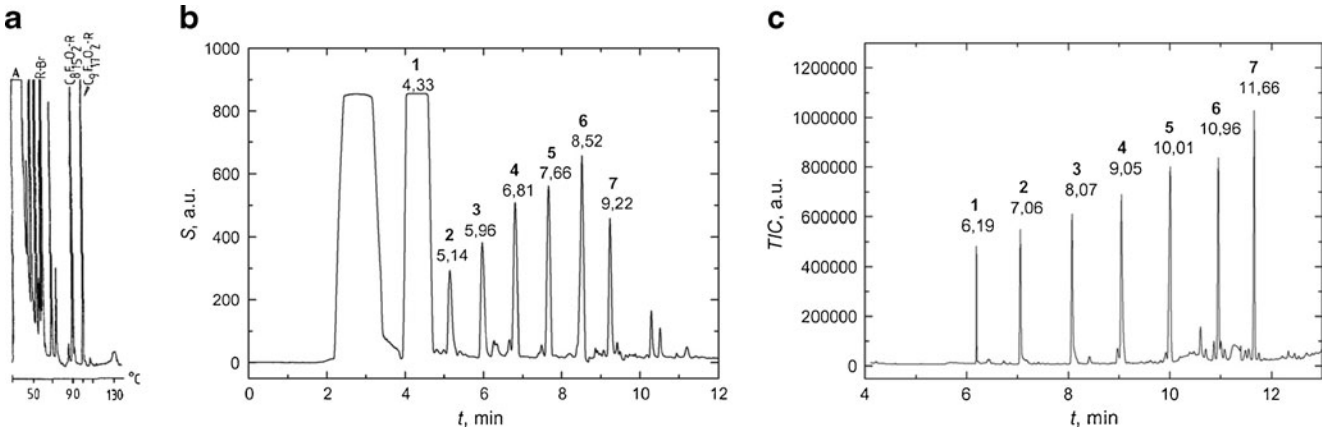


**Fig. 7** Comparison of application of gas chromatography with different detection methods for determination of PFCAs. **a** Chromatogram recorded in the system with flame ionization detection for separation of benzyl esters of PFOA and perfluorononanoic acid in blood plasma [60]. **b** Chromatogram recorded in the system with electron capture detection for mixture of C6 to C12 PFCAs 10 mg·L$^{-1}$ each derivatized to isobutyl esters [63]. **c** GC-EI-MS chromatogram recorded for mixture of C6 to C12 PFCAs 10 mg·L$^{-1}$ each derivatized to isobutyl esters [63]

avoid solvent-induced response enhancements, which resulted in instrumental limits of detection of <0.2 pg [68]. In earlier work on determination of airborne fluorinated organics kit was shown that both positive and negative modes of chemical ionization were useful for the determination of all target analytes [69].

As examples of GC/MS determinations of PFASs in different matrices without derivatization, one can indicate the determination of PFOS and fluorotelomer alcohols with chemical ionization in outdoor air [69] (see example chromatograms in Fig. 8), or 8:2 telomer alcohol in animal plasma and tissues with electron impact ionization [70]. On the other side, with the use of appropriate derivatization and chemical ionization, the GC/MS was employed for PFCAs determination in water matrices, including seawater, with ion-pair solid-phase micro-extraction and in-port derivatization with butanol [71], and in harbor sediment with the derivatization using methanol and the pressurized fluid extraction [72]. For analysis of waters it was shown that PFCAs can be determined at ng·L$^{-1}$ levels [71], and satisfactory results were reported for effluents from wastewater treatment plants (0.05–8.2 μg·L$^{-1}$) and harbor seawater.

## Capillary electrophoresis methods

Another modern method of high-performance separation, which found so far rather limited applications in determination of PFASs, is a capillary electrophoresis (CE). By offering the separation efficiency in the range between HPLC and GC methods, from this point of view CE should be an attractive tool for analysis of polar and ionized PFASs, including isomers with branched alkyl chains. This is proved by numerous applications in environmental analysis, and especially analysis of biological samples, of which hundreds can be found in current analytical literature. In its simplest instrumental forms, which can be employed with commercial instruments with absorptive spectrophotometric detections, its most significant drawback is a very poor detectability. This results first of all from a very short optical pathway for absorptive measurements. In case of determination of

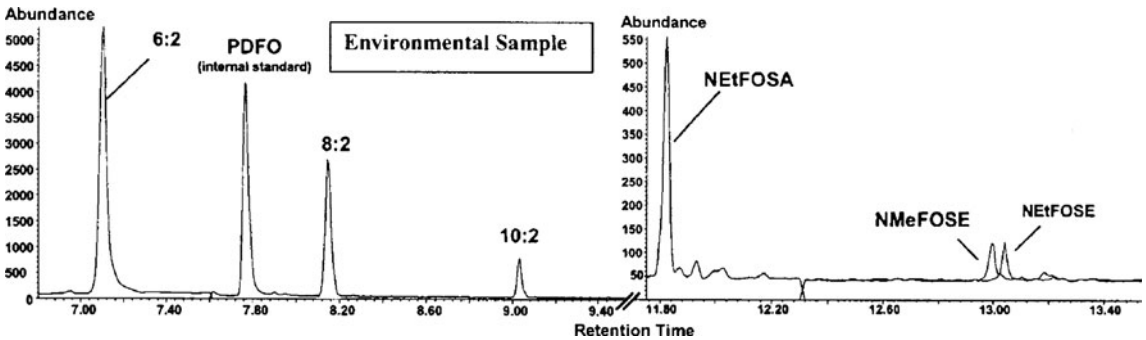


**Fig. 8** Extracted and overlaid SIM chromatograms recorded in GC/MS system for determination of volatile fluorinated organics in air samples collected on XAD 2 resin and eluted with ethyl acetate [69]

PFCAs an additional limiting factor is a weak absorption of UV/Vis radiation. In optimized conditions of pH and background electrolyte (BGE), a satisfactory separation was reported for C6 to C12 PFCAs, but for direct UV detection at 190 nm the limits of detection were in the range 2–33 mg·L$^{-1}$, only [73].

Approximately 10-fold improvement of detectability was obtained in optimized conditions for indirect UV detection [74]. Using BGE containing 2,4-dinitrobenzoic acid as a chromophore, the UV detection at 270 nm, the base-line resolution was obtained for C6-C12 PFCAs (Fig. 9a). The LOD values in this case were in the range 0.6 to 2.4 mg·L$^{-1}$. If such determination would be accompanied by efficient preconcentration of analytes (2–3 orders of magnitude), then MDL for PFCAs might be at the level close to that occurring for PFCAs in blood serum [75, 76]. Further improvement of sensitivity of such determination can be expected by employing a special design of flow-cells with longer pathway, or with the application of laser induced fluorescence (LIF) detection with appropriate derivatization, as it was discussed above for HPLC methods. A substantial improvement of the detection limit in CE determination with indirect UV detection of PFOA, where also PFOS was determined, was recently reported with the use of non-aqueous BGE [77] (see example recording in Fig. 9b). Employing a field-amplified sample injection and SPE preconcentration on C18 cartridges, the LOD at the level 0.26 and 0.28 μg·L$^{-1}$ was achieved for PFOA and PFOS, respectively. The possibility of the application of developed method was shown for analysis of river water samples spiked with 1 nmol·L$^{-1}$ of PFOA and PFOS.

In these considerations of application of electromigration methods, it should not be omitted some perspective aspects concerning further developments of instrumentation for routine monitoring of PFASs for environmental protection. A very important trend in development of electromigration methods is the miniaturization down to microfluidic format with the use of different detection methods. A first attempt of determination of PFCAs in microfluidic chip was demonstrated with the conductivity detection [78]. In the optimized conditions C6-C12 PFCAs were resolved and determined with LOD values in the range of 0.15–2.9 mg·L$^{-1}$. The application of a more sensitive detection preconcentration may result in essential lowering those values.

## Determination of Total Organic Fluorine (TOF)

The presence of a very large number of different PFASs at trace or ultra-trace level, especially in environmental samples, makes their monitoring a very difficult and time-consuming task. Already at early stage of increasing interest in the monitoring of those compounds in environment, using $^{17}$F NMR and LC/MS$^2$ it was demonstrated that determination of several most common analytes, gives insufficient information about the presence of that group of compounds in analyzed samples [30]. This implies the considering of determination of a Total Organic Fluorine as a novel total index of water quality, which might be considered as informative measure of whole content of fluorinated organic compounds in analyzed samples. Total indices are widely used in modern analytical chemistry in environmental, food, clinical and process analysis, to describe the content of group of chemical compounds of similar nature and properties, and exhibiting similar functions in particular media [79]. The most commonly used total indices in the environmental analysis include e.g. Adsorbable Organic Halogens (AOX), Extractable Organic Halogens (EDX), and Total Organic Chlorine (TOCl) [80].

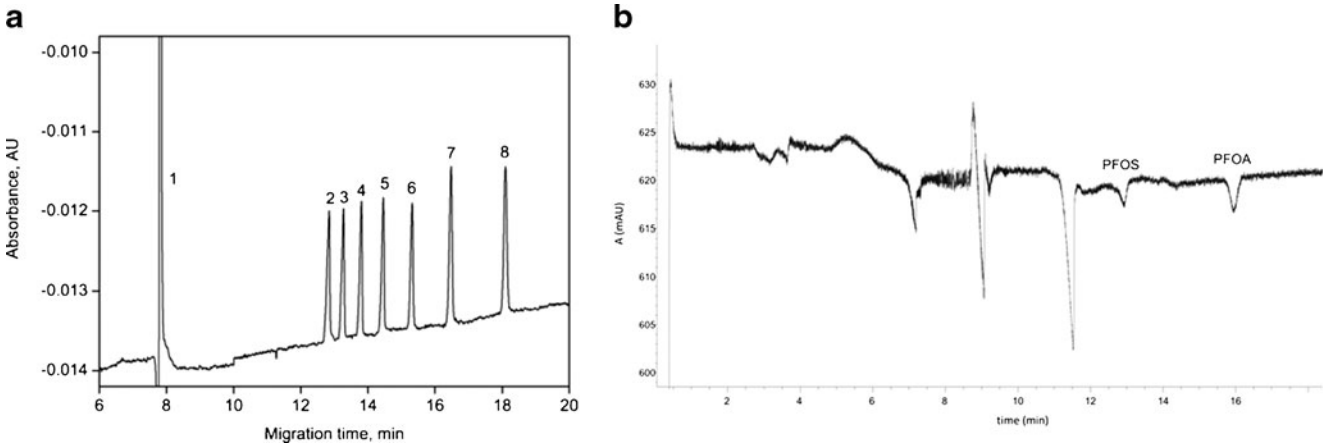


**Fig. 9** Examples of application of capillary electrophoresis with indirect UV detection in determination of PFCAs. **a** Electropherogram recorded in for mixture of C6 to C12 PFCAs 0.1 mmol·L$^{-1}$ each using as background electrolyte 50 mmol·L$^{-1}$ Tris buffer of pH 9.0 with 7 mmol·L$^{-1}$ 2,4-dinitrobenzoic acid and 50 % methanol [74]. **b** Electropherogram recorded employing a large-volume sample stacking for mixture containing PFOA and PFOS 0.5 μmol·L$^{-1}$ each using as background electrolyte solution of 5 mmol·L$^{-1}$ NSA and 10 mmol·L$^{-1}$ TEA in ACN/MeOH (50:50 v/v) [77]

Methods of the determination of a total content of fluorinated organic compounds are being developed since the middle of previous century, and their first stage is the release of fluorine from organic compounds by various techniques [81]. Most commonly for this purpose are employed combustion methods [82–86]. The hydrogen fluoride formed is adsorbed in an alkaline solution, and fluoride can be conventionally titrated by thorium (IV) [84], or determined by fluoride ion-selective electrode (ISE) [85, 86]. Fluoroorganic compounds can be also first adsorbed on carbon sorbent, and then burned together with sorbent in an oxygen atmosphere [85]. Besides various confined combustion methods, in determination of total fluoride in biological matrices there were also employed digestions with acid or alkali, fusion with alkali method or

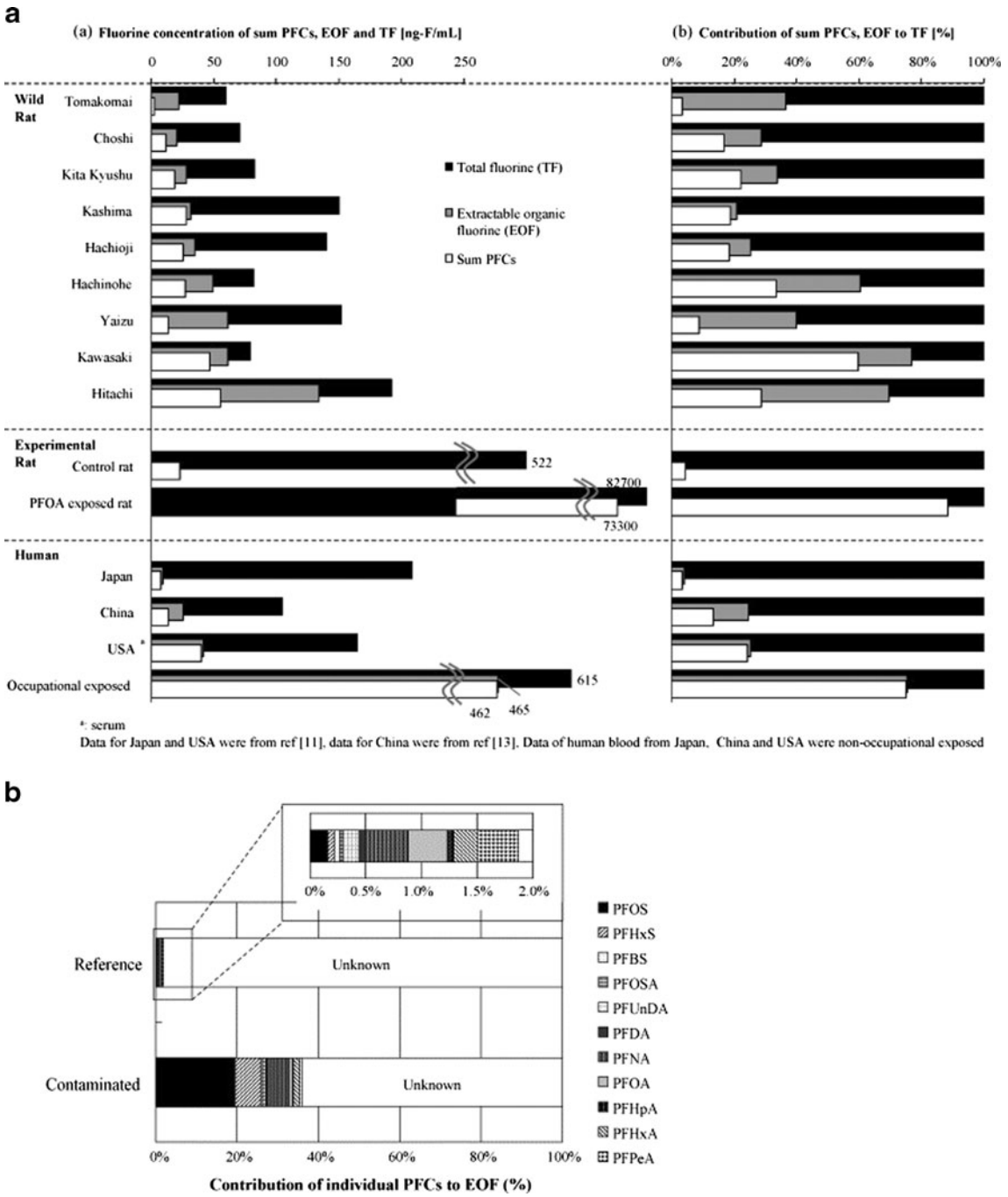


**Fig. 10** Results of determination of PFASs in different samples using combustion ion-chromatography with conductivity detection. **a** Concentration (a) and contribution (b) of sum PFCs, extractable organic fluorine (EOF) and total fluorine (TF) in whole blood [90]. **b** Contribution of known PFASs to extractable organic fluorine in seawater determined with combustion ion-chromatography system [89]

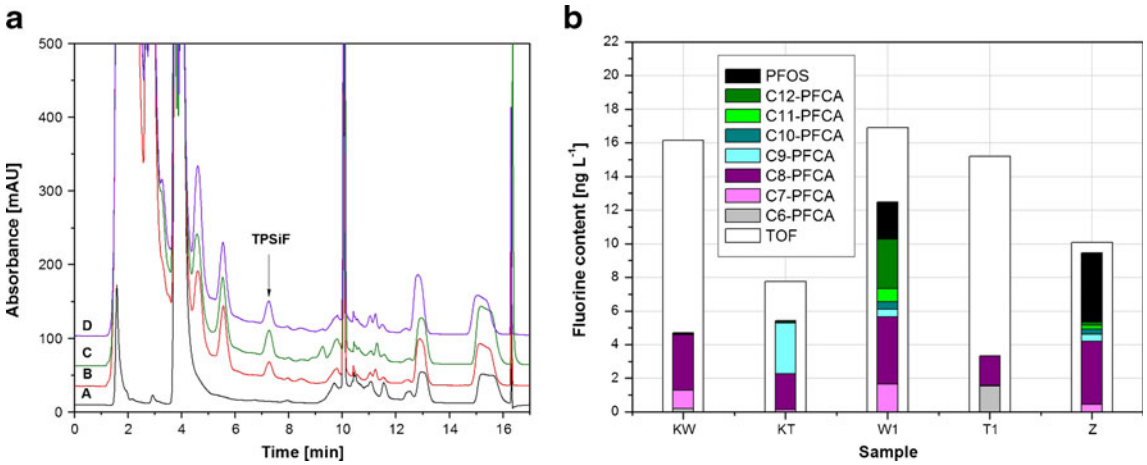


**Fig. 11** Application of HPLC method with SBP defluorination in determination of total organic fluorine (TOF). **a** Chromatograms recorded with UV detection at 222 nm for determination of PFASs as fluoride, derivatized to TPSiF [97]. A – blank without SBP, B – blank after defluorination with SBP and derivatization with TPSiOH, C – PFOA standard solution after defluorination and derivatization, D – river water sample after defluorination and derivatization. **b** Comparison of TOF values determined by HPLC (white bars) in samples of natural waters with the content of individual PFASs identified and quantified by the LC/MS method [92]. KW – tap water from Warsaw, KT – tap water from city Tarnow (Poland) , W1 – river water from Vistula , T1 – surface water from Tarnow, Z – well water from Tarnow

reduction with alkali metals in organic solvents [82]. As the example of the last mentioned option, can be the application of sodium biphenyl (SBP) in determination of covalently bound fluorine in organic compounds [87]. This method was successfully employed for the determination of PFOA in human plasma sample spiked with 10 $mg \cdot L^{-1}$ analyte, and extraction with ether prior to reaction with SBP. The released fluoride was determined by fluoride ISE. Among other methods used for the defluorination one can find, for instance defluorination by magnesium in supercritical carbon dioxide, the using Ti-catalyzed reactor with borohydride, photodegradation in $H_2O_2$ solution, or radical reduction by electron beam.

The combustion method in recent years was employed in determination of total content of fluoroorganic compounds in the system hyphenated with ion-chromatography as the combustion ion-chromatography (CIC). Determinations were carried out in whole blood and serum plasma [88], and also in costal seawaters [89]. In the analysis of human blood, besides the total content of fluorine, the content of organic fluorine was determined in extracts obtained with methyl-tert-butyl ether and hexane. The organic layer was analyzed by CIC method and LC/MS. It was found that PFASs measured by LC/MS/MS accounted for about 80 % of total fluorine in fluoroorganic compounds present in extracts [88]. In similar determinations carried out in seawaters, a much larger contribution of unknown fluoroorganic compounds in organic extracts was demonstrated besides 11 species determined by LC/MS [89] (Fig. 10a). Reference and contaminated samples were taken from different locations around Japan, where total content of extractable organic fluorine was about 0.1 and 0.56 $\mu g \cdot L^{-1}$, respectively. Later on, the same method was employed in studies of PFASs in the blood of wild and PFOA-exposed rats [90], reporting the presence of other forms of organic fluorine in addition to known PFASs determined by LC/MS/MS (Fig. 10b). The CIC method was also used recently for the investigation of trophic magnification of poly- and perfluorinated compounds in a subtropical food web [91].

A simple method of determination of a total content of fluoroorganic compounds can be also based on reported earlier defluorination with SBP [87], and determination of released fluoride after hydrolysis of the post-reaction mixture. The attempts to determine the released fluoride using flow-injection analysis methods with potentiometric and fluorimetric detections did not allow the obtaining a satisfactory LOD [92], hence chromatographic methods were employed for this purpose. In procedures of determinations of PFCAs in natural

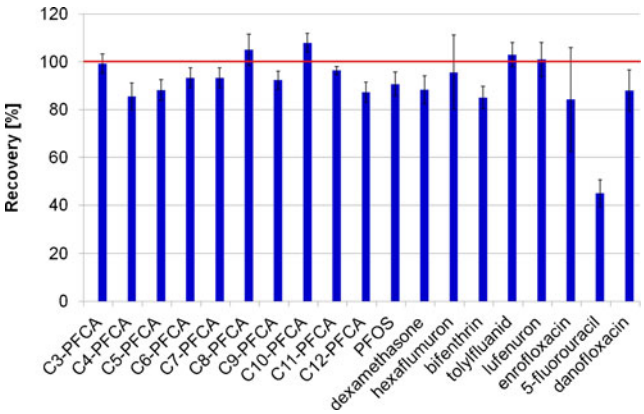


**Fig. 12** Recovery of determination of fluorinated organic compounds (20 $\mu mol \cdot L^{-1}$ each) as TOF using defluorination reaction with SBP, derivatization with TPSiOH, and final determination in GC system with FID detection [105]. GC measurements were carried out in optimized conditions according to Ref. [99]

waters, the first stage is sorption of analytes on appropriate non-polar sorbent. If it is carbon-based sorbent, such as it was reported for quaternary ammonium surfactants [93], but also for perfluoroalkyl substances [94–96], a further reaction with SBP can be carried out directly on the sorbent bed. When silica-based or polymeric sorbents are used, then retained analytes are flushed with organic solvent and reaction with SBP is carried in a solvent phase. Fluoride is determined in the obtained hydrolyzate. As the application of ion-chromatography in determination of fluoride in hydrolyzate was unsuccessful [97], the use of other modes of chromatography for determination of fluoride required a derivatization to fluorosilane derivative [97, 98]. The obtained derivative can be determined both by RP-HPLC with UV detection [97], as well as GC with FID or MS detection [99]. For PFOA the MDL value for whole procedure with preconcentration and HPLC determination was evaluated as 20 $ng \cdot L^{-1}$ [97], and Fig. 11a shows example chromatograms recorded for triphenylsilyl fluoride (TPSiF). In determinations of PFOA with GC/MS, the MDL value was evaluated as 43 $ng \cdot L^{-1}$ [99]. Similarly to results of works reported above for CIC method, in examined natural water samples the obtained TOF values indicate the presence of larger amounts of perfluoroalkyl substances, than sum of 8 most commonly occurring PFASs determined with LC/MS (Fig. 11b).

In determinations of a total content of fluoroorganic compounds both using CIC method and HPLC with SBP-based defluorination, the obtained results were confronted with determination of content of most commonly occurring PFASs. Due to extreme stability especially this group of fluorinated organic compounds is intensively investigated in recent decade. Numerous other fluorinated organic compounds find, however wide applications as pharmaceuticals [100–102], as crop protection agents [103]. In 2004 17 % of all commercially available herbicides were fluorine-containing compounds [100]. Therefore an increasing attention is also focused on the determination of those compounds in environment and their ecotoxicology [104]. Then one can also expect that they form part of TOF in environmental and biological samples. It was shown that selected fluorinated pharmaceuticals and herbicides are defluorinated with SBP with the acceptable yield, hence their presence in analyzed sample may contribute to the determined TOF values (Fig. 12) [105].

## Conclusions

Determination of PFASs in different matrices is a very tough challenge for analytical chemists. In spite of a great progress in development of new methods and application of increasingly sophisticated instrumentation, as it is shown above and in other recent reviews [28, 29], still numerous problems and challenges remain to solve. Trace analytical determinations always encounter the danger of contamination, and in many cases in ultra-trace determinations of PFCs this problem is reported. Another difficulty is a limited number of available standards, and especially of the certified reference materials. From one side it is necessary to develop new methods and improve instruments e.g. for separation of isomers of PFASs, but on the other hand there is need for much simpler methods and instruments, enabling wide routine monitoring of those pollutants in environment.

Similarly to other POPs, authorities often demand much lower detection limits, than those which can be gained with commonly employed instruments [106]. The importance of risk assessment of perfluoroalkyl substances is evident from the number of regulations and countermeasures in various countries [107], and number of 60 to 70 papers published annually on toxicity of PFASs. Still of great importance is identification novel fluorochemicals in different matrices, e.g. [108]. Their large variety in analyzed samples, makes those determinations very difficult and time consuming, hence it seems that for common monitoring a very helpful alternative can be evaluation of such total indices as Extractable Organic Fluorine [88–90], or Total Organic Fluorine [92, 97]. The trend observed in last years is also increasing interest in determination of PFASs in foods for tracking the pathways of human exposure [109].

The common occurrence of fluorochemicals in environment is also a cause of increasing interest in development of methods of their removal from waters and wastes [110]. The evaluation of yield and final products of such processes is another area of application of analytical methods for determination of fluorinated organic compounds.



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