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# Analysis of Emerging Contaminants of Municipal and Industrial Origin

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**Abstract** Besides recognized pollutants, numerous other chemicals are continuously released into the environment as a result of their use in industry, agriculture, consumer goods or household activities. The presence of these substances, known as emerging contaminants, has become an issue of great concern within the scientific community during the last few years. For this reason, the availability of sensitive, accurate and reliable analytical techniques is essential in order to assess their occurrence, removal and fate in the environment.

In this chapter, the state of the art of the analytical techniques used to determine a wide range of emerging contaminants in several environmental matrices will be overviewed.

**Keywords** Emerging contaminants · Instrumental analysis · Sample preparation techniques

**Abbreviations**

| | |
|---|---|
| ADBI | 4-Acetyl-1,1-dimethyl-6-*tert*-butylindane |
| AED | Atomic emission detector |
| AHMI | 6-Acetyl-1,1,2,3,3,5-hexamethylindane |
| AHTN | 7-Acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene |
| AP | Alkylphenol |
| APCI | Atmospheric pressure chemical ionization |
| APEC | Alkylphenoxy carboxylate |
| APEO | Alkylphenol ethoxylate |
| APPI | Atmospheric pressure photoionization |
| ATII | 5-Acetyl-1,1,2,6-tetramethyl-3-isopropylindane |
| BSA | *N*,*O*-Bis(trimethylsilyl)-acetamide |
| BSTFA | *N*,*O*-Bis(trimethylsilyl)-trifluoroacetamide |
| BTEX | Benzene, toluene, ethylbenzene and xylenes |
| CAPEC | Dicarboxylated alkylphenoxy ethoxylate |
| CAR | Carboxen |
| CDEA | Coconut diethanolamide |
| CID | Collision-induced dissociation |
| CLLE | Continuous liquid–liquid extraction |
| CSIA | Compound-specific stable isotope analysis |
| CW | Carbowax |
| DAI | Direct aqueous injection |
| DEET | *N*,*N*-Diethyl-*m*-toluamide |
| DI-SPME | Direct solid-phase microextraction |
| DMIP | Dummy molecularly imprinted polymer |
| DPMI | 6,7-Dihydro-1,1,2,3,3-pentamethyl-4-(5*H*)-indanone |
| DVB | Divinylbenzene |
| ECD | Electron capture detector |

| | |
|---|---|
| EI | Electron impact |
| ELISA | Enzyme-linked immunosorbent assay |
| EPA | Environmental Protection Agency |
| ESI | Electrospray ionization |
| EU | European Union |
| FAS | Fluorinated alkyl substance |
| FID | Flame ionization detector |
| F NMR | Fluorine nuclear magnetic resonance |
| FTOH | Fluorotelomer alcohol |
| GC | Gas chromatography |
| GCB | Graphitized carbon black |
| GC×GC | Comprehensive two-dimensional gas chromatography |
| GC-MS | Gas chromatography–mass spectrometry |
| GPC | Gel permeation chromatography |
| HHCB | 1,2,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyrane |
| HLB | Hydrophilic–lipophilic balanced |
| HPLC | High-performance liquid chromatography |
| HS | Headspace |
| HSGC | Headspace gas chromatography |
| HS-SPME | Headspace solid-phase microextraction |
| IA | Immunoaffinity |
| IDA | Information-dependent acquisition |
| IPPC | Integrated Prevention and Control of the Contamination Directive |
| KOH | Potassium hydroxide |
| LAS | Linear alkyl sulphonate |
| LC | Liquid chromatography |
| LC/ESI-MS | Liquid chromatography–electrospray mass spectrometry |
| LLE | Liquid–liquid extraction |
| MAE | Microwave-assisted extraction |
| MCF | Methyl chloroformate |
| MCX | Mixed-mode cation exchange |
| MIMS | Membrane-introduction mass spectrometry |
| MIP | Molecularly imprinted polymer |
| MMLLE | Microporous membrane liquid–liquid extraction |
| MRM | Multiple reaction monitoring |
| MSPD | Matrix solid-phase dispersion |
| MSTFA | *N*-Methyl-*N*-trimethylsilyltrifluoroacetamide |
| MTBE | Methyl *tert*-butyl ether |
| MTBSTFA | *N*-(*tert*-Butyldimethylsilyl)-*N*-methyltrifluoroacetamide |
| NCI | Negative chemical ionization |
| NI | Negative ionization |
| NP | Normal phase |
| NPEC | Nonylphenoxy carboxylate |
| OECD | Organization for Economic Co-operation and Development |
| PA | Polyacrylate |
| PAH | Polycyclic aromatic hydrocarbon |
| PAM-MS | Purge-and-membrane inlet mass spectrometry |
| PBDE | Polybrominated diphenyl ether |
| PCB | Polychlorinated biphenyl |
| PCI | Positive chemical ionization |

| | |
|---|---|
| PCP | Personal care product |
| PDMS | Polydimethylsiloxane |
| PEEK | Polyetheretherketone |
| PFA | Pentafluoropropionic acid anhydride |
| PFDA | Perfluorodecanoic acid |
| PFO | Perfluorooctane sulphonate |
| PFOA | Perfluorooctanoate |
| PI | Positive ionization |
| PID | Photoionization detector |
| PLE | Pressurized-liquid extraction |
| PPY | Polypyrrole |
| PTFE | Polytetrafluoroethylene |
| PTV | Programmable temperature vaporization |
| P&T | Purge and trap |
| Q-LIT | Quadrupole–linear ion trap |
| QqQ | Triple quadrupole |
| Q-TOF | Quadrupole–time of flight |
| RAM | Restricted access material |
| RIA | Radioimmunoassay |
| RP | Reversed phase |
| SAX | Strong anion exchange |
| SEC | Size-exclusion chromatography |
| SFE | Supercritical-fluid extraction |
| SIM | Selected ion monitoring |
| SNUR | Significant new use rule |
| SPE | Solid-phase extraction |
| SPME | Solid-phase microextraction |
| SRM | Selected reaction monitoring |
| TBA | *tert*-Butyl alcohol |
| TBBPA | Tetrabromobisphenol A |
| TBF | *tert*-Butyl formate |
| TBS | *tert*-Butyldimethylsilyl |
| TFC | Turbulent flow chromatography |
| TMS | Trimethylsilyl |
| TMS-DEA | *N*,*N*-Diethyltrimethylamine |
| TrBA | Tri-*n*-butylamine |
| UPLC | Ultra-performance liquid chromatography |
| UV | Ultraviolet |
| VOC | Volatile organic compound |
| WAX | Mixed mode weak anion exchange |
| WWTP | Wastewater treatment plant |

## 1 Introduction

During the last three decades, the impact of chemical pollution has focused almost exclusively on the conventional "priority" pollutants, which have long been recognized as posing risks to human health, due to their toxicity, car-

cinogenic and mutagenic effects, and their persistence in the environment. Legislation and long-established standards and certified analytical methods, set by the Environmental Protection Agency (EPA) and the International Organization for Standardization (ISO), are already available for the determination of these priority pollutants. Besides recognized contaminants, numerous other chemicals are continuously released into the environment as a result of their use in industry, agriculture, consumer goods or household activities. The identification, analysis and characterization of the risks posed by these substances, classified as the so-called emerging contaminants, has focused attention and awakened concern among the scientific community during the last few years. This group of compounds, including pharmaceuticals and personal care products, surfactants, gasoline additives, fire retardants and fluorinated organic compounds, among others, is still unregulated. These contaminants may be candidates for future regulation, depending on research on their potential health effects and monitoring data regarding their occurrence.

Several studies have demonstrated that wastewater treatment plants (WWTPs) are major contributors to the presence of emerging contaminants in the environment. As these substances are used in everyday life, they are continuously introduced into the aquatic media via sewage waters mainly through industrial discharges (surfactants, fire retardants), excretion (pharmaceuticals, hormones and contraceptives, personal care products) or disposal of unused or expired substances [1]. Methyl *tert*-butyl ether (MTBE) and other gasoline additives also enter the aquatic environment due to anthropogenic activities, mainly via accidental spills and leakage of corroded tanks at gasoline stations or refineries.

Due to their continuous introduction into the environment, emerging contaminants can be considered as "pseudo-persistent" pollutants, which may be able to cause the same exposure potential as regulated persistent pollutants, since their high transformation and removal rates can be compensated by their continuous input into the environment [2]. Consequently, there is a growing need to develop reliable analytical methods, which enable their rapid, sensitive and selective determination in different environmental compartments at trace levels.

This chapter aims to overview the state of the art of the most recent analytical methodologies developed in the last few years for the analysis of emerging contaminants in environmental samples, using advanced chromatographic techniques and detection systems. Since it is impossible to cover all analytes, we have just focused our attention on selected classes of contaminants, which are currently the most widely studied and ubiquitous in the environment. Trends in sample preparation and instrumental analysis for each group of compounds will be described.

## 2
## Sampling and Sample Preparation

Sample preparation is one of the most important steps within an analytical methodology. Selectivity of stationary phases used for the isolation and preconcentration of target compounds is a key parameter to take into account when analysing emerging contaminants at trace levels from complex environmental samples, since the reduction of co-extracted compounds results in a better sensitivity, achieving lower limits of detection. In the following section, a summary of the trends in stationary phases and materials used for the analysis of emerging contaminants in both aqueous and solid samples will be described.

### 2.1
### Sampling Strategies

Generally, to determine surface waters (river, lake, sea) grab samples are used, whereas for wastewaters composite samples are often collected over sampling periods of 6 h to several days. Some studies reported that the addition of 1% of formaldehyde to water samples prevents degradation of target compounds until analysis. Before sample enrichment, water samples are filtered through glass fibre or cellulose filters. Depending on the nature of the water sample (wastewater, surface water or seawater) and its organic matter content, different pore size filters are used.

In the case of sediments or soil samples, depending on the objective of the study (determination of vertical distribution profiles or concentrations in a surface layer), either core or grab samples are taken. Usually, water is removed and then the solid matrix is stored in the dry state. Removal of water from the sediments before extraction was found to be crucial in obtaining good recoveries [3]. Freeze-drying is an accepted and commonly used procedure for drying solid matrices, but it is not known how this affects the levels of target compounds measured, especially those that are relatively volatile [4].

When small fish, mussels or other bivalves are analysed, several individual species are homogenized to form a pool of tissues, from which sub-samples are taken for extraction. Removal of water is also generally performed by freeze-drying [5].

However, for aqueous matrices, grab samples may not be representative and moreover, a relatively large number of samples must be taken from a given location over the entire duration of sampling [6]. Therefore, a good alternative to overcome this problem could be the use of passive samplers. These devices are based on the free flow of analyte molecules from the sampled medium to a collecting one, as a result of a difference in chemical potentials of the analyte between the two media. Although they have only been applied for the determination of some organic pollutants and pesticides, their application in aqueous and gaseous phases is constantly increasing [6–10].

In passive samplers, the concentration of the analyte is integrated over the whole exposure time, making it immune to accidental or extreme variations of pollutant concentrations [6]. Other advantages against grab sampling are that decomposition of the sample during transport and storage is minimized and that passive sampling and/or extraction methods are simple to perform as, after the isolation and/or enrichment step, no further sample preparation is usually required [6]. Devices used today are based on diffusion through a well-defined diffusion barrier or permeation through a membrane, the former being the most popular ones.

## 2.2 Analysis of Emerging Contaminants in Water Samples

Extraction of target compounds from water matrices is generally achieved by solid-phase extraction (SPE) and solid-phase microextraction (SPME). For SPE, several stationary phases can be used, ranging from mixtures of different polymers (such as divinylbenzene–vinylpyrrolidone) to octadecylsilica ($C_{18}$) or more selective tailor-made materials, such as immunosorbents, molecularly imprinted polymers (MIPs) and restricted access materials (RAMs).

The use of tailor-made materials is very useful when performing single group analysis, as they enhance the selectivity for the compounds of interest in the sample preparation process, reducing the amount of co-extracted material and, as a result, increasing the sensitivity. However, when the aim of the analytical methodology is to analyse a wide spectrum of compounds with different physico-chemical properties, polymeric or $C_{18}$ sorbents are the most recommended ones.

The use of automated on-line systems, which integrate extraction, purification and detection, has increased over the past several years. One option is on-line coupling of SPE and LC, utilizing special sample preparation units, such as PROSPEKT (Spark Holland) and OSP-2 (Merck). This technique has been successfully applied to the analysis of pesticides, estrogens and progestogens in water samples [11–17]. Similarly, on-line coupling of SPE and SPME to GC is a promising approach with good prospects [18, 19].

### 2.2.1 Immunosorbents

The immunosorbents, such as polyclonal antibodies, are immobilized on silica-based supports, activated Sephadex gels, synthetic polymers, sol/gel materials, cyclodextrins, or RAMs and packed into cartridges or pre-columns [20, 21]. Immunoaffinity extraction coupled with LC/ESI-MS has been used for the analysis of pesticides [12, 22–24] and β-estradiol and estrone in wastewater [25]. Immunosorbents have also the potential to be applied to the determination of drugs in aqueous samples. In fact, most on-line

immunosorbent applications correspond to pharmaceutical and biomedical trace analysis [26]. Therefore, a high number of pharmaceuticals [27, 28] and hormones [29, 30] have been determined in biological samples using immunoaffinity SPE coupled to on-line LC-MS. With these materials, humic and fulvic acids are not co-extracted and thus no further clean-up is necessary. Moreover, cross-reactivity of the antibody can be advantageous, because it not only extracts a determined substance, but also all compounds within a given class, being then separated and quantified individually by coupling with chromatographic techniques [31].

### 2.2.2 Molecularly Imprinted Polymers (MIPs)

During the last few years, MIPs have appeared as new selective sorbents for SPE of organic compounds in complex materials [32, 33]. Both on-line and off-line MIP-SPE protocols have been developed to determine organic pollutants in environmental waters, mainly pesticides and hormones [34–39].

Molecular imprinting is a rapidly developing technique for the preparation of polymers having specific molecular recognition properties [40–43]. First, the template and the monomer form a stable template–monomer complex prior to polymerization. Then the complex is polymerized in the presence of a cross-linking agent. The resulting MIPs are matrices possessing microcavities with a three-dimensional structure complementary in both shape and chemical functionality to that of the template [44, 45]. After polymerization, the template, which consists of one of the target analytes or related analogues, is removed, generating specific binding sites. Then, the polymer can be used to selectively rebind the template molecule, the analyte or structurally related analogues. The specific binding sites in MIPs are formed by covalent or, more commonly, non-covalent interactions between the imprinting template and the monomer [32].

Apart from their high selectivity for target compounds, MIPs possess other advantages, such as low cost, high stability, ability to be reused without loss of activity, high mechanical strength, durability to heat and pressure and applicability in harsh chemical media [46, 47].

MIPs can be prepared in a variety of physical forms, but the conventional approach is to synthesize the MIP in bulk, grind the resulting polymer and sieve the particles into the desired size ranges [48, 49]. However, this method is tedious and time-consuming, often produces particles that are irregular in size and shape and some interaction sites are destroyed during grinding. In order to overcome these problems, alternative methods have been developed, such as using multi-step swelling procedures, suspension and precipitation polymerization, respectively, to obtain uniform spherical particles [50–55].

In MIP-SPE processes, the sample medium, during the loading step, has an important influence on the recognition properties of the MIP. If the an-

alyte of interest is presented in an aqueous medium, the analyte and other interfering compounds are retained non-specifically on the polymer. Therefore, to achieve the selectivity desired, a clean-up step using organic solvents is required prior to elution [32].

One of the main disadvantages of MIP-SPE is the difficulty in removing the entire template molecule, even after extensive washing, and therefore a leakage of template molecule can occur, which is an obstacle in the determination of target compounds. To overcome this problem, a structural analogue of the target molecule can be imprinted to make a "dummy molecularly imprinted polymer" (DMIP), distinguishing then any leakage of target compound [56].

### 2.2.3 Restricted Access Materials (RAMs)

RAMs are a class of SPE materials that possess a biocompatible surface and a pore size that restricts big molecules from entering the interior extraction phase based on size [26]. Simultaneously, an extraction phase located on the inner pore surface is responsible for isolation of the low molecular weight compounds [26]. Koeber et al. [57] applied this approach in combination with MIP and used an on-line mode to analyse pesticides from environmental samples. There are various references reporting the use of RAMs for direct injection of biological samples [58–60], but few applications have been reported for environmental matrices.

### 2.2.4 Solid-Phase Microextraction (SPME)

Several reviews have been devoted to the application of SPME in environmental analysis [6, 61–66]. SPME is a simple and effective adsorption/absorption and desorption technique which eliminates the need for solvents and combines sampling, isolation and enrichment in one step [66]. Depending on the analyte and matrix, SPME of water samples can be performed in different modes: direct-immersion extraction (for less volatile compounds and relatively clean samples), headspace extraction (for more volatile compounds and dirtier samples), membrane-protected SPME (for the extraction of analytes in heavily polluted samples), in-tube SPME [5, 67] and thin-film microextraction (use of a thin sheet of PDMS membrane) [68].

In-tube SPME has been applied for the determination of a variety of environmental pollutants [69–75] and is based on the use of a fused-silica capillary column as the extraction device. Target analytes in aqueous matrices are directly extracted and concentrated by the coating in the capillary column by repeated withdrawal and expulsion of the sample solution, and can be directly transferred to LC or GC columns for analysis.

The major part of SPME applications has been developed for GC, as the coupling to HPLC is more complex and requires specifically designed interfaces to desorb analytes from the fibres and also because not all fibres can be used for LC, due to solubility and swelling of the fibre coatings in organic solvents [5].

Several fibre coatings are commercially available for the analysis of non-polar organic compounds, such as BTEX, PAHs and pesticides, and polar compounds like phenols, alcohols, etc. [66], including polydimethylsiloxane (PDMS), polyacrylate (PA), divinylbenzene (DVB), Carboxen (CAR) and Carbowax (CW). On the other hand, a polypyrrole (PPY) coating is used to extract polar or ionic analytes [67], which is mainly addressed to the coupling of SPME to LC.

Another way to determine polar compounds by SPME is presented by SPME derivatization, which includes three different approaches: in-coating, direct or on-fibre derivatization. The difference between these techniques is that while in direct derivatization, the derivatizing agent is first added to the sample vial and the derivatives are then extracted by the SPME fibre coating, for on-fibre derivatization, the derivatizing agent is loaded on the fibre, which is subsequently exposed to the sample and extracted [66]. This approach is now widely used for the analysis of organic pollutants in the environment, such as acidic herbicides [76, 77], and has been recently reviewed by Stashenko [78] and Dietz [79].

## 2.3 Analysis of Emerging Contaminants in Solid Samples and Biota

### 2.3.1 Extraction Techniques

Organic contaminants present in solid environmental samples, such as sediments, soils, sludge and biota, are determined by exhaustive extraction with appropriate solvents. Liquid–liquid extraction (LLE), Soxhlet, sonication, pressurized-liquid extraction (PLE), microwave-assisted extraction (MAE) and supercritical-fluid extraction (SFE) are the techniques most commonly used [5]. Also methods based on HS-SPME have been developed to determine volatile and semi-volatile compounds.

Soxhlet has been widely used, as it is considered as the reference method, is inexpensive and is easy to handle. However, new trends are focused on the use of "low-solvent, low-time and low-cost" techniques, amenable to automation, such as PLE, MAE and SFE. These techniques use elevated temperature and pressure, which results in improved mass transfer of the analytes and, consequently, increased extraction efficiency. SFE and MAE are not suitable for highly polar organic compounds or matrices with high water content. Therefore, nowadays PLE, also termed accelerated solvent extraction, is the preferred technique, because it is automated, it consumes low amounts of sol-

vent and because older extraction procedures can be easily adapted. However, it offers some disadvantages, such as its cost, as commercial PLE equipment may be expensive and, moreover, some thermolabile compounds may suffer degradation. A good alternative to PLE would be MAE, as it is more affordable, fast and consumes little solvent, but extracts need to be filtered and microwave heating is uneven and restricted to matrices that adsorb this radiation. SFE with solid-phase trapping has been used for different groups of organic pollutants. Although good results and unique improved selectivity were obtained for selected applications, the method did not find acceptance. This is because the extraction conditions depend on the sample, requiring complicated optimization procedures [5, 80].

### 2.3.2
### Extract Clean-up and Purification

Due to the complexity of samples and the exhaustive extraction techniques used, a substantial number of interfering substances present in the matrix are found in the extracts. Therefore, a clean-up and purification step after extraction is indispensable to remove these compounds and enhance selectivity, in order to reduce ion-suppression effects when working with ESI-MS detection and to improve the separation of analytes from impurities.

#### 2.3.2.1
#### Solid Samples

The conventional approach used is based on solid/liquid adsorption, using either long open columns or disposable cartridges packed with different sorbents, depending on the physico-chemical properties of the analytes of interest. Purification can be also performed by off-line SPE cartridges packed with polymeric materials, $C_{18}$, $NH_2$-, CN-modified silica or anionic exchange materials, by reversed-phase (RP) or normal-phase (NP) liquid chromatography, generally using alumina, silica or Florisil as the packing material, or size-exclusion chromatography (SEC) [5]. When high selectivity for one compound or related analogues is desired, MIPs and RAMs are also appropriate materials to use for the clean-up of crude extracts.

Purification based on two tandem SPE procedures is a widespread approach, which generally consists of the use of anionic exchange cartridges and other polymeric materials. Moreover, when extracts contain high amount of lipids and organic matter, such as sewage sludge and biota, non-destructive and destructive methods are generally used prior to instrumental analysis. The former include gel permeation and column adsorption chromatography, generally using polystyrene–divinylbenzene copolymeric columns. Other neutral adsorbents commonly used are silica gel, alumina and Florisil® [81]. Destructive lipid removal methods consist of sulphuric acid treatment, either

directly to the extract or via impregnated silica columns, and saponification of extracts by heating with ethanolic KOH [82].

#### 2.3.2.2 Biota

The analysis of biota, such as fish or mussels, could be an indicator of the water quality, as lipophilic organic contaminants tend to accumulate in the tissues with high lipid content. Isolation of organic compounds from biological tissues is a complicated and laborious task because of the nature of the matrix. Disruption of a cellular structure of biological samples results in an abundance of lipids and proteins. Extraction methods often yield high concentrations of lipids and, therefore, an exhaustive purification is required to achieve the selectivity and sensitivity desired. For this reason, treatment with sulphuric acid and saponification are frequently used for the removal of lipids prior to the purification using the same techniques as for solid samples (RP or NP, LC, SPE, SEC, MIP or RAM). However, in some cases, this step has to be avoided as some target compounds may be destroyed.

A simultaneous extraction and clean-up step was proposed by Eljarrat et al. [83] for the determination of PBDEs in fish. This methodology is based on the inclusion of alumina in the PLE cells, so that both purification and isolation of target analytes is achieved in a single step, speeding up sample preparation considerably.

Another approach to conduct simultaneous disruption and extraction of solid and semi-solid samples involves matrix solid-phase dispersion (MSPD), a technique that combines in one step extraction, concentration and clean-up by blending a small amount of sample with the selected sorbent. It has been successfully applied to the analysis of penicillins, sulphonamides, tetracycline antibiotics [5] and ionic [5, 84, 85] and non-ionic surfactants in fish and mussels.

## 3 Instrumental Analysis and Quantitation

### 3.1 Chromatographic Separation

Both gas chromatography (GC) and liquid chromatography (LC) are techniques par excellence in environmental analysis. Even though the former is more addressed to the analysis of non-polar and volatile compounds (PBDEs and MTBE), non-volatile compounds, such as pharmaceuticals, surfactants, personal care products, estrogens and others, can also be determined after a derivatization step.

### 3.1.1 Gas Chromatography

GC was one of the first chromatographic separation techniques to be developed, and today is still widely used and has not lost its eminence in the environmental field. The popularity of GC is based on a favourable combination of very high selectivity and resolution, good accuracy and precision, wide dynamic range and high sensitivity. Columns mainly used in GC consist of narrow-bore capillary columns [86–88].

In GC, the three most frequently used injection systems are splitless, on-column and programmable temperature vaporization (PTV). In splitless injection, the transfer of the analytes into the analytical column is controlled by the volume of the liner and by the injected volume. In on-column injection, extracts are directly injected into the column or in a glass insert fitted into a septum-equipped programmable injector kept at low temperature. Finally, PTV is a split/splitless injector which allows the sample to be introduced at a relatively low temperature, thus affording accurate and reproducible sampling. After injection, the PTV is rapidly heated to transfer the vaporized components into the capillary column.

Nowadays, headspace GC (HSGC) and comprehensive two-dimensional GC (GC×GC) have gained popularity in the environmental field. The main advantages presented by the former, against GC, is the ability to increase efficiency and drastically reduce analysis time [89]. On the other hand, GC×GC has a great capability to separate and identify organic compounds in complex environmental samples. This technique has been mainly employed for the determination of MTBE and other oxygenated and aromatic compounds in gasoline-contaminated ground waters [90] and for the determination of PBDEs [91]. In this technique, two GC separations based on distinctly different separation mechanisms are used, with the interface, called modulator, between them. Then, the effluent from the first column is separated into a large number of small fractions, and each of these is subsequently separated on the second column, which is much faster than the first separation. In principle, all kinds of stationary phases can be used in the first dimension of a GC×GC system, but generally, non-polar phases are the preferred ones. Concerning the second dimension, a variety of phases can be selected depending on the desired analyte–stationary phase interactions. However, most applications showed that the combination between a non-polar and (medium) polar phase is by far the most popular option. Concerning column size, samples are generally first separated on a 15–30 m × 0.25–0.32 mm ID × 0.1–1 μm film ($d_f$) column. After modulation, each individual fraction is injected onto a much shorter, narrower column, with dimensions typically 0.5–2 m × 0.1 mm ID × 0.1 μm $d_f$.

### 3.1.2 Liquid Chromatography

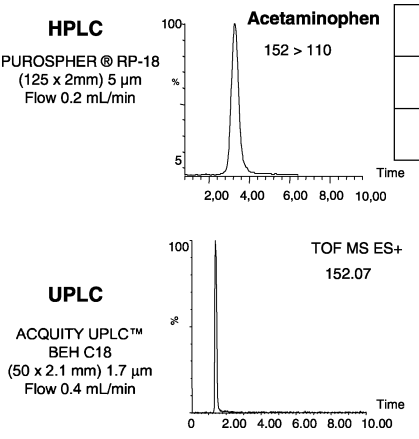
Besides the advantages offered by GC, nowadays reversed-phase HPLC is the technique of choice for the separation of polar organic pollutants, silica-bonded columns being preferred [92]. The size parameters of the columns are typically as follows: (1) length in the range 10–25 cm, (2) internal diameter 2.1–4.6 mm and (3) particle sizes 3–5 μm. Gradient elution represents the most common strategy in separation. The mobile phases generally used are acetonitrile, methanol or mixtures of both solvents, obtaining in the latter case shorter retention times and better resolution of the analytes. In order to obtain an efficient retention of the analytes in the column and to improve the sensitivity of MS detection, mobile phase modifiers, buffers and acids are recommended and widely used. The selection of such modifiers strongly depends on the physico-chemical properties of target compounds and their p$K_a$ values. The most common ones include ammonium acetate, ammonium formiate, tri-*n*-butylamine (TrBA), formic acid and acetic acid. Typical concentrations of the salts range from 2 to 20 mM, since it has been observed that higher concentrations could lead to a reduction of the signal intensities [92].

Shortening the analysis times is important for attaining the high sample throughput often required in monitoring studies. This objective can be achieved by shortening the columns and increasing the flow velocity, decreasing the particle size of the stationary phase and finally increasing the temperature, which enhances diffusivity thus allowing working at higher flow rates. These principles are both applied in the Acquity UPLC (ultra-performance liquid chromatography) system, produced by Waters Corporation (Manchester, UK) and in the 1200 Series RRLC (rapid resolution LC) from Agilent Technologies. Both systems use rather short columns (50–100 mm, 4.6 mm ID) packed with sub-2-μm porous particles, allowing very short chromatographic runs. However, the negative effect of using a small particle size is high back-pressure generation (reducing the particle size by a factor of 3 results in an increase in the backpressure by a factor of 27) [92]. Even though the application of UPLC is promising, its application to environmental analysis is still rare. Petrovic et al. [93] developed a UPLC-QqTOF-MS method for screening and confirmation of 29 pharmaceutical compounds belonging to different therapeutic classes in wastewaters, including analgesics and anti-inflammatories, lipid-regulating agents, cholesterol-lowering statin agents, psychiatric drugs, anti-ulcer agents, histamine $H_2$ receptor antagonists, antibiotics and beta-blockers. UPLC, using columns packed with 1.7-μm particles, enabled elution of target analytes in much narrower, more concentrated bands, resulting in better chromatographic resolution and increased peak height. The typical peak width was 5–10 s at the base, permitting very good separation of all compounds in

10 min, which represented an approximate threefold reduction in the analysis time in comparison to conventional HPLC as shown in Fig. 1.

One of the main problems encountered in quantitative LC analysis and a main source of pitfalls is the existence of matrix effects in general, and the ion suppression phenomenon in particular. The ionization suppression or enhancement may severely influence the sensitivity, linearity, accuracy and precision of quantitative LC analysis. Therefore, any study dealing with analysis of complex samples should include a matrix effect study, and if relevant ion suppression (or signal enhancement) occurs, additional procedures should be applied for correction and/or minimization of inaccurate quantification.

There are several strategies to reduce matrix effects, i.e. selective extraction, effective sample clean-up after the extraction, or improvement of the chromatographic separation. Sometimes, these approaches are not the appropriate solutions because they could lead to analyte losses as well as long analysis times [94]. Recently, several strategies have been adopted as standard practices [95–98]. The most often applied approach consists of the use of suitable calibration, such as external calibration using matrix-matched samples, standard addition or internal standard calibration using structurally similar unlabelled pharmaceuticals or isotopically labelled standards. Other approaches include a decrease of the flow that is delivered to the ESI interface, as well as the dilution of sample extracts. However, the most recommended and versatile approach is isotope dilution, which consists of the use of an isotopically labelled standard for each target compound [99]. But such an approach is expensive and in many cases suffers from a lack of isotopically labelled compounds for all target analytes.




| Separation technique | Peak width | Chromatographic run |
|---|---|---|
| HPLC | 0.5 – 1 min | 30 min separation<br>Total run **45 min** |
| UPLC | 5 - 10 s | 10 min separation<br>Total run **14 min** |

**Fig. 1** UPLC versus HPLC chromatograms for the determination of the analgesic acetaminophen (paracetamol) in the PI mode, showing the reduced peak width and increased peak height achieved with UPLC, which results in an improved sensitivity, reduced spectral overlap in complex mixtures and improved MS spectral data

### 3.2 Detection Systems

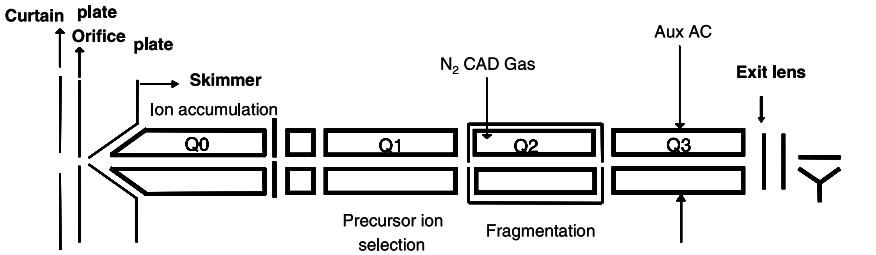
The rapid developments in the field of tandem MS/MS have transformed it into a key technique for environmental analysis, replacing other detectors widely used in the past, such as fluorescence and UV detectors for LC and flame ionization (FID), electron capture (ECD) and photoionization (PID) detectors for GC. While tandem MS/MS is mainly coupled to LC, replacing LC-MS due to its higher sensitivity and selectivity, single mass spectrometry is generally attached to GC, mainly using quadrupole, ion trap (IT) and time of flight (TOF) analysers. The latter is mainly applied when working with GC×GC devices.

With regard to LC-MS/MS, triple quadrupole (QqQ) mass analysers have become the most widely used analytical tool in the determination of emerging contaminants in environmental samples. Triple quadrupole instruments gather a variety of scan functions and modes, such as product ion scan, precursor ion scan, neutral loss and multiple reaction monitoring (MRM) mode. LC-MS/MS (QqQ) has been mostly applied to the determination of target analytes, using the selected reaction monitoring (SRM) mode and reaching typically ng $L^{-1}$ detection limits [92].

Although the sensitivity, selectivity and efficiency of the MRM approach are excellent, qualitative information, needed to support the structural elucidation of compounds other than target analytes, is lost [92]. This drawback can be overcome by using the hybrid MS systems, such as QqTOF or QqLIT. The acceptance of QqTOF-MS for environmental analysis in the last few years has been significantly improved and the number of methods reported in the literature is steadily increasing [92].

QqTOF is mainly used as an unequivocal tool for confirmation of contaminants detected. Its unique characteristic of generating full scan and product ion scan spectra with exact masses is excellent for the elimination of false positives and avoiding interpretation ambiguities. The main field of application is the identification of unknowns and elucidation of structures proposed for transformation products, where the amount of information obtained allows secure identification of compounds [92]. Regarding its quantitative performance, QqTOF has a lower linear dynamic range (over two orders of magnitude) with respect to QqQ instruments (typically > four orders of magnitude) [92]. However, when the application requires a high degree of certainty or is aimed at multiple tasks, such as target analysis combined with qualitative investigation of unknowns, its use could be a viable choice.

Regarding QqLIT, its unique feature is that the same mass analyser Q3 can be run in two different modes, retaining the classical triple quadrupole scan functions such as MRM, product ion, neutral loss and precursor ion while providing access to sensitive ion trap experiments [100] (see Fig. 2). This allows very powerful scan combinations when performing information-




| Scan Type | Q1 | Q2 | Q3 |
|---|---|---|---|
| Q1 Scan | Resolving Scan | RF-only | RF-only |
| Q3 Scan | RF-only | RF-only | Resolving (Scan) |
| Product Ion Scan (PIS) | Resolving (Fixed) | Fragment | Resolving (Scan) |
| Precursor Ion Scan (PI) | Resolving (Scan) | Fragment | Resolving (Fixed) |
| Neutral Loss Scan (NL) | Resolving (Scan) | Fragment | Resolving (Scan Offset) |
| Selected Reaction Monitoring (SRM) | Resolving (Fixed) | Fragment | Resolving (Fixed) |
| Enhanced Product Ion Scan (EPI) | Resolving (Fixed) | Fragment | Trap/Scan |
| $MS^3$ | Resolving (Fixed) | Fragment | Isolation/frag trap/scan |
| Time delayed frag capture Product Ion (TDF) | Resolving (Fixed) | Trap/No frag | Frag/trap/scan |
| Enhanced Q3 single MS (EMS) | RF-only | No frag | Trap/Scan |
| Enhanced Resolution Q3 Single MS (ERMS) | RF-only | No frag | Trap/Scan |
| Enhanced Multiply Charged | RF-only | No frag | Trap/empty/scan |

**Fig. 2** Scheme of the QqLIT instrument (QTRAP, Applied Biosystems/Sciex) and description of the various triple quadrupole and trap operation modes

dependent data acquisition. In the case of small molecules, qualitative and quantitative work can be performed concomitantly on the same instrument. The very fast duty cycle of QqLIT provides a superior sensitivity over that of traditional QqQ and ion trap and allows one to record product ion scan spectra for confirmation purposes without compromising signal-to-noise (S/N) ratio. Also the resolution and accuracy are higher and these peculiarities improve the ion selection capability for complex mixtures, i.e. improve the instrumental selectivity. Although environmental applications are still scarce, a few recent papers reported on the application of a hybrid QqLIT for trace level determination of emerging contaminants, such as perfluorinated chemicals, herbicides and pharmaceuticals [92].

### 3.3 Ionization Sources

For GC-MS instruments, the most common ionization sources employed are electron impact (EI) or chemical ionization, either in negative (NCI) or positive mode (PCI). GC-NCI-MS is mainly used for compounds containing bromine or chlorine ions, such as PBDEs.

As concerns the LC-MS and LC-MS/MS techniques, API interfaces, such as electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI), are the ones most commonly used. In ESI, a liquid containing target analytes, dissolved in a large amount of solvent, is pushed through a very small, charged and usually metal capillary. The analyte exists as an ion in solution and as charges repel, the liquid pushes itself out of the capillary and forms an aerosol, a mist of small droplets about 10 μm across. An uncharged carrier gas such as nitrogen is sometimes used to help nebulize the liquid and evaporate the neutral solvent in the droplets. As the solvent evaporates, the analyte molecules repel each other and break up the droplets. This process repeats until the analyte is free of solvent and is a lone analyte ion. This process is known as Coulombic fission because it is driven by Coulombic forces between charged molecules. On the other hand, in APCI analytes are already vaporized when introduced into the detector. In this technique, the mobile phase containing eluting analytes is heated to a relatively high temperature (above 400 °C) and sprayed with high flow rates of nitrogen, generating an aerosol cloud which is subjected to a corona discharge to generate analyte ions. These techniques are especially suitable for the determination of low volatility and thermolabile compounds as well as polar substances. ESI is very useful for the analysis of macromolecules because it overcomes the propensity of such molecules to fragment when ionized.

Recently, a new API interface has been developed, the so-called atmospheric pressure photoionization (APPI) interface [101, 102]. APPI is a modification of the APCI source in which the corona is replaced by a gas discharge lamp, emitting radiation in the UV region that is able to selectively ionize the analytes in the presence of the LC mobile phase. Improved performance of APPI can be achieved by adding a dopant, which is a mobile phase additive, like acetone or toluene, which is first ionized itself and then aids ionization of the analytes in further reactions [103]. Compounds like naphthalene, acridine, diphenyl sulphide and 5-fluorouracil could be ionized by an APPI source. Despite being a very new approach, APPI-MS is expected to become an important complementary technique to APCI for low and non-polar analytes in the future [103].

## 4
## Emerging Contaminants

### 4.1
### Fluorinated Alkyl Substances (FASs)

FASs are a group of compounds of anthropogenic origin used in many industrial and consumer products, such as polymers and surfactants. They have

been widely used to synthesize products that resist heat, oil, stains, grease and water, due to their unique properties [104].

FASs include the perfluoroalkyl sulphonates (perfluorooctane sulphonate (PFO) and related chemicals, such as *N*-methyl and *N*-ethyl perfluorooctanesulphonamidoethanol, and also short- and long-chain perfluoro sulphonate acids), the perfluoroalkyl carboxylates (perfluorooctanoate (PFOA) and fluorotelomer alcohols (FTOHs)) and the short- and long-chain perfluoroalkyl acids (e.g. perfluorodecanoic acid (PFDA) [105]). Other substances, such as PFHS and PFBS, considered as "related substances" to PFOs because they have the same moiety ($C_8F_{17}SO_2$ group), are included in the group of PFAs as, once present in the environment, they may decompose to generate PFOs. Many of the degradation products of FASs have been found in the environment throughout the world, but PFOs and PFOA are the two most widely detected groups. Because of the strong carbon–fluorine (C–F) bond associated with their chemical structure, they are environmentally persistent substances and have been detected in human blood, water, soils, sediments, air and biota [105].

Due to their high production worldwide, in October 2000 the US EPA proposed a significant new use rule (SNUR) for 88 PFO-related substances [105]. On the other hand, PFOs and related substances have also been on the agenda of the Organization for Economic Co-operation and Development (OECD) since the year 2000 [105]. In the EU, there is currently no legislation on their use associated with their potential environmental and/or human health effects. However, some legislation which generally applies to the release of substances to the environment may be relevant to the release of PFOs. Therefore, the IPPC Directive 96/61/EC includes fluorine and its compounds in the "indicative list of the main polluting substances to be taken into account if they are relevant for fixing emission limit values". There are several reviews devoted to their analysis in environmental samples [105, 106]. However, these compounds present several difficulties during their analysis, as indicated in the section below.

### 4.1.1 Background Contamination Problems

The analysis of PFAs is rather difficult due to several background contamination problems not only coming from the materials used for sample collection and preparation, but also from the instrumental techniques [104, 107–109]. Therefore, one source of experimental contamination is the use of materials made of, or containing, fluoropolymers, such as polytetrafluoroethylene (PTFE) or perfluoroalkoxy compounds, which should be avoided. Taniyasu et al. [107] performed several experiments to assess possible sources of contamination, from sample collection materials to solvents used. They found that polypropylene sample bottles used for sample collection and storage con-

tained PFOA. In the evaluation of two widely employed SPE cartridges, the Oasis hydrophilic–lipophilic balanced (HLB) and Sep-Pak $C_{18}$, considerable amounts of PFOA, PFOs, PFHS and PFBS were detected, the latter being the one showing higher concentrations. Even purified water was found to be another possible source of contamination. In the light of these concerns, water samples are collected in polyethylene or polypropylene bottles rinsed with methanol and deionized water prior to use. Glass is avoided because analytes tend to bind it and some authors centrifuge water samples, as an alternative to filtration, to avoid possible adsorption of PFOs onto the filter and subsequent loss of analyte [110].

Moreover, during instrumental analysis, especially when working with LC-MS or tandem MS/MS detection, significant instrumental contamination problems can occur. Yamashita et al. [109] determined that the HPLC tubing, internal fluoropolymer parts and autosampler vial septum were potential sources of PFA contamination during LC analysis. Therefore, it is recommended to replace the PTFE HPLC tubing with stainless steel and polyetheretherketone (PEEK). Moreover, the same authors isolated the degasser and solvent selection valves, which contain fluoropolymer coatings and seals from the HPLC system, and the solvent inlet filters were replaced by stainless steel ones. Finally, autosampler vial caps made of Viton fluoropolymers or polyethylene were used, as they reduced considerably the instrumental blank concentrations.

### 4.1.2 Sample Preparation

Fluorinated alkyl substances have been mainly analysed in biological samples and environmental waters [105]. Concerning their determination in aqueous matrices, liquid–liquid extraction (LLE) and solid-phase extraction (SPE) are the traditional methods used for enrichment and isolation of target analytes, mainly using Oasis HLB, octadecyl $C_{18}$ bonded silica and Oasis WAX adsorbents (see Table 1) [105]. On-line direct analysis using diverse preconcentration columns has been proposed by several authors [18, 106, 111–113], to speed up sample preparation.

Only Higgins et al. [114] have determined the presence of fluorinated compounds in sediments. Extraction was performed using a heating sonication bath and afterwards a clean-up procedure with $C_{18}$ SPE cartridges. These compounds have also been determined in sludges by Higgins et al. [114] and Schröder et al. [115]. The former applied the same treatment as for the sediments. The latter compared the efficiency of three extraction techniques (Soxhlet, hot vapour and PLE), PLE being the one yielding better performances. After extraction, crude extracts are purified, generally using SPE with $C_{18}$ cartridges (see Table 2).

**Table 1** Representative methods, indicating the extraction and detection techniques, for the determination of the selected groups of emerging contaminants in environmental waters

| Compounds | Matrix | Extraction method | Purification or derivatization for GC | Detection | GC/LC column | LC mobile phase | LOD (ng/L) | Refs. |
|---|---|---|---|---|---|---|---|---|
| MTBE, degradation products and other gasoline additives | Influent/ effluent wastewaters | P&T | – | GC-EI-MS | | | | [362] |
| | Influent/ effluent wastewaters | HS-SPME | – | GC-EI-MS | | | | [351] |
| | Ground water | P&T with Tenax® silica gel–charcoal at room temperature. Desorption with He at 225 °C | – | GC-EI-MS | Capillary fused silica DB-624 (75 m × 0.53 mm) | | 1–110 | [347] |
| PFOs | Surface water | SPE (Presep-C cartridges) | – | LC-ESI-MS | Zorbax XDB $C_{18}$ (2.1 × 150 mm) | AcN-$H_2O$ (10 mM $NH_4Ac$) | 0.04–0.1 | [111, 112] |
| PFOs, *N*-EtFOSAA | Wastewater | SPE (Waters, Oasis HLB 1 g) | – | LC-ESI-MS/MS | Zorbax SB $C_8$ (3.0 × 150 mm) | A: MeOH/AcN (50%) 0.15% HOAc B: Water 0.15% HOAc | 0.06–0.1 | [363] |

**Table 1** (continued)

| Compounds | Matrix | Extraction method | Purification or derivatization for GC | Detection | GC/LC column | LC mobile phase | LOD (ng/L) | Refs. |
|---|---|---|---|---|---|---|---|---|
| PFNA<br>PFOSA<br>FTOHS | Seawater | SPE<br>(Oasis WAX) | – | LC-ESI-MS/MS | Guard column:<br>XDB-$C_8$<br>(2.1×12.5 mm)<br>Column:<br>Betasil-$C_{18}$<br>(2.1×150 mm) | A: $H_2O$<br>(2 mM<br>$NH_4Ac$)<br>B: MeOH | 1.8 pg/L<br>1pg/L<br><br>0.01–1 | [107] |
| E1, E2,<br>17$\alpha$-E2, EE | Surface water<br>Drinking water<br>STP effluent | SPE<br>(Lichrolut EN) | Derivatization with 10% PFBCl in toluene | GC-NCI-MS | DB5MS<br>(60m×0.32 mm,<br>0.25 μm) | – | 0.05–0.15 | [185] |
| E1, E2, E3, EE | Ground water | SPE (Oasis HLB) | Derivatization with PFBBR + TMSI (LLE with water and hexane) | GC-NCI-MS/MS | DB5-XLB<br>(60m×0.25 mm,<br>0.25 μm) | – | 0.2–0.6 | [134] |
| E1, E2, EE | Drinking, ground, surface and wastewater | SPE<br>(Bakerbond $C_{18}$) | For WWTP influent SPE (silica gel) | LC-ESI (NI) MS/MS | RP-$C_8$<br>Hypersil MO5<br>(100×2.1 mm,<br>5 μm) | A: ACN/MeOH<br>B: $H_2O$ | 0.1–2 | [167, 168] |
| E1, E2, E3, EE, DES, E2-17G, E1-3S, E2-17 Acet. | Ground, river and treated waters | Fully automated on-line SPE (PLRP-s) | – | LC-ESI (NI) MS/MS | Purospher STAR-RP18e<br>(125×2 mm,<br>5 μm Merck) | A: ACN<br>B: $H_2O$ | 0.01–0.38 | [138] |

**Table 1** (continued)

| Compounds | Matrix | Extraction method | Purification or derivatization for GC | Detection | GC/LC column | LC mobile phase | LOD (ng/L) | Refs. |
|---|---|---|---|---|---|---|---|---|
| E1, E2, E3 + PROG + six androgens | Ground and river water | SPE (Carbograph) | – | LC-APCI (PI) MS/MS | Alltima $C_{18}$ (250×4.6 mm, 5 μm Alltech) | A: ACN B: $H_2O$ 5 mM $NH_4Ac$ | 0.5–1 | [364] |
| Antibiotics, β-blockers, psychiatric drugs, anti-inflammatories | Hospital effluent wastewaters | pH adjustment (pH 7) SPE (Oasis HLB) | – | LC-ESI (NI) and (PI) MS/MS | Purospher STAR-RP18e (125×2 mm, 5 μm Merck) | **ESI(+)** A: ACN B: Aq-Formic acid **ESI(–)** A: ACN B: $H_2O$ | 4–47 | [200] |
| Anti-inflammatories, lipid regulators, anti-epileptic, β-blockers, antibiotics and other contaminants | River and wastewaters | Natural water pH SPE Oasis HLB | – | LC-ESI (NI) and (PI) MS/MS | Purospher STAR-RP18e (125×2 mm, 5 μm Merck) | **ESI(+)** A: ACN/MeOH (2:1) B: $NH_4Ac$ 5 m/ HAc **ESI(–)** A: MeOH B: $H_2O$ | 0.5–47 RW 1–60 WW | [2] |
| Analgesics/ anti-inflammatories, lipid regulators, β-blockers, antibiotics, anti-epileptics | Surface water | Sample acidified at pH = 3 SPE Oasis MCX | – | LC-ESI (NI) and (PI) MS/MS | | **ESI(+)** and **ESI(–)** A: MeOH B: 2 mM $NH_4Ac$ | 5–25 | [365] |

**Table 1** (continued)

| Compounds | Matrix | Extraction method | Purification or derivatization for GC | Detection | GC/LC column | LC mobile phase | LOD (ng/L) | Refs. |
|---|---|---|---|---|---|---|---|---|
| Tetracycline and sulphonamide antibiotics | Wastewaters | Addition of $Na_2EDTA$ and citric acid (pH<3) SPE Oasis HLB | – | LC-ESI (PI) MS/MS | | **ESI(+)** A: AcN B: 0.1% formic acid | 30–70 | [366] |
| All musk (no metabolites) | Wastewaters | LLE with hexane SEC (Bio Beads SX-3) | Silica purification | GC/EI-MS | VR-5MS (30 m×0.25 mm, 0.25 μm) | | NR | [258] |
| HHCB, AHTN, ATII, ADBI, AHMI, DPMI, MX, MK | WWTP effluent and surface water | SLLE with pentane, DCM, DCM (at pH 2) Dried with sodium sulphate | – | GC/EI-MS | BPX-5 (30 m×0.25 mm, 0.25 μm) | | NR | [234, 235] |
| HHCB, AHTN | Ground water | SPE ($C_{18}$) Eluent: acetone/hexane (3:17 VR) | Silica purification | GC/EI-MS | XTI-5 (30 m×0.25 mm, 0.25 μm) | | NR | [197] |
| BDE-15, BDE-28, BDE-47, BDE-100, BDE-99, BD-154, BDE-153, BDE-183 | Tap and river water | HF-MMLLE using *n*-undecane as solvent. Extraction time: 60 min; stirring rate: 1200 rpm | – | GC/EI-MS | HP-5 ms (30 m×0.25 mm, 0.25 μm) | | 0.2–0.9 | [320] |
| BDE-47, BDE-100, BDE-99, BDE-85, BDE-154, BDE-153 | River, sea and wastewater | SPME using polydimethylsiloxane (PDMS) rods | – | GC-ECD-MS | HP-5 (30 m×0.32 mm, 0.25 μm) | | 0.3–5 | [367] |

**Table 1** (continued)

| Compounds | Matrix | Extraction method | Purification or derivatization for GC | Detection | GC/LC column | LC mobile phase | LOD (ng/L) | Refs. |
|---|---|---|---|---|---|---|---|---|
| α, β, γ-HBCD | Landfill leachate | LLE using DCM<br>SPE<br>Abselut Nexus | – | LC-ESI-MS/MS | Develosil C30-UG-5 (150 mm×2 mm) | **ESI**(–) A: ACN B: $H_2O$ | NR | [368] |
| APEO, APEC, AP, halogenated derivatives | Surface drinking, and wastewaters | SPE<br>$C_{18}$ | – | LC-ESI (NI)/APCI-MS | Lichrospher RP-18 100 (250×4 mm, 5 μm) | **ESI**(–)<br>A: MeOH<br>B: $H_2O$<br>**APCI**<br>A: MeOH/ACN (1:1) B: $H_2O$ | 5–20 μg for river sediment<br>5–25 μm for sewage sludge | [277] |
| AEO, NPEO, CDEA, LAS, NPEGNP, OP | Coastal waters | SPE<br>Lichrolut $C_{18}$ | – | LC-ESI (NI)/APCI-MS | Lichrospher RP-18 100 (250×4 mm, 5 μm) | **AEO, NPEO, CDEA APCI**<br>A: MeOH/ACN (1:1) B: $H_2O$<br>**LAS, NPEC, NP, OP**<br>**ESI**(–)<br>A: MeOH; B: $H_2O$ | 10–150 | [279] |

**Table 2** Representative methods for the determination of the selected groups of emerging contaminants in solid samples, indicating the extraction, purification procedures and detection systems

| Compounds | Matrix | Extraction method | Purification or derivatization for GC | Detection | GC/LC column | LC mobile phase | LOD | Refs. |
|---|---|---|---|---|---|---|---|---|
| MTBE, degradation products and other gasoline additives | Soil | P&T with Tenax® silica gel–charcoal at room temperature. Desorption with He at 225 °C | – | GC-EI-MS | Capillary fused silica DB-624 (75 m×0.53 mm) | | 0.01–1.44 μ/kg | [350] |
| PFOs | Sediments | 3 extractions with 90:10 (v/v) MeOH and 1% HOAc | SPE $C_{18}$ | LC-ESI-MS/MS | Targa Sprite $C_{18}$ (40×2.1 mm) | MeOH-$H_2O$ 2 mM $NH_4Ac$ | 0.04–0.07 ng/L 0.109 ng/g | [114] |
| PFOA, PFHS, *N*-MeFO, SAA, *N*-EtFOSAA, anionic, non-ionic | Sewage sludge | PLE [EtOAc/DMF (8:2), MeOH/$H_3PO_4$ (95:5), MeOH/$H_3PO_4$ (99:1), MeOH/$H_3PO_4$ (99:1)] 150 °C, 10 714 kPa | – | LC-ESI-MS | PF-$C_8$ column (150×4.6 mm) filled with spherical perfluorinated RP-$C_8$ material (5 μm) | A: MeOH B: MeOH/$H_2O$ (80:20) (2 mM diethyl ammonium) | 0.6 ng/g | [115] |
| E1, E2, α-E2, E3, MES (+BPA, NP) | River sediment | Ultrasonication (acetone/DCM, 1:1) | LLE with DCM + silica gel fractionation. Derivatization: PFPA | GC-EI-MS | HP-5MS (30 m×0.25 mm, 0.25 μm) | | 0.6–2.5 ng/g | [151] |

**Table 2** (continued)

| Compounds | Matrix | Extraction method | Purification or derivatization for GC | Detection | GC/LC column | LC mobile phase | LOD | Refs. |
|---|---|---|---|---|---|---|---|---|
| E1, E2, EE, MES | Sludge | Ultrasonication (MeOH + acetone) | GPC Biobeads SX-3<br>SPE (silica gel)<br>Derivatization: MSTFA/TMSI/ DTE (1000:2:2, v/v/w) | GC-(IT)-MS/MS | XTI-5 (30 m×0.25 mm, 0.25 μm) | | 2–4 ng/g | [149] |
| 17G, E2–3, 17diS E1, E2 | Estuary sediment | Sonication (MeOH) | SPE (Lichrolut EN + BondElut $C_{18}$) + NP-LC fractionation | LC-ESI (NI)-TOF-MS | Betasil C18 (150×2.1 mm, 3 μm, Keystone Scientific) | A: AcN<br>B: $H_2O$ | 0.03–0.04 ng/g | [152] |
| E1, E2, E3, EE, DES (+ progestins) | River sediment | Sonication (acetone: methanol, 1:1) | SPE ($C_{18}$) | LC-ESI (NI)-MS | Lichrospher 100 RP-18 (250×4 mm, 3 μm, Merck) | A: AcN<br>B: $H_2O$ | 1–2 ng/g | [153] |
| Tetracycline, macrolide and sulphonamide antibiotics | Agricultural soils | PLE MeOH/citric acid (1:1, v/v) adjusted to pH = 4.7 with NaOH | Dilute PLE extracts to MeOH content < 10%. Purification with SAX-Oasis HLB in tandem | LC-ESI (PI)-MS/MS | X-terra MS-$C_{18}$ (100×2.1 mm, 3.5 μm, Merck) | A: MeOH<br>B: Aq. formic acid | 8–22 μg/L | [194] |

**Table 2** (continued)

| Compounds | Matrix | Extraction method | Purification or derivatization for GC | Detection | GC/LC column | LC mobile phase | LOD | Refs. |
|---|---|---|---|---|---|---|---|---|
| Tetracycline, sulphonamides, fluoro-quinolone antibiotics and trimethoprim | Arable soils fertilized with manure | **TCs, SAs and TMP** MeOH/EDTA-McIlvaine buffer pH = 6 (90:10, v/v) **FQs** AcN acidified with 2% HCOOH | **TCs, SAs and TMP** SPE $C_{18}$ **FQs** LLE with hexane | **TCs, SAs and TMP** LC-ESI (PI) MS/MS **FQs** LC-ESI (PI) MS | **TCs, SAs and TMP** Luna (Phenomenex) $C_8$ (150×2 mm, 5 μm) **FQs** Luna (Phenomenex) $C_8$ (150×3 mm, 5 μm) | **TCs, SAs and TMP** A: ACN B: $H_2O$ C: 0.5% HCOOH 10 mM $NH_4OAc$ **FQs** A: ACN 0.01% HCOOH B: $H_2O$ 0.01% HCOOH | 1.6–18 (ng/mL) | [369] |
| Analgesics and anti-inflammatories, lipid regulators, antibiotics and ivermectin | River sediment | Ultrasound **Acidic compounds** Acetone/HAc (20:1, v/v) + ethyl acetate **Antibiotics** MeOH/acetone + ethyl acetate | Dilute extracts **Acidic compounds** Acidify at pH = 2 SPE Oasis MCX **Antibiotics** Acidify at pH = 3 SPE Lichrolut EN + $C_{18}$ **Ivermectin** | **Acidic compounds** LC-ESI (NI) MS/MS **Antibiotics** LC-ESI (PI) MS | All compounds Lichrospher RP-18 (125×3 mm, 5 μm, Merck) | **Acidic compounds** A: ACN B: $H_2O$ pH = 2.9 (with HAc) **Antibiotics** A: Eluent B + AcN B: 20 mM $NH_3$ at pH = 5.7 with HAc | **Acidic compounds** 0.4–20 ng/g **Antibiotics** 3–20 ng/g | [195] |

**Table 2** (continued)

| Compounds | Matrix | Extraction method | Purification or derivatization for GC | Detection | GC/LC column | LC mobile phase | LOD | Refs. |
|---|---|---|---|---|---|---|---|---|
| | | | Add $NH_4Ac$ buffer<br>SPE Lichrolut EN | | | **Ivermectin**<br>A: ACN 10% B<br>B: 15 mM $NH_4$ AC + HAc (pH = 4) | | |
| All musks and metabolites (except DPMI) | Activated sludge | LLE with hexane | Silica purification | GC-MS/MS<br>GC-EI-MS | DB-1 (60 m×0.25 mm, 0.25 μm) | | NR | [265, 370] |
| HHCB, AHTN, ATII, ADBI, AHMI, DPMI, MX, MK, MA, MM, MT | Digested sludge | Dried with sodium sulphate<br>Soxhlet extraction with DCM<br>Sulphur removed with copper in flask during extraction | Silica/alumina purification (layered)<br>SEC (Bio Beads S-X3)<br>Silica/alumina purification | GC-EI-MS | HP-5MS (30 m×0.25 mm) | | NR | [261] |
| All musks | Sludge | SFE with acetone/DCM (1:1) | Silica purification<br>Sulphur removed with copper | GC-NCI/MS<br>GC-EI-MS | HP-5MS (30 m×0.25 mm, 0.25 μm) | | NR | [371] |

**Table 2** (continued)

| Compounds | Matrix | Extraction method | Purification or derivatization for GC | Detection | GC/LC column | LC mobile phase | LOD | Refs. |
|---|---|---|---|---|---|---|---|---|
| Mono-hepta-BDEs (39 compounds) | Marine and river sediment | PLE (Cu + $Al_2O_3$ 1:2) using DCM:C6 (1:1) as solvent | – | GC-NCI-MS | HP-5MS (30 m×0.25 mm, 0.25 $\mu$m) | | 1–46 pg/g | [326] |
| α, β, γ-HBCD | Sediments | Soxhlet (acetone:C6, 3:1) | LLE with $H_2SO_4$ + GP + $SiO_2$ | LC-ESI (**NI**) MS | Luna $C_{18}$ (150×2 mm, 5 μm, Merck) | A: AcN + 10 mM $NH_4OAc$ B: $H_2O$ + 10 mM $NH_4OAc$ | NR | [372] |
| Di-hexa BDEs + deca-BDEs (14 compounds) | Sewage sludge | PLE (DCM:C6, 1:1) | $H_2SO_4$ + $SiO_2$ $H_2SO_4$ + $Al_2O_3$ | **Di-hexa BDE:** GC-MS/MS **Deca-BDE:** GC-NCI-MS | NR | | NR | [373] |
| Mono-deca BDEs (40 compounds), total HBCD | Fish tissue | PLE ($Al_2O_3$, DCM:C6, 1:1) | – | GC-NCI-MS | HP-5MS (30 m×0.25 mm, 0.25 μm) | | 2–19 pg/g (wet-weight) | [306] |
| Tri-deca BDEs (27 compounds) | Fish tissue | PLE (DCM) | GPC + $SiO_2$ | GC-NCI-MS | NR | | NR | [374] |
| Non-ionic surfactants, NPEO, AEO, CDEA | Sewage sludge | Sonication (DCM/MeOH, 3:7) | SPE $C_{18}$ | LC-ESI (NI)/APCI-MS | Lichrospher RP-18 100 (250×4 mm, 5 μm) | **ESI** (–) A: MeOH B: $H_2O$ **APCI** A: ACN B: $H_2O$ | 5–25 μg/kg | [277] |

**Table 2** (continued)

| Compounds | Matrix | Extraction method | Purification or derivatization for GC | Detection | GC/LC column | LC mobile phase | LOD | Refs. |
|---|---|---|---|---|---|---|---|---|
| APEO, APEC, AP, halogenated derivatives | River sediment, sludge | Sonication (DCM/MeOH, 3:7) | SPE $C_{18}$ | LC-ESI (NI)/APCI-MS | Lichrospher RP-18 100 (250×4 mm, 5 μm) | **ESI(–)** A: MeOH B: $H_2O$ **APCI** A: MeOH/ ACN (1:1) B: $H_2O$ | 20–100 μ/kg | [277] |
| Ionic surfactants LAS, SPC | Marine sediment | Soxhlet (MeOH) | SPE $C_{18}$ | LC-FL | Lichrosorb RP-18 (250×4.6 mm, 10 μm) | A: MeOH/$H_2O$ (80:20) with 1.25 mM tetraethyl-ammonium B: $H_2O$ | 5–10 μ/kg | [375] |

### 4.1.3 Instrumental Analysis

Fluorinated surfactants can be detected by $^{19}F$ NMR, gas and liquid chromatography–mass spectrometry and liquid chromatography coupled to tandem mass spectrometry [105], the latter two being the most widely employed.

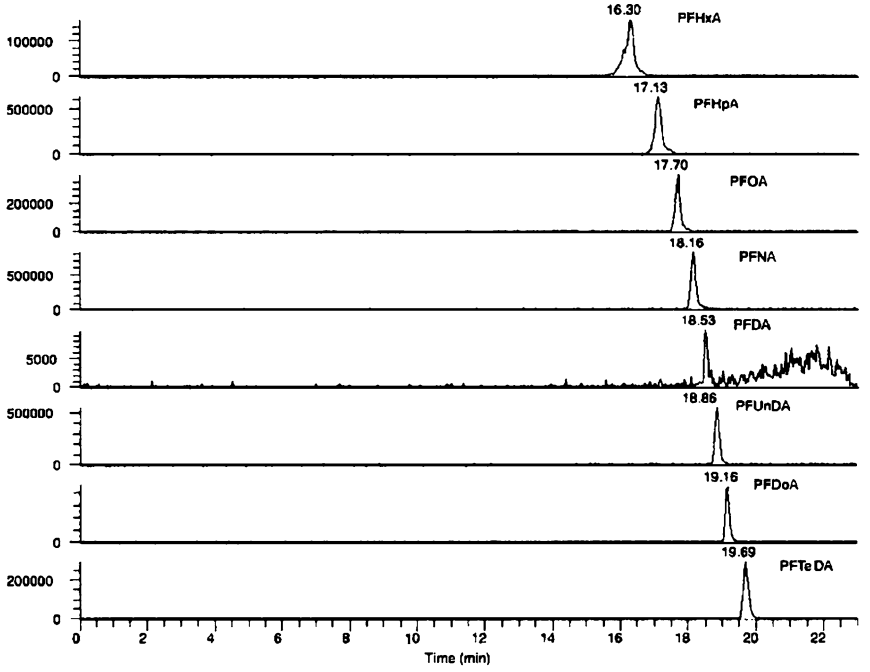
$^{19}F$ NMR spectroscopy is a non-specific method, as it determines the presence of $CF_2$ and $CF_3$ moieties [116, 117]. Moody et al. [117] compared the results achieved by this technique with LC-MS/MS, showing discrepancies between the two methods. With $^{19}F$ NMR the total content of perfluorinated compounds was higher than that calculated by LC-MS/MS, attributed to the presence of other surfactants in the samples which yielded a similar $^{19}F$ NMR spectrum to perfluoroalkanesulphonates and perfluorocarboxylates [105].

Gas chromatography–mass spectrometry can be used for the direct determination of neutral and volatile FASs, such as sulphonamides or fluorotelomer alcohols, which have high vapour pressures [105]. Perfluorocarboxylates have been quantitatively determined by GC-MS after derivatization of the carboxylates to their methyl esters [116, 117]. However, PFOs was not able to be detected by such a method [117]. Although perfluoroalkane sulphonate esters may be formed during the derivatization step, the esters are unstable because of the excellent leaving group properties of perfluoroalkane sulphonates [105]. Thus, despite the fact that some fluorinated surfactants can be analysed by GC-MS, this technique is not so useful for multi-residue analysis of all groups of PFAs [105]. The drawbacks offered by both $^{19}F$ NMR and GC-MS and the multiple advantages presented by LC-MS and LC-MS/MS, in terms of sensitivity and selectivity, have made these techniques the preferred tools for the instrumental analysis of PFAs in environmental samples. Other detectors coupled to LC include fluorescence detection for the determination of perfluorocarboxylic acids [118], ion-exclusion chromatography with conductimetric detection for perfluorocarboxylic acid and perfluorosulphonates [119, 120] and LC with conductimetric detection for perfluorosulphonates [121].

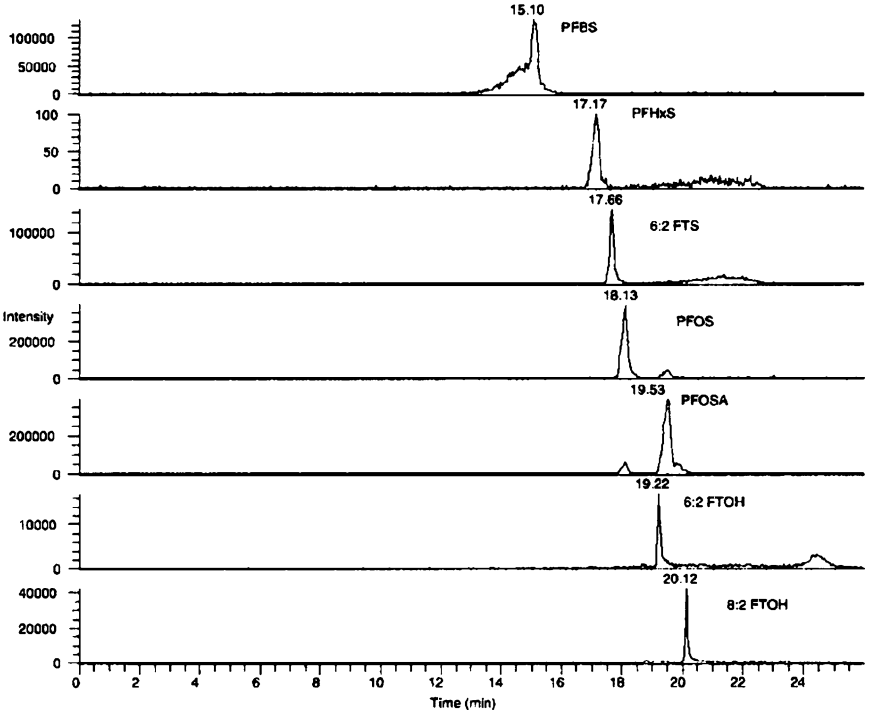
Electrospray ionization (ESI) working in the negative ion (NI) mode is the interface most widely used for the determination of anionic perfluorinated surfactants. APCI is not suitable for the determination of PFOs due to their ionic nature. The ESI interface has also been optimized for the determination of neutral compounds, such as the sulphonamides PFOSA, Et-PFOSA and *t*-Bu-PFOs [122]. Takino et al. [110] developed a method based on an APPI interface, which would alleviate matrix effects found with ESI interfaces.

Chromatographic separation of fluorinated compounds has been mainly carried out using both RP-$C_{18}$ and RP-$C_8$ materials. However, RP-$C_{18}$ presented some interferences, enhancing analyte signals and, therefore, the

**Fig. 3** LC-ESI(NI)-MS chromatograms obtained in the SIM mode for a standard solution containing **a** perfluorocarboxylic acids and **b** sulphonates and neutral FASs. Reprinted with permission from [376] ▶


16.30
PFHxA
100000
0
17.13
PFHpA
500000
0
17.70
PFOA
200000
0
18.16
PFNA
500000
0
18.53
PFDA
5000
0
18.86
PFUnDA
500000
0
19.16
PFDoA
0
19.69
PFTeDA
200000
0
0 2 4 6 8 10 12 14 16 18 20 22
Time (min)

a


15.10
PFBS
100000
50000
0
17.17
PFHxS
100
50
0
17.66
6:2 FTS
100000
0
18.13
PFOS
Intensity
200000
0
19.53
PFOSA
200000
0
19.22
6:2 FTOH
10000
0
20.12
8:2 FTOH
40000
20000
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (min)

b

RP-$C_8$ ones are more recommended. Nevertheless, using RP-$C_{18}$ branched isomers can be distinguished, while RP columns with shorter alkyl chains ($C_8$) are not so efficient. This effect can be minimized by increasing the LC column temperature from 30 to 40 °C [110, 112, 123]. Comparison of the retention times of a $C_8$ column and an end-capped $C_8$ one indicated that the interaction of FASs with the residual silanol groups in the non-end-capped column played an important role in providing a good separation of the analytes [115].

Moreover, in reversed-phase LC columns, the FAS standards display a characteristic chromatographic pattern with two unresolved signals or shoulders adjacent to the major signal (see Fig. 3). This is due to the fact that most commercially available standards are mixtures of linear and branched isomers (approximately 70% linear), which contain impurity isomers with the same alkyl chain lengths. It is assumed that the response factor for branched and linear isomers is equivalent and that the standard mixtures are representative of those identified in the samples [124]. Regarding mobile phases, mixtures of acetonitrile–water and methanol–water, often modified with ammonium acetate (1.0–20 mM) are the ones most commonly employed.

In the fragmentation pattern of FASs, the deprotonated molecules $[M - H]^-$ are the predominant ions. Typical ions and fragmentations monitored for PFOs and related substances correspond to $[SO_3]^-$, $[FSO_3]^-$ and $[M - SO_3]^-$ ions. For PFOSA and PFOA, $[SO_2N]^-$ and $[MCOOH]^-$ ions are the most abundant ones, respectively [105].

## 4.2
## Steroid Estrogens, Pharmaceuticals and Personal Care Products

### 4.2.1
### Steroid Estrogens (Hormones and Contraceptives)

Estrogens have often been identified as the compounds responsible for the estrogenic effects that have been observed in different wildlife species, such as intersex in carp, high levels of plasma vitellogenin in fish, etc. [125].

Chemical analysis has focused on the investigations of free estrogens, both natural (estradiol, estrone and estriol) and synthetic (basically ethynyl estradiol, mestranol and diethylstilberol). In contrast, conjugated estrogens and halogenated derivatives have been seldom studied, maybe due to their lower estrogenic effect and recent identification.

#### 4.2.1.1
#### Sample Preparation

There are multiple reviews devoted to the analysis of esteroid estrogens in environmental samples [25, 126–133]. An important precaution that should be

taken into account when analysing steroid estrogens in tap water, or water samples that could contain chlorine, is the addition of sodium thiosulphate immediately after collection in order to avoid losses of target analytes [134].

Extraction of estrogens from water samples has usually been carried out by off-line SPE using either disks or, most frequently, cartridges (see Table 1), with octadecyl $C_{18}$-bonded silica, polymeric graphitized carbon black (GCB) and Oasis HLB being the most widely employed cartridges [134–136]. On the other hand, many works are based on the use of on-line SPE [129, 137, 138], using the same extraction materials as indicated for off-line SPE. To elute compounds trapped in the SPE cartridges, methanol is the solvent generally used. However, Isobe et al. [136] determined that adding 5 mM of TEA to 10 mL of methanolic solution, as an ion pair reagent, improved the efficiency of elution, thus achieving higher recoveries for conjugates which were not effectively removed by only using methanol.

Other widely employed materials to isolate steroid estrogens from water samples are molecularly imprinted polymers (MIPs) [25, 38, 139]. Some recent works have also proposed the use of SPME, using fibre and in-tube SPME, in combination with either LC or GC instruments [140, 141, 143].

As concerns the determination of esteroid estrogens in solid samples, the analytical methods are generally adapted from those developed for water samples, incorporating additional purification steps of crude extracts prior to instrumental analysis [144]. Extraction techniques more commonly used are pressurized liquid extraction (PLE) [145, 146], microwave-assisted extraction (MAE) [147] and, more frequently, ultrasonication [148–153], using methanol [148, 152], methanol/acetone [145, 146, 149, 153], acetone/dichloromethane [151], ethyl acetate [154, 155] or dichloromethane/water [150] as extraction solvents. Some of the most representative methods are summarized in Table 2.

Purification of extracts is generally carried out by liquid–liquid extraction (LLE) [156–158], HPLC fractionation [156, 159–162], gel permeation chromatography (GPC) [158], immunoaffinity (IA) extraction [25] or SPE using Florisil [136, 157], $C_{18}$ sorbents [132, 156, 159, 160], silica gel [163–169] and restricted access materials (RAMs).

#### 4.2.1.2 Instrumental Analysis

In the past, the techniques most commonly used for the environmental analysis of estrogens have been immunoassays and, to a greater extent, GC-MS. The former are simple and sensitive but they can have false positive results due to the influence of coexisting materials present in the sample matrix. On the other hand, GC-MS and GC-MS/MS are also highly sensitive methods, but derivatization is required prior to analysis [141]. Moreover, these methodologies are mainly based on the determination of unconjugated (i.e. free)

estrogens, unless intermediate hydrolysis steps are performed [136, 170]. LC-MS and especially LC-MS/MS are the preferred tools nowadays [171, 172], which allow the determination of both conjugated and free estrogens without derivatization and hydrolysis.

Enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA) are by far the most common *bioassays* used for the determination of estrogens. Several recent works have reported their application in the analysis of estrogens in environmental matrices, such as water [173–176], sludge and manure, although they have been more extensively used for the analysis of biological samples in clinical studies. Their main advantages are ease of use, relatively simple protocol and fairly good sensitivity. Bioassays are also used to measure the estrogenic (endocrine disrupting) activity of sample extracts or of chemicals. The in vitro and in vivo assays available for this purpose have been recently reviewed [177, 178]. Many bioassays show potential for development as biosensors [179, 180].

On the other hand, GC separation has been performed with a variety of capillary columns (DB5-MS, XTI-5, HP Ultra II, etc.), using helium as carrier gas. Both conventional MS and MS/MS detection have been accomplished in most instances in the electron impact (EI) mode at 70 eV. The use of negative ion chemical ionization (NICI) has been reported on fewer occasions [134, 165, 181–184]. However, it has been observed that the highest sensitivity for the GC-NICI-MS methods is obtained when estrogens have pentafluorobenzyl (PFB) [181, 182], pentafluorobenzoyl [184, 185] and other fluorine-containing derivatives.

Derivatization is generally carried out in the –OH groups of the steroid ring, performed by silylation with reagents such as *N*,*O*-bis(trimethylsilyl)-acetamide (BSA), *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA), *N*,*O*-bis(trimethylsilyl)-trifluoroacetamide (BSTFA), or *N*-(*tert*-butyldimethylsilyl)-*N*-methyltrifluoroacetamide (MTBSTFA), which lead to the formation of trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (TBS) derivatives [186]. Some authors reported breakdown of some TMS derivatives with various solvent–reagent combinations, pyridine and dimethylformamide being the most suitable ones [186–188].

LC has been performed by octadecyl silica stationary phases. As mobile phases, mixtures of water/methanol and, more frequently, water/acetonitrile have normally been used, sometimes with added modifiers such as 0.1% acetic acid, 0.2% formic acid or 20 mM ammonium acetate. The interfaces most widely employed are electrospray ionization (ESI) in the negative ion (NI) mode and, to a lesser extent, atmospheric pressure chemical ionization (APCI) in the positive ionization (PI) mode. These API interfaces have been applied in a variety of MS analysers, including quadrupole, ion-trap, orthogonal-acceleration time-of-flight (oaTOF), and combinations of them. Single and triple quadrupole analysers have been the most widely used for the analysis of estrogens, the latter being preferred nowadays. Some works

**Table 3** MRM transitions monitored for the determination of steroid estrogens and pharmaceuticals in environmental samples using LC-ESI-MS/MS (QqQ) instruments

| Group of substances | Compound | MRM 1 | MRM 2 |
|---|---|---|---|
| Steroid estrogens | Estriol | 287>171<br>Loss of $C_6H_{12}O_2$ | 287>145<br>Loss of $C_8H_{14}O_2$ |
| | Estradiol | 287>145<br>Loss of $C_8H_{14}O$ | 281>183<br>Loss of $C_5H_{12}O$ |
| | Estrone | 269>145<br>Loss of $C_8H_{12}O$ | 269>143<br>Loss of $C_8H_{14}O$ |
| | Ethynyl estradiol | 295>145<br>Loss of $C_9H_{12}O$ | 295>159<br>Loss of $C_{10}H_{14}O$ |
| *Anti-inflammatory/ analgesic/antiphlogistic* | Ibuprofen | 205>161<br>Loss of $CO_2$ | – |
| | Ketoprofen | 253>209<br>$[M\text{-}H\text{-}CO_2]^-$ | 253>197 |
| | Naproxen | 229>185<br>$[M\text{-}H\text{-}CO_2]^-$ | 229>170<br>$[M\text{-}H\text{-}C_3H_2O_2]^-$ |
| | Indomethacin | 356>312<br>$[M\text{-}H\text{-}CO_2]^-$ | 356>297<br>$[M\text{-}H\text{-}C_3H_2O_2]^-$ |
| | Diclofenac | 294>250<br>$[M+H\text{-}H_2O]^+$ | 294>214 |
| | Acetaminophen | 152>110<br>Loss of $CH_2CO$<br>150>107<br>Loss of $COCH_3$ | 152>93<br>– |
| | Fenoprofen | 241>197 | 241>93 |
| | Mefenamic acid | 240>196<br>Loss of $CO_2$ | 240>180<br>$[M\text{-}H\text{-}CO_2\text{-}CH_3]^-$ |
| | Propyphenazone | 231>189<br>$[M\text{-}C_3H_7+H]^+$ | 231>201 |
| | Phenylbutazone | 309>160<br>$[M\text{-}(C_6H_5\text{-}N\text{-}(C_4H_9)]^+$<br>362>276 | 309>181<br>362>316 |
| *Lipid regulating agents* | Bezafibrate | 360>274<br>Loss of $C_4H_6O_2$ | 360>154<br>Loss of $C_{12}H_{14}O_3$ |
| | Clofibric acid | 213>127<br>$[C_6O_4ClO]^-$ | 213>85 |
| | Gemfibrozil | 249>121<br>$[M\text{-}H\text{-}C_7H_{12}O_2]^-$ | – |
| *Psychiatric drugs* | Carbamazepine | 237>194<br>Loss of HNCO | 237>192 |
| | Fluoxetine | 310>44<br>$[M\text{-}F_3C_7H_4OC_8H_8]^+$ | 310>148<br>$[M\text{-}F_3C_7H_4O]^+$ |
| | Paroxetine | 330>192<br>$[M\text{-}C_7H_5NO_3]^+$ | 330>123<br>$[M\text{-}C_{12}H_4NOF]^+$ |
| | Diazepam | 285>257<br>$[M\text{-}CO+H]^+$ | 285>154 |

**Table 3** (continued)

| Group of substances | Compound | MRM 1 | MRM 2 |
|---|---|---|---|
| *Macrolide antibiotics* | Erythromycin-$H_2O$ | 716>522 $[M\text{-}DS\text{-}2H_2O+H]^+$ | 716>558 $[M\text{-}DS\text{-}H_2O+H]^+$ |
| | Clarythromycin | 750>116 $[CL\text{-}OCH_3+H]^+$ | 750>592 $[M\text{-}DS+H]^+$ |
| | Roxythromycin | 838>158 $[DS+H]^+$ | 838>680 $[M\text{-}DS+H]^+$ |
| | Oleandomycin | 689>545 [M-oleandrose+H]$^+$ | 689>158 $[DS+H]^+$ |
| | Tylosin | 916>723 $[M\text{-}MY+H]^+$ | 916>174 $[DS\text{-}O\text{-}MY+H]^+$ |
| *Tetracycline antibiotics* | Chlortetracycline | 479>444 | 479>462 |
| | Doxycycline | 445>428 | 445>410 |
| | Oxytetracycline | 461>426 | 461>443 |
| | Tetracylcline | 445>410 $[M\text{-}H_2O\text{-}NH_3+H]^+$ | 445>427 $[M\text{-}H_2O+H]^+$ |
| *Quinolone antibiotics* | Ciprofloxacin | 332>314 $[M\text{-}H_2O+H]^+$ | 332>288 $[M\text{-}H_2O\text{-}CO_2+H]^+$ |
| | Ofloxacin | 362>344 $[M\text{-}H_2O+H]^+$ | – |
| | Norfloxacin | 320>302 $[M\text{-}H_2O+H]^+$ | 320>302 $[M\text{-}CO_2+H]^+$ |
| | Enrofloxacin | 360>342 $[M\text{-}H_2O+H]^+$ | 360>316 $[M\text{-}CO_2+H]^+$ |
| *Sulphonamide antibiotics* | Sulphamethoxazole | 254>156 $[H_2NPhSO_2]^+$ | 254>92 $[H_2NPhO]^+$ |
| | Sulphamethazine | 279>186 $[M\text{-}H_2NPh]^+$ | 279>124 [aminodimethyl-pyridine+H]$^+$ |
| | Sulphadiazine | 251>156 $[H_2NPhSO_2]^+$ | 251>108 $[H_2NPhO]^+$ |
| *Penicillins* | Dicloxacillin | 487>160 $[F1+H]^+$ | 487>311 $[F2+H]^+$ |
| | Nafcillin | 432>171 [ethoxynaphthyl]$^+$ | 432>199 [ethoxynaphtyl-carbonyl]$^+$ |
| | Amoxycillin | 366>208 $[M\text{-}NH_3+H]^+$ | 366>113 $[F1+H]^+$ |
| | Oxacillin | 419>144 [phenylisoxazolyl+H]$^+$ | 419>243 [aminodimethyl-pyridine+H]$^+$ |
| | Penicillin G | 352>160 $[F1+H]^+$ | 352>176 $[F2+H]^+$ |
| | Penicillin V | 368>114 $[F1\text{-}CO_2+H]^+$ | 368>160 $[F1+H]^+$ |

**Table 3** (continued)

| Group of substances | Compound | MRM 1 | MRM 2 |
|---|---|---|---|
| *Other antibiotics* | Chloramphenicol | 323>152 [nitrobenzyl alcohol carbanion]$^-$ | 323>176 [194-$H_2O$]$^-$ |
| | Trimethoprim | 291>230 [M-2$CH_3O$]$^+$ | 291>213 [M-trimethoxy-phenyl]$^+$ |
| β-blockers | Atenolol | 267>190 [M-$H_2O$-$NH_3$-isopropyl+2H]$^+$ | 267>145 [190-CO-$NH_3$]$^+$ |
| | Sotalol | 273>255 [M-$H_2O$+H]$^+$ | 273>213 [M-$C_3H_9N$+H]$^+$ |
| | Metoprolol | 268>133 [$C_6H_{15}NO_2$]$^+$ | 268>159 [$C_8H_{17}NO_2$]$^+$ |
| | Propranolol | 260>116 [(*N*-isopropyl-*N*-2-hydroxypropyl-amine)+H]$^+$ | 260>183 |
| *Other drugs* | Salbutamol | 240>166 [M+H-$(CH_3)$2C-$CH_2$-$H_2O$]$^+$ | 240>148 [166-$H_2O$]$^+$ |
| | Ranitidine | 315>176 [M-$C_8H_{12}NO$]$^+$ | 315>130 [M-$C_8H_{12}NO$-$NO_2$]$^+$ |
| | Omeprazole | 346>136 [M-$H_3CO$-($C_7H_4N_2$)-SO-$CH_2$]$^+$ | 346>198 [M-$H_3CO$-$C_7H_4N_2$]$^+$ |

are available using Q-TOF analysers [152], but this technique has not been routinely employed yet.

In most cases, the base peak selected for quantitation of estrogens in SIM and MRM modes, when operating with an ESI (NI) and APCI (PI) interface, corresponds to the deprotonated molecule $[M-H]^-$ and to the $[M+H-H_2O]^+$ ion ($[M+H]^+$ for estrone). In Table 3, the most common fragmentations monitored in LC-MS/MS analysis, using triple quadrupole instruments, are summarized for the most studied steroid estrogens.

### 4.2.2 Pharmaceuticals

A large number of reports and reviews are devoted to the occurrence, fate and risk assessment of pharmaceuticals in the environment [92, 93, 127, 189–

193]. While their occurrence in the aquatic environment has been extensively studied, data regarding their presence in solid samples are still scarce, veterinary antibiotics being the ones most commonly investigated in such matrices [194–199].

Most of the analytical methods available in the literature are focused on the analysis of particular therapeutic groups. However, the general trend in recent years is the development and application of generic methods that permit simultaneous analysis of multiple-class compounds [2, 99, 200–209]. Multi-residue methods provide wider knowledge about their occurrence, necessary for further understanding of their removal, partition and ultimate fate in the environment. Nevertheless, simultaneous analysis of compounds from diverse groups with different physico-chemical properties requires a compromise in the selection of experimental conditions for all analytes studied.

#### 4.2.2.1 Sample Preparation

In such multi-residue methods, simultaneous extraction of all target analytes in one single SPE step from water samples is the approach most widely employed [190]. Another option consists of the combination of two SPE materials operating either in series or classifying target compounds into two or more groups, according to their physico-chemical properties [190]. In both situations Oasis HLB or $C_{18}$ cartridges are the most widely employed materials for pre-concentration and extraction of target compounds. For the former, neutral sample pH is advisable to achieve good recoveries for all compounds, whereas for $C_{18}$, sample pH adjustment prior to extraction is required depending on the acidic, neutral or basic nature of the analytes. The less common cartridges employed are Lichrolut ENV+, Oasis MCX and StrataX. While these materials generally need sample pH adjustment and sometimes special elution conditions (mixtures of methanol/ammonia, acidified or basified methanol), Oasis HLB provides good performances at neutral sample pH and elution with pure organic solvents, generally methanol (see Table 2).

When these methods include the determination of antibiotics, some precautions have to be taken into account during the analytical procedure. As tetracycline, sulphonamides and polypeptide antibiotics form complexes with metal ions, the addition of some chelating agent before SPE, such as $Na_2EDTA$, is recommended to avoid important losses during analysis. When analysing tetracycline, it should be highly recommended to use PTFE instead of glass materials, since they tend to bind to the glass, resulting in significant losses [93, 189, 190]. Additional problems are the formation of keto–enol tautomers in alkaline aqueous solutions [210] and the formation of 4-epimer isomers in acidic ones [211]. For this reason, it is advisable to work at neutral sample pH.

MIPs and immunosorbents could be a useful tool to provide high selectivity for target analytes when performing single group analysis. Although these materials have been widely employed to selectively isolate clenbuterol, aniline β-agonists, tetracycline and sulphonamide antibiotics, β-agonists and β-antagonists from biological samples, few applications have been reported for environmental matrices [212–215].

With regard to their analysis in solid samples, most of the methods available in the literature are based on sonication and PLE as the extraction technique followed by a clean-up procedure. The extraction solvents used generally consist of pure organic solvents, such as methanol and acetonitrile, or mixtures of polar solvents with water, acidified water (acetic acid, orthophosphoric acid), or buffers (citric acid) in different proportions. An important issue to consider is that when extracting tetracycline and macrolide antibiotics by PLE, temperature control is required, since temperatures higher than room temperature can cause their transformation into epi- or anhydrous forms for TCs. Moreover, values higher than 100 °C promote the degradation of macrolides [127].

For the extraction of tetracycline antibiotics, special precautions have to be taken into account. As they tend to form complexes with metal ions, extraction solvents consist of mixtures with organic solvent, generally methanol, with citric acid and McIlvaine buffer (mixture of citric acid with $Na_2HPO_2$), also containing $Na_2EDTA$ [194].

After extraction, a purification step is required and is generally performed by SPE, using the same cartridges and conditions as the analysis of pharmaceuticals in water samples. Sample extracts are therefore diluted with an appropriate volume of MilliQ water, until the organic solvent content is below 10%, in order to avoid losses of target compounds during SPE [194]. Cartridges mainly used consist of Oasis HLB (see Table 2). However, some authors use either SAX or MCX [189] cartridges in tandem with the polymeric Oasis HLB [194], in order to remove negatively charged humic material (in the SAX material) and organic matter (in the MCX cartridge), and therefore selectively retain target compounds in the Oasis HLB material. When SAX cartridges are employed, samples are acidified at pH values ranging from 2 to 3 to ensure an efficient removal of the humic material (see Table 2).

Elution of target compounds from SPE cartridges is achieved with a large variety of organic solvents, according to the physico-chemical properties of the compounds analysed, methanol and acetonitrile being the most common ones (see Tables 1 and 2).

#### 4.2.2.2 Instrumental Analysis

LC-MS/MS is the instrumental method of choice due to its versatility, specificity and selectivity, replacing GC-MS and LC-MS [190]. GC-MS can only

be successfully applied for a limited number of non-polar and volatile pharmaceutical compounds, requiring a time-consuming derivatization step for the determination of polar pharmaceuticals [216–219]. Among LC-MS/MS techniques, triple quadrupole (QqQ) and ion trap (IT) instruments are in common use [92], the former being the most widely used, working in selected reaction monitoring (SRM) mode and typically reaching ng/L detection limits. More recent approaches in LC-MS/MS are linear ion traps (LITs), new generation triple quadrupoles, and hybrid instruments, such as quadrupole–time of flight (QqTOF) and quadrupole–linear ion trap (QqLIT) [92, 220].

The main applications of QqTOF instruments are focused on the elucidation of structures proposed for transformation products or are used as a complementary tool to confirm positive findings obtained by a QqQ screening method. Recently, Eichhorn et al. [221] reported on the structural elucidation of the metabolites of the antimicrobial trimethoprim. Stolker et al. [203], Marchese et al. [222], Petrovic et al. [93] and Gómez et al. [223] used QqTOF to identify the presence of various pharmaceuticals in environmental waters. Recently, Pozo et al. [224] evaluated the potential of a QqTOF instrument to confirm positive findings in the analysis of penicillin and quinolone antibiotics in surface and ground water samples. An example of the analysis of selected pharmaceuticals in an urban wastewater by UPLC-QqTOF-MS is shown in Fig. 4.

As concerns QqLIT, Seitz et al. [225] developed a method for the determination of diclofenac, carbamazepine and iodinated X-ray contrast media using direct analysis (among other contaminants), reaching LODs of 10 ng/L. Nikolai et al. [226] used QqLIT operating in QqQ mode for stereoisomer quantification of β-blockers in wastewater. On the other hand, Gros et al. [212] developed an analytical methodology for trace analysis of eight β-blockers in wastewaters using MIPs for pre-concentration of target compounds combining different functions of QqQ. Quantitative analysis was performed using a 4000QTRAP tandem mass spectrometer in SRM mode. Using the information-dependent acquisition (IDA) function in the software, a large amount of data for unequivocal identification and confirmation of the target compounds were generated at high sensitivity. An example of an IDA experiment for the determination of atenolol in an influent wastewater sample is shown in Fig. 5.

Regarding LC, reversed-phase LC is mainly used, $C_{18}$ columns being the preferred ones. Only one method, targeted to acidic drugs, was based on ion-pair reversed-phase LC with a Phenyl–Hexyl column [227]. As mobile phases, acetonitrile, methanol, or mixtures of both solvents are normally used. In order to improve the sensitivity of MS detection and give an efficient retention, mobile phase modifiers, buffers and acids are widely employed, with ammonium acetate, tri-*n*-butylamine (TrBA), formic acid and acetic acid being the more common ones. Typical concentrations of salts range from 2 to

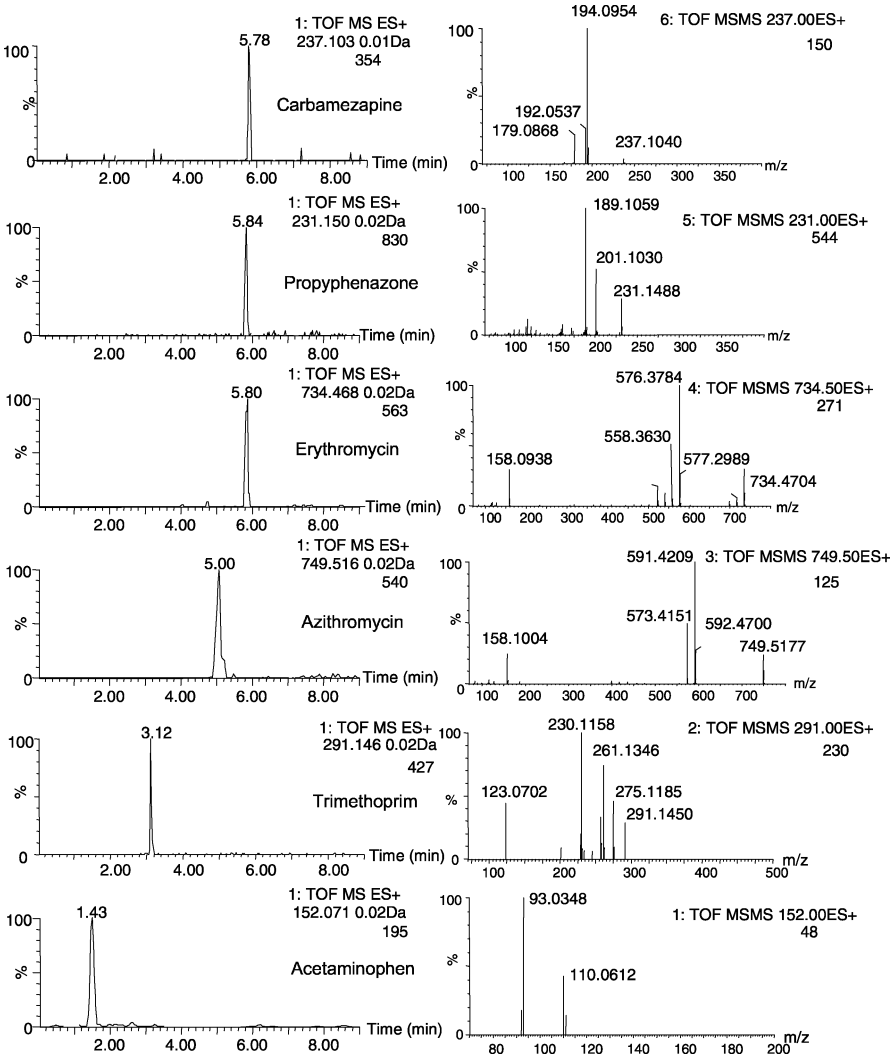



**Fig. 4** Confirmation of several pharmaceuticals in an urban wastewater. *Left panel*: narrow window extracted ion chromatograms (nwXICs) of $[M+H]^+$ obtained in the TOF mode for $m/z$ 152.071 (acetaminophen), $m/z$ 291.146 (trimethoprim), $m/z$ 749.516 (azithromycin), $m/z$ 734.468 (erythromycin), $m/z$ 231.150 (propyphenazone) and $m/z$ 237.103 (carbamazepine). *Right panel*: product ion spectra obtained in the Q-TOF mode

20 mM, since it has been observed that higher concentrations could lead to a reduction of signal intensities [190].

Shortening the analysis time is important for attaining the high sample throughput often required in monitoring studies. This can be achieved by

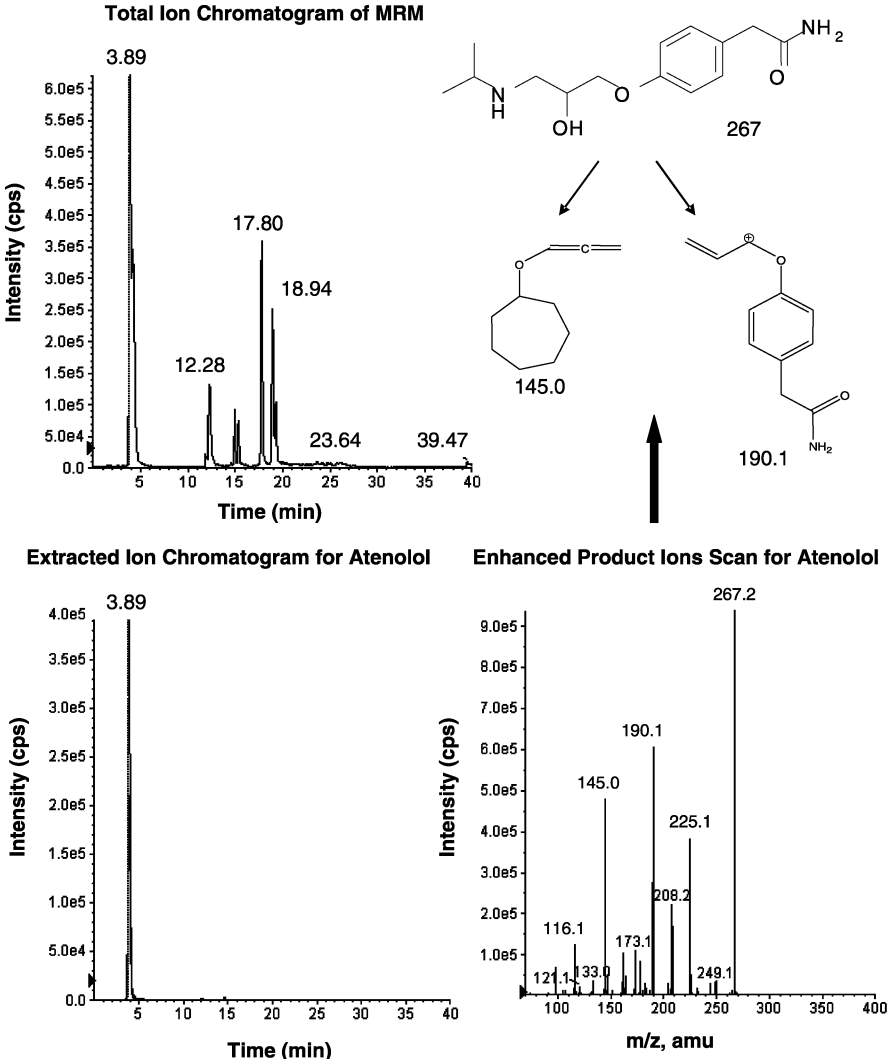



**Fig. 5** Information-dependent acquisition (IDA) experiment for the determination of atenolol in an influent wastewater sample

using short columns and increased flow velocity, decreasing the particle size of stationary phases or increasing temperature. These approaches are applied in two newly developed instruments, UPLC (ultra-performance LC) and by RRLC (rapid resolution LC). For the moment, only one publication presented by Petrovic et al. [93] describes the use of UPLC coupled to a QqTOF system for the multi-residue analysis of 29 pharmaceuticals in environmental waters. Compounds more frequently detected in multi-residue methods and their MRM transitions are summarized in Table 3.

### 4.2.3
### Personal Care Products (PCPs)

This group of compounds includes synthetic musk fragrances (nitro and polycyclic musk fragrances), antimicrobials (triclosan and its metabolites and triclocarban), sunscreen agents (ultraviolet filters), insect repellents (*N*,*N*-diethyl-*m*-toluamide, known as DEET) and parabens (*p*-hydroxybenzoic esters), which are basically substances used in soaps, shampoos, deodorants, lotions, toothpaste and other PCPs. The nitro musk fragrances were the first to be produced and include musk xylene, ketone, ambrette, moskene and tibetene. In the environment, the nitro substituents can be reduced to form amino metabolites of these compounds. The polycyclic musk fragrances, which are used in higher quantities than nitro musks, include 1,2,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyrane (HHCB), 7-acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene (AHTN), 4-acetyl-1,1-dimethyl-6-*tert*-butylindane (ADBI), 6-acetyl-1,1,2,3,3,5-hexamethylindane (AHMI), 5-acetyl-1,1,2,6-tetramethyl-3-isopropylindane (ATII) and 6,7-dihydro-1,1,2,3,3-pentamethyl-4-(5*H*)-indanone (DPMI). Parabens are the most common preservatives used in personal care products and in pharmaceuticals and food products. This group of substances includes methylparaben, propylparaben, ethylparaben, butylparaben and benzylparaben.

These substances have been analysed in various environmental matrices, such as water, sediments, sewage sludge and aquatic biota. The hydrophobicity of many of these compounds indicates their potential for bioaccumulation [228].

#### 4.2.3.1
#### Sample Preparation

Methods used for the extraction of PCPs from water samples are based on liquid–liquid extraction (LLE) [1, 52–67], continuous liquid–liquid extraction (CLLE), SPE [219, 229–231] and SPME [232, 233]. When LLE and CLLE are applied, various organic solvents are used for the extraction of target compounds, dichloromethane, pentane [234, 235], hexane [236–238], toluene [239, 240], cyclohexane [233] and petroleum ether [241], and mixtures of them in appropriate proportions, being the most widely employed (see Table 2). Extraction of target compounds using these techniques is performed either at ambient pH or by acidifying the sample, generally to values ranging from pH 2 to 3 [219, 228]. For the extraction of UV filters, LLE with cyclohexane at pH 3 is the most common procedure [228].

For SPE, a wide range of sorbents are used, including $C_{18}$ [219, 230, 231, 242–248] at ambient and acidic (pH<3) sample pH, Abselut Nexus [249, 250] (Varian, Palo Alto, CA, USA), Isolute ENV+ [231], Oasis MAX [241], Bio Beads

SM-2 [251–253] (Bio-Rad Laboratories, Hercules, CA, USA), XAD-2 [254] (Supelco, St. Louis, MO, USA), SDB-XC [255, 256] and XAD-4/XAD-8 [254, 257]. Elution of target compounds from these materials is achieved with a large variety of organic solvents, according to the physico-chemical properties of the compounds analysed, with acetone, methanol, toluene, hexane, mixtures of dichloromethane/acetone and methanol, hexane/acetone or hexane/ethyl acetate and acetone/ethyl acetate being the most widely used [228]. When analysing antimicrobials with Oasis MAX, the sample is acidified (pH 3) prior to extraction, washed with methanol/sodium acetate solution and eluted with pure methanol. For parabens, few methods are reported relevant to environmental matrices, but their analysis is mainly based on SPE extraction using Oasis HLB.

Sometimes, when using these techniques, sample purification prior to instrumental analysis is necessary, generally using SPE with silica and alumina [228]. The most common techniques used for their extraction from sewage sludge include PFE [197, 231, 241, 244, 245, 252, 258, 259], SFE [230, 241] (using $CO_2$), sonication, Soxhlet [240, 260–263], LLE [264, 265] and MAE [266]. Sometimes, before extraction of target compounds, copper is added to remove sulphur content in the samples. Generally, after extraction, a purification step with silica columns or size-exclusion chromatography (SEC) followed by Bio Beads SX-3 or silica columns is required. Hexane, ethyl acetate, acetone, cyclohexane and mixtures of them are the solvents mainly used for the elution of target compounds [228].

On the other hand, SPME has also been a widespread technique for the extraction of PCPs in environmental waters and solid samples, using either direct (DI-SPME) or headspace (HS-SPME) methods [228, 248, 267, 268]. The materials most commonly used are polydimethylsiloxane (100 μm) (PDMS) for DI-SPME, and PDMS-DVB (65 μm), Carboxen-PDMS (75 μm), Carbowax-DVB (65 μm) and Carbowax-PDMS (65 μm) for both types of SPME, PDMS-DVB being the one yielding higher recoveries [228].

The extraction techniques used for the analysis of biota samples are the same as those used for solid samples but after extraction, removal of the lipid content is essential, generally performed by SEC in tandem with Bio Beads SX-3 cartridges. For the determination of nitro musks, lipids cannot be removed destructively with $H_2SO_4$ since important losses of target compounds could occur.

#### 4.2.3.2 Instrumental Analysis

Synthetic musk fragrance standards and deuterated musk xylene and AHTN standards are commercially available for use as recovery or injection standards. There have been reports of problems with the use of the deuterated AHTN (AHTN-$d_3$) due to the occurrence of proton exchange during sample

processing [228]. A variety of other recovery and injection standards have been used for the analysis of synthetic musk fragrances, including pentachloronitrobenzene, deuterated polycyclic aromatic hydrocarbons (PAHs), and various labelled and unlabelled polychlorinated biphenyls (PCBs).

PCPs are most commonly analysed by GC-EI-MS, but GC-NCI-MS is more sensitive for nitro musk fragrances. These compounds have also been analysed by GC-FID, GC-ECD, and high-resolution and ion-trap tandem mass spectrometry (MS/MS). Common GC phases are 5% phenylmethylpolysiloxane and dimethylpolysiloxane [228].

Triclosan and its chlorinated metabolites are also determined by GC-EI-MS with and without derivatization, LC-MS and LC-MS/MS. When derivatizing, *N*,*N*-diethyltrimethylamine (TMS-DEA), *N*,*O*-bis(trimethysilyl)trifluoroacetamide (BSTFA), pentafluorinated triclosan and *tert*-butyldimethylsilyl triclosan are the ether derivatives generated after reaction with methyl chloroformate (MCF), pentafluoropropionic acid anhydride (PFA) and *N*-*tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamide (MTBSTFA), respectively [228].

GC-based techniques dominate the analysis of UV filters and insect repellents, using DB-5 and 5% polyphenylmethylsilicone columns, respectively. Almost all UV filters are amenable to GC except octyl triazone, avobenzone, 4-isopropyldibenzoylmethane and 2-phenylbenzimidazole-5-sulphonic acid, some of them being determined by HPLC-UV. Although there are few methods published dealing with the analysis of parabens in environmental samples, the methods reported are based on LC-MS/MS under NI conditions using a $C_{18}$ column.

## 4.3 Surfactants

A number of books and reviews are already available on the determination of surfactants in wastewaters, sludges, sediments and biological samples, using GC-MS, LC-MS or LC-MS/MS techniques [4, 269–271]. Among the various surfactant classes, both non-ionic and ionic substances are the most widely employed in both industry (e.g. alcohol ethoxylates (AEOs), alkylphenol ethoxylates (APEOs) and different fatty amine or acid ethoxylates [269]) and household applications (linear alkylbenzene sulphonates (LASs)).

From the environmental point of view, APEOs and LASs are the ones deserving especial attention due to their ubiquity and ecotoxicological relevance. Sixty percent of APEOs that enter mechanical or biological sewage or sewage sludge treatment plants are subsequently released into the environment, 85% being in the form of the potentially estrogenic metabolic products, alkylphenols (APs), alkylphenol carboxylates (APECs) and alkylphenol dicarboxylates (CAPECs) [272–275]. Moreover, numerous studies have confirmed that alkylphenolic compounds can mimic endogenous hormones. APEOs and

their biodegradation products are transformed into halogenated by-products during chlorination disinfection in wastewater or drinking water treatment plants, in the presence of bromide ion [276, 277].

### 4.3.1 Sample Preparation

Both ionic and non-ionic surfactants are generally isolated from water samples by SPE, at natural sample pH, Lichrolut $C_{18}$ cartridges (Merck, Darmstadt, Germany) being the most widely employed. For halogenated derivatives, SPE using Lichrolut $C_{18}$ is also widely employed [278]. Elution is usually performed using pure solvents, with methanol the most common one [5].

Analysis of surfactants and their halogenated derivatives from solid samples is challenging due to their strong adsorption on the soil/sludge particles by hydrophobic and electrostatic interactions. Most of the methods available in the literature are based on sonication and PLE as the extraction technique followed by a clean-up procedure, generally using SPE $C_{18}$, ENV+, strong anion exchange (SAX) or polymeric cartridges [5, 279–281]. The former has been widely employed for the analysis of LASs, NPEOs and their degradation products nonylphenol carboxylates (NPECs) and NPs, AEOs, and coconut diethanolamides (CDEAs) [282]. On the other hand, PLE methods have been optimized for LASs, NPEOs and their neutral and acidic metabolites, AEOs and alkylamine ethoxylates (ANEOs) [282]. Pure solvents, such as methanol and dichloromethane, and mixtures of organic solvents (hexane/acetone or methanol/dichloromethane) are mainly used for the extraction of surfactants from solid matrices (see Table 2). Other methods based on extraction with pressurized (supercritical) hot water as well as SFE with solid-phase trapping, using $CO_2$ and methanol or water as modifier, have been described in the literature for the simultaneous extraction of several surfactant classes [282].

### 4.3.2 Instrumental Analysis

Commercial mixtures of surfactants comprise several tens to hundreds of homologues, oligomers and isomers. For LASs, mixtures of secondary isomers with alkyl chain lengths of 10–13 carbons are available.

GC and LC coupled to MS detection systems are now the commonly used methods to identify and quantitate surfactants in both aqueous and solid matrices. Although GC-MS is adopted in many analytical methodologies, it cannot be applied for the direct determination of several classes of surfactants since derivatization of low volatility compounds is required. This is why, in surfactants analysis, GC-MS methods are partially substituted with LC-MS or LC-MS/MS [269, 283]. However, most of the methods available focus on one

or two classes of surfactants which are similar in nature, generally including their main degradation products. Only recently, several efforts have been made to develop generic methods that allow simultaneous determination of a broad range of surfactant types.

Gas chromatography–mass spectrometry has been widely used for the analysis of alkylphenolic compounds and anionic surfactants (LASs). Alkylphenolic substances, which mainly include the most volatile compounds AP, APEO, AEO and ANEO with fewer than four ethoxy groups, and the rest of the non-ionic surfactants can be determined without derivatization, while for anionic surfactants derivatization prior to analysis is required [284]. Derivatization is usually performed by transforming parent compounds to the corresponding trimethylsilyl ethers, methyl ethers, acetyl esters and pentafluorobenzoyl or heptafluorobutyl esters [5, 285, 286]. After derivatization, NPEO derivatives can be analysed by GC-MS in the EI or NCI modes [130]. GC-CI-MS, using ammonia as reagent gas for the detection of $NPE_nC$, gave intense ammonia–molecular ion adducts of the methyl esters, at *m/z* 246, 310, 354 and 398 for $NPE_1C$, $NPE_2C$, $NPE_3C$ and $NPE_4C$, respectively, with little or no secondary fragmentation [5]. Moreover, GC-CI-MS spectra of the NPECs with isobutene as reagent gas showed characteristic hydride-ion-abstracted fragment ions shifted 1 Da from those in the corresponding EI mass spectra. On-line direct GC injection-port derivatization with ion-pair reagents (tetraalkylammonium salts) has also been reported [287].

As concerns liquid chromatography, even though LC-MS/MS is more specific and sensitive than LC-MS, the majority of studies dealing with the analysis of surfactants in environmental samples are based on LC-MS [128, 270]. However, several papers describing the application of tandem MS to the unambiguous identification and structural elucidation of alkylphenolic compounds have been published [275, 288–291].

The analysis of LASs by LC-MS operating in the ESI and NI modes is particularly attractive due to their anionic character. MS analysis of commercial LAS mixtures shows four ions at *m/z* 297, 311, 325 and 339, corresponding to deprotonated molecules of $C_{10}$–$C_{13}$ LAS homologues [282]. With increasing cone voltage using in-source collision-induced dissociation (CID), the spectra show additional fragment ions at *m/z* 183 and 80, which were assigned to styrene-4-sulphonate and $[SO_3]^-$. The analysis of APEOs by LC-MS in the PI mode yields a characteristic pattern of equally spaced signals with mass differences of 44 Da (one ethoxy unit), which is a diagnostic fingerprint for this group of compounds. Using an ESI interface and aprotic solvent, APEOs predominantly give evenly spaced sodium adducts $[M + Na]^+$ [270], which are relatively stable and generally no further structurally significant fragmentation is provided in the mass spectrum. Some authors used ammonium acetate as mobile phase in order to enhance the formation of ammonium adducts over sodium or proton adducts, which give fragments in CID processes, enabling a more specific detection of APEOs [275].

On the other hand, alkylphenoxy carboxylates ($APE_nC$) are generally determined by ESI operating in the NI mode, and less frequently by the PI mode [282]. For the analysis by NI, two types of ions, one corresponding to the deprotonated molecule and the other corresponding to deprotonated alkylphenols, are obtained. For the determination of AEOs, some authors used LC-MS operating in APCI mode [282] to analyse AEOs with alkyl chains from $C_{10}$ to $C_{14}$ and from $C_{10}$ to $C_{18}$.

Like their non-halogenated analogues, halogenated APEOs show a great affinity for alkali metal ions when analysed by LC-MS in ESI mode, and they give exclusively evenly spaced (44 Da) sodium adduct peaks $[M + Na]^+$ with no further structurally significant fragmentation [277]. Fully de-ethoxylated degradation products, octylphenol (OP) and nonylphenol (NP), were detected under NI conditions with both APCI and ESI interfaces. However, sensitivity was higher when using an ESI source than an APCI one [5].

Diagnostic ions used for the analysis of XAPEOs under NI conditions using LC-MS corresponded to the cleavage of the alkyl moiety ($CH_2$ group), leading to a sequential loss of *m/z* 14, the most abundant fragments being at *m/z* 167 for $^{35}Cl$ and *m/z* 169 for $^{37}Cl$.

In LC-tandem MS, compounds analysed under NI conditions (AP, APEC and their halogenated derivatives) were analysed by ESI-MS/MS, while for APEO, detected in the PI mode, no fragmentation was obtained using an ESI source. These compounds were determined by APCI-MS/MS. Using ESI-MS/MS, the CID spectrum of NP shows fragments at *m/z* 147, 133, 110 and 93, attributed to the progressive fragmentation of the alkyl chain [5]. For APEC, an intense signal at *m/z* 219 is observed for NPEC, produced after the loss of the carboxylated (ethoxy) chain, and other peaks at *m/z* 133 and 147, due to the sequential fragmentation of the alkyl chain [128, 275, 288]. LC-tandem MS was also used to determine halogenated surfactants, obtaining the same product ions as for LC-MS, with *m/z* 167 for $^{35}Cl$ and *m/z* 169 for $^{37}Cl$, with a relative ratio of intensities of 3.03, being the most abundant fragment ions.

LC-ESI-IT-MS and LC-(PI)-APCI-IT-MS have been used to determine LASs and SPCs, and APEOs, AEOs and cationic surfactants, respectively, in several environmental matrices [292–296]. These instruments permit $MS^n$, which makes them suitable for identification and quantitation purposes. On the other hand, MALDI-TOF and MALDI-Q-IT have been used to determine APEOs [297, 298]. Ayorinde et al. [292] used α-cyano-4-hydroxycinnamic acid as a matrix to determine NPEO (with 2–120 ethoxy units).

## 4.4 Polybrominated Diphenyl Ethers (PBDEs)

Polybrominated flame retardants are chemicals used in large quantities as they are added to polymers, which are used in plastics, textiles, electronic circuitry and other materials, to prevent fires, due to their fire retarding

properties [299]. Several studies have reported that these substances tend to bioaccumulate in biota and humans due to their lipophilicity [300–311]. Moreover, PBDEs are suspected to cause endocrine dysfunction by interfering with thyroid hormone metabolism [312, 313]. In 2003, the European Union banned the use of the PBDE commercial mixtures PentaBDE and OctaBDE. Nowadays, the only remaining unregulated PBDE mixture in production is DecaBDE [314].

### 4.4.1 Sample Preparation

Analytical methods developed for the determination of PBDEs are very similar to those used for PCBs, due to their similarity in physico-chemical properties. As they are non-polar compounds, their occurrence has been widely reported in solid samples, such as sewage sludge, soil and sediments. For this reason, the determination of PBDEs in liquid samples is mainly focused on the analysis of human milk or plasma, while few studies have analysed them in natural and sewage waters [81].

BDE congeners typically measured in human tissues are associated primarily with the PentaBDE mixture, and to some extent with the OctaBDE mixture. One of the greatest challenges to measuring PBDEs in environmental samples has been developing methods to accurately quantify BDE 209. While analytical methods are readily available for quantifying tribrominated through heptabrominated congeners found in the PentaBDE and OctaBDE mixtures, the analysis of brominated compounds has proven to be difficult. Currently, there are several reviews available in the scientific literature devoted to the analysis of PBDEs in different environmental matrices [81, 82, 299].

The techniques used are mainly based on liquid–liquid extraction (LLE) [315–319], with mixtures of non-polar and polar solvents. Recently, headspace solid-phase microextraction (HS-SPME) and microporous membrane liquid–liquid extraction (MMLLE) have been proposed as suitable techniques [320]. Other techniques used consist of saponification with ethanolic KOH, especially for their analysis in human milk [299]. Similar procedures involving protein denaturation with HCl/isopropanol and extraction with hexane/methyl *tert*-butyl ether have been used for the determination of neutral and phenolic brominated compounds from human serum [321].

Extraction of PBDEs from solid and biological samples is generally performed using non-polar solvents, such as hexane, toluene, dichloromethane or hexane/acetone mixtures. Binary solvent mixtures, combining a non-polar and a polar solvent, are most commonly used for their known extraction efficiency, especially for biota and wet sediment samples, as non-polar solvents are not able to penetrate the organic matter and therefore desorb contaminants. Soxhlet [322–324], supercritical-fluid extraction (SFE) [325], acceler-

ated solvent extraction [326, 327] and microwave-assisted extraction (MAE) are the techniques mainly used [328].

Extracts obtained using these techniques need a clean-up step prior their analysis by chromatographic techniques. Therefore, extracts from sediments, sewage sludge or soil samples may contain sulphur that has to be removed as it could disturb the GC analysis. Typical methods used for this purpose are treatment with copper powder, silica modified with $AgNO_3$ in a multilayer silica column, desulphuration with mercury or reaction with tetrabutylammonium sulphite [81, 82, 299]. In the case of Cu powder, it is generally added in the Soxhlet beaker or PLE cell.

On the other hand, in the case of sewage sludge, extracts contain a high amount of lipids and organic matter, which should be removed prior to instrumental analysis, by either non-destructive or destructive methods. The former include gel permeation and column adsorption chromatography, using polystyrene–divinylbenzene copolymeric columns and dichloromethane or mixtures of dichloromethane/hexane and ethyl acetate/cyclohexane as eluents. Other neutral adsorbents commonly used are silica gel, alumina and Florisil® [323, 329]. Destructive lipid removal methods consist of sulphuric acid treatment, either directly to the extract or via impregnated silica columns, and saponification of extracts by heating with ethanolic KOH. Since PBDE concentrations are generally related to the amount of lipids, the lipid content is often measured gravimetrically prior to the clean-up step, or determined separately by a total lipid determination [299, 323].

It is important to remark that when analysing BDE 209 special precautions should be taken, as it is sensitive to UV light and it may also adsorb to small dust particles. Therefore, incoming sunlight into the laboratory should be blocked and all glassware covered with aluminium foil, to prevent dust particles and UV light entering either the solutions or samples. The use of isooctane for the extraction should be avoided due to the insolubility of BDE 209 in this solvent. Moreover, it is recommended not to evaporate extracts until dryness because it may not completely re-dissolve after that step even when using toluene.

### 4.4.2 Instrumental Analysis

Like perfluorinated alkyl substances, standards available for PBDE determination consist of a mixture of several congeners of different degrees of bromination. As reported by Stapleton [314], about 160 of the 209 possible BDE congeners are currently commercially available. Isotopically labelled standards to be used for internal standard calibration purposes are scarce, and therefore some authors have used $^{13}C$-labelled bromobiphenyls and chlorinated diphenyl ethers as an alternative.

Owing to their vapour pressure and polarity, GC coupled to ECD, NCI-LRMS and EI-LRMS detectors has become a standard analytical separation method for the analysis of PBDEs. The three most common injection techniques for PBDEs are split/splitless, on-column and programmable temperature vaporization (PTV) injection. When working with split/splitless injection, the high inlet temperature can lead to thermal degradation and discrimination of higher molecular weight PBDEs, particularly the fully brominated BDE 209. This problem can be solved by using on-column injection, which consists of the direct injection of the sample, dissolved in a carrier solvent, onto the head of the column [314, 330]. PTV inlets have become a more popular choice for injection over the past 5 years, where higher injection volumes can be used, thus improving detection limits.

Both on-column and PTV injections require the use of a guard column, composed either of untreated silica with active silanol groups or deactivated fused silica. Short DB columns (10–15 m) with thin (0.1 μm) stationary phases are the most commonly used and the ones providing higher sensitivity for measuring the entire range (low to high bromine substitution). However, longer columns are not well suited for higher molecular weight PBDEs, as they can degrade [314]. Again, BDE 209 should receive special attention, due to its susceptibility to degrade at higher temperatures in the GC system.

ECNI-LRMS provides higher sensitivity than EI-LRMS, the LODs for the former being at least one order of magnitude lower than for the latter. However, EI-LRMS provides higher specificity and accuracy in quantification, as isotopically labelled standards can be used for the isotope dilution approach.

GC/ECNI-LRMS mass spectra for all PBDEs rely upon selective ion monitoring (SIM) of $Br^-$ ions [$^{79}Br$ and $^{81}Br$]. By contrast, EI provides more structural information, giving the molecular ions and the sequential losses of bromine atoms (molecular clusters for mono- to tri-BDEs and $[MBr_2]^+$ for tetra- to hepta-BDEs).

The presence of potential interferences in the NCI and EI approaches has been widely studied [314, 331, 332]. In general, EI-MS is affected by chlorinated interferences, especially PCBs, as analytical procedures developed for PBDE analysis are mainly based on the methods already available for PCBs. Thus, purified extracts may contain both PCBs and PBDEs. Alaee et al. [332] found that the isotopic cluster of $[M - Cl_2]^+$ from heptachlorinated biphenyls contains the same mass fragments found in tetrabrominated diphenyl ethers $[M - Br_2]^+$ and resolving powers of 25 000 ($m/\Delta m$) were required to differentiate them.

Such interferences are illustrated in Figs. 6 and 7, where the chromatograms obtained following the injection of a PBDE standard mixture and PCB standard mixtures are depicted. As can be observed, some hepta-CBs (CB-180) and octa-CBs (CB-199) elute with tetra-BDEs. Furthermore, some octa-CBs (CB-194) elute with penta-BDEs [82].

When using NICI-LRMS, such chlorinated interferences do not occur, but due to the presence of different brominated compounds, such as MeO-BDEs,

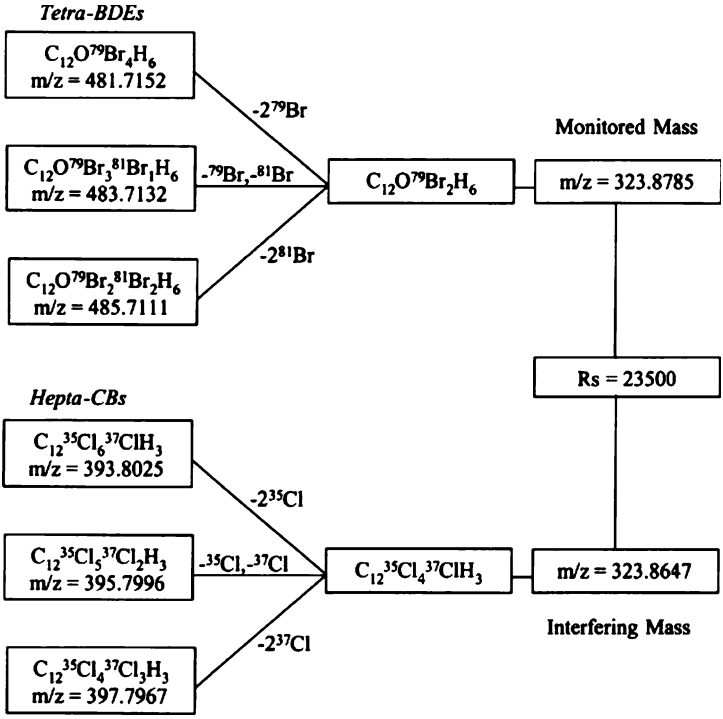



**Fig. 6** Interferences between tetra-BDEs and hepta-CBs. Reprinted with permission from Elsevier [331]

can produce the same fragment ion and confound analysis of PBDEs. Several papers have reported the co-elution of 2,2′4,4′,5′5-hexabromobiphenyl (PBB 153) and TBBPA with BDE 154 and of tetrabromobisphenol A with BDE 153 [81, 323, 333–336] on 15- and 30-cm capillary columns. Moreover, naturally produced brominated compounds, such as halogenated bipyrroles and brominated phenoxyanisoles, can be considered as potential interferences.

High-resolution instruments operating in the EI mode offer the best selectivity for PBDE measurements, with a mass resolution of approximately 10 000, resulting in fewer co-eluting interferences [337]. Moreover, they also allow the use of isotope dilution with $^{13}$C-labelled BDE standards due to the reduction of interferences.

Tandem mass spectrometers using ion traps have also been reported for the analysis of PBDEs [338, 339], offering the advantage of increased sensitivity at low mass resolution because analytes are fragmented twice, minimizing the chance of isobaric interferences and reducing background noise. In this equipment, precursor ions, which are typically $[M]^+$ or $[M - Br_2]^+$, are fragmented yielding $[M - COBr]^-$ ions.

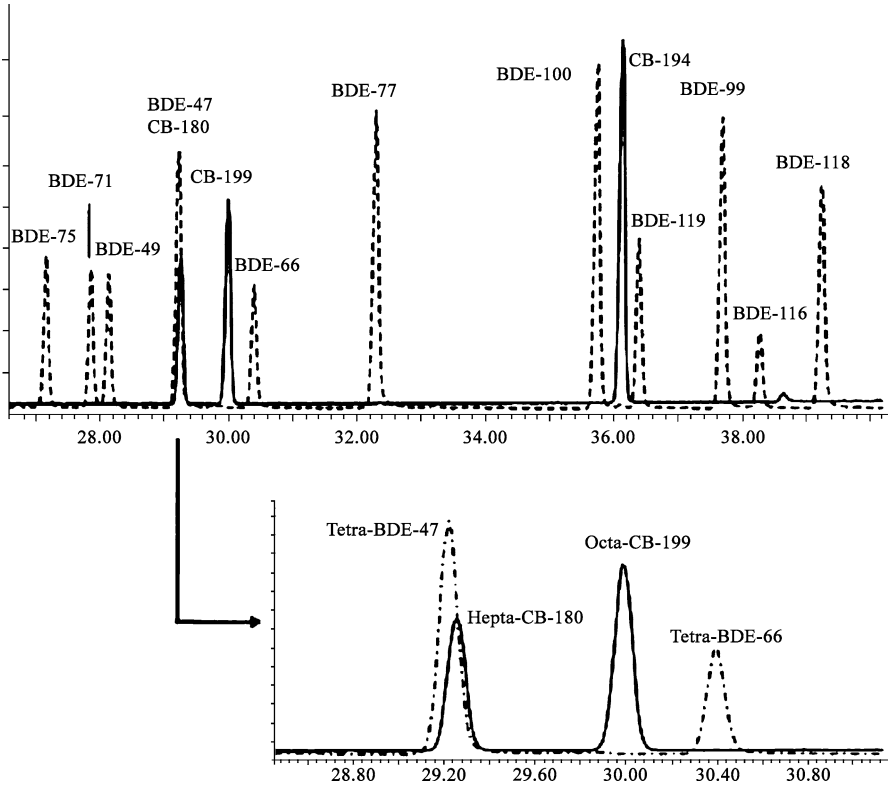



**Fig. 7** TIC obtained following the co-injection of PBDE and PCB standard mixtures. Hepta- and octa-CBs eluted within the chromatographic window are defined for tetra- and penta-BDEs. BDE-47 and CB-180 eluted at the same retention time. Reprinted with permission from Elsevier [331]

HR-TOF mass spectrometers have also been used to determine PBDEs in environmental samples, with detection limits comparable to those of most other MS techniques [340, 341]. Alternative analytical techniques are LC-MS, LC-MS/MS [342, 343] and GC×GC [336, 340]. The former two are promising, but use atmospheric pressure photoionization (APPI), as PBDEs do not ionize well with either ESI or APCI. When working with APPI, both negative and positive ionization modes are suitable for their analysis, depending on the degree of bromine substitution. However, the analysis of metabolites, such as hydroxylated BDEs (OH-BDEs), can be successfully conducted when operating in ESI mode. Finally, GC×GC could be very useful to avoid the co-elution problems found in standard GC-MS methods [344].

## 4.5 Methyl *tert*-Butyl Ether (MTBE) and Other Gasoline Additives

MTBE, and gasoline additives in general, are not usually analysed in wastewaters, but this section was included as they are an important group of compounds to be considered when dealing with emerging contaminants. Fuel oxygenates have been added to gasoline since the 1970s, mainly as octane enhancers that increase the combustion efficiency and reduce toxic air emissions, such as lead compounds or carbon monoxide. Since the ban on tetraalkyl lead compounds, MTBE has become the most commonly used oxygenate and the one with the highest production volume worldwide [345].

Among fuel additives, MTBE is the ether with higher solubility and lower sorption and Henry's law constant, enhancing its higher mobility (nearly as fast as that of ground water) and the difficulty in removing it from water by aeration or degradation processes [346]. For this reason, as well as its intense use, MTBE has become one of the most frequently detected volatile organic compounds (VOCs) in ground water which can be adsorbed on subsurface solids [346].

Besides the health effects, toxicity and carcinogenicity at high concentrations [347], there is much interest in the aesthetic implications of MTBE in drinking water. Taste and odour thresholds for this compound in water have been reported at very low concentrations, approximately 25–60 μg/L for flavour and 40–70 μg/L for odour at 25 °C [347]. For this reason, the US Environmental Protection Agency (EPA) established a drinking water advisory for aesthetic concerns at 20–40 μg/L [347]. To date, there are no regulations for MTBE in water, air or soil in Europe but some countries are establishing their own guidelines.

Analytical methodologies dealing with the analysis of MTBE also include the determination of its main degradation products, *tert*-butyl alcohol (TBA) and *tert*-butyl formate (TBF), as well as other gasoline additives present in fuel, such as the oxygenate dialkyl ethers, for example ethyl *tert*-butyl ether, *tert*-amyl methyl ether and diisopropyl ether, and the aromatic compounds benzene, toluene, ethylbenzene and xylene (BTEX).

### 4.5.1 Analysis in Environmental Samples

There are some reviews devoted to the analysis of MTBE and other gasoline additives in environmental samples [346, 348, 349]. Even though MTBE is more likely to be present in ground and surface waters as well as soil samples, due to its physico-chemical properties (high mobility and solubility), some studies also revealed its presence in wastewaters [350, 351].

The most crucial step in trace analysis of VOCs is definitely enrichment and sampling. For MTBE analysis, samples do not need to be preserved, as biodegradation is very slow [352]. However, special precautions have to be

taken in VOC analysis to avoid losses and prevent contamination. Bottles used to collect samples are filled to the top, avoiding air bubbles passing through the sample, to prevent volatilization of target compounds [347].

As to enrichment techniques, some methodologies, including direct aqueous injection (DAI), membrane-introduction mass spectrometry (MIMS), headspace (HS) analysis, purge and trap (P&T), solid-phase microextraction (SPME) by direct immersion or headspace compound-specific stable isotope analysis (CSIA), which is an emerging tool in environmental sciences, have been proposed and discussed by [353, 354] as appropriate methods to be used. These techniques are recommended when VOCs are found at lower concentrations and they mainly operate coupled to an instrumental technique. As VOCs, fuel oxygenates are almost exclusively analysed by GC and MS detection. Other detectors, such as flame ionization (FID), photoionization (PID) and atomic emission (AED), can also be used, but MS is the preferred one due to its higher sensitivity and selectivity [350]. In Tables 1 and 2, some of the most representative methods for the analysis of MTBE and other gasoline additives in water and solid samples, respectively, are described.

The selection of one technique or another depends on the type of matrix analysed, the concentration range and the need for compliance with the regulations [350]. P&T and SPME were the methods that obtained the best accuracy in a MTBE inter-laboratory study with 20 European participating laboratories and, when coupled with mass spectrometry, were the ones offering the best results according to the quality state assurance/quality control requirements [350, 355]. When P&T is used, VOCs are purged from water with helium, and generally they are subsequently adsorbed onto a Tenax® silica gel–charcoal trap. After sample loading, trapped components are desorbed at high temperatures and transferred directly to the GC-MS system [347].

For the analysis of MTBE and gasoline additives in solid samples, the same techniques as for water samples (P&T, SPME, etc.) are used [350]. Pressurized-liquid extraction (PLE) has also been used for the determination of higher concentrations (mg/kg) of BTEX (Application note 324) in soils using hexane/acetone (1:1). A semi-automatic purge-and-membrane inlet mass spectrometric (PAM-MS) instrument [377] provided good sensitivity and accuracy for some BTEX compounds and MTBE. Among the ifferent types of P&T instruments assembled for the analysis of VOCs in solid matrices [356–361], closed-system P&T is directed to determine low concentrations (<200 μg/kg), as indicated in the EPA Method 5035 [350].

Quantitative analysis of MTBE, its degradation products and other gasoline additives is performed by operating the mass spectrometer in EI mode, generally at 70 eV. In order to increase sensitivity and selectivity, samples are injected in time scheduled SIM mode. Due to the rather high energy transfer in the EI ionization mode, fuel oxygenates do not yield molecular ions. Typical fragments obtained correspond to the α-cleavage $[M - CH_3]^+$ or $[M - CH_5]^+$, taken as base peaks in the mass spectra [347]. Typical columns

used in the GC separation are fused-silica capillary DB-624 columns (75 m × 0.53 mm ID) with a 3-μm film thickness.

## 5 Conclusions

Among modern analytical techniques, GC and LC, coupled to both MS and tandem MS, are the key techniques for the determination of emerging contaminants in complex environmental samples. These techniques, combined with appropriate sample preparation procedures, allow the detection of target compounds at the low environmental levels. Furthermore, the introduction of new chromatographic techniques, such as fast LC, fast GC, and GC×GC, has improved the analysis of complex mixtures. However, current analytical methods only focus their attention on parent target compounds and rarely include metabolites and transformation products. The question is whether chemical analysis of only target compounds is sufficient to assess contaminants present in the environment. Recent developments in the mass spectrometry field, such as the introduction of Q-TOF and Q-LIT instruments, allow the simultaneous determination of both parent and transformation products. Exact mass measurements provided by Q-TOF and the ability to combine several scan functions are a powerful tool to provide a more accurate identification of target compounds in complex samples, as well as to enable structural elucidation of unknown compounds. However, general screening for unknown substances is time-consuming and expensive, and is often shattered by problems, such as lack of standards and mass spectral libraries. Therefore, effect-related analysis, focused on relevant compounds, nowadays seems to be a more appropriate way to assess and study environmental contamination problems.

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