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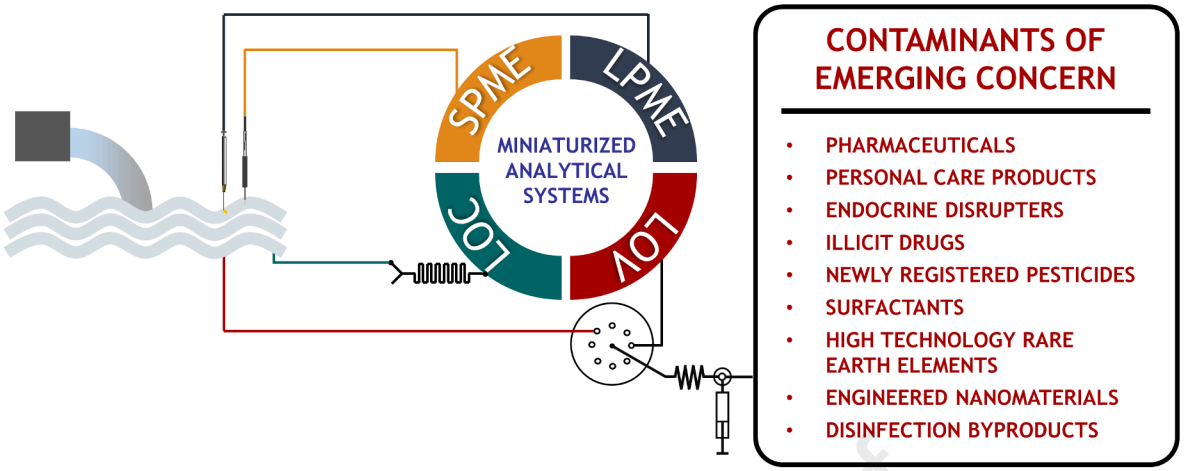
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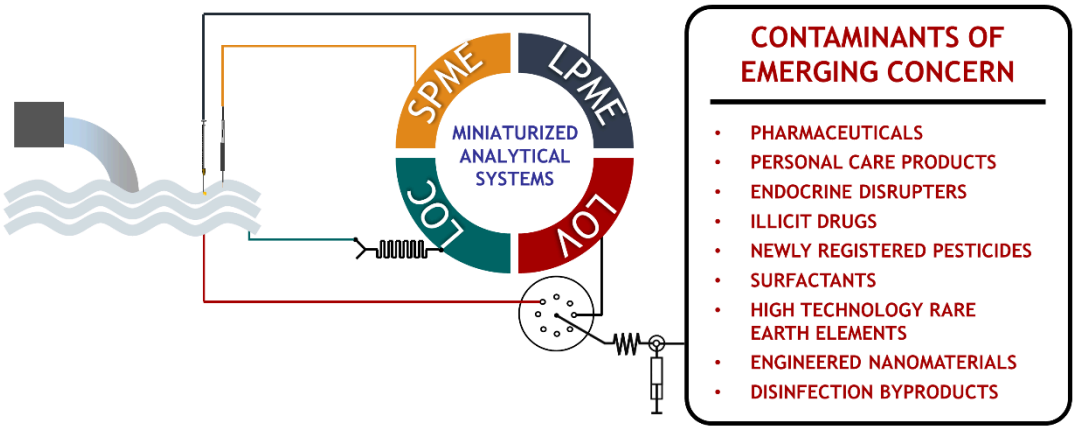
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Graphical abstract

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Abbreviations:

AμE, adsorptive microextraction; AChE, acetylcholinesterase; AEEC, automated extraction and electrospray ionization chip; BAμE, bar adsorptive microextraction; BHF, bundled

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polypropylene hollow fiber array; BI, bead injection; CAR, carboxen; CE, capillary electrophoresis; CECs, contaminants of emerging concern; CIAME, cold-induced aggregation microextraction; CRMs, certified reference materials; D-µSPE, dispersive micro-solid phase extraction; DAD, diode array detection; DBPs, disinfection by-products; DES, deep eutectic solvents; DI, direct immersion; DLLME, dispersive liquid-liquid microextraction; DSDME, directly suspended droplet microextraction; DVB, divinylbenzene; E1, estrone; E2, estradiol; E3, estriol; EA, electro-assisted; ECD, electron capture detection; EDs, endocrine disruptors; EE2, ethinylestradiol; EFSA, European Food Safety Authority; EME, Electromembrane extraction; ENMs, engineered nanomaterials; ESI, electrospray ionization; ETAAS, electrothermal atomic absorption spectrometry; ETV, electrothermal vaporization; FAAS, flame atomic absorption spectrometry; FID, flame ionization detection; FLD, fluorescence detection; GC, gas chromatography; HF, hollow fiber; HS, headspace; IC, ion chromatography; ICP, inductively coupled plasma; IL, ionic liquid; ISFME, *in situ* solvent formation microextraction; IT, in-tube; IUPAC, International Union of Pure and Applied Chemistry; L/SME, liquid/solid phase microextraction; LC, liquid chromatography; LDR, linear dynamic range; LLE, liquid-liquid extraction; LLME, liquid-liquid microextraction; LLLME, liquid-liquid-liquid microextraction; LOC, lab-on-a-chip; LOD, limit of detection; LOQ, limit of quantification; LOV, lab-on-valve; LPME, liquid-phase microextraction; MAE, microwave-assisted extraction; MCE, microfluidic chip electrophoresis; MEKC, micellar electrokinetic chromatography; MEPS, microextraction by packed sorbent; MIP, Molecularly imprinted polymer; MOF, metal-organic framework; MS, mass spectrometry; MSAµE, adsorptive microextraction in multiple spheres; MSPE, Magnetic solid-phase extraction; NNIs, neonicotinoids; NOM, natural organic matter; NPD, nitrogen-phosphorous detection; NPs, nanoparticles; NSAIDs, non-steroidal anti-inflammatory drugs; NTD, needle trap device; PA, polyacrylate; PAD, paper-based device; µPAD, Microfluidic paper-based analytical device; PBDEs, polybrominated diphenyl ethers; PCPs, personal care

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products; PDMS, polydimethylsiloxane; PIL, polymeric ionic liquid; PLE, pressurized liquid extraction; PS, paper spray; QDs, quantum dots; Q-TOF, quadrupole time-of-flight ; RCA, rolling circle amplification; REEs, rare earth elements; RSD, relative standard deviation; SBME, solvent bar microextraction; SBSDμE, stir bar sorptive-dispersive microextraction; SBSE, stir-bar sorptive extraction; SDME, single drop microextraction; SERS, for surface-enhanced Raman spectroscopy; SFODME, solidified floating organic drop microextraction; SLE, solid-liquid extraction; SLM, supported liquid membrane; SPE, solid phase extraction; SPME, solid phase microextraction; STPs, sewage treatment plants; SUPRASs, supramolecular nanosolvents; TFME, thin film microextraction; TGA, thioglycolic acid; UHPLC, ultra-high-performance liquid chromatography; UNODC, United Nations Office on Drugs and Crime; US, ultrasound; UV, ultraviolet detection; VALLME, vortex-assisted liquid-liquid microextraction; WWTPs, wastewater treatment plants; XRF, X-ray fluorescence spectrometry.

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Abstract

The determination of contaminants of emerging concern (CECs) in environmental samples has become a challenging and critical issue. The present work focuses on miniaturized analytical strategies reported in the literature for the determination of CECs. The first part of the review provides brief overview of CECs whose monitoring in environmental samples is of particular significance, namely personal care products, pharmaceuticals, endocrine disruptors, UV-filters, newly registered pesticides, illicit drugs, disinfection by-products, surfactants, high technology rare earth elements, and engineered nanomaterials. Besides, an overview of downsized sample preparation approaches reported in the literature for the determination of CECs in environmental samples is provided. Particularly, analytical methodologies involving microextraction approaches used for the enrichment of CECs are discussed. Both solid phase- and liquid phase-based microextraction techniques are highlighted devoting special attention to recently reported approaches. Special emphasis is placed on newly developed materials used for extraction purposes in microextraction techniques. In addition, recent contributions involving miniaturized analytical flow techniques for the determination of CECs are discussed. Besides, the strengths, weaknesses, opportunities and threats of point of need and portable devices have been identified and critically compared with chromatographic methods coupled to mass chromatography. Finally, challenging aspects regarding miniaturized analytical methods for determination of CECs are critically discussed.

Keywords: Emerging contaminants; Microextraction; Microfluidics; Millifluidics; Miniaturization; Sample preparation

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1. Introduction

Regulated contaminants are worldwide monitored and controlled by means of reference analytical methods. These methodologies enable to discern whether a contaminant is present at toxicologically acceptable levels in analyzed samples. Ensuring contaminant levels below their maximum contaminant levels set by widely recognized agencies is therefore fundamental to implement public health protection. Apart from regulated contaminants, a number of unregulated chemicals that have been classified as contaminants of emerging concern (CECs) are receiving increasing attention. The term 'contaminants of emerging concern' is commonly employed to refer to those chemicals that, in spite of not being currently regulated, might be considered in future regulations due to their potential risk for human health and environment. This term is not only employed to consider newly developed compounds but also refers to those chemicals consistently used and increasingly released to the environment that may pose concerns to the environment, food safety and human health [1].

CECs have awakened much interest in a wide range of scientific and technological areas, environmental sciences, chemistry and chemical engineering representing ca. 70% of the total number of contributions as shown in **Figure 1**A-B. In particular, the number of publications devoted to their determination has steadily increased in the last decade, as can be observed in **Figure 1**C-D. The development of analytical methods that enable the sensitive and selective determination of CECs is therefore of paramount importance.

A significant number of review articles on CECs written from different perspectives can be found in the literature. Thus, readers can find relevant information on the occurrence and fate of CECs [2,3], strategies for their removal [4–7] or chemical analysis [8–12]. Regarding analytical methods, several reviews focus on the methodologies devoted to the determination of a given group of CECs (*e.g.* personal care products (PCPs) or disinfection by-products (DBPs))

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[11–14], or deal with the determination of CECs in a specific sample type (*e.g.* water, sewage sludge, marine organisms, atmospheric or clinical samples) [8,11,13,15], but little or no attention is paid in these contributions to miniaturized approaches employed for determination of CECs.

The miniaturization of analytical methodologies is, in fact, a matter of much interest. Reducing dimensions of conventional analytical systems is not the only driving force toward miniaturization, but also widely reducing the amounts of reagents and solvents used per analysis and, consequently, decreasing the amounts of generated wastes, among other aspects. In this sense, a number of downscaled sample preparation approaches broadly encompassed under the denomination of microextraction techniques have been developed to overcome the limitations of conventional sample preparation counterparts [16,17]. On the other hand, miniaturized flow-based approaches such as lab-on-valve (LOV) and lab-on-a-chip (LOC) systems enable to integrate several steps of the analytical process [18,19] thus showing high potential for the determination of CECs.

The present work provides an overview of CECs, paying special attention to their occurrence and fate (section 2), the developments in (solid- and liquid-phase) microextraction techniques for enrichment from environmental samples (section 3) and miniaturized flow-based analytical systems for their determination (section 4). In addition, the strengths, weaknesses, opportunities and threats of recently reported point of need and portable devices for CECs determination as alternatives to conventional chromatographic methods is discussed (section 5).

2. Occurrence and fate of contaminants of emerging concern

A brief overview of CECs whose monitoring is of particular significance, namely pharmaceuticals, PCPs, endocrine disruptors (EDs), newly registered pesticides, illicit drugs, surfactants, high technology rare earth elements (REEs), natural and engineered nanomaterials (ENMs) and DBPs, is provided in this section. Additional information on the sources of CECs,

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their transport and degradation, environmental and health-related issues, as well as remediation strategies for CECs can be found in several recent review articles [2,3,24,25,4–7,20–23].

2.1. Pharmaceuticals

Pharmaceuticals are a group of anthropogenic chemicals that include, among others, anti-inflammatories and analgesics, antibiotics, antiepileptics, antidepressants, lipid lowering agents, antihistamines and β-blockers, and represent one of the largest environmental inputs [26,27]. Pharmaceuticals are widely present in all water bodies, ranging from a few ng L^{-1} to high μg L^{-1} [28]. Their concentration levels depend on the studied location and the prescription profile in the corresponding area [29]. Pharmaceuticals have also been detected in other compartments of the environment, including soils, where pharmaceuticals are present at lower concentrations than those found in water resources, and aquatic organisms [30]. Even though pharmaceuticals are generally found at very low concentrations in the environment, their continuous release to the environment is a matter of much concern. Furthermore, the acute risk posed by a single drug molecule is not necessarily the same as when the molecule is present in the environment together with other pollutants, resulting in their synergistic action [31].

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2.2. Personal care products

PCPs are another important family of CECs, which include a number of chemicals used in cosmetics and daily care products such as fragrances, plasticizers, synthetic musks, UV-filters and preservatives. PCPs have been frequently detected in environment waters worldwide [32]. Nitro musks are compounds potentially toxic to aquatic species that are slowly being phased out, while polycyclic musks are produced and used in very large quantities [26]. Both types of musk products are ubiquitous in the environment and show estrogenic activity [33]. UV filters have unique properties because they can absorb, reflect and/or diffuse UV radiation, thus protecting

human skin and our health. As CECs, UV filters are of great concern and their detection in the aquatic environment indicates their high chemical stability and persistence [34]. Several UV filters have been detected in all environmental compartments [35] and, due to their high lipophilicity and relative stability to biodegradation, UV filters have been shown to accumulate in the suspended particles contained in water, sediments, sludge or in the food chain. Moreover, UV filters can alter the endocrine system of aquatic fauna [13]. Although UV filters should be stable to UV exposure, research has shown that several organic UV filters are not resistant and decompose, mainly by photolysis, but also by reaction with chlorine in marine medium [36]. The process of UV filters photolysis in natural waters is slow, but it can be accelerated with the help of photosensitisers. The resulting decomposition products of UV filters represent an additional environmental stress [34].

2.3. Endocrine disruptors

EDs include a collection of chemicals capable of interfering hormone biosynthesis and thus affecting the balance of the endocrine systems of wildlife and humans even at very low concentrations. EDs are widely used in industrial, domestic and agricultural applications and are easily released into the environment from the time they are manufactured until they are used and discarded [37]. EDs are mainly in gaseous phase, while compounds of semi-volatile nature are more likely to be associated with airborne particles [38]. On the other hand, many EDs are soluble in water and their presence has been regularly reported in the aquatic environment around the world. Their occurrence depends on the close presence of cities and agriculture/industrial areas, being wastewater treatment plants (WWTPs) effluents a significant point source of many of these EDs [37,39]. Moreover, EDs might interact with sediments by hydrophobic partition and, thus, lipophilic EDs can be found at higher concentrations in this compartment [40]. EDs can also be directly transferred to soil due to land application of

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biosolids and manure, irrigation with reclaimed water or effluents from WWTPs. Once in soil, certain EDs have the potential to be taken up by plants. Thus, during the EDs cycle in the environment, some EDs can enter the food chain and could pose a risk to human health [41–43].

2.4. Illicit drugs

Illicit drugs are CECs which have an adverse influence on environment, ecology and human health. According to the United Nations Office on Drugs and Crime (UNODC) publication Terminology and Information on Drugs, illicit drugs are non-prescribed or psychotropic drugs with their production, sale and use prohibited by the universal drug control laws [44]. The illicit drug consumption has increased worldwide since the 1990s, and its growth rate has greatly exceeded that of the normal population [44]. Common illicit drugs and their metabolites include, among others, cocaine, benzoylecgonine, morphine, codeine, 6-acetylmorphine, methadone, amphetamine, methamphetamine, 3,4-methylenedioxyamphetamine and 3,4-methylenedioxymethamphetamine. Illicit drugs and their metabolites are released into the environment eventually following their metabolism in the human body or by direct disposal. They will go through various processes in the environment, including adsorption, degradation, leaching and transportation in natural waters, accompanied by interaction with different substances [45]. There is a potential high risk of accidental toxicity to aquatic life. So far, plenty of illicit drugs have been determined in environmental waters, sewage sludge and air, which confirms the wide distribution of illicit drugs worldwide. Furthermore, the low removal efficiency of WWTPs is another important reason for the widespread occurrence of illicit drugs and metabolites in the environment [46]. It is suggested that the treatment schemes of WWTPs do not completely remove these CECs and can cause a problem of restricted waterways in rapidly urbanizing regions [45]. Consequently, the corresponding legislations and policies should

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be strengthened to regulate illicit drugs and strenuous efforts should be devoted to improving sewage removal efficiency of illicit drugs.

2.5. Newly registered pesticides

Pesticides to be commercialized must be first registered and their potential for health and ecological effects evaluated. Newly registered pesticides include new pesticide chemicals or different uses of existing chemicals. In addition, already registered pesticides must be re-evaluated periodically to ensure that they continue to be safe. As a remarkable example, neonicotinoids (NNIs) can be considered a relatively new class of insecticides. The first NNIs were approved in the EU in 2005 and since then, they have become one of the most commonly pesticides used worldwide and, within them, imidacloprid has been the world's largest selling insecticide. Thus, it is not surprising that studies have confirmed the widespread contamination by NNIs over the world in several environmental compartments. The occurrence of NNIs in soil is mainly related to their use in agricultural soils. Since NNIs are highly water soluble, residues remaining in the soil might move into surface waters or leached into groundwater. NNIs have been frequently detected in several types of water reservoirs, effluents from WWTPs, and tap water. Besides, NNIs can enter the atmosphere from treated seeds during planting, tillage or wind erosion events [47–51]. The presence of NNIs has been linked to the loss of biodiversity and the reduction of insects, particularly affecting pollinator species like bees [52]. At this regard, in 2013, the use of clothianidin, imidacloprid and thiamethoxam was severely restricted to protect honeybees**.** Later, the European Food Safety Authority (EFSA) was commissioned to carry out risk assessments for the use of the above-mentioned NNIs and their impact on bees. On the basis of that study, the European Union banned in 2018 all outdoor uses of such NNIs in order to protect honeybees and only their use in permanent greenhouses remained possible. From

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this example, it is clear that there is a need for permanent quality monitoring data of potential environmental pollutants to evaluate their occurrence and impact on the environment.

2.6. Surfactants

Surfactants are a group of chemicals that show solubility in polar and nonpolar liquids, amphiphilicity, ability to form micelles, and adsorption at phase boundaries. They are produced and consumed in huge quantities, especially as key components of (bio)detergents and cleaners, and for other industrial applications. Monitoring their distribution, behavior and final fate once they reach aquatic environments is of particular relevance [53–55]. At concentrations above the critical micelle concentration level, namely, the threshold concentration at which surfactant molecules aggregate into micelles, surfactants can solubilize large amounts of hydrophobic organic compounds present in the aqueous phase. Surfactant degradation by microorganisms is the primary transformation process occurring in the environment, as well as in WWTPs. During biodegradation, the microorganisms can either utilize surfactants as substrates to obtain nutrients and energy, or cometabolize the surfactants by microbial metabolic reactions [55]. The occurrence, levels and fate of surface active compounds in the environment are described in detail in several review papers [54–56].

2.7. High technology rare earth elements

REEs are referred to a group of 17 elements, including Sc, Y and the 15 lanthanoids (La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu), in accordance with the International Union of Pure and Applied Chemistry (IUPAC) [119]. REEs show paramount importance in the transition process to a low-carbon technology [57]. Their unique properties make them critical for the development of technological devices, among other uses [121,122]. The increasing demand of REEs (expected annual growth rate of 13.7% between 2017 and 2021) is, however, a

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source of concern. Particularly, the demand of REEs is not in balance with their natural abundance, leading to an economic issue known as "balance problem" [58]. In this sense, REEs present at very low amounts (*e.g*. Dy, with an estimated crustal abundance of 3.0-7.5 parts per million) are highly required, whereas more abundant REEs (*e.g*. Y, with an estimated abundance that is an order of magnitude higher) are currently less demanded [59]. The widespread use of REEs is leading to increased concentration levels in the different environmental compartments [60,61]. REEs can be bio-accumulated through the food chain, being detected in human hair, nails and biofluids [60]. Several deleterious effects have been associated to human exposure to REEs, including damages to nephrological system, dysfunctional neurological disorder, fibrotic tissue injury, pneumoconiosis or male sterility [60].

2.8. Natural and engineered nanomaterials

Nanoparticles (NPs) are materials showing a length of 1 to 100 nm in at least one dimension that occur naturally in the environment. Depending on the environmental conditions (*e.g*. presence of natural organic matter (NOM), pH, temperature and light), metal NPs and their oxides/sulfides can be formed spontaneously in different compartments by biogeochemical processes [62]. Remarkably, the mass of naturally occurring NPs formed per year has been estimated to be several orders of magnitude higher than the amount of ENMs produced annually [62]. Based on their composition, ENMs can be classified as carbon-containing NPs, such as fullerenes, carbon nanotubes and graphene; and inorganic NPs, including elemental metals (*e.g*. gold and silver NPs, zero-valent iron NPs), metallic and metalloid oxides (*e.g*. TiO_2, SiO_2 and iron oxides) and metal salts. The release of ENMs to the environment is expected to increase significantly in the years to come due to the growing relevance of nanotechnology. Once in the environment, ENMs can suffer physical, chemical and biological transformations and, consequently, their size, morphology and even stability can be significantly affected [63–65]. The toxicity of ENMs can

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be significantly different from the one of natural NMs, due to differences in the type of capping agents present at their surfaces, among other factors [62]. Moreover, ENMs transformed in the environment can show enhanced risk to the environment and human health due to the release of toxic metals, or adsorption of environmental pollutants, among others [64,66,67].

2.9. Disinfection by-products

Disinfection of water is a treatment process carried out to inactivate pathogenic microorganisms present in water bodies aimed at avoiding waterborne diseases and increasing the quality of water for its consumption. However, disinfection of waters can lead to the unintended generation of potentially toxic DBPs by reactions of disinfectants (e.g. chlorine, chloramine, chlorine dioxide, ozone, and UV irradiation) with NOM, halides and other anthropogenic compounds (*e.g.* pesticides, pharmaceuticals, surfactants or estrogens) [68,69]. A small number of DBPs are currently regulated, with maximum concentration levels that vary substantially among countries [70]. DBPs regulated by the USEPA include trihalomethanes, haloacetic acids, and inorganic oxyanions such as chlorite and bromate [71]. Even though more than 700 DBPs have been identified, the number of identified DBPs accounts for less than half of the total organic halide contents [68]. Unregulated DBPs such as haloacetonitriles, haloketones and halonitromethanes are widely distributed in drinking waters around the world with concentration levels that vary substantially [72]. Most of studies involving halogenated DBPs have focused on chlorine-containing DBPs, although brominated and, especially, iodinated DBPs often show higher toxicity than their chlorinated analogues [68]. In addition, nitrogenous DBPs derived from waters containing significant levels of organic nitrogen content have raised concerns due to their higher cytotoxicity and genotoxicity than analogous carbonaceous DBPs [14]. DBPs have received much attention in recent years owing to their toxicity and widespread distribution in the environment. Thus, researchers have placed strong emphasis on the identification and

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determination of these CECs as well as on the assessment of their formation pathways [68,69,73].

3. Downsized sample preparation approaches for determination of contaminants of emerging concern

In this section, an overview of downsized sample preparation approaches is provided. In particular, solid-phase and liquid-phase based microextraction approaches are reviewed and relevant applications involving microextraction approaches for determination of target CECs in environmental samples are summarized in **Tables 1** and **2**.

3.1. *Solid phase-based microextraction techniques*

3.1.1. *Solid-phase microextraction*

SPME was introduced by Pawliszyn and Arthur in 1990 [74] and has become one of the most used sample preparation techniques in analytical laboratories worldwide. SPME is based on the partitioning of target analytes from the sample to the coating of a small fiber, presenting some inherent advantages related to the combination of sampling, analyte isolation and enrichment in a single step as well as environmental friendliness and expeditiousness. Since its introduction, SPME has undergone modifications expanding both the nature of the samples and the variety of analyzed compounds. In this sense, many examples of the applications of SPME for determination of CECs in liquid, gaseous and solid environmental samples, including *in vivo* sampling, are available in the literature and some recent relevant applications are mentioned in **Table 1**.

Direct immersion-SPME (DI-SPME), in which a coated fiber is immersed in an aqueous sample, has been widely used in the analysis of CECs. The direct immersion mode is recommended for extracting analytes present in clean matrices, irrespective of their volatility.

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Experimentally, after fiber conditioning, the SPME fiber is immersed into the sample solution, as shown in **Figure 2**A. After extraction for a prescribed time, analytes can be thermally desorbed from the fiber at the GC injector port or eluted with an appropriate solvent for further analysis. In most cases, subsequent separation and quantification is carried out by GC usually coupled to MS or by LC coupled to UV, diode array detection (DAD) or MS detection [75–84].

The SPME performance is directly related to the fiber coating type and thickness. In this regard, a large variety of commercially available fibers such as polyacrylate (PA) and divinylbenzene-carboxen-polydimethylsiloxane (DVB/CAR/PDMS) have been successfully used for the analysis of numerous CECs in different environmental matrices by DI-SPME [76,77]. In the last years, the use of custom-made fibers has been an area of intense activity in order to overcome some drawbacks of commercial coatings, namely the deterioration caused by fouling and the limited reproducibility and selectivity. For instance, an easy approach to prepare low cost home-made fibers was to fix a piece of well-cut PDMS tube at one end of a piece of clean stainless-steel wire by epoxy resin glue. Such fibers were conceived as disposable with a cost less than 1 US$ for each piece [85]. In another approach, eleven analytes (pesticides, industrial chemicals and pharmaceuticals) of different polarities were simultaneously extracted by a home-made Sylgard® 184 overcoated PDMS/DVB fiber with both ends sealed by a PDMS layer. Such approach allowed to decrease the coating fouling process during direct immersion in complex matrices and, as a result, increased fiber lifetime [78].

Molecularly imprinted polymer (MIP)-based fibers for SPME provide a superior selectivity for the extraction of CECs. Generally, these home-made MIP-fibers are prepared in an easy manner by polymerization in molds, as a capillary or glass tube [86]. It has been shown that MIP fibers can be used up to 100 times without losing efficiency [80,87], showing excellent adsorption capacity and high selectivity compared to that provided by commercial fibers [79,81,82]. Some examples of applications include the analysis of imidazolinones in food and

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soil samples [79] and the determination of antiviral drugs in effluents [82]. Although MS detection is usually performed, the use of selective fibers allows the detection by LC coupled to UV or DAD [79–81,83], even for complex matrices as sewage [81].

SPME is also a promising technique for *in vivo* analysis due to its reduced size, slight invasiveness, improved sensitivity and precision. Moreover, it is a nonlethal sampling approach that provides a more precise information of what is occurring in a complex living system. The *in vivo*-SPME technique (**Figure 2**B) has been mainly used for fish tissue sampling. In brief, SPME fibers are inserted (after conditioning) into the organism with the help of a cannula or the needle of a hypodermic syringe to a depth of 1.5-2 cm. Fishes are anaesthetized before the introduction of the fiber into the dorsal-epaxial muscle. Then, the needle is carefully withdrawn back to let the fiber be exposed in the muscle. After a certain period of time, the fish is re-anaesthetized to remove the fiber, which is rinsed with deionized water before thermal or liquid desorption [88–95].

Although commercial SPME fibers have been successfully used for *in vivo* sampling [93], efforts have been made to prepare biocompatible materials. These materials are aimed at avoiding both undesirable local or systemic reactions in the living organisms and biofouling that slows down the extraction kinetics. In this sense, several approaches for the preparation of home-made fibers that meet such requirements have been proposed. One example of an easy and low-cost (less than 1 US$) home-made fiber is a PDMS tubing attached to the epoxy-glue-coated stainless-steel wire. Such fibers were applied to the extraction of synthetic musks in tilapia (*Oreochromis mossambicus*) and aloe (*Aloe chinensis* Baker) [88], and anesthetics in tilapia [92]. However, other custom-made fibers have been described in the literature providing better results in terms of extraction efficiency. In one example, fibers were prepared from 5 µm C_{18} particles glued with polyacrylonitrile onto a stainless-steel wire until the coating reached a thickness of 45 µm. This approach exhibited much higher extraction efficiency toward fluoroquinolones, *ca.* 9-

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31 times higher than a 165 μm PDMS coating, and was applied to fish (*Takifugu obscurus*) [90]. In another relevant approach, a modified metal-organic framework (MOF) with amino groups (MIL-101(Cr)-NH_2) was synthesized and subsequently attached onto the surface of a quartz fiber. Such custom-made fibers were applied to the extraction of six antibiotics in tilapia providing extraction efficiencies higher than those obtained with commercial fibers [95]. As an interesting alternative, the preparation of fibers that rely on the presence of an external polymer coating inspired by the composition of adhesive proteins in mussels has been proposed. Bioinspired coatings were prepared based on the works of Lee *et al.* [96] and Taskin *et al.* [97] by self-polymerization of norepinephrine providing hydrophilicity and bio-interface properties. Such fibers possess anti-biofouling ability and were used for *in vivo* sampling of pharmaceuticals in fish and vegetables [89,91]. Additionally, the combination of bioinspired fibers with conductive materials as polypyrrole permitted the application of an electric field for electrosorption enhancement *in vivo* SPME. The major advantage of such combination is the ultrafast extraction procedure that reduces the extraction time to one min. With this method, ionized pharmaceuticals were analyzed in living tilapia for a monitoring period of 360 h opening the way to temporal studies without animal sacrifice [94]. Notably, all the bioinspired custom-made SPME fibers described above exhibited much higher extraction efficiency as compared to PDMS fibers with satisfactory stability and reproducibility.

Headspace SPME (HS-SPME) displays some advantages over DI-SPME due to the possibility of selectively extracting volatile and semivolatile compounds from the samples, which can be in solid state [98,99]. Generally, the SPME fiber is exposed to the headspace above the sample for a certain extraction time, volatilized analytes being extracted and concentrated in the fiber (**Figure 2**C). Due to the volatile character of many CECs, HS-SPME has been often coupled to GC, even though liquid desorption and analysis with other instrumentation can also

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be performed. The headspace mode facilitates the use of harsh conditions for extraction and/or derivatization such as extreme pH values without fiber deterioration.

HS-SPME has been used for the analysis of volatile and semivolatile CECs such as trimethyl phosphate, synthetic musk fragrances and UV filters in a wide range of environmental samples [100–103]. Commercially available fibers such as PA or PDMS/DVB have been broadly used for the analysis of CECs [101,104]. Additionally, the use of the SPME arrow device for the determination of synthetic musk fragrances in fish was evaluated. SPME arrow combines a larger sorption phase capacity with the main benefits of conventional SPME thus achieving a sensitivity 10 times higher than that obtained with conventional SPME and similar to pressurized liquid extraction (PLE) and QuEChERS, reaching LODs of 0.5-2.5 ng g^{-1} [102].

The use of custom-made fibers for HS-SPME has been reported to a lesser extent. A Prussian blue NPs-doped graphene oxide composite was prepared by hydrothermal reaction and used as a fiber coating for the determination of hazardous pollutants in environmental waters [103]. MIP fibers were used for the ultrasensitive determination of trimethyl phosphate in environmental water samples. The extraction performance of this highly polar compound onto MIP fiber was better than that onto commercial PDMS and PA coatings and without substantial deterioration after being used more than 110 times. An ultrasensitive determination was achieved with LODs of 0.36 ng L^{-1} by means of GC with nitrogen-phosphorous detection (NPD) [105]. Besides, crosslinked polymeric ionic liquids (PILs)-based materials have been reported as alternative SPME fibers for determination of UV filters in waters, showing comparable performance to that of commercial PA fibers [106].

Vacuum-assisted HS-SPME was developed to accelerate the extraction kinetics, thus achieving an increased sample throughput without raising the sample temperature. The SPME fiber is inserted into the air-evacuated vial and exposed to the headspace of the sample. Such strategy was applied for the determination of pollutants in soil samples without any previous

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sample preparation step and better sensitivity, precision, and accuracy than that obtained with traditional HS-SPME [107].

Alternative configurations have been reported in the literature to overcome, among other drawbacks, the brittleness of coatings used in SPME. In this sense, capillaries coated with materials of different nature on its inner surface led to the development of a technique named as in-tube SPME (IT-SPME) [108–111]. A wide range of materials have been used as capillary coatings, *e.g*. nanomaterials, MIPs, MOFs, ionic liquids (ILs) or graphene [111]. IT-SPME offers direct on-line coupling to LC systems, thus leading to improved accuracy and precision with a reduced analysis time. Exemplary applications of IT-SPME include, among others, the extraction and preconcentration of phthalate esters (PAEs) and their degradation products [112], UV filters [113] and carboxylic acid-containing gold NPs [114] from environmental waters.

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3.1.2. *Thin film microextraction*

Among downsized sample preparation approaches, thin film microextraction (TFME), illustrated in **Figure 2**D, offers some interesting advantages in comparison with conventional SPME such as an increased extraction phase volume and surface area-to-volume ratio. Thus, the enhanced extraction efficiency achievable by this technique makes it a good candidate for ultra-trace and fast analysis. Since the first TFME setup developed in 2003, efforts have been made to improve the fiber geometry but also to automate both extraction and desorption [115].

TFME has been applied for the analysis of CECs in various environmental samples. TFME can be performed in either direct or headspace extraction mode, after which solventless thermal desorption can be performed, even though an adapter is required to accommodate the larger extraction phase size to the GC inlet [116]. Alternatively, liquid desorption can be performed and the eluate can be further concentrated and re-dissolved prior to GC analysis [116–118] or directly injected into a LC system [119–124].

Analogously to SPME, the extraction efficiency of TFME depends on the nature of the extraction phase. Since the first sorbent proposed, PDMS, several alternatives have been described in literature. In this sense, a sorbent phase prepared easily and in an economic manner was a polyurethane thin film cut into pieces of 2×2 cm, which has been applied to the extraction of pyrethroids from Chrysanthemum tea [117]. In addition, the use of biosorbent materials such as different kinds of recycled resources have emerged as a more environmentally friendly approach. For instance, a green sorbent based on recycled diatomaceous was used for the analysis of bisphenol A, benzophenone, triclocarban, 4-methylbenzylidene camphor and 2-ethylhexyl-p-methoxycinnamate [120]. Alternatively, recycled disposable stoppers or natural cork were used for the extraction of 3-(4-methylbenzylidene) camphor, ethylparaben, triclocarban and bisphenol A [123]. Remarkably, the use of hydrophilic-lipophilic balance particles, PDMS and carbon mesh membranes has demonstrated excellent performance for the simultaneous enrichment of both polar and nonpolar compounds of varying volatility [125].

Functionalization of the sorbent can provide enhanced selectivity. Thus, magnetic NPs functionalized with histamine enabled the selective extraction of six EDs [122]. Furthermore, a current trend is the production of the sorbent phase by electrospinning. Such technique is frequently used for the production of polymers with nanoscale fibrous structures, so called electrospun nanofibers [126]. In this sense, a polyimide nanofiber membrane was prepared and applied to the determination of phenols in environmental water samples and wastewaters [116]. In another study, an acrylonitrile butadiene styrene nanofiber was prepared in one step on an aluminum foil for the analysis of industrial wastewater samples [118]. Similarly, a polyacrylonitrile/zeolite imidazolate-8 film was prepared for the determination of bisphenol A in environmental water samples [124].

The combination of TFME with a 96-well plate system has been reported allowing the simultaneous extraction/desorption of up to 96 samples. Such high-throughput analysis permits

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the automation of the procedure as well as the reduction of the analysis time for series of samples. With this technique, several CECs were studied in environmental water samples with a small volume of sample required (1.5 mL) and analysis of almost 200 samples per working day [120,122,123].

3.1.3. *Needle trap device*

A number of needle-based alternatives to SPME have also been reported in the literature to overcome the problems associated with the SPME method, including in-needle capillary adsorption trap, solid phase dynamic extraction and needle trap device (NTD) [127]. NTD is a solvent-free sample preparation approach developed for sampling and preconcentration of volatile compounds [128]. Nevertheless, NTD is more robust than SPME fibers since the sorbent is protected inside a steel needle. The efficiency of NTD extraction can be increased by increasing sorbent and/or sampling volumes (active sampling) [129,130]. NTD provides high sensitivity, simplicity and time-efficiency, while avoiding solvent usage. Besides, NTD integrates extraction, desorption and analysis [131,132]. Compared to SPME, NTD overcame deficiencies such as fiber brittleness, limited fiber capacity, and inability of active sampling [127,131].

During the extraction process, a certain volume of air passes through the NTD leaving the analytes trapped on the surface of the adsorbent [131]. Removal of retained analytes is performed by thermal desorption for analysis [128].

The selection of the appropriate sorbent is one of the key factors for achieving high enrichment factors. Commercial sorbents such as PDMS, CAR, DVB, Carboxen 1000, Carbopack X, and Tenax TA are currently in use [128,129], although the application of novel materials tends to overcome certain limitations of commercial sorbents such as limited extraction efficiency and selectivity [132]. Thus, materials such as aerogels (silica aerogel [133–135],

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hybrid aerogels [136,137]), metal NPs, carbon nanotubes, and graphene [138,139] have been recently employed as NTD sorbents and the development of materials with enhanced extraction ability is currently under development [128,132]. The use of these materials may significantly improve the reusability of NTDs and reduce the time of analysis [132].

NTD has proven to be a very effective tool for monitoring of air quality in workplaces. In addition, NTD can also be used to capture particles and aerosols from air, as opposed to insufficiently effective SPME. NTD can be successfully adapted to sampling of pen-sized sampler thanks to its small size and straightforward sampling procedure [140]. These approaches have been applied in the sampling and analysis of various environmental pollutants [141–143].

3.1.4. *Microextraction by packed sorbent*

Microextraction by packed sorbent (MEPS) is a simple and fast sample preparation approach introduced by Abdel-Rehim [144,145] that has demonstrated its convenience for determining CECs in environmental samples [145–147]. MEPS is actually a downsized approach derived from SPE that shows some significant differences with its conventional counterpart. Particularly, the sorbent is integrated directly into the syringe in MEPS and not into a separate column. This fact enables the application of laboratory robotics. The amount of sorbent in MEPS is very small (1-2 mg) and can be used more than 100 times. Because MEPS allows the use of small sample volumes (10-1,000 μL), it has found its place in analytical forensic toxicology where sample quantity is often limited [148]. The amount of solvent required to elute the retained analytes is quite small (from mL to μL) making MEPS more environmentally friendly than conventional extraction techniques. Besides, MEPS can be fully automated and coupled on-line to GC, LC or capillary electrochromatography [149]. Also, analysis with MEPS is more cost-effective than with SPE [144].

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A typical MEPS is designed in the form of a syringe [149,150], as depicted in **Figure 2**E. Since both MEPS and SPE are based on the same principles, it is easy to transfer methods from traditional SPE to MEPS. A main difference between SPE and MEPS is that while in SPE the solution only flows downwards, the sample flows in two directions (up and down) in MEPS, so optimizing both washing and elution steps is crucial [149].

Due to the high similarity of MEPS with SPE, it is to be expected that MEPS uses the same sorbents as those used in SPE. The most widely used are silica-based sorbents (C2, C8 and C18) as well as polymeric sorbents. A major problem with the application of these common sorbents is the lack of selectivity, which has been successfully solved by preparing MIPs by imprinting of target molecules [147,149,151].

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3.1.5. *Stir bar sorptive extraction*

Stir-bar sorptive extraction (SBSE) is an efficient sample preparation method described for the first time by Baltussen *et al.* in 1999 [152]. In general, SBSE is based on the use of a magnetic stir bar covered with an appropriate sorbent material. Stir bars used in SBSE have three essential parts, namely a magnetic stirring rod, a thin glass jacket that covers the stirring rod and a layer of appropriate sorbent (usually PDMS or ethylene glycol-modified silicone material) into which the analytes are extracted [153]. The extraction mechanism of SBSE is based on sorptive extraction, where analytes are extracted from the aqueous sample into a PDMS coating supported on a stir bar, depending on their octanol–water partitioning coefficient. The technique has been applied successfully to the analysis of samples of varying complexity. Extremely low LODs can be obtained thanks to the high extraction phase volume used [154,155].

The extraction process is kinetically controlled being influenced by the sample volume, stir bar dimensions and stirring speed. After extraction, both thermal or liquid desorption can be performed [153,155,156]. Preconcentration of numerous analytes by SBSE has been described in

the literature [157]. SBSE also enables the development of multiresidue methods for simultaneous preconcentration and subsequent determination of dozens of xenobiotics [155,158].

Several approaches based or related with SBSE have been described recently. SBSE with freeze concentration, named as ice concentration linked with extractive stirrer, uses a PDMS stir bar for the extraction in aqueous sample. During this process, pure water is frozen, while solutes are gradually concentrated in the remaining (liquid) part of the sample [154,159]. Another modification of SBSE, namely solvent-assisted SBSE, uses solvent-swollen PDMS stir bars. In this approach, the solvent, which is mixed into the PDMS phase, acts not only as a PDMS modifier, but also as an additional extraction medium [154,160]. An alternative approach named stir bar sorptive-dispersive microextraction (SBSDμE) combines the principles and benefits of SBSE and D-μSPE based on magnetically modified graphene. Hence, SBSDμE enables an effective mixing in large sample volumes as well as quick and convenient collection of the sorbent [161]. Besides, rotating-disk sorptive extraction is based on the analyte extraction onto a small rotating disk made of Teflon containing a sorbent phase of PDMS on one of its surfaces with no risk of adsorbent layer damage during stirring. This approach has been used for the determination of parabens in water samples [162]. SBSE has been employed in the analysis of samples of different complexity, even though the extraction of hydrophilic analytes remains challenging. Hence, a significant number of novel coatings, *e.g.* carbon based-materials, functional polymers and MOFs, have been proposed [163]. Recently published review papers covering SBSE procedures and applications can be found elsewhere [153–155,163].

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3.1.6. *Bar adsorptive microextraction*

Alternative adsorptive microextraction (AμE) techniques were introduced in 2010 by Neng *et al.* [164]. AμE can be performed with two different geometric configurations, namely bar adsorptive microextraction (BAμE) and adsorptive microextraction in multiple spheres (MSAμE). In

BAμE, adsorbents are fixed by adhesive films on polypropylene hollow cylindrical substrates, whereas in MSAμE polystyrene spherical substrates are covered with the adsorbents and subsequently fixed by heat treatment [164]. A wide range of materials can be used in AμE approaches including, for instance, activated carbon, polystyrene DVB copolymer, silica, alumina, zeolites, ionic exchange resins or carbon nanotubes [165,166].

The enrichment of several classes of compounds, ranging from polar to non-polar, is performed by means of AμE devices under the floating sampling technology, demonstrating excellent stability and reproducibility [167]. AμE techniques have been employed for determination of pharmaceuticals, hormones, plasticizers and UV filters in environmental samples [165,167,168].

AμE encompasses a number of advantages, including low amount of solvent required (*ca.* 30-100 times less than the volume needed for elution in SPE), possibility to select a variety of adsorbents that enable the enrichment of compounds with different polarities, and the possibility to carry out sampling, isolation and enrichment in a single-step [165,169]. Besides, the AμE device has been recently downsized, thus leading to a reduction of the solvent volume needed to perform liquid desorption and, as a consequence, minimizing the loss of sensitivity due to dilution of the extract [165].

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3.1.7. *Magnetic solid-phase extraction, dispersive micro-solid phase extraction and immunomagnetic separation*

Magnetic solid-phase extraction (MSPE) was firstly introduced by Safarikova and Safarik in 1999 [170]. In this technique, magnetic adsorbents suspended (dispersed) in the analyzed solution or suspension can efficiently extract target analytes. Due to the magnetic properties of the adsorbents used and the diamagnetic properties of the majority of target molecules and accompanying impurities in solutions and suspensions analyzed, MSPE can be successfully used

for extraction purposes even from difficult to handle samples. Magnetic adsorbents can be rapidly, efficiently and selectively separated using an appropriate magnetic separator. Analytes are subsequently eluted from the recovered adsorbent and analyzed [171,172]. MSPE has developed rapidly due to its easy operation, high extraction efficiency and the potential reusability of adsorbents [173].

Later on, Anastassiades *et al.* introduced a complementary analytical procedure involving nonmagnetic adsorbents generally called dispersive solid phase extraction [174]. The dispersed adsorbent can capture target analytes from the bulk sample and extracted analytes can be subsequently eluted from the adsorbent collected by filtration or centrifugation for analysis. When a reduced amount of adsorbent (in units of mg range) is applied, the procedure is usually called dispersive micro-solid phase extraction (D-μSPE) or dispersive solid phase microextraction [175].

Adsorbents play an extremely important role during MSPE and D-μSPE. They have to exhibit high affinity for the target analyte but, at the same time, the adsorbed analyte has to be desorbed easily. The adsorption efficiency depends on the adsorbent surface area and, therefore, nanostructured adsorbents provide higher adsorption capacity in comparison with micrometer-sized materials. Adsorbents used in D-μSPE and MSPE have to be dispersed properly in the sample in order to accelerate the extraction process. Mechanical treatment (*i.e.*, stirring, vortexing, shaking or US application) is usually employed for this purpose [175–177]. A recently described D-μSPE/MSPE procedure employed a magnetic graphitic carbon nitride nanocomposite dispersed into the aqueous sample solution by air bubbles, which improved the extraction of target analytes [178]. Alternatively, SBSDμE with magnetically modified graphene as the sorbent was applied to isolation of pesticides [161]. In addition, effervescence-assisted D-μSPE, based on the efficient dispersion of the sorbent *via* effervescent reaction, has been reported [175].

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Adsorbents used in standard SPE procedures (*e.g*. octadecyl silica (C_{18}), aminopropyl (-NH_2) and cyanopropyl (-CN) materials, strong anion exchangers or neutral alumina) can be successfully used in D-μSPE, in addition to many newly developed adsorbents such as IL modified carriers, silica coated with polyaniline or MIPs. Also, various types of other nano- and micromaterials including carbon-based nanostructures (carbon fibers, pristine and functionalized single or multi-walled carbon nanotubes and graphene nanosheets), layered double hydroxides, MOFs, hollow porous MIPs, dendrimers and special hybrid materials have been assessed [175,179–182].

Magnetic solid phase (micro)extraction employs various types of magnetically responsive nano- and microsized composite adsorbents, where the magnetic moiety is based on ferrimagnetic iron oxides magnetite or maghemite. Alternatively, various types of ferrites can be also used. Specific adsorbents can be prepared by the immobilization of affinity ligands on magnetic nano- or microparticles. In addition, immobilized specific antibodies (monoclonal, polyclonal or genetically engineered ones) enable to capture target analytes or cells via antigen/antibody interaction during immunomagnetic separation/extraction. Alternatively, standard SPE adsorbents can be magnetically modified using appropriate postmagnetization procedure, *e.g*. magnetic fluid treatment [183,184] or microwave-assisted magnetization procedure [185].

MSPE is well suited for automation since it enables easy handling of magnetic adsorbents using appropriate arrangement of permanent magnets or electromagnets. Both batch [186,187] and flow-through systems [188,189] can be successfully implemented.

Both MSPE and D-μSPE involving different materials have been successfully applied for extraction and subsequent determination of CECs. More detailed information can be found in several comprehensive review articles summarizing the progress in MSPE [171–173,190–193]

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and D-μSPE [175,181,194]. Reviews dealing with (nano)materials applicable as adsorbents for both extraction techniques are also available [173,182,195–197].

Classical immunoassays performed, *e.g*. in microtitration plates can be converted to the magnetic version being mainly performed in test tubes with the aid of magnetic separators. Two types of magnetic-particle-based immunoassays can be distinguished, namely immunomagnetic assays, where an appropriate antibody is immobilized on a magnetic carrier (instead of in the wells of the microtitration plates), or magnetoimmunoassays, where magnetic particles serve as a detectable label (instead of enzymes, radionuclides or luminescent molecules used in standard immunoassays). Immunomagnetic assays are very similar to standard microtitration plate assays, the main difference being that specific antibodies are bound to the magnetically responsive particles, which can be separated from the suspension using appropriate magnetic separators based on strong rare-earth permanent magnets [156,198].

Immunomagnetic kits for the determination of a variety of pollutants are commercially available [199,200]. Further information about the use of immunomagnetic techniques for determination of xenobiotics and cells in water and for magnetic decoration and labeling of cells is available [156,198].

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3.2. *Liquid phase-based microextraction techniques*

3.2.1. *Single drop microextraction and related techniques*

Single drop microextraction (SDME) was introduced as a downsized version of conventional LLE where a microdrop of extractant phase is used for the extraction and preconcentration of target analytes. Since the seminal works by Dasgupta [201,202] and Jeannot and Cantwell [203,204], a number of SDME modes were developed where the extractant phase, held from the needle of a syringe, has a nearly spherical shape during the extraction process. The use of a syringe as the drop holder enables to integrate several steps, including the exposure of the drop

to the sample for analyte enrichment, retraction of the enriched microdrop and injection for analysis. The first developed SDME mode, commonly known as immersed or direct SDME (DI-SDME) [203], involves the exposure of an immiscible microdrop of extractant phase to a continuously stirred sample solution (**Figure 3**A). Selection of an appropriate extractant phase is of paramount importance since it significantly affects the extractability of relevant compounds. Different possibilities have been considered, including mainly hydrophobic organic solvents, but also ILs and, more recently, deep eutectic solvents (DES), which are solvents commonly considered as IL analogues derived from, at least, two solid compounds. Recommendations for solvent selection can be found elsewhere [205]. The direct mode can be used for both volatile and non-volatile analytes. In order to extract charged analytes, derivatization can be applied in the sample or in the drop to yield uncharged extractable compounds. DI-SDME has been used for enrichment of a variety of target analytes, reaching acceptable enrichment factors. However, experimental variables that could improve the extractability (*e.g.* stirring rate, temperature or extraction time) have been reported to affect the stability of the drop at the syringe needle, and hence the potential of this technique for preconcentration is limited by technical aspects. Thus, authors have progressively turned to more efficient alternatives to DI-SDME, as reflected by the decreased number of publications involving this SDME mode. Few recent examples involving DI-SDME for extraction of CECs prior to their determination can be pointed out. For instance, DI-SDME has been used to extract ranitidine from environmental waters prior to its determination by LC-MS/MS [206].

Alternative three phase SDME modes have been developed to achieve a more selective extraction of target compounds. Thus, volatile and semi-volatile analytes (or volatile derivatives of non-volatile analytes) can be extracted by a microdrop of extractant phase exposed to the headspace above a sample solution (**Figure 3**B). This mode, named as headspace SDME (HS-SDME), allows achieving excellent enrichment factors while avoiding interferences from non-

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volatile compounds present in environmental samples (*e.g*. NOM). The number of extractant phases amenable to be used in HS-SDME is higher than that in DI-SDME as solvents are physically separated from the sample and, therefore, miscible solvents are also usable. However, the non-negligible evaporation of several organic solvents represents an important constraint for the selection of appropriate extractant phases in HS-SDME. Thus, organic solvents with low vapor pressures, ILs, DES or aqueous drops have been used as extractant phases in HS-SDME. Several contributions dealing with HS-SDME for the enrichment of volatiles have been reported in the literature. For example, a HS-SDME-GC-MS method has been reported for determination of residual 2-phenoxyethanol in fish tissues [207]. Besides, HS-SDME and electrothermal atomic absorption spectrometry (ETAAS) enabled the determination of CdTe quantum dots (QDs) (and Te(IV)) in environmental waters. The method involved iodine-induced oxidation of CdTe to Te(IV) and subsequent H_2Te generation, with trapping of the evolved hydride by an aqueous microdrop of Au(III) [208]. The mass transfer of volatile and semi-volatile analytes can be improved in different ways in HS-SDME, commonly by fast agitation, addition of salts, increasing temperatures or US irradiation. Even though strategies are mainly focused on increasing the mass transfer from the sample solution to the headspace, it has been recently demonstrated that the mass transfer from the headspace to the extractant phase microdrop is also of paramount relevance and should not be neglected. In particular, interfacial gas constraints can be significantly decreased under reduced pressure conditions and, hence, extraction times can be greatly reduced. Vacuum-assisted HS-SDME can therefore be used for extraction of volatile and semi-volatile pollutants in significantly reduced sampling times [209].

Besides, a three phase SDME mode introduced by Ma and Cantwell [210], namely liquid-liquid-liquid microextraction (LLLME), has been employed to achieve a selective extraction of ionizable compounds (**Figure 3**C). LLLME involves extraction of the analyte in its neutral form into an extractant phase immiscible with the sample (commonly an organic solvent with lower

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density than water) followed by back-extraction into a microdrop of acceptor phase (commonly an aqueous drop). Appropriate adjustment of the pH of both the sample and the acceptor phase is key to ensure an efficient mass transfer. Even though this SDME mode has been mainly used for extraction of acidic and basic analytes from biological samples, a number of applications devoted to the analysis of environmental samples can also be highlighted. For example, LLLME has been combined with liquid chromatography quadrupole time-of-flight mass spectrometry (LC-Q-TOF-MS) for determination of five statins in river water samples. High enrichment factors (350 to 1712) were achieved in only 4 min, leading to LODs in the range of 0.03 to 2.00 ng L^{-1} [211].

The instability of the microdrop at the syringe needle during the extraction process represents the main limitation of immersed SDME modes (*i.e.*, DI-SDME and LLLME). In fact, dislodgement of microdrops occurs when fast agitation, increased temperatures and extended microextraction times were used. As all these experimental parameters favorably affect the extraction kinetics, it is reasonable to infer that the development of more efficient alternative microextraction approaches was needed to achieve more sensitive and expeditious analytical methodologies. LPME approaches where the microdrop is directly exposed to the sample without being held by the syringe while maintaining its nearly spherical configuration were firstly introduced [212]. Two and three phase directly suspended droplet microextraction (DSDME) modes were applicable in an analogous way to DI-SDME and LLLME. Two phase DSDME is shown in **Figure 3**D. Some works involving DSDME modes have been reported in the literature. Thus, the extraction of silver NPs by a microvolume of 1-octanol and subsequent back-extraction (and oxidation) of the enriched organic phase into an acidic and oxidizing aqueous phase was recently reported. Non-significant differences were observed when extracting silver NPs of different size (4-63 nm) and surface coatings (citrate-silver NPs, cysteine-silver NPs, polyvinylpyrrolidone-silver NPs and silver sulfide NPs), thus leading to the determination of the total concentration of silver NPs in environmental water samples at the fM level [213].

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Besides, the three phase DSDME mode has been combined with UV-vis spectrophotometry for determination of tramadol hydrochloride in water samples [214]. The main limitation of DSDME, however, is associated to the difficulty to collect the enriched microdrop at the end of the extraction process. In addition, the restriction to use only water immiscible solvents with lower density than water could also affect the extractability of certain analytes.

3.2.2. *Membrane-assisted LPME*

Microporous hollow fiber membranes were also proposed to improve the stability and reliability of LPME approaches. The use of membranes results in additional protection of the acceptor phase and microfiltration through the pores of the hollow fiber, thus leading to higher enrichment factors and cleaner extracts [215].

Hollow fiber liquid-phase microextraction (HF-LPME) can be performed in two-phase sampling configuration, where target analytes are extracted from an aqueous sample to a water immiscible extraction solvent which is immobilized in the pores and lumen of the hollow fiber (**Figure 3**E). The acceptor solution can be directly analyzed by GC or LC, but also by CE after evaporation of the solvent and reconstitution in an aqueous medium. Examples of CECs analyzed in two-phase configuration include the extraction of PAEs [216] and β-blockers from environmental waters [217], or the assessment of regulated DBPs and emerging iodinated trihalomethanes formed in water samples subject to different treatment processes [218]. Applications of this sample preparation approach for mixtures of different families of CECs have been scarcely reported. Nevertheless, HF-LPME was successfully applied to the determination of 27 CECs in effluents from STPs and surface water with enrichment factors from 6 to 4,177 and LODs in the range from 1.09 to 98.15 ng L^{-1} [219].

Furthermore, in order to increase the volume capacity for LPME, nine hollow fibers were held together compactly in a bundle to develop a bundled polypropylene hollow fiber array (BHF) that was used for the extraction of estrogens in influent and effluent of a WWTP. The

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LODs obtained, within the range of 0.251-0.440 ng L^{-1}, were lower or similar to those previously reported in microextraction methods or conventional SPE methods [220].

HF-LPME can also be performed in three-phase mode (HF-LLLME), where analytes are extracted from an aqueous sample through an extraction solvent immobilized in the pores of the hollow fiber, and back extracted into an acceptor aqueous phase inside the lumen of the hollow fiber. This configuration is limited to ionizable analytes and, thus, the adjustment of the pH of the donor and acceptor phases is critical because the migration of the analytes is pH-dependent, the acceptor phase being compatible with LC or CE analysis. This approach has been successfully applied for determination of sulfonamides in influent and effluent waters of three STPs [221] and salicylic acid in estuarine and riverine waters [222]. Additionally, the coupling of HF-LLLME with an on-column preconcentration approach as on-line sweeping micellar electrokinetic provided enrichment factors higher than 3,100 for target triazines in honey, tomato and environmental water samples [223].

The selection of an appropriate acceptor phase is key to achieve efficient extraction in HF-LPME. In this sense, organic solvents such as 1-octanol [216,219–222], n-decane [223] and heptanol [217] have been commonly used for extraction of CECs. However, volatile organic solvents pose potential environmental, health and safety risks, so different alternatives such as ILs have been proposed because of their significant advantages (*e.g.* low vapor pressure, wide range of miscibility with other organic solvents, good thermal stability, and dual natural polarity). For example, 1-alkyl-3-methylimidazolium hexafluorophosphate ILs have been used for extracting bisphenol A and diethylstilbestrol [224] and triazine herbicides [225]. Additionally, the use of the ultra-hydrophobic IL 1-hexyl-3-methylimidazolium tris(pentafluoroethyl)trifluorophosphate was more effective for the extraction of chlorophenols than other commonly used ILs, providing LODs lower than 0.5 ng mL^{-1} [226].

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Alternatively, the use of supramolecular nanosolvents (SUPRASs) as the liquid membrane phase shows much interest due to their unique properties, allowing the coextraction of acidic, basic and amphiprotic analytes from aqueous environmental samples [227].

Solvent bar microextraction (SBME) has been proposed as a modification of the original HF-LPME where a short piece of hollow fiber sealed at both ends is impregnated with the organic solvent and then freely stirred in the aqueous sample solution. As the extraction device moves freely during sampling, the transference of analytes is enhanced and higher enrichment factors can be obtained in a shorter time [228]. Bandforuzi *et al.* proposed a two phase-SBME using a non-ionic surfactant in the extraction phase for extraction of PAEs from environmental aqueous samples. In this work, the extractant phase was a reverse micelle of the non-ionic surfactant which promoted the partition process by non-ionic intermolecular forces such as polar and hydrophobicity interactions. As a result, LODs of 0.012-0.03 ng mL^{-1} and high enrichment factors in the range of 285-314 were achieved [229].

Electromembrane extraction (EME) consists of a three-phase configuration HF-LPME, where one electrode is placed in the sample solution and the other electrode in the acceptor solution which is placed inside the lumen (**Figure 3**F). Ionized analytes move across the supported liquid membrane by electrokinetic migration under an applied voltage providing enhanced extraction speed [230]. In this regard, a combination of EME and electro-assisted liquid-liquid microextraction (EME-EA-LLME) was proposed for the determination of antidepressants (namely, imipramine and clomipramine) in urine and wastewater samples (**Figure 3**G). This approach provided enrichment factors above 561 and LODs of 0.15 ng mL^{-1} with an analysis time less than 10 min [231].

Alternatively, the use of a SPME fiber inside the lumen of the hollow fiber improves the preconcentration and cleanup, and simultaneously avoids the direct contact of the fiber with the sample. As an example, a tailor-made silica fiber was applied for the extraction of chlorophenols

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from water and wastewater samples. Analytes were extracted in this work through the hollow fiber membrane containing n-decane and reached the acceptor phase where analytes were extracted and derivatized on the fiber [232]. Similarly, a tailor-made methacrylic-based polymeric fiber was used to perform a microwave-assisted extraction-hollow fiber liquid/solid phase microextraction (MAE-HF-L/SME) for determination of 54 CECs (including pharmaceuticals and PCPs) in fish samples. Up to 22 different pharmaceuticals and PCPs were detected in fish samples, sedatives being present at the highest concentrations in analyzed samples [233].

Furthermore, the use of MIPs, tailor-made materials with selective recognition sites able to rebind target analytes, has been proposed to improve the selectivity of microextraction methods [234]. The combination of MIP-SPME with HF-LPME offers the advantages of high selectivity of MIP-SPME and enrichment and sample cleanup ability of the HF-LPME into a single device [235]. Apart from the MIP fiber, the selective sorbent can be prepared in other configurations. For instance, MIP was prepared in the walls of a porous hollow fiber to take advantage of the high loading capacity compared with SPME fibers [236]. Additionally, few milligrams of imprinted beads were packed into the lumen of the hollow fiber in order to protect and separate them from aqueous media [237]. Both approaches were used for the determination of triazines in environmental water samples with LODs within the range of 0.022-0.1 μg mL^{-1}.

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3.2.3. *Dispersive liquid-liquid microextraction and related techniques*

As commented on previous sections, the limited stability of the extractant phase in LPME (immersed) modes represented an important constraint in terms of sensitivity and analysis time. The search for advantageous alternatives probably reached a turning point with the development of dispersive liquid-liquid microextraction (DLLME), introduced by Rezaee *et al*. in 2006 [238]. As shown in **Figure 3**H, in this technique a mixture of an immiscible organic solvent showing

higher density than water (typically a halogenated organic solvent) that behaves as extractant phase and a dispersion solvent (*e.g.* methanol, acetone or acetonitrile) showing significant miscibility with both the sample and the organic solvent is rapidly injected into the sample, thus forming a cloudy solution. The dramatically increased interfacial area enables a drastic improvement of liquid-liquid mass transfer rates. After emulsion breakdown, commonly by centrifugation but also by solvent-based de-emulsification [239], the enriched extractant phase is collected for further analysis. Many contributions devoted to the determination of CECs have employed DLLME for enrichment and sample clean-up, including, among others, pharmaceuticals [240], PCPs [241], UV filters [241], illicit drugs [242], pesticides [243], REEs [244], nanomaterials [245] and DBPs [246].

Several alternatives to the conventional DLLME approach aimed at greening and improving the microextraction procedure have been developed. The search for approaches allowing the formation of cloudy solutions thus increasing the interfacial area for mass transfer while avoiding the use of dispersive solvents was mostly pursued. For this purpose, different strategies leading to the development of novel DLLME-related approaches were followed, including the use of US irradiation, vortex mixing, rotor-stator mixing devices, temperature control, *in situ* formation of immiscible extractant phases and effervescence reaction. US irradiation has proved useful for efficiently dispersing the extractant phase and enhancing mass transfer by cavitation [247]. Different DLLME approaches involving US irradiation have been recently reviewed [248]. Among other applications, US-assisted DLLME microextraction approaches have been employed for the determination of pharmaceuticals in waters [249]. Vortex-assisted liquid-liquid microextraction (VALLME) [250,251] makes use of vortex mixing to disperse the immiscible extractant phase into the sample. The technique has been employed, *e.g.* for extraction of bisphenol A and replacements in indoor dust of public environments [252]. More recently, a laboratory homogenizer has been proposed with this aim [253]. In fact, rotor-

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stator mixers can act as dispersing devices, leading to the formation of small solvent drops with narrow size distributions. In addition, the turbulent flows and shear forces occurring inside the homogenizer cause an enhancement of mass transfer rates. Microextraction approaches derived from DLLME based on temperature control also enabled the extraction of target pollutants. This is the case of solidified floating organic drop microextraction (SFODME) [254], where temperature control simplifies the collection of the enriched extract. SFODME makes use of extractant phases with melting points near room temperature (*e.g.* 1-dodecanol) [254]. Thus, extraction is performed at a temperature significantly higher than the melting point of the solvent to keep the solvent in its liquid state (analogously to DSDME), whereas the collection is performed in an ice bath where solidification of the extract occurs. Similarly, cold-induced aggregation microextraction (CIAME) exploits the ILs solubility dependence on temperature. Thus, the hydrophobic IL is fully dispersed along the sample by increasing the sample temperature, whereas a subsequent decrease in temperature facilitates the phase separation of the enriched extract. *In situ* formation of immiscible extractant phases has also been exploited in DLLME and related approaches. This is the case of *in situ* solvent formation microextraction (ISFME), in which a hydrophobic IL is formed by addition of a hydrophilic IL and an appropriate ion-pairing agent to the sample, leading to the instantaneous formation of a cloudy solution [255]. For example, the simultaneous addition of a hydrophilic 1-alkyl-3-methylimidazolium bromide and lithium bis[trifluoromethyl)sulfonyl]imide resulted in the formation, by metathesis reaction, of a hydrophobic 1-alkyl-3-methylimidazolium bis[trifluoromethyl)sulfonyl]imide, that enabled the rapid enrichment of eight UV filters from aqueous samples [256]. Effervescence has also been employed to disperse the microvolume of extractant phase in DLLME and related approaches. This approach, based on the *in situ* formation of CO_2 in the sample, has been applied to extract surfactants from environmental waters [257].

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On the other hand, halogenated solvents commonly used in DLLME have found some remarkable replacements. In its classical version, DLLME involves solvents as extractant phases with higher density than water (*e.g.* chloroform or carbon tetrachloride). In spite of the reduced volumes of extractant phase used in DLLME, environmental, health and safety issues of the organic solvents used in DLLME have prompted the search for alternatives. For example, the development of different modes of DLLME, such as VALLME, SFODME or in-syringe DLLME [258], enables the use of solvents with lower density than water, thus expanding the potential applicability of these LPME approaches. In addition, the full automated in-syringe DLLME process makes it robust and versatile [258]. A variety of ILs, hydrophobic DES and SUPRASs have been proposed in recent contributions. ILs have been extensively used in DLLME, and even certain DLLME-related approaches such as CIAME [259] or ISFME [255] were derived from their use. Hydrophobic ILs are commonly used bearing in mind that most of analyzed environmental samples are aqueous or, at least, of hydrophilic nature. Nevertheless, hydrophilic ILs have also been used in sample pretreatment and/or formation of hydrophobic ILs by metathesis reaction. Magnetic ILs have also recently found application in DLLME and related approaches [260]. Magnetic ILs are a type of ILs with tunable properties that remarkably respond to magnetic fields. They have proved highly efficient for extraction purposes in DLLME since analyte-enriched magnetic IL can be magnetically separated, and hence, centrifugation steps are avoided. Additional strategies are, however, needed to make the extract compatible with certain analytical instrumentation [260]. On the other hand, SUPRASs, *i.e.* solvents typically produced from coacervation of decanoic acid aqueous vesicles in the presence of tetrabutylammonium cation, have received considerable attention [252]. In addition, an increasing number of works make use of DES as extractant phases in DLLME [261].

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4. Miniaturized analytical flow-based approaches for determination of contaminants of emerging concern

4.1. *Millifluidic platforms*

The bead injection technique is based on the use of automatically renewable solid-phases, bearing functional group or ligands with (bio)chemical nature [262]. The main asset of this concept is that a fresh portion of sorbent can be used for each sample through automatic microfluidic manipulation. Several platforms have been proposed to implement bead injection, but the most successful so far is the LOV format [263].

LOV consists of a methacrylate (or other material compatible with organic solvent) micro-machined piece, placed atop a selection valve (**Figure 4**). Recently, 3-D printing techniques have also been applied to tailor LOV devices [264,265]. Similarly to sequential injection analysis systems [266], all fluids are manipulated in or out the peripheral ports through the central channel, which is connected to a pumping device.

For implementation of the bead injection concept, particles must be retained in one of the peripheral ports, using frits or filters with pore size lower than the size of particles [267] (typically between 10 to 300 μm), or even tubing with narrow diameter [268] that allows the passage of fluids but not of particles. Concerning the type of particles/sorbents, despite the fact that initial works advocated the use of spherical particles with homogenous size distribution, the practice has shown that any type of material can be used, ranging from homogeneous OASIS HLB (co-polymer of polystyrene-divinylbenzene-N-vinylpyrrolidone) [269] to irregularly shaped MIPs [270]. For environmental analytical applications, octadecyl derivatized silica (Bond Elut C18) [271] and functionalized agarose (polysaccharide polymer) [272] have also been used.

One of the main features of LOV systems is their versatility concerning the integration of sample treatment and detection steps. Several detectors can be designed into the LOV piece, namely optical detection through CCD miniaturized spectrometers (**Figure 4**B) in μTAS configurations. Moreover, on-line or at-line connection to separative techniques (LC or GC) can

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be easily attained by directing the eluate of microextraction procedures to one of the lateral ports, connected to the injection valve or to the auto-sampler of other instrument [273].

An important issue when analyzing environmental samples is the need to achieve low LODs, so relatively high sample volumes (5-10 mL in microextraction techniques) are required. LOV systems are able to handle such volumes, without sorbent fouling or clogging, as it is renewed for each analyzed sample [274]. Concerning the application to CECs, some recent examples can be presented. Two different approaches using LOV systems have been proposed for evaluation of estrogens in wastewater and seawater. In the first approach, E1, E2, E3, and EE2, were retained in a commercially available MIP and eluted in 400 µL of MeOH which were directly injected into LC-UV [275]. In the second approach, the same compounds were retained in a C18 sorbent and eluted using 200 µL of ACN. After eluate drying and reconstitution, extracts were loaded onto a GC-MS auto-sampler for derivatization and quantification [271]. Determination at µg L^{-1} levels was feasible, with good recoveries (80.5-113.3%) and full automation of sample extraction.

The LOV system has also been exploited to evaluate the leaching kinetics of CECs (methyl paraben, butyl paraben, diclofenac, and triclosan) from exposed mussels [276]. Pulverized mussel tissue was placed in a large-bore column percolated by simulated gastrointestinal fluid. Aliquots of this fluid were then cleaned up, and the analytes were pre-concentrated onto the sorbent (Oasis PRIME-HLB) captured into the channels of the LOV mesofluidic platform. The eluate (ACN/MeOH (90:10, v/v)) was automatically transferred and analyzed by LC-MS/MS. This approach for dynamic bioaccessibility testing offered a significant shortening of the extraction time in comparison with the batch method (28 *vs* 240 min). Moreover, the renewable capabilities of the system avoided the overestimation of potentially bioavailable fractions that can potentially occur upon accumulation of interfering compounds

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(*e.g.* phospholipids). Using a similar approach, determination of butylparaben and triclosan was performed in seawater using a porous carbon-coated titanium dioxide nanotubes [277].

Miniaturized immuno-extraction as part of an ELISA protocol has been successfully implemented for determination of carbamazepine in wastewater [272]. Apart from solution preparation, all assay steps were fully automated with no need for error-prone manual washing. Microbeads carrying anti-carbamazepine antibodies were trapped in the LOV, placed in the optical path of an in-built detection cell. Real-time monitoring of enzymatic detection using a carbamazepine-horseradish peroxidase conjugate was implemented, enabling the analysis of urban wastewater without any treatment at μg L^{-1} levels. Besides requiring minimal sample treatment, a short time-to-result interval (11 min) was achieved. Moreover, the discard of the solid material at the end of each analysis increased sample throughput as no support regeneration is performed, thereby avoiding memory effects, support fouling and cross-contamination.

In summary, millifluidic platforms have the potential to handle the challenges offered by CECs analysis in different types of matrices, as flexible extraction protocols can be envisioned through computer control and programmable flow. 3D-printing is also opening new opportunities for innovation and design of new platforms with integrated detection systems.

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4.2. *Microfluidic platforms*

Microfluidics is a technology for precise control and manipulation of microscale fluids [278]. The basic operation units such as preparation, extraction, reaction and detection in various analysis processes are integrated onto a microchip. Through the micromachining process, the micro- to sub-millimeter-level fluid channels, pumps, valves, filters, sensors, detectors and other units can be fabricated on the substrate of silicon, metal, polymer, glass or other materials [279].

The microfluidic platforms can be classified into capillary, pressure-driven, centrifugal, electrokinetic and acoustic systems on the basis of their liquid propulsion principles [280]. So

far, microfluidic platforms have been applied using various detection techniques including electrochemical analysis, mass spectrometry, chemiluminescence, fluorescence analysis and UV-vis spectrophotometry [281]. Because microfluidics provides the benefits of cheapness, portability, disposability, rapid response, high precision, low reagent consumption and high-throughput parallel processing, it has spread into emerging interdisciplinary research fields such as biology, chemistry, medicine, fluid, electronics, materials and machinery.

The overuse of some pharmaceuticals may accelerate the occurrence of multi-resistant bacteria when accumulated in the environment. Microfluidic platforms have been applied for the analysis of pharmaceutical compounds. Liyong He *et al.* developed a microfluidic chip-based aptasensor for kanamycin detection in milk and fish, where a stir bar and rolling circle amplification (RCA) were used for sorptive extraction and signal amplification separately. The synthesis principle of the circular DNA template and the detection mechanism of the platform are shown in **Figure 5**A. Based on microfluidic chip electrophoresis (MCE), kanamycin can be quantified in a linear range of 0.0008–10 ng mL^{-1} with a LOD of 0.3 pg mL^{-1}. Remarkably, the detection assay can be completed in 3 min consuming only a small sample volume of 150 pL [282]. A microfluidic cartridge system was also reported for surface-enhanced Raman spectroscopy (SERS) determination of sulfamethoxazole in tap, river and lake water with an improved LOD of 2.2 nM [283]. Although the LOD is below the allowed concentration in tap water (200 nM), there is risk that the inorganic cations and anions in surface water can interact with the silver surface, thus causing the formation and aggregation of silver NPs. Therefore, strategies to improve silver surface stability remain to be explored. In addition, a single-use foil-based microfluidic flow cell combined with an automated spectrometric detection unit for diclofenac detection in wastewater was developed [284]. Fluorescence detection of diclofenac in the concentration range of 10-50 μM was achieved, which is in agreement with that recorded by the microscope, thus indicating the great potential for on-site detection of diclofenac. Soon after,

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oxytetracycline and norfloxacin were determined on microfluidic paper-based analytical devices, which are based on the filtration and concentration of reagents and food contaminants such as antibiotic residues. A LOD as low as 1 ppm was achieved for target detection in pork, which is quite appropriate for food safety surveillance [285].

PCPs widely used in daily life may cause a serious threat to the environment by entering the food chain [46]. The interest in PCPs detection in water systems continues to grow. Thus, Yazdi and White proposed an automated optofluidic SERS microsystem for detection of melamine and thiram in field water [286]. As illustrated in **Figure 5**B, the microsystem consists of packed microspheres, an integrated micromixer, and integrated fiber optic cables. The platform shows up to 2 orders of magnitude improvement in the LOD relative to a conventional open microfluidic SERS device, which is more beneficial for on-site detection of water contaminants. Nevertheless, the problem regarding silver NPs clogging with long time for sample loading and device fabrication remains to be solved.

Apart from PCPs, detection of EDs has also been reported. For example, simultaneous capture, detection and removal of polybrominated diphenyl ethers (PBDEs) in seawater has been demonstrated on a microfluidic platform involving the competitive immunoassay-linked binding between PBDE and horseradish peroxidase modified PBDE [287]. The platform not only allows obtaining a LOD similar to that in a commercial colorimetric test (0.019 ng mL^{-1} *vs* 0.018 ng mL^{-1}), but also requires less reagent and shorter analysis time. Further studies should be performed to develop an automated detection platform, given that the competitive immunoassay used here is usually more complicated than label-free methods for PBDE detection.

Waters, soil, and farm products are easily contaminated with common pesticides, which may lead to poisoning related to kidney damage, neurotoxicity and cancer. A series of papers have been published for monitoring pesticides. Kamrul Islam *et al.* [288] developed a microchip capillary electrophoresis system for separation and amperometric detection of triazines in soil.

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Separation and detection are completed within only 1.25 min, which provides an effective and reliable platform for rapid determination of pesticides. A microfluidic silicon rubber polyaniline extraction system combined with GC–MS was also proposed for triazines detection in natural water [289]. Notably, the developed method consumed the least sample volume (0.5 mL) and organic solvent volume (3.3 μL) among the relevant extraction methods. In contrast, its extraction time is almost 3 times longer than that achieved by the SPE–DLLME method (60 min *vs* 23 min), thus more attempts should be made to shorten the extraction time. Besides, a microfluidic device involving a central chip unit with an aligned microchannel was fabricated for triazines determination in river, sea and paddy water [290]. The device was designed in a sandwiched format to hold the electrospun polyamide/titania hollow nanofibers sheets as micro–extractive phases. The device provided a 10-fold improvement in sensitivity (0.01-0.03 ng mL^{-1}) compared with the previous device (0.2-0.5 ng mL^{-1}). Apart from triazines, multiplexed determination of carbamates in river, lake and irrigation water was also demonstrated on a microchip with a LOD of 0.7-1.2 μM [291]. The microchip offers an analysis time within 6 min for carbamates, provided that press-transferred carbon black NPs were used as highly efficient transducers in the microchip. Wei *et al*. [292] developed an automated extraction and electrospray ionization (ESI) chip (AEEC) for pesticide detection, containing a SPE zone, seven pneumatic valves, one monolithic ESI nozzle, apart from other components. The platform was able to accomplish pesticide detection within 5 min with fewer random errors due to the automated SPE and on-line MS investigation in AEEC-MS.

Both filtration and label-free sensing of cationic surfactant in river water have been demonstrated on a microfluidic device with a LOD of 0.5 μM [293]. A perfluorinated microporous membrane isorefractive to water is placed across two channels to filter the sample solution and avoid the clogging of the membrane pores. It took only a few minutes to quantify adsorbing substances when testing samples containing high levels of environmental particles,

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which reveals numerous possibilities for developing large-scale environmental monitoring platforms. Moreover, more efforts are required to optimize the production and cleaning processes of the membrane for higher affinities and sensitivities.

In summary, microfluidic devices have many advantages, *i.e.*, cheapness, rapid response, high sensitivity, high precision, operation simplicity, short analysis time, low sample and reagent consumption as compared to conventional methods. However, further efforts should be devoted to exploring more methods for improving sensitivity and specificity, strengthening detection stability and enrichment efficiency, optimizing production and cleaning processes, shortening fabrication and analysis time to extend the applications for monitoring CECs. **Table 3** displays a summary of microfluidic platforms for determination of CECs in environmental samples. In addition, despite the challenges to be faced, there is an urgent need to develop low-cost automated microfluidic platforms for high-throughput on-site monitoring of CECs.

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4.3. *Paper-based analytical devices*

Microfluidic paper-based analytical devices (μPADs) have shown significant promise for monitoring CECs, for example a multiplexed chemical analysis utilizing μPAD has been described early in 2007 [294]. A μPAD is a device that controls a small volume of sample through the fiber network through capillary action, with its flow path defined by patterned hydrophobic area [295]. Recently, numerous papers have described the determination of CECs by μPADs.

μPADs have been applied for effective monitoring of pharmaceuticals in the environment. Wang *et al.* [294] reported a ratiometric paper-based device (PAD) combined with a digital fluorescence detector for multiple detection of aminoglycoside antibiotics in river water. As shown in **Figure 6**A, the device consists of five layers and four parallel channels, which are used for sample addition, pH control, targets acquisition, 'stop-flow' control and detection

region, respectively. The LOD of this low-cost platform is 0.023-0.069 ng mL^{-1} for aminoglycoside detection, which is comparable to those obtained by methods involving expensive equipment. Moreover, the device provides a powerful platform for on-site simultaneous detection of antibiotics while the commercialized ELISA kit can only detect one antibiotic at a time.

Tetracyclines are among the most common antimicrobials in various fields. Due to the abuse of tetracyclines, their residues in the environment may result in antibiotic resistance and allergic reactions. A PAD system based on fluorescent analysis was created for screening total tetracyclines in river, surface and tap water [295]. The LOD for total tetracyclines was 4.5 ng mL^{-1} with electrokinetic stacking, which is 250-fold lower than that without this procedure. It took only 5 min to prepare the paper channel, process and analyze water samples using the system, which is more suitable for field-testing of total tetracyclines compared with previous instrumental methods. However, some measures should be taken to reduce interferences from other substances because some species that co-exist in the samples may interfere with fluorescent detection under the field amplification stacking conditions.

The occurrence of EDs in the environment is of great concern because they can interfere with the endocrine or hormonal systems. An electrochemical paper-based immunocapture assay was demonstrated for EE2 determination in river water [296]. The μPAD modified with silica NPs and anti-EE2 specific antibodies was applied to capture, preconcentrate and detect EE2. An appropriate linear range of 0.5–120 ng L^{-1} with a LOD of 0.1 ng L^{-1} for EE2 detection was reported. The platform offers a suitable LOD for EE2 quantification in river water, which will open up a new path for on-site monitoring of CECs. In contrast, the linear range of the assay is much narrower than that obtained by other methods, indicating that the assay is not appropriate for quantifying high-concentration levels.

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Most μPADs recently described for pesticide detection rely on the inhibition of AChE, which is an enzyme essential for controlling the normal transmission of nerve impulses [295]. Colorimetric analysis involving acetylcholinesterase (AChE) has been described to quantify organophosphorus pesticides in natural waters, which is based on a μPAD combined with a cell phone and an on-site image processing app [297]. A scheme of the μPAD for organophosphates detection is depicted in **Figure 6**B. Outstandingly, the platform allows the display of real-time results when integrated with a public website, which provides a beneficial platform for real-time water quality monitoring. Even so, more attempts should be made to improve the LODs for complex water matrices because there is a shift towards higher concentrations for these matrices. In the same year, a MIP based lab-on-paper device was applied for dichlorvos determination [298]. The schematic procedure for preparing MIP on paper is shown in **Figure 6**C. The μPADs can be fabricated in high production, followed by the MIP layer synthesized and adsorbed on the paper. Based on the chemiluminescence enhancement of luminol-H_2O_2, dichlorvos has been measured at levels as low as 0.8 ng mL^{-1}, which are consistent with those achieved by LC analysis. Apilux *et al.* [299] proposed a water-soluble thioglycolic acid (TGA)-capped CdTe QD paper-based device for the detection of organophosphorus and carbamate pesticides. It took only 25 min to accomplish the whole assay, which depends on the change in the fluorescence intensity of TGA-capped CdTe QDs, which can be determined by the naked eye under UV-black light. Although the LODs (0.01-0.05 ppm) meet the requirement for pesticide detection in contaminated agricultural products, the reported recoveries (60-80%) are obviously lower than those obtained by GC-MS/MS (88-114%). Arduini *et al.* [300] presented a three-dimensional origami multiple paper-based electrochemical device for pesticide detection. Two different office paper-based screen-printed electrodes and multiple filter paper-based PADs were integrated to load enzymes and enzymatic substrates. Only a few microliters of untreated sample or distilled water were needed for measurements. These pesticides have been measured at the ppb level in

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river water with a satisfactory accuracy. Hua *et al.* [301] developed a flow control-based 3D μPAD for paraoxon-ethyl detection in river water, using wax-printed channels for flow rate control. The assay only needs a single step involving sample addition, which is promising for rapid on-site pesticide detection. Nevertheless, the LOD here is remarkably higher than that achieved by the bidirectional lateral flow dipsticks for organophosphate pesticide detection (25.0 μg L^{-1} *vs* 0.01 μg L^{-1}). Therefore, further studies should be performed to improve the detection capability of the device.

Notably, Damon *et al.* [302] carried out multiplexed detection of illicit drugs, corrosion inhibitors, and pesticides by creating 2D solid wax patterns on paper. The 2D wax-printed paper substrates were used for paper spray mass spectrometry analysis. For illicit drugs, the LODs from dried urine samples were at least 2 times lower than those from fresh urine samples due to the reduced ion suppression effects. The LODs achieved by wax-printed paper spray (PS)-MS analysis were at least 3 times lower than those obtained from the un-waxed PS-MS analysis. Besides, LODs ranged from 0.09 pg mL^{-1} to 0.68 pg mL^{-1}, respectively for Duomeen and 4.9-5.2 ng mL^{-1} for metaldehyde in real water samples. This work raises the prospects of disposable μPADs for on-site MS analysis for environmental pollutants.

The occurrence of NPs in the environment brings about a harmful influence on the health of diverse organisms. NPs can cause inflammation and lesions once entering the body. Othman *et al.* [303] proposed a paper-based and microarray-printed multifunctional platform for capture and detection of ceria NPs in chemical mechanical planarization slurries and wastewaters. Design concept of the paper-based platform and capture mechanism with fabrication and measurement procedures are shown in **Figure 6**D. Using either catechol or ascorbic acid as ligands, the platform was fabricated based on the use of redox-active ligands containing o-dihydroxy functionality. The platform indicates a concentration range of 23×10^{11} - 9.2×10^{13} NP mL^{-1} for colorimetric analysis of ceria NPs with LODs of 14.9×10^{11}-19.2×10^{11} NP mL^{-1}

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for catechol and ascorbic acid, respectively. Although the LOD achieved by X-ray fluorescence spectrometry (XRF) analysis is 10 times more sensitive than that by colorimetric analysis, colorimetric analysis is more user-friendly than XRF analysis.

In summary, paper-based platforms can meet the requirements of the ASSURED criteria (affordable, sensitive, specific, user-friendly, robust, equipment-free, delivered), which are more suitable for field-testing of CECs than instrumental methods, and have widely applicable prospects in the resource-limited regions lacking advanced equipment and skilled technicians. Nevertheless, it is essential to improve the analytical performance of PADs to offer reliable results. Further measures should be taken to improve the analytical performance for complex environmental matrices by reducing interferent effects. **Table 3** shows the summary of paper-based platforms for determination of CECs in environmental samples. The future looks bright for real-time environmental monitoring by integrating PADs, intelligent portable electronic equipment and publicly accessible website.

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5. Point of need and portable devices for determination of CECs: A comparison with chromatographic methods coupled to mass spectrometry

Chromatographic techniques coupled to mass spectrometry are definitely the gold standard for determination of CECs in the environment. Nevertheless, they suffer from several limitations and, to provide a fair comparison towards point of need and portable devices, a SWOT analysis was undertaken (**Figure 7**).

Sample preparation is definitely one aspect to look into. Generally, for portable methods, sample preparation requirements are kept to a minimum in order to foster simple and in field application. On the contrary, for methods employing chromatography and mass spectrometry detectors, sample preparation is time-consuming. This step is of utmost importance to avoid

matrix effects. Hence, it focuses on eliminating matrix constituents and lowering the analytical range to nanogram per litre.

The analytical range expected for CECs in environment is indeed a challenge. This is in fact an Achilles' heel of point of need/portable devices because, most of the time, colorimetric detection is not capable of providing the low detection limits required. Other more sensitive detection strategies may be employed (fluorescence, electrochemistry associated to a biochemical element - biosensor) and here there is a clear opportunity for introduction of new materials, able to perform preconcentration and also work as a platform for detection.

Other aspect to be considered is all the costs associated to the analytical procedure. GC/LC-MS requires a continuous investment on equipment, not only for acquisition, but also to maintain it in suitable working conditions that meet the low CECs levels expected in environmental samples. Moreover, trained operators are required, also to analyse and validate obtained data. Point of need/portable devices for CECs analysis are in an opposite position. The design is generally thought to have a low cost and to be used by low trained operators. Other current idea is that this type of devices can be used to implement the "science of citizens" where anyone from the general society would gather environmental data and contribute to map the presence of CECs. Finally, GC/LC-MS are so far restricted to the laboratory, despite efforts to make this hyphenation more portable and downscaled.

Concerning precision and robustness, GC/LC-MS is definitely the best approach, with clear guidelines for implementation of quality assurance/quality control (QA/QC) procedures. Also, GC- and LC-MS equipment are commercially available from different companies. Point of need/portable devices for CECs analysis are still one step back regarding acceptance by regulatory agencies and commercial availability. This is a clear opportunity for entrepreneurship in the analytical area.

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Finally, an increased amount of information can be extracted from GC/LC-MS as compared to point of need/portable devices. Focusing on analysis of CECs in environmental samples, GC/LC-MS offers the possibility to investigate the pathway of degradation of a given compound in a single run, considering the multi-analyte capability for quantitative and qualitative analysis. This would require HRMS or tandem MS configurations, which are not available in most routine laboratories. In this context, point of need/portable devices for CECs analysis has a clear role as a screening technique, that can be used before transportation of sample to the lab and that would decrease the analytical burden in the lab if only confirmatory/more detailed analysis were performed for positive samples.

6. Concluding remarks and outlook

An overview of recent advances toward the miniaturization of analytical methods for determination of CECs in environmental samples is provided herein. A number of analytical systems reported for CECs determination, comprising both downsized sample preparation techniques and miniaturized analytical flow systems, are described and recent developments discussed. In spite of the progress achieved so far, a number of challenging aspects are expected to be faced in the years to come by exploiting the potential of miniaturized analytical systems.

Notable efforts have been undertaken to determining CECs by means of miniaturized analytical systems. However, the degree of compliance with the requirements is highly dependent on the type of analyte considered. Thus, while a considerable number of methodologies are described for some CECs, there is still plenty of room for the development of methods capable of accurately determining certain types of CECs (*e.g.* engineered NPs, certain DBPs, etc.). Besides, the development of methods capable of determining CECs in matrices of increasing complexity at trace and ultratrace levels entail special difficulties. Rigorous validation of such methods is of paramount importance to provide evidence of their reliability. This aspect

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can be constrained by the lack of availability of certified reference materials (CRMs) and reference methods for determination of numerous CECs. The preparation of candidate CRMs that enable the quality control of developed procedures would be therefore of much interest.

On the other hand, the development of more sensitive and selective methods, in which downsized sample preparation techniques can be particularly advantageous, can be valuable to elucidate the environmental and health issues of non-regulated compounds; monitoring their presence in environmental compartments and to study the formation and degradation of potential CECs (*e.g*. DBPs).

Miniaturization of analytical methodologies is a matter of particular relevance. Shrinking conventional analytical systems is far from being the only driving force behind miniaturization. Instead, several desirable features can be identified for miniaturized methodologies, including a widely reduced consumption of sample and chemicals per analysis (with the subsequent reduction in wastes generation), integration of steps, simplification, enhanced portability, reduced human manipulation and adequate performance. Different levels of miniaturization can be attained in the analytical process, from downsized specific steps to fully miniaturized, integrated, analytical systems [304]. In spite of the degree of miniaturization achieved in methods of analysis devoted to the determination of CECs there is certainly still room for improvement. In fact, analytical methods claimed to be miniaturized usually involve bulky, not miniaturized, apparatus. While fully miniaturized analytical systems would be highly desirable, it should be kept in mind that controlling liquids becomes challenging under these conditions. In this sense, accomplishing the detection of analytes at realistic concentration levels is hard due to limitations in the sensitivity of detectors and the low sample volumes (*i.e.* low mass of analytes per sample volume).

Some additional important aspects should be increasingly considered in future contributions regarding method development. Firstly, analytical methods should move toward

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higher levels of automation and portability bearing in mind their benefits for analyte determination in general and CECs monitoring in particular. Besides, the development and implementation of novel materials that might overcome the limitations of commercially available alternatives in miniaturized analytical systems could acquire special interest and importance. The development of such materials could help in achieving improved analytical characteristics and sample throughput. Attention should also be paid to the removal or replacement of harmful chemicals in the developed methodologies. Thus, within the context of green analytical chemistry, researchers should consider with greater conviction the removal or replacement of harmful chemicals by greener alternatives. This aspect should not be limited to the application of the analytical method, but to every aspect related to it. Thus, features such as the preparation of advanced materials to be used in miniaturized analytical systems should be carefully considered from the viewpoint of green chemistry. The search for more sustainable methods is, in fact, of much importance to avoid the troubling situation that methods devoted to the determination CECs in environmental samples may significantly aggravate environment issues.

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Figure captions:

Figure 1. Evolution of publications devoted to CECs classified by year (A) and by subject area (B). Evolution of publications devoted to methods for CECs determination classified by year (C) and by subject area (D).

Figure 2. Schematic representation of solid phase-based microextraction and related techniques employed for determination of CECs. A) DI-SPME. B) *In vivo*-SPME [92]. C) HS-SPME. D) TFME. F) MEPS [149]. Reprinted with permission from Elsevier.

Figure 3. Schematic representation of liquid phase-based microextraction techniques employed for determination of CECs. A) DI-SDME. B) HS-SDME. C) LLLME. D) DSDME [212]. E) HF-LPME [215]. F) EME [230]. G) EME-EA-LLME [231]. H) DLLME [238]. Reprinted with permission from Elsevier and the American Chemical Society.

Figure 4. Schematic representation of LOV systems employed for CACs determination. A) LOV systems used for at-line micro-extraction. B) LOV systems used for micro-extraction and *in situ* detection of analytes.

Figure 5. Examples of various LOC systems designed for determination of CECs in the environment. A) A schematic of the synthesis principle of the circular DNA template and the detection mechanism of the platform [282]. B) An optofluidic SERS microsystem consisting of packed microspheres, an integrated micromixer, and integrated fiber optic cables [286]. Reprinted with permission from the Royal Society of Chemistry and the American Chemical Society.

Figure 6. Examples of various PAD systems designed for determination of CECs in the environment. A) Simulation diagram and structure illustration of the ratiometric paper-based device [294]. B) A schematic of the μPAD for the detection of organophosphates in natural waters [297]. C) The schematic procedure for preparing MIP on paper [298]. D) Design concept

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of the paper-based platform and capture mechanism with fabrication and measurement procedures [303]. Reprinted with permission from Elsevier and the American Chemical Society.

Figure 7. SWOT analysis regarding point of need and portable devices *vs*. chromatographic methods coupled to mass spectrometry for analytical purposes, particularly for analysis of CECs.

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Table 1

Selected applications of solid phase-based microextraction approaches for determination of CECs in environmental samples (classified by technique)

Analytes (number)	Analytical method	LOD	LOQ	LDR	Repeatability (RSD, %)	Environmental samples analyzed	Concentration levels	Recoveries (%)	Ref.
EDCs (10)	DI-SPME-GC–MS	1-42.5 ng g^{-1}	4-50 ng g^{-1}	1-3,000 ng g^{-1}	≤12.1	Biosolids	<LOD-786.7 ng g^{-1}	--	[76]
UV filters (14)	DI-SPME-GC–MS/MS	0.000045-0.0082 µg L^{-1}	0.00015-0.027 µg L^{-1}	0.002-1 µg L^{-1}	≤ 11	River and sea water	<LOD-258 µg L^{-1}	85-106	[77]
Synthetic and natural hormones (6)	MIP-DI-SPME-LC-UV	0.21-0.80 µg L^{-1}	0.69-2.6 µg L^{-1}	10.0 – 1,000 µg L^{-1}	≤ 6.6	Sewage of wastewater plant	< LOD	89-105	[81]
Abacavir (antiviral drug)	MIP-DI-SPME-LC-MS	10.1-13.6 ng L^{-1}	33.3-43.9 ng L^{-1}	50-1,000 ng L^{-1}	1.1-9.7	River, lake, sea and waste water	< LOD	88-99	[82]
Pharmaceuticals (12)	*In vivo*-SPME-LC-MS/MS	0.16-5.35 ng g^{-1}		1-5,000 ng g^{-1}	2-10	Fish and vegetable	~1-3,500 ng g^{-1}		[89]
UV filters (11)	HS-SPME-GC-MS/MS	0.001-0.087 ng g^{-1}	0.004-0.15 ng g^{-1}	0.01-50 ng g^{-1}	≤13	Beach sand	<LOD-670 ng g^{-1}	71-119	[101]

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Analytes (number)	Analytical method	LOD	LOQ	LDR	Repeatability (RSD, %)	Environmental samples analyzed	Concentration levels	Recoveries (%)	Ref.
Synthetic musk fragrances (9)	HS-SPME-GC-MS/MS	0.5-2.5 ng g^{-1}	2.5-5 ng g^{-1}	2.5-250 ng g^{-1}	≤ 23	Fish	<LOD-17.5 ng g^{-1}	--	[102]
Trimethyl phosphate	MIP-HS-SPME-GC-NPD	0.00012 µg L^{-1}	0.00036 µg L^{-1}	0.02–50 µg L^{-1}	≤6.9	River, lake, rain and waste water	<LOD-1.22 µg·L^{-1}	89-103	[105]
UV filters (9)	PIL-SPME-GC-MS	2.8-26.0 ng L^{-1}	8.5-183 ng·L^{-1}	1-6,000 ng·L^{-1}	2.5-15	Lake water	<LOD-42 ng·L^{-1}	63.5-120	[106]
Acidic pharmaceuticals (10)	*In vivo*-SPME-LC-MS/MS	0.13-8.44 ng g^{-1}	0.44-28.1 ng g^{-1}	1-5,000 ng g^{-1}	1.6-10.3	Fish (tilapia)	100-1400 ng g^{-1}	--	[91]
Diclofenac	IT-SPME-nanoLC-DAD	1.0 µg L^{-1}	3.3 µg L^{-1}	3.3-400 µg L^{-1}	4	River water	<LOD	100	[305]
UV filters (5)	IT-SPME-LC-DAD	0.04-0.26 µg L^{-1}	0.12-0.87 µg L^{-1}	0.25-200 µg L^{-1}	1.7-9.7	Lake, river and waste water	<LOD-5.46 µg L^{-1}	70.5-119	[113]
Carboxylic group-containing gold NPs	IT-SPME-ICP-MS	3.97 ng L^{-1} as Au (24.2 fmol L^{-1} as gold NPs)	--	0.02-20 µgL^{-1}	5.1	River and lake water	< LOD	77-103	[114]

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Analytes (number)	Analytical method	LOD	LOQ	LDR	Repeatability (RSD, %)	Environmental samples analyzed	Concentration levels	Recoveries (%)	Ref.
Pyrethroids (8)	TFME-GC-ECD	0.05-0.5 µg L^{-1}	0.15-1.5 µg L^{-1}	1-500 µg L^{-1}	≤ 8.3	Chrysanthemum tea	<LOD-0.082 µg L^{-1}	85-104	[117]
Bisphenol A	TFME-LC-DAD	0.05 µg L^{-1}	0.15 µg L^{-1}	0.15-50 µg L^{-1}	≤ 7.2	River and wastewater	<LOD-0.31 µg L^{-1}	81-95	[119]
N-nitrosamines (4)	NTD-GC-MS	1.0-10 ng L^{-1}	3.3-33.3 ng L^{-1}	50-3,000 ng L^{-1}	< 14.2	Air	<LOD-2,954 ng L^{-1}	82.2-109.3	[142]
Synthetic musk fragrances (9)	NTD-GC-MS/MS	2.5-12 ng L^{-1}	5-25 ng L^{-1}	Up to 5,000 ng mL^{-1}	3-11	Waste water	<LOD-1,160 ng L^{-1}	--	[143]
PAEs (5)	MEPS-GC-FID	0.02-0.1 ng mL^{-1}	0.07-0.25 ng mL^{-1}	0.07-100 ng mL^{-1}	4.8-8.3	Tap, river and mineral water	<LOD-4.5 ng mL^{-1}	85.5-99.2	[306]
PAEs (5)	MEPS-DLLME-GC-FID	0.001-0.01 ng mL^{-1}	0.003-0.03 ng mL^{-1}	0.003-200 ng mL^{-1}	5.7-8.9	Tap, river and mineral water	<LOD-7.8 ng mL^{-1}	90.3-98.8	[307]
Parabens (5)	MEPS-	0.06-0.09 µg L^{-1}	0.2-0.3 µg L^{-1}	0.2-20 µg L^{-1}	1.5-19.2	Tap, lake, swimming pool and wastewater	<LOD-4.6 µg L^{-1}	82.3-119.2	[308]

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Analytes (number)	Analytical method	LOD	LOQ	LDR	Repeatability (RSD, %)	Environmental samples analyzed	Concentration levels	Recoveries (%)	Ref.
Perfluorinated compounds (6), preservatives (4), plasticizers (2), surfactants (7), flame retardant (1), hormones (4), pharmaceuticals (14), UV filter (1), pesticides (9)	SBSE-LC-MS/MS	3.6-53 ng L^{-1}	12-177 ng L^{-1}	--	1-20	River water	<LOD-2,326 ng L^{-1}	63-120	[157]
Pharmaceuticals (27)	SBSE-LC-MS	--	1.25-5.0 ng L^{-1}	1.25-1,250 ng L^{-1}	0.9-20.2	Waste water	<LOD-43,860 ng L^{-1}	--	[158]
Parabens (4)	RDSE-GC-MS	0.02-0.05 µg L^{-1}	0.06-0.15 µg L^{-1}	--	2.5-9.7	Waste water	<LOD-0.87 µg L^{-1}	79-91	[162]
NSAIDs (4)	BAµE-CE-DAD	0.3 µg L^{-1}	1.0 µg L^{-1}	2.5-320 µg L^{-1}	0.3-4.4	Sea, estuary and river water	<LOD	10.4-94.1	[309]
Pharmaceuticals (3), hormones (7), plasticizers (2), flame retardant (1)	BAµE-UHPLC-MS/MS	0.012-0.6 µg L^{-1}	0.04-2.0 µg L^{-1}	0.04-40.0 µg L^{-1}	2-19	River water	<LOD-4.2 µg L^{-1}	74-118	[167]
Steroid hormones (9)	BAµE-LC-DAD	50.0-100.0 ng L^{-1}	165.0-330 ng L^{-1}	0.2-24.0 µg L^{-1}	3-14	Sea, underground, estuary, waste water	<LOD-4.30 µg L^{-1}	93-101	[165]

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Analytes (number)	Analytical method	LOD	LOQ	LDR	Repeatability (RSD, %)	Environmental samples analyzed	Concentration levels	Recoveries (%)	Ref.
UV filters (2)	BAμE-LC-DAD	0.04-0.20 μg L^{-1}	0.16-0.80 μg L^{-1}	0.16-80.0 μg L^{-1}	< 12	Sea, estuarine and waste water	<LOD	~33-75	[168]
REEs (6)	μ-SPE-ICP-MS	0.01-1.2 ng L^{-1}	--	0.1-10,000 ng L^{-1}	2.5-6.3	Lake and waste water	0.03-3.12 μg L^{-1}	93-107	[310]

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Table 2

Selected applications of liquid phase-based microextraction approaches for determination of CECs in environmental samples (classified by technique)

Analytes (number)	Analytical method	LOD	LOQ	LDR	Repeatability (RSD, %)	Environmental samples analyzed	Concentration levels	Recoveries (%)	Ref.
Ranitidine	DI-SDME-LC-MS/MS	3.0 μg L^{-1}	8.8 μg L^{-1}	8.8-4,716 μg L^{-1}	4-6	Superficial and waste water	<LOD	98.3-101.3	[206]
2-phenoxyethanol	HS-SDME-GC-MS	0.2 μg mL^{-1}	0.66 μg mL^{-1}	0.1-6.0 μg mL^{-1}	<5.0	Fish tissues	<LOD-6 μg mL^{-1}	97.7-102.4	[207]
CdTe QDs (1)	HS-SDME-ETAAS	0.03 μg L^{-1}	0.11 μg L^{-1}	--	3.0	Superficial, ground and lake water	<LOD	95-116	[208]
Statins (pharmaceuticals) (5)	LLLME-LC-Q-TOF-MS	0.03-2.00 ng L^{-1}	--	0.1-1,000 ng L^{-1}	3.6-5.3	River water	<LOD	88.3-105.6	[211]
Silver NPs	DSDME-FAAS	4 μg L^{-1}	--	10-120 μg L^{-1}	6.8	Tap, river and waste water	<LOD	90-104	[213]
Tramadol	Three phase-DSDME-UV-vis	8 μg L^{-1}	--	0.5-8 μg mL^{-1}	4.9	Tap and river water	<LOD	97.6-98.2	[214]
Phthalic acid esters (9)	HF-LPME-GC-MS/MS	1 μg L^{-1}	--	1-100 μg L^{-1}	< 20	Mineral, pond and waste water	<LOD-2.46 μg L^{-1}	74-120	[216]
β-blockers (6)	HF-LPME-LC-UV	0.08-0.5 μg L^{-1}	0.160-1.00 μg L^{-1}	0.160-200 μg L^{-1}	1.0-2.2	Waste water	<LOD->LOQ	96-108	[217]
Regulated DBPs (4) and	HP-LPME-GC-	1-44 ng L^{-1}	3-65 ng	0.01-45	3-22	Drinking water	<LOD-83.9 ng L^{-1}	96.5-105.2	[218]

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Analytes (number)	Analytical method	LOD	LOQ	LDR	Repeatability (RSD, %)	Environmental samples analyzed	Concentration levels	Recoveries (%)	Ref.
iodinated trihalomethanes (6)	μECD		L^{-1}	μg L^{-1}					
Pesticides (15), pharmaceuticals (5), PCP (2), industrial products (4) and lifestyle products (1)	HF-LPME-UHPLC-MS/MS	1.09-98.15 ng L^{-1}	2.13-126.50 ng L^{-1}	1-100 μg L^{-1}	2.7514.98	Sewage treatment plant and river water	<LOD-68.87 μg L^{-1}	80-127	[219]
Estrogens (4)	BHF-LPME-UHPLC-MS/MS	0.251-0.440 ng L^{-1}	0.995-1.82 ng L^{-1}	5-10,000 ng L^{-1}	7.25-8.13	Waste water	<LOD-145 ng L^{-1}	41-123	[220]
Sulfonamides (8)	HF-LLLME-UHPLC-FLD	3.1-1.2 ng L^{-1}	10.3-37.3 ng L^{-1}	0.05-5 μg L^{-1}	< 19	Sewage treatment plant water	<LOD-6.934 μg L^{-1}	56-113	[221]
Triazine herbicides (7)	HF-LLLME-sweeping-MEKC	0.07-0.69 μg L^{-1}	--	0.3-100 μg L^{-1}	7.4-12.1	Lake and pond water, honey and tomato	<LOD	85.2-114	[223]
Chlorophenols (3)	HF-LLLME-LC-UV	0.3-0.5 μg L^{-1}	--	5-1,000 μg L^{-1}	4.3-5.7	Canal water	<LOD	80-102	[226]
Pharmaceuticals (2)	EME-EA-LLME-GC-FID	0.15 μg L^{-1}	0.5 μg L^{-1}	0.5-750 μg L^{-1}	6.9-12.2	Waste water	<LOD	92.0-92.3	[231]
Chlorophenols (4)	HF-SPME-GC-ECD	0.36-1,200 ng L^{-1}	0.9-4,100 ng L^{-1}	0.02-500 μg L^{-1}	5.7-12.2	Tap, well and waste water	<LOD-30 μg L^{-1}	88- 97	[232]
Pharmaceuticals and PCPs (54)	MAE-HF-L/SME	0.01-0.50 ng g^{-1}	0.05-2.00 ng g^{-1}	0.5-50 ng g^{-1}	2.1-14.2	Fish	<LOD-7.81 ng g^{-1}	56.3-119.9	[233]
Triazine herbicides (5)	SLM-protected-MIP-MSPE	0.022-0.030 μg L^{-1}	--	--	5.8-10.6	Reservoir, well and tap water	<LOD	77.6-102.9	[237]
NSAIDS (3)	DLLME-LC-DAD-FLD	17-95 μg L^{-1}	57-316 μg L^{-1}	100-50,000 μg L^{-1}	2-3	Tap and river water	<LOD	89.8-103.0	[240]
Pesticides (5)	SLE-DLLME-LC-ESI-MS/MS	0.0015-0.0090 ng	0.005-0.030 ng	0.015-200 ng	8.5-13.9	Soil	0.03-197 ng g^{-1}	87-114	[243]

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Analytes (number)	Analytical method	LOD	LOQ	LDR	Repeatability (RSD, %)	Environmental samples analyzed	Concentration levels	Recoveries (%)	Ref.
		g^{-1}	g^{-1}	g^{-1}					
Cocaine	DLLME-LC-DAD-FLD	0.1 µg L^{-1}	0.3 µg L^{-1}	15-195 µg L^{-1}	4.6-7.6	Hospital effluent	0.4-4.9 µg L^{-1}	98.3-102.6	[242]
PCPs (13) and UV filters (6)	DLLME-GC-MS/MS	0.1-20.0 ng L^{-1}	0.2-66.7 ng L^{-1}	4-1,500 ng L^{-1}	<12	Tap, river, sea and waste water	<LOD-5,801 ng L^{-1}	83-120	[241]
DBPs (11)	DLLME-GC-MS	0.22-1.19 µg L^{-1}	0.75-3.98 µg L^{-1}	0.5-40 µg L^{-1}	4.0-15.5	Drinking water	<LOD-<LOQ	75.0-119.5	[246]
REEs (6)	DLLME-ETV-ICP-MS	0.08-150 ng g^{-1}		--	--	Geological samples	0.14-90.5 µg g^{-1}	75-105	[244]
Pharmaceuticals (12)	US-DLLME-UHPLC-MS/MS	0.006-0.091 µg L^{-1}	0.018-0.281 µg L^{-1}	0.04-200 µg L^{-1}	1.6-8.8	Drinking, running, river and waste water	<LOD-16.26 µg L^{-1}	76.77-99.97	[249]
Bisphenol A and emerging replacements (6)	VALLME-LC-MS/MS	0.5-10 ng g^{-1}	1-20 ng g^{-1}	1-10,000 ng g^{-1}	--	Dust	<LOD-4,444 ng g^{-1}	69.0-108.1	[252]
EDs (5)	AA-DLLME-SFO-LC-PDA	0.96-2.30 µg L^{-1}	2.92-7.02 µg L^{-1}	3-300 µg L^{-1}	<4.7	River and tap water	<LOD	90.1-104.4	[311]

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Table 3
Selected methods involving miniaturized analytical flow-based approaches for determination of CECs in environmental samples (classified by technique)

Analytes (number)	Analytical method	LOD	LOQ	LDR	Repeatability (RSD, %)	Environmental samples analyzed	Concentration levels	Recoveries (%)	Ref.
Estrogens (4)	LOV-BI-LC-UV	2-3 μg L^{-1}	6-9 μg L^{-1}	6.5-100 μg L^{-1}	< 4.9 (intra-day), < 12.1 (inter-day)	Waste water	<LOD-100 μg L^{-1}	80.5-113.3	[275]
Estrogens (4)	LOV-BI-GC-MS	0.05-0.3 μg L^{-1}	0.2-1 μg L^{-1}	0.2-500 μg L^{-1}	< 7.0 (intra-day), < 8.8 (inter-day)	Sea water	<LOD	91-110	[271]
Methyl paraben, butyl paraben, diclofenac, triclosan	LOV-BI-LC-MS/MS	n.a.	n.a.	2.5-300 μg L^{-1}	< 8	Mussels	243-882 μg kg^{-1}	89-132	[276]
Carbamazepine	LOV-BI-ELISA	n.a.	1.0 μg L^{-1}	1.0-50 μg L^{-1}	< 8.5	Waste water	1.7-2.2 μg L^{-1}	93-110	[272]
Butylparaben and triclosan	LOV-μSPE-LC-MS	0.5-0.6 ng L^{-1}	1.7-2.0 ng L^{-1}	1.7-250 ng L^{-1}	1.1-5.8	Sea water	<LOD-8.7 ng L^{-1}	97-107	[277]
Kanamycin	LOC-RCA-MCE	0.3 pg mL^{-1}	0.96 pg mL^{-1}	0.0008–10 ng mL^{-1}	3.9-4.7	fish	--	89.5-103.9	[282]
Sulfamethoxazole	LOC-SERS	0.2 nM	--	--	--	Tap, river and lake water	<LOD	--	[283]
Melamine and Thiram	LOC-SERS-chemical analysis	0.05-63 ppb	--	0.001–125 ppm	--	Field water	8 ppb	--	[286]
PBDEs	LOC-electrochemical analysis	0.019 μg L^{-1}	--	0.025-1.0 μg L^{-1}	5.1-9.6	Sea water	<LOD	94.1-103.0	[287]
Triazines (3)	LOC-electrochemical analysis	0.36-0.55 nM	--	1 nM-100 mM	--	Soil	<LOD	--	[288]
Triazines (3)	μSPE-LOC-GC–MS	0.2-0.5 ng mL^{-1}	0.5-2 ng mL^{-1}	0.5–1000 ng mL^{-1}	6.5–12.5	Natural water	1-3.5 ng mL^{-1}	97-101	[289]
Triazines (3)	μSPE-LOC-GC-MS	0.01-0.03	0.04-0.1	0.1-500	2.8–5.6	River, sea and	<LOD	89-98	[290]

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Analytes (number)	Analytical method	LOD	LOQ	LDR	Repeatability (RSD, %)	Environmental samples analyzed	Concentration levels	Recoveries (%)	Ref.
		ng mL^{-1}	ng mL^{-1}	ng mL^{-1}		paddy water			
Carbamates (3)	μSPE-LOC-electrochemical analysis	7-12 μM	21-27 μM	25-125 μM	5-11	Lake, river and irrigation water	<LOD	87-106	[291]
Pesticides (10)	μ-AEEC-MS	0.10-0.75 ng μL^{-1}	--	0.586-8.0 ng μL^{-1}	0.45-17	Sorghum plant	0.586 ng μL^{-1}	--	[292]
Cationic surfactant	LOC-Scattering Phantom Interface	0.5 μM	--	--	--	River water	1-4 μM	--	[293]
Aminoglycoside antibiotics (3)	Ratiometric PAD-FLD	0.023-0.069 ng mL^{-1}	--	0.01-150 ng mL^{-1}	0.92-5.97	River water	<LOD	99.4−102.6	[294]
Total tetracyclines	μ-PAD-field amplification sample stacking-fluorescent analysis	4.5 ng mL^{-1}	--	5-80 ng mL^{-1}	4.1-16.3	River, surface and tap water	<LOD-13.1 ng mL^{-1}	87-112	[295]
EE2	PAD-based immunocapture assay-electrochemical analysis	0.1 ng L^{-1}	--	0.5-120 ng L^{-1}	<4.9	River water	3.91-14.56 ng L^{-1}	97-104	[296]
Organophosphate pesticides (2)	μ-PAD-colorimetric analysis	10 nM	--	10-1,000 nM	--	Lake and ground water	<LOD->0.19 mg L^{-1}	--	[297]
Dichlorvos	MIP-based PAD-chemiluminescent analysis	0.8 μg L^{-1}	--	3.0-1,000 μg L^{-1}	4.0	Vegetables	222–524 μg L^{-1}	97.0-104.2	[298]
Pesticides (3)	μ-PAD-fluorescent analysis	0.01-0.05 ppm	--	--	--	Lettuce and choy	0.1–2.5 ppm	60-80	[299]
Pesticides (3)	μ-PAD-electrochemical analysis	2-50 ppb	--	2-600 ppb	--	River water	<LOD	76-95	[300]
Paraoxon-ethyl	μ-PAD-colorimetric analysis	25.0-46.7 μg L^{-1}	--	25.0-200 μg L^{-1}	2.63	River water	<LOD	86-131	[301]

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Analytes (number)	Analytical method	LOD	LOQ	LDR	Repeatability (RSD, %)	Environmental samples analyzed	Concentration levels	Recoveries (%)	Ref.
Metaldehyde	μ-PAD-PS-MS	4.9-5.2 ng mL^{-1}	--	4.9-150 ng mL^{-1}	<10%	Real water	<LOD	--	[302]
Ceria NPs	μ-PAD-colorimetric analysis	14.9×10^{11} -19.2×10^{11} NP mL^{-1}	--	23×10^{11}-9.2×10^{13} NP mL^{-1}	--	River water, slurries and wastewater	<LOD	91.68-94.65	[303]

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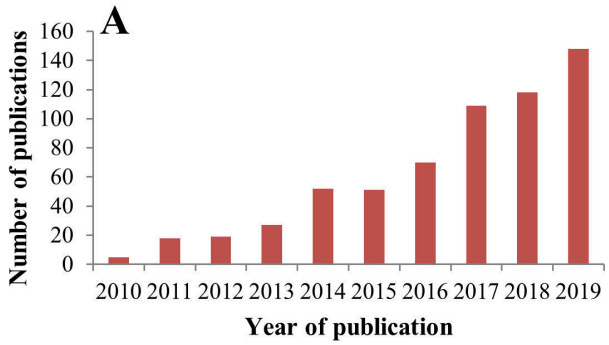
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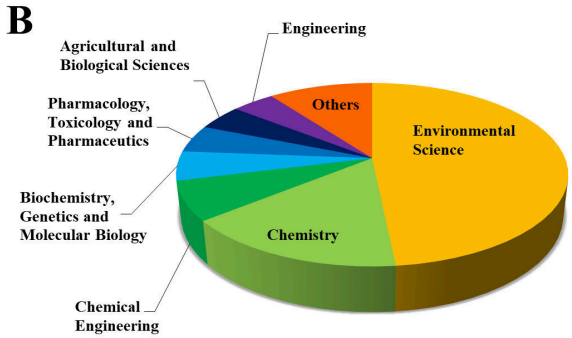


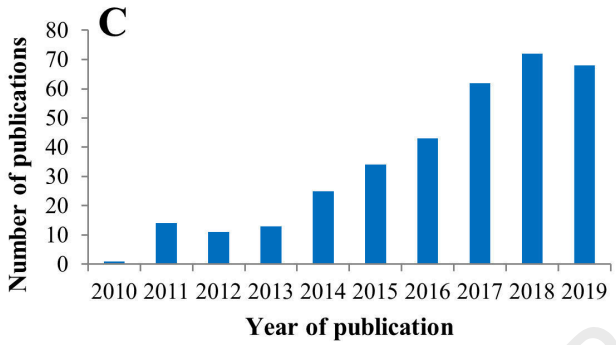


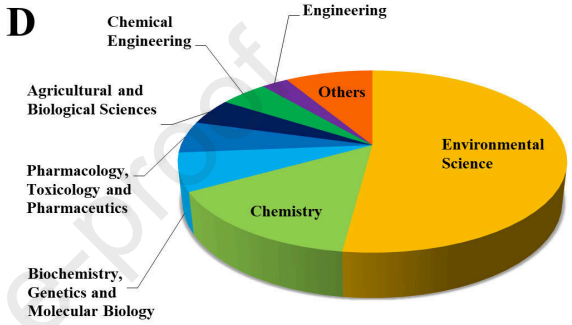
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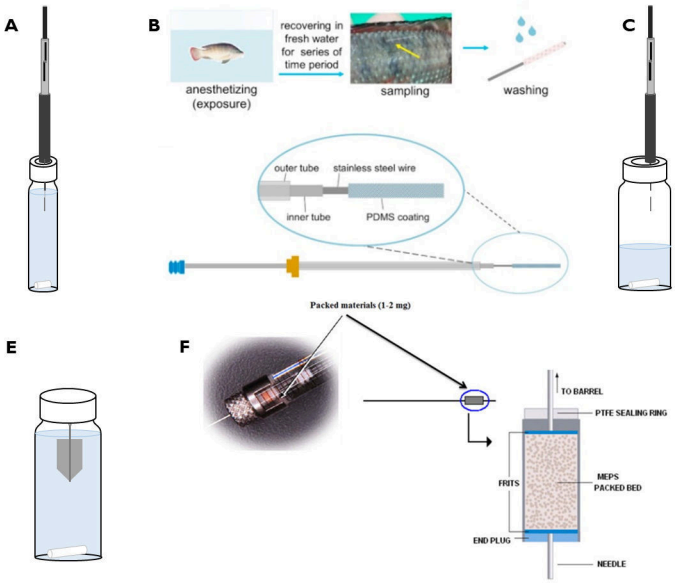




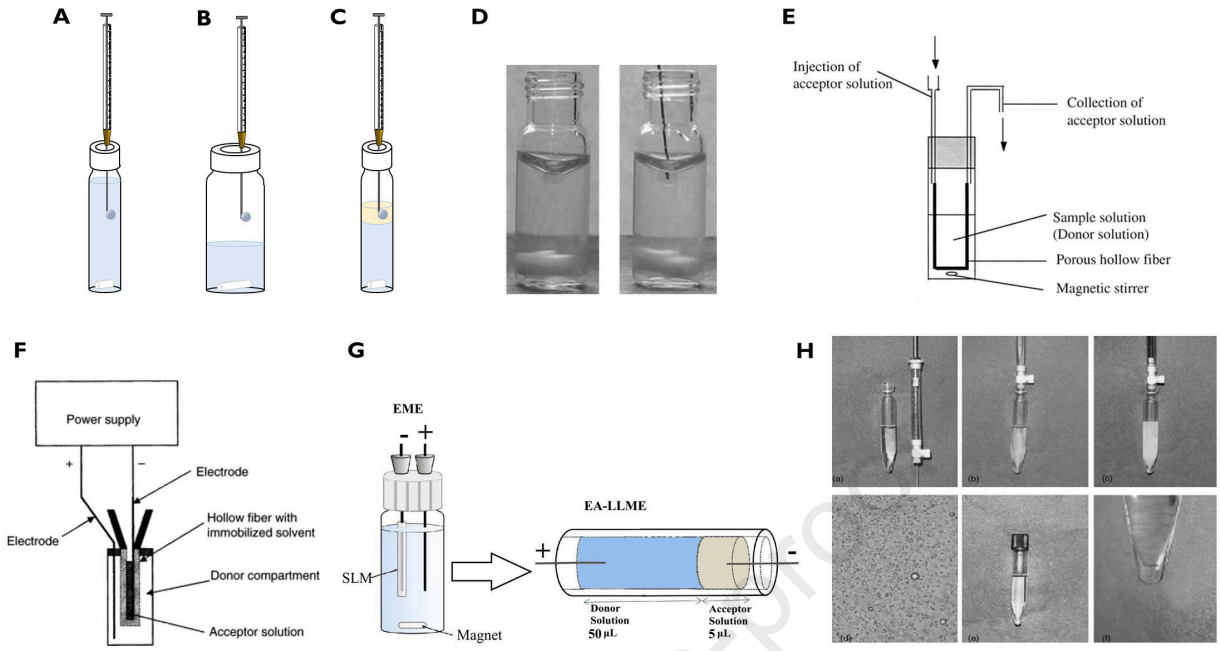




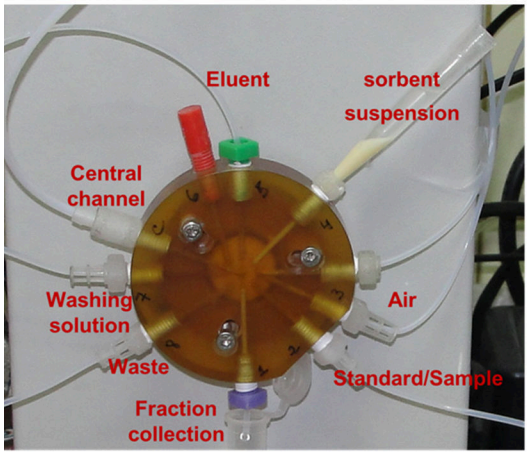
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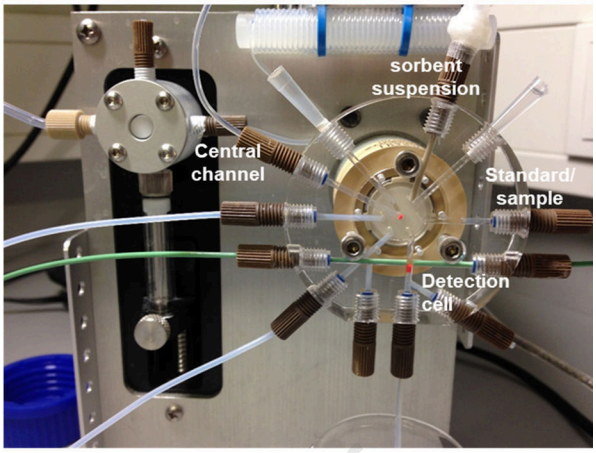


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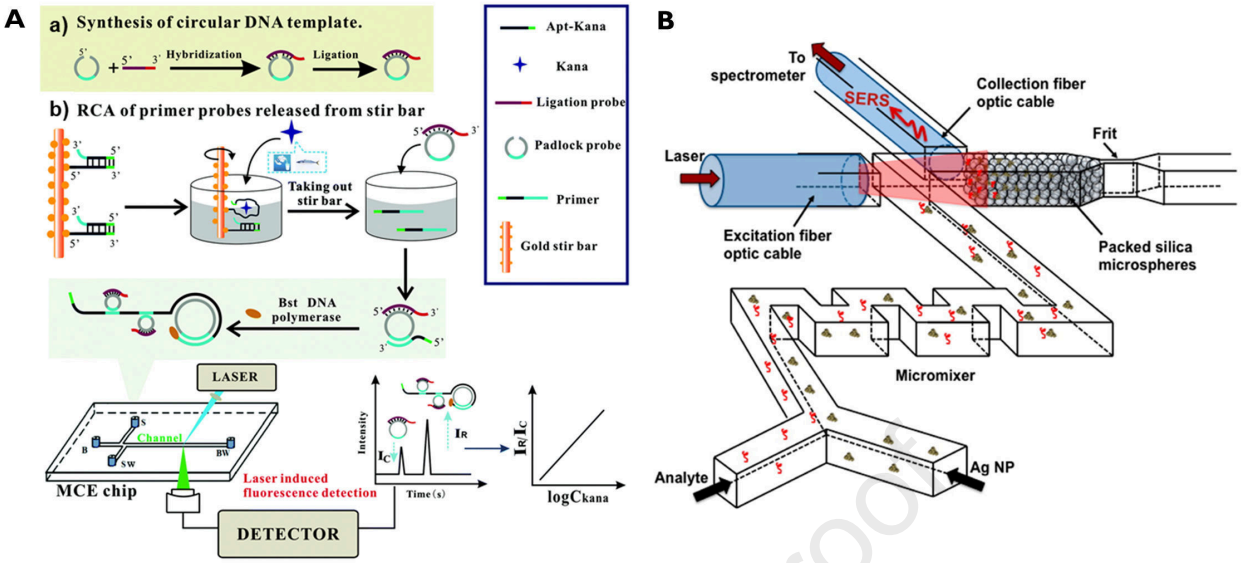


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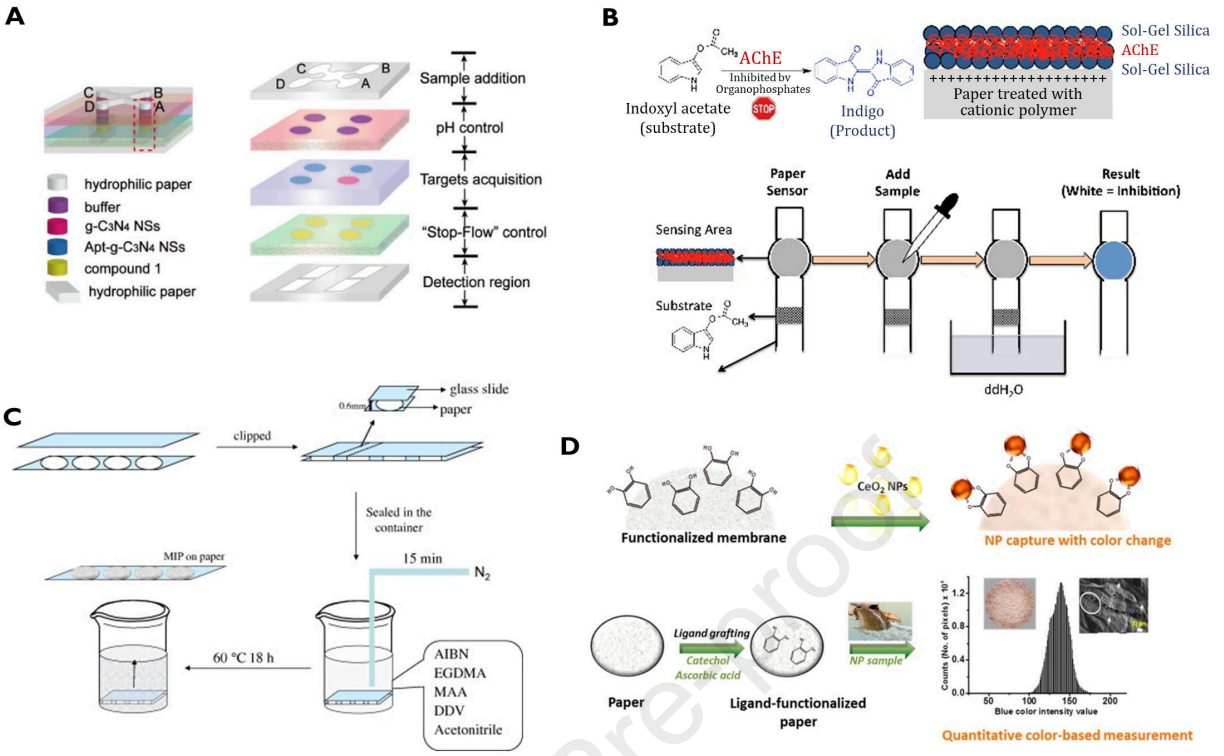




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POINT OF NEED AND PORTABLE DEVICES	
STRENGTHS • Miniaturization and/or downscaling • Field deployment • Low cost • Frequently available as open source hardware/software • Complies with Green Analytical Principles	**WEAKNESSES** • Methods with moderate to low precision • Constraints in selectivity and sensitivity • Application to known analytes and well characterized matrices
OPPORTUNITIES • Good match with large number of samples fostered by environmental analysis • Implementation of citizen science • Screening method before GC/LC-MS, reducing the number of samples analysed in the lab • Enables the creation of big data sets at low cost for environmental studies • Contributions from material sciences provide new platforms for portable devices	**THREATS** • Passive samplers offer more information compared to single measurements • Lack of approval from law enforcement agencies • Lack of stability of sensing elements • Few commercially available set-ups for environmental CECs analysis
CHROMATOGRAPHIC METHODS COUPLED TO MASS SPECTROMETRY	
STRENGTHS • Several CECs are determined individually in the same analysis/run • Robust and precise methods • Amenable for implementation of QA/QC procedures • Compatible with low concentrations found in environmental samples • Simultaneous quantitative and qualitative analysis	**WEAKNESSES** • High cost, high maintenance equipment • Requires specialized operators • Data treatment requires more time • Laboratory-based technique, not adequate for in field analysis • Possibility of sample degradation during transportation to the lab • Not environmentally friendly as organic solvents are commonly employed
OPPORTUNITIES • Equipment is becoming more portable • Automation and integration of sample treatment, enhancing throughput • Potential for assessing the formation pathway of CECs • Targeted and untargeted analysis of environmental samples	**THREATS** • HRMS or tandem settlements are required for confirmatory and identification analysis

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Miniaturized analytical methods for determination of environmental contaminants of emerging concern– A Review

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Highlights

- Microextraction, millifluidic and microfluidic approaches used for CECs determination are reviewed
- The occurrence and fate of CECs in the environment is described
- Challenging aspects of miniaturized analytical approaches are identified and discussed
- Relevant applications to the determination of CECs in environmental samples are discussed

Antonio Martín-Esteban is Senior Researcher and Head of Department of Environment & Agronomy at INIA (Madrid, Spain). He is author/co-author of over 80 publications including original research papers, reviews and book chapters. His current research is focused on the development of improved sample preparation methods, including the use of molecularly imprinted polymers, for the determination of organic compounds both in environmental and food samples by chromatographic techniques.

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Carlos Bendicho is a Professor at the Food and Analytical Chemistry department and the marine research center at the Vigo University. His current research focuses on the design of new nanosorbents and optical nanosensors for trace metal analysis and speciation in food, environmental and biological samples. He is author of about 180 scientific articles, 175 Congress communications, 15 reviews and 10 book chapters. His Hirsch-index is 43 (Scopus).

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Dragana Mutavdžić Pavlović is Full Professor at the Faculty of Chemical Engineering and Technology University of Zagreb (Croatia) since 2018. Her main research interest is in the field of environmental analytical chemistry, primarily focusing on modern sample preparation techniques (SPE, SBSE, MAE, USE, MSPD), the development of chromatographic methods for the determination of organic micropollutants in environmental samples and study of their behaviour in the environment (sorption phenomenon). She has participated in several national and international research projects. She has published 40 papers in SCI journals (Hirsch Index 15) and published 5 book chapters. She is reviewer of several SCI journals.

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Elefteria Psillakis is Professor in Water Chemistry at the School of Environmental Engineering, Technical University of Crete, Greece. She was selected for a Fulbright Research Fellowship and used it at Caltech, USA. Her research activities focus on understanding the fundamentals and developing new sample preparation methods and monitoring the environmental fate of organic contaminants. She is currently the Head of the EuChemS-DAC Sample Preparation Task Force and Network.

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Francisco Pena-Pereira received his Ph.D. (2009) in Chemistry from the University of Vigo (Spain). He then joined the Center for Environmental and Marine Studies (CESAM), University of Aveiro (Portugal) & Gdańsk University of Technology (Poland) as a postdoctoral fellow (2011–2015). At present, he focuses on the implementation of nanomaterials in miniaturized systems for analyte sensing at the University of Vigo (Spain) as distinguished researcher. He has published 66 scientific papers, 8 book chapters and 2 books (as Editor). His Hirsch-index is 28 (Scopus).

Journal Pre-proof

Ivo Safarik, Prof., PhD., DSc., received his PhD. degree in biochemistry from Institute of Chemical Technology in Prague in 1984, and in 1993 he became Associate Professor in biochemistry at the same institution. In 2008 he became Full Professor in biochemistry at Palacky University in Olomouc. DSc. degree in biochemistry was awarded by the Czech Academy of Sciences in 2001. His research interest is mainly focused on the development and characterization of new types of magnetically responsive (bio)materials and their use in various areas of biosciences, biotechnology and environmental technology. He has published 246 journal papers and book chapters.

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Professor **Jon Cooper** holds The Wolfson Chair in Biomedical Engineering and Emeritus Vice Principal at the University of Glasgow. He has published over 280 papers with an ISI H index of 53. He was elected as a Fellow of the Royal Academy of Engineering (UK's National Academy of Engineering) as well as a Fellow of the Royal Society of Edinburgh (Scotland's National Academy of Arts, Humanities and Sciences).

Journal Pre-proof

Kristýna Pospíšková, MSc., PhD., received her PhD. degree in biochemistry at Palacký University Olomouc (Faculty of Science) in 2013. Her research interest is mainly focused on the preparation of magnetic composite materials (including methods of magnetic modification of nonmagnetic materials) and other (nano)composites for environmental applications, bioapplications and analytical applications (carriers for immobilization of enzymes and cells, adsorbents of xenobiotics and reactive sorbents, magnetic modification of enzymes and cells, biosensors, isolation of biologically active compounds, preconcentration of analytes, etc.). She is also interested in preparation of biochar-based carbon composites for environmental and catalytic applications.

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Marcela Segundo is Professor at Faculty of Pharmacy, University of Porto and Head of the Analytical Development Group at REQUIMTE – PT Government Associate Laboratory. She received the FIA award for Science (2016) and she is the Secretary of the Division of Analytical Chemistry - EuChemS (2018). She is author or coauthor of > 125 peer-reviewed publications. Her scientific interests are focused on sample treatment, miniaturization of analytical devices, and hyphenation of flow techniques for high-throughput analysis. https://orcid.org/0000-0003-2938-0214

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Myriam Díaz-Álvarez received her Bachelor of Science degree in Biology from the Complutense University of Madrid, Spain in 2004. In 2006, she joined the Department of Environment at the Spanish National Institute for Agriculture and Food Research and Technology (INIA) in Madrid, where she continues working as a laboratory technician. She is the co-author of 20 publications, including original research papers and book chapters. The current research of her group is focused on the development of miniaturized sample preparation procedures, including the use of molecularly imprinted polymers, for the determination of pesticides, antibiotics and personal care products in environmental and food samples.

Journal Pre-proof

Yuwei Pan received a B.E. degree in Biomedical Engineering from University of Electronic Science and Technology of China in 2017. She is pursuing her Ph.D. in Biomedical Engineering at University of Glasgow (UK) and is currently a visiting student at Cranfield University. Her current research interest focuses on developing microfluidic paper-based analytical devices for point-of-car pathogen detection. She is also interested in electrochemical biosensors for monitoring water quality.

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Dr **Zhugen Yang** is faculty member at Cranfield University (UK), heading up a UKCRIC sponsored Sensors Laboratory. His group is developing low-cost and point-of-use sensors (e.g. paper-origami device) for environmental science (e.g. microbial contamination, AMR), public health (e.g. drug of abuse, COVID-19 for wastewater epidemiology), and biomedical diagnostics (e.g. infectious disease). He is recently involved UK national wastewater epidemiology surveillance programme (N-WESP) for COVID-19. His research has been featured in Science magazine and public media including BBC, Washington Post, Daily Mail etc.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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