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Review

Trends in analytical methodologies for the determination of alkylphenols and bisphenol A in water samples

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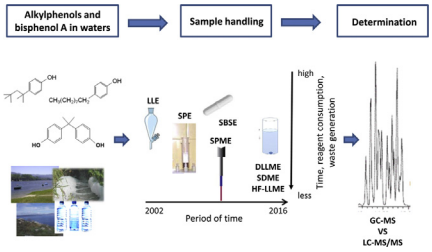
HIGHLIGHTS

- Trends in analytical methods for APs and BPA determination in waters are reviewed.
- Aspects related to sampling, extraction, clean-up and detection are discussed.
- Microextraction techniques are now the most used because of their remarkable advantages.
- Further research is required to achieve an effective method for APs and BPA water analysis.

GRAPHICAL ABSTRACT



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ABSTRACT

In the last decade, the impact of alkylphenols and bisphenol A in the aquatic environment has been widely evaluated because of their high use in industrial and household applications as well as their toxicological effects. These compounds are well-known endocrine disrupting compounds (EDCs) which can affect the hormonal system of humans and wildlife, even at low concentrations. Due to the fact that these pollutants enter into the environment through waters, and it is the most affected compartment, analytical methods which allow the determination of these compounds in aqueous samples at low levels are mandatory. In this review, an overview of the most significant advances in the analytical methodologies for the determination of alkylphenols and bisphenol A in waters is considered (from 2002 to the present). Sample handling and instrumental detection strategies are critically discussed, including analytical parameters related to quality assurance and quality control (QA/QC). Special attention is paid to miniaturized sample preparation methodologies and approaches proposed to reduce time- and reagents consumption according to Green Chemistry principles, which have increased in the last five years. Finally, relevant applications of these methods to the analysis of water samples are examined, being wastewater and surface water the most investigated.

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Contents

1. Introduction

A significant rise in chemical production has aroused special concern during decades because of the worldwide economic progress and technological advances. One clear example are plasticizers, additives used in plastic manufacture to improve its properties (i.e. flexibility, stability, resistance). Some of these additives, such as alkylphenols (APs) and bisphenol A (BPA), are considered endocrine disrupting compounds (EDCs) due to the fact that they can affect the hormonal system of human and wildlife at low concentrations.

Alkylphenols are a great family of organic compounds formed by a substituted phenolic ring and an alkyl chain ($n = 1–12$). The alkyl chain can be attached at various locations around the phenolic ring and therefore, *meta*-, *ortho*- and *para*-alkylphenols (also called 2-, 3- and 4-alkylphenols, respectively) can be distinguished. Among all APs, 4-octylphenols (4-OP) and 4-nonylphenols (4-NP) are the most important APs because of their higher use in industrial and household applications (more than 80% of total APs production) as well as their higher disruption capabilities [1]. These compounds are employed in plastic manufacture such as high density polyethylene (HDPE), polyethylene terephthalate (PET) and polyvinyl chloride (PVC) and also in the production of textiles, paper and agricultural chemical products [2]. Moreover, APs are the main degradation products of alkylphenol ethoxylates (APEOs), one of the most important non ionic surfactants used as detergents, dispersants or solubilizers [3].

Branched and linear isomers can be identified depending on the structure of the octyl- and nonyl- alkyl group. Whereas branched 4-OP (4-*tert*-OP) is a unique compound, more than 211 isomers are part of branched 4-NP (technical mixture). Although linear isomers (4-*n*-OP and 4-*n*-NP) are scarcely used for industrial purposes, they are present in aquatic system and can be bio accumulated in organisms as it was demonstrated in different environmental and ecotoxicological studies [4,5]. For all these reasons, both linear and branched 4-OP and 4-NP have been selected as representative alkylphenols in this critical review.

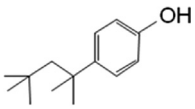
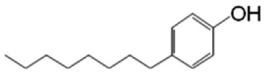
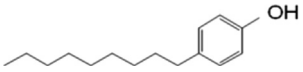
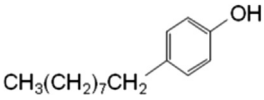
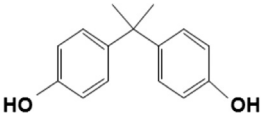
The other considered compound is BPA, with the chemical name 2,2-(4,4-dihydroxydiphenyl)propane, one of the most important monomers used worldwide in the manufacture of epoxy resins, phenol resins, polycarbonates, polyesters and also in flame retardants. Thus, this EDC is present in electronic components, construction materials, drinking bottles, food containers and medical devices [6].

These pollutants are partially eliminated in wastewater treatments plants (WWTP) and therefore, they enter into the aquatic environment and have negative impacts on surface and marine water bodies. Water is the most affected environmental compartment but of course, because of their physical and chemical properties (Table 1) they can be also associated to sediment and bio accumulated in biota, damaging human health at last step [7–9]. To preserve the environment and guarantee public safety, 4-OPs and 4-NPs have been included in the list of 45 priority substances set in the new European water legislation (Directive 2013/39/EU) [10]. Nevertheless, BPA has not been included in this Directive, although several investigations confirm different effects of this pollutant in organisms and humans such as sexual maturation, altered development and tissue organization of mammary glands [11]. Nowadays, the environmental impact of BPA is still in question and more studies are needed to support an adequate assumption.

Taking into account all the facts mentioned above, research based on the behaviour, distribution and transport of these EDCs in the aquatic system have become a significant issue for environmental and toxicological sciences. To achieve the low environmental levels of APs and BPA, sensitive and selective analytical methodologies are required. Fastness, simplicity and economical aspects are other ideal characteristics for methods, as well as low consumption of reagents and low waste generation. In this context, the main objective of this review is to critically discuss the state of the art and future trends in analytical methods for the determination of linear and branched 4-APs (4-*tert*-OP, 4-*n*-OP, 4-*n*-NP and NP) and BPA in water samples. This detailed recompilation of published methods for the analysis of these EDCs in the aquatic environment could provide significant information for initial assays because characteristics related to sample handling and instrumental detection are mentioned. Although some previous reviews were focused on some of these aspects (i.e. sample preparation, separation techniques) for some selected EDCs [12–14], the detailed information here discussed has not been included in any of them. Consequently, this review can be interesting and helpful for researchers who analyze these compounds (or similar ones) in environmental, food, biological and ecotoxicological studies in order to select an adequate method depending on the aimed application.

Hereby, a total of 75 analytical methods for APs and/or BPA analysis (from 2002 to the present) were recompiled, taking into account their scientific contribution to the topic as well as the number of citations achieved. As it can be seen in Fig. 1, a clear

Table 1
CAS-Number, physico-chemical properties and chemical structures of alkylphenols and bisphenol A.

Compounds of interest	CAS number	Molecular weight	Water solubility 25 °C (mg L^{-1})	log K_{ow}	Chemical structures
4-*tert*-octylphenol (4-tOP)	140-66-9	206	19.00[a]	5.28[b]	
4-*n*-octylphenol (4-*n*-OP)	1806-26-4	206	12.60[a]	5.56[b]	
4-*n*-nonylphenol (4-*n*-NP)	104-40-5	220	4.90[a]	5.76[b]	
4-Nonylphenol (NP)	84852-15-3	220	5.43[a]	5.99[b]	
Bisphenol A (BPA)	80-05-7	228	200[c]	3.32[c]	

log K_{ow}: octanol-water partition coefficient.
[a] Ref [7].
[b] Ref [8].
[c] Ref [9].

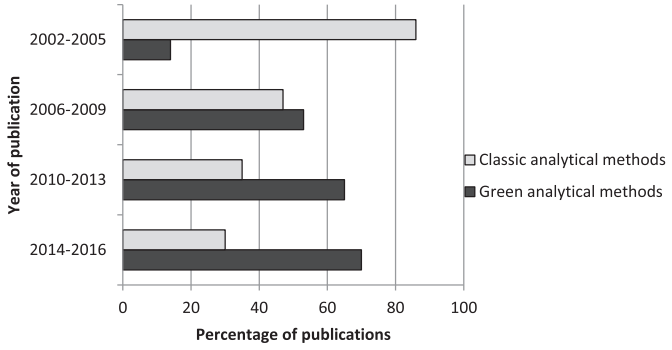


Fig. 1. Percentage of scientific papers based on classic and green methodologies for the analysis of alkylphenols and bisphenol A in water samples: from 2002 to 2005 (n = 19), from 2006 to 2009 (n = 16), from 2010 to 2013 (n = 29) and from 2014 to 2016 (n = 11).

evolution in analytical methodologies for the determination of APs and BPA in waters took place in the last decades. From 2002 to 2006, more than the 85% of the reported methods were based on classical analytical methods including common extraction techniques such as liquid liquid extraction (LLE) or solid phase extraction (SPE). As an example, the two standardized protocols established by the International Organization of Standardization (ISO) for this purpose, based on LLE [15] and SPE [16] followed by GC-MS determination. However, environmental friendly strategies have been extensively used since that time because of all their advantages (i.e. less time, less solvent consumption and simplicity). Thus, while only the 14% of the analytical methods based on microextraction techniques were published before 2006, more than 50% were achieved since 2011, increasing to 86% in the last two years (2014–2016).

Regarding the target compounds, marked tendencies can be observed in the analysis of these EDCs. The most analyzed compound is NP, followed by 4-tOP and BPA, considered in the 62%, 55% and 53% of the 75 reviewed methods. Nevertheless, lower percentages of methodologies include the analysis of 4-*n*-OP (37%) and 4-*n*-NP (24%). These results indicate the need of encouraging the determination of linear APs and the development of analytical methods that include these isomers, in order to resolve questions about their environmental and toxicological impacts.

2. Sample treatment

Sample preparation techniques are normally selected taking into account the physico-chemical properties of the target compounds, their environmental levels and the complexity of the analyzed matrices. Sample treatment is crucial in water sample analysis, because the analyte should be isolated from other matrix components and pre-concentrated in order to achieve the low environmental levels of pollutants.

Among the 75 reviewed methodologies for the determination of APs and BPA, both solid-liquid extraction (SLE) and liquid-liquid extraction (LLE) techniques have been selected as sample handling procedure. As it can be seen in Fig. 2, SLE procedures (75%) have been more employed than LLE techniques (25%), being the most common SLE technique solid phase extraction (SPE) (49%). Solid phase microextraction (SPME), stir bar sorptive extraction (SBSE) and other SLE techniques such as micro solid phase extraction or microextraction by packed sorbents (MEPS) are less applied for APs and BPA determination (5%, 8% and 4% respectively). Regarding LLE techniques, classic LLE (1%) has been replaced by liquid-liquid microextraction (LLME) techniques which minimize time- and reagent consumption according to Green Chemistry principles. Up to date, the most employed LLME procedure is dispersive liquid-liquid microextraction (DLLME) followed by membrane liquid-liquid microextraction (MLLME), hollow fiber microextraction (HF-LLME) and other techniques like single drop microextraction (SDME) with percentages of 15%, 7%, 4% and 7%, respectively.

The characteristics of all the selected methodologies, the compounds of interest and the analytical aspects related to quality

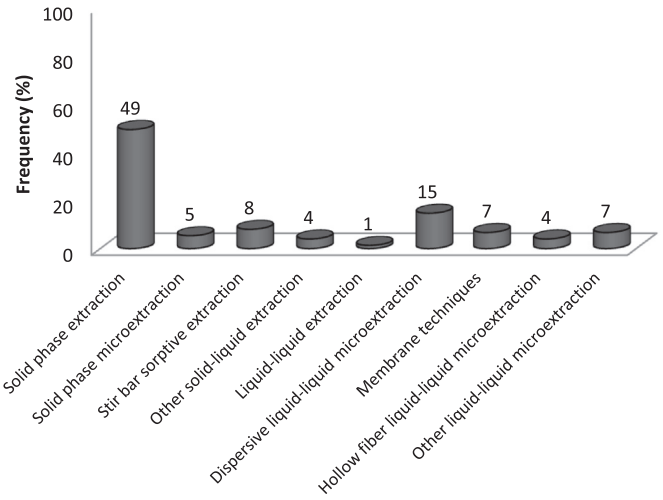


Fig. 2. Solid-liquid (micro)extraction techniques (SLE) and liquid-liquid (micro) extraction techniques (LLE) employed for the determination of alkylphenols and bisphenol A in water samples.

assurance and quality control (QA/QC) are reported in Table 2 (SLE techniques) and Table 3 (LLE techniques) and discussed in the following lines, in order to establish a critical comparison between methods. As it is shown in these Tables, among all extraction techniques are enough exhaustive to isolate the target compounds from the rest of matrix components, usually in combination with an adequate chromatographic separation technique and followed by a sensitive and selective mass spectrometric detection. However, a clean-up step can be needed when a complex matrix is analyzed, because of the presence of matrix interferences that can have influence in the determination, in spite of the strategy used for the quantitation (i.e. surrogate internal standards, matrix calibration and/or standard addition). In almost all cases, SPE is chosen as clean-up strategy, being the most common sorbents silica [17,18] and Florisil® [19] employed for the analysis of seawater/surface water and wastewater, respectively. It must be also mentioned that some analytical methods ("multi-residue" methods) were developed and applied to the analysis of alkylphenol precursors (APs ethoxylates or APs carboxylates [20,21]) and also for different pollutants in waters such as sexual hormones [3,22], phthalates [23] or polycyclic aromatic hydrocarbons [24]; although this fact is remarked in Tables, it is not detailed along the manuscript, because this discussion is out of scope of this review.

2.1. Solid-liquid (micro)extraction techniques

As commented before, SPE is the most common technique used for the determination of APs and BPA in waters. Besides its versatility and flexibility which can be explained by the wide range of available sorbents, SPE allows the isolation and pre-concentration of target compounds in only one step, reducing the analysis time in comparison with classical techniques (i.e. liquid-liquid extraction). The most employed sorbents in off-line SPE are C_{18} [5,18,20,21,23–36] followed by Oasis HLB® [3,17,37–44] and other polymeric sorbents (i.e. divinylbenzene) [25,45]. Although polymeric sorbents exhibit multiple retention characteristics and higher binding capacities as compared to silica-based packing materials [39], C_{18} seems to be adequate for APs and BPA determination because of the strong interactions between the sorbent and the aromatic ring (π-bond) of the target compounds [26]. Alternative and more specific sorbents such as mixed hemimicelles [46] and molecularly imprinted polymeric materials (MIPs) [47] were recently applied to the determination of target compounds in order to improve the selectivity and efficiency of the extraction step. Regarding the elution solvent, acetone, dichloromethane, methylbuthyleter and methanol are commonly used and therefore, a concentration step and re-dissolution in a compatible solvent with the instrumental technique could be required.

A limiting issue in off-line SPE applications is the volume of sample needed to achieve the low expected levels of target EDC: volumes of 250 [33,42], 500 [36,43], 1000 [11,37] and >4000 mL [5,17] of water were reported, which undoubtedly complicate sampling, transport and storage of samples. To minimize these problems, passive sampling devices were also employed in APs and BPA determination. One of the most common devices is polar organic chemical integrative sampler (POCIS), composed of two sheets of microporous polyethersulfone membrane encasing a solid phase sorbent, which is usually Oasis HLB® for the determination of target compounds [48,49]. The main drawback of passive sampling is up to date the interpretation of results, which are clearly related to the sampling time, diffusion parameters and the statistical tools applied [20].

However, the best way to solve all drawbacks of off-line SPE (i.e. tedious procedure, co-eluting interferences) is automatized the experimental procedure. Developing an on-line sample preparation procedure is a good way to reduce procedural errors, contamination, and analysis time [50]. In almost all published on-line SPE methods for APs and BPA determination [50–53], a polymeric precolumn (i.e. polystyrene divinylbenzene) is employed to isolate the target compounds, which are eluted with LC mobile phase in the same step, generally methanol or acetonitrile and water. Although on-line SPE is particularly attractive when large numbers of samples and/or sample series have to be routinely analyzed with high sensitivity, the cost of the equipment and the impossibility of (re) inject the extracts several times limit its application.

Nowadays, SPE is partially replaced by other microextraction techniques used for APs and BPA determination, which comply with Green Chemistry principles. Generally, these techniques are based on the adsorption of analytes onto sorbent materials, followed by a desorption process, usually with high temperature or low volume of solvents. Depending on the physical support where sorbents are fixed (i.e. fibre, syringe, stir bar) different techniques can be considered. One of the first known microextraction technique applied to APs and BPA determination was solid phase microextraction (SPME) in which the sorbent coating (10–150 μm) is applied over a thin silica fibre on a syringe needle [54]. Although polydimethylsiloxane (PDMS) is the most common sorbent used in SPME because of its suitability for extracting compounds with log $K_{ow} > 3–4$, PDMS was replaced by other polymeric materials in the determination of target compounds in order to improve the efficiency of the extraction. Taking into account their physico-chemical properties, more polar phases can be suitable for the determination of APs and BPA [55–58], such as polyacrilate [56] or carbowax template resin (CW/TPR) [57]. Other alternative fibres were coated in house, using sorbents like copolymer-polyaniline (CPANI) [55] and ionic liquids [58], obtaining also satisfactory results. Besides of its coupling with GC [56], SPME can be also coupled with LC [57,58], using the LC mobile phase in the desorption process, reducing sample handling and the analysis time (<60 min). One of the main drawbacks related to SPME is its limited efficiency in comparison with other techniques such as SPE because of the small amount of coating available; however when a GC-MS is selected as instrumental technique, all extracted analytes are injected in the GC and therefore, similar method quantitation limits can be obtained.

Other alternative microextraction technique for APs and BPA

Table 2
Methodologies based on solid-liquid (micro)extraction techniques for 4-APs and BPA analysis in water samples (from 2002 to the present, Web of Science™).

SLE technique	Extraction characteristics	Compounds of interest	Type of waters	Sample volume (mL)	Instrumental technique	Analytical quality parameters		Ref
						Relative recovery%	MDL/MQL ($\mu g\ L^{-1}$)	
SPE	C_{18} cartridges. Elution with 2 × 5 mL MeOH:DCM (9:1 v/v)	4-tOP, NP (APEOs and APECs)	Seawater	NM	LC-MS/MS, ACN/water:water (80:20 v/v, 5 mM acetic acid)	81–91	0.15 (MDL)	[20]
SPE	C_{18} cartridges. Elution with 2 × 4 mL MeOH	4-OP, NP (APEOs and EDCs)	Wastewater	500	LC-MS/MS, ACN:water	85–88	0.1 (MDL)	[25]
SPE	C_{18} cartridges. Elution with 2 × 4 mL MeOH	NP	Drinking water	500	LC-MS/MS, MeOH:water	85	0.001 (MDL)	[26]
SPE	C_{18} cartridges (500 mg, 6 mL). Elution with 3 mL propanol	4-OP, NP	Wastewater	4000	LC-MS and LC-FLD, ACN:water (58:42 v/v)	91–96	<0.15 and <1.2 (MQL)	[27]
SPE	C_{18} cartridges (1000 g, 6 mL). Elution with 5 mL acetone + 2 × 5 mL MTBE:MeOH (9:1 v/v)	4-*n*-NP, BPA (APEOs)	Wastewater	500	LC-MS, ACN:MeOH/water (10 mM ammonium acetate)	80–100	<0.003 (MDL)	[28]
SPE	C_{18} cartridges (500 mg, 6 mL). Elution with 2 × 5 mL ACN	4-tOP, NP, BPA (other EDCs)	Surface water	500	LC-MS, ACN:water	71–125	0.09–0.15 (MDL)	[29]
SPE	C_{18} cartridges (500 mg, 3 mL). Elution with 6 mL diethylether: MeOH (9:1)	4-tOP, 4-OP, 4-*n*-NP, NP; BPA (other EDCs)	Wastewater	500	GC-MS, Derivatization: BSTFA	95–105	0.02–0.15 (MQL)	[23]
SPE	C_{18} cartridges (500 mg). Elution with 5 mL MeOH	BPA	Wastewater	1000	LC-MS, MeOH:water	>85	0.38 (MDL)	[30]
SPE	C_{18} cartridges. Elution with 4 × 2 mL DCM:hexane (4:1)	4-*n*-NP, BPA (other EDCs)	Wastewater	100	GC-MS, Derivatization: BSTFA	33–93	0.11–0.48 (MQL)	[31]
SPE	C_{18} cartridges. Elution 5 mL MeOH	NP	Wastewater bottle water	200	UPLC-MS/MS, MeOH:water (0.01% ammonia + 0.1 mM ammonium acetate)	83–108	<0.290 (MQL)	[32]
SPE	C_{18} cartridges. Elution 2 mL MeOH	4-tOP, 4-OP, 4-*n*-NP, BPA	Seawater	4000	UPLC-FLD, ACN:water	85–104	<0.045 (MQL)	[5]
SPE	C_{18} cartridges. Elution 2 mL MeOH	4-tOP, 4-OP, 4-*n*-NP, NP	Surface water, Wastewater	250	LC-MS/MS, ACN/THF: water (1 mM formic acid)	67–92	0.002–0.004 (MDL)	[33]
SPE	Supelclean ENVI-18 cartridges (500 mg, 3 mL). Elution with 8 mL ethylacetate	4-NP, BPA	Tap and bottle water	1000	GC-MS, Derivatization: PFBOCl-	74–118	<0.007 (MQL)	[34]
SPE	RP-C_{18} and EN (100 mg) cartridges (200 mg). Elution with 1.9 mL ACN	4-NP	Surface water, Wastewater	1000	GC-MS, Derivatization: K_2CO_3+acetic acid	96–113	<0.002 (MDL)	[35]
SPE	RP-C_{18} cartridges (200 mg). Elution with 3 × 10 mL ethylacetate:hexane (50:50 v/v)	4-tOP, NP; BPA (other EDCs)	Wastewater snow	500	GC-MS, No derivatization	111–129	<0.033 (MQL)	[36]
SPE	Oasis HLB® glass column. Elution with MeOH and DCM	4-tOP, NP (APEOs)	Wastewater	1000	LC-MS/MS, MeOH:water (3 mM ammonium acetate)	60–75	<0.004 (MDL)	[37]
SPE	Oasis HLB® cartridges (200 mg, 6 mL). Elution with 3 mL methylbuthylether	4-tOP, 4-OP, 4-*n*-NP, BPA (other EDCs)	Surface water, Wastewater and tap water	500	LC-MS/MS, ACN:water	887–106	0.02–0.4 (MQL)	[38]
SPE	Oasis HLB® cartridges (200 mg, 6 mL). Elution with 2 × 3 mL propanol:methylbuthylether (10:90 v/v)	4-tOP, 4-OP, 4-*n*-NP, BPA (other EDCs)	Surface water, Wastewater	500	LC-MS/MS, ACN: water/ACN (80:20 v/v, 1 mM ammonium formate)	80–106	<0.04 (MQL)	[39]
SPE	Oasis HLB® cartridges. Elution with 200 mL acetone:MeOH (80:20 v/v). Clean-up: silica gel (3 g)	4-tOP, NP, BPA (other EDCs)	Seawater	5000	LC-MS/MS, MeOH:water (2.5 mM ammonium acetate)	20–80	<0.00014 (MDL)	[17]
SPE	Oasis HLB® cartridges (200 mg, 6 mL). Elution with MeOH:Acetone:ethylacetate (2:2:1)	4-OP, 4-*n*-NP, NP; BPA (APEOs and APECs)	Wastewater industrial effluents	1000	LC-MS/MS, ACN:water (0.1% acetic acid)	NM	<0.01 (MDL)	[40]
SPE	Oasis HLB® cartridges (200 mg, 6 mL). Elution with 2 × 5 mL acetone	4-tOP, 4-OP, NP, BPA (other EDCs)	Wastewater	500–1000	GC-MS, Derivatization: BSTFA	72–115	<0.007 (MDL)	[3]
SPE	Oasis HLB® cartridges (500 mg, 6 mL).	4-tOP, 4-*n*-, NP, BPA (other EDCs)	Surface water, seawater, Wastewater	2000	GC-MS, Derivatization: MTSTFA	57–91	<0.001 (MDL)	[41]

(*continued on next page*)

Table 2 (*continued*)

SLE technique	Extraction characteristics	Compounds of interest	Type of waters	Sample volume (mL)	Instrumental technique	Analytical quality parameters		Ref
						Relative recovery%	MDL/MQL ($\mu g\ L^{-1}$)	
	Elution with 12 mL DCM:ethylacetate:MeOH (2:2:1)							
SPE	Oasis HLB® cartridges. Elution with 3 mL acetone+2 mL DCM	4-tOP, 4-*n*-NP	Wastewater	250	GC-MS, Derivatization: acetic acid	70–135	0.03–0.05 (MQL)	[42]
SPE	Oasis HLB® cartridges (200 mg). Elution with 8 mL ethylacetate + 8 mL hexane	4-tOP, NP; BPA (other EDCs)	Wastewater	500	GC-MS, Derivatization: BSTFA	69–121	<0.055 (MDL)	[43]
SPE	Oasis HLB® cartridges (200 mg). Elution with 10 mL (DCM:hexane 50:50 v/v + 10 mL acetone:DCM 50:50 v/v)	4-OP, NP, BPA (other EDCs)	Tap water	1000	GC-MS, No derivatization	88–112	<0.029 (MQL)	[44]
SPE	ISOLUTE® ENV + cartridges (500 mg, 6 mL). Elution with 12 mL DCM + 12 mL MeOH + 12 mL acetone	4-OP, NP	Surface water	4000	LC-MS/MS, MeOH:water/MeOH (50:50 v/v, 10 mM ammonium acetate)	95–110	0.002–0.003 (MDL)	[21]
SPE	LiChrolut® EN cartridges (200 mg). Elution with 5 mL ACN	4-tOP, 4-NP, BPA	Surface water, seawater, Wastewater	500	LC-MS, ACN:water (0.05% acetic acid)	40–93	0.001–0.3 (MDL)	[45]
SPE	Ionic Par (1 mM). C_{18} cartridges. Elution with 2 mL acetone. Clean-up silica (0.5 g)	4-tOP, NP	Surface water	20	GC-MS, Derivatization: PFBBr	92–108	<0.076 (MDL)	[18]
SPE	Micelles formation: SDS (pH = 2). Sorbent: alumina. Elution with 2 mL MeOH	OP, NP (APECs)	Surface water, Wastewater	500	LC-MS, MeOH:water	95–104	0.07–0.11 (MDL)	[46]
SPE	AffiniMIP® sorbent (200 mg). Elution 3 mL MeOH	4-OP, NP, BPA	Surface water	250	LC-MS, MeOH:water (0.15% ammonium hydroxide)	80–120	<0.0064 (MQL)	[47]
SPE (passive sampling)	POCIS. Oasis HLB® cartridges (240 mg). Elution with 20 mL MeOH. Extraction in 6 weeks (15 m depth)	OP, NP (PAHs)	Seawater	Passive sampling	GC-MS, Derivatization: PFBOCl	NM	<0.0143 (MDL)	[20]
SPE (passive sampling)	POCIS. Oasis HLB® cartridges (100 mg). Elution with 3 × 10 mL MeOH. Extraction in 10 days (50–100 cm depth)	BPA	Surface water, Wastewater	Passive sampling	GC-MS, No derivatization	80–87	<0.000487 (MDL)	[48]
SPE (passive sampling)	POCIS. Oasis HLB® cartridges (100 mg). Elution 50 mL acetone. Extraction in 28 days	4-tOP, 4-OP, NP, BPA	Surface water, seawater, Wastewater	Passive sampling	GC-MS, Derivatization: BSTFA	77–105	NM	[49]
On-line SPE	Polystyrene-divinylbenzene pre-column. Elution with mobile phase.	4-tOP, NP, BPA	Surface water, seawater, Wastewatertap water	100	HPLC-UV, MeOH:water (1% acetic acid)	41–97	0.01–0.1 (MQL)	[50]
On-line SPE	On-line. SPE polystyrene-divinylbenzene cartridges. Elution with mobile phase	4-tOP, NP (other EDCs)	Surface water, tap water	20	LC-MS, ACN:water	74–93	<0.065 (MDL)	[51]
On-line SPE	C_{18} pre-column. Elution with mobile phase.	BPA	Surface water, Wastewater tapwater	1000	LC-MS, ACN:MeOH:water (30:20:50)	85–100	<0.115 (MDL)	[52]
On-line SPE	C_{18} and C_8 pre-column. Elution with mobile phase	4-tOP, 4-*n*-OP, 4-NP (APEOs and APECs)	Wastewater	NM	LC-MS/MS. MeOH:water (20:80 v/v)	59–105	0.050–0.085 (MDL)	[53]
SPME	CPANI fiber. Extraction time, 150 min. Temperature, 30 °C. Desorption with mobile phase	4-tOP, 4-*n*-NP, BPA	Surface water, tap water	10	HPLC-FLD, ACN:water (75:25 v/v)	84–123	<0.091 (MDL)	[55]
SPME	Polyacrylate fiber. Extraction time, 30 min. Temperature, 65 °C.	4-tOP, 4-*n*-NP, NP	Tap water, lake water	2	GC-MS, Derivatization: MTBSTFA	91–115	<0.00385 (MDL)	[56]
SPME	CW/TPR fiber. Extraction time, 60 min. Temperature, 40 °C. Desorption with mobile phase during 14 min	NP, BPA	Tap water	40	HPLC-FLD, ACN:water	95–113	0.34–0.90 (MQL)	[57]
(IL)-SPME	Polymeric ionic liquid. Extraction during 60 min a Temp. 20°	4-tOP, 4-OP, NP	Tap water, Bottle water, swimming pool	20	GC-FiD	82–105	0.055–1.5 (MDL)	[58]
SBSE	Stir bar PDMS. Agitation during 60 min. Temp. 20°	4-tOP, 4-OP, NP, BPA	River	10	TD-GC-MS, derivatization acetic acid	85–106	0.032 (MDL)	[60]
SBSE	PDMS stir bar. Extraction during 240 min. Desorption with ethyl acetate	4-tOP, 4-OP, 4-*n*-NP, NP, BPA (other EDCs)	Surface water, Wastewater, tap water	15	GC-MS, Derivatization: MTSTFA	11–24	<0.021 (MDL)	[61]
SBSE	Stir bar PDMS. Agitation during 15 h, 600 rpm	4-tOP, 4-OP, NP, BPA (other EDCs)	Seawater, Wastewater	100	TD-GC-MS, Derivatization: BSTFA	99–147	<0.021 (MQL)	[62]
SBSE		NP, BPA (other EDCs)		100	GC-MS, derivatization MTSTFA	83–111	<0.011 (MDL)	[63]

Table 2 (*continued*)

SLE technique	Extraction characteristics	Compounds of interest	Type of waters	Sample volume (mL)	Instrumental technique	Analytical quality parameters		Ref
						Relative recovery%	MDL/MQL ($\mu g\ L^{-1}$)	
	Stir bar PDMS. Agitation during 8 h at 900 rpm. Desorption: ethylacetate		Surface water, Seawater, Wastewater					
SBSE	PDMS stir bar. Extraction during 300 min at 500 rpm	4-tOP, 4-*n*-NP, NP, BPA (other EDCs)	Wastewater	10	TD-GC-MS, Derivatization: acetic acid	40–118	0.002 (MDL)	[64]
RDSE	PTFE Disk + PDMS stir bar. Agitation during 20 min. Desorption with MeOH a 45 °C, 20 min	NP	Wastewater	250	GC-MS, no derivatization	84–122	0.09 (MDL)	[65]
μ-SPE	0.05 mL sorbent (Chromosorb®). Extraction 2400 min. Elution with MeOH	4-tOP, 4-OP, NP (APEOs)	Surface water, tap water	10	GC-FiD	47–97	0.7–1 (MDL)	[66]
MEPS	C_{18} as sorbent (2 mg). Elution ethylacetate:hexane (50:50v/v)	4-tOP, NP, BPA (other EDCs)	Wastewater snow	5	GC-MS, no derivatization	94–97	<0.121 (MQL)	[36]
MEPS	C_{18} as sorbent (4 mg). Elution ethylacetate: dichloromethane (50:50v/v)	4-tOP, 4-OP, 4-*n*-NP, NP, BPA (other EDCs)	Surface water, Wastewater	0.8	GC-MS, derivatization 2BSTFA	78–96	<0.013 (MDL)	[22]

Abbreviations: ACN, acetonitrile; APEOs, alkylphenol polyethoxylates; APECs, alkylphenol ethoxycarboxylates; BSTFA, N, O-bis(trimethylilyl)trifluoroacetamide; BPA, bisphenol A; CPANI, composite polyaniline; CW/TPR, cabowax template resin; DAD, diode array detector; DCM, dichloromethane; EDCs, endocrine disrupting compounds; FiD, flame ionization detector; FLD, fluorescence detector; GC, gas chromatography; HPLC, high performance liquid extraction; IL, ionic liquid; LC, liquid chromatography; MDL, method detection limit; MeOH, methanol; MEPS, microextraction by packed sorbents; MQL, method quantitation limit; MS(/MS), (tandem) mass spectrometry; μ-SPE, micro solid phase extraction; MSTFA, *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide; MTBE, methyl tert-butyl ether; NM, not mentioned; NP, nonylphenol technical mixture; 4-NP, 4-*n*-NP, nonylphenol (linear isomer); OP, octylphenol; 4-tOP, 4-tert-octylphenol; 4-OP, 4-*n*-OP, 4-octylphenol (linear isomer); PDMS, Polydimethylsiloxane; PFBBr, Pentafluorobenzylbromide, PFBOCl, Pentafluorobenzoylchloride; POCIS, Polar Organic Chemical Integrative Sampler; RDSE, rotating disk sorptive extraction; SBSE, stir bar sorptive extraction; SPE, solid phase extraction; SPME, solid phase microextraction; TD, thermal desorption; UPLC, ultra performance liquid chromatography.

determination is stir bar sorptive extraction (SBSE), based on a stir bar coated with PDMS as an extracting phase [59]. In comparison with SPME, the amount of sorbent is increased and therefore, the extraction efficiency is improved; however, higher extraction time (60 min–15 h [58–65] are needed to achieve the equilibrium between phases. After the extraction, target compounds were usually desorbed quantitatively into a GC-MS by thermal (TD) [58,62,64] or solvent desorption [61,63]. In the first case, a TD equipment is needed increasing the analysis cost; however, the whole extract can be injected which improves the method quantitation limits. When solvent desorption is applied, a small volume of solvent (normally ethylacetate) is used and only an aliquot of the extract can be injected. A weakness of SBSE is the limited stir bar coatings available, which reduces the applications of this technique. As an alternative, a made in-house rotating disk coated with PTFE and PDMS was applied to the determination of NP in wastewaters [65]. The combination of these two sorbents allows the extraction of a higher range of compounds with different polarity avoiding derivatization of more polar compounds.

Miniaturized-SPE techniques such as micro-solid phase extraction (μ-SPE) [66] and microextraction by packed sorbents (MEPS) [22,36] were also proposed for the determination of these EDCs in waters. In the μ-SPE, a volume of 10 mL was passed through a low amount of the porous polymer (10–50 mg) and extracted with methanol (<1 mL) [66]. In the case of MEPS, a small sample volume (<1 mL) was passed through a lower amount of C_{18} (2–4 mg [22]) placed into a microsyringe. After the analytes are absorbed to the sorbents, they are directly eluted with a minor volume of solvents or a mixture of solvents (≈50 μL) and analyzed by GC-MS. Because of the large volume of injection (LVI) employed in MEPS applications, method quantitation limits similar to other techniques (i.e. SPE) can be achieved using lower sample volume. Moreover, a reduction in time and labour effort in sample preparation and analysis can be achieved by a fully automated method using MEPS, which should be considered as a promising approach.

2.2. Liquid-liquid (micro) extraction techniques

Although LLE was employed for the determination of APs and BPA in water samples [67], nowadays its use is limited to routine analysis and standardized protocols. Because of its tedious experimental procedure, the high analysis time, reagent consumption (normally 150–200 mL of dichloromethane) and volume of sample needed (500–1000 mL), LLE has been replaced by other liquid-liquid microextraction techniques (LLME) which minimize these disadvantages. LLME techniques are based on the same principle as LLE, but using less than 200 μL of extraction solvents [68–70]. Different strategies can be selected to improve the efficiency of the extraction like modification of pH and/or salinity. Thus, salts (i.e. tetramethylammonium hydroxide [68]) or solvents were usually added to water sample (donor phase) to facilitate the diffusion of analytes to the acceptor phase (i.e. chloroform or acetonitrile).

Taking into account the mechanisms used to expose the extraction solvent to water samples, different LLME techniques can be distinguished [71]. One of them is single drop microextraction (SDME) which consisting of a drop of extractant solvent exposed to the aqueous phase from a microsyringe needle [72]. For the extraction of APs and BPA, low volumes (<4 μL) of long alkyl chain alcohols (i.e. octanol [73] and decanol [74]) were selected as extraction solvent, because of their water immiscibility. Although satisfactory recoveries were obtained, difficulties in the formation of the drop can affect the precision of the analytical method and consequently, other alternatives were proposed to minimize SDME disadvantages.

Consequently, dispersive liquid-liquid microextraction (DLLME) was also proposed for APs and BPA determination [74–84]. In fact, this technique is the most used LLME technique for this purpose due to its low cost, simplicity, short extraction time and higher enrichment factors. DLLME is based on the extraction of analytes in aqueous samples by an appropriated mixture of extraction solvent and dispersant agent producing a cloudy solution [75]. Whereas

Table 3
Methodologies based on liquid-liquid (micro)extraction techniques for 4-APs and BPA analysis in water samples (from 2002 to the present, Web of Science™).

LLE technique	Extraction characteristics	Compounds of interest	Type of waters	Sample volume (mL)	Instrumental technique	Analytical quality parameters		Ref
						Relative recovery%	MDL/MQL (μg L^{-1})	
LLE	3 × 50 mL DCM	4-tOP, NP, BPA (other EDCs)	Bottled water	1000	GC-MS, derivatization: BSTFA	77–92	0.02 (MDL)	[67]
LLME	Tetramethylammonium hydroxide (donor). Chlorotoluene (acceptor). Agitation: 50 min	4-tOP, 4-*n*-NP, BPA	Tap water, lagoon water	14	HPLC-FLD, ACN:water (0.05 M ammonium phosphate)	92–105	<0.017 (MDL)	[68]
LLME	Ionic par (3 mM TBAB) + 0.002 mL chloroform:octanol (50:50 v/v)	4-OP, BPA (other EDCs)	Surface water	3	GC-MS, No derivatization	NM	0.2–1.3 (MQL)	[69]
IL-LLME	Formation of ionic liquid and extraction con 200 μL ACN	4-tOP, 4-OP, NP, BPA (other EDCs)	Seawater	2	HPLC-DAD, ACN:water	94–100	4.6–9.8 (MQL)	[70]
SDME	Extraction with 4 μL of octanol:octane (90:10) during 40 min	4-OP, 4-NP, BPA (other EDCs)	Surface water	10	HPLC-DAD, ACN:water	92–111	0.33 (MDL)	[73]
SDME	2.5 μL decanol (extractant). Agitation during 60 min 100 rpm	4-tOP,4-OP, 4-*n*-NP, BPA	Seawater	5	HPLC-UV, ACN:water	91–114	4-9 (MDL)	[74]
DLLME	150 μL ACN (dispersant) + decanol (extractant). Centrifugation (5 min, 3600 rpm)	4-tOP,4-OP, 4-*n*-NP, BPA	Seawater	5	HPLC-UV, ACN:water	96–121	0.7–1.6 (MDL)	[74]
DLLME	2 mL acetone (dispersant) + 142 μL chloroform (extractant). Centrifugation (5 min, 6000 rpm)	BPA	Surface water, tap water	10	HPLC-UV, ACN:water (55:44)	93–98	0.07 (MQL)	[75]
DLLME	0.5 mL MeOH:pyridine (dispersant) + 50 μL chloroform (extractant). Centrifugation	4-tOP, NP	Surface water	5	GC-MS, no derivatization	88–106	0.007–0.08 (MDL)	[76]
DLLME	Extraction with 100 μL octanol during 5 min at 1200 rpm + Centrifugation	4-tOP, 4-OP, 4-*n*-NP, NP, BPA	Seawater	30	LC-MS/MS, MeOH:water (0.05% ammonia)	80–104	0.005–0.03 (MQL)	[77]
DLLME	1.5 mL acetone (dispersant) + 50 μL trichloroethylene (extractant). Centrifugation (10 min, 5000 rpm)	OP, NP (APEOs)	Surface water, tap water	5	HPLC-FLD, MeOH:ACN:water (50:15:35)	75–77	0.10–0.33 (MQL)	[78]
DLLME	10 μL hexadecanethiol. Agitation during 90 s. Centrifugation (2 min, 5000 rpm)	4-tOP, 4-*n*-NP	Surface water	5	HPLC-DAD, ACN:water	82–108	0.8–1.5 (MDL)	[79]
DLLME	25 μL heptanoic acid (dispersant) + ammonium hydroxide (extractant). Agitation + Centrifugation	4-tOP, NP	Wastewater	5	HPLC-UV, MeOH:water (phosphate buffer)	92–107	0.5–0.7 (MDL)	[80]
IL-DLLME	Extraction with ionic liquid at Temp. 80 °C + Centrifugation	4-tOP, NP, BPA	Surface water, Wastewater, snow	10	HPLC-FLD, MeOH:water (75:25)	86–116	0.23–0.48 (MDL)	[81]
US-DLLME	200 μL acetone (dispersant) + 100 μL DCM (extractant). Agitation + Centrifugation (3min, 6000)	4-tOP, 4-NP, BPA (other EDCs)	Wastewater	5	GC-MS/MS, derivatization BSTFA	82–97	<0.05 (MQL)	[82]
VALLME	50 μL octanol. Agitation 2 min + Centrifugation (2 min, 3500 rpm)	OP, NP, BPA	Surface water, Wastewater, tap water	20	HPLC-FLD, ACN:water (80:20)	66–110	0.01–0.07 (MDL)	[83]
DLLME-SFO	80 μL 1-undecnol (dispersant) + 500 μL MeOH (extractant). Agitation + Centrifugation + Cooling	BPA (other EDCs)	Surface water, tap water	10	LC-MS/MS, MeOH:water (5 mM ammonium acetate)	>80	<1.44 (MDL)	[84]
MMLE	Microporous membrane PTFE system. Extraction with hexane	4-tOP, 4-*n*-NP (APEOs)	Surface water, Wastewater, tap water	0.96	HPLC-FLD, ACN:water (70:30 v/v)	74–110	0.05–0.1 (MDL)	[85]
MASE	Membrane HDPP. Extraction 500 μL hexane. Agitation during 60 min at 750 rpm.	4-tOP, 4-OP, 4-*n*-NP, NP, BPA	Surface water, seawater, tap water	15	LC-MS/MS, MeOH:water (0.05% ammonia)	81–108	0.0005–0.032 (MQL)	[86]
MASE	Membrane LDPE. Extraction 800 μL chloroform. Agitation during 60 min at 600 rpm. Clean-up: Florisil®	4-tOP, 4-OP, NP, BPA (other EDCs)	Wastewater	130	LC-MS/MS, MeOH:water (0.05% ammonium hydroxide)	74–137	<0.030 (MDL)	[19]
MASE	Extraction with 400 μL ethylacetate	4-tOP, 4-OP, NP	Surface water, Wastewater	130	GC-MS, derivatization BSTFA	83–124	<0.0296 (MDL)	[87]
MASE	LDPE membrane. Extraction with 80 μL chloroform. Agitation during 60 min at 600 rpm	4-tOP, 4-OP, NP, BPA (other EDCs)	Surface water, Wastewater, seawater	15	GC-MS, derivatization BSTFA	42–124	<0.050 (MDL)	[88]
HF-LLME	Fiber PP with dihexylether (acceptor)	4-*n*-OP, 4-*n*-NP		50	HPLC-FLD, MeOH:water (5% formic acid)	60–90	1.76–1.83 (MDL)	[90]

Table 3 (*continued*)

LLE technique	Extraction characteristics	Compounds of interest	Type of waters	Sample volume (mL)	Instrumental technique	Analytical quality parameters		Ref
						Relative recovery%	MDL/MQL (μg L^{-1})	
			Surface water, Wastewater, tap water					
HF-LLME	Fiber PP with dodecane (acceptor).	4-OP, 4-*n*-NP	Surface water, tap water	50	HPLC-FLD, MeOH:water (75:30)	97–100	0.1–0.2 (MDL)	[91]
HF-LLME	Fiber PP with octanol (acceptor)	4-tOP, NP, BPA	Surface water, wastewater, drinking water	100	UPLC-MS/MS, MeOH:water (0.01% ammonia)	89–113	0.01–0.06 (MQL)	[92]

Abbreviations: ACN, acetonitrile; BSTFA, N, O-bis(trimethylilyl)trifluoroacetamide; BPA, bisphenol A; DAD, diode array detector; DCM, dichloromethane; DLLME, dispersive liquid liquid microextraction; EDCs, endocrine disrupting compounds; FLD, fluorescence detector; GC, gas chromatography; HDPP, high density polypropylene, HF-LLME, hollow fiber liquid-liquid microextraction; HPLC, high performance liquid extraction; IL, ionic liquid; LC, liquid chromatography; LDPE, low density polyethylene; LLE, liquid-liquid extraction; LLME, liquid liquid microextraction; MASE, membrane assisted solvent extraction; MDL, method detection limit; MeOH, methanol; MQL, method quantitation limit; MMLE, microporous membrane liquid extraction; MS(/MS), (tandem) mass spectrometry; NM, not mentioned; NP, nonylphenol technical mixture; 4-NP, 4-*n*-NP, nonylphenol (linear isomer); OP, octylphenol; 4-tOP, 4-tert-octylphenol; 4-OP, 4-*n*-OP, 4-octylphenol (linear isomer); PP, polypropylene; SDME, single drop microextraction; SOF, solidification of floating drop; TBAB, tetrabutylammonium bromide; UPLC, ultra performance liquid chromatography; US, ultrasonic; UV, ultraviolet visible; VALLME, vortex assisted liquid liquid microextraction.

dispersant agent should be miscible with aqueous phase (i.e. acetone [75], ACN [74], MeOH [78]), extraction solvent must not be miscible with them (i.e. chloroform [76], decanol [74]). The main problem is the correct selection of the mixture of solvents because losses of analytes can take place and therefore, some authors suggest the replacement of the dispersant agent by an agitation step like ultrasonic [82] and vortex [77,83] to carry out the formation of the cloudy solution. Other alternative to avoid the third solvent is the use of ionic liquids (ILs) as extraction solvent (i.e. 1-octyl-3-methylimidazolium hexafluorophosphate), achieving the formation of the cloudy solution with controlled changes of temperature [81]. More recent option is DLLME based on solidification of floating drop (SFO), in which low temperatures were used to freeze the drop and facilitate the separation of the extraction solvent prior to the analysis [84]. Membrane extraction techniques were also suggested for APs and BPA determination [85–89]. The first proposed was microporous membrane liquid extraction (MMLE), based on an aqueous-organic extraction system with a hydrophobic PTFE microporous membrane. In this way, the organic solvent (i.e. hexane) fills the pores of the membrane and contacts with aqueous sample and extracts the target analytes [85]. Other technique based on the same principle is called membrane assisted solvent extraction (MASE) [86–89]. Hydrophobic porous or non-porous polymeric membranes are the most common devices used in MASE [89]. Although porous membranes can be employed as a filter, non-porous membranes are not only considered as a barrier for particles, macromolecules and polar species; they can also provide selectivity and specificity in terms of permeation and transport through the membrane [86]. Although there is one MASE device commercially available, which consists of a 20 mL glass vial with membranes of HDPP, made in-house membranes with other polymeric materials (i.e. LDPE) were also proposed by some authors in order to achieve lower method detection limits increasing the sample volume [19]. Regarding extraction solvent, low volumes (<1 mL) of hexane [86], chloroform [19] and ethylacetate [87] were employed.

One more recent technique selected for APs and BPA extraction is hollow fiber liquid liquid microextraction (HF-LLME) [90–92], based on the diffusion of compounds from the sample (donor phase) to an organic solvent (acceptor phase), which is contained inside the hollow fibre normally made of PP [93]. After HF-LLME, the liquid extract is injected in a LC. The enhancement of extraction efficiency because of the extended contact area between solvent and sample and easy handling are the main advantages of this technique [92]. Most common extraction solvent are dihexylether [90], dodecane [91] and octanol [92] and consequently, more applications of this technique in which non-toxic solvents were used are expected.

2.3. Comparison between extraction techniques

As it was commented before, a high number of extraction techniques can be employed for the determination of APs and BPA and therefore, researches should select the most suitable option for their applications considering different criteria such as simplicity, versatility, fastness and analysis cost. Taking into account its versatility, robustness and relative low cost, SPE is a good option to carry out multiresidue analysis when the analysis time is not a limitation factor [25–47]. Thus, this technique (and in a lesser extent LLE) is still used in standardized protocols [15,16], instead of some disadvantages (i.e. higher analysis time or high reagent consumption). However, when a high number of samples have to be analyzed, a less tedious extraction technique reducing the analysis time and waste generation can be a right alternative. Although some of them can be followed by both GC-MS and LC-MS determination, low detection limits are usually obtained when SLE techniques are coupled to GC-MS, as it was shown for SPME [56], SBSE [60–64] and MEPS [22,36]; however, the moderate cost of the equipments can be an important disadvantages for modest laboratories. Meanwhile, if a LC-MS is used for the determination of compounds, LLME techniques present more advantages than SLE techniques. Between all of them, DLLME [74–82] and recently HF-LLME [90–92] seems to be the favourite options because of its simplicity, fastness and versatility. In any case, the application of these extraction techniques to the determination of APs and BPA is still low in some cases and therefore, more studies are needed to find an ideal technique, especially in context of new sorbents and techniques modifications (i.e. DLLME-SFO [84]).

3. Analytical determination

3.1. Gas chromatography

To determine the low concentrations of APs and BPA in waters, a sensitive and selective instrumental technique is mandatory, being gas chromatography coupled to mass spectrometry (GC-MS) the most employed [3,10,18,22,23,34–36,41–44,48,49,56,58,61–67,69,76,82,87,88].

Besides its higher sensitivity, GC can be easily coupled with microextraction techniques such as SPME [56,58] and SBSE (when a thermal desorption equipment is available) [58–65], reducing blank contamination problems, sample handling and the analysis time and allowing the injection of whole extract and the achievement of lower method quantitation limits. The main disadvantage of GC-MS is the derivatization step needed when moderate polar or non-polar compounds are analyzed, especially in the case of BPA. Although some authors avoid this step [36,44], the vast majority employed it to obtain symmetric chromatographic peaks and good precision and to improve the separation and detection of these EDCs [3,41,94]. Silylation is the more common derivatization route, using N, O-bis(trimethylilyl)trifluoroacetamide (BSTFA) [3,47] and *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) as derivatizing agents [41]. Regarding the separation column, diphenyldimethyl (5–95%) polysiloxane capillary columns [3,60] are the most employed. However, a remarkable problem is related to the determination of NP using this stationary phase. Because more than 211 isomers are present in branched NP, a group of peaks is obtained when this mixture is analyzed by GC-MS; all these peaks should be considered in the quantitation of this pollutant which difficult the interpretation and can cause great errors and lower precision in the obtained result. Nowadays, investigations are directed to the individual quantitation of these branched isomers because some of them seem to be more estrogenic than others [95]. To achieve this aim, two dimensional gas chromatography followed by mass spectrometry was applied and, although the tentative identification of more than 100 isomers was achieved, the cost associated to this equipment have limited the use of this technique [96]. Recently, a cheaper option based on chiral cyclodextrin GC capillary columns were employed and the enantioselective separation of eight target isomers were identified [97]. In any case, further research is needed to separate and reliably identify all NP branched isomers.

3.2. Liquid-chromatography

The analysis of APs and BPA was also carried out by high performance liquid chromatography coupled to a fluorescence detector (HPLC-FLD) [5,55,57,83,85,90,91] or an ultraviolet–visible detector (HPLC-UV/Vis) [50,75,80]. However, the complexity of some waters (i.e. wastewater or seawater) can hinder the identification and quantitation of target compounds due to the fact that inadequate chromatograms with overlapping and tailing peaks can be obtained. In these cases, an exhaustive extraction and/or clean-up technique are required, increasing the analysis time and the consumption of toxic reagents. Limitations of these detectors and GC-MS can be avoided using liquid chromatography (tandem) mass spectrometry (LC-MS/MS) [17,19,21,24–30,37–40,45–47,51–53,84,92]: on the one hand, low detection limits are achieved without derivatization step and on the other hand, only one peak is detected when NP is analyzed by LC-MS/MS (and LC separation is carried out by reversed-phase) because of the separation of compounds according to the character of the hydrophobic moiety. Consequently, oligomers containing the same hydrophobic moiety elute in one peak, increasing the peak intensity and therefore, the sensitivity of the determination [98]. Besides its sensitivity and selectivity, the emergence of new ionization techniques which allow the soft ionization of a wide range of substances, have encouraged the use of LC-MS/MS in the last years and up to date, more than 70% of published works for APs and BPA analysis are based on this determination technique. The most employed ionization technique is electrospray (ESI), followed by atmospheric pressure chemical ionization (APCI) and atmospheric pressure photoionization (APPI). The main advantage of ESI source is that allows the ionization of a wide range of compounds (including polar compounds); however, the matrix effects associated to ESI are higher than the observed with the other types of ionization techniques [39]. When LC-MS/MS is selected as determination strategy, multiple reaction monitoring (MRM) or selected reaction monitoring (SRM) are usually employed as acquisition modes, improving selectivity and sensitivity. Other way to improve the sensitivity of the determination and also the chromatographic separation is the addition of some modifiers to the mobile phases; for APs and BPA determination, acid acetic [40,45], ammonium salts [19,21,47] and ammonia [32,77,86] were usually used as LC modifiers. Recently, some authors demonstrated a basic pH (pH > 8) highly increased the signal obtained for APs and therefore, ammonia seems to be the best modifier for LC-MS determination [77,92]. Some authors employed also derivatizing agents (i.e. dansyl chloride or pentafluorobenzyl bromide PFFBr [99]) to increase the signal intensity; however, temperature and pH should be critically controlled to guarantee the success of this step [100].

Moreover, advances in equipment and accessories were performed and improved in the last years and therefore, alternative separation and determination techniques are currently used in APs and BPA determination. For example, ultra-high performance liquid chromatography mass spectrometry (UPLC-MS) has been employed to increase the elution speed with superior resolution and sensitivity using columns packed with smaller particles and/or applying higher flow rates [32,99]. Although its advantages, few methods based on this determination technique can be found in the literature for APs and BPA analysis. Other important research line is focused on qualitative and quantitative analysis of target and non-target compounds; nevertheless, screening methodologies based on gas or liquid chromatography high resolution mass spectrometry (GC-HRMS; LC-HRMS) are also scarcely employed for APs and BPA determination [101]. Consequently, these novel techniques deserve further exploration for the analysis of target compounds.

4. Quality assurance/quality control (QA/QC)

A quality assurance/quality control (QA/QC) protocol must be established in order to guarantee reliable and precise results. Although some authors make reference to different European reports (i.e. Decision Commission 2002/657/EC for veterinary drugs residues) in order to justify the performance of analytical methods and the interpretation of results [102], QA/QC procedures were scarcely detailed in the vast majority of the reviewed works.

Different guidelines can be followed for the identification and confirmation of target compounds depending on the instrumental technique employed. Thus, for GC or LC coupled to MS, which are the most common techniques employed for APs and BPA determination, the retention time (t_R) and the number of identification points must be taken into account for their identification. Moreover, the ratio between mass transitions is the most studied parameter for confirmation purposes [102]. Regarding the quantitation of target EDCs, internal standards [33,61], surrogate internal standards (SIS) [77,86,92] and matrix calibration [50,60] were selected according to matrix effects, especially in LC-MS(/MS) determination. Consequently, when matrix effects are low, SIS allows a reliable quantitation of APs and BPA; however, in the analysis of complex waters such as wastewater or seawater, matrix calibration can be needed for quantitation. In any case, the selection of an adequate strategy for quantitation of compounds is mandatory and can avoid a subsequent clean-up step. One notorious aspect related with APs and BPA analysis is blank contamination. Because of their ubiquity, these pollutants are also present in research laboratories. Substantial peaks observed even without sample are usually encountered during 4-tOP, NP and BPA

determination, which can cause errors in quantitation when low concentrations are analyzed. For example, problems in quantitation of NP at levels lower than 0.1 μg L^{-1} were reported in a laboratory intercomparison study focused on the analysis of OP and NP in surface water [103]. The main sources of APs and BPA seemed to be detergents and plastics and therefore, this material should be avoided along all steps of the experimental procedure in order to maintain blank contamination below a critical value. However, other sources were identified depending on the selected extraction and determination techniques. Whereas some authors support the employment of glass columns in SPE [104], others selected plastic commercial cartridges and kept the blanks under control [27]. Sources of 4-tOP, NP and BPA in LC-MS/MS analysis were also investigated and while mobile phases (both organic phase and ultrapure water) mainly contributed to blank contamination, septum and LC plastic connections did not have influence in blanks [2].

Because of the absence of certified reference materials (CRMs) for APs and BPA in waters, spiked real samples are commonly used for optimization and validation studies of these types of matrices. Among all analytical quality parameters, recoveries (%) and method detection and quantitation limits (MDL/MQL) are mainly mentioned in the recompiled methods. In general, satisfactory recoveries (80−120%) were obtained with proposed methodologies, except some cases (R% < 40%) [45,105] that consider seawater and/or wastewater analysis, probably because of matrix effects. Problems related to matrix effects were demonstrated by applying the same technique (i.e. SPE, MASE [19]) to different types of water samples. Concerning MDL/MQL, MQL was mentioned in almost all cases at values ranged between 0.001 μg L^{-1} [26] and 1.83 μg L^{-1} [90]. In the vast majority of the works, the criteria followed for MQL estimations were mentioned; however, few works proved experimentally the calculated MQL values [77]. Estimations based on three times the ratio S/N [61,81], three times the standard deviation (SD) of a spiked water (low concentration) [60] and the average ± three times the standard deviation (SD) of blank water samples (no concentrations of target compounds expected) [77] seemed to be the most employed criterion. Nevertheless, and taking into account the MQL depends on the analytical methodology, the analyzed matrix and the calculation used for its estimation, a common criterion in MQL estimations seems to be mandatory in order to establish a harmonized comparison between analytical methodologies. In any case, more than 50% of total recompiled methods do not achieve the environmental quality standards (EQS) established by European water legislation (Directive 2013/39/EU) for APs analysis. In addition, if the technical specifications for chemical analysis set by Directive 2009/90/EC are considered (MQL should be lower than 30% of EQS [106]), only 30% of reviewed methodologies could be incorporated in monitoring programs for water analysis.

5. Application to water analysis

The 75 reviewed methodologies were applied to the analysis of APs and BPA in different types of water samples. The applicability and practicability of almost 50% of methods were proved for only one type of water [3,63,87] whereas the 30% and 20% of methods were employed to the analysis of two [88,89] or more than two kind of waters [56,90], respectively. Wastewater was the most analyzed one (31%) due to the fact that wastewater treatment plants are one of the main sources of contamination of these compounds in the aquatic environment. Similar percentage was attributed to surface water (30%) followed by tap water (18%) and seawater (14%). The lower percentage of seawater samples can be attributed to the complexity of the matrix as well as the low concentrations usually found in marine ecosystem. In the last years, and considering the possible migration of these plasticizers from bottled waters to the aqueous phase and the resulting damage to human health, different analytical methods focused on this purpose have been published (4%)). Taking into account the aforementioned percentages, more research based on analytical methods for seawater and bottled drinking water analysis are needed to obtain more information about the behaviour of these EDCs and in this way, preserve marine ecosystem and guarantee public safety. Finally, other type of waters such as lagoon water, snow and swimming-pool water were scarcely considered (3%); however, the concentrations of NP found in almost of them suggested these kind of waters would be the basis of new research fields.

6. Conclusions

Water is the environmental compartment mainly affected by APs and BPA pollution and consequently, investigations focused on the distribution and behaviour of these EDCs in the aquatic system are required to preserve the environment and protect human health. In this context, analytical methods which allow the determination of these compounds at low concentrations have been developed in the last years, according to trends in analytical techniques as well as the marked goal in each application.

Solid phase extraction is the main solid-liquid extraction technique used for APs and BPA analysis. However, and in order to reduce the volume of sample needed and the amount of reagents consumed, the use of microextraction techniques has been highly increased, especially in the last five years. Among all of them, DLLME is up to date the most employed technique. IL-based extraction and other miniaturized strategies such as MEPS are included in new trends for APs and BPA analysis.

Regarding the instrumental determination, LC-MS/MS was chosen in the vast majority of the analytical methods, because of its sensitivity and selectivity as well as the avoidance of the derivatization step. New tendencies are directed to increase signal intensity and reduce analysis time (i.e UPLC) and to achieve an individual quantitation of NP isomers using an adequate chromatographic column followed by GC-MS (i.e. cyclodextrin capillary columns).

One hinder gap in water analysis is related to the establishment of a QA/QC protocol. Because of its significance, more details of analytical parameters should be included in new research to guarantee reliable, precise and comparable results. Special attention should be paid to the blank contamination problems and matrix effects. Furthermore, more sensitive methods are needed to be included in monitoring programs to reach the low EQS established for APs (<2 μg L^{-1}) in European water legislation (Directive 2013/39/EU). On the other hand, and taking into account the number and types of water analyzed, analytical methods which can be applied to different types of waters as well as to seawater are needed to understand these complex aquatic ecosystems.

Finally, further research is needed to develop an effective multiresidue methodology for the determination of APs (including individual isomers) and BPA in water samples with a view to promote environmental and eco toxicological investigations.

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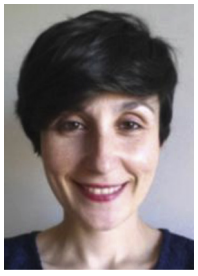

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