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REVIEW

Recent advances in analysis of bisphenols and their derivatives in biological matrices

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Abstract

Biomonitoring is a very useful tool to evaluate human exposure to endocrine-disrupting compounds (EDCs), like bisphenols (BPs), which are widely used in the manufacture of plastics. The development of reliable analytical methods is key in the field of public health surveillance to obtain biomonitoring data to determine what BPs are reaching people's bodies. This review discusses recent methods for the quantitative measurement of bisphenols and their derivatives in biological samples like urine, blood, breast milk, saliva, and hair, among others. We also discuss the different procedures commonly used for sample treatment, which includes extraction and clean-up, and instrumental techniques currently used to determine these compounds. Sample preparation techniques continue to play an important role in the analysis of complex matrices, for liquid matrices the most commonly employed is solid-phase extraction, although microextraction techniques are gaining importance in this field, and for solid samples ultrasound-assisted extraction. The main instrumental techniques used are liquid and gas chromatography coupled with mass spectrometry. Finally, we present data on the main parameters obtained in the validation of the revised methods. This review focuses on various methods developed and applied for trace analysis of bisphenols, their conjugates, halogenated derivatives, and diglycidyl ethers in biological samples to enable the required selectivity and sensitivity. For this purpose, a review is carried out of the most recent relevant publications from 2016 up to present.

Keywords Bisphenols · Halogenated derivatives · Biological samples · Sample preparation techniques · Chromatography · Mass spectrometry

Introduction

Bisphenols (BPs) are a large family of chemicals commonly used in the manufacture of numerous consumer products. They are important industrial chemicals used as plasticizers in epoxy resins, polyvinyl, and polycarbonate plastics. The most widely used is bisphenol A (BPA) and it has attracted relevant attention by the scientific community for its toxicity. Several studies demonstrated estrogen-like property of BPA, correlating the BPA exposure with diabetes, heart diseases, obesity, breast and prostate cancer, lowered sperm quality, neurotoxicity problem, and polycystic ovarian syndrome [1, 2]. The exposure to BPA of different age groups humans, including infants, is through consumption of canned foods, reusable food and drink containers, bottled water, and other minor exposure sources (e.g., environment, dental sealants, thermal paper receipts) [3].

Due to the numerous routes of exposure to BPA through consumer products and industrial applications, concerns about the human health risks are increasing, and its extended use has led to industry replacing it with structurally similar chemicals [4]. In recent years, over 20 presumably less toxic, more sustainable, and more environmentally friendly bisphenol analogues including bisphenol C (BPC), bisphenol S (BPS), bisphenol F (BPF), bisphenol AF (BPAF), etc., have been produced to partially replace the known toxic BPA [5]. Unfortunately, their toxicity is similar to BPA [6], and some of them are more potent than BPA itself in activating the estrogen receptor [7].

In response to the widespread use of BPA and bisphenol-based alternatives, a significant amount of work has been conducted to determine bisphenols in biological samples (e.g.,

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urine, blood, saliva, and breast milk), also known as human biomonitoring, and develop reliable analytical methods to detect and quantify these chemicals.

Most of the analytical methods to determine BPs and their halogenated and diglycidyl ether derivatives in biological matrices involve sample treatment, separation, and detection. Sample treatment, which includes extraction and clean-up, is still a critical step, and its main objectives are extracting the target analytes and removing potential matrix interferences to obtain extracts suitable for quantitative analysis. Biological matrices are rich in undesired components that may be co-extracted with the analytes and affect their response. In addition, most BPs are commonly present in biological samples at low concentration levels (trace levels). To overcome these problems, the use of sample preparation techniques is usually required, which makes these studies more challenging. Separation and detection are performed mostly by liquid chromatography (LC) or gas chromatography (GC), usually coupled to mass spectrometry (MS) or tandem mass spectrometry (MS/MS), due to the selectivity, specificity, and sensitivity achieved.

This paper aims to review the recent methods to determine BPs, their conjugates, halogenated derivatives, and diglycidyl ethers in biological samples published from 2016 up to the present. Detailed information on studies carried out before 2016 can be found in other reviews [3, 4].

Compounds

Table S1 (see the Electronic Supplementary Material, ESM) shows the structures and physicochemical properties of the BPs and their halogenated and diglycidyl ether derivatives covered by this review. Chlorinated derivatives mainly result from the reaction of bisphenols with sodium hypochlorite, used as a bleaching agent in paper factories and water disinfection, and bisphenol diglycidyl ethers are the primary chemical building blocks for epoxy resins, epoxy-based lacquers, or vinylic organosol (PVC) resins [4].

Bisphenols and derivatives constitute a group of chemicals with quite different physicochemical properties, a feature common to all of them is the presence of aromatic moieties, most of them are in the neutral form in biological samples [4] and are hydrophobic (log K_{ow} around 3–8) which indicates their potential for bioaccumulation. Most of them are stable in solution [8], except for diglycidyl ethers which have a high reactivity triggered by external factors making them difficult to analyze, so appropriate storage conditions, solvents for sample preparation, and storage time between analyses should be selected carefully. It has been reported that their stability decreases with increasing solution water content, and the use of low storage temperatures (e.g., 4 and − 20 °C) is recommended; also it is advisable to prepare the standard solutions just before commencing any further instrumental or biological studies [9].

Standards

Most bisphenols, their halogenated and diglycidyl ether derivatives have become available as commercial compounds. Conjugated BPs including glucuronides and sulfates are more difficult to find and they are available for BPA and BPS. In some cases, these standards were synthesized. Ho et al. reported the chemical synthesis and characterization of the conjugates BPA-monoglucuronide, BPA-monosulfate, BPA-diglucuronide, and BPA-disulfate [10].

Internal standards

Currently, several internal standards (IS) for quantifying bisphenols are available. The most commonly used are deuterated BPA (BPA-d_4, BPA-d_8, BPA-d_{14}, BPA-d_{16}), deuterated BPA analogues (BPS-d_8, BPF-d_{10}, BPAF-d_4, DCBPA-d_{12}), and a variety of ^{13}C isotopically labeled bisphenols (BPA-$^{13}C_4$, BPS-$^{13}C_4$, BPF-$^{13}C_4$, BPAF-$^{13}C_4$, BPB-$^{13}C_4$, BPA-$^{13}C_{12}$, BPB-$^{13}C_{12}$, BPF-$^{13}C_{12}$, BPS-$^{13}C_{12}$, TCBPA-$^{13}C_{12}$, TBBPA-$^{13}C_{12}$), but these last are used less frequently. Since isotopically labeled bisphenols are not always available, they can be synthesized as was proposed by Sosvorova et al. for BPS-d_4 [11]. Additionally, other compounds have been used as IS for quantification like phenobarbital-d_5 in LC-MS and triphenyl phosphate in GC-MS. Isotopically labeled compounds should be used as internal standards to compensate for the matrix effect due to the complexity of the biological samples, and the quantification of bisphenols by external standard calibration is not recommended when LC and GC coupled with MS are employed [12], but it was applied with LC-UV [13–15] and LC-FLD [16, 17].

Regarding conjugated bisphenols (glucuronide and sulfate), only the glucuronides BPA-G-$^{13}C_{12}$ and BPS-G-d_8 have been used. Consequently, development and further marketing of a wider range of isotopically labeled conjugates for use as surrogate and internal standards is an important need for the assessment of human exposure to BPA analogues [3, 18].

Background contamination

Due to the extended use of BPs, background contamination is a common problem in the determination of these compounds at low concentrations that arises from the widespread use of polycarbonate plastics and epoxy resins in laboratory materials and equipment. There is concern that determinations of BPs could be biased due to external contamination of the samples during sample collection and/or analyses [4]. Indeed, contrary to most other analytes, these compounds might be contained in virtually several products used in daily life. To prevent this problem, basic precautions should be taken:

all glassware used must be previously washed and sequentially rinsed (several times) with different organic solvents, high purity solvents should be used, and a set of operational blanks should be processed to monitor for contamination from the laboratory environment and/or any other sources [19–21]. Pednekar et al. recommend that all the glassware must be heated at 120 °C for 3 h in addition to being rinsed with methanol and wrapped in aluminum foil until analysis [22]. A meticulous protocol was proposed by Caballero-Casero et al., in which sample preparation was performed in a room designated exclusively for bisphenol working; laboratory benches were cleaned with methanol every day and covered with aluminum foil, over which clean materials were left; the personnel always wore nitrile gloves; glassware and other materials were washed with soap, and sequentially rinsed (twice each step) with tap water, ultra-pure water (filtrated with SPE styrene-divinylbenzene disks), and methanol; and if procedural blanks gave signals higher than noise, labware was re-subjected to the cleaning protocol and retested again [23].

Finally, as a precautionary measure, Ballesteros-Gómez et al. used a LC system in which an additional column is inserted between the pump and injector to trap BPA that could be released from the equipment [20].

Analytical methods

BP concentrations in biological matrices are mostly in the ng/mL and ng/g ranges, depending on the type of sample which means that sensitive analytical methods are required. Extraction techniques are needed to clean the biological sample and to extract and preconcentrate the analytes followed by their best chromatographic separation and detection; they are used as a countermeasure to matrix effects by removing the interferences. Currently, the most commonly used technique for extracting BPs from liquid samples is solid-phase extraction (SPE) and for solid samples is ultrasound-assisted extraction (UAE). After the extraction, the analytes are often derivatized to improve sensitivity. Subsequently, the methods are validated to confirm that the analytical procedure employed is suitable for its intended use. The main validation parameters evaluated are linearity, accuracy, precision, LOD, and LOQ, and the results obtained can be used to demonstrate the quality, reliability, and competence of the analytical method. All these analytical steps will be presented and discussed in the following sections.

Sample preparation and clean-up for liquid samples

The majority of the studies for biomonitoring have a preference for liquid samples, mainly by urine (54%) followed by blood (serum 17%, plasma 7%, whole 2%), breast milk (11%), and saliva (4%), among others (Fig. 1). Blood is commonly considered an ideal sample because it is in contact with all body tissues, but it has the disadvantage of being an invasive matrix. Human breast milk is an important matrix due to compounds being transferred to breast milk from plasma. In addition, it is easily collected, and its monitoring is essential because breast milk is the first food for newborns. Saliva represents another biological matrix easily collectible through a non-invasive procedure, but it has the disadvantage that it is a very dilute fluid [24]. Urine is the preferred sample because the sampling is non-invasive, and the collection of urine samples is easy. BPs are excreted in urine as glucuronide and sulfate conjugates [3] and deconjugation is usually done by enzymatic digestion with β-glucuronidase to achieve accurate measurements of the total (free and conjugated) BPs in urine. In some cases, the pretreatment is a simple dilution of the urine with acetonitrile for protein precipitation [19, 25], and this dilution reduces variability between sample matrix that could affect analyte recovery.

Common sample preparation techniques are employed because there are many interfering compounds co-extracted with the analytes that can reduce the precision and accuracy of the method. Tables 1, 2, and 3 show a summary of the techniques applied to liquid samples in relevant analytical methods proposed in the current literature for urine, blood, and other matrices, respectively. Extraction techniques range from classic liquid–liquid extraction (LLE) to recent developments in the field of miniaturized methods (e.g., dispersive liquid–liquid microextraction (DLLME), hollow fiber liquid-phase microextraction (HF-LPME), and salting-outliquid–liquid microextraction (SALLME), among others). Sometimes an additional clean-up step is needed to get a cleaner extract; for this purpose, SPE is the technique of choice.

Figure 1 shows that from 2016 to 2021, SPE (43%), LLE (15%), *d*-SPE (14%), and microextraction techniques (17%) are the most used techniques for BP analysis. A percentage breakdown of the solvent-based microextraction techniques used for the determination of BPs in biological samples is shown in Fig. 1. DLLME (33%) is clearly the predominant microextraction technique of choice using conventional organic solvents as extraction phase, as its rapidness is one of the main advantages over the other approaches. These sample preparation techniques and their applications will be discussed in the next sections.

Liquid–liquid extraction

Liquid–liquid extraction (LLE) is a relatively simple and effective extraction method that makes use of solvents to extract the analyte from the sample matrix. Though it is well-known that is time-consuming, requires large volumes of organic solvents, and is difficult to automate, this technique has broad

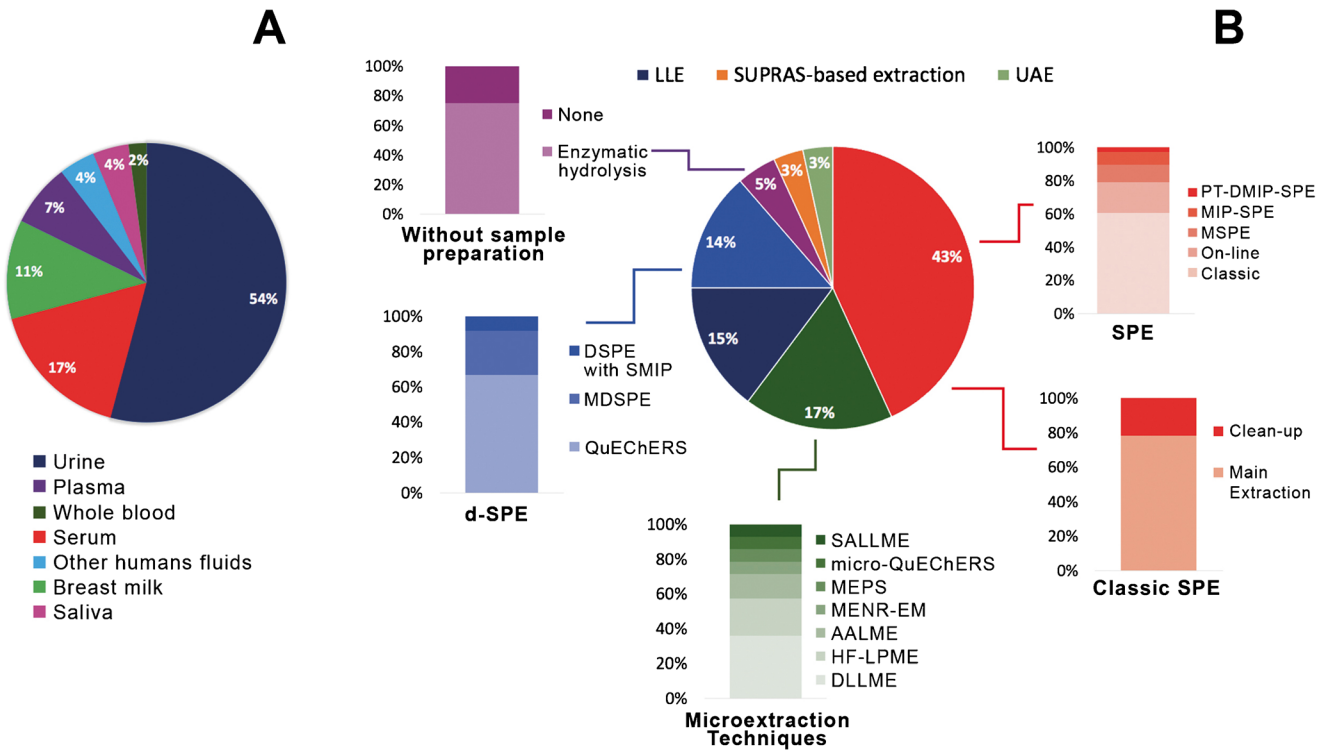

Fig. 1 (**A**) Liquid biological samples and (**B**) Sample preparation techniques used in the analytical methods for BPs biomonitoring

application for the extraction of BPs from urine, plasma, serum, and amniotic fluid. Ethyl acetate [10, 26, 40, 45, 65, 67, 71], methyl tert-butyl ether [11], methyl tert-butylether/ethyl acetate 5:1, v/v [44] and 1:1, v/v [92], methanol/acetonitrile (1:1, v/v) [72], and dichloromethane [38] have been employed as extraction solvents.

Wang et al. developed a method for the simultaneous extraction of 8 BPs and 26 other EDCs in human serum using an optimized extraction procedure. Samples were prepared using an extraction procedure consisting of LLE followed by SPE and promptly analyzed. Analysis by LC-MS/MS revealed recoveries ranging from 45.8 to 120% for BPs spiked at three different concentrations (0.5, 2.5, and 10 ng/mL). Furthermore, detection limits ranging from 0.003 to 0.016 ng/mL were achieved for the 8 BPs analyzed [72].

Louis and co-workers determined endocrine-disrupting chemicals (three BPs, five benzophenones, nine environmental phenols, and 15 phthalates) in seminal plasma using LLE and LC-MS/MS and obtaining LODs for BPs between 0.018 and 0.048 ng/mL [92].

Solid-phase extraction

Undoubtedly, solid-phase extraction (SPE) is by far the most usual sample preparation technique for liquid samples (i.e., urine, blood, saliva, and breast milk), with both off-line and on-line configurations, which can be used as extraction or clean-up before analysis of BPs. It is well suited to extracting many compounds with a wide range of polarities and physicochemical properties, as is the case with BPs, and it provides better selectivity and higher recoveries than conventional LLE. Some SPE parameters (e.g., sorbent, sample volume, pH, and elution solvent) have to be optimized to get the best analyte recovery and a clean extract.

Most applications to determine BPs are based on off-line SPE [18, 21, 22, 54, 56, 74, 76, 85], but for large-scale biomonitoring studies, high throughput with suitable sensitivity is necessary. For this purpose, on-line SPE techniques have been proposed [27, 28, 42, 47, 48, 57, 58]. This technique enables the quantitative transfer of the analytes in the analytical column and avoids loss of analytes, which is common for manual handling.

Although some conventional bonded silica sorbents are still in use (C8 [58], XBridge C18 [27], Betasil C18 [42], C18 [48], MAYI-ODS [57], amino silica S2907i-QuipNH2 [74]), these are being replaced by polymeric materials which enabled highly selective extraction for different compounds; among these, we have divinylbenzene (DVB) [22], hydrophilic-lipophilic balance polymeric material (e.g., Oasis HLB [21, 54, 76], Oasis MAX [18], Oasis WAX [56], Cleanert PWAX [85] or Strata X [28]), and polymeric anion exchanger HR-XAW [79]. Also, new sorbents are being developed like polycaprolactone nano-/microfiber composite with a polydopamine coating [47].

Simonelli et al. applied a method to determine urinary and peritoneal fluid concentration levels of BPA using SPE using

Table 1 Determination of bisphenol analogues in urine

Analytes	Sample preparation technique	Instrumental analysis	Accuracy (% recovery)	Precision(RSD)	LOD	LOQ	Reference
BPA	LLE and clean-up with SPE	GC-MS	86–103	4.5–6.7	2.0 ng/L	NR	[26]
BPA, CBPA, DCBPA, TCBPA, TTCBPA	On-line SPE	LC-MS/MS	54.7–75.7	2.9–16.4	NR	0.025–0.25 ng/mL	[27]
BPA-G	SPE	LC-MS/MS	90.1–103.3	6.9–11.7	1 ng/mL	5 ng/mL	[18]
BPA, BPS, BPAF, BPB, BPF	Enzymatic hydrolysis and on-line SPE	LC-MS/MS	101–108	17.6–14.2	0.005–0.39 ng/mL	NR	[28]
BPA, BPF	DLLME	GC-MS	94–109	7.1–9.7	0.011–0.041 ng/mL	NR	[29]
BPA	Enzymatic hydrolysis and SPE	LC-MS/MS	102.2–107.1	2.8–8.7	0.03 ng/mL	0.09 ng/mL	[30]
BPA, BPS, BPF, BPZ, BPP, BPAF, BPAP	DLLME	LC-MS/MS	90–112	1.9–14.8	0.005–0.2 ng/mL	0.02–0.5 ng/mL	[31]
BPA	Enzymatic hydrolysis, PT-DMIP-SPE	GC-MS	50.7	8.2–14.2	NR	50 ng/mL	[32]
BPA	Enzymatic hydrolysis and HF-LPME	GC-MS	NR	13.9–17.1	1.82 ng/mL	3.04 ng/mL	[33]
BPA	Enzymatic hydrolysis, and RAM-VOL-SUPRAS-based microextraction	LC-MS/MS	96–107	4.5	0.015 ng/mL	0.025 ng/mL	[34]
BPA, BPA-monoglucuronide, BPA-monosulfate, BPA- diglucuronide, BPA-disulfate	BPA: LLE, and clean-up with SPE BPA glucuronide and sulfate conjugates: SPE	BPA: GC-MS/MS BPA glucuronide and sulfate conjugates: LC-MS/MS	71.1–94.4	1.4–7.9	1.1–3.3 ng/g creatinine	5.6–17.0 ng/g creatinine	[10]
BPA	Enzymatic hydrolysis and SPE	GC-MS/MS	104.4	1.5–9.7	0.05 pg/μL	NR	[35]
BPA	Enzymatic hydrolysis and SPE	GC-MS with injection port butylation	95–101	2–9	0.03 ng/mL	0.1 ng/mL	[36]
BPA	Micro-QuEChERS	GC-MS	74–118	3–10	0.13 μg/L	0.43 μg/L	[37]
BPA, BPB, BPE, BPF, BPS, BPAF	Enzymatic hydrolysis and LLE	LC-MS/MS	NR	0.3–20.2	0.04–6.4 ng/mL	NR	[38]
BPA	On-line SPE	LC-MS/MS	95.8–108	4.5–13.5	0.4 ng/mL	1.5 ng/mL	[39]
BPA, BPS, BPF, BPZ, BPB, BPAP, BPP, BPAF	Enzymatic hydrolysis and LLE	LC-MS/MS	95.6–112	11.8–19.0	0.03–0.79 ng/mL	0.10–2.61 ng/mL	[40]
BPA, BPS, BPAP, BPP, BPF, BPAF, BPZ.	AALLME	LC-MS/MS	91–113	0.2–11.4	0.01–0.08 ng/mL	0.03–1.0 ng/mL	[41]
BPA, BPS, BPF, BPB, BPAF	Enzymatic hydrolysis and on-line SPE	LC-MS/MS	83–154	3.6–19	0.02–0.10 ng/mL	0.05–0.4 ng/mL	[42]
BPA	Enzymatic hydrolysis and MDSPE	LC-FLD	92.3	1.5	1.0 ng/mL	NR	[17]
BPA	MIP-SPE	LC-DAD	90.5–103.8	1.2–6.2	2.6 ng/mL	NR	[14]
BPA, BPB, BPAF, BPAP, BPE, BPF, BPP, BPS, BPZ	Enzymatic hydrolysis and SPE	LC-MS/MS	81.18–115.80	0.26–12.31	0.03–0.26 ng/mL	0.12–0.81 ng/mL	[43]
BPA, BPS, BPP, BPZ, BPAP, BPB	Enzymatic hydrolysis and LLE	LC-MS/MS	80.9–116.9	3.9–12.6	0.10–0.50 ng/mL	NR	[44]
BPA	SALLME	LC-MS/MS	95–108	6	0.1 ng/mL	0.2 ng/mL	[20]
BPA	Enzymatic hydrolysis, LLE and clean-up with SPE	LC-MS/MS	106–108	1.0–5.0	0.04 μg/L	0.20 μg/L	[45]
BPA, BPS, BPF, BPB, BPAF, BPZ, BPE, BPAP	Enzymatic hydrolysis and DLLME	GC-MS	62–103	1–20	0.03–4.55 μg/L	0.1–15 μg/L	[46]
BPS, BPA, BPC, BPZ, BPM, BPAF, BPAP, BPBP,	On-line SPE	LC-DAD	NR	0.12–8.42	NR	NR	[47]
BPA	Enzymatic hydrolysis and on-line SPE	LC-MS/MS	95.8–108	4.5–13.5	0.4 μg/L	NR	[48]

Table 1 (continued)

Analytes	Sample preparation technique	Instrumental analysis	Accuracy (% recovery)	Precision(RSD)	LOD	LOQ	Reference
BPA, BPS, BPAP, BPP, BPF, BPAF, BPZ	Enzymatic hydrolysis and LDS–AALLME	LC-MS/MS	96–115	1–12	0.003–0.30 ng/mL	0.01–0.10 ng/mL	[49]
BPA, BPF, BPS	Enzymatic hydrolysis	LC-MS/MS	85–104	3–15	0.066 ng/mL	0.2 ng/mL	[50]
BPA, BPF, BPS	Enzymatic hydrolysis and SPE	LC-MS/MS	96–104	2–12	0.06–0.23 ng/mL	0.8–1.5 ng/mL	[51]
BPA, BPAP, BPAF, BPP	MDSPE	LC-DAD	47–108	1–13	0.6–1.5 ng/mL	NR	[15]
BPA, BPF, BPS, BPZ, BPP, BPAF, BPAP	VADLLME	LC-MS/MS	80–106	1.5–8.1	0.05–0.09 ng/mL	0.14–0.20 ng/mL	[52]
BPA	Enzymatic hydrolysis and SPE	LC-MS/MS	Urine: 98–108	Urine: 0.2–1	NR	1.25 ng/mL	[53]
BPA, BPS, BPF, BPB	Enzymatic hydrolysis and SPE	LC-MS/MS	98–118	7–25	0.004–0.01 ng/mL	0.05–0.5 ng/mL	[54]
BPA	Enzymatic hydrolysis and SPE	LC-MS/MS	87.2–95.8	4.9–8.3	NR	0.50 μg/L	[55]
BPAF, BPF, BPA, BPB, BPZ, BPS, BPAP	Enzymatic hydrolysis and SPE	GC-MS/MS	86–115	2–12	NR	0.02–0.3 ng/mL	[56]
BPA, BPS, BPF	Enzymatic hydrolysis and on-line SPE	LC-MS/MS	98.3–113.4	2.2–9.2	0.13–0.24 ng/mL	NR	[57]
BPS, BPS-G	On-line SPE	LC-MS/MS	BPS: 80–96 BPS-G: 80–96	9–17	NR	Urine BPS: 0.5 ng/mL Urine BPS-G: 5 ng/mL	[58]
TBBPA	Enzymatic hydrolysis and SPE	LC-MS/MS	74.7–120.3	3.8–10.6	0.029 ng/mL	NR	[59]
BPA	Microwave hydrolysis and SALLE	GC-MS	86–110	0.49–2.07	0.3 ng/mL	1.0 ng/mL	[60]
BPA, BPS, BPAP, BPAF	Enzymatic hydrolysis and MEPS	LC-MS/MS	91–112	1–16	0.005–0.02 ng/mL	0.02–0.07 ng/mL	[61]
BPE, BPF, BPAP, BFDGE-$2H_2O$	MNER-EM	LC-FLD	87.4–106.1	1.2–5.7	0.019–0.028 ng/mL	0.063–0.094 ng/mL	[62]
BPA, BPS, BPF, BPB, BPAF	Enzymatic hydrolysis and centrifugation	LC-MS/MS	83–112	7–9	NR	0.6–10.8 ng/mL	[63]
BPA	MSPE	LC-UV	100.4–113.2	3.5–8.6	2.0 ng/mL	5.0 ng/mL	[64]
BPA, BPS, BPZ, BPAF, BPAP, BPP, BPB	Enzymatic hydrolysis and LLE	LC-MS/MS	80–110	3–16	NR	0.01–0.2 ng/mL	[65]
BPA	LLE (protein precipitation)	LC-MS/MS	84.32–102.00	1.07–14.87	0.001 ng/mL	0.005 ng/mL	[25]
21 compounds: bisphenols, chlorinated derivatives, and bisphenol diglycidyl ethers	SUPRAS-based microextraction	LC-MS/MS	76–108	1–9	NR	0.019–0.19 ng/mL	[23]
BPA	d-SPE with S-MIPs	LC-DAD	77.3–87.8	2.8–7.2	1.7 μg/L	NR	[66]
BPZ, BPP, BPM, BPS, BPF, BDP, TBBPA, BPAP, BPAF, BPDP	Enzymatic hydrolysis, LLE	LC-MS/MS	81–105	3–9	0.3–0.5 ng/mL	NR	[67]
BPA	d-SPE	LC-UV	95.15	2	1.0 ng/mL	NR	[68]
BPA, BPF, BPS	Enzymatic hydrolysis and SPE	GC-MS/MS	NR	1.0–6.8	NR	0.03–0.25 ng/mL	[21]

G glucuronide; *NR* data not reported, *LLE*liquid-liquid extraction; *SPE*solid-phase extraction; *MSPE* magnetic solid-phase extraction; *MDSPE* magnetic dispersive solid-phase extraction; *MIP-SPE* molecularly imprinted polymer solid-phase extraction; *PT-DMIP-SPE* pipette tip dummy molecularly imprinted polymer solid-phase extraction; *QuEChERS* quick, easy, cheap, effective, rugged, and safe; *d-SPE* dispersive solid-phase extraction; *HF-LPME* hollow fiber liquid-phase microextraction; *SALLME*salting-outliquid–liquid microextraction; *DLLME* dispersive liquid–liquid microextraction; *AALLME*air-assistedliquid–liquid microextraction; *MNER-EM* magnetic effervescent reaction-enhanced microextraction; *VADLLME*vortex-assisted dispersive liquid–liquid microextraction; *SUPRAS* supramolecular solvents; *RAM-VOL-SUPRAS* restricted access-volatile supramolecular solvents; *S-MIPs*solvent-responsive molecularly imprinted polymers; *MEPS* microextraction by packed sorbent; *LDS–AALLME*low-density solvent air-assistedliquid–liquid microextraction; *LC-UV* liquid chromatography with ultraviolet detector; *LC-DAD* liquid chromatography with diode array detector; *LC-FLD* liquid chromatography with fluorescence detector; *LC-MS/MS* liquid chromatography coupled to tandem mass spectrometry; *GC-MS* gas chromatography coupled to mass spectrometry; *GC-MS/MS* gas chromatography coupled to tandem mass spectrometry

Table 2 Determination of bisphenol analogues in blood (serum, plasma and whole blood)

Analytes	Sample preparation technique	Instrumental analysis	Accuracy (% recovery)	Precision (RSD)	LOD	LOQ	Reference
Serum							
BPA, BPB, BPE, BPF, BPS, BPAF, BPZ, TBBPA	UAE-QuEChERS	LC-MS/MS	62–91	2.6–5.5	0.1–1.0 ng/mL	0.3–2.5 ng/mL	[69]
BPS, BPF, BPA, BPB, BPAF	MSPE	LC-MS	93.0–107.8	1.2–6.9	1.0–78.1 ng/L	3.2–260.3 ng/L	[70]
BPA, BPB, BPE, BPF, BPS, BPAF	Enzymatic hydrolysis and LLE	LC-MS/MS	NR	0.2–27.0	0.14–2.5 ng/mL	NR	[38]
BPA	Enzymatic hydrolysis and SPE	LC-MS/MS	83.9–128	4.7–24.8	0.4 ng/mL	1.0 ng/mL	[39]
BPA, BPC, BPE, BPF, BPG, BPM, BPP, BPS, BPZ, BPFL, BPBP	LLE (protein precipitation)	LC-MS/MS	87.6–134.6	1.2–15	0.008–0.039 ng/mL	0.024–0.12 ng/mL	[19]
BPA	Enzymatic hydrolysis and MDSPE	LC-FLD	90.8	7.3	2.0 ng/mL	NR	[17]
BPS, BPA, BPC, BPZ, BPM, BPAF, BPAP, BPBP	On-line SPE	LC-DAD	NR	0.12–8.42	NR	NR	[47]
BPA, BPS, BPF, BPE, BPB, BPZ, BPAF, BPAP	Enzymatic hydrolysis, LLE and clean-up with MIP-SPE	LC-MS/MS	71.2–118.9	1.1–12.4	0.05–0.19 ng/mL	0.18–0.63 ng/mL	[71]
BPA, BPS, BPF, BPP, BPZ, BPB, BPAF, BPAP	LLE (protein precipitation) and clean-up with SPE	LC-MS/MS	45.8–120	0.5–13.3	0.003–0.016 ng/mL	0.010–0.053 ng/mL	[72]
BPA	Enzymatic hydrolysis and SPE	LC-MS/MS	90–102	0.8–4	NR	1.25 ng/mL	[53]
BPS, BPF, BPB, BPZ, BPAP, BPP, BPAF, TBBPA, TBBPS, TCBPA	UAE and clean-up with SPE	LC-MS/MS	66.6–101.0	0.80–14.0	0.001–0.197 ng/mL	0.002–0.658 ng/mL	[73]
BPA	SPE	LC-MS	95.46–98.35	2.5–17.8	0.02 ng/mL	0.05 ng/mL	[74]
BPE, BPF, BPAP, BFDGE-2H_2O	MNER-EM	LC-FLD	83.5–106.2	1.1–6.8	0.019–0.028 ng/mL	0.063–0.094 ng/mL	[62]
BPA, BPS, BPZ, BPAF, BPAP, BPP, BPB	Enzymatic hydrolysis and LLE	LC-MS/MS	80–110	3–16	NR	0.01–0.2 ng/mL	[65]
21 compounds: bisphenols, chlorinated derivatives, and bisphenol diglycidyl ethers	SUPRAS-based microextraction	LC-MS/MS	72–107	1–10	NR	0.019–0.19 ng/mL	[23]
Plasma							
BPA, BPA-monoglucuronide, BPA-monosulfate, BPA-diglucuronide, BPA-disulfate	LLE, and clean-up with SPE	BPA: GC-MS/MS BPA glucuronide and sulfate conjugates: LC-MS/MS	85–105	NR	0.021 ng/mL	NR	[10]
BPA, BPS, BPF, BPAF	LLE	LC-MS/MS	93.0–113.1	1.7–11.2	NR	41.6–150.8 pg/mL	[11]
BPA	SPE	GC-MS	83.31–104.01	5.97–15.25	NR	1 ng/mL	[22]
BPA	LLE (protein precipitation)	LC-MS/MS	87.72–106.6	2.89–11.01	5 ng/mL	10 ng/mL	[75]
BPA, MCBPA, DCBPA, TCBPA, TTCBPA	SPE	LC-MS/MS	31–92	3–17	NR	0.005–0.1 ng/mL	[76]
BPS, BPS-G	On-line SPE	LC-MS/MS	BPS: 80–96 BPS-G: 80–96	9–17	BPS: 0.02 ng/mL BPS-G: 0.14 ng/mL	BPS: 0.05 ng/mL BPS-G: 0.5 ng/mL	[58]
16 bisphenol analogues	UAE and clean-up with SPE	LC-MS/MS	85.7–110	4–10	Plasma: 1–32 pg/g	NR	[77]
BPA, BPB, BPF, BPS, BPAF	Direct injection	LC-MS/MS	87.72–111.7	2.07–11.9	5 ng/mL	10 ng/mL	[78]
BPA-G, BPF-G, BPS-G	On-line SPE	LC-MS/MS	80–121	3–30	0.023–0.038 ng/mL	0.046–0.052 ng/mL	[79]
Whole blood							
BPA	LLE and clean-up with SPE	GC-MS	82–104	4.1–7.5	2.1 ng/L	NR	[26]
BPA, BPS, BPF, BPB, BPAF, BPZ, BPE, BPAP	Enzymatic hydrolysis and DLLME	GC-MS	74–116	2–19	0.03–4.55 μg/L	0.1–15 μg/L	[46]

G glucuronide; *NR* data not reported, *LLE*liquid-liquid extraction; *SPE*solid-phase extraction; *MSPE* magnetic solid-phase extraction; *MDSPE* magnetic dispersive solid-phase extraction; *MIP-SPE* molecularly imprinted polymer solid-phase extraction; *QuEChERS* quick, easy, cheap, effective, rugged, and safe; *d-SPE* dispersive solid-phase extraction; *UAE*ultrasound-assisted extraction; *DLLME* dispersive liquid–liquid microextraction; *MNER-EM* magnetic effervescent reaction-enhanced microextraction; *SUPRAS* supramolecular solvents; *LC-DAD* liquid chromatography with diode array detector; *LC-FLD* liquid chromatography with fluorescence detector; *LC-MS* liquid chromatography coupled to mass spectrometry; *LC-MS/MS* liquid chromatography coupled to tandem mass spectrometry; *GC-MS* gas chromatography coupled to mass spectrometry; *GC-MS/MS* gas chromatography coupled to tandem mass spectrometry

Table 3 Determination of bisphenol analogues in other biological liquid matrices

Analytes	Sample preparation technique	Instrumental analysis	Accuracy (% recovery)	Precision (RSD)	LOD	LOQ	Reference
Breast milk							
BPA, BPF, BPS	DLLME	LC-MS/MS	94.5–110.4	5.1–14.8	0.1 ng/mL	0.4–0.5 ng/mL	[80]
BPA	UA-MSPE	LC-UV	89.1–99.4	0.5–3.7	0.75 ng/mL	2.5 ng/mL	[13]
24 bisphenols	Enzymatic hydrolysis and QuEChERS	LC-MS/MS	86.11–119.05	0.59–13.49	0.0003–0.067 ng/mL	0.001–0.200 ng/mL	[81]
BPA	SPE	LC-MS/MS	85.8–106	3.6–19.6	0.3 ng/mL	1.0 ng/mL	[39]
BPA, BPF, BPS	QuEChERS	LC-MS/MS	97–115	6–13	NR	0.10–0.25	[82]
BPS, BPA, BADGE, BADGE-2H_2O, BADGE-2HCl	QuEChERS	LC-MS/MS	70–>130	5–15	0.10 and 0.54 ng/mL for BPS and BPA, respectively	0.01–27.65 ng/mL	[83]
BPA, BPF, BPS	QuEChERS	LC-MS/MS	35–102	7–17	NR	0.10–0.25 ng/mL	[84]
BPA, BPS, BPF, BPAF	SPE	LC-MS/MS	76–105	NR	0.06–0.37 ng/mL	NR	[85]
BPA, BPS, BPF, BPB	Enzymatic hydrolysis and QuEChERS	LC-MS/MS	41.5–113.9	5.3–7.2	NR	25–53 ng/mL	[86]
BPA, BPS, BPF, BPAF	Enzymatic hydrolysis and QuEChERS	LC-MS/MS	77.4–84.1	2.5–7.9	0.01–0.20 ng/mL	0.03–0.67 ng/mL	[87]
Saliva							
BPA	Enzymatic hydrolysis	LC-MS/MS	NR	2.8–4	0.1 ng/mL	NR	[88]
BPA, BPS, BPAF, BPAP, BPP, BPZ	DLLME	LC-MS/MS	85–114	2–19	0.01–0.10 ng/mL	0.10–0.40 ng/mL	[89]
BPA and 12 bisphenol analogues and derivatives	SUPRAS-based microextracti-on	LC-MS/MS	95–105.6	0.6–16	0.012–0.049 μg/L	0.024–0.098 μg/L	[90]
BPA	HF-LPME	GC-MS	93	7.36–13.02	0.070 ng/mL	0.24 ng/mL	[91]
Amniotic fluid							
BPA, BPS, BPZ, BPAF, BPAP, BPP, BPB	Enzymatic hydrolysis and LLE	LC-MS/MS	80–110	3–16	NR	0.01–0.2 ng/mL	[65]
Follicular fluid							
BPA	Enzymatic hydrolysis and SPE	LC-MS/MS	99–110	0.3–3	NR	1.25 ng/mL	[53]
Peritoneal fluid							
BPA	Enzymatic hydrolysis and SPE	GC-MS/MS	103.5	1.4–5.8	0.015 pg/μL	NR	[35]
Seminal fluid							
BPA, BPF, BPS	Enzymatic hydrolysis and LLE	LC-MS/MS	NR	NR	0.018–0.048 ng/mL	NR	[92]

LLE liquid-liquid extraction; *SPE* solid-phase extraction; *UA-MSPE* ultrasound-assisted magnetic solid-phase extraction; *QuEChERS* quick, easy, cheap, effective, rugged, and safe; *d-SPE* dispersive solid-phase extraction; *HF-LPME* hollow fiber liquid phase microextraction; *DLLME* dispersive liquid–liquid microextraction; *SUPRAS* supramolecular solvents; *LC-UV* liquid chromatography with ultraviolet detector; *LC-MS/MS* liquid chromatography coupled to tandem mass spectrometry; *GC-MS* gas chromatography coupled to mass spectrometry; *GC-MS/MS* gas chromatography coupled to tandem mass spectrometry

Strata C18-E cartridges followed by GC-MS/MS; recoveries and LODs obtained were > 103.5 and 0.015–0.05 pg/μL, respectively [35].

Dima and co-workers developed a method for the simultaneous determination of BPA and six phthalates in serum, urine, and follicular fluid using SPE with Oasis HLB

cartridges and LC-MS/MS; recoveries and LOD for BPA were > 90% and 1.25 ng/mL, respectively [53].

Magnetic solid-phase extraction

The use of magnetic materials in SPE has become increasingly important and popular because of the advantages of this approach over conventional SPE, i.e., they avoid sorbent packing problems, high back pressure, or clogging. Magnetic solid-phase extraction (MSPE) consists of a magnetic sorbent dispersed into a liquid sample for a defined time to allow the adsorption of the analytes and equilibrium, then the sorbent is easily recovered by the application of a magnetic field, centrifugation, or filtration, followed by a washing and elution step [93]. Filippou et al. fabricated a magnetic-activated carbon as sorbent through the impregnation of a micro-meso-porous activated carbon with magnetite (Fe_3O_4) to determine BPA in breast milk with ultrasonic-assisted magnetic solid-phase extraction (UA-MSPE) and LC-UV. The method recoveries were between 89.1–99.4% and LOD 0.75 ng/mL [13]. Yang et al. synthesized magnetic porous aromatic frameworks with a core–shell structure (PAF-6 MNPs) and used them as a sorbent to determine BPA and other four phenols in urine using MSPE and LC-UV; for BPA, recoveries were between 100.4–113.2% and LOD 2.0 ng/mL [64].

Molecularly imprinted polymer solid-phase extraction

To increase the selectivity of SPE, molecularly imprinted polymers (MIPs) have been used as sorbents in the so-called technique molecularly imprinted polymer solid-phase extraction (MIP-SPE). MIPs are synthesized via polymerization process, which uses a template molecule and a functional monomer for copolymerization in the presence of a cross-linking agent; the use of MIPs decreases the non-specific interactions because tailor-made recognition sites are generated with a memory of the shape, size, and functional groups of the template molecules and they have been widely applied because of their high selectivity and accuracy [94]. Despite all their advantages, there are few applications on MIPs and BPs in biological samples. One example is that of Yang et al., who fabricated a phenolphthalein-imprinted polymer using 4-vinylpyridine(4-VP) as the functional monomer by bulk polymerization for highly selective extraction of BPA from human urine. MIP-SPE followed by LC-DAD revealed recoveries ranging from 90.5 to 103.8% for BPs spiked at two different concentrations (100 and 500 ng/mL), and LOD was 2.6 ng/mL [14]. Tan et al. used LLE for extraction, MIP-SPE as clean-up, and LC-MS/MS for the determination of eight BPs in serum samples. MIPs were prepared using 1,1,1-tris(4-hydroxyphenyl)ethane (THPE) as the template, and 4-VP as the functional monomer. In this study, the matrix effect was eliminated to a great extent and recoveries ranged from 71.2 to 118.9% at three different concentrations (0.8, 8, and 20 ng/mL) while LOD ranged from 0.05 to 0.19 ng/mL [71]. In addition to the usual SPE configuration, MIPs have been used in pipette tip dummy molecularly imprinted polymer solid-phase extraction (PT-DMIP-SPE) for the analysis by GC-MS of BPA in urine samples. The template was BPA and the functional monomer was aminopropyl-triethoxysilane (APTES). For this method, recoveries ranged from 8.2 to 14.2 and LOQ was 50 ng/mL [32].

Recently, Cui et al. fabricated solvent-responsive molecularly imprinted polymers (S-MIPs) employing a dynamic cross-linker with solvent-responsiveness and using beta-cyclodextrin derivative as functional monomer, and methacrylic acid (MAA) was added to strengthen the selective sites. The synthesis of the S-MIPs was easy and of low cost, and the adsorption character of S-MIPs can be regulated by adjusting the solvent composition. The prepared S-MIPs were used for the determination of BPA in human urine by *d*-SPE and LC-DAD, obtaining recoveries between 77.3 and 87.8% and LOD of 1.7 μg/L [66].

Dispersive solid-phase extraction

Dispersive solid-phase extraction (*d*-SPE) is one of the variations of the SPE technique that simplifies the procedure and reduces the extraction/clean-up. In this approach, the sorbent is dispersed into the liquid sample, making big the surface contact area between the sorbent and the analytes, avoiding the conditioning step, and thus reducing the extraction time. After extraction, the sorbent is recovered by centrifugation and then dispersed in an appropriate solvent to elute the analytes [95]. Despite the advantages of *d*-SPE, it is not widely used. Cui et al. developed a method to determine BPA in human urine with *d*-SPE and LC-DAD using MIPs as sorbent yielding an excellent enrichment capability and satisfactory recovery (> 77%) [66]. Shi et al. developed a facile and low-cost method for the preparation of activated carbon (AC) from peanut shell showing good adsorbing performance and is recycled naturally. Peanut shell-derived AC was used as a sorbent for the analysis of BPA in urine using *d*-SPE and LC-UV with the method showing recovery of around 95.15% and LOD 1.0 ng/mL [68].

Su et al. prepared BPA-specific nanoparticles by functionalization of Fe_3O_4@SiO_2 with ssDNA aptamer, named as Apt-MNPs, which exhibited an excellent magnetic response and were used as the specific sorbent to analyze BPA in human serum and urine using magnetic dispersive solid-phase extraction (MDSPE) and LC-FLD. The recoveries of BPA in the spiked serum and urine samples were around 90.8% and 92.3%, respectively; also, LODs for serum and urine were 2.0 and 1.0 ng/mL, respectively [17]. Baile et al. prepared a zeolite-based magnetic composite modified with the hexadecyltrimethylammonium bromide surfactant, named

as HDTMA-ZSM-5/Fe_2O_3. This composite was applied like a sorbent for MDSPE followed by LC-DAD for the analysis of BPA, BPAP, BPAF, and BPP in urine. The LODs of the method were from 0.6 to 1.5 ng/mL and the recoveries were between 81 and 108%, except for BPP with recoveries between 47 and 59% [15].

Quick, easy, cheap, effective, rugged, and safe

The quick, easy, cheap, effective, rugged, and safe (QuEChERS) method involves two steps. The first is an extraction step based on partitioning via salting-out where an equilibrium is established between an organic solvent (mainly acetonitrile) and aqueous sample. The second is a clean-up step with *d*-SPE using several combinations of porous sorbents (e.g., primary/secondary amine (PSA), C18, alumina) and salts (e.g., $MgSO_4$, NaCl, sodium citrate) to remove matrix interferents [96].

This method is mostly used for breast milk mainly because of the results achieved and the simplicity of the technique. Niu et al. developed a highly sensitive method based on QuEChERS and LC-MS/MS for the simultaneous determination of 14 bisphenol analogues as well as 9 of their halogenated derivatives in breast milk using a small sample volume (200 μL). This method showed recoveries ranged from 86.11 to 119.05% and LODs between 0.0003 and 0.067 ng/mL [81]. Dualde et al. developed a method to determine four parabens, BPA, BPF, and BPS in breast milk based on QuEChERS followed by LC-MS/MS; the recoveries varied between 97 and 115% for BPs using three spiked levels from 0.1 to 50 ng/mL and LOQs from 0.10–0.25 ng/mL [82]. Tuzimski et al. developed a method to determine BPA, BPS, and three BPA diglycidyl ethers in breast milk using QuEChERS and LC-MS/MS. Acceptable analytical performance was observed only for BPA and BPS, with recoveries (spiked levels from 25 to 500 ng/mL) in the range of 70–92% and LOQs were between 0.20 and 1.35 ng/mL. For diglycidyl ethers, further methodology optimization was necessary because recoveries were significantly overstated (> 130%) and LOQs were between 0.01 and 0.10 ng/mL, except for BADGE-2HCl which LOQ was 27.65 ng/mL [83]. More recently, Tuzimski et al. proposed another method based on QuEChERS followed by LC-DAD and LC-FLD for the qualitative analysis of BPs and BPA diglycidyl ethers and LC-MS/MS for the quantitative analysis of BPs [86].

Song et al. developed an ultrasound-assisted method based on QuEChERS (UAE-QuEChERS) followed by LC-MS/MS for the simultaneous determination of eight bisphenol analogues in serum. For this method, a satisfactory extraction efficiency was obtained for the energy provided by ultrasound and the LODs were between 0.1 and 1.0 ng/mL and the recoveries were between 86.11 and 119.05% [69].

Miniaturization of this technique (micro-QuEChERS) followed by GC-MS has also recently been applied for the fast determination of BPA in urine. The conditions were 1.5 mL of sample, 3 mL of acetonitrile, and 750 mg of salts, obtaining recoveries between 74 and 118% at three spiking levels (10, 20, and 50 μg/L) and LOD of 0.13 μg/L [37].

SUPRAS-based microextraction

Nanostructured supramolecular solvents (SUPRASs) are green water-immiscible solvents composed of amphiphile aggregates. They are produced through sequential self-assembly of amphiphilic molecules, induced by changes in external stimuli (modifications in pH, temperature, or salt addition). In the last few years, the range of applications of SUPRAS-based extraction has extended because they are excellent solvents for the extraction of organic compounds from complex matrices such as biological and environmental samples [97].

Romera-García and co-workers employed SUPRAS-based microextraction and LC-MS/MS for the biomonitoring of 13 free bisphenol analogues and chlorinated derivatives in saliva. In this study, saliva was used to induce the growth of inverted aggregates of hexanol in THF, and saliva played the dual role of the inductor of the self-assembly process and the sample to be analyzed. The sample treatment was simple, fast, and with low sample and solvents consumption (1005 μL of saliva, 45 μL of hexanol, and 450 μL of THF), and the performance of the method was adequate with recoveries between 95 and 105.6% and LODs between 0.012 and 0.049 μg/L [90].

Caballero-Casero and Rubio developed a method with SUPRAS-based microextraction and LC-MS/MS for the determination of 21 BPs, chlorinated derivatives, and diglycidyl ethers in urine and serum. The sample volume used was 1500 μL and the volumes of the solvents were 100 μL of hexanol and 400 μL of THF. External calibration was applied to quantify because the method was matrix-independent with recoveries > 72% for all analytes and LODs between 0.019 and 0.19 ng/mL [23].

Salatti-Dorado and co-workers developed a method based on restricted access-volatile supramolecular solvents (RAM-VOL-SUPRAS) followed by LC-MS/MS to determine BPA in urine. RAM-VOL-SUPRAS were synthesized in urine by addition of hexanol (83 μL) in THF (150 μL), and they allowed the fast removal of protein and phospholipids and efficient extraction of BPA. Recoveries were within the range of 96–107% for urine sample spiked at 0.4 ng/mL, and LOD was 0.015 ng/mL [34].

Other microextraction techniques

Miniaturization of extraction techniques has become a major trend of green analytical chemistry to reduce organic solvent volumes and diminish the environmental impact. For this

reason, several microextraction techniques have been applied for the analysis of BPs in biological samples. Among them, we have microextraction by packed sorbent (MEPS), salting-outliquid–liquid microextraction (SALLME), dispersive liquid–liquid microextraction (DLLME), vortex-assisted dispersive liquid–liquid microextraction (VADLLME), air-assistedliquid–liquid microextraction (AALLME), hollow fiber liquid-phase microextraction (HF-LPME), and magnetic effervescent reaction-enhanced microextraction (MNER-EM). Notably, no literature was found regarding the utilization of solid-phase microextraction (SPME) or stir bar sorptive extraction (SBSE), which are popular microextraction techniques commonly used in liquid samples.

MEPS is a miniaturized technique where the packing is integrated directly into a liquid-handling syringe. It uses the same sorbents as conventional SPE columns; so most existing SPE methods can be adapted to MEPS by scaling down the reagent and sample volumes. An additional advantage is that it can be fully automated [98]. Despite the advantages, the use of MEPS for the extraction of BPs from biological matrices is uncommon. Silveira et al. developed a method for the simultaneous determination of various classes of endocrine-disrupting chemicals (four bisphenols, seven parabens, four benzophenones, and triclocarban) in human urine based on MEPS combined LC-MS/MS. The conditions were C18 sorbent, 250 μL of the sample, five draws-eject cycles, and 100 μL of CH_3OH–H_2O 80:20 (v/v) as an elution solvent. Recoveries and LODs for bisphenols were 91–112% and 0.005–0.02 ng/mL, respectively [61].

SALLME is an alternative technique to the conventional LLE in which the analytes are extracted into an organic solvent miscible with water, after induced phase separation with the addition of inorganic salt. It is simple and produces clean extracts as most solvents and salts used are capable of precipitating proteins before the phase separation, leaving most of the matrix interferents unextracted [99]. Ballesteros-Gómez and Rubio developed a method based on SALLME and LC-MS/MS for the determination of BPA in urine. The conditions were 1 mL of sample, 145 mg of NaCl, and 650 μL of tetrahydrofuran as extracting solvent. Recoveries of the method were between 95 and 108% and LOD 0.1 ng/mL [20].

DLLME is the miniaturized form of LLE in which the amount of organic solvent is reduced. This approach is based on a ternary solvent system: the extraction solvent (non-miscible in water), the aqueous sample, and the disperser solvent (miscible in both extraction and aqueous phases). A suitable mixture of extraction and dispersive solvents is injected quickly into the aqueous sample with a syringe. The extraction solvent is spread through the aqueous sample by the dispersive solvent, and small drops of the extraction solvent are formed. Then, the extraction solvent can easily be isolated by centrifugation [100]. Due to this technique is simple and fast, it has been applied in several liquid samples like urine, blood, breast milk, and saliva. Pastor-Belda and co-workers developed a method using DLLME in combination with GC-MS for the determination of BPA and BPF in urine. The method parameters were 2 mL urine, 1 mL acetone as disperser solvent, and 100 μL chloroform as extractant solvent; the recoveries were between 94 and 109% and LODs 0.011–0.041 ng/mL [29]. Gonzalez and co-workers proposed two methods based on DLLME and GC-MS for the analysis of eight BPs in blood and urine samples; the conditions for blood were 500 μL of the sample, 1.5 mL of acetonitrile (dispersive agent), and 85 μL of tetrachloroethylene (extractant solvent); the conditions for urine were 5 mL of sample, 1325 μL of acetonitrile, and 85 μL of tetrachloroethylene; and both methods showed suitable performance with recoveries > 62% and LODs between 0.03–4.55 μg/L [46]. Rocha et al. proposed a biomonitoring method combining DLLME and LC-MS/MS for the determination of seven BPs in urine. The conditions were 5 mL of urine (diluted to 10 mL with 10% NaCl aqueous solution), 750 μL of acetone as disperser solvent, and 500 μL of 1,2-dichloroethane as extraction solvent; the recoveries were between 90 and 112% and LODs 0.005–0.2 ng/mL [31]. Vela-Soria and co-workers developed a method based on DLLME and LC-MS/MS for the determination of endocrine-disrupting chemicals (three BPs, four parabens, and six benzophenones) in human milk. The conditions were 10 mL of pre-treated sample (protein denaturation), 750 μL of acetone as a disperser solvent, and 750 μL of trichloromethane as an extraction solvent; the recoveries and LOD for BPs were 94.5–110.4% and 0.1 ng/mL, respectively [80]. De Oliveira et al. reported a method to determine endocrine-disrupting chemicals (six BPs, five parabens, five benzophenones, and triclocarban) in saliva using DLLME and LC-MS/MS. Conditions include using 500 μL of the sample (diluted with 500 μL of water), and 2 mL of a mixture containing acetone (dispersant solvent) and trichloromethane (extraction solvent) 3:1 (v/v); the recoveries and LODs for BPs were 85–114% and 0.01–0.10 ng/mL [89].

Even though DLLME has several advantages like its high enrichment factors, low cost, easy application, and fast reach of equilibrium, its main drawback is its low selectivity and the need for a disperser solvent that normally decreases the partition coefficient of the analytes in the extraction solvent. To overcome these problems, other studies have proposed the use of vortex mixing (VADLLME) as dispersing force of the extraction solvent, avoiding the use of a disperser solvent. VADLLME is a solvent miniaturized technique in which the suspension obtained by LLME is subjected to vortex stirring to favor the dispersion of the extractant phase in the aqueous sample. The analytes are extracted in the small droplets formed, then the suspension is centrifuged to separate the two phases; this technique has the inherent advantage of reaching equilibrium conditions in just a few minutes and high efficiency in the extraction is obtained [101]. Bocato and co-

workers developed a method using VADLLME and LC-MS/MS for the determination of endocrine disruptor compounds (seven BPs, seven parabens, five benzophenones, and two antimicrobials) in urine; the conditions were 1 mL of sample, 150 μL of dichloromethane (extractant solvent), 250 μL of 2-propanol (dispersant), and stirring time of 20 s. The BPs recoveries were between 80 and 106% (at three levels 1.0, 12.5, and 20.0 ng/mL) and LODs ranged from 0.05 to 0.09 ng/mL [52].

AALLME is another improvement of the classical DLLME; in this technique, a hydrophobic extraction solvent is dispersed into the sample solution by performing sucking/dispersing cycles several times with the aid of a syringe, and thus, there is no need to use a disperser solvent [102]. Rocha et al. developed a method based on AALLME combined with LC-MS/MS for the analysis of multiple endocrine-disrupting chemicals (seven BPs, seven parabens, five benzophenones, and two antimicrobials) in human urine. The method conditions were 5 mL of sample, 750 μL of 1,2-dichloroethane (extraction solvent), and three aspiration–dispersion cycles. This method effectively extracted BPs and was characterized by its simplicity and speed; the recoveries and LODs obtained for BPs were 91–113% and 0.01–0.08 ng/mL, respectively [31].

In the AALLME technique, chlorinated solvents are commonly selected as extraction solvents to obtain high extraction efficiency. However, the toxicity of this kind of solvents discourages their use. For this reason, LDS–AALLME emerged as an improvement to make the procedure eco-friendly. Rocha et al. developed a simple method for the simultaneous analysis of endocrine-disruption compounds (seven BPs, seven parabens, five benzophenones, and two antimicrobials) in human urine by using LDS–AALLME followed by LC-MS/MS. The method conditions were 2 mL of sample, 300 μL of 1-octanol (low-density extraction solvent), and three aspiration–dispersion cycles. The performance of the method was suitable; the recoveries and LODs obtained for BPs were 96–115% and 0.003–0.30 ng/mL [49].

Liquid-phase microextraction (LPME) is a miniaturization of LLE; this technique decreases the extraction solvent volume in relation to the sample volume, and a newer mode of LPME is HF-LPME which has a higher efficiency attributed to the enhancement of mass transfer process under strong stirring during extraction when hollow fiber is used. These methods can be categorized in two-phase and three-phase modes. In the two-phase mode, the analytes are isolated from the aqueous sample (donor phase) and dispersed into the organic solvent impregnated in the supported liquid membrane (SLM) in the hollow fiber, the analytes are then transferred into the organic solvent (acceptor phase) inside the lumen of the hollow fiber. In the three-phase mode, the analytes are extracted from the aqueous sample (first phase) into the thin organic film (second phase) and restrained in the hollow fiber pores (SLM) in its deionized form. The analytes are then converted to their ionized form and moved to a different organic solvent (third phase) residing in the hollow fiber lumen [103]. Moreira Fernandez and co-workers proposed a method to determine BPA and eight phthalates in urine using HF-LPME and GC-MS. The method conditions were 10-cm hollow fiber, 35 μL of octanol as the extraction solvent, 16 mL of sample volume, pH of the sample at 2, extraction time 70 min, and stirring at 700 rpm. The method was precise and sensitive, and the LOD for BPA was 1.82 ng/mL [33]. Messias Gomes et al. developed a method to analyze BPA and 13 phthalates in saliva using HF-LPME and GC-MS. The method conditions used were 7-cm hollow fiber, 15 μL of octanol-ethyl octanoate (1:1, v/v) as the extraction solvent, 9 mL of sample volume, pH of the sample at 2, extraction time 55 min, and stirring at 2000 rpm; the recovery and LOD for BPA were 93% and 0.070 ng/mL, respectively [91].

Recently, several novel dispersive solvent-free microextraction techniques were developed such as effervescence-assisted DLLME. This method involves the in situ generation of carbon dioxide (the disperser) from acid and alkaline reaction to promote the close contact between the aqueous sample (donor phase) and the solvent extractant (acceptor phase), and also the products of the reaction contribute to the ionic strength and may produce a salting-out effect and thus enhance extraction of the analytes. To enhance this technique, magnetic nanoparticles can be added to the extractant and used to recover the extractant from the sample avoiding the centrifugation process [104]. Tan and co-workers developed a novel method referred to as MNER-EM followed by LC-FLD to determine endocrine disruptor compounds (BPE, BPF, BPAP, BFDGE-$2H_2O$, estriol, and 17-α-ethinylestradiol) in urine and serum. They synthesized $NiFe_2O_4$@COF (covalent organic framework) magnetic nanocomposites (MNCs) and used it as an independent adsorbent, which improved the extraction because it offered a larger surface area and more active sites in the external layer of COF. The superparamagnetism of $NiFe_2O_4$@COF MNCs leads to a quick separation/collection by a magnet. The experimental conditions were 5 mL of sample, a magnetic effervescent tablet (0.24 g of NaH_2PO_4, 0.212 g of Na_2CO_3, and 0.01 g of $NiFe_2O_4$@COF), 3 min for the effervescent reaction process, 500 μL acetonitrile as an elution solvent (twice). The method gave high recoveries (> 83.5%) and low LODs (0.019–0.028 ng/mL) for both matrices [62].

Sample preparation and clean-up for solid samples

In the case of solid samples, biomonitoring studies are focused mostly on hair (70%), followed by placenta (20%) and adipose tissue (10%). Hair is a non-invasive matrix easy to

sample; it has the advantages of sample stability at room temperature, easily handled and transported, and information on short and long-term exposure can be obtained. The compounds present in blood can be incorporated into hair structure through capillary blood vessels surrounding hair follicles making hair a suitable sample for bioanalysis. However, there is a problem that compounds can be deposited on hair from the environment, pollution, or physical contact, among others. Therefore, the pretreatment and preparation of hair sample before the instrumental analysis is very important. Commonly, the hair is washed to eliminate external contamination, and it can be pulverized or cut into small pieces [24]. Placenta is a tough fibrous tissue, and important steps in its pretreatment involve disruption and homogenization [24]. It has been shown that BPA conjugates can passively cross the placenta in a bidirectional mode between maternal and fetal compartments, and they can be accumulated [3].

Table 4 shows the most relevant publications from 2016 onwards about the sample preparation techniques used for solid samples. Figure 2 shows that conventional solid–liquid extraction (SLE, 45%) and ultrasound-assisted extraction (UAE, 55%) are the two sample preparation techniques almost exclusively employed in recent methods for the analysis of BPs. Co-extracted matrix components are usually found in sample extracts, which leads to an additional clean-up step with SPE. These techniques and their applications will be discussed in the next sections.

Solid–liquid extraction

SLE is the most popular technique for the analysis of solid biological samples such as hair, placenta, and adipose tissue due to its simplicity and the fact that it requires no expensive equipment. The main step of SLE consists in homogenizing a proportion of the solid sample with the appropriate solvent through a careful procedure. Thus, the analytes and other solid matrix components pass from the solid sample to the liquid phase of the homogenate solution. To clean this solution, additional steps can be employed including centrifugation, evaporation, filtration, and application of another extraction technique like SPE [112].

The efficiency of SLE depends mainly on the nature of the extractant solvent used; methanol and acetonitrile are the most common but, in some cases, solvent mixtures are necessary to extract analytes with a wider range of polarity. Extraction time is another key factor in assuring quantitative extractions; this varies from minutes to several hours, and a centrifugation step usually needed after SLE to separate the extract causes an increase in procedure time.

Lee et al. developed a method for the simultaneous determination of BPA and three estrogens in hair samples based on SLE for extraction, SPE for clean-up, and LC-MS/MS. The experimental conditions used were 100 mg of sample, 1 mL of

Table 4 Determination of bisphenol analogues in biological solid samples

Analytes	Sample preparation technique	Instrumental analysis	Accuracy (% recovery)	Precision(RSD)	LOD	LOQ	Reference
Hair							
BPA	UAE	LC-MS/MS	77–82	3–15	1.8 ng/g	6.1 ng/g	[105]
BPA	SLE and clean-up with SPE	LC-MS/MS	90.0–103.6	3.0–8.1	3.49 ng/g	11.5 ng/g	[106]
BPA	UAE and clean-up with SPE	LC-FLD	85	< 10%	NR	2.0 ng/g	[16]
BPA	UAE	LC-MS	77.9–107.8	9.8–19.8	0.2 pg/mg	0.7 pg/mg	[107]
BPA	UAE	LC-MS/MS	77	3–15	1.8 ng/g	6.1 ng/g	[108]
BPA, BPS	UAE	LC-MS	BPA: 98.5 BPS: 63.0	8.1–13.3	0.6 pg/mg	1.8 pg/mg	[109]
BPA, BPS	SLE	BPA: GC-MS/MS BPS: LC-MS/MS	BPA: 106–112 BPS: 92–120	6–16	NR	BPA: 50 pg/mg BPS: 9 pg/mg	[110]
BPZ, BPP, BPM, BPS, BPF, BDP, TBBPA, BPAP, BPAF, BPDP	SLE	LC-MS/MS	86–101	3–9	0.04–0.5 ng/g	NR	[67]
Placenta							
BPA	Enzymatic hydrolysis and SLE	LC-MS/MS	80.3–103	3.3–17.1	0.3 ng/g	1.0 ng/g	[39]
16 bisphenol analogues	UAE and clean-up with SPE	LC-MS/MS	69.6–95.3	3–8	1–80 pg/g	NR	[77]
Adipose tissue							
BPA	UAE	LC-MS/MS	93	0.5	0.14 ng/g	NR	[111]

NR data not reported; *SLE* solid–liquid extraction; *SPE* solid-phase extraction; *UAE* ultrasound-assisted extraction; *LC-FLD* liquid chromatography with fluorescence detector; *LC-MS* liquid chromatography coupled to mass spectrometry; *LC-MS/MS* liquid chromatography coupled to tandem mass spectrometry

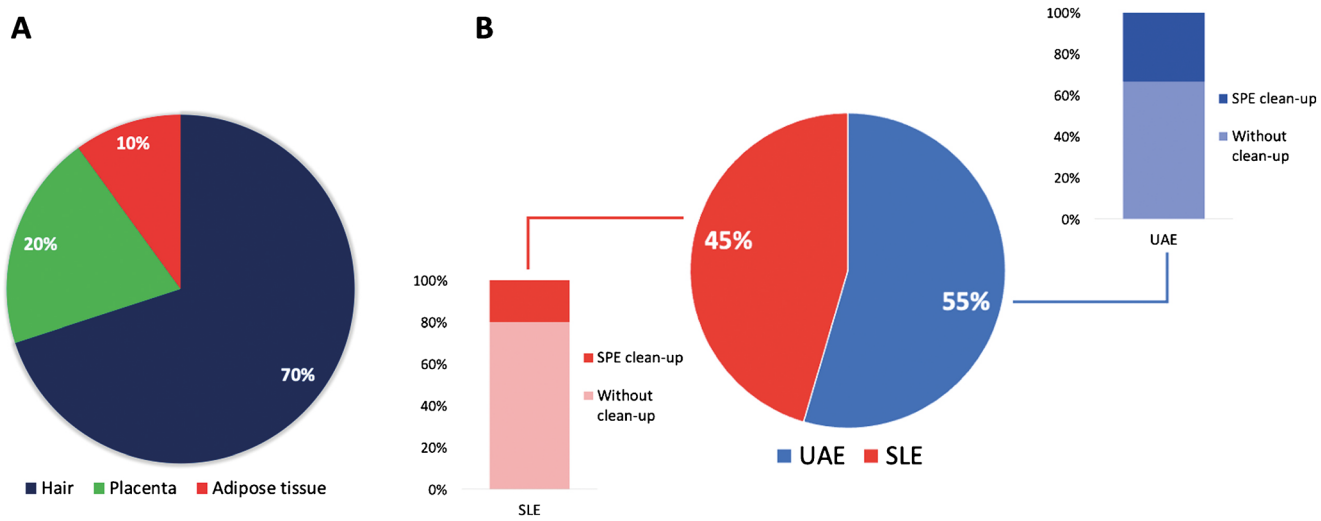

Fig. 2 (**A**) Solid biological samples and (**B**) Sample preparation techniques used in the analytical methods for BPs bioanalysis

1 N HCl as an extracting solvent, temperature extraction 45 °C, extraction time 30 min, and clean-up with an Oasis HLB cartridge, to achieve recoveries and LOD for BPA of 90.0–103.6% and 3.49 ng/g, respectively [106]. Peng and co-workers applied a method to determine BPA, BPS, four polychlorinated biphenyls, and seven polybrominated diphenyl ethers in hair using SLE followed by GC or LC tandem MS. In this method, the conditions were 50 mg of sample, 1 mL of an acetonitrile-water mixture (80:20, v/v), temperature extraction 40 °C, and overnight as extraction time; recoveries and LODs for BPs were > 92% and 9–50 pg/mg, respectively [110].

Li et al. applied a method to determine ten BPs and six phthalates in hair based on SLE and LC-MS/MS, the experimental conditions were 0.1 g of sample, 10 mL of ethyl acetate as extracting solvent, extraction time 10 min; the recoveries and LODs for BPs were > 81% and 0.04–0.5 ng/g, respectively [67]. Lee et al. applied a method to analyze BPA in human placenta using SLE and LC-MS/MS, and the method conditions were 1 g of sample, 5 mL of ethyl acetate as an extracting solvent, extraction time 10 min; the recoveries and LODs for BPA were 80.3–103% and 0.3 ng/g, respectively [39].

Ultrasound-assisted extraction

UAE procedures entail the application of ultrasound radiation to the extraction of analytes from solid samples. The cavitation process produced by the ultrasound radiation reduces considerably the extraction time and enhances recovery of the analytes. The extraction solvent and irradiation conditions (temperature, solid/liquid ratio, amplitude of sonication, and time) are important parameters commonly optimized; the experimental conditions should be controlled to avoid degradation of the analytes that may occur during the extraction procedure. After extraction, centrifugation and filtration are usually required [113].

UAE has been widely applied over the last few years in the analysis of BPs in biological samples. Martín et al. developed a method to extract endocrine-disrupting compounds (BPA, three parabens, six perfluoroalkyl compounds, and a brominated flame retardant) in human hair by UAE and LC-MS/MS; the method conditions were 100 mg of sample, incubation with MeOH-acetic acid (85:15, v/v) at 38 °C, 3 mL of ACN as extraction solvent, and 10 min of extraction time; recoveries and LOD obtained for BPA were 77–82% and 1.8 ng/g, respectively [105]. Nehring and co-workers proposed a method to determine BPA and two alkylphenols in hair using UAE followed by LC-FLD. The method conditions were 0.1 g of sample, 8 mL of MeOH mixed with 2 mL of 0.01 M ammonium acetate solution containing chloric acid (VII) as an extraction solvent, 10 min of extraction time, and clean-up with SPE using HLB cartridges; recovery and LOQ obtained for BPA were 85% and 2.0 ng/g, respectively [16]. Karzi et al. developed a method to determine BPA, triclosan, and perfluorooctanoic acid in hair using UAE followed by LC-MS; the method conditions were 100 mg of sample, 2 mL of MeOH as extraction solvent (twice), and 2 h of extraction time; recoveries at five concentration levels (10, 25, 50, 100, and 250 pg/mg) and LOD obtained for BPA were 77.9–107.8% and 0.2 pg/mg, respectively [107]. Katsikantami and co-workers employed a method to analyze BPA, BPS, and seven phthalates in hair based on UAE and LC-MS; the experimental conditions were 100 mg of sample, 2 mL of MeOH as extraction solvent, and 2 h of extraction time; recoveries at seven concentration levels (5, 10, 25, 50,

100, 250, and 500 pg/mg) and LOD obtained for BPs were > 63% and 0.6 pg/mg, respectively [109]. Artacho-Cordón and co-workers applied a method to determine BPA, seven parabens, and eight phenols in adipose tissue; the method conditions were 100 mg of sample, 2 mL of MeOH followed by 2 mL of acetone as extraction solvent, and 10 min of extraction time. Then an additional treatment was performed for removal of the remaining lipids, 200 μL of MeOH–20% HCOOH (1:1) and 300 μL of 1 M ammonium acetate buffer were added, and the solution was centrifuged at 4 °C. Recovery and LOD obtained for BPA were 93% and 0.14 ng/g, respectively [111].

Derivatization

Derivatization aims to improve the physicochemical properties of analytes through organic reactions to make them suitable for GC or LC and to enhance their analysis in terms of sensitivity and specificity. This process is usually performed after extraction and it may be affected by different experimental parameters (e.g., temperature, time, pH, and reaction agent); therefore, it is necessary to optimize derivatization conditions to avoid undesirable derivatization by-products to achieve reliable analytical results [114]. Tables 5 and 6 summarize the reagents used to derivatize BPs in sample extracts for GC or LC analysis.

Regarding GC analysis, in most of the studies, BPs are derivatized to form trimethylsilylethers by using silylating reagents like N-methyl-N-(trimethylsilyl) trifluoroacetamide (MSTFA) [21], N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) [56], and BSTFA with 1% trimethylchlorosilane (TMCS) [10, 22, 26, 32, 33, 35, 37, 91].

Another study reported derivatization of BPA and BPS with the alkylating reagent 2,3,4,5,6-pentafluorobenzyl bromide (PFBBr) [110] to convert them into their halogenated derivatives, which have the potential to form stable radicals that are of particular importance in quantitative analysis by mass spectrometry [114]. Another kind of derivatization consists of acetylation of the hydroxyl groups to reduce their polarity and improve the chromatographic response; this was used as in situ derivatization with acetic anhydride for the analysis of BPA and BPF in urine [29] and eight BPs in urine and blood [46]. Another mode is the injection port derivatization, which is an on-line derivatization that occurs in the high-temperature GC injection port. It has the advantages of being simple, high reaction efficiency, and less consumption of reagents. This modality was applied using tetrabutylammonium hydroxide (TBAOH) as a derivatization reagent for the determination of BPA, 4-*tert*-octylphenol, and 4-nonylphenols by injection port butylation and GC-MS [36].

On the other hand, sulfonyl chlorides are commonly used derivatizing reagents for the LC analysis of BPs, because of their selective reactivity with phenolic hydroxyl groups and compatibility with aqueous reactions and it has been reported that this kind of derivatization improved 180 times the sensitivity of BPA [81]; among them, the most used is dansyl chloride (DNS-Cl) [11, 58, 71, 79, 106]. Faÿs et al. proposed a method to determine BPA, BPF, and BPB in urine using 1-methylimidazole-2-sulfonyl chloride (MIS-2-Cl) as the derivatizing reagent to enhance BP detection [54]. However, there is one study involving the determination of 24 bisphenols including their chlorinated derivatives in breast milk, where four sulfonyl chlorides were compared, DNS-Cl, pyridine-3-sulfonyl chloride (PS-Cl), 1,2-dimethylimidazole-4-sulfonyl chloride (DMIS-4-Cl), and 1, 2-dimethylimidazole-5-sulfonyl chloride (DMIS-5-Cl). Results showed that the optimal derivatizing reagent was PS-Cl with the highest selectivity and outstanding sensitivity (response improved around 1–250 times) for the analysis of BPs [81].

Instrumental analysis

Due to the complexity of biological matrices, an analytical separation technique is required to analyze the extracts, and for this purpose, chromatographic techniques are undoubtedly the choice. Chromatography enables a selective determination, since some co-extracted compounds can still be present after the extraction process, and also, they allow the simultaneous determination of BPs with different physicochemical properties.

The analytical methods commonly employ liquid chromatography (LC, 83%) and gas chromatography (GC, 17%) as can be seen in Fig. 3. Among these, the most used are LC coupled to tandem mass spectrometry (LC-MS/MS, 76%) and gas chromatography coupled to mass spectrometry (GC-MS, 73%). The low concentration of the analytes in biological samples requires high sensitivity. Therefore, MS detection is the most suitable for the determination of these compounds in such complex matrices because lower limits of detection are obtained when compared to other more traditional detectors, such as ultraviolet (UV) detector.

Tables 5, 6, and 7 list matrix types, target analytes, internal standards, derivatization agents, and chromatographic conditions reported in recent studies. Due to the relatively low

Table 5 Chromatographic conditions of the methods using LC coupled to MS and tandem MS used to determine bisphenol analogues in biological samples

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
LC-MS	Hair	BPA	Phenobarbital-d_5	Not used	1. Injection volume: NR, 2. Column: Discovery C18 (250 mm, NR), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (quadrupole), APCI (negative)	Phenobarbital-d_5: 236.05, BPA: 133.05, 259.15, 227.15	[107]
	Hair	BPA, BPS	Phenobarbital-d_5	Not used	1. Injection volume: 20 μL, 2. Column: Discovery C18 column (250× 4.6 mm, 5 μm), 3. Mobile phase: acetonitrile with 0.1% formic acid-water with 0.1% formic acid (gradient mode), 4. Detector: MS (QqQ), APCI (negative)	Phenobarbital-d_5: 236.05, BPA: 227.15, 259.10, BPS: 249.05, 285.05	[109]
	Serum	BPA	Not used	Not used	1. InjectioJ15:J18n: 10 μL, 2. Column: C18 (100 ×2.1 mm, 5 μm), 3. Mobile phase: acetonitrile-water with 1% ammonia (70:30) (isocratic mode), 4. Detector: MS (QqQ), ESI (negative)	227.1→212.2	[74]
LC-MS/MS	Hair	BPA	BPA-d_{14}	Not used	1. Injection: NR, 2. Column: Zorbax Eclipse XDB-C18 Rapid Resolution HT (50×4.6 mm, 1.8 μm), 3. Mobile phase: methanol-water with 5 mM ammonium acetate (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA: 227.3→133.0	[105]
	Urine	BPA	$^{13}C_{12}$-BPA	Not used	1. Injection volume: 10 μL, 2. Column: Atlantis C18 (150× 2.1 mm, 5 μm), 3. Mobile phase: methanol-water (gradient mode),	$^{13}C_{12}$-BPA: 239→ 224, BPA: 227→ 212	[30]

Table 5 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
					4. Detector: MS (QqQ), ESI (negative)		
	Urine	BPA, BPS; BPF, BPZ, BPP, BPAF, BPAP	BPA-d_{16}	Not used	1. Injection volume: 10 μL, 2. Column: Ascentis Express C18 (75× 2.1 mm, 2.7 μm), 3. Mobile phase: methanol-water with 0.1% of ammonium hydroxide (v/v) (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-d_{16}: 241→223, BPA: 227→212, BPS: 249→108, BPF: 199→93, BPZ: 267→173, BPP: 345→330, BPAF: 335→265, BPAP: 289→273	[31]
	Breast milk	BPA, BPF, BPS	BPA-d_{16}	Not used	1. Injection volume: 10 μL, 2. Column: Gemini C18 (100×2 mm, 3 μm), 3. Mobile phase: acetonitrile-water with 0.025% of ammonia (v/v) (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-d_{16}: 241.1→ 223.1, BPA: 227.1 →212.0, BPF: 199.0→92.9, BPS: 249.0→ 108.0	[80]
	Adipose tissue	BPA	BPA-d_8	Not used	1. Injection volume: 100 μL, 2. Column: Hypersil Gold aQ (50× 4 mm, 3 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), APCI (negative)	BPA-d_8: 235→137, BPA: 227→133	[111]
	Saliva	BPA	BPA-d_{16}	Not used	1. Injection volume: 3 μL, 2. Column: Vision HT C18 (100×2.0 mm, 1.5 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-d_{16}: 241→142, BPA: 227→212	[88]
LC-MS/MS	Plasma, urine	BPA-mono glucuronide, BPA-monosulfate, BPA-diglucuronide,	BPA-d_{16}	Not used	1. Injection volume: 10 μL, 2. Column: Waters XBridge C18 (50× 3.0 mm, 2.5 μm), 3. Mobile phase: acetonitrile with 0.1% ammonium	BPA-d_{16}: 243→223, BPA-mono glucuronide: 403→227, BPA-monosulfate: 307→227, BPA-diglucuronide: 579 →403,	[10]

Table 5 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
		BPA-disulfate			hydroxide-water with 0.1% ammonium hydroxide (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-disulfate: 387→307	
	Hair	BPA	BPA-d_{16}	DNS-Cl	1. Injection volume: 5 μL, 2. Column: CAPCELL PAK C18 (100×2 mm, 3 μm), 3. Mobile phase: acetonitrile-water (gradient mode), 4. Detector: MS (QqQ), ESI (positive)	Dn-BPA: 695→171	[106]
	Breast milk	24 bisphenols	BPA-$^{13}C_{12}$, BPB-$^{13}C_{12}$, BPF-$^{13}C_{12}$, BPS-$^{13}C_{12}$, BPAF-d_4, TCBPA-$^{13}C_{12}$, TBBPA-$^{13}C_{12}$	PSCl	1. Injection volume: 10 μL, 2. Column: BEH C18 column (100×2.1 mm, 1.7 μm), 3. Mobile phase: acetonitrile-water with 0.1% formic acid (gradient mode), 4. Detector: MS (QqQ), ESI (positive)	Ps-BPA: 511→212, Ps-BPB: 525→212, Ps-BPC: 539→240, Ps-BPE: 497→198, Ps-BPF: 483→199, Ps-BPM/BPP: 629→276, Ps-BPS: 533→327, Ps-BPZ: 551→224, Ps-BPAF: 619→344, Ps-BPAP: 573→196, Ps-BPBP: 635→274, Ps-BPFL: 633→349	[81]
	Urine	BPA	BPA-$^{13}C_{12}$	Not used	1. Injection volume: 10 μL, 2. Column: ACE C18-PFP column (150×3 mm, 3 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QIT), ESI (negative)	BPA-13C12: 239→224, BPA: 227→212	[34]
	Serum	BPA, BPB, BPE, BPF, BPS, BPZ, BPAF, TBBPA	BPA-$^{13}C_{12}$, TBBPA-$^{13}C_{12}$	Not used	1. Injection volume: 5 μL, 2. Column: ACQUITY UPLC BEH C18 (100×2.1 mm, 1.7 μm), 3. Mobile phase: acetonitrile-water with 10 mM ammonium acetate (gradient mode), 4. Detector: MS	BPA-$^{13}C_{12}$: 239→139, TBBPA, $^{13}C_{12}$: 555→297, BPA: 227→133, BPB: 241→147, BPE: 213→197, BPF: 199→93, BPS: 249→108, BPZ: 267→173, BPAF: 335→69, TBBPA: 543→420	[69]

Table 5 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
					(QqQ), ESI (negative)		
	Plasma	BPA, BPS, BPF, BPAF	BPA-d_{16}, BPS-d_4	DNS-Cl	1. Injection volume: 50 μL, 2. Column: Kinetex C18 (150×3 mm, 1.7 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), ESI (positive)	Dn-BPA-d_{16}: 709→171, Dn-BPS-d_4: 721→171, Dn-BPA: 695→171, Dn-BPS: 717→171, Dn-BPF: 667→171, Dn-BPAF: 803→171	[11]
LC-MS/MS	Seminal fluid	BPA, BPF, BPS	Labeled internal standard for all analytes	Not used	1. Injection volume: NR, 2. Column: Ultra AQ C18 (100×2.1 mm, 3 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	NR	[92]
	Serum	BPS, BPF, BPA, BPB, BPAF	BPA-d_{16}	Not used	1. Injection volume: 10 μL, 2. Column: Hypersil GOLD C18 (150×2.1 mm, 5 μm), 3. Mobile phase: methanol-water with 0.01% ammonium hydroxide (v/v) (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-d_{16}: 241.1→223.12, BPS: 248.9→108.12, BPF: 198.9→93.12, BPA: 227.0→211.99, BPB: 241.0→211.01, BPAF: 334.9→264.90	[70]
	Serum and urine	BPA, BPB, BPE, BPF, BPS, BPAF	BPA-d_{16}	Not used	1. Injection volume: NR, 2. Column: Hypersil Gold (50×2.1 mm, 1.9 μm), 3. Mobile phase: acetonitrile-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPS: 249→108, BPF: 199→93, BPE: 213→198, BPA: 227→213, BPB: 241→212, BPAF: 335→265	[38]
	Serum, urine, placenta, breast milk, umbilical cord serum	BPA	BPA-$^{13}C_{12}$	Not used	1. Injection volume: 10 μL, 2. Column: Shiseido ACR C18 (150×2 mm, 3 μm), 3. Mobile phase: acetonitrile with 0.1% acetic acid-water with 0.1% acetic acid (gradient mode), 4. Detector: MS	NR	[39]

Table 5 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
					(QqQ), ESI (negative)		
	Serum	BPA, BPC, BPE, BPF, BPG, BPM, BPP, BPS, BPZ, BPFL, BPBP	BPA-$^{13}C_{12}$	Not used	1. Injection volume: 5 μL, 2. Column: Ascentis Express C18 (150× 2.1 mm, 2.7 μm), 3. Mobile phase: methanol with 0.01% ammonia (v/v)-water with 0.01% ammonia (v/v) (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-$^{13}C_{12}$: 239.1→224.0, BPA: 227.3→212.1, BPC: 255.3→240.15, BPE: 213.0→198.15, BPF: 199.3→93.0, BPG: 311.1→295.3, BPM: 345.0→330.2, BPP: 345.0→330.2, BPS: 249.0→108.1, BPZ: 267.1→173.1, BPFL: 349.1→256.1, BPBP: 351.1→274.2	[19]
LC-MS/MS	Urine	BPA, BPS, BPF, BPZ, BPB, BPAP, BPP, BPAF	BPA-$^{13}C_{12}$, BPS-$^{13}C_{12}$	Not used	1. Injection volume: 10 μL, 2. Column: Betasil C18 (100× 2.1 mm, 5 μm), 3. Mobile phase: methanol-water with 1% ammonium hydroxide (v/v) (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-$^{13}C_{12}$: 239→224, BPS-13C12: 261→114, BPA: 227→212, BPS: 249→108, BPF: 199→93, BPZ: 267→173, BPB: 241→212, BPAP: 289→274, BPP: 345→330, BPAF: 335→265	[40]
	Urine	BPA, BPS, BPAP, BPP, BPF, BPAF, BPZ.	BPA-d_{16}	Not used	1. Injection volume: 10 μL, 2. Column: Atlantis T3 dC18 (75× 2.1 mm, 3 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-d_{16}: 241.115→223.000, BPA: 227.017→212.151, BPS: 248.943→107.988, BPAP: 289.057→273.958, BPP: 345.123→329.968, BPF: 199.004→93.231, BPAF: 334.991→264.913, BPZ: 267.073→172.996	[41]
	Urine	BPA, BPS, BPF, BPB, BPAF	BPA-$^{13}C_4$, BPS-$^{13}C_4$, BPF-$^{13}C_4$, BPAF-$^{13}C_4$, BPB-$^{13}C_4$	Not used	1. Injection volume: 80 μL (on-line SPE), 2. Column: Zorbax Eclipse Plus C18 (50× 2.1 mm, 1.8 μm), 3. Mobile phase: acetonitrile-water with 1 mM ammonium fluoride (gradient mode), 4. Detector: MS	BPA-$^{13}C_4$: 239.2→224.0, BPS-$^{13}C_4$: 261.2→98.0, BPF-$^{13}C_4$: 211.1→99.1, BPAF-$^{13}C_4$: 347.1→277.1, BPB-$^{13}C_4$: 253.2→224.0, BPA: 227.3→212.0, BPS: 249.3→92.0, BPF: 199.2	[42]

Table 5 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
					(QqQ), ESI (negative)	→93.1, BPB: 241.3→212.1, BPAF: 335.2→265.0	
	Urine	BPA, BPB, BPAF, BPAP, BPE, BPF, BPP, BPS, BPZ	BPA-d_4, BPF-d_{10}, BPS-$^{13}C_{12}$, BPAF-$^{13}C_{12}$	Not used	1. Injection volume: NR, 2. Column: Acquity UPLC BEH C18 (100× 2.1 mm, 1.7 μm), 3. Mobile phase: methanol with 0.1% ammonium-water with 0.1% ammonium (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-d_4, 231.20→216.20, BPF-d_{10}, 209.15→97.10, BPS-$^{13}C_{12}$, 261.00→113.95, BPAF-$^{13}C_{12}$: 346.05→276.05, BPA, 227.00→212.00, BPB, 240.90→212.05, BPAF, 335.95→266.00, BPAP, 289.10→274.05, BPE, 212.95→198.00, BPF, 198.85→77.05, BPP, 345.05→330.15, BPS, 248.75→108.00, BPZ: 266.95→173.10	[43]
	Urine	BPA, BPS, BPP, BPZ, BPAP, BPB, BPAF	BPA-$^{13}C_{12}$, BPS-$^{13}C_{12}$	Not used	1. Injection volume: 5 μL, 2. Column: Betasil C18 (100× 2.1 mm, 3 μm), 3. Mobile phase: acetonitrile-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-$^{13}C_{12}$: 239.1→224.1, BPS-$^{13}C_{12}$: 261.1→114.0, BPA: 227.1→212.1, BPS: 249.1→108.0, BPP: 345.2→330.1, BPZ: 267.2→223.0, BPAP: 289.1→274, BPAF: 335.2→265.0, BPB: 241.1→212.2	[44]
	Urine	BPA	BPA-$^{13}C_{12}$	Not used	1. Injection volume: 30 μL, 2. Column: Symmetry Shield TM RP 18 (50× 2.1 mm, 3.5 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QIT), ESI (negative)	BPA-$^{13}C_{12}$: 239→144.9, BPA: 227→132.9	[20]
	Urine	BPA	BPA-$^{13}C_{12}$	Not used	1. Injection volume: 10 μL, 2. Column: Atlantis C18 (150× 2.1 mm, 5 μm), 3. Mobile phase: methanol with 5% acetonitrile (v/v)-water with 10 mM	BPA-$^{13}C_{12}$: 239→139, BPA: 227→133	[45]

Table 5 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
					ammonium acetate (gradient mode), 4. Detector: MS (QqQ), ESI (negative)		
	Saliva	BPA, BPS, BPAF, BPAP, BPP, BPZ	BPA-d_{16}	Not used	1. Injection volume: 10 μL, 2. Column: Atlantis T3 dC18 (75× 2.1 mm, 3 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-d_{16}: 241→223, BPA: 227→212, BPS: 249→107, BPAF: 335→264, BPAP: 289→273, BPP: 345→329, BPZ: 267→172	[89]
	Breast milk	BPA, BPF, BPS	BPA-d_{14}, BPF-d_{10}, BPS-d_8	Not used	1. Injection volume: 20 μL, 2. Column: Symmetry C18 column (150× 2.1 mm, 5 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), APCI (negative)	BPA-d_{14}: 241.2→ 141.9, BPF-d_{10}: 209.0→97.0, BPS-d_8: 257.0→ 112.0, BPA: 227.1 →133.0, BPF: 199.1→105.0, BPS: 249.1→ 108.0	[82]
	Infant urine	BPA	BPA-$^{13}C_{12}$	Not used	1. Injection volume: 10 μL, 2. Column: Shiseido ACR C18 column (150×2 mm, 3 μm), 3. Mobile phase: acetonitrile with 0.1% acetic acid-water with 0.1% acetic acid (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	NR	[48]
LC-MS/MS	Hair	BPA	BPA-d_{14}	Not used	1. Injection volume: 10 μL, 2. Column: Zorbax Eclipse XDB–C18 Rapid Resolution HT (50 ×4.6 mm, 1.8 μm), 3. Mobile phase: methanol-water with 5 mM ammonium acetate (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA: 227→133.0	[108]
	Urine		BPA-d_{16}	Not used			[49]

Table 5 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
		BPA, BPS, BPAP, BPP, BPF, BPAF, BPZ			1. Injection volume: 10 μL, 2. Column: Ascentis Express C18 (100 ×4.6 mm, 2.7 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-d_{16}: 241→223, BPA: 227→212, BPS: 249→108, BPAP: 289→274, BPP: 345→330, BPF: 199→93, BPAF: 335→265, BPZ: 267→173	
	Saliva	BPA and 12 bisphenol analogues and derivatives	BPA-$^{13}C_{12}$	Not used	1. Injection volume: 10 μL, 2. Column: ACE 3, C18-PFP (150× 3 mm, 3 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-$^{13}C_{12}$: 239→ 224.1, BPA: 227 →212.0, BPB: 241→212.0, BPE: 213→198.0, BPF: 199→93.0, BPP: 345→330.0, BPS: 249→108.0, BPZ: 267→173.0, BPZ: 267→173.0, BPAF: 335→ 265.0, BPAP: 289 →274.0	[90]
	Urine	BPA, BPF, BPS	BPA-d_{16}, BPF-d_{10}, BPS-d_8	Not used	1. Injection volume: 20 μL, 2. Column: Luna C18(2) (150× 2 mm, 5 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), APCI (negative)	BPA-d_{16}: 241.2→ 141.0, BPF-d_{10}: 209.0→97.0, BPS-d_8: 257.0→ 112.0, BPA: 227.1 →133.0, BPF: 199.0→105.1, BPS: 249.1→92.1	[50]
	Serum	BPA, BPS, BPF, BPE, BPB, BPZ, BPAF, BPAP	BPA-$^{13}C_{12}$, BPS-$^{13}C_{12}$, BPAF-$^{13}C_{12}$	DNS-Cl	1. Injection volume: NR, 2. Column: Hypersil GOLD C18 (150× 2.1 mm, 5 μm), 3. Mobile phase: acetonitrile-water (gradient mode), 4. Detector: MS (QqQ), ESI (positive)	BPA-$^{13}C_{12}$: 707→ 171, BPS-$^{13}C_{12}$: 729→171, BPAF-$^{13}C_{12}$: 815 →171, BPA: 695 →171, BPS: 717 →171, BPF: 667 →171, BPE: 681 →171, BPB: 709 →171, BPZ: 735 →171, BPAF: 803 →171, BPAP: 757 →171	[71]
	Breast milk	BPS, BPA, BADGE, BADGE-2-H_2O, BADGE-2-HCl	BPA-d_{16}	Not used	1. Injection volume: 10 μL, 2. Column: Poroshell 120 EC-C18 (100× 3 mm, 2.7 μm), 3. Mobile phase: acetonitrile and water with 5 mM ammonium acetate (9:1,	BPA-d_{16}: 241→225, BPS: 249→108, BPA: 227→212, BADGE: 358→ 191, BADGE-2H_2O: 394→209, BADGE-2HCl: 430→227	[83]

Table 5 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
					v/v)-water with 5 mM ammonium acetate (gradient mode), 4. Detector: MS (QqQ), ESI (negative for BPs and positive for BADGEs)		
	Breast milk	BPA, BPF, BPS	BPA-d_{16}, BPF-d_{10}, BPS-d_8	Not used	1. Injection volume: 10 μL, 2. Column: Scherzo SM-C18 (100× 3 mm, 2.7 μm), 3. Mobile phase: acetonitrile with 50 mM formic acid-water with 50 mM formic acid (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-d_{16}: 241→225, BPF-d_{10}: 209→199, BPS-d_8: 249→257, BPA: 227→212, BPF: 209→199, BPS: 249→108	[84]
LC-MS/MS	Urine	BPA, BPF, BPS	BPA-$^{13}C_{12}$, BPS-$^{13}C_{12}$, BPF-$^{13}C_{12}$	Not used	1. Injection volume: 5 μL, 2. Column: Kinetex Phenyl-Hexyl (100 ×2.1 mm, 1.7 μm), 3. Mobile phase: methanol-water with 0.2 mM ammonium fluoride and 10% methanol (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-$^{13}C_{12}$: 239→139, BPS-$^{13}C_{12}$: 261→98.0, BPF-$^{13}C_{12}$: 205→99.0, BPA: 227→133, BPF: 199→93.0, BPS: 249→92.0	[51]
	Serum	BPA, BPS, BPF, BPP, BPZ, BPB, BPAF, BPAP	BPA-d_{16}, BPAF-d_4	Not used	1. Injection volume: 5 μL, 2. Column: BETASIL C18 (100×2.1 mm, 5 μm), 3. Mobile phase: acetonitrile-water with 0.05% acetic acid (v/v) (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-d_{16}: 241→223, BPAF-d_4: 339→269, BPA: 227→133, BPS: 249→108, BPF: 199→93, BPP: 345→330, BPZ: 267→173, BPB: 241→212, BPAF: 335→265, BPAP: 289→274	[72]
	Plasma	BPA	BPA-d_{16}	Not used	1. Injection volume: 2 μL, 2. Column: Gemini-NX C18 (150×2 mm, 5 μm), 3. Mobile phase: methanol-water with 2 mM of	BPA-d_{16}: 240.877→142.100, BPA: 227.119→211.700	[75]

Table 5 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
					ammonium acetate (gradient mode), 4. Detector: MS (QIT), ESI (negative)		
	Urine	BPA, BPF, BPS, BPZ, BPP, BPAF, BPAP	BPA-d_{16}	Not used	1. Injection volume: 10 μL, 2. Column: Brownlee Aq C18 (100×4.6 mm, 5 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-d_{16}: 241.115→223.000, BPA: 227.017→212.151, BPF: 199.004→93.231, BPS: 248.943→107.990, BPZ: 267.073→172.996, BPP: 345.123→329.968, BPAF: 334.991→264.913, BPAP: 289.057→273.958	[52]
	Plasma	BPA, MCBPA, DCBPA, TCBPA, TTCBPA	BPA-d_{16}, DCBPA-d_{12}	Not used	1. Injection volume: 20 μL, 2. Column: Acquity CSH C18 (100×2.1 mm, 1.7 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-d16: 241.078→222.900, DCBPA-d12: 306.988→224.900, BPA: 226.967→211.800, MCBPA: 260.896→181.700, DCBPA: 294.869→243.700, TCBPA: 364.794→313.700, TTCBPA: 328.713→249.700	[76]
	Serum, urine, follicular fluid	BPA	BPA-$^{13}C_{12}$	Not used	1. Injection volume: 6 μL, 2. Column: Zorbax Eclipse Plus C18 (50×2.1 mm, 1.8 μm), 3. Mobile phase: methanol and acetonitrile (1:1, v/v)-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-$^{13}C_{12}$: 239→224, BPA: 227→212	[53]
	Urine	BPA, BPS, BPF, BPB	BPA-d_{16}, BPF-d_{10}, BPS-d_8	MIS-2-Cl	1. Injection volume: NR, 2. Column: BEH C18 (100×2.1 mm, 1.7 μm)3. Mobile phase: acetonitrile-water with 0.1% of formic acid (gradient mode), 4. Detector: MS	NR	[54]

Table 5 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
					(QqQ), ESI (positive)		
LC-MS/MS	Urine	BPA	BPA-d_8	Not used	1. Injection volume: 2 μL, 2. Column: Accucore Phenyl-X (150× 2.1 mm, 2.6 μm), 3. Mobile phase: acetonitrile with 0.02% acetic acid-water with 0.02% acetic acid (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-d_8: 235.0→220.0, BPA: 227.0→212.0	[55]
	Breast milk	BPA, BPS, BPF, BPAF	BPA-$^{13}C_{12}$, BPS-$^{13}C_{12}$	Not used	1. Injection volume: 10 μL, 2. Column: BEH Shield RP C18 (100×2.1 mm, 1.7 μm), 3. Mobile phase: methanol-water with 2 mM ammonium acetate (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-$^{13}C_{12}$, 239→224, BPS-$^{13}C_{12}$: 261→114, BPA: 227→212, BPS: 249→108, BPF: 199→77, BPAF: 335→265	[85]
	Urine	BPA, BPS, BPF	BPA-d_{16}	Not used	1. Injection: LVI (on-line SPE), 2. Column: ACE 5 sp;2.1 mm, 5 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), APCI (negative)	BPA-d_{16}: 241.1→142.2, BPA: 227.1→113.2, BPS: 249.1→91.9, BPF: 199.4→105.1	[57]
	Plasma, urine	BPS, BPS-G	BPS-d_8, BPS-G-d_8	For urine: DNS-Cl	1. Injection: LVI (on-line SPE), 2. Column for plasma: Acquity CSH C18 (100× 2.1 mm, 1.7 μm), 3. Column for urine: Acquity Phenyl-Hexyl (100 ×2.1 mm, 1.7 μm), 4. Mobile phase: acetonitrile-water (gradient mode), 5. Detector: MS (QqQ), ESI (positive for urine, negative for plasma)	BPS-d_8: 257.10→112, BPS-G-d8: 433.16→257, BPS: 249.10→108, BPS-G: 425.16→249, Dn-BPS-d8: 725→171, Dn-BPS-G-d8: 668→171	[58]

Table 5 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
	Serum	BPS, BPF, BPB, BPZ, BPAP, BPP, BPAF, TBBPA, TBBPS, TCBPA	BPAF-d_4, TBBPA-d_{10}	Not used	1. Injection volume: 5 μL, 2. Column: Symmetry C18 (150×2.1 mm, 3.5 μm), 3. Mobile phase: methanol-water with 2 mM ammonium acetate (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPAF-d_4: 339→269, TBBPA-d_{10}: 553→427, BPS: 249→108, BPF: 199→105, BPB: 241→212, BPZ: 267→173, BPAP: 289→274, BPP: 345→330, BPAF: 335→265, TBBPA: 542.8→418, TBBPS: 564.6→485, TCBPA: 365→314	[73]
	Urine	TBBPA	TBBPA-$^{13}C_{12}$	Not used	1. Injection volume: 10 μL, 2. Column: Poroshell 120 EC-C18 (100×4.6 mm, 2.7 μm), 3. Mobile phase: acetonitrile-water with 5 mM ammonium acetate (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	TBBPA-$^{13}C_{12}$: 555.0→79.0, TBBPA: 543.0→79.0	[59]
LC-MS/MS	Plasma, placenta	16 bisphenol analogues	BPA-$^{13}C_{12}$, BPS-$^{13}C_{12}$, BPF-$^{13}C_{12}$, BPAF-$^{13}C_{12}$, BPB-$^{13}C_{12}$, TBBPA-$^{13}C_{12}$	Not used	1. Injection volume: 5 μL, 2. Column: XBridge C18 (100×2.1 mm, 3.5 μm), 3. Mobile phase: methanol-water with 0.5 mM ammonium acetate (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-$^{13}C_{12}$: 239.1→224.1, BPS-$^{13}C_{12}$: 261.0→114.0, BPF-$^{13}C_{12}$: 211.0→105.0, BPAF-$^{13}C_{12}$: 346.8→277.0, BPB-$^{13}C_{12}$: 253.2→224.1, TBBPA-$^{13}C_{12}$: 554.8→81.0, BPA: 227.1→211.9, BPAF: 334.8→265.0, BPAP: 289.2→274.1, BPE: 213.1→197.0, BPC: 254.8→147.0, BPP: 345.2→315.2BPZ: 267.1→173.1, BPM: 345.2→251.1BPB: 241.2→212.1, BPF: 199.0→93.0, BPS: 248.8→108.0	[77]
	Hair	BPS	Thiabendazole-$^{13}C_6$		1. Injection volume: NR, 2. Column: NR, 3. Mobile	NR	[110]

Table 5 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
					phase: NR, 4. Detector: NR		
	Urine	BPA, BPS, BPAP, BPAF	BPA-d_{16}	Not used	1. Injection volume: 10 μL, 2. Column: Atlantis T3 dC18 (75× 2.1 mm, 3 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-d_{16}: 241.115→ 223.000, BPA: 227.017→ 212.151, BPS: 248.943→ 107.988, BPAP: 289.057→ 273.958, BPAF: 334.991→ 264.913	[61]
	Urine	BPA, BPS, BPF, BPB, BPAF	BPA-$^{13}C_4$, BPS-$^{13}C_4$	Not used	1. Injection volume: NR, 2. Column: Kinetex F5 (125× 4.6 mm, 2.6 μm)3. Mobile phase: methanol with 0.1% acetic acid and 5% water-water with 0.1% acetic acid and 1% methanol (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA: 227.0→133.0, BPS: 249.1→ 92.0, BPF: 199.0 →105.0, BPB: 241.1→211.0, BPAF: 335.0→ 265.0	[63]
	Breast milk	BPA, BPS, BPF, BPB	Not used	Not used	1. Injection volume: 5 μL, 2. Column: Zorbax Eclipse XDB-C18 (50× 4.6 mm, 1.8 μm), 3. Mobile phase: acetonitrile with ammonium acetate buffer 5 mM (9:1, v/v)-water with 5 mM ammonium acetate (gradient mode), 4. Detector: MS (QTOF), ESI (negative)	NR	[86]
LC-MS/MS	Plasma	BPA, BPB, BPF, BPS, BPAF	Not used	Not used	1. Injection volume: 2 μL, 2. Column: Gemini-NX C18 (150×2 mm, 5 μm), 3. Mobile phase: methanol-water with 2 mM ammonium acetate (gradient mode), 4. Detector: MS (QIT), ESI (negative)	NR	[78]
	Urine, serum, amniotic fluid	BPA, BPS, BPZ, BPAF,	BPA-$^{13}C_{12}$, BPS-$^{13}C_{12}$, BPAF-$^{13}C_{12}$	Not used	1. Injection volume: 10 μL, 2. Column: Betasil	BPA: 227→212, BPS: 249→108, BPZ: 267→173,	[65]

Table 5 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
		BPAP, BPP, BPB			C18 (100× 2.1 mm, 5 μm), 3. Mobile phase: methanol-water with 0.1% formic acid (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPAF: 335→265, BPAP: 289→274, BPP: 345→330, BPB: 241→211	
	Urine	BPA	BPA-$^{13}C_{12}$	Not used	1. Injection volume: 20 μL, 2. Column: Agilent Pursuit 3 pentafluorophenyl propyl (100× 3 mm, 3 μm), 3. Mobile phase: methanol-water with 2 mM ammonium acetate (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA-$^{13}C_{12}$: 239.2→224.1, BPA: 227.0→132.8	[25]
	Urine	21 compounds: Bisphenols, chlorinated derivatives, and bisphenol diglycidyl ethers	BPA-$^{13}C_{12}$, BADGE-d_6	Not used	1. Injection volume: 10 μL, 2. Column: ACE 3 C18-PFP (150× 3 mm, 3.5 μm), 3. Mobile phase: methanol-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative for Bisphenols, chlorinated derivatives), ESI (positive for diglycidyl ethers)	BPA-$^{13}C_{12}$: 239→224.1, BADGE-d_6: 364→197.2, BPA: 227→212.0, BPB: 241→212.0, BPE: 213→198.0, BPF: 199→93.0, BPP: 345→329.9, BPS: 249→108.0, BPZ: 267→172.9, BPAF: 335→264.9, BPAP: 289→273.9, BADGE: 359→190.9, BADGE-2H2O: 394→209.0, BADGE-2HCl: 430→227.1	[23]
LC-MS/MS	Breast milk	BPA, BPS, BPF, BPAF	Not used	Not used	1. Injection volume: 5 μL, 2. Column: Hypersil Gold C18 (100× 2.1 mm, 1.9 μm), 3. Mobile phase: acetonitrile-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	BPA: 227→133, BPS: 249→108, BPF: 199→93, BPAF: 335→265	[87]
	Plasma	BPA-G, BPF-G, BPS-G	BPS-G-d_8, BPA-G-$^{13}C_{12}$	DNS-Cl	1. Injection: LVI (on-line SPE), 2. Column: Acquity UPLC CSH	Dn-BPS-G-d_8: 668→492, Dn-BPA-G-$^{13}C_{12}$: 650→474,	[79]

Table 5 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
					Phenyl-Hexyl (100 ×2.1 mm, 1.7 μm), 3. Mobile phase: acetonitrile with 0.1% formic acid-water with 0.1% formic acid (gradient mode), 4. Detector: MS (QqQ), ESI (positive)	Dn-BPA-G: 638→462, Dn-BPF-G: 610→434, Dn-BPS-G: 660→484	
	Urine, hair	BPZ, BPP, BPM, BPS, BPF, BDP, TBBPA, BPAP, BPAF, BPDP	BPA-$^{13}C_{12}$	Not used	1. Injection: 10 μL, 2. Column: Eclipse plus C18, (100×2.1 mm, 3.5 μm), 3. Mobile phase: acetonitrile-water (gradient mode), 4. Detector: MS (QqQ), ESI (negative)	NR	[67]

NR data not reported, *LC-MS* liquid chromatography coupled to mass spectrometry; *LC-MS/MS* liquid chromatography coupled to tandem mass spectrometry; *ESI* electrospray ionization; *APCI* atmospheric pressure chemical ionization; *QqQ* triple quadrupole; *TOF* time of flight; *QIT* quadrupole ion trap; *LVI*large-volume injection; *on-line SPE*on-line solid-phase extraction; *DNS-Cl* dansyl chloride; *PSCl*pyridine-3-sulfonyl chloride; *MIS-2-Cl*1-methylimidazole-2-sulfonyl chloride; *Dn* derivatized with dansyl chloride; *Ps* derivatized with pyridine-3-sulfonyl chloride

volatility of BPs, liquid chromatography (LC) is a suitable technique for their detection, and as can be seen in Fig. 3, LC coupled to tandem mass spectrometry (LC-MS/MS) is the most used chromatographic technique for their determination. As can be seen in Tables 5 and 7, reversed phase chromatography with C18 columns were the most used by far in the analysis of BPs, although a variety of other columns have also been used such as C8 [13], C12 [28], amide [18], phenyl-hexyl [51, 58, 79], phenyl-X [55], pentafluorophenyl [25, 62], and C18-pentafluorophenyl [57]. Most of the works presented here use a binary mobile phase with methanol-water delivered in gradient mode [20, 23, 27, 34, 52, 65, 70, 76, 82, 88, 105, 107, 111]. However, the use of acetonitrile and water is also very common and has been employed in several works [15, 18, 39, 42, 48, 54, 55, 71, 79–81, 83, 87, 106, 109]. To obtain satisfactory ionization and improved sensitivity, the following have been used: ammonium acetate [18, 59, 69, 73, 75, 77, 83, 85, 105, 108], ammonium hydroxide [10, 19, 31, 40, 43, 70, 80], ammonium fluoride [42, 51, 79, 109], formic acid [54, 65, 81, 84], or acetic acid [28, 39, 48, 55, 62, 72] is often included as a mobile phase additive (see Table 5).

LC-MS/MS has been mainly used with the electrospray ionization (ESI) source either in negative mode for underivatized BPs and chlorinated derivatives [18, 27, 45, 52, 67, 70, 88, 89, 92] or positive mode for derivatized BPs and BADGEs [11, 23, 71, 81, 83], although atmospheric pressure chemical ionization (APCI) in negative mode [50, 57, 82, 107, 109] has been used in some cases. The MS analyzer most used by far is triple quadrupole (QqQ), although single quadrupole [107], quadrupole ion trap (QIT) [20, 34, 75, 78], and quadrupole time of flight QTOF [86] have also been used.

Regarding GC, it has been extensively coupled to MS as is presented in Table 6 [22, 26, 29, 32, 33, 36, 37, 46, 91]; more sophisticated GC-MS/MS has also been used but in less often [10, 21, 35, 56, 110]. For the analytes' injection, besides splitless mode, which is the most used, other modes applied in BPs' analysis include split [26, 32], pulsed splitless mode [21, 29, 56, 110], and programmed temperature vaporizer (PTV) [36]. The columns commonly used in the GC separation of BPs have a non-polar stationary phase with 5%-diphenyl/95%-dimethylpolysiloxane and low bleed characteristics (ZB-5, DB-5 MS, HP-5 MS, Rtx-5 Sil MS, and VF-5 MS); other column used was ZB-XLB with stationary phase 5% silphenylene (Si-arylene) silicone polymer which has alternative selectivity to standard 5-type phases [37]. The column dimensions are usually 30 m × 0.25 mm × 0.25 μm, although a

Table 6 Chromatographic conditions of the methods using GC coupled to MS and tandem MS used to determine bisphenol analogues in biological samples

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
GC-MS	Urine, whole blood, breast milk	BPA	Triphenyl phosphate	BSTFA + 1% TMCS	1. Injector: split mode (1:20 ratio), injection volume of 1 μL, 2. Column: DB-5 MS (30 m×0.25 mm, 0.25 mm), 3. Detector: MS (quadrupole), EI	NR	[26]
	Urine	BPA, BPF	BPZ	Acetic anhydride (in situ derivatization)	1. Injector: pulsed splitless mode, injection volume of 2 μL, 2. Column: HP-5 MS (30 m×0.25 mm, 0.25 mm), 3. Detector: MS (quadrupole), EI	BPF: 107, 242, BPA: 228, 270	[29]
	Urine	BPA	BPA-d_{16}	BSTFA + 1% TMCS	1. Injector: split mode (1:3 ratio), injection volume of 1 μL, 2. Column: HP-5 MS (30 m×0.25 mm, 0.25 mm), 3. Detector: MS (quadrupole), EI	BPA-d_{16}: 368, 386, 217, BPA: 357, 372, 177	[32]
	Urine	BPA	Not used	BSTFA + 1% TMCS	1. Injector: splitless mode, injection volume: NR, 2. Column: DB-5 MS (60 m× 0.25 mm, 0.25 mm), 3. Detector: MS (quadrupole), EI	357, 372, 207	[33]
	Urine	BPA	BPA-d_{16}	TBAOH (Injection port butylation)	1. Injector: injection volume of 10 μL (PTV), 2. Column: DB-5 MS (30 m× 0.25 mm, 0.25 mm), 3. Detector: MS (ion trap), EI	Bu-BPA-d_{16}: 337, Bu-BPA: 325	[36]
	Urine	BPA	BPA-$^{13}C_{12}$	BSTFA + 1% TMCS	1. Injector: splitless mode, injection volume of 2 μL, 2. Column: ZB-XLB (30 m× 0.25 mm, 0.25 mm), 3. Detector: MS (ion trap), EI	BPA-$^{13}C_{12}$: 364, 383, BPA: 357, 372	[37]
	Plasma	BPA	BPA-d_6	BSTFA + 1% TMCS	1. Injector: splitless mode, injection volume of 1 μL, 2. Column: Rtx-5 Sil MS (30 m× 0.25 mm, 0.25 mm), 3. Detector: MS (quadrupole), EI	BPA-d_6: 360, 378, BPA: 357, 372	[22]
GC-MS	Urine, blood	BPA, BPS, BPF, BPB, BPAF, BPZ, BPE, BPAP	BPA-d_{16}	In situ derivatization with acetic anhydride	1. Injector: splitless mode, injection volume of 1 μL, 2. Column: DB-5MS (30 m× 0.25 mm, 0.25 mm), 3. Detector: MS (quadrupole), EI	BPA-d_{16}: 224, 242, 284, 266, 326, BPA: 213, 228, 255, 270, 312, BPS: 250, 334, 292, 141, 186, BPF: 200, 284, 242, 152, 107, BPB: 213, 255, 297, 281, 326, BPAF: 267, 420, 336, 359, 197, BPZ: 268, 352, 310, 225, 251, BPE: 199, 256, 298, 214, 241, BPAP: 275, 317, 312, 359, 374	[46]
	Saliva	BPA	Not used	BSTFA + 1% TMCS	1. Injector: splitless mode, injection volume: NR, 2. Column: HP-5 MS (30 m× 0.25 mm, 0.25 mm), 3. Detector: MS (ion trap), EI	357, 372, 207	[91]
	Urine	BPA	NR	BSTFA	NR	NR	[60]
GC-MS/MS	Plasma, urine	BPA	BPA-d_{16}, pyrene-d_{10}	BSTFA + 1% TMCS	1. Injector: splitless mode, injection volume of 2 μL, 2. Column: VF-5 MS (30 m×	pyrene-d_{10}: 212→208, BPA-d16-TMS: 368→73, BPA-TMS: 357→73	[10]

Table 6 (continued)

Instrumental analysis	Matrix	Analytes	Internal standard	Derivatization	Instrumental conditions	MS/MS transition (quantifier) or SIM ions	Reference
					0.25 mm, 0.25 mm), 3. Detector: MS (QqQ), EI		
	Urine, peritoneal fluid	BPA	BPA-d_{16}	BSTFA + 1% TMCS	1. Injector: splitless mode, injection volume of 1 μL, 2. Column: ZB-5 (30 m × 0.25 mm, 0.25 mm), 3. Detector: MS (ion trap), EI	BPA-d_{16}: 368.2→197.5BPA: 357.10→191.5	[35]
	Urine	BPAF, BPF, BPA, BPB, BPZ, BPS, BPAP	BPA-$^{13}C_{12}$, BPF-$^{13}C_{12}$, BPS-$^{13}C_{12}$, BPB-$^{13}C_{12}$	BSTFA	1. Injector: pulsed splitless mode, injection volume of 1 μL, 2. Column: DB-5 MS (30 m × 0.25 mm, 0.25 mm), 3. Detector: MS (QqQ), EI	BPAF: 480.3→411.2, BPF: 344.2→179.2, BPA: 357.2→191.2, BPB: 386.2→357.2, BPZ: 412.3→203.2, BPS: 394.2→229.2, BPAP: 419.3→341.2	[56]
	Hair	BPA, BPS	BPA-d_{16}	PFBBr	1. Injector: pulsed splitless mode, injection volume of 2 μL, 2. Column: HP-5 MS (30 m × 0.25 mm, 0.25 mm), 3. Detector: MS (QqQ), CI (negative)	NR	[110]
	Urine	BPA, BPF, BPS	BPA-d_4, BPF-$^{13}C_{12}$, BPS-$^{13}C_{12}$	MSTFA	1. Injector: pulsed splitless mode, injection volume of 2 μL, 2. Column: DB-5 MS (30 m × 0.25 mm, 0.25 mm), 3. Detector: MS (QqQ), EI	BPA-d_4: 386>368, BPF-$^{13}C_{12}$: 356>185, BPS-$^{13}C_{12}$: 406>391, BPA: 357>191, BPF: 344>179, BPS: 394>379	[21]

NR data not reported, *GC-MS* gas chromatography coupled to mass spectrometry; *GC-MS/MS* gas chromatography coupled to tandem mass spectrometry; *EI* electron ionization; *QqQ* triple quadrupole; *TOF* time of flight; *QIT* quadrupole ion trap; *FLD* fluorescence detector; *PTV* programmed temperature vaporization; *BSTFA* N,O-bis(trimethylsilyl)trifluoroacetamide; *MSTFA* N-methyl-N-(trimethylsilyl)trifluoroacetamide; *TBAOH* tetrabutyl ammonium hydroxide; *PFBBr* 2,3,4,5,6-pentafluorobenzyl bromide; *Bu* derivatized with tetrabutyl ammonium hydroxide

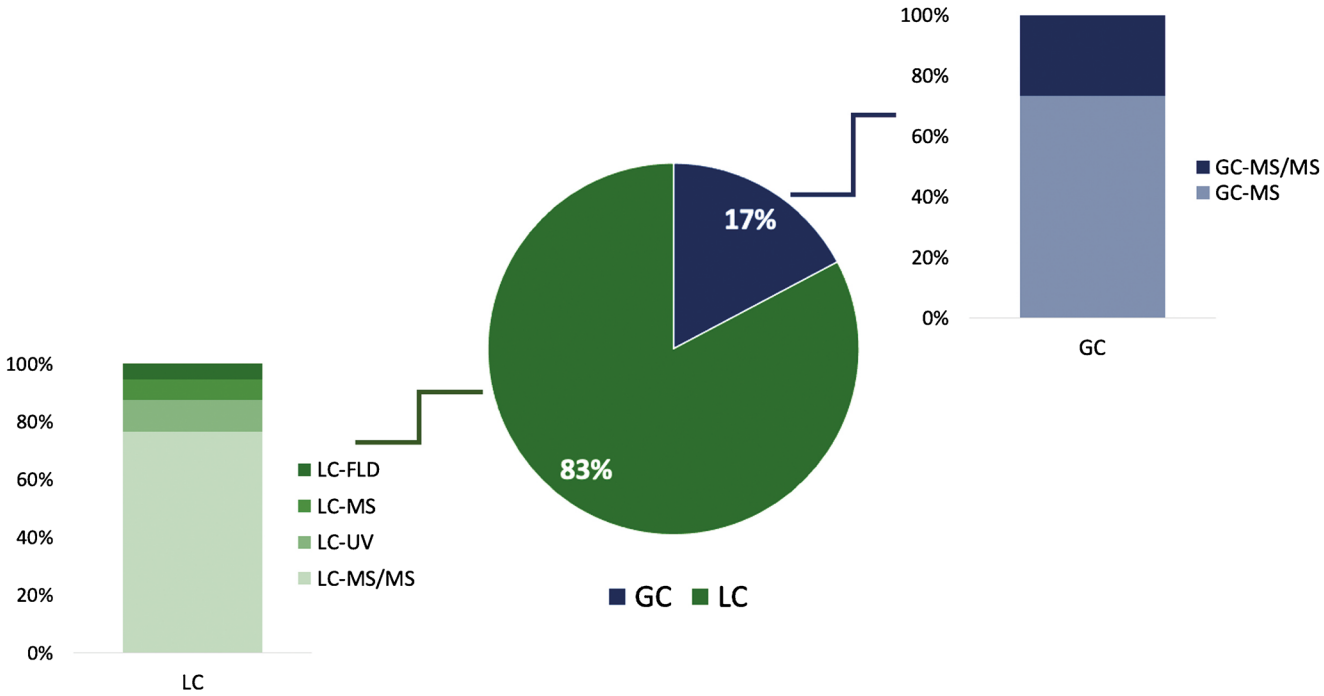

Fig. 3 Chromatographic analysis used in the methods for BPs bioanalysis

longer column was used to achieve better separation between BPA and eight phthalates [33]. The most common source for MS is electron ionization (EI) and on scarce occasions chemical ionization (CI) is used [110]. The mass analyzers single quadrupole, ion trap, and triple quadrupole (QqQ) have all been used in GC-MS and GC-MS/MS study of BPs; although time of flight (TOF) is commercially available, it has not been applied recently for the analysis of BPs.

Method performance

Initial method validation will provide parameters of method performance, such as accuracy, precision, LOQs, and LODs. Continual use of QC samples (e.g., method blank and spiked samples) are not only important to monitor and to maintain the routine performance of the method but also important to ensure that there is minimal matrix effect for the samples analyzed.

Matrix effect

The most outstanding limitation of chromatography systems coupled to MS is the susceptibility of interfaces to co-extract matrix components, which can strongly vary with the matrix affecting the data quality and result in poor analytical accuracy and precision. The matrix effect (ME) refers to a difference in MS response for an analyte in a standard solution versus the response for the same analyte in a biological matrix. It might be caused by the interaction between the target analytes and those co-extracted matrix components during sample preparation and in the ionization chamber, which can affect chromatographic behavior and the ionization of target compounds, resulting in ion suppression or enhancement [12, 115].

Regarding LC-MS (or tandem MS), ESI is the most commonly used for trace analysis of BPs in biological samples; although it is the most susceptible to signal suppression and enhancement by matrix components, this matrix effect can be compensated using isotopically labeled compounds. APCI may be an alternative ionization interface to ESI since it has been reported to be generally less sensitive to the ME because is less susceptible to ion suppression, but it is not widely used due to a decreased sensitivity. APCI also needed the use of surrogate standards for some analytes to compensate for significant ion enhancement. On the other hand, in GC-MS the enhancement or decrease in the analytes' response can be produced in the injector, column, or ionization chamber. ME can be caused by a blockage of active sites in the injector by matrix components, which prevents thermal degradation/adsorption of the analytes, or in the analytical column, which results in a faster elution of the analytes with a sharper peak shape [12].

It is essential to address this issue when developing and validating analytical methods in biological matrices, and there are various ways to appraise the ME [115].

Battal et al. evaluated the ME for BPA in urine using LLE and LC-ESI-MS/MS at three different concentrations (50,

Table 7 Chromatographic conditions of the LC methods with UV, DAD, and FLD detectors to determine bisphenol analogues in biological samples

Instrumental analysis	Matrix	Analytes	Instrumental conditions	Reference
LC-UV	Breast milk	BPA	1. Injection volume: 20 μL. 2. Column: Intertsil C8 (250×4.0 mm, 5 μm). 3. Mobile phase: acetonitrile-water (67:33, v/v) (isocratic mode). 4. Detector: UV (230 nm)	[13]
	Urine	BPA	1. Injection volume: 10 μL. 2. Column: Unitary C18 (250×4.6 mm, 5 μm). 3. Mobile phase: methanol-water (55:45, v/v) (isocratic mode). 4. Detector: UV (270 nm)	[64]
	Urine	BPA	1. Injection volume: NR. 2. Column: EC-C18 (250×4.6 mm, 4 μm). 3. Mobile phase: acetonitrile-water (isocratic mode). 4. Detector: UV (NR)	[68]
LC-DAD	Human urine	BPA	1. Injection volume: 20 μL. 2. Column: Zorbax SB-C18 (250×4.6 mm, 5 μm). 3. Mobile phase: methanol-water (65:35, v/v) (isocratic mode). 4. Detector: UV (225 nm)	[14]
	Urine, serum	BPS, BPA, BPC, BPZ, BPM, BPAF, BPAP, BPBP	1. Injection volume: 10 μL. 2. Column: Kinetex Biphenyl (150×4.6 mm, 5 μm). 3. Mobile phase: methanol-water (gradient mode). 4. Detector: UV (230 nm)	[47]
	Urine	BPA, BPAP, BPAF, BPP	1. Injection volume: 20 μL. 2. Column: Synergy™ Fusion-RP C18 (250×4.6 mm, 4 μm). 3. Mobile phase: acetonitrile-water (gradient mode). 4. Detector: UV (210 nm)	[15]
	Urine	BPA	1. Injection volume: 10 μL. 2. Column: Zorbax SB-C18 (250×4.6 mm, 5 μm). 3. Mobile phase: methanol-water (60:40, v/v). (isocratic mode). 4. Detector: UV (224 nm)	[66]
LC-FLD	Hair	BPA	1. Injection volume: NR. 2. Column: HYPERSIL Gold C18 PAH (250×4.6 mm, 5 μm). 3. Mobile phase: acetonitrile-water (gradient mode). 4. Detector: FLD (emission: NR, excitation: NR)	[16]
	Serum, urine	BPA	1. Injection volume: NR, 2. Column: XDB-C18 (Dimensions: NR), 3. Mobile phase: acetonitrile-water (50:50, v/v) (isocratic mode), 4. Detector: FLD (excitation 229 nm, emission: 315 nm)	[17]
	Urine, serum	BPE, BPF, BPAP, BFDGE-$2H_2O$	1. Injection volume: 20 μL, 2. Column: Zorbax Eclipse SB-C18 (150×4.6 mm, 5 μm), 3. Mobile phase: acetonitrile-water (gradient mode), 4. Detector: FL (excitation: 280 nm, emission: 310 nm)	[62]

Internal standard and derivatization were not used in the studies

NR data not reported; *LC-UV* liquid chromatography with ultraviolet detector; *LC-DAD* liquid chromatography with diode array detector; *LC-FLD* liquid chromatography with fluorescence detector

200, and 400 ng/mL). Various lots of real matrices (n = 6) were used to calculate the relative ME, which was expressed as CV% of the slopes of the calibration curves. They concluded no matrix effect was observed because it was less than ± 13.6% [25].

Caballero-Casero and Rubio developed a method to analyze BPs, their chlorinated derivatives, and BADGEs in urine using SUPRAS-based extraction and LC-ESI-MS/MS; the ME was calculated by measuring signal suppression or enhancement (SSE) by comparing mass response for analytes in samples and standards in solvent mixtures. The SSE calculated in this manner may be referred to as an absolute ME; percentages higher than 100 indicate ion enhancement, while percentages lower than 100 are indicative of ion suppression. SSE values obtained were in the range 88–110%; the signal was within the interval recommended for analysis of contaminants (e.g., 70–120%) indicating no matrix effect was observed and the method is matrix-independent [23].

Cambien et al. developed a method to determine BPA and its chlorinated derivatives in plasma using SPE followed by LC-ESI-MS/MS. They evaluated the ME as the ratio of the relative areas of the analytes in the blank plasma extract and standard solutions and found ME were low to moderate from 54 to 99%. However, they were satisfactorily corrected with the internal standards [76].

Brigante et al. investigated the matrix effect for BPA in urine using GC-EI-MS; they employed six lots of blank urine to calculate a matrix factor (MF) for each matrix lot by calculating the ratio between the peak area of the analyte in the presence of the matrix and the peak area of the analyte in the absence of the matrix, at low and high BPA concentrations (100 and 200 ng/mL). The IS-normalized MF was also calculated by dividing the analyte MF by the IS MF. The CV of the IS-normalized MF calculated from the matrix lots should not be greater than 15%; they concluded no matrix effect was found because CV was 7.8% and 13.9% for low and high concentrations, respectively [32].

Accuracy and precision

Significant differences in the physicochemical properties of BPs, chlorinated derivatives, and BADGEs lead to a wide range

of recovery rates in multi-residue methods, and low RSDs (< 20%) and high recovery rates (between 80% and 120%) were achieved for most of the compounds in most of the methods and matrices here reported (see Tables 1, 2, 3, and 4).

Precision is concentration dependent and most of the methods measured it at different concentrations, commonly at two or three levels, and typically, the better precision was obtained at a higher level. Remarkably, acceptable precision was obtained even though most of the methods evaluated it at trace level.

Authors often look for a compromise, seeking the conditions for obtaining good recoveries for most compounds. Grignon et al. determined BPA and its chlorinated derivatives in urine, and the obtained recoveries varied from 54.7 to 75.7%, with the lower values obtained for the chlorinated derivatives [27]. Martín et al. developed a method to determine BPA and other endocrine-disrupting compounds in hair and obtained BPA recoveries from 77 to 82%, being 77 ± 5% for the lower level evaluated (0.25 mg/g) [105]. Brigante et al. determined BPA in urine, even though MIPs were employed to improve selectivity, recovery was around 50% [32]. Song et al. developed a method to determine eight BP analogues in urine; the lowest recoveries (around 69%) were obtained for the chlorinated compound and BPF [69]. Tuzimski et al. developed a method to analyze BPA, BPF, BPS, BPB, and BADGEs and in breast milk, but the method was not suitable for all analytes because very low recoveries were obtained for BPB (around 15%), and BADGEs (< 10%) [84].

Limits of detection and quantitation

Analysis of BPs and derivatives in biological samples is a difficult task, as is hard to get low LODs and LOQs for all the analytes, especially taking into account the physicochemical differences between them.

Tables 1, 2, 3, and 4 summarize the LODs and LOQs obtained in each study; the limits obtained were in the sub-ng/g or ng/mL range despite the presence of BPs in blanks due to the ubiquity of these compounds. LODs and LOQs are highly dependent on the matrix analyzed; most of the methods reported both parameters, and others only one of them to show the sensitivity of the methods, mainly LOD, but some studies presented here without even reporting how the limits were calculated. It is recommended to state LOQ for best evaluation of method performance since this parameter with adequate precision and accuracy determines their suitability.

Future perspectives

There is a need to develop more analytical methods for the biomonitoring of mixtures of bisphenols, chlorinated derivatives, and BADGEs, and optimizing especially the recovery of chlorinated derivatives which are difficult to extract. SUPRAS-based methods seem promising for this purpose, but they only have been tested in matrices with low lipid content like urine, serum, and saliva. As far as we know, microextraction techniques very popular for liquid samples, like solid-phase microextraction (SPME) and stir bar sorptive extraction (SBSE), and matrix-solid-phase dispersion (MSPD) for solid samples, have not been recently used for BPs in biological samples.

Finally, capillary electrophoresis (CE) is an instrumental technique that has not been recently explored for the analysis of BPs in biological matrices, despite its many advantages as high separation efficiency, short analysis times, low waste generation, and its versatility for the analysis of diverse types of analytes (cationic, anionic, and neutral). In addition, it offers a wide range of separation modes in combination with various detection techniques like UV detector or MS.

Conclusions

As interest grows in biomonitoring for assessing human exposure to BPs and their derivatives, demand increases for analytical methods to identify and to quantify them in biological matrices. Within this field, the methods able to determine simultaneously multiple compounds with different physicochemical properties (e.g., BPs, chlorinated derivatives, and BADGEs) are scarce. This could be a future trend in this area of analytical chemistry. Sample preparation for liquid biological samples is dominated by SPE, with conventional silica-bonded sorbents and polymeric materials. One trend for these types of methods is the development of on-line techniques for rapid analyses. On the other hand, ultrasound-assisted extraction is the most used for solid biological samples, because of its high extraction efficiency, although classic SLE continues to be used due to its simplicity.

LC-MS/MS is the prevailing technique for quantifying and confirming the analytes in biological matrices. Although ESI in negative mode is the most widely used ionization mode (because it does not require analytes' derivatization), APCI in negative mode has also been employed. As for detection, QqQ is used most often, as it offers the required selectivity and sensibility for the determination and the quantification of BPs and their derivatives with adequate accuracy and precision.

Researchers have used quite different miniaturized analytical approaches, although most are based on solvent extraction. The sensitivity and selectivity afforded are suitable for BP trace analysis and recovery is also very good, except for chlorinated derivatives. Urine and hair have been the preferred

samples for analysis, because the sampling is non-invasive, and the collection of the samples is easy.

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Declarations

Conflict of interest The authors declare no competing interests.

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