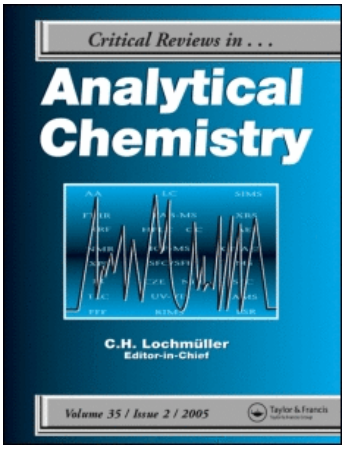

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A Review on the Analysis of Emerging Contaminants in Aquatic Environment

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A Review on the Analysis of Emerging Contaminants in Aquatic Environment

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The occurrence of emerging contaminants in the aquatic environment is of increasing interest, as mordern sensitive techniques are employed worldwide for their determination. This review covers the current status and future prospects about the application of modern analytical instruments (such as GC-MS or LC-MS) for the analysis of emerging contaminants in aquatic system, in the past 2 years. The various sample preparation techniques will be compared and discussed as well.

Keywords emerging contaminants, water samples, gas chromatography, liquid chromatography, mass spectrometry

INTRODUCTION

In recent years, pollutants in aquatic environment, are of major concern since they potentially adversely affect human health or ecosystem safety. Emerging contaminants, belonging to pollutants, have long been present in the environment but had not gained scientific or public attention until recently. Some of the emerging contaminants have been regulated for water quality monitoring, according to U.S. EPA standard and the World Health Organization (WHO) guideline. However, most of these pollutants are not yet covered under worldwide routine monitoring programs. Depending on the ecotoxicity results and data regarding their occurrence and fate in the environment, they may be candidates for future regulations (1).

ADVANCED INSTRUMENT

With the need to study the occurrence, transport, and fate of the emerging contaminants in the environment, it is necessary to unambiguously identify the structures of emerging contaminants and determine their amount. Chromatography, including gas chromatography (GC) and high performance liquid chromatography (HPLC), is the dominant modern analytical technique. HPLC has been employed since the late 1960s, in which the liquid mobile phase is mechanically pumped through a column that is packed with the stationary phase. HPLC is routinely employed for the analysis of non-volatile ionic compounds from the smallest ions to large biological molecules. In the GC system, different components in the mixtures are separated based on the different absorptive interaction between the components in the gas stream and the stationary phase. Mass spectrometry (MS) is the one of the most valuable detection techniques, because it provides information on the compound's molecular structure and it is also highly sensitive and selective. The combination of chromatograph, with MS can separate mixtures into their individual components and subsequently analyze each compound in the mixtures, qualitatively and quantitatively.

In GC analysis, by comparing their mass spectra with mass spectral libraries, the full scan mode of MS is employed for identifying compound structures, based on interpreting abundant fragment-ion patterns. For quantification, selective ion mode (SIM) of MS can be applied to achieve high sensitivity. More recently, to improve determination selectivity and sensitivity, triple quadrupole (QqQ) MS has been introduced in GC analysis. For unbiased determination and confirmation of chemical structures of metabolites, biodegradation, and transformation products, high-resolution MS is also employed. In traditional LC analysis, QqQ MS or ion-trap MS is usually applied for structure elucidation and quantitative analysis (2). Recently, more advanced MS such as time of flight MS (TOF-MS), etc. are introduced, making a new powerful identification tool be available; one new hybrid quadrupole-time of flight mass spectrometer (QqToF) permits the acquisition of full-scan product ion spectra, with the accurate mass of the product ions. Based on the product ion spectra, structure elucidation of unknown compounds as well as identification of target compounds can be obtained with a much higher degree of certainty (3).

GC-MS and LC-MS have been widely employed for the analysis of emerging contaminants including pharmaceuticals and

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metabolites, endocrine disrupting compounds (EDCs), drinking water disinfection by-products (DBPs), UV filters, brominated flame retardants, etc. (4–14).

SAMPLE PREPARATION

To analyze the emerging contaminants in aquatic enviromental samples with complex matrices, sample preparation is a primary step. There are several goals of sample extraction prior to instrument analysis (15). Firstly, it is frequently necessary to separate the target organic compounds from a complex aqueous matrix such as sewage and marine water samples to remove the interference. Secondly, enrichment of the target analytes is important, especially when analytes in trace levels are to be determined. Sample extraction and concentration steps are applied to improve determination sensitivity. Finally, the compatibility between the sample matrix and the instrumental analysis must be considered. For example, generally aqueous samples are not immediately analyzed with GC analysis in which a solvent extraction procedure is normally applied.

Usually, sample preparation includes liquid-liquid extraction (LLE), solid-phase extraction (SPE), solid-phase microextraction (SPME), stir-bar sorptive extarction (SBSE), liquid-phase microextraction (LPME), etc.

LLE is a traditional technique to extract organic compounds from aqueous samples (16). LLE is based on the partition of the dissolved analytes between the organic solvent and the aqueous sample according to their partition coefficients. Due to its tedious operation procedure and large amount of organic solvent consumed, LLE is being replaced by other techniques.

Compared to LLE, SPE is a more modern extraction technique (17–20) and has become the most common sample preparation technique in environmental analysis. The principle is based on the sorption of analytes on the sorbent. In this procedure, organic compounds are initially trapped on the sorbent while the aqueous sample is passed through the cartridge or disk. Then the target compounds are eluted with a suitable solvent. Therefore, separation and enrichment can be obtained. Compared to LLE, SPE offers the advantages in the following (21):

- Higher recoveries;
- Improved selectivity, specificity, and reproducibility;
- Elimination of emulsions;
- Less organic solvent usage;
- Shorter sample preparation time;
- Easier operation and the possibility of automation.

In the SPE procedure, the choice of sorbent is critical since it controls selectivity, affinity, and capacity. Classical SPE sorbents include chemically bonded silica with the C8 or C18 organic group, carbon, and ion-exchange materials. More recently, polymeric materials, immunosorbents, molecularly-imprinted polymers, and restricted access materials have been introduced and improved, the extraction efficiency of target compounds (21). Based on the characters of target compounds such as polarity, different SPE sorbents can be chosen.

SPME is a modern equilibrium extraction method. A fused silica fiber coated with a polymeric phase is usually utilized in SPME (22). In SPME, generally, there are three modes of operation: direct immersion extraction, headspace extraction, and the less commonly used membrane-protected SPME (22). There are some advantages for SPME: firstly, SPME completely eliminates the usage of organic solvents; secondly, it is a simple operation procedure since it incorporates sampling, extraction, concentration, and sample introduction into a single step. However, there are still limitations such as short fiber lifetime, high cost, fragility, and carry-over effects. Furthermore, it lacks selectivity when extracting analytes in complex matrices (22).

SBSE is a solventless extraction technique in which a magnetic stir bar coated with an absorbent material is uesd (23). Polydimethylsiloxane (PDMS) is widely used as the sorptive extraction phase. During extraction procedure, the stir bar is added to the sample and stirred. After extraction and thermal desorption, the analyte can be introduced for analysis, typically by GC-MS. Compared to SPME, SBSE provides higher sensitivity and slower desorption process because of the extended extraction phase (23).

LPME, a microscale LLE, is introduced to reduce the consumption of organic solvent (24–26). In this procedure, only a small amount of organic solvent is involved for exatrction. It is an equilibrium extraction technique rather than an exhaustive extraction technique. LPME is basically divided into two general methods: droplet-based LPME and membrane-based LPME. In the former method, a discrete suspended drop of immiscible solvent was used as the extraction phase without a supporting membrane. In the latter method, the extraction solvent is confined in a porous membrane.

EMERGING CONTAMINANTS

Pharmaceuticals and Their Metabolites

Among new emerging contaminants, pharmaceuticals (Table 1) (21) have raised concerns due to their pharmacological activity. In addition, the widespread usage of pharmaceuticals and continual input into the aquatic environment has made them to be "pseudo" persistent pollutants (27). After metabolizing in living organisms, pharmaceuticals are usually excreted in their parent forms or as metabolites. Biodegradation and transformation (such as hydrolysis or photolysis of pharmaceuticals and metabolites) can also occur in aquatic environments (27).

Due to the polarity of most pharmaceuticals, either LC-MS (or LC-MS-MS) or GC-MS (or GC-MS-MS) combined with derivatization is normally used for analysis. Togola and Budzinski used GC-MS (SIM) to determine 18 drugs inclduing anti-inflammatories, anti-depressants and hypolipidic drugs after derivatization with *N*-methyl-*N*-(trimethylsylil)

TABLE 1
Classes of Pharmaceuticals (11)

Therapeutic classes	Examples
Veterinary and human antibiotics	
-β-lactams	Amoxicillin, ampicillin, benzylpenicillin
-macrolides	Erythromycin, azithromycin, tylosin
-sulfonamides	Sulfamethazine, sulfadiazine, sulfaguanidine
-tetracyclines	Oxytetracycline, tetracycline
Analegesics and anti-inflammatory drugs	Codeine, ibuprofen, acetoaminofen, diclofenac, fenoprofen
Lipid regulators	Bezafibrate, clofibric acid, fenofibric acid
Psychiatric drugs	Diazepam
B-blockers	Metoprolol, propranolol, timolol, solatol
X-ray contrast media	Lopromide, lopamidol, diatrizoate
Anti-depressants	Fluoxetine
Hormones	Estradiol, estrone, estriol, diethylstilbestrol

trifluoroacetamide (MSTFA). The optimized procedure has been successfully applied to the analysis of wastewaters, surface waters, and drinking waters from the Cortiou rocky inlet (South coast of France), highly impacted by the Marseilles wastewater treatment plant effluent, and the H'erault watershed (28). Sebők et al. reported a multi-residue analysis procedure which permited the identification and quantification of 63 water-soluble pollutants (including ibuprofen, caffeine, gemfibrozil, fenoprofen calcium salt hydrate, naproxen, ketoprofen, diclofenac sodium salt, etc.) (29). Their trimethylsilyloxime ether/ester derivatives were analyed by GC-MS after SPE. In this method, limit of quantitation values ranged from 0.92 (4-hydroxyphenylacetic acid) to 600 ng/L (dehydrocholic acid). Reproducibilities, characterized with the relative standard deviations (RSDs) of measurements, varied between 0.71 and 10%, with an average of 4.38% RSD. This method was applied for the identification and quantification of the pollutants of Hungarian influent and effluent wastewaters (for six consecutive months) and that of the Danube River (for 2 months).

Compared with GC-MS, LC-MS-MS was more favorable in the analysis of pharmaceuticals and metabolites. Schultzt and Furlong developed a method for the determination of trace levels of anti-depressants in environmental aquatic matrices using SPE coupled with LC-ESI-MS-MS (30). Recoveries of parent anti-depressants from matrix spiking experiments for the individual anti-depressants varied from 72 to 118% at low concentrations (0.5 ng/L) and 70 to 118% at high concentrations (100 ng/L) for the SPE. Method detection limits for the individual anti-depressant compounds ranged from 0.19 to 0.45 ng/L. The method was applied to test wastewater effluent and samples collected from a wastewater-dominated stream. Venlafaxine was the predominant antidepressant observed in wastewater and river water samples. Individual antidepressant concentrations found in the wastewater effluent ranged from 3 (duloxetine) to 2190 ng/L (venlafaxine), whereas individual concentrations in the waste-dominated stream ranged from 0.72 (norfluoxetine) to 1310 ng/L (venlafaxine). Van De Steene and Lambert used LC-ESI-MS-MS combined with SPE for the simultaneous analysis of nine basic pharmaceuticals (flubendazole, pipamperone, cinnarizine, ketoconazole, miconazole, rabeprazole, itraconazole, domperidone, and propiconazole) in environmental waters (31). In this method, standard addition was employed for accurate quantification to reduce matrix effects. Limits of detection and quantification were in the range of <0.05–1 and 0.05–10 ng/L, respectively. Good precision and accuracy were obtained. Recoveries were in the range of 60–100%. This method was applied for identifying and quantifying target pharmaceuticals in wastewater and surface water. A simple on-line method was developed by Viglino et al. for the analysis of pharmaceuticals, pesticides, and some metabolites in drinking, surface, and wastewater samples (32). The technique was based on the use of on-line SPE combined with LC-ESI(PI)-MS-MS (positive electrospray ionization). Only 1 mL of filtered water sample was injected. Total analysis time was 20 min, including the period required to flush the SPE cartridge with organic solvent and reconditioning the LC column. Method detection limits were in the range of 2 to 24 ng/L for the compounds of interest. Chang et al. established a sensitive method, in which LC-ESI-MS-MS combined with SPE and silica cartridge cleanup was used for the analysis of 16 sulfonamides and trimethoprim in various water matrices (33). Signal suppression of all target analytes in sewage treatment plant influent, effluent, and river water was improved by this method. The method detection limits for 17 analytes were 20–200 pg/L for influent, 16–120 pg/L for effluent and 8.0–60 pg/L for river water with overall mean recoveries of 62–102% in all studied matrices. This method was used to analyze residual sulfonamides and trimethoprim in wastewater and river samples from Japan. Hao et al. created a high-throughput method for the determination of 51 emerging organic pollutants (EOPs) in environmental waters. The method was validated for the analysis of 38 pharmaceutically active, 10 endocrine disrupting, and three perfluoroalkylated compounds with LC-MS-MS (34). They applied this method to the analysis of effluents and samples downstream of a wastewater treatment plant (WWTP) and more than 35 target EOPs were quantified. A novel analytical method was established for the determination of six basic anti-depressants (venlafaxine, sertraline, paroxetine, citalopram, amitriptyline, and fluoxetine) and four of their metabolites (O-desmethylvenlafaxine, desmethylsertraline, nortriptyline, and norfluoxetine) in raw

sewage and roughly primary-treated wastewater by Lajeunesse et al. (17). All the target compounds at concentrations of 2–346 ng/L were found at WWTP in Montreal. The target anti depressants were also detected in samples taken from the effluent receiving waters (i.e., the St. Lawrence River), but at lower concentrations (0.41–69 ng/L). Pedrouzo et al. developed a method for the analysis of 11 pharmaceuticals in various water sources by SPE followed by LC-ESI-MS-MS (35). The limits of detection for river water samples were 5 ng/L for sulfadiazine, trimethoprim, sulfamethazine, sulfamethoxazole, and ranitidine and 10 ng/L for the other compounds. The highest concentrations found in river waters were for sulfamethoxazole (50 ng/L). In influent sewage waters, ranitidine was the most commonly detected compound with a maximum value of 0.24 μg/L. Wu et al. reported a method for the simultaneous determination of 36 pharmaceuticals (histamine receptor antagonists, psychoactive stimulants, anti-epileptics, anti-hypertensive, non-steroidal anti-inflammatories, analgesics and anti-pyretics, lipid regulator anti-biotics, anti-bacterials, skin care ingredient and metabolites of nicotine and lipid regulators) in surface water using SPE and LC-MS-MS (36). The optimized method was used to determine the occurrence of target analytes in surface water from the coastal Lake Erie in Oregon, northwest Ohio. Seventeen analytes were detected with concentrations up to hundreds of nanograms per liter in stream and lake water samples. A sensitive and highly selective method for the simultaneous determination of sulfonamides, macrolides, fluoroquinolones, and trimethoprim in wastewater and river water was developed by Senta et al. (37). The method was successfully applied to the analysis of raw municipal wastewater, wastewater effluents, and river waters. Stulten et al. developed a method for the analysis of diclofenac and two of its hydroxylated metabolites, 4'-hydroxy diclofenac (4'-OHD) and 5-hydroxy diclofenac (5-OHD), together with the lactam of 4'-OHD, 4'-hydroxy diclofenac dehydrate (4'-OHDD) using SPE followed by LC-ESI-MS-MS (38). The metabolites were detected in the samples in median concentration ranges of <LOQ to 0.71 ng/L, <LOQ to 0.45 ng/L, and <LOQ to 0.42 ng/L for 4'-OHD, 5-OHD, and 4'-OHDD, respectively, while median diclofenac concentrations ranged from 1.3 to 3.3 ng/L. It was found that the wide occurrence of its metabolites was highly relevant on account of their structural similarity and the toxicological properties of diclofenac. Choi et al. used the LC-ESI-MS-MS for the analysis of 11 pharmaceuticals, including acetaminophen, caffeine, carbamazepine, cimetidine, diltiazem, trimethoprim, and five sulfonamide antibiotics in real water samples (39). It was observed that levels of pharmaceutical residues in the influents were the highest for acetaminophen (average 27,089 ng/L), followed by caffeine (23,664 ng/L), cimetidine (8045 ng/L), and sulfamethoxazole (523 ng/L). Levels of acetaminophen and caffeine in STP effluents were very low compared to the influent concentrations. Conley et al. measured 14 analytes (acetaminophen, atorvastatin, caffeine, carbamazepine, ciprofloxacin, diltiazem, fluoxetine, levofloxacin, lovastatin, norfluoxetine, ranitidine, sertraline, sulfamethoxazole, and trimethoprim) with LC-MS-MS (40). In addition, they investiagated the spatial and temporal variations in the concentration of target pharmaceuticals. Busetti et al. developed a rapid direct injection LC-MS-MS method for real water sample analysis of iodinated X-ray contrast media comprising iopamidol, iothalamic acid, diatrizoic acid, iohexol, iomeprol, iopromide, ioxaglic acid, and iodipamide (41). Xiao et al. used LC-ESI-MS-MS combined with SPE for the senstive determination of 20 quinolone and fluoroquinolone anti-biotics (pipemidic acid, flerofloxacin, ofloxacin, pefloxacin, enoxacin, norfloxacin, ciprofloxacin, danofloxacin, enrofloxacin, lomefloxacin, difloxacin, sarafloxacin, gatifloxacin, sparfloxacin, moxifloxacin, cinoxacin, oxolinic acid, nalidixic acid, flumequine, and piromidic acid) in influent, effluent, and river waters (42). Kovalova et al. established a method for the determination of the cytostatics 5-fluorouracil, cytarabine, and gemcitabine and human metabolites uracil 1-beta-D-arabinofuranoside and 2',2'-difluorodeoxyuridine in wastewater using SPE combined with LC-ESI-MS-MS (43). Tong et al. developed a method for determining multi-residues of four classes of widely used anti -biotics in pig farms [sulfonamides (SAs), fluoroquinolone (FQs), tetracycline (TCs), and chloramphenicol (CAP)] with SPE combined with LC-MS-MS (44). The average antibiotics concentrations in groundwater, lake water, final effluent, and influent swine wastewater were, respectively, 1.6–8.6, 5.7–11.6, 7.9–1172.3 and 8.5–21692.7 ng/L in summer and 2.0–7.3, 6.7–11.7,5.8-409.5, and 32.8–11276.6 ng/L in winter.

Recently, more and more ultra performance liquid chromatography (UPLC) methods were developed for the analysis of pharmaceuticals, due to the shorter run times needed and smaller amount of solvents consumed compared with other previously reported HPLC-based methods. Among them, Conley et al. described a new method for the detection of 13 different pharmaceuticals and one metabolite in surface water at low ng/L levels with UPLC-MS-MS (45). Mean method detection limits were as low as 4.10 ng/L. Application of this method for the detection of pharmaceuticals in Tennessee River surface water determined that caffeine, sulfamethoxazole, and carbamazepine were frequently detected (100% of samples). Trimethoprim was moderately detected (30% of samples); acetaminophen, atorvastatin, and lovastatin were infrequently detected (10% of samples); and ciprofloxacin, diltiazem, fluoxetine, levofloxacin, norfluoxetine, ranitidine, and sertraline were not detected. This study reported the first detection of lovastatin in surface water. Kasprzyk-Hordern et al. introduced a new technique, UPLC-ESI-MS-MS, for the determination of multi-residue compounds including multiple classes of pharmaceuticals (acidic, basic, and neutral compounds: analgesic/anti-inflammatory drugs, anti-biotics, anti-epileptics, beta-adrenoceptor blocking drugs, lipid regulating agents, etc.), personal care products (sunscreen agents, preservatives, disinfectant/antiseptics), and illicit drugs (amphetamine, cocaine, and benzoylecgonine) in surface water and wastewater (46). The usage of the novel UPLC system with a 1.7-μm particle-packed column allowed for good

resolution. SPE with the usage of Oasis MCX (Waters, Milford, MA, USA) strong cation-exchange mixed-mode polymeric sorbent was selected. The influence of mobile phase composition, matrix-assisted ion suppression in ESI-MS, and SPE recovery on the sensitivity of the method was extensively studied. The method limits of quantification were at low ng/L and ranged from tenths to tens of ng/L in surface water and from single to a few hundreds of ng/L in wastewater. The method was successfully applied for the determination of pharmaceuticals in the River Taff (South Wales) and a wastewater treatment plant (WWTP Cilfynydd). A rapid and sensitive method was developed for the analysis of 48 human prescription active pharmaceutical ingredients and 6 metabolites of interest, utilizing selective SPE and UPLC-MS-MS by Batt et al. (18). The single-cartridge extraction step was developed using Oasis MCX and validated in both wastewater effluent and surface water. Method detection limits ranged from 1.0 to 51 ng/L. The analysis showed that effluent concentrations varied from 7 to 2950 ng/L and surface water concentrations ranged from 10 to 140 ng/L. Tamtam et al. developed a method for the determination of 17 anti-biotics belonging to five different antibiotic groups: quinolones (oxolinic acid, nalidixic acid, pipemidic acid, flumequine), fluoroquinolones (enoxacin, ciprofloxacin, norfloxacin, ofloxacin, enrofloxacin, sarafloxacin, danofloxacin, difloxacin, lomefloxacin), sulphonamides (sulphamethoxazole, sulphamethazine), nitroimidazole (ornidazole) and diaminopyrimidine (trimethoprim) in natural waters with UPLC-MS-MS (47). The separation of all compounds was achieved within 10 min. Performances of the method (recoveries, detection limit, quantification limit, and relative standard deviation) and matrix effects were studied. Results demonstrated that the method was suitable for routine analysis of anti-biotics in surface water. Samples analysis from the Seine River (France) confirmed the interest of anti-biotic contamination evaluation in that area.

Matrix effect is a major issue in the LC-MS-MS method since the matrix co-extracted with the analytes can alter the signal response, causing either suppression or enhancement, thus resulting in poor analytical accuracy, linearity, and reproducibility. During method development, it is of critical importance to diminish matrix effects as much as possible. Van De Steene and Lambert evaluated matrix effects from aqueous environmental samples in simultaneous analysis of a group of nine specific pharmaceuticals (flubendazole, propiconazole, pipamperone, cirmarizine, ketoconazole, miconazole, rabeprazole, itraconazole and domperidone) with LC-ESI-MS-MS and UPLC-ESI-MS-MS (48). Matrix effects could not be compensated for even though analogue internal standards were used during LC-MS-MS analysis. Therefore, the standard addition approach was necessary for accurate quantification. However, in UPLC, matrix effects could be lower or even eliminated due to the better resolution and more narrow peaks, since analytes will co-elute less with interferences during ionization (48). Results in this paper showed that matrix effects were almost eliminated if internal standards (structural analogues) in UPLC were used, therefore simplying the overall method with HPLC. To reduce matrix effect, Cappiello et al. proposed the direct electron ionization liquid chromatography-mass spectrometry (direct-EI LC-MS) interface, in which the ionization process was based on electron impact ionization (49). Since ionization occured in the gas phase, it was not influenced by coeluted matrix compounds. The authors also quantitatively evaluated matrix effects on enriched environmental and biological samples with different extraction procedures, using ESI and direct-EI LC-MS. They found that the samples analyzed with direct-EI were not affected by matrix composition, whereas with ESI either signal suppression or enhancement was observed, depending on the sample nature.

For identification and sensitive determination of pharmaceutical metabolites, there are several papers published regarding the application of more advanced hybrid mass spectrometry such as TOF-MS, QqToF, quadrupole linear ion-trap-mass spectrometry (QqLIT-MS), and the hybrid linear ion trap FT Orbitrap mass spectrometry (LTQ FT Orbitrap MS). Ibáñez et al. developed a method using UPLC coupled to TOF-MS for screening of non-target organic pollutants in water samples (50). The great accuracy and the resolution provided by a TOF analyzer allowed accurate measurement of the mass of any ionizable component in a sample. Anti-biotics (e.g., ofloxacin or ciprofloxacin) and drugs of abuse (e.g., benzoylecgonine, which is a cocaine metabolite) were detetced in several types of water samples. The results demonstrated that UPLC-TOF-MS was an efficient technique for the rapid screening of multi-class organic pollutants in water. Additionly, full-acquisition MS data obtained by TOF-MS provided valuable qualitative information, which facilitated the safe identification of many different compounds in samples. Ibáñez et al. explored QqTof-MS coupled to UPLC for the screening and confirmation of anti-biotics in water samples (51). In this paper, several types of water samples (surface water, influent and effluent wastewaters) were analyzed. Several anti-biotics were found in the samples, such as ofloxacin, ciprofloxacin, clarythromycin, or erythromycin. Moreover, the full spectrum data provided by TOF-MS acquisition enabled searching for many other pharmaceuticals that could be present in the samples in a "post-target" way. In all, this approach permited the detection and confirmation of paracetamol, omeprazole, and codeine, among others. For QqLIT-MS, Gros et al. created a method for the simultaneous detection and identification of 73 pharmaceutical residues, coveting various therapeutic groups, in both surface and wastewaters (52). The method was based on the simultaneous extraction of all target compounds by SPE, using a hydrophilic-lipophilic balanced polymer followed by LC-QqLIT-MS. Quantitative analysis was conducted using the 4000 Qtrap tandem mass spectrometer in selected reaction monitoring (SRM) mode, monitoring two SRM transitions to fulfill EC guidelines, as well as to ensure an accurate identification of target compounds in the samples. Quantitation was performed by the internal standard approach,

indispensable to correct matrix effects. Moreover, to obtain an extra tool for confirmation and identification of the studied pharmaceuticals, an information dependent acquisition (IDA) experiment was performed. This method demonstrated high sensitivity (limits of detection ranging from 0.1–55 ng/L) and selectivity. The method was sucessfully applied to the analysis of various influent and effluent wastewaters as well as river waters from Spain. Radjenović et al. developed a method for the analysis of the biodegradation of the β-blocker atenolol and the hypoglycaemic agent glibenclamide (53). The biodegradation tests were performed in batch reactors under aerobic conditions, using as inocculums sewage sludge from a conventional activated sludge treatment and a laboratory-scale membrane bioreactor. Pharmaceuticals were used as sole carbon sources, spiked at 50 ng/L and 10 mg/L concentrations. UPLC combined with QqTof-MS was used for the screening and the structural elucidation of biodegradation products. A microbial metabolite of atenolol with $[M+H]^+$ at 268 was detected in the positive electrospray ionization mode. This new compound was determined to be a product of microbial hydrolysis of the amide of the parent compound. Biodegradation of glibenclamide by activated sludge proceeded via bacterial hydroxylation of the cyclohexyl ring, which resulted in the formation of a metabolite with a protonated molecule, $[M+H]^+ = 510$. MS^3 experiments performed by LC-QqLIT-MS enabled further structural elucidation of the identified metabolites. Moreover, the highly sensitive QqLIT instrument in the MRM mode enabled the detection of parent compounds and one of the microbial metabolites identified in real wastewater samples. The methodology used in this study permitted for the first time the identification and detection of biodegradation product of β-blocker atenolol in real wastewater samples. Díaz-Cruz et al. developed a highly sensitive analytical method for the determination of nine sulfonamide antibiotics and one N-4-acetylated metabolite in environmental waters (wastewater, surface water, and groundwater) and bottled mineral water with LC-QqLIT-MS (54). Method limits of detection obtained for sulfonamides were in the range 0.01–1.13 ng/L and for the metabolite 0.08–461 ng/L. Hogenboom et al. applied LTQ FT Orbitrap MS for the target search for pharmaceuticals, benzotriazoles, illicit drugs, and for the identification of unknown compounds in water samples (55). In this study, a two-pronged strategy in MS research was employed: firstly, searching for accurate masses corresponding to target compounds known from priority lists or the scientific literature, and exploring effluent, surface, ground- and drinking-water samples; secondly, full-scan screening of water samples in search of "unknown" or unexpected masses, followed by MS^n experiments to elucidate the structure of the unknowns. The applications of accurate mass screening and identification described in this article demonstrated that the LC-LTQ FT Orbitrap MS was well equipped to meet the challenges posed by newly emerging polar contaminants.

Endocrine Disrupting Compounds (EDCs)

EDCs refer to natural and synthetic chemicals which have the ability to mimic hormones and are able to interfere or disrupt normal hormonal functions (4). EDCs include natural estrogens, natural androgens, phytosteroids, isoflavenoids, synthetic estrogens, pesticides, phthalates, alkylphenol ethoxylate surfactants, dioxins, coplanar polychlorinated biphenyls (PCBs), parabens, bisphenol A, and organotins (4). Because of their ecotoxicological potencies, EDCs have increased in interest. It is found that EDCs exsit in aquatic environments, through wastewater discharges.

To determine EDCs in environmental water samples, GC-MS and LC-MS-MS have been widely used. For GC-MS, recently, Van Hoeck et al. developed a multi-residue method for screening EDCs with GC-MS (56). In this method, SBSE was employed, followed by derivatization with BSTFA. In scan-mode MS, the limits of detection were in the range of 1–500 ng/L. Zhao et al. established an analytical method for the analysis of EDCs using GC-MS coupled with the negative chemical ionization (NCI) technique in water samples (57). Derivatization using pentafluorobenzoyl chloride (PFBOCl) before GC-MS analysis were applied and optimized for phenolic compounds. 4-Tert-octylphenol (4-t-OP), 4-nonylphenol (4-NP), bisphenol-A (BPA), estrone (E1), estradiol (E2), and triclosan (TCS) were detected at trace or ultra trace levels in the water samples. The highest concentrations of the phenolic compounds were found at 3,150 ng/L for 4-t-OP, 11,300 ng/L for 4-NP, 1,040 ng/L for BPA, 79 ng/L for El, 7.7 ng/L for E2, and 355 ng/L for TCS. To identify the decomposition of EDCs including estrone (E1), 17 beta-estradiol (E2), estriol (B), nonylphenol (NP), and bisphenol A (BPA) during ozonation of municipal sewage, Zhang et al. developed a method for determining the estrogenicity in the wastewater samples (58). The original estrogenicity, expressed as the E2 equivalent concentration (EEQC), in the primary effluents was 315–1018 ng/L. Results indicated that the EEQC can be reduced rapidly to below 10 ng/L after ozonation. To undoubtly determine EDCs, high-resoution GC-MS-MS has been employed by Ikonomou et al. (59). Detection limits were in the low- to mid-ng/L range, and recoveries were greater than 60% for most target analytes. This new method allowed for high through-put analysis of many organic wastewater contaminants in a complex matrix with relative standard deviation of less than 15% for most measurable compounds.

Although GC-MS is still being employed for the determination of EDCs, LC-MS-MS is increasingly applied. Hao et al. recently developed a high through-put LC-MS-MS method for the determination of 51 emerging organic pollutants in environmental waters including 10 EDCs (34). Kuster et al. developed a method for investigating the presence of 21 emerging contaminants of various chemical groups (seven estrogens and three progestogens included) in the Llobregat river basin (NE Spain), in which SPE was used as extraction method followed by LC-MS-MS analysis (60). Method detection limits were

$\leq$ 0.85 ng/L for estrogens and $\leq$ 3.94 ng/L for progestogens. Of the estrogens and progestogens analyzed, only estrone-3-sulfate, estrone, estriol, and progesterone were found to be present in the low nanogram per liter range in some of the samples investigated. Mieğe et al. studied estrogenic disrupting potency in rivers and wastewaters in the Orge catchment area near Paris, in which LC-MS-MS was used for the determinations of natural estrogens and synthetic estrogen (ethinylestradiol) (61). The estrone in all samples was in the range of 0.1–15.7 ng/L, while β-estradiol, was measured at a lower level (0.1–2.3 ng/L). No α-estradiol was detetced. Ethinylestradiol was only detected in WWTP effluent at 0.2 ng/L, estriol in WWTP effluent at 12.1 ng/L and downstream effluent at 4.9 ng/L.

Drinking Water Disinfection By-Products (DBPs)

DBPs are potentially toxic chemical compounds that are formed in extremely low concentrations during the disinfection of water supplies. They are the products of the reaction between disinfectants and natural, or sometimes man-made, organic and inorganic substances present in water (62). Toxicologically important DBPs include brominated, iodinated, and nitrogen-containing products (4). Studies have shown that some of DBPs are carcinogenic. It is also found that brominated DBPs are more carcinogenic than their chlorinated analogues and iodinated DBPs may be more toxic than their brominated analogues (4). Although concentrations of DBPs in drinking water are extremely low, it has been suggested that prolonged exposure to very low doses might have the same effect as short-term exposure to high doses (62).

Speicific DBPs that are of current interest include iodo acids, bromonitrometanes, haloaldehydes, haloamides, and nitrosodimethylamines (NDMAs), formed in chloraminated or chlorinated water, but is classified as a probable carcinogen (4). There are several papers published regarding the determination of DBPs. Zhang et al. developed a fast selective method for the detection of polar brominated DBPs in drinking water (63). In this work, negative ion ESI-MS-MS (setting precursor ion scans of m/z: 79 and 81) was used without LC separation. The results demonstrated that the ESI-MS-MS precursor ion scan was an effective tool for the selective detection of electrospray ionizable bromine-containing compounds in a complex mixture. Many polar/highly polar bromine-containing DBPs were tentatively found in two drinking water samples, and some of them may be new brominated DBPs that have not been previously reported. This method was also extended for the selective detection of polar bromine-containing compounds/contaminants in groundwater, surface water, and wastewater. Heffner et al. reported a method for identifying potential DBPs, in which gas chromatography fourier transform ion cyclotron resonance mass spectrometry (GC-FT-ICR-MS) was used (64). In this method, both LLE and SPME techniques were utilized for sample preparation prior to GC-MS analyses. Six DBPs were detected and their molecular compositions were assigned at a high level of confidence.

NDMAs, recently discovered to be DBPs in drinking water, have been determined by GC-MS or LC-MS-MS. A method was developed to determine nine NDMAs in wastewater based on SPE and LC-MS-MS with LTQ Orbitrap hybrid instrument at high mass resolution by Krauss and Hollender (65). In this method, due to better sensitivity, the molecular ions were usually used for quantification, and the product ions for confirmation. An actual mass resolving power of 25,000–40,000 ensured a sufficient selectivity to distinguish all molecular and product ions from interfering background ions. The optimized method allowed the quantification of nine NDMAs in drinking water and wastewater samples with method detection limits of 0.3–3.9 ng/L. In two wastewater treatment plants, N-Nitrosodimethylamine and N-nitrosomorpholine were the most abundant compound at 3–22 ng/L, in which another four nitrosamines (N-nitrosopyrrolidone, -piperidine, -diethylamine, and -dibutylamine) were also found. These results demonstrated that LTQ Orbitrap was a powerful instrument to quantify NDMAs at the picogram level in complex matrixes with both a high sensitivity and selectivity. Hu et al. developed three methods for the determination of NDMAs (66). In the first method, pulsed splitless gas chromatography-nitrogen phosphorus detector (GC-NPD) was used, in which high sensitivity can only be achieved when the NPD bead is extremely clean. In the second method, large volume injection (LVI) GC-MS was employed. The results demonstrated that PTV-GC-MS equipped with dual column of DB-5MS (30 m $\times$ 250 mm $\times$ 0.25 mm) and OV-1701 (30 m $\times$ 250 mm $\times$ 0.25 mm) could overcome the matrix interference for the trace analysis. In the third method, PTV-GC-MS-MS was employed. It was found that the PTV-GC-MS-MS system could efficiently remove the interference on a single DB-5MS (30 m $\times$ 250 mm $\times$ 0.25 mm) column with good sensitivity and selectivity. Planas et al. developed a method for the analysis of nine NDMAs in water samples, on the basis of automated SPE and isotope dilution GC-MS with high resolution (67). Quality requirements for isotope dilution-based methods were accomplished for most analyzed nitrosamines, regarding to trueness (80–120%), method precision (<15%), and method detection limits (0.08–1.7 ng/L).

UV Filters

UV filters are compounds used for absorbing UV light (organic UV filters) or reflecting/scattering UV light (inorganic UV filter: TiO_2, ZnO) in sunscreens, cosmetics, and other personal care products (4). Due to their presence in aquatic environments and growing concern about UV radiation and skin cancer, UV filters have attracted more attention.

For UV filters, there are several reviews published. Giokas et al. mentioned that UV filters may be systematically absorbed through the skin surface or enter into the aquatic environment during bathing and washing activities, etc. (68). Thus, it was necessary to investigate the magnitude and effects of skin penetration as well as accumulation in the water environment. In this paper, they reviewed the analytical methods on UV-filter

determination in biological and environmental samples (68). Another review (69) described the processes undergone by UV filter compounds once released into the environment. In addition, the instrumental methods, based on chromatography and MS, for their determination in environmental samples were included. The metabolites, photodegradates, and by-products of wastewater treatment were also discussed in detail in this paper.

For the measurement of UV filters, both GC-MS and LC-MS-MS have been employed. Cuderman and Heath developed a method using SPE and GC-MS for analyzing UV filters with the commercial name Eusolex (homosalate, 4-methylbenzylidenecamphor, benzophenone-3, octocrylene, butylmethoxydibenzoylmethane, ethylhexyl methoxycinnamate) and two common anti-microbial agents, clorophene and triclosan (70). After SPE, extracted compounds were then derivatized before analysis by GC-MS. Limits of detection of 13–266 ng/L for UV filters were obtained. It was found that the most abundant UV filter was benzophenone-3 (11–400 ng/L) in environmental samples. Rodil and Moeder developed a method using SBSE combined with thermal desorption GC-MS for the determination of nine UV filters in water samples (71). A sample volume of 20 mL was used and detection limits were between 0.2 and 63 ng/L. Rodil et al. established a novel analytical method for the determination of UV sunscreen agents including three very polar sulfonates (e.g., 2-phenylbenzimidazole-5-suffonic acid) and six other less polar compounds (e.g., benzophenone-3, octocrylene....) in the water environment, based on SPE and LC-ESI-MS-MS (72). Detection limits between 7 and 46 ng/L were achieved. Benzophenone-4 was found in environmental water samples at 237–1481 ng/L. Kawaguchi et al. developed a method for the simultaneous measurement of benzophenone sunscreen compounds and its derivatives 2,4-dihydroxybenzophenone, 2-hydroxy-4-methoxybenzophenone, 2-hydroxy-4methoxy-4'-methylbenzophenone, 2-hydroxybenzophenone, 3-hydroxybenzophenone, and 4-hydroxybenzophenone in water samples using SBSE with in situ derivatization followed by thermal desorption GC-MS (73). The detection limits of 0.5–2 ng/L for the seven target compounds were obtained. To determine the fate of UV filters, Negreira et al. studied the stability of three UV filters: 2-ethylhexyl salicylate, 2-ethylhexyl 4-(dimethylamino) benzoate, and 2-hydroxy-4-methoxybenzophenone and its metabolite, 2,4-dihydroxybenzophenone, in water samples containing low concentrations of free chlorine, in which SPE was used as the extraction method and GC-MS after silylation was employed as the detection instrument (74). It was observed that ES showed an acceptable stability whereas the rest of species reacted with free chlorine at significant rates following pseudo-first-order kinetics. A relatively simple degradation pathway for 2-ethylhexyl 4-(dimethylamino) benzoate was established: it consisted of aromatic substitution of one atom of hydrogen per chlorine or bromide. The same reaction pattern was observed for 2-hydroxy-4-methoxybenzophenone leading, in this case, to mono- and di-halogenated by-products. In addition, several halogenated forms of 3-methoxyphenol were identified as BP-3 cleavage by-products.

Brominated Flame Retardants

Brominated flame retardants are a group of organic flame retardants that contain bromine. They are applied to prevent electronics, clothes, and furniture from catching fire. Brominated flame retardants include polybrominated diphenyl ethers (PBDEs), polybrominated biphenyls (PBBs), brominated cyclohydrocarbons, decabromodiphenyl ethers (*De*BDEs), hexabromocyclododecanes (HBCDs), and tetrabromobisphenol A (TBBPA) (4). Because of their widespread presence in the environment and their potential toxicity to humans and animals, increasing concern has prompted many countries to ban some of them (4).

Due to the hydrophobic characters of brominated flame retardants, GC-MS or GC-MS-MS is usually used for their determination. Serodio et al. developed a method for the determination of eleven PBDEs, from tetra to nona congeners (BDE-47, BDE-100, BDE-99, BDE-85, BDE-154, BDE-153, BDE-183, BDE-197, BDE-196, BDE-207, and BDE-206), in environmental matrices by using GC-MS after SBSE and liquid desorption (75). Low detection limits (0.3–203.4 ng/L) were achieved for the 11 congeners studied. The proposed method was applied for the determination of ultra-trace levels of PBDEs in waste water, sediments, and printed board circuit matrices. Prieto et al. created a SBSE for the determination of PBDEs and PBBs in water samples, in which GC-MS was employed (76). In this method, statistical design of experiments was used for the optimization of extraction conditions. Recovery at 82–106% and repeatability (less than 18%) was achieved. Detection limits of 1.1–6.0 ng/L were obtained for the congeners studied. López et al. developed several methods for measuring bromoanisoles, bromotoluenes, bromoalkanes, and 1,5,9–cyclododecatriene, in which extraction methods were LLE, SPE, and SPME, in which GC-MS with electron capture negative ionization or electron impact was used for quantification (77). It was observed that detection limits at the low ng/L for most of the target analytes were achieved. For LC analyis, Li et al. developed a new method using single-drop microextraction, one mode of LPME, and HPLC for the determination of decabromodipherryl ether (BDE-209) in water samples (78). Under optimal extraction conditions, the limit of detection was 0.7 ng/mL. Gomara et al. reported a method for the enantiomer specific determination of HBCDs by LC-ESI-MS-MS (ion trap analyz was used) (79). The method was based on the formation of a chlorine adduct (m/z 676.6) of the (+/-) alpha-, (+/-)beta-, and (+/-)gamma-HBCD enantiomers and their further fragmentation into their stable quasi-molecular ion (m/z 640.6). In this way, problems related to the ion trap low mass cutoff and variable amounts of other adduct peaks in the samples were solved. The detection limits were from 1.5 and 4.3 ng/mL. Guerra et al. developed a method for the simultaneous determination of HBCD diastereoisomers and TBBPA and its derivatives by LC-QqLIT-MS (80). Two different experiments

were developed. In the first one, a SRM method was used, in which the two most abundant transitions were selected for each analyte. In the second, the ion trap was used for the storage and subsequent fragmentation of precursor ions, obtaining an enhanced product ion (EPI) experiment. Limits of detection were in the range of 0.1–1.8 pg and 0.01–0.5 pg for the SRM and EPI experiments, respectively.

Recently, the occurrence, transport, and fate of brominated flame retardants were investigated. Petreas and Oros studied the occurrence of PBDEs in California wastestreams (81). Based on measurement of PBDEs in samples of such waste streams, the consumption of PBDEs of assumption were estimated. Compared with the reported consumption of PBDEs in California, about half of the PBDEs could not be accounted for in the waste streams examined, suggesting that additional waste streams, such as household wastes, should be evaluated for their PBDEs content. Ueno et al. developed a method for determining the occurrence of hydroxylated-PBDEs (OH-PBDEs) (metabolites of PBDEs) in abiotic environment (82). In this study, OH-PBDEs were determined in samples of surface water and precipitation (rain and snow) collected from sites in Ontario, Canada. The results in this study suggested that OH-PBDEs were ubiquitous in the abiotic environment and most likely were produced through reaction of PBDEs with atmospheric OH radicals. As well, they may be present in surface waters near STPs due to oxidation of PBDEs and inflows from metabolism by humans and animals. Guan et al. studied the riverine inputs of PBDEs from the Pearl River Delta to the coastal ocean (83). It was found that the sigma(17)-PBDEs (sum of 17 BDE congeners, i.e., BDE-28, -47, -66, -85, -99, -100, -138, -153, -154, -183, -196, -197, -203, -206, -207, -208, and -209) concentrations varied from 344 to 68,000 pg/L, with those of BDE-209, BDE-47, and BDE-99 being 335-65, 200, 3–143, and <1–200 pg/L, respectively. Based on the concentration of PBDEs, the consumptions were estimated. Wang et al. investigated the effect of municipal sewage treatment plant effluent on bioaccumulation of PBDEs and PCBs in the recipient waters (84). The results suggested that bioaccumulations of PBDEs and PCBs were found in aquatic species. The logarithm bioaccumulation factor (BAF) decreased with the number of bromines in PBDEs molecules, while the log BAF versus the number of chlorines in PCBs appears to be parabolic. However, it was not obvious that biomagnifications of these compounds existed in the food web.

CONCLUSIONS

In recent years, advanced instruments such as GC-MS, GC-MS-MS, LC-MS, LC-MS-MS, etc., have been developed and widely employed in analysis of emerging contaminants in aquatic environments. It is demonstrated that these advanced instruments are helpful in the quantification of trace levels of emerging contaminants with high precision and sensitivity. In addition, more advanced extraction techniques such as SPE, SPME, SBDE, and LPME are used for sample preparation in the analysis of emerging contaminants. Among them, SPE is the most popular and well-established technique because it is robust and highly selective. The automated SPE has been widely used in environmental analyses.

However, due to the unknown structures of emerging contaminants metabolities and their existence in complex environmental matrix with trace level, it is a challenge to develop a rapid and accurate analytical method. Therefore, further research is needed to improve the structure elucidation as well as method accuracy and sensitivity.

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