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Review

Analytical methods for the determination of mixtures of bisphenols and derivatives in human and environmental exposure sources and biological fluids. A review

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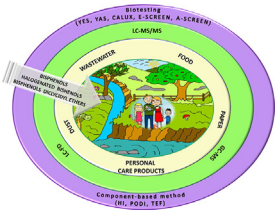
HIGHLIGHTS

- Analytical methods for the (bio) monitoring of mixtures of bisphenols are reviewed.
- LC and CG coupled to MS are the preferred techniques.
- Method-dependent sample treatments are required to remove matrix effects.
- Toxicity is evaluated in terms of receptor activation, cell proliferation and physiological responses.
- Simpler, generalized (bio)monitoring methods are lacking for assessing exposure to bisphenols.

GRAPHICAL ABSTRACT



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ABSTRACT

Bisphenol A (BPA) is ubiquitous in humans and the environment. Its potential adverse effects through genomic and non-genomic pathways have fostered BPA replacement by bisphenol analogs that, unfortunately, exert similar adverse effects. Many of these analogs, as well as their derivatives, have already found in humans and the environment and major concerns have arisen over their low dose- and mixture-related effects. This review aims to discuss the characteristics of the main analytical methods reported so far for the determination of mixtures of bisphenol analogs and/or derivatives in human and environmental exposure sources and biological fluids. Approaches followed for removal of background contamination, sample preparation and separation and detection of mixtures of bisphenols and derivatives are critically discussed. Sample treatment is matrix-dependent and common steps include analyte isolation, removal of interferences, evaporation of the extracts and solvent reconstitution. Separation and quantification has been almost exclusively carried out by liquid chromatography tandem mass spectrometry (LC-MS/MS) or gas chromatography mass spectrometry (GC–MS), in the last case prior derivatization, but LC-fluorescence detection has also found some applications. Main characteristics, advantages and drawbacks of these methods will be comparatively discussed. Although at an early stage, some approaches for the assessment of the risk to mixtures of bisphenols, mainly based on the combination of chemical target analysis and toxicity evaluation, have been already applied and they will be here presented. Current knowledge gaps hindering a reliable assessment of human and environmental risk to mixtures of bisphenols and derivatives will be outlined.

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1. Introduction

1.1. Bisphenols: uses and properties

Bisphenol A (BPA) is a high-production volume industrial chemical mainly used as a monomer in the production of polycarbonate plastics (~80%) and epoxy resins (~18%) [1–3]. Both of these polymers are widely used as food contact materials (viz. polycarbonate plastics in reusable food and drink containers, in tableware, and in water pipes, and epoxy resins as inner coatings of cans and lids of glass jars and bottles for food and beverages) [4–6].

No complete polymerization and/or polymer degradation account for leaching of BPA from consumer products to the surroundings. The serious concerns about the adverse effects of BPA on human health and aquatic life have led to industry to replace it with other bisphenols in some applications (Table 1) [7–9]. Because of the similarity in structure to BPA, the same or improved technical product properties as BPA can be obtained with the bisphenols included in Table 1. Unfortunately, toxicity profiles are also similar to BPA, with the disadvantage of being even less well-known within the scientific community [10].

Many other bisphenol-related compounds will undoubtedly contribute to the human and environmental exposure to bisphenols, namely chlorinated derivatives and bisphenol diglycidyl ethers. Chlorinated derivatives mainly result from the reaction of bisphenols with sodium hypochlorite, used as bleaching agent in paper factories and water disinfection (Table 1 shows as an example the chlorinated derivatives of BPA). Bisphenol diglycidyl ethers are the primary chemical building blocks for epoxy resins, epoxy-based lacquers or vinylic organosol (PVC) resins. The structures of bisphenol A and bisphenol F diglycidyl ethers (BADGE and BFDGE, respectively), as well as their hydrolytic and chlorinated derivatives, generated when the coating comes into contact with water and hydrochloric acid of the foodstuff during heat stabilization and storage, are also shown in Table 1 [11,12].

Properties of interest for the extraction, separation and detection of mixtures of bisphenols and derivatives (e.g. octanol–water partition coefficients and acid dissociation constants) are included in this table. Most of bisphenols are in the neutral form in samples and their mixtures encompass a wide range of polarity (eg. log K_{ow} 1.254–6.564).

1.2. Levels for human and environmental exposure to bisphenols

Human and environmental exposure to bisphenols and their derivatives can be assessed either from estimated daily intakes [13–20] or biomonitoring [12,21,22]. Table 2 shows the concentrations found in the literature for bisphenols, chlorinated derivatives of BPA and diglycidyl ethers of BPA and BPF in human exposure sources, grouped according to the route of exposure (e.g. ingestion, dermal, inhalation), environmental compartments and biological samples. Only studies including more than one bisphenol or derivative, analyzed in at least 10 samples, have been considered for calculation of the results reported in Table 2 [12,14,15,23–61]. These results are expressed as arithmetic or geometric mean depending on the data reported in the respective studies. Also the whole range of concentrations found for the target compounds as well as their frequency of detection are shown in the table. When available, both free and total bisphenol concentrations have been included. These results are expected to give a rough picture of current human and environmental exposure to mixture of bisphenols.

Human exposure to bisphenols occurs primarily through ingestion of canned food and beverages [15,23–27,29–37,49–56,59,62–65] but also through skin absorption [14,66–68] and inhalation of dust [60] (Table 2). According to the results shown in Table 2, BPA continues being the bisphenol at the highest concentration and detection rate in foodstuffs, but

Table 1
Chemical structures, octanol–water partition coefficients (log $K_{o/w}$) and ionization constants (pK_a) for bisphenols, bisphenol A chlorinated derivatives and bisphenols diglycidyl ethers.

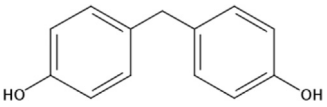
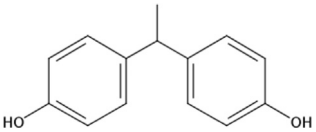
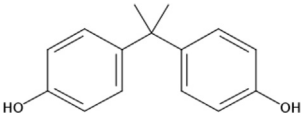
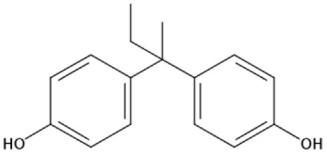
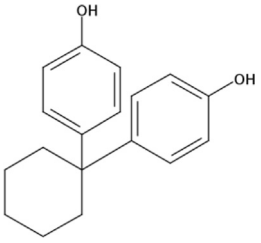
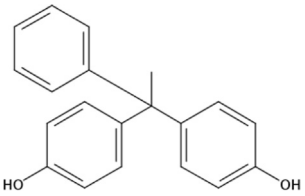
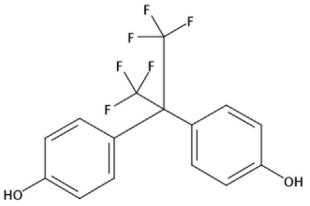
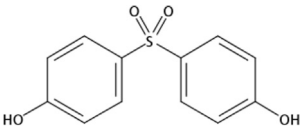
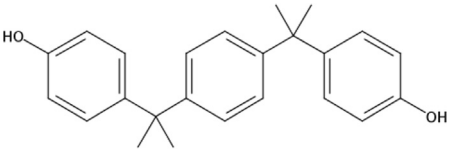
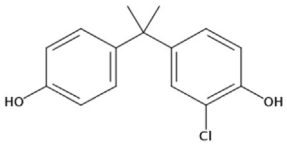
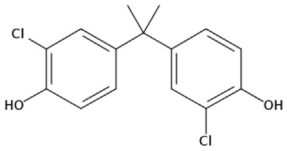
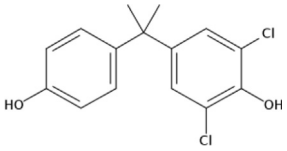
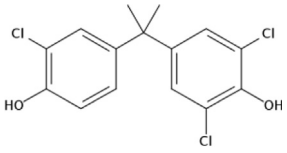
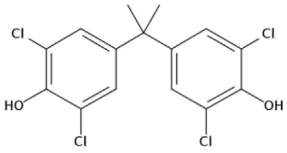
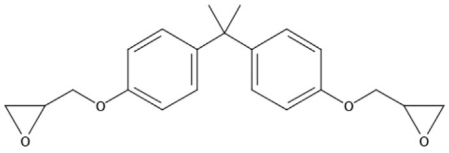
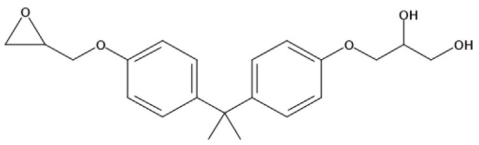
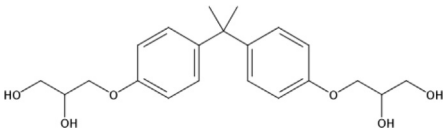
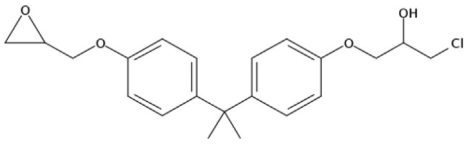
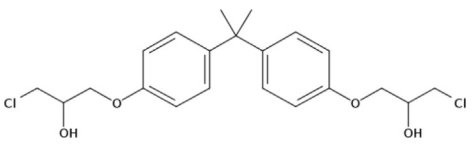
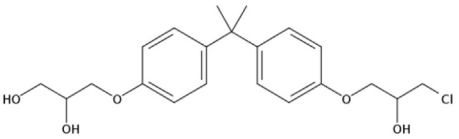
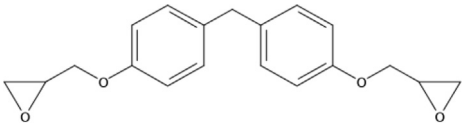
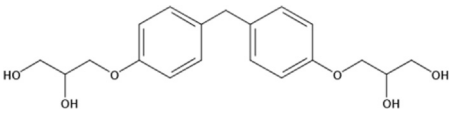
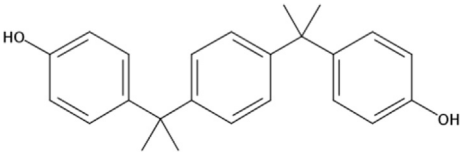
Chemical name	Chemical structure	CAS number	log K_{ow}	pK_a
Bisphenols				
4,4′-Dihydroxydiphenylmethane (BPF)		87139-40-0	2.764	9.91
4,4′-Ethylidenebisphenol (BPE)		2081-08-5	3.230	10.10
2,2′-Bis(4-hydroxyphenyl)propane (BPA)		80-05-7	3.641	10.29
2,2′-Bis(4-hydroxyphenyl)butane (BPB)		77-40-7	4.150	10.27
1,1′-Bis(4-hydroxyphenyl)-cyclohexane (BPZ)		843-55-0	4.870	9.91
1,1′-Bis(4-hydroxyphenyl)-1-phenyl-ethane (BPAP)		1571-75-1	4.331	10.22
2,2′-Bis(4-hydroxyphenyl)hexafluoropropane (BPAF)		1478-61-1	3.975	8.74
Bis(4-hydroxyphenyl)sulfone (BPS)		80-09-1	2.139	7.64
1,4-Bis(2-(4-hydroxyphenyl)-2-propyl)benzene (BPP)		2167-51-3	6.564	10.31
Bisphenol A chlorinated derivatives				

Table 1 (*continued*)

Chemical name	Chemical structure	CAS number	log K_{ow}	pK_a
2-Chloro-4-[1-(4-hydroxyphenyl)-1- methylethyl]phenol (MCBPA)		74192-35-1	4.335	9.79
4,4'-(1-Methylethylidene)bis[2-chlorophenol (DCBPA)		79-98-1	5.030	9.44
2,6-Dichloro-4-[1-(4-hydroxyphenyl)-1-methylethyl]phenol (DCBPA)		14151-65-6	5.027	8.98
2,6-Dichloro-4-[1-(3-chloro-4-hydroxyphenyl)-1-methylethyl]phenol (TCBPA)		40346-55-2	5.721	8.93
4,4'-(1-methylethylidene)bis[2,6-dichloro-Phenol (TeCBPA)		79-95-8	6.413	8.59
Bisphenol diglycidyl ethers				
2,2′-Bis(4-glycidyloxyphenyl)propane (BADGE)		1675-54-3	3.710	–
2-[4-(2,3-Dihydroxypropyloxy)phenyl]-2-[4-(glycidyloxy)phenyl]propane (BADGE·H_2O)		76002-91-0	3.185	13.53
2,2′-Bis[4-(2,3-dihydroxypropoxy)phenyl]propane (BADGE·$2H_2O$)		5581-32-8	2.515	13.23
2-[4-(3-Chloro-2-hydroxypropyloxy)pheny]-2-[4-(glycidyloxy)phenyl]propane (BADGE·HCl)		13836-48-1	4.025	13.33
2,2′-Bis[4-(3-chloro-2-hydroxypropoxy)phenyl]propane (BADGE·2HCl)		4809-35-2	4.340	12.83

(*continued on next page*)

Table 1 (*continued*)

Chemical name	Chemical structure	CAS number	log K_{ow}	pK_a
2-[4-(3-Chloro-2-hydroxypropyloxy)phenyl]-2-[4-(2,3-dihydroxypropyloxy)phenyl] propane (BADGE·HCl·H_2O)		227947-06-0	3.500	13.13
Bis[4-(glycidyloxy)phenyl]methane (BFDGE)		2095-03-6	2.449	–
Bis[4-(2,3-dihydroxypropoxy)phenyl]methane (BFDGE·2H_2O)		72406-26-9	1.254	13.23
Bis[4-(3-chloro-2-hydroxypropoxy)phenyl]methane (BFDGE·2HCl)		374772-79-9	3.093	13.52

other bisphenols as BPP show mean concentrations nearly those of BPA. Dust is, at present, an important source for BPA, BPF and BPS.

Human exposure to chlorinated derivatives of bisphenols occurs primarily through the consumption of tap water [25,69,70] (Table 2). Concerning bisphenol diglycidyl ethers and derivatives, ingestion of canned food continues being the highest route for human exposure. Among the analyzed diglycidyl ethers, BADGE.2H_2O and BFDGE occur at the highest concentration (Table 2).

In general, bisphenols and derivatives mainly enter the environment through wastewater [71–75]. Soils can become contaminated by farmland fertilization with sewage sludge. Both, wastewater and leaching from landfill sites containing these compounds are the major sources of contamination of ground waters, rivers, streams and, eventually, drinking water [76]. Levels found for bisphenols in sediments and sewage vary over a wide range as it can be seen in Table 2.

The measurement of total bisphenols (unconjugated and their glucuronidated and sulphated conjugates) in urine has been the most used parameter for their biomonitoring, although differential measurements for free bisphenols and metabolites have been also reported. Table 2 shows the levels reported for the target bisphenols and derivatives in urine. Other biological fluids such as serum have been less used for biomonitoring purposes [77].

On the other hand, there is a great concern about exposure of human fetuses, neonates, and infants to bisphenols because of the sensitivity of the developing organs and brain to endocrine disrupting chemicals. Considering that bisphenols can cross the placental barrier, the fetus remains exposed to these compounds. Also, neonates and infants are exposed to bisphenols through breast milk. The evaluation of “in utero exposure” to bisphenols, through the analysis of biological fluids from pregnant or nursing mother (i.e. blood, urine, breast milk, colostrum), the fetus or newborn infant (i.e. meconium, umbilical cord blood, neonatal urine), and from both the fetus and the mother (i.e. placental tissues, amniotic fluid), would allow for a better understanding and a more concrete picture into the exposure of the most vulnerable segment of the human population. The reported levels of bisphenols and BPA chlorinated derivatives in some of these types of samples are shown in Table 2.

1.3. Dose-related effects of bisphenols

Concerning the effects of bisphenols and derivatives on human health and the environment, those produced by BPA have been so far the most investigated [78–83]. BPA exhibits both estrogenic and antiandrogenic effects [84] and many studies have examined correlations between elevated levels of BPA and negative impacts on reproduction, neurobehavioral development, and metabolic diseases (e.g. obesity, diabetes, heart disease, thyroid and liver function) [85]. A lot of information is also available in the literature on the adverse effects on animals (viz. rats and mice), following exposure to low doses of BPA [86,87]. These health effects are not fully understood yet and there are strong controversies in their interpretation, even governmental decisions are sometimes contradictory [78].

Regarding the effects of bisphenols, other than BPA, the information is quite scarce but the few studies reported confirm that human and environmental toxicity and exposure pathways are similar to those of BPA [87–90]. Studies involving BPA by-products suggest that they could be even more cytotoxic than BPA [91]. On the other hand, bisphenol diglycidyl ethers have lower estrogenic potency compared to bisphenols but some studies indicate that they seem to induce adverse effects in humans at estimated intake levels [92].

On the whole, the effects reported for bisphenols and derivatives, mainly those in the low dose range, as well as their simultaneous presence in different sources, strength the need to no longer consider them individually for both human and environmental exposure and legislative provisions.

1.4. International and national provisions regarding bisphenols and derivatives

The European Union (EU) has set food migration limits for BPA (0.6 mg kg^{-1} [93]), BADGE and its hydrolysis products (9 mg kg^{-1}, [94]) and chlorinated BADGE byproducts (1 mg kg^{-1}, [94]). In 2011,

Table 2
Levels of bisphenols, bisphenol A chlorinated derivatives and bisphenol diglycidyl ethers in human exposure sources (ingestion, dermal, inhalation) and environmental and biological samples.

Analyte		Ingestion			Dermal		Inhalation	Environmental		Biological						Ref.
		Packed food (ng g^{-1})	Beverages (ng mL^{-1})	Drinking water (ng mL^{-1})	Personal care (ng g^{-1})	Paper (ng g^{-1})	Dust (ng g^{-1})	Sediments (ng g^{-1})	Sewage sludge (ng g^{-1})	Urine (ng mL^{-1})	Serum (ng mL^{-1})	Placental tissue (ng g^{-1})	Breast milk (ng mL^{-1})	Adipose tissue (ng g^{-1})	Colostrum (ng mL^{-1})	
Bisphenols																
BPA	n	871	97	62	36	16	284	172	76	50[c] 40	58	59	33	20	21	[14,15,23–28,30,32–37,40–43,45–48,52–55,57,59–61]
	Mean[a]/ GM[b]	21.2[a]	1.92[a]	0.02[a]	20.9[a]	10511[a]	1000[a]	117[a]	459[a]	1.06[a,c] 4.47[a]	2.91[a]	7.49[a]	0.43[a]	5.83[a]	1.87[a]	
	Range	nd-521	nd-46.4	nd-0.128	nd-88.3	nd-70000	9.6–32000	nd-13370	6.48–4700	nd-4.3[c] nd-40	nd-7.12	nd-34.9	<0.01–3.29	nd-12.01	nd-6.12	
	F (%)	66.4	43.3	95.2	55.6	88	100	84.9	100	40[c] 57.5	51.7	37.3	100	55	90.5	
BPB	n	686	76		29		284	172	76	20[c] 20	58					[15,23,24,26–28,36,37,42,43,48,57,59–61]
	Mean[a]/ GM[b]	17.4[a]	0.09[a]		0.01[a]		<1[a]	0.06[a]	0.97[a]	nd[c] 0.68[a]	5.15[a]					
	Range	nd-85.7	nd-0.16		nd-0.014		<1–8.4	nd-10.6	nd-5.6	nd[c] nd-1.15	nd-11.94					
	F (%)	4.6	19.7		3.45		1	0.6	1.4	0[c] 10	27.6					
BPE	n	16	10													[24,59]
	Mean[a]/ GM[b]	nd	nd													
	Range	nd	nd													
	F (%)	0	0													
BPF	n	641	67		29		284	172	76							[15,23,24,33,35,48,54,55,59–61]
	Mean[a]/ GM[b]	3.37[a]	0.16[a]		0.13[a]		1000[a]	69.7[a]	17.2[a]							
	Range	nd-623	nd-0.26		nd-0.79		<1-110000	nd-9650	nd-242							
	F (%)	17.3	7.5		5		83	62.2	68.0							
BPP	n	464	35		29		284	172	76							[15,23,48,60,61]
	Mean[a]/ GM[b]	1.15[a]	0.025[a]		nd		<2[a]	nd	1.06[a]							
	Range	nd-73.1	nd-0.03		nd		<2–9.4	nd	nd-6.4							
	F (%)	5.4	2.8		0		nr	0	4.2							
BPS	n	500	31		29	8	284	172	76				30			[14,15,23,24,40,48,58,60,61]
	Mean[a]/ GM[b]	6.3[a]	0.007[a]		0.04[a]	11025[a]	220[a]	12.37[a]	34.5[a]				0.23[a]			
	Range	nd-175	nd-0.007		nd-0.04	1000–60000	<2-21000	nd-1970	nd-1480				nd-0.23			
	F (%)	25.8	3.2		13.8	100	100	28.5	84				3.3			
BPZ	n	474	45		29		284	172	76							[15,23,35,48,60,61]
	Mean[a]/ GM[b]	0.69[a]	0.09[a]		nd		<0.5[a]	0.37[a]	1.81[a]							
	Range	nd-2.6	nd-0.09		nd		<0.5	nd-63.3	nd-66.7							
	F (%)	3.6	2.2		0		nr	0.6	1.4							
BPAF	n	464	35		29		284	172	76							[15,23,48,53,60,61]
	Mean[a]/ GM[b]	0.02[a]	0.006[a]		0.03[a]		3.1[a]	0.05[a]	6.01[a]							
	Range	nd-0.76	nd-0.009		nd-0.07		<0.1–54	nd-4.23	nd-72.2							
	F (%)	12	6.45		10.3		73	4.1	46							
BPAP	n	464	35		29		284	172	76							[15,23,48,60,61]
	Mean[a]/ GM[b]	0.89[a]	nd		0.19[a]		0.38[a]	1.71[a]	nd							
	Range	nd-127	nd		nd-1.01		<0.5–4.5	nd-252	nd							

(*continued on next page*)

Table 2 (*continued*)

Analyte		Ingestion			Dermal		Inhalation	Environmental		Biological						Ref.
		Packed food (ng g^{-1})	Beverages (ng mL^{-1})	Drinking water (ng mL^{-1})	Personal care (ng g^{-1})	Paper (ng g^{-1})	Dust (ng g^{-1})	Sediments (ng g^{-1})	Sewage sludge (ng g^{-1})	Urine (ng mL^{-1})	Serum (ng mL^{-1})	Placental tissue (ng g^{-1})	Breast milk (ng mL^{-1})	Adipose tissue (ng g^{-1})	Colostrum (ng mL^{-1})	
	F (%)	9.5	0		31		1	7.6	0							
Bisphenol A chlorinated derivatives																
MCBPA	n			62						31		59	33	20	21	[40,41,44–47,58]
	Mean[a]/ GM[b]			0.005[a]						0.055[b]		9.45[a]	nd	3.05[a]	nd	
	Range			0.0002 –0.027						nd-1.68		nd-21.4	nd	nr	nd	
	F (%)			100						16.1		40.7	0	15	0	
DCBPA	n			62						31		59	33	20	21	[40,41,44–47,58]
	Mean[a]/ GM[b]			0.001[a]						0.048[b]		23.3[a]	2.53[a]	9.21[a]	1.96[a]	
	Range			nd-0.006						nd-1.06		nd-58.8	<0.4–4.13	nr	<0.4–4.13	
	F (%)			98.4						19.4		40.7	100	80	100	
TCBPA	n			62						31		59	33	20	21	[40,41,44–47,58]
	Mean[a]/ GM[b]			0.002[a]						0.047[b]		11.3[a]	0.68[a]	0.74[a]	0.17[a]	
	Range			nd-0.008						nd-0.675		nd-31.2	nd-0.68	nr	<0.4–0.68	
	F (%)			58.1								39.0	33.3	10	11	
TeCBPA	n			62								59		20		[41,46,47]
	Mean[a]/ GM[b]			0.0005[a]								nd		nd		
	Range			nd-0.005								nd		nd		
	F (%)			48.4								0		0		
Bisphenol diglycidyl ethers																
BADGE	n	134					158			127[c] 303						[12,29–32,34,38,39, 49–52,56,59,60]
	Mean[a]/ GM[b]	32.63[a]					3.47[b]			0.116[b,c] 2.63[b]						
	Range	nd-440					nd-7750			0.027 –0.497[c] nd-295						
	F (%)	36					91.1			100[c] 68						
BADGE·H_2O	n	129					158			127[c] 227						[12,29–32,34,38,39, 49–51,56,59,60]
	Mean[a]/ GM[b]	48.33[a]					40.5[b]			0.06[b,c] 0.221[b]						
	Range	nd-179					nd-8850			nd-0.37[c] nd-3.7						
	F (%)	14					99.4			79.5[c] 57.7						
BADGE·$2H_2O$	n	110					158			127[c] 303						[12,29–3234,38,39, 49,50,56,59,60]
	Mean[a]/ GM[b]	104.3[a]					1310.7[b]			0.537[b,c] 6.59[b]						
	Range	nd-675					35–59900			nd-5.24[c] nd-1450						
	F (%)	64					100			99.2[c] 91.2						
BADGE·HCl	n	129								100						[12,29–32,34,38,39, 49–51,59]
	Mean[a]/ GM[b]	21.43[a]								<2						
	Range	nd- 74.42								nd - <2						

	F (%)	13		3	
BADGE·2HCl	n	128			[29–32,34,49–51,59]
	Mean[a]/ GM[b]	42.4[a]			
	Range	nd-810			
	F (%)	39			
BADGE·HCl·H_2O	n	128	158	127[c] 227	[12,29–32,34,38,39,49–51,59,60]
	Mean[a]/ GM[b]	39.1[a]	229.1[b]	0.042[b,c] 0.138[b]	
	Range[c]	nd-533	5–24300	nd-1.265[c] nd-3.412	
	F (%)	64	100	44.1[c] 52.8	
BFDGE	n	73			[29,59]
	Mean[a]/ GM[b]	81[a]			
	Range	nd-314			
	F (%)	21.9			
BFDGE·H_2O	n	10			[50]
	Mean[a]/ GM[b]	nd			
	Range	nd			
	F (%)	0			
BFDGE· $2H_2O$	n	19			[29,34,50]
	Mean[a]/ GM[b]	0.6[a]			
	Range	nd-0.81			
	F (%)	26			
BFDGE·HCl	n	10			[50]
	Mean[a]/ GM[b]	nd			
	Range	nd			
	F (%)	0			
BFDGE· 2HCl	n	57			[29,34,49,50,59]
	Mean[a]/ GM[b]	69.5[a]			
	Range	nd-120			
	F (%)	3.5			
BFDGE·HCl·H_2O	n	10			[50]
	Mean[a]/ GM[b]	nd			
	Range	nd			
	F (%)	0			

n: number of samples; F: frequency of detection; nd: not detected; nr: not reported;
[a] Arithmetic mean.
[b] Geometric mean.
[c] Free bisphenols.

on the basis of the precautionary principle, the EU restricted the production and sale of BPA-based polycarbonate baby bottles [95].

Since 2006, the European Food Safety Authority (EFSA) has conducted several scientific assessments on BPA. The last scientific opinion, published in January 2015, consists of three separate documents, namely Executive Summary [79]; Part I-Exposure assessment [96] and Part II-Toxicological assessment and risk characterization [80]. In this opinion, the EFSA Panel on Food Contact Materials, Enzymes, Flavorings and Processing Aids has established a temporary Tolerable Daily Intake (t-TDI) of 4 μg kg^{-1} body weight per day and it has concluded that there is no consumer health risk from BPA exposure. Nevertheless, bans on the use of BPA for food packaging intended for young children (zero to three years old) have been proposed by several EU Member States (viz. Denmark, Sweden, France, Belgium and Austria) [96].

The U.S. Environmental Protection Agency (EPA) and U.S. Food and Drug Administration (FDA) have chosen not to regulate BPA due to insufficient scientific evidence of adverse human health effects at low-levels of exposure [97,98], despite provisions for its elimination from some products such as baby bottles [98]. The National Sanitation Foundation (NSF) recommends a BPA drinking water criterion of 0.1 mg L^{-1} total allowable concentration and 0.01 mg L^{-1} single-product allowable concentration [99]. BADGE is not regulated by the EPA or FDA but the NSF recommends a drinking water criterion of 1 mg L^{-1} total allowable concentration and 5 mg L^{-1} short term exposure level [99].

1.5. Combination effects of chemical mixtures

It is becoming increasingly evident that, in combination, some chemicals can cause harmful effects in wildlife species, laboratory animals, and humans, at concentrations considered safe for the individual chemicals [100–102]. In view of this evidence, the traditional chemical-by-chemical approach to risk assessment is hard to justify, and the ground is prepared to seriously consider group-wise regulation of chemicals [103–111].

Regarding the number of bisphenols and derivatives used in the market as monomers or additives of plastic materials and other consumer products (and also the many possible byproducts generated), and considering the strong previous experimental evidence that endocrine disruptors chemicals (EDCs) of relatively low potency and at low exposure levels can still work together to produce significant combination effects when they are present in sufficient number, it seems that the current approach of assessing human and environmental risk to bisphenols through the t-TDI set for BPA (the only legislated bisphenol) may underestimate the actual risk to these compounds.

Bisphenol mixtures meet several of the criteria set by the EC to be considered as a mixture of potential concern [111]. Thus, exposure of the human population and the environment to bisphenols is widespread; they are pseudo-persistent; there is potential for adverse effects to the likely exposure levels; as EDCs, there is scientific base to predict that they will probably act similarly; and, except for BPA, threshold limits for the effects of mixture components have been not established.

2. Analytical methods for the determination of mixtures of bisphenols and derivatives

Chemical analysis is essential in the assessment of wildlife and humans exposure to a mixture of bisphenols. The components to be analyzed differ greatly in their physical and chemical properties (Table 1) and are generally present at trace concentrations in complex matrices (Table 2), that requiring highly selective and sensitive analytical methods for their quantification. Adding greatly to the complexity, and to the number of bisphenols in our environment, are the unknown potential byproducts that can be formed via human and environmental transformations.

Table 3 gives an overview of the analytical methods reported in the literature for the determination of mixtures of bisphenols and derivatives in human and environmental exposure sources and biological samples. Packed food, aquatic environment and biological fluids have been the areas receiving the greatest attention, although interesting methods involving other human exposure sources such as beverages, drinking water, personal care products, paper and dust, have been also reported. There have been substantial differences among the mixture of bisphenols or derivatives selected for analysis depending on the matrix. Thus, separate mixtures of bisphenols or diglycidyl ethers have been preferentially analyzed in packed food, while bisphenols and BPA chlorinated derivatives have been jointly analyzed in aquatic environments. Methods reported for biological samples have been mainly devoted to the determination of mixtures of BPA plus chlorinated derivatives and BPA plus diglycidyl ethers. Very few methods have included BPE as a component in the mixtures investigated.

Common steps in sample treatment for most of the analytical methods reported for mixtures of bisphenols and derivatives include sample pretreatment, extraction of analytes from the matrix, cleanup of the extracts to remove interferences, and concentration to achieve the desired sensitivity. Analyte separation and quantification has been almost exclusively carried out by LC-MS/MS or GC–MS, in the last case prior derivatization, but LC-fluorescence detection has also found some applications. Below, we summarize the state-of-the-art of the analytical methodologies developed, including strategies for removal of background contamination, sample preparation and separation and detection of mixtures of bisphenols and derivatives.

2.1. Sources and removal of background contamination

Background contamination of bisphenols occurs at ng μg L^{-1} levels during sample collection, preservation, handling and/or quantitation. Bisphenols are inherently ubiquitous in the lab environment due to the widespread use of polycarbonate plastics and epoxy resins in lab materials and equipment. The random pattern of this contamination makes it difficult to identify specific sources, often compromising the accurate quantification of bisphenols. As a general rule, contact of the sample with material susceptible of leaching bisphenols should be avoided. Otherwise, contamination has to be controlled or eliminated using appropriate laboratory procedures and designated work areas. Procedural blanks should be conducted for each sample batch to account for background contamination.

Commonly reported specific sources of contamination for bisphenols include, among others, labware, gloves, plastic and microcentrifuge tubes, SPE cartridges, syringe metal needles (owing to the epoxy-resin based adhesive used to fix the needle to the glass syringe), solvents, reagents, ultra-high-quality water (contamination arises from the purification system), pipes and connections in instruments [25,112–114].

Where possible, replacement of bisphenol-leaching materials (e.g. use of glassware, nitrile gloves, metallic connections, etc) is the most adequate strategy to deal with background contamination. Before use, glassware must be rinsed several times with organic solvents and treated at high temperature (400–500 °C) during 2–4 h [26,27,115]. Biological samples (e.g.blood) are susceptible to be contaminated during collection, so it is recommended to use vacuum containers as Vacu-test® [28]. The contamination arising from SPE cartridges (e.g. Oasis HLB) can be effectively removed by their pre-washing with an organic solvent such as methanol [25].

Table 3
Analytical methods reported for the determination of mixtures of bisphenol and derivatives.

Sample type (size)	Analytes	Sample treatment	Separation/detection	RSD (%)	R (%)	Detection limits	Ref.
Packed food							
Canned vegetables and fruits (10 g, total content for fruits; solid portion for vegetables)	BPA, BPB	Sample + water, 5 mL; stirring and centrifugation QuEChERS extraction: AcN, 10 mL; $MgSO_4$, 4 g; NaCl, 1 g; shaking 15 min Centrifugation DLLME: 1 mL AcN extract as dispersive solvent and 50 μL T4CE as extractive solvent; add to 3 ml of water and shake Centrifugation	GC-EI-MS(SIM) Derivatization agent: AA Column: DB-5MS (30m × 0.25 mm, 0.25 μm) Matrix-matched calibration (BPA-d16)	4–20[a]	69–104	MDL = 0.1–0.6 ng g^{-1} MQL = 1 ng g^{-1}	[26]
Canned seafood (10 g, total content except for tuna)	BPA, BPB	Fat removal: sample + n-heptane, 5 mL + water, 10 mL; stirring and centrifugation QuEChERS extraction: AcN, 10 mL; $MgSO_4$, 4 g; NaCl, 1 g; shaking 15 min; centrifugation; AcN extract + $MgSO_4$, 1.2 g + C18, 120 mg + GCB, 50 mg; stirring Centrifugation DLLME: 1 mL AcN extract (dispersive solvent)+ K_2CO_3, 5% to pH > 10 + 50 μL T4CE (extractive solvent); add to 4 ml of water and shake Centrifugation	GC-EI-MS(SIM) Derivatization agent: AA Column: DB-5MS (30m × 0.25 mm, 0.25 μm) Matrix-matched calibration (BPA-d16)	10–21[a]	68–104	MDL = 0.2–0.4 ng g^{-1} MQL = 1 ng g^{-1}	[27]
Canned peeled tomatoes (20 g, total content)	BPA, BPB	Extraction: AcN, 2 × 150 mL Clean up: n-hexane, 3 × 60 mL (fat removal); solvent evaporation; reconstitution water: AcN (90:10), 6 mL; SPE,C-18 Strata E; elution MeOH 4 × 5mL, solvent evaporation, reconstitution hexane: EA (96:4), 6 mL; SPE, Forisil; elution EA 4 × 5mL Solvent evaporation Reconstitution AcN, 20 mL	LC-UV-FD (λ 228 nm) (λex 273 nm, λem 300 nm) Mobile phase: AcN/water (isocratic) Column: Synergi Fusion-RP80 Å (250 × 4.6 mm; 4 μm) External calibration	0.04–2.82[a] 0.2–2.96[b]	94.3–95.7	UV MDL = 15.4–20 ng g^{-1} MQL = 51.3–66.9 ng g^{-1} FD MDL = 0.7–1.1 ng g^{-1} MQL = 2.3–3.7 ng g^{-1}	[36]
Canned powdered infant (10 mL)	BPA, BPB	Reconstitution with water Precipitation of protins and fats: TCA 10% in MeOH, 5 mL; stirring; centrifugation Upper layer at pH ≥ 10 with potassium carbonate, 5%; take 10 mL Extraction: DLLME (extractive solvent: T4CE, 30 μL; dispersive solvent: AcN, 440 μL)	Heart cutting-GC-EI-MS(SIM) Derivatization agent: AA Column 1: DB-5HT (5m × 0.32 mm, 0.1 μm) Column 2: DB-5MS (15m × 0.25 mm, 0.25 μm) Matrix-matched calibration (BPA-d16)	7–15[a]	68–114	MDL = $3 \cdot 10^{-2}$ – $6 \cdot 10^{-2}$ ng g^{-1} MQL = 0.1–0.2 ng g^{-1}	[37]
Canned fish, meat, pasta, fruits, vegetables, etc. (20 g, total content)	BPA, BPF	Extraction: AcN:n-heptane (fat removal) (50:50), 40 mL; n-heptane washing with AcN, 20 mL; AcN extrats combinated and treated with anhydrous sodium sulphate Solvent evaporation to 5 mL Dilution: water, 50 mL Derivatization Extraction: n-heptane, 5 mL	GC-EI-MS(SIM) Derivatization agent: AA Column: HP-5MS (30m × 0.25 mm, 0.25 μm) External calibration (BPA-d14)	5.2[a]	61–128	MDL = 2–10 ng g^{-1}	[33]

(*continued on next page*)

Table 3 (*continued*)

Sample type (size)	Analytes	Sample treatment	Separation/detection	RSD (%)	R (%)	Detection limits	Ref.
Canned infant formula (10 g)	BPA, BPF	Extraction: AcN, 20 mL+10 mL Solvent evaporation to 5 mL Dilution: water, 50 mL Derivatization Extraction: n-heptane, 5 mL	GC-EI-MS(SIM) Derivatization agent: AA Column: HP-5MS (30m × 0.25 mm, 0.25 μm) External calibration (BPA-d14)	5.2[a]	61–128	MDL = 2–10 ng g^{-1}	[33]
Canned tomato paste and corn (10 g, total content)	BPA, BPF	Extraction: AcN:water (90:10), 15 mL Preconcentration: HS-SPME (SWCNT) of the extract and derivatization	GC-EI-MS(SIM) Derivatization agent: AA Column: HP-5MS (30m × 0.25 mm, 0.25 μm) Matrix-matched calibration (BPA-d14)	<12[b]	79–86	LOD = 0.1 ng g^{-1} LOQ = 0.3 ng g^{-1} MDL = 0.045 ng g^{-1}	[54]
Canned corn, tomato paste, stew, tuna fish (10 g, total content)	BPA, BPF	Extraction: AcN:water (90:10), 15 mL Preconcentration: HS-SPME (–) of the extract and derivatization	GC-EI-MS(SIM) Derivatization agent: AA Column: HP-5MS (30m × 0.25 mm, 0.25 μm) Standard method addition (BPA-d14)	nr	79–86	LOD = 0.1 ng g^{-1} LOQ = 0.3 ng g^{-1} MDL = 0.045 ng g^{-1}	[55]
Milk, lactic acid milk drinks and carbonated drinks (10 mL)	BPA, BPAF	Sample+26 mg magnesium sulphate/centrifugation Extraction: SUPRAS (octanol in THF), 500 μL Dilution of SUPRAS to 1 mL with AcN	LC-UV/Vis (λ 240 nm) Mobile phase: AcN/water (gradient) Column: C18 (150 × 4.6 mm; 5 μm)	3.98 –5.64[a]	91–105	MDL = 0.14–0.32 ng mL^{-1} MQL = 0.41–1.02 ng mL^{-1}	[53]
Canned vegetables (solid portion, 2 g; liquid portion, 10 mL)	BPS, BPA	Solid portion + water, 10 mL Liquid portion + water, 4 mL Extraction: SPME (PA fiber, 85 μm) Desorption in the injection port at 280 °C	GC-EI-MS(SIM) Derivatization agent: BSTFA Column: SLB-5MS (30m × 0.25 mm, 0.25 μm) External calibration	4.47 –5.12[a]	84–112	MDL = 0.0025–0.016 ng mL^{-1} MQL = 0.0083–0.055 ng mL^{-1}	[118]
Canned vegetables (2 mL, liquid portion)	BPA, BPF, BPZ	Dilution to 10 mL with water Extraction: SBSE (PDMS) Desorption: thermal desorption unit equipped with an autosampler	GC-EI-MS(SIM) Derivatization agent: AA Column: HP-5MS (30m × 0.25 mm, 0.25 μm) External calibration	1.90 –3.59[a] 3.11 –5.80[b]	86–122	LOD = $0.9 \cdot 10^{-3}$–$2.5 \cdot 10^{-3}$ ng mL^{-1} LOQ = $3.2 \cdot 10^{-3}$ –$8.4 \cdot 10^{-3}$ ng mL^{-1}	[35]
Cereals and cereal products, meat and meat products, fish and seafood, eggs, bean products, fruits, vegetables, cookies/snacks, cooking oils,etc (1–4 g)	BPA, BPAF, BPAP, BPB, BPF, BPP, BPS, BPZ	Samples were freeze–dried Extraction: AcN, 2 × 6 mL; shaking; centrifugation; solvent evaporation; reconstitution DCM:hexane (10:90), 2 mL Clean up: SPE, Strata NH2; elution MeOH:acetone (80:20), 5 mL Solvent evaporation Reconstitution: MeOH, 0.5 mL	LC-ESI(–)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: Betasil C18 (100 × 2.1 mm; 5 μm) External calibration (BPA-$^{13}C_{12}$)	<15[a]	62–126	MQL = 0.01–0.05 ng g^{-1}	[15,23]
Milk and milk products (3 g)	BPA, BPAF, BPAP, BPB, BPF, BPP, BPS, BPZ	Extraction: AcN, 6 mL (sample:acetonitrile = 1:2, v/v); shaking; centrifugation; solvent evaporation to 4 mL Dilution to 10 mLwith formic acid, 0.2% (pH = 2.5) Clean up: SPE, Oasis MCX Concentration of eluate to 0.5 mL	LC-ESI(–)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: Betasil C18 (100 × 2.1 mm; 5 μm) External calibration (BPA-$^{13}C_{12}$)	<15[a]	62–126	MQL = 0.01–0.05 ng g^{-1}	[15,23]
Fish, meat (5 g, total content)	BADGE, BADGE·$2H_2O$, BADGE·H_2O	Extraction: pentane 3 × 2 mL/solvent evaporation Clean up: MeOH, 3 × 5mL Solvent evaporation Reconstitution: mobile phase, 0.5 mL	LC-FD (λ_{ex} 275 nm, λ_{em} 305 nm) Mobile phase: CH/TBME (for BADGE) and AcN/water/MeOH (for hydrolysis products) Column: Hibar Lichrosorb Si60 (250 × 4.6 mm; 5 μm) for BADGE and Hibar Lichrosorb Diol (250 × 4.6 mm; 5 μm) for	1.9 –5.7[a]	90–114	LOD: 10 ng g^{-1}	[56]

Table 3 (*continued*)

Sample type (size)	Analytes	Sample treatment	Separation/detection	RSD (%)	R (%)	Detection limits	Ref.
			hydrolysis products External calibration				
Canned tuna (10 g, total content)	BADGE, BADGE·2H_2O, BADGE·H_2O, BADGE·HCl·H_2O, BADGE·2HCl, BADGE·HCl,	Extraction: AcN, 40 mL; stirring; add NaCl and stirring Centrifugation	LC-FD (λ_{ex} 275 nm, λ_{em} 305 nm) Mobile phase: AcN/water (gradient) Column: Spherisorb ODS2 (100 × 4.6 mm; 5 μm) Matrix-matched calibration	5–9[a]	95–99	MDL = 10–20 ng g^{-1} MQL = 30–50 ng g^{-1}	[31]
Fish and meat (2 g)	BADGE, BADGE·H_2O, BADGE·HCl·H_2O, BADGE·2HCl, BADGE·HCl, BFDGE	Extraction: MAE (hexane, 5 mL + acetone, 3 mL; 20 min at 105 °C and 200 W)/Centrifugation Clean up: supernatant washing with AcN, 2 × 5 mL/solvent evaporation/redissolution with water:MeOH (90:10), 3 mL/SPE, PS-DVB; elution AcN, 5 mL Solvent evaporation Reconstitution: MeOH, 1 mL	LC-FD (λ_{ex} 230 nm, λ_{em} 301 nm) Mobile phase: AcN/water (gradient) Column: Lichrospher C18 (150 × 2.1 mm; 5 μm) External calibration	0.29 –8.64[a]	70.46 –103.44	LOD = 0.79–3.77 ng g^{-1} LOQ = 2.75–10.92 ng g^{-1}	[51]
Canned fruits and vegetables (3 g, total content)	BADGE, BADGE·2H_2O, BADGE·H_2O, BADGE·HCl·H_2O, BADGE·2HCl, BADGE·HCl, BFDGE, BFDGE·2H_2O, BFDGE·2HCl	Extraction: EA, 6 mL; 5 mL to dryness Reconstitution: MeOH: water (50:50), 1 mL	LC-ESI(+)-MS/MS(SRM) Mobile phase: MeOH/ 25 mM formic acid-ammonium formate buffer (pH 3.75) (gradient) Column: Fused Core™Ascentis Express C18 (50 × 2.1 mm; 2.7 μm) External calibration	3–20[a]	60–90	MQL = 1–4 ng g^{-1}	[112]
Fish and meat (10 g, total content)	BADGE, BADGE·2H_2O, BADGE·H_2O, BADGE·HCl·H_2O, BADGE·2HCl, BADGE·HCl, BFDGE, BFDGE·2HCl	Sample + diatomaceous earth Extraction: PLE (hexane-acetone (4:1), 100 °C, 1500 psi and 5 min static time and two cycles) Concentration to 10 mL under nitrogen Clean up: AcN, 3 × 2 mL; SPE (C18 + NH2), elution AcN-MeOH (1:1) Solvent evaporation Reconstitution: AcN: water (1:1), 0.2 mL	LC-APCI(+)-MS/MS(SRM) Mobile phase: AcN/water (isocratic) Column: Kromasil C18(100 × 2.1 mm; 3.5 μm) External calibration	5–10[a]	82–101	LOD = 0.25–1 ng g^{-1} LOQ = 0.8–3.5 ng g^{-1}	[49]
Canned fish (2 g, total content)	BADGE, BADGE·H_2O, BADGE·2H_2O, BADGE·HCl•H_2O, BADGE·2HCl, BADGE·HCl, BFDGE, BFDGE·2H_2O, BFDGE·2HCl	Extraction: AcN:n-hexane (1:1), 20 mL; stirring; centrifugation Solvent evaporation of 1 mL of AcN layer Reconstitution: ammonium formate (0.01M), 0.5 mL	LC-ESI(+)-MS/MS(MRM) Mobile phase: MeOH/ ammonium formate (0.01M) (gradient) Column: Synergy MAX-RP (100 × 2 mm; 2.5 μm) Matrix-matched calibration	5.8 –9.5[a] 6.7 –12[b]	90–110	MDL = 0.5–3.1 ng g^{-1} MQL = 1.8–10.3 ng g^{-1}	[29]
Fish, meat, vegetables and peanut butter (5 g)	BADGE, BADGE·2H_2O, BADGE·H_2O, BADGE·HCl·H_2O, BADGE·2HCl, BADGE·HCl, BFDGE, BFDGE·2H_2O, BFDGE·H_2O, BFDGE·HCl·H_2O, BFDGE·2HCl, BFDGE·HCl	Extraction: MAE (hexane, 10 mL + acetone, 5 mL; 10 min at 105 °C; 5 min 800 W) Centrifugation Clean up: AcN, 2 × 5 mL Solvent evaporation Reconstitution: AcN: water (50:50), 1 mL	UPLC-ESI(+)-MS/ MS(MRM) QTRAP Mobile phase: AcN/ formic acid solution (0.2%) (gradient) Column: ACQUITY UPLC™ BEH C18 (100 × 2.1 mm, 1.7 μm) Matrix-matched calibration	2.9 –7.8[a]	65.4 –101.8	LOD = 0.19–1.27 ng g^{-1} MDL = 0.24–1.84 ng g^{-1}	[50]
Milk (10 mL)	BPA, BADGE	Sample + MeOH, 10 mL and sonication (emulsion destabilization) Dilution to 100 mL (water) Extraction: SPE, C18 Clean up: SPE, Forisil Solvent evaporation Reconstitution: EA, 0.3 mL	GC-EI-MS(SIM) Column: HP-5MS (30m × 0.25 mm, 0.25 μm) External calibration (BEHP-d4)	6.6 –17.6[b]	81–119	MDL: 0.15–0.36 ng mL^{-1}	[52]

(*continued on next page*)

Table 3 (*continued*)

Sample type (size)	Analytes	Sample treatment	Separation/detection	RSD (%)	R (%)	Detection limits	Ref.
Milk (10 mL)	BPA, BPB, BPF, BADGE,BFDGE	Sample + MeOH,10 mL and sonication (emulsion destabilization) Dilution to 100 mL (water) Extraction: SPE, Chromabond C18; elution AcN, 5 mL	LC-FD (λ 228 nm) (λex 273 nm, λem 300 nm) Mobile phase: AcN/water (isocratic) Column: SynergiFusion-RP (250 × 4.6 mm; 4 μm) Matrix-matched calibration	0.05 −2.98[a] 0.018 −2.99[b]	93–106	LOD = 0.3–4.2 ng mL^{-1} LOQ = 1–14 ng mL^{-1}	[119]
Canned peas, tuna, olives, maize, artichokes and palm hearts (10 ml, liquid portion)	BPA, BADGE, BFDGE BADGE·diol, BADGE·2HCl, BFDGE·diol	Sample +0.75 g of sodium chloride Extraction: SPME (carbowax, 65 μm) Desorption: 150 μL mobile phase or in the desorption chamber of SPME-LC interface	LC-FD (λ 228 nm) (λex 275 nm, λem 305 nm) Mobile phase: AcN/water (isocratic) Column: XTerra MS C18 (100 × 4.6 mm; 5 μm) Standard addition method	14 −32[a]	7–65	LOD = 0.7–2.4 ng mL^{-1} LOQ = 2.5–7.2 ng mL^{-1}	[120]
Canned vegetables, sauces, fish, others (2 −5 g, total content)	BPA BADGE, BADGE·H_2O, BADGE·2H_2O, BADGE·HCl·H_2O, BADGE·2HCl, BADGE·HCl	Extraction: AcN - Clean up: SPE, Oasis HLB Solvent evaporation Reconstitution: AcN: water (40:60), 1 mL	LC-ESI(−)-MS/MS(MRM) Mobile phase: AcN/water (gradient) Column: Acquity BEH C18 (50 × 2.1 mm; 1.7 μm) LC-ESI(+)-MS/MS(MRM) Mobile phase: MeOH/ ammonium acetate (5 mM) (gradient) Column: Acquity BEH C18 (50 × 2.1 mm; 1.7 μm)	1.22 −2.18[a]	93(BPA) 69–103	LOD = 0.3 (BPA) ng g^{-1} MQL = 0.39–0.69 ng g^{-1}	[30]
Canned fish, meat, fruits and vegetables (5 g)	BPA, BADGE, BADGE·2H_2O, BADGE·H_2O, BADGE·HCl·H_2O, BADGE·2HCl, BADGE·HCl	Extraction: AcN, 40 mL Clean up: n-hexane, 75 mL; n-hexane washing with AcN, 30 + 20 mL; solvent evaporation; reconstitution MeOH: water (5:95), 3 mL; SPE, Oasis HLB; elution MeOH 2 × 2mL, MeOH: EA (50:50) 2 mL, EA 2 mL Solvent evaporation Reconstitution: AcN: water (90:10), 1 mL	LC-FD (λ_{ex} 235 nm, λ_{em} 317 nm) Mobile phase: AcN/water (gradient) Column: Nucleosil-100C18 (250 × 4 mm; 5 μm) External calibration	0.04 −2.82[a] 0.2 −2.96[b]	86.07 −114.06	MDL = 4.5–7.9 ng g^{-1} MQL = 13.7–24.1 ng g^{-1}	[32]
Canned fish and meat (1.25 g, total content)	BPA, BADGE, BADGE·2H_2O, BADGE·H_2O, BADGE·HCl·H_2O, BADGE·2HCl, BADGE·HCl, BFDGE, BFDGE·2H_2O, BFDGE·2HCl	Sample + 10 g anhydrous sodium sulphate Extraction: DCM 2 × 30 mL; solvent evaporation; reconstitution DCM:CH (50:50), 25 mL Clean up: (2 mL) Gel permeation chromatography(Bio-Beads S-X3); elution DCM:CH (50:50) Eluate evaporation Reconstitution: AcN, 0.5 mL	LC-FD (λex 233 nm, λem 310 nm) Mobile phase: AcN/water (gradient) Column: LiChrospher250-4 (250 × 4 mm; 5 μm) External calibration	2.3–3[a]	75–92	MDL = 3 ng g^{-1} MQL = 10 ng g^{-1}	[34]
Canned vegetables, fruits, fish, grains and meat (0.2 g)	BPA, BPB, BPE, BPF, BADGE, BADGE·2H_2O, BADGE·H_2O, BADGE·HCl, BADGE·HCl·H_2O, BADGE·2HCl, BFDGE, BFDGE·2HCl	Extraction: 0.6 mL SUPRAS (tetradecanoic acid, 40% THF, v/v) stirring. Centrifugation	LC-FD (λex 276 nm, λem 303 nm) Mobile phase: acetonitrile/water (gradient) Column: Ultrabase C18 (250 × 4.6 mm; 5 μm) External calibration	1.8 −6.8[a] 4.4 −8.1[b]	80–110	MDL = 0.9–3.5 ng g^{-1} MQL = 0.3–1.1 ng g^{-1}	[59]
Beverages							
Canned cola, energetic drinks, carbonated drink and no carbonated flavor drink (10 mL)	BPA, BPB	Sample at pH ≥ 10 with potassium carbonate, 5% Extraction: DLLME (extractive solvent: T4CE, 30 μL; dispersive solvent: AcN, 440 μL)	Heart cutting-GC-EI-MS(SIM) Derivatization agent: AA Column 1: DB-5HT (5m × 0.32 mm, 0.1 μm) Column 2: DB-5MS (15m × 0.25 mm, 0.25 μm) Matrix-matched calibration (BPA-d16)	2–8[a]	82–111	MDL = $2 \cdot 10^{-3}$ – $5 \cdot 10^{-3}$ ng mL^{-1} MQL = $7 \cdot 10^{-3}$ – $1 \cdot 10^{-2}$ ng mL^{-1}	[37]

Table 3 (*continued*)

Sample type (size)	Analytes	Sample treatment	Separation/detection	RSD (%)	R (%)	Detection limits	Ref.
Canned soft drinks (50 mL)	BPA, BPF	Degasification Derivatization Extraction: n-heptane, 5 mL	GC-EI-MS(SIM) Derivatization agent: AA Column: HP-5MS (30m × 0.25 mm, 0.25 μm) External calibration (BPA-d14)	5.2[a]	61–128	MDL = 2–10 ng mL^{-1}	[33]
Canned soda, tonic water, beer, sports drink, tea and cola (2 mL)	BPA, BPF, BPZ	Degasification Centrifugation Dilution to 10 mL with water + derivatization agent Extraction: SBSE (PDMS), 3 h Desorption: unit of thermal desorption connected to the autosampler	GC-EI-MS(SIM) Derivatization agent: AA Column: HP-5MS (30m × 0.25 mm, 0.25 μm) External calibration	1.90 –3.59[a] 3.11 –5.80[b]	86–122	LOD = $0.9\cdot10^{-3} - 2.5\cdot10^{-3}$ ng mL^{-1} LOQ = $3.2\cdot10^{-3}$ –$8.4\cdot10^{-3}$ ng mL^{-1}	[35]
Canned soda, tonic water, beer, sports drink, tea, cola and beer (1 mL)	BPA, BPF, BPE, BPB,BPS	Extraction: SPE on-line, C18; loading solvent MeOH:water (5:95)	LC-ESI(−)-MS/MS(SRM) Mobile phase: MeOH/water (gradient) Column:: Fused Core™Ascentis Express C18 (50 × 2.1 mm; 2.7 μm) Matrix-matched calibration (BPA-d16)	2.5 –10[a]	93–98	MDL = $5\cdot10^{-3}$ –$5\cdot10^{-2}$ ng mL^{-1} MQL = $1.5\cdot10^{-2}$ – 0.167 ng mL^{-1}	[24]
Juice, liquor, coffee drinks, bottled water, soft drink, fruit juice, beer and wine (5 g)	BPA, BPB, BPF BPAF, BPAP, BPP, BPS, BPZ	Extraction: EA, 2 × 6 mL; solvent evaporation; Reconstitution DCM:hexane (10:90), 2 mL Clean up: SPE, Strata NH2; elution MeOH:acetone (80:20), 5 mL Solvent evaporation Reconstitution: MeOH, 0.5 mL	LC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: Betasil C18 (100 × 2.1 mm; 5 μm) External calibration (BPA-$^{13}C_{12}$)	n.r	78–122	MQL = 0.01–0.05 ng g^{-1}	[15,23]
Canned soda, beer, cola, tea and tonic water (3 mL)	BADGE, BADGE·$2H_2O$, BADGE·H_2O, BADGE·HCl·H_2O, BADGE·2HCl, BADGE·HCl, BFDGE, BFDGE·$2H_2O$, BFDGE·2HCl	Degasification by sonication Extraction: SPE, Oasis HLB; elution MeOH, 4 mL Solvent evaporation Reconstitution: MeOH:water (50:50), 1 mL	LC-ESI(+)-QQQ(SRM) Mobile phase: MeOH/25 mM formic acid-ammonium formate buffer (pH 3.75) (gradient) Column: Fused Core™Ascentis Express C18 (50 × 2.1 mm; 2.7 μm) External calibration	3–20[a]	70–95	MQL = 0.13–1.6 ng mL^{-1}	[112]
Drinking water							
Tap water (100 mL)	BPA, BPF, BPB,BPS	Extraction: SPE (C18); elution AcN, 5 mL Solvent evaporation Reconstitution: MeOH (70%), 1 mL	UPLC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: ACQUITY BEH C8 (50 × 2.1 mm, 1.7 μm) External calibration (BPA-$^{13}C_{12}$)	1.26 –3.67[a]	89.2 –106.9	MDL = 0.25–1 ng mL^{-1}	[121]
Personal care products							
Cosmetic and personal hygiene products (0.12 g)	BPA, BPF, BPZ	Sample + water, 10 mL + NaCl, 1 g and sonication Extraction: SBSE (EG-silicone), 3 h at 900 rpm Water washing Desorption: unit of thermal desorption connected to the autosampler	GC-EI-MS(SIM) No derivatization step Column: HP-5MS (30m × 0.25 mm, 0.25 μm) External calibration (BP)	1.2 –2.9[a]	89–114	MDL = 8–8.7 ng g^{-1} MQL = 26.7–29.2 ng g^{-1}	[66]
Cosmetic and personal hygiene products (0.2–0.5 g)	BPA, BPB, BPF, BPP, BPS, BPZ, BPAF, BPAP	Extraction: MTBE, 2 × 5 mL; shaking; centrifugation; water washing, 2 mL Solvent evaporation	LC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: Betasil C18	n.r.	74–122	MQL = 0.25–1 ng g^{-1}	[67]

(*continued on next page*)

Table 3 (*continued*)

Sample type (size)	Analytes	Sample treatment	Separation/detection	RSD (%)	R (%)	Detection limits	Ref.
		Reconstitution: DCM:hexane (1:9), 3 mL Clean up: SPE (Silica gel); elution DCM:ethyl acetate (1:1), 10 mL Solvent evaporation to 1 mL	(100 × 2.1 mm, 5 μm) External Calibration (BPA-$^{13}C_{12}$)				
Paper							
Paper (0.12 g)	BPA, BPS	Air-drying in an oven at 105 °C for 24 h	Py-GC-EI-MS(SIM) Derivatization agent: TMAH Column: DB5 fused silica (30m × 0.25 mm, 0.25 μm) External calibration	n.r	n.r.	LOD = $0.5\cdot10^3$–$0.6\cdot10^3$ ng g^{-1} LOQ = $1.3\cdot10^3$–$1.4\cdot10^3$ ng g^{-1}	[122]
Dust							
Houses, offices and laboratories (0.05 −0.1 g)	BPA, BPAF, BPAP, BPB, BPF, BPP, BPS, BPZ	Extraction: MeOH:water (5:3), 5 + 3 mL; shaking; centrifugation Solvent evaporation to ~ 4 mL Dilution to 10 mL with formic acid (0.2%, pH = 2.5) Clean up: SPE (Oasis MCX); elution MeOH, 5 mL Solvent evaporation to 1 mL	LC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: Betasil C18 (100 × 2.1 mm) External calibration (BPA-$^{13}C_{12}$)	<20[a]	51–137	MQL = 0.5–2 ng g^{-1}	[18]
Houses, offices, cars, air conditioner, and laboratories (0.1 g)	BPA, BPAF, BPAP, BPB, BPF, BPP, BPS, BPZ	Extraction: [MeOH:water (5:3), 5 mL; shaking; centrifugation] x 3 times. Solvent evaporation to ~4 mL Dilution to 10 mL with formic acid (0.2%, pH = 2.5) Clean up: SPE (Sep-Pack C18); elution MeOH, 4 mL + THF:MeOH (4:6), 3 mL + THF, 3 mL Solvent evaporation to 1 mL	LC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water (0.1% ammonium) (gradient) Column: Betasil C18 (100 × 2.1 mm) External calibration (BPA-$^{13}C_{12}$)	<20[a]	78.3 −104.8	LOD = 0.05–0.2 ng g^{-1} LOQ = 0.5–2 ng g^{-1} MDL = 0.07–1 ng g^{-1}	[60]
Houses, offices and laboratories (0.05 −0.1 g)	BPA, BADGE, BADGE·H_2O, BADGE·HCl·H_2O, BFDGE·$2H_2O$	Extraction: MeOH:water (5:3), 5 + 3 mL; shaking; centrifugation Solvent evaporation to ~ 4 mL Dilution to 10 mL with formic acid (0.2%, pH = 2.5) Clean up: SPE (Oasis MCX); elution MeOH, 5 mL Solvent evaporation to 1 mL	LC-ESI(+)-MS/MS(MRM) Mobile phase: MeOH/MeOH:ammonium acetate 2 mM 1:9 v/v (gradient) Column: Betasil C18 (100 × 2.1 mm) External calibration (BPA-$^{13}C_{12}$)	<15[a]	86–115	MQL = 0.2 ng g^{-1}	[20]
Environmental							
Lake water (100 mL)	BPA, BPF, BPB,BPS	Extraction: SPE (C18); elution AcN, 5 mL Solvent evaporation Reconstitution: MeOH (70%), 1 mL	UPLC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: ACQUITY BEH C8 (50 × 2.1 mm, 1.7 μm) External calibration (BPA-$^{13}C_{12}$)	1.26 −3.67[a]	89.2 −106.9	MDL = 0.25–1 ng mL^{-1}	[121]
River water (250 mL)	BPA, BPE, BPF, BPM,TCBPA	Filtration Extraction: SPE (MISPE, BPE-MIP) Elution: HAc (5% in MeOH), 4 mL Solvent evaporation Reconstitution: AcN, 0.1 mL	LC-UV-VIS (λ 232 nm) Mobile phase: NH_4Ac (10 mM, pH 5.8)/methanol (gradient) Column: Capcell Pack C18 (250 × 4.6 mm; 5 μm) External calibration	1.8 −11.6[a] 2.5 −13.9[b]	86–97	MQL = $2.5\cdot10^{-3}$ – $5\cdot10^{-3}$ ng mL^{-1}	[128]
River water (1 mL)	BPA, MCBPA, DCBPA, TCBPA,TeCBPA	Extraction: SPE on-line, Hypersil Golg C18	LC-ESI(−)-MS/MS(SRM) Mobile phase: AcN/MeOH/water (gradient) Column: Fused Core™Ascentis Express C18 (50 × 2.1 mm; 2.7 μm)	3–14[a]	85–100	MQL = $5.7\cdot10^{-3}$ –0.18 ng mL^{-1}	[125]

Table 3 (*continued*)

Sample type (size)	Analytes	Sample treatment	Separation/detection	RSD (%)	R (%)	Detection limits	Ref.
			External calibration (BPA-d16)				
River water (300 mL)	BPA, BPF, BPB,BPS, BPAF, TCBPA	pH = 3–7 with HCl (1 M) Extraction: SPE (Oasis HLB); elution ammonia (2% in MeOH), 6 mL Clean up: (extract+1.5 mLwater) SPE (Oasis MAX); elution formic acid (2% in MeOH), 6 mL Solvent evaporation Reconstitution: MeOH:water (50:50), 1 mL	UPLC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: ACQUITY BEH C18 (100 × 2.1 mm, 1.7 μm) Standard addition method (TCBPA-$^{13}C_{12}$) (BPA-d4)	2.9 −16.9[a] <18.1[b]	80.6 −107.3	MDL = 0.02–0.45 ng mL^{-1} MQL = 0.05–1.49 ng mL^{-1}	[126]
River water (10.8 mL)	BPA, BPF, BADGE, BFDGE	Extraction: SUPRAS (decanoic acid, 60 mg in THF, 1.2 mL)+sample at pH = 2; stirring Centrifugation	LC-FD (λex 280 nm, λem 306 nm) Mobile phase: AcN/water (gradient) Column: Hipersil ODS C18 (150 × 4.6 mm; 5 μm) External calibration	2–5[a]	79–95	MDL = 0.03–0.035 ng mL^{-1}	[124]
River water, drinking water reservoir (10 −50 mL)	BPA, BPB, BPF, BPP, BPS, BPZ, BPAF, BPAP	Extraction: SPE (Oasis HLB); elution MeOH, 5 mL	LC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: Betasil C18 (50 × 2.1 mm, 5 μm) Standard addition method (BPA-$^{13}C_{12}$)	<20[a]	73–111 (43–54 BPP)	MQL = $1 \cdot 10^{-4}$-0.05 ng mL^{-1}	[76]
Sewage sludges (0.1 −0.2 g)	BPA, BPB, BPF, BPP, BPS, BPZ, BPAF, BPAP	Extraction: [MeOH:water (5:3), 5 mL; shaking; centrifugation] x 2 times. Solvent evaporation to ~4 mL Dilution to 10 mL with formic acid (0.2%, pH = 2.5) Clean up: SPE (Oasis MCX); elution MeOH, 5 mL	LC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water (1% ammonium hydroxide, v/v) (gradient) Column: Betasil C18 (100 × 2.1 mm, 5 μm) External calibration (BPA-$^{13}C_{12}$)	n.r	78–103	MQL = 78–103 ng g^{-1}	[61]
Sewage sludges (1 g)	BPA, MCBPA, DCBPA, TCBPA,TeCBPA	Dried samples Extraction: PLE (EA), 100 °C, 1000 psi, preheating period 2 min, 8 min static time, 3 cycles; final volume 15 mL Solvent evaporation Reconstitution: mobile phase, 0.5 mL Centrifugation	LC-APCI(−)-MS/MS(MRM) Mobile phase: MeOH (ammonia 0.025% v/v)/ 0.025% (v/v) ammoniacal aqueous solution (gradient) Column: Gemini C18 (100 × 2.0 mm; 3 μm) Matrix-matched calibration (BPA-d16)	0.7 −4.6[a] 0.9 −5.7[b]	97.7 −100.6	MDL = 0.004–0.008 ng g^{-1} MQL = 0.014–0.026 ng g^{-1}	[71]
Sewage sludges (1 g)	BPA, MCBPA, DCBPA, TCBPA,TeCBPA	Dried samples Extraction: PLE (EA), 100 °C, 1000 psi, preheating period 2 min, 8 min static time, 3 cycles; final volume 15 mL Solvent evaporation Reconstitution: mobile phase, 0.5 mL Centrifugation	LC-APCI(−)-MS/MS(MRM) Mobile phase: MeOH (ammonia 0.025% v/v)/ 0.025% (v/v) ammoniacal aqueous solution (gradient) Column: Gemini C18 (100 × 2.0 mm; 3 μm) Matrix-matched calibration (BPA-d16)	0.7 −4.6[a] 0.9 −5.7[b]	97.7 −100.6	MDL = 4–8 ng g^{-1} MQL = 14–26 ng g^{-1}	[72]
Sewage sludges (1 g)	BPA, MCBPA, DCBPA, TCBPA,TeCBPA	Dried samples Extraction: EA, 10 mL; stirring; sonication Centrifugation Solvent evaporation Reconstitution: mobile phase, 0.5 mL Centrifugation	LC-APCI(−)-MS/MS(MRM) Mobile phase: MeOH (ammonia 0.025% v/v)/ 0.025% (v/v) ammoniacal aqueous solution (gradient) Column: Gemini C18 (100 × 2.0 mm; 3 μm) Matrix-matched calibration (BPA-d16)	0.4 −2.1[a] 1.3 −3.4[b]	97.9 −103.1	MDL = 2–4 ng g^{-1} MQL = 8–14 ng g^{-1}	[72]

(*continued on next page*)

Table 3 (*continued*)

Sample type (size)	Analytes	Sample treatment	Separation/detection	RSD (%)	R (%)	Detection limits	Ref.
Sewage sludges (1 g)	BPA, MCBPA, DCBPA, TCBPA,TeCBPA	Dried samples Extraction: MAE (EA, 10 mL + water, 0.4 mL); 10 min (10 min for holding) at 90 °C; 1000 W Centrifugation Solvent evaporation Reconstitution: mobile phase, 0.5 mL centrifugation	LC-APCI(−)-MS/MS(MRM) Mobile phase: MeOH (ammonia 0.025% v/v)/ 0.025% (v/v) ammoniacal aqueous solution (gradient) Column: Gemini C18 (100 × 2.0 mm; 3 μm) Matrix-matched calibration (BPA-d16)	0.4 −3.5[a] 1.5 −5.3[b]	97 −101.4	MDL = 6–9 ng g^{-1} MQL = 20–30 ng g^{-1}	[72]
Sewage sludges (0.1 g)	BADGE, BADGE·H_2O, BADGE·HCl, BADGE·$2H_2O$, BADGE·2 HCl, BADGE·H_2O·HCl, BFDGE, BFDGE·2HCl, BFDGE·$2H_2O$	Dried samples Extraction: MeOH, 3 × 5 mL; shaking Centrifugation Extraction: SPE (ENVI-Carb); elution methanol 3 × 2 mL Solvent evaporation	LC-ESI(+)-MS/MS(MRM) Mobile phase: MeOH/ water:MeOH (9:1 v/v, ammonium acetate 2 mM) (gradient) Column: Betasil C18 (50 × 2.1 mm, 5 μm) Standard addition method (BADGE-d6)	n.r.	74–150	MQL = 4.55–9.10 ng g^{-1}	[75]
Sediments and sludges (0.5 and 0.2 g)	BPA, BPF, BPB,BPS, BPAF, TCBPA	Dried samples + MeOH:acetone (50:50), 2 × 10 mL and sonication Centrifugation Solvent evaporation to 1 mL Dilution to 10 mL with water Extraction: SPE (Oasis HLB); elution ammonia (2% in MeOH), 6 mL Clean up: (extract+1.5 mLwater) SPE (Oasis MAX); elution formic acid (2% in MeOH), 6 mL Solvent evaporation Reconstitution: MeOH:water (50:50), 1 mL	UPLC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/ water (gradient) Column: ACQUITY BEH C18 (100 × 2.1 mm, 1.7 μm) Standard addition method (TCBPA-$^{13}C_{12}$) (BPA-d4)	3.5 −16.8[a] <18.1[b]	57.1 −103.2	MDL = 0.02–0.86 ng g^{-1} MQL = 0.06–2.83 ng g^{-1}	[126]
Sediments (0.2–0.5 g)	BPA, BPB, BPF, BPP, BPS, BPZ, BPAF, BPAP	Extraction: MeOH:water (5:3), 3 × 5 mL; shaking; centrifugation, extract combination Solvent evaporation to ~4 mL Dilution: formic acid (2%, pH = 2.5), 10 mL Clean up: SPE (Oasis MCX); elution MeOH, 5 mL Solvent evaporation to 1 mL	LC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/ water (gradient) Column: Betasil C18 (100 × 2.1 mm; 5 μm) External calibration (BPA-$^{13}C_{12}$)	<10[a]	82–138	MQL = 0.25–1 ng g^{-1}	[48]
Sludges from wastewater treatment plants (0.1 g)	BPA, BPB, BPF, BPP, BPS, BPZ, BPAF, BPAP	Dried samples Extraction: Methanol:water (5:3), 3 × 5 mL; shaking Centrifugation Solvent evaporation to 4 mL Dilution: formic acid (2%, pH = 2.5), 10 mL Clean up: SPE (Oasis MCX); elution MeOH, 5 mL Solvent evaporation to 1 mL	LC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/ water (gradient) Column: Betasil C18 (50 × 2.1 mm, 5 μm) External calibration (BPA-$^{13}C_{12}$)	n.r.	55.9 −157	MQL = 0.5–2 ng g^{-1}	[73]
Influent and effluent of sewage treatment plant (400 mL)	BPA, BPF	Sample containing TBAC 5 mM Extraction: SPE (hemimicelles of SDS on alumina) Elution: MeOH, 1 mL	LC-FD (λex 278 nm, λem 306 nm) Mobile phase: AcN/water (gradient) Column: Waters Nova-Pack C18 (150 × 3.9 mm; 4 μm) External calibration	n.r.	96–106	MDL = 0.01–0.015 ng mL^{-1}	[123]

Table 3 (*continued*)

Sample type (size)	Analytes	Sample treatment	Separation/detection	RSD (%)	R (%)	Detection limits	Ref.
Dringking water treatment plants (250 mL)	BPA, MCBPA, DCBPA, TCBPA	Sample + sodium thiosulphate (20 mg L-1)for the removal of residual chlorine Sample + MeOH 1.25 mL Extraction: SPE (C18 upti-clean)); elution hexane:DCM (1:1), 2 × 2 mL + MeOH:acetone:EA (2:2:1), 2 × 2 mL Solvent evaporation Reconstitution: water:MeOH (50:50), 0.250 mL	UPLC-APCI(−)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: Supercosil ABZ® (150 × 4.6 mm; 3 μm) External calibration (BPA-d16)	7.19[a] 13 −21[b]	88−108	MDL = 0.3 ·10^{-3} − 2.3 ·10^{-3} ng mL^{-1} MQL = 1 ·10^{-3} − 6.8 ·10^{-3} ng mL^{-1}	[127]
Influent (100 mL) and effluent (300 mL) of sewage treatment plant	BPA, BPF, BPB,BPS, BPAF, TCBPA	pH = 3−7 with HCl (1 M) Extraction: SPE (Oasis HLB); elution ammonia (2% in MeOH), 6 mL Clean up: (extract+1.5 mLwater) SPE (Oasis MAX); elution formic acid (2% in MeOH), 6 mL Solvent evaporation Reconstitution: MeOH:water (50:50), 1 mL	UPLC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: ACQUITY BEH C18 (100 × 2.1 mm, 1.7 μm) Standard addition method (TCBPA-$^{13}C_{12}$) (BPA-d4)	2.9 −13.5[a] <18.1[b]	75.8 −114.3	MDL = 0.02−0.82 ng mL^{-1} MQL = 0.06−1.65 ng mL^{-1}	[126]
Industrial effluent (paper recycling plant) (1 mL)	BPA, MCBPA, DCBPA, TCBPA,TeCBPA	Extraction: SPE on-line, Hypersil Golg C18	LC-ESI(−)-MS/MS(SRM) Mobile phase: AcN/MeOH/water (gradient) Column: Fused Core™Ascentis Express C18 (50 × 2.1 mm; 2.7 μm) External calibration (BPA-d16)	3.14[a]	85−100	MQL = 5.7 ·10^{-3} −0.18 ng mL^{-1}	[125]
Dringking water treatment plants (100 mL)	BPA, MCBPA, DCBPA, TCBPA,TeCBPA	Sample + sodium thiosulphate (20 mg L-1)for the removal of residual chlorine Extraction: SPE (Oasis HLB); elution MTBE:MeOH (1:1), 4 mL Derivatization Reconstitution: AcN, 0.5 mL	UPLC-ESI(+)-MS/MS(MRM) Mobile phase: AcN/water (0.1% formic acid) (gradient) Column: AcquityUPLC BEH C18 (100 × 2.1 mm; 1.7 μm) External calibration (BPA-d4)	≤10[b]	102 −109	LOD = 0.001−0.03 ng mL^{-1} MQL = 2 ·10^{-5} −5 ·10^{-5} ng mL^{-1}	[25]
Influent and effluent of sewage treatment plant (10.8 mL)	BPA, BPF, BADGE, BFDGE	Extraction: SUPRA (decanoic acid, 60 mg in THF, 1.2 mL)+sample at pH = 2; stirring Centrifugation	LC-FD (λex 280 nm, λem 306 nm) Mobile phase: acetonitrile/water (gradient) Column: Hipersil ODS C18 (150 × 4.6 mm; 5 μm) External calibration	2−5[a]	78−96	MDL = 0.03−0.035 ng mL^{-1}	[124]
Biological samples							
Urine (5 mL)	BPA, BPB (free and total concentration)	Sample* +K2CO3, 5% to pH > 10 DLLME: 1.325 mL AcN (dispersive solvent)+ 50 μL T4CE (extractive solvent)+0.125 μL derivatization agent; inject into the sample; shaking; centrifugation *for total concentration, previous deconjugation using β-glucuronidase/sulfatase	Heart cutting-GC-EI-MS(SIM) Derivatization agent: AA Column 1: DB-5HT (5m × 0.32 mm, 0.1 μm) Column 2: DB-5MS (15m × 0.18 mm, 0.18 μm) Matrix-matched calibration (BPA-d16)	7−20[a]	71−93	MDL = 0.03−0.05 ng mL^{-1} MQL = 0.1 ng mL^{-1}	[42]
Urine (0.1 mL)	BPA, BPF, BPS (free and total concentration)	Sample* to 1 mL with formic acid 0.1 M; stirring; centrifugation Extraction: SPE on-line, LiChrosfer RP-18 ADS;	LC-APCI(−)-MS/MS Mobile phase: MeOH/10 mM ammonium acetate (gradient) Column: Chromolith®	5.4 −12.1[b]	91−107	MDL = 0.03−1 ng mL^{-1}	[131]

(*continued on next page*)

Table 3 (*continued*)

Sample type (size)	Analytes	Sample treatment	Separation/detection	RSD (%)	R (%)	Detection limits	Ref.
		injection volume 0.350 mL *for total concentration, previous deconjugation using β-glucuronidase/sulfatase	C18 (100 × 4.6 mm) External calibration (BPA-$^{13}C_{12}$) (BPS–$^{13}C_{12}$)				
Urine (0.3 mL)	BPA, MCBPA, DCBPA, TCBPA, TeCBPA (free concentration)	Sample + ACN, 0.6 mL; shaking; +ammonium formate 10 M, 0.150 mL; stirring Centrifugation Solvent evaporation of 0.4 mL organic layer Reconstitution: water (0.1 mL)	UPLC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: Acquity CSH™ C18 (100 × 2.1 mm, 1.7 μm) Matrix-matched calibration (BPA-d16) (DCBPA-d12)	3–15[a] 4–20[b]	33–45	MDL = 0.009–0.048 ng mL^{-1}	[43]
Urine (5 mL)	BPA, MCBPA, DCBPA, TCBPA, TeCBPA, BPS (free and total concentration)	Sample* to 10 mL with NaCl 10%; pH = 2 with HCl 0.1 M DLLME: 0.5 mL acetone (dispersive solvent)+ 0.750 μL TCM (extractive solvent); inject into the sample; shaking; centrifugation Solvent evaporation of organic layer Reconstitution: MeOH (0.1% ammonia): water (0.1% ammonia) (60:40) (0.1 mL) *for total concentration, previous deconjugation using β-glucuronidase/sulfatase	UPLC-ESI(+,-)-MS/MS(MRM) Mobile phase: MeOH (ammonia 0.1% v/v)/0.1% (v/v) ammoniacal aqueous solution (gradient) Column: Acquity UPLC® BEH C18 (50 × 2.1 mm, 1.7 μm) Matrix-matched calibration (BPA-d16)	1.9–13.8[b]	94–106	MDL = 0.1–0.6 ng mL^{-1}	[57]
Urine (0.5 mL)	BPA, BPADS, BPADG, MCBPA, DCBPA, TCBPA,	Sample + EI, 0.05 mL + ammonium acetate buffer (1 M, pH = 5),1 mL + formic acid buffer (1 M, pH = 1), 0.24 mL + water, 1.21 mL For BPA and BPA chlorides: Extraction: SPE (Oasis HLB); elution MeOH, 5 mL Solvent evaporation to 0.5 mL For BPAG and BPADS Extraction: SPE (Strata NH2+Sep-Pak C18 in series) Elution Strata NH2: NH_4OH (5% in MeOH), 3 mL; pH to 7 with formic acid; concentration to 1 mL (fraction containing BPADS) Elution Sep-Pak C18: MeOH), 5 mL; concentration to 1 mL (fraction containing BPAG)	LC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/10 mM ammonium acetate (gradient) Column: Betasil C18 (100 × 2.1 mm, 3 μm) External calibration (BPA-$^{13}C_{12}$)	2–19[a]	76–129	LOD = 0.003–0.02 ng mL^{-1} LOQ = 0.01–0.05 ng mL^{-1}	[44]
Urine (0.2 mL)	BADGE, BADGE·H_2O, BADGE·$2H_2O$	Extraction: EA:hexane (1:1), 2 mL; stirring; centrifugation Solvent evaporation Reconstitution: initial mobile phase, 0.2 mL	LC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH (5 mM ammonium acetate)/water (5 mM ammonium acetate) (gradient) Column: Luna C18 (50 × 2 mm, 3 μm) External calibration (BPA-$^{13}C_{12}$) (BPS–$^{13}C_{12}$)	0.7–14.4[a]	51–114	MQL = 0.05–0.2 ng mL^{-1}	[131]
Urine (0.5 mL)	BADGE, BADGE·H_2O, BADGE·HCl·H_2O, BFDGE·$2H_2O$ (free and total concentration)	Sample*+ammonium acetate 1 M, 0.3 mL Extraction: EA, 3 × 3 mL; centrifugation; combination of extracts Wash: water, 1 mL	LC-ESI(+)-MS/MS(MRM) Mobile phase: MeOH/MeOH:ammonium acetate 2 mM 1:9 v/v (gradient) Column: Betasil C18	<15[a]	72–107	LOQ = 0.01–0.03 ng mL^{-1}	[12]

Table 3 (*continued*)

Sample type (size)	Analytes	Sample treatment	Separation/detection	RSD (%)	R (%)	Detection limits	Ref.
		Solvent evaporation Reconstitution: MeOH (0.5 mL) *for total concentration, previous deconjugation using β-glucuronidase/sulfatase	(100 × 2.1 mm) External calibration (BP-3-$^{13}C_{12}$)				
Urine (0.5 mL)	BADGE, BADGE·H_2O, BADGE·HCl·H_2O, BADGE·$2H_2O$, BADGE·HCl (total concentration)	Deconjugation using β-glucuronidase/sulfatase Extraction: EA, 3 × 3 mL; centrifugation; combination of extracts Wash: water, 1 mL Solvent evaporation Reconstitution: MeOH (0.5 mL)	LC-ESI-MS/MS(SRM) Mobile phase: Column: Betasil C18 (100 × 2.1 mm; 5 μm) External calibration (BADGE-d6)	nr	nr	LOQ = 0.5–2 ng mL^{-1}	[38]
Urine (0.5 mL)	BADGE, BADGE·H_2O, BADGE·HCl·H_2O, BADGE·$2H_2O$, BADGE·HCl, BADGE·2HCl, BFDGE, BFDGE·2HCl, BFDGE·$2H_2O$, BPA, BPAP, BPAF, BPP, BPS, BPZ (total concentration)	Deconjugation using β-glucuronidase/sulfatase Extraction: EA, 3 × 3 mL; centrifugation; combination of extracts Wash: water, 1 mL Solvent evaporation Reconstitution: MeOH (0.5 mL)	LC-ESI(+)-MS/MS(MRM) Mobile phase: MeOH/water: MeOH (9:1) (1.5% ammonium acetate) (gradient) Column: Betasil C18 (100 × 2.1 mm; 5 μm) LC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water: MeOH (9:1) (1.5% ammonium acetate) (gradient) Column: Betasil C18 (100 × 2.1 mm; 5 μm) LC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: Betasil C18 (100 × 2.1 mm; 5 μm) External calibration (BADGE-d6)	nr	nr	MQL = 0.01–2 ng mL^{-1}	[39]
Serum (0.3 mL)	BPA, BPB (free concentration)	Sample + mobile phase, 0.150 mL + perchloric acid (25%), 0.150 mL(for protein precipitation); stirring Centrifugation	LC-FD (λ_{ex}273 nm, λ_{em} 300 nm) Mobile phase: AcN/phosphate buffer (pH 6) (isocratic) Column: Onyx Monolithic C18 (100 × 4.6 mm) External calibration	3.9–4.2[a]	86–88	LOD = 0.15–0.18 ng mL^{-1} LOQ = 0.5–0.6 ng mL^{-1}	[28]
Serum (0.5 mL)	BPA, BPADS, BPADG, MCBPA, DCBPA, TCBPA,	Sample + EI, 0.05 mL + ammonium acetate buffer (1 M, pH = 5),1 mL + formic acid buffer (1 M, pH = 1), 0.24 mL + water, 1.21 mL Extraction: SPE (Strata NH2+ Oasis MCX in series) Elution Strata NH2: NH4OH (5% in MeOH), 3 mL; pH to 7 with formic acid; concentration to 1 mL (fraction containing BPADS) Elution Oasis MCX: MeOH, 5 mL; concentration to 1 mL (fraction containing BPA,BPAG and BPA chlorides)	LC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/10 mM ammonium acetate (gradient) Column: Betasil C18 (100 × 2.1 mm, 3 μm) External calibration (BPA-$^{13}C_{12}$)	3–18[a]	76–129	LOD = 0.003–0.02 ng mL^{-1} LOQ = 0.01–0.05 ng mL^{-1}	[44]
Plasma (5 mL)	MCBPA, DCBPA, TCBPA, TeCBPA	Dilution to 15 with water Proteins precipitation: $ZnSO_4$ (10%), 1 ml + NaOH (0.1 M), 1 mL, centrifugation, supernatant filtration Acidification: HCl (0.1 M), pH = 3–3.5; water to 20 mL Extraction: SPME (PA 85 μm)	GC-EI-MS(SIM) Derivatization agent: BSTFA Column: HP1 (30m × 0.25 mm, 0.25 μm) Standard addition method	3.8–4.5[a]	94–107.2	MDL = 0.5–3 ng mL^{-1} MQL = 0.8–5 ng mL^{-1}	[130]

(*continued on next page*)

Table 3 (*continued*)

Sample type (size)	Analytes	Sample treatment	Separation/detection	RSD (%)	R (%)	Detection limits	Ref.
		Desorption: thermal desorption Derivatization in the GC injector port					
Plasma (venous blood and umbilical cord blood) (0.2 mL)	BADGE, BADGE·H_2O, BADGE·$2H_2O$	Extraction: EA:hexane (1:1), 2 mL; stirring; centrifugation Solvent evaporation Reconstitution: initial mobile phase, 0.2 mL	LC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH (5 mM ammonium acetate)/water (5 mM ammonium acetate) (gradient) Column: Luna C18 (50 × 2 mm, 3 μm) External calibration (BPA-$^{13}C_{12}$) (BPS−$^{13}C_{12}$)	4.2 −13.7[a]	51−114	MQL = 0.05−0.2 ng mL^{-1}	[131]
Plasma (0.5 mL)	BPA, BADGE, BADGE·H_2O, BADGE·HCl·H_2O, BADGE·$2H_2O$, BADGE·HCl, BADGE·2HCl, BFDGE, BFDGE·$2H_2O$, BADGE·2HCl	Extraction: EA, 3 × 3 mL; shaking; centrifugation; water washing, 1 mL Solvent evaporation Reconstitution: methanol, 0.5 mL	LC-ESI(±)-MS/MS(MRM) Mobile phase: MeOH/water: MeOH (9:1) (2 mM ammonium acetate) (gradient) Column: Betasil C18 (100 × 2.1 mm) External calibration (BPA-$^{13}C_{12}$) (BP-3-$^{13}C_{12}$) (BADGE-d6)	<15[a]	94−107	MQL = 0.25−2.5 ng mL^{-1}	[77]
Placental tissue (1.5 g)	BPA, MCBPA, DCBPA, TCBPA	Homogenization: sample + water, 1.5 mL; stirring Extraction: EA,3 mL; stirring; centrifugation Solvent evaporation of the organic layer Reconstitution: amonia in MeOH (0.1%), 1 mL (containing the I.E.)+ amonia in water (0.1%), 1 mL; shaking Centrifugation	LC-APCI(−)-MS/MS(MRM) Mobile phase: ammoniacal aqueous (0.1%)/ammonia in MeOH (0.1%) (gradient) Column: Gemini C18 (100 × 2 mm, 3 μm) Standard addition method (BPA-d16)	1.8 −8.1[a]	97−105	MDL = 0.2−0.6 ng g^{-1} MQL = 0.5−2 ng g^{-1}	[46]
Placental tissue (0.250 g)	BPA, MCBPA, DCBPA, TCBPA, TeCBPA	Lyophilized tissue + silica, 0.75 g; manual grounding Extraction: MSPD (mixture into a polypropylene cartridge containing PSA, 0.75 g as clean up sorbent); extraction MeOH, 12.5 mL Solvent evaporation Reconstitution: MeOH:water (containing ammonia 0.1%) (60:40), 0.1 mL; stirring; centrifugation	UPLC-ESI(+/−)-MS/MS(SRM) Mobile phase: ammoniacal aqueous (0.1%)/ammonia in MeOH (8.5 mM) (gradient) Column: Acquity BEH C18 (50 × 2.1 mm, 1.7 μm) Matrix-matched calibration (BPA-d16)	6.1 −14.8[b]	97−105	MDL = 0.1 ng g^{-1} MQL = 0.3−0.4 ng g^{-1}	[41]
Human breast milk (3 g)	BPA, BPB, BPAP, BPAF, BPBP, BPC, BPC12, BPE, BPPH, BPS, BPF, DHDPE, BPFL, BPZ, BPM, BPP, BP4,4′,BIS2 (total concentration)	Deconjugation using β-glucuronidase/sulfatase Protein precipitation: Acetone, 5 + 3 mL Evaporation of organic layer Extraction: SPE, CHROMABOND HR-X; elution AcN, 14 mL Clean up: SPE, MIP(MACHEREY BPA); elution MeOH, 10 mL Solvent evaporation Reconstitution AcN, 0.1 mL Derivatization	GC-EI-MS(SRM) Derivatization agent:MSTFA Column: Optima®-17-MS (30m × 0.25 mm, 0.25 μm) External calibration (BPA-$^{13}C_{12}$)	13 −20[b]	90−109	MDL = 0.001−0.03 ng g^{-1} MQL = 0.003−0.1 ng g^{-1}	[40]
Human breast milk (0.5 mL)	BPA, MCBPA, 2,6-DCBPA, 2,2′-DCBPA, TCBPA,	Stirring Extraction: MeOH,4 mL; stirring; sonication; centrifugation Solvent evaporation of supernatant Reconstitution: water:MeOH (70:30), 1 mL	UPLC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: Acquity CSH™ C18 (100 × 2.1 mm, 1.7 μm) Matrix-matched	1−20[a] 11 −19[b]	81−119	MDL = 0.01−0.09 ng mL^{-1} MQL = 0.4 ng mL^{-1}	[58]

Table 3 (*continued*)

Sample type (size)	Analytes	Sample treatment	Separation/detection	RSD (%)	R (%)	Detection limits	Ref.
		Clean up: SPE on-line, Xbridge C8; injection volume 0.050 mL; loading solvent MeOH:water (20:80)	calibration (BPA-d16)				
Adipose tissue (0.2 g)	BPA, MCBPA, DCBPA, TCBPA	Homogenization: sample + n-hexane, 6 mL; Extraction: AcN, 2 mL; shaking Separation of phases Solvent evaporation Reconstitution water, 15 mL Clean up: SPE, AccuBONDII ODS-C18; elution DEE:MeOH:DCM (9:1), 3 mL Solvent evaporation Reconstitution EA, 0.120 mL Derivatization	GC-EI-MS(SIM) Derivatization agent: BSTFA/TMCS (1:1) Column: ZB-5MS Zebron(30m × 0.25 mm, 0.25 μm) Standard addition method	3.8–4.5[a]	95–105	LOD = 0.5–3 ng g^{-1}	[47]
Adipose tissue (0.2–0.3 g)	BPA, BADGE, BADGE·H_2O, BADGE·HCl·H_2O, BADGE·$2H_2O$, BADGE·HCl, BADGE·2HCl, BFDGE, BFDGE·$2H_2O$, BADGE·2HCl	Extraction/homogenization: acetone, 5 mL (in a mortar); methanol washing, 2 mL Acetone evaporation Separation of lipids at −20 °C (15 min) Centrifugation Solvent evaporation to 0.5 mL	LC-ESI(±)-MS/MS(MRM) Mobile phase: MeOH/water: MeOH (9:1) (2 mM ammonium acetate) (gradient) Column: Betasil C18 (100 × 2.1 mm) External calibration (BPA-$^{13}C_{12}$) (BP-3-$^{13}C_{12}$) (BADGE-d6)	<15[a]	98–125	MQL = 0.16–4 ng g^{-1}	[76]
Colostrum (0.5 mL)	BPA, MCBPA, 2,6-DCBPA, 2,2′-DCBPA, TCBPA	Extraction: MeOH,4 mL; stirring; sonication; centrifugation Solvent evaporation of supernatant Reconstitution: water:MeOH (50:50), 1 mL Clean up: SPE on-line, Xbridge C8; injection volume 0.050 mL; loading solvent MeOH:water (20:80)	UPLC-ESI(−)-MS/MS(MRM) Mobile phase: MeOH/water (gradient) Column: Acquity CSH™ C18 (100 × 2.1 mm, 1.7 μm) External calibration (BPA-d16)	≤20[b]	80–120	LOD = 0.01–0.09 ng mL^{-1} LOQ = 0.4 ng mL^{-1}	[45]

Abbreviations: AA: acetic anhydride; AcN: Acetonitrile; APCI: atmospheric-pressure chemical ionization; BEHP: bis(2-ethylhexyl) phthalate; BP-3: 2-hydroxy-4-methoxybenzophenone; BSTFA: bis-(trimethylsilyl)trifluoroacetamide); CH: cyclohexane; DCM: dichloromethane; DEE: diethyl ether; DLLME: dispersive liquid–liquid microextraction; EA: ethylacetate; EI: electron impact; ESI: electronspray ionization; FD: fluorescence detection; GC: gas chromatography; GCB: graphitized carbon black; HAc: acetic acid; HLB: hydrophilic-lipophilic balance; HS-SPME: headspace solid-phase microextraction; LC: liquid chromatography; LOD: instrumental detection limit; LOQ: instrumental quantitation limit; MAE: microwave-assisted extraction; MAX: mixed-mode anion-exchange; MCX: mixed-mode cation-exchange; MDL: method detection limit; MeOH: methanol; MIP: molecularly imprinted polymer; MISPE: molecularly imprinted solid-phase extraction; MQL: method quantitation limit; MRM: multiple reaction monitoring; MS: mass spectrometry; MSTFA: N-methyl-N(trimethylsilyl)-trifluoroacetamide); MTBE: methyl tert-butyl ether; n.r.: not reported; PA: polyacrylate; PDMS: polydimethylsiloxane; PLE: pressurized liquid extraction; PSA: poly secondary amine; PS-DVB: polystyrene-divinylbenzene; Py: pyrolysis; QTRAP: hybrid triple quadrupole/linear ion trap mass spectrometer; SBSE: stir bar sorptive extraction; SDS: dodecilsulfato sódico; SIM: single ion monitoring; SLB-5MS: poly (5%-diphenyl, 95%-methyl siloxane); SPE: solid-phase extraction; SPME: solid-phase microextraction; SRM: selected reaction monitoring; SWCNT: single wall carbon nanotubes; T4CE: tetrachloro ethylene; TBAC: tetrabutylammonium chloride; TBME: *tert*-Butylmethylether; TCA: trichloroacetic acid; TCM: Trichloromethane; THF: tetrahydrofuran; TMAH: trimethylammonium hydroxide; TMCS: trimethylchloro silane; TMSH: trimethylsulphonium hydroxide; UPLC: ultra performance liquid chromatography.

[a] Intra-day.

[b] Inter-day precision.

Filtration of the ultra-high-quality water through a hydrophobic membrane (Empore disk) has proved efficient to obtain bisphenol-free water [116].

Organic solvents used as mobile phases in LC represent an important source of contamination of bisphenols. An effective approach for removing or minimizing this contamination is the use of a C18 pre-column between the LC pump and the injection valve. In this way, bisphenols coming from the solvents making up the mobile phase are retained in the precolumn and elute after the respective bisphenols coming from the sample [117].

2.2. Sample preparation

2.2.1. Packed food

Sample treatment is somewhat different for solid and liquid foodstuffs. Solid foodstuffs are usually homogenized and sometimes freeze–dried [15,23]. Canned food containing both liquid and solid portions (e.g. vegetables) can be filtered and treated separately [118] or the whole sample taken for analysis [33]. The amount of food required for analysis is usually in the range 1–20 g for solid samples [e.g. 15, 33], and 10 mL for liquid samples such as

bottled milk [53] and the liquid portion of canned vegetables [118]. Many methods have been developed for specific food matrices such as seafood [27], vegetables [35,118], infant formula [33,37], tuna [31], milk [52,119] etc, but various of them are applicable to a range of samples [23,50,59].

Solvent extraction is the most common technique for the isolation of mixtures of bisphenols and diglycidyl ethers from solid foodstuffs (Table 3). Among solvents, acetonitrile is usually preferred for the extraction of bisphenols [23,33,54] while pentane [56], hexane-acetone [49,51] and ethyl acetate [112], in addition to acetonitrile [31], have been proposed for the extraction of diglycidyl ethers. Typically, conventional solvent extraction using stirring or sonication is applied and repeated extractions are usually necessary to ensure the complete isolation of both bisphenols and diglycidyl ethers. Other strategies reported include the application of the QuECHERS method to the extraction of mixtures of bisphenols [26,27], and the use of auxiliary energies, such as microwave [50,51] and pressure [49], in the extraction of diglycidyl ethers. Benefits of using microwave assisted extraction (MAE) and pressurized liquid extraction (PLE) include increased extraction rates and considerable reduction in solvent consumption [49–51]. On the other hand, very low enrichment factors have been achieved for the extraction of mixtures of bisphenols using the QuECHERS approach [26,27]. To overcome this problem, dispersive liquid–liquid microextraction (DLLME), using tetrachloroethylene as extractant and acetonitrile as dispersive solvent, has been applied to the QuECHERS extracts, after removal of interferences by dispersive solid-phase extraction with C18 and graphitized carbon black.

Supramolecular solvents (SUPRAS), as an alternative to organic solvents, have been also proposed for the extraction of mixtures of bisphenols plus diglycidyl ethers from foodstuffs [59]. SUPRAS have outstanding properties for microextraction of a wide polarity range of compounds, mainly arising from the mixed-mode mechanisms and high number of binding sites they offer to solutes. Because of the restricted access properties of some SUPRAS, isolation of analytes and sample cleanup can be simultaneously performed, this greatly simplifying sample treatment [59].

Although some methods report the direct analysis of solvent extracts using LC and GC separation techniques [59,31], in most cases additional sample cleanup and concentration steps are required to achieve the desired selectivity and sensitivity. Thus, removal of lipids from the extract is essential for samples of animal origin (e.g. fish, meat) since they can significantly reduce the analytical performance of LC and GC. Lipidic material affects the active surface of the stationary phase in LC and degrades the resolution power of the column. In GC/MS, lipids accumulate in the injection port, column and ion source. Fat removal is mainly made by liquid–liquid extraction with n-heptane [27,33] and n-hexane [36].

Solid phase extraction (SPE) cleanup is the most commonly reported technique to achieve selectivity in the determination of mixtures of both bisphenols and diglycidyl ethers in solid foodstuffs. Gel permeation chromatography [34] and solvent extraction [50] have been also proposed. Non-selective sorbents such as chemically bonded reversed-phase silica, C18 [27,36,49], magnesium silicate, Florisil [36], strata NH_2 [23,49], mixed-mode cation exchange OASIS MCX [15], polystyrene-divinylbenzene, PS-DVB [51] and divinylbenzene/N-vinylpyrrolidone copolymer, OASIS HLB [30,32] have been used, singly or sequentially, for SPE cleanup. After removal of interferences, evaporation of eluates, reconstitution with organic solvent and filtration complete sample treatment.

A variety of techniques have been reported for isolation of mixtures of bisphenols and diglycidyl ethers from liquid foodstuffs (e.g. bottled milk and the liquid portion of canned vegetables, Table 3). They include SPE with non-selective sorbents such as C18 [52,119], solid-phase microextraction, SPME, on fibers of polyacrylate [118] or carbowax [120], stir bar sorptive extraction, SBSE, on fibers of polydimethyl siloxane [35], DLLME with tetrachloroethylene-acetonitrile [37] and SUPRAS-based microextraction using inverted hexagonal aggregates of octanol [53]. Prior to SPE, milk samples are usually mixed with methanol and sonicated for emulsion destabilization and then diluted with water to reduce viscosity. In this way, a better flow rate is achieved during SPE [52,119]. Sample cleanup is also preferentially carried out using SPE [15,23,52,119].

On the whole, except for some methods based on sorbent [35,118,120] or solvent [53,59] microextraction, the overall consumption of solvent, including analyte isolation and cleanup, is high and more green sample treatments should be developed for analysis of foodstuffs. Recoveries for both bisphenols and diglycidyl ethers are in the range 61–126%.

2.2.2. Beverages

Among methods reported for analysis of beverages (including juice, soft, carbonated and alcoholic drinks), those related to the determination of mixtures of bisphenols predominate (Table 3). Both solvent-based extraction (e.g. heptane [33], ethylacetate [15,23], DDLME with tetrachloroethylene-acetonitrile [37]) and sorbent-based extraction (e.g. SPE on C18 [24] or OASIS HLB [112], SBSE on polydimethyl siloxane [35]) have been proposed for analyte isolation. Degasification of carbonated drinks by sonication is required before extraction [112,33,35]. Sorbent-based extraction methods [24,35,112] usually provide eluates clean enough and no further sample treatment is necessary for interference removal. On the contrary, many of the extracts obtained from solvent-based extractions require further cleanup (usually by SPE [15,23]) for accurate determination of bisphenols. Recoveries were in the range 61–128%.

2.2.3. Other human exposure sources

Insufficient attention has been paid to the development of methods for the determination of mixtures of bisphenols and diglycidyl ethers in human exposure sources other than foodstuffs and beverages (e.g. drinking water, personal care products, paper and dust, Table 3). Minute amounts of samples are used for analysis of personal care products (e.g. 120 mg [66]) and dust (e.g 50–100 mg [18,20]). Sample treatment for tap water is simple; it involves C18-based SPE, solvent evaporation and reconstitution in 70% methanol [121]. Dust is a more complex matrix and it requires extraction with a mixture of methanol: water (5:3, v/v), cleanup on SPE (OASIS MCX) and solvent evaporation [18,20]. Analysis of paper only required its pyrolysis after air-drying in an oven at 105 °C [122]. SBSE on EG-silicone has been proposed for the extraction of BPA, BPF and BPZ from cosmetic and personal care products once the sample is dispersed in sodium chloride-containing water by sonication [66]. General recoveries reported for samples were good except for bisphenols in dust, which were in the range 51–137% [18].

2.2.4. Environmental samples

Analytical methods reported for the determination of bisphenols in samples of environmental interest have included natural waters (e.g. rivers and lakes), residual waters (e.g. domestic and industrial influents and effluents), sediments and sewage sludge. Although some of these methods were intended to determine mixtures of bisphenols [122,123] or bisphenols plus diglycidyl ethers [124], most of them involved the determination of mixtures of BPA and chlorinated-BPA derivatives (Table 3). Minute amounts of samples were taken for analysis of sediments (0.2–05 g) and

sewage sludge (1 g). The volume of water samples required for analysis was in the range 100–400 mL except for those methods using on-line SPE (1 mL, [125]) or SUPRAS-based extraction (around 11 mL, [124]).

SPE has been the primary technique for the extraction of mixture of bisphenols in both natural and residual waters. Mixed-mode sorbents such as OASIS HBL [25,126] and hemimicelles/admicelles [123] are particularly valuable for this application, although other sorbents such as C18 [121,125,127], both in on-line [125] and off-line [121,127] modes, and molecular imprinted polymers [128] have been also proposed. The double retention mechanism (e.g. hydrophilic and lipophilic interactions) provided by OASIS HLB permitted the extraction of a mixture of seven bisphenols and chlorinated derivatives (log Kow in the range 1.2–7.2) from river and residual water with overall recoveries in the range 75.8–114.3% [126]. Interferences causing ion suppression in LC-MS/MS were removed by SPE-based sample cleanup on OASIS MAX (a mixed-mode reversed-phase/strong anion-exchange sorbent).

Hemimicelles and admicelles (i.e. surfactant-coated mineral oxides) also offer different microenvironments for solute solubilization [129]. Hemimicelles of dodecyl sulphate adsorbed onto alumina have been proposed for the SPE of BPA and BPF from sewage influents and effluents [123]. Formation of mixed aggregates between dodecyl sulphate and tetrabutylammonium provided a mixed-mode retention mechanism for bisphenols (e.g. dispersion and π-cation interactions), that permitting their quantitative extraction (i.e. recoveries 96–106%) with preconcentration factors of 400 without the need for solvent evaporation.

Similarly, SUPRASs offer different microenvironments for solute solubilization and a SUPRAS made up of hexagonal inverted aggregates of decanoic acid has been proposed for the extraction of BPA, BPF, and their corresponding diglycidyl ethers (BADGE and BFDGE) from wastewater and river water (~11 mL), prior to their determination by LC-FD [124]. The procedure is robust (extractions are no dependent on the ionic strength, temperature or matrix components), simple (treatment of samples only require the extraction of bisphenols for 5 min and no clean-up of extracts or solvent evaporation are necessary) and fast (each complete extraction procedure takes about 15–20 min and several samples can be simultaneously extracted. The method achieves actual concentration factors in the range 87–102 and the recoveries in samples ranged between about 80 and 92%.

Relatively few analytical methods have been reported for the determination of mixtures of bisphenols in sewage sludge [74,75,126,71,72] and sediments [47,126]. Mixtures of BPA and BPA-chlorinated derivatives are efficiently extracted with ethylacetate assisted by auxiliary energies such as sonication, microwaves and pressure [71,72]. Recoveries were in the range around 97–107%. On the other hand, extraction of mixtures of bisphenols from sediments and sludge can be carried out with methanol–acetone [126] or methanol–water [48] but recoveries in these cases decrease (e.g. 57–103% [126] and 82–138% [48]), and one-two steps SPE-based sample cleanup, using mixed-mode mechanism sorbents (e.g. OASIS HBL-OASIS MAX [126] and OASIS MCX [48]), is required to achieve selectivity.

2.2.5. Biological samples

Although urine has received the highest attention regarding biomonitoring of mixtures of bisphenols, some analytical methods involving other biological samples such as serum, plasma, placenta, human breast milk, colostrum and adipose tissue have been also reported (Table 3). Most of these methods involved the determination of mixtures of BPA plus BPA-chlorinated derivatives, and only a few dealt with mixtures of bisphenols or diglycidyl ethers.

In biological samples, bisphenols and derivatives can exist in both the conjugated and the unconjugated form. Both glucuronides and sulphates are the most common conjugates, the first one being the predominant. Usually, both free and total concentration of bisphenols is calculated. So, methods to determine total concentration require an enzymatic deconjugation using a mixture of β-glucuronidase and sulphatase. Even if a study is focused only on free bisphenols, the information on total or conjugated bisphenols is needed for quality control purposes. Additional quality criteria include the information on extraction recovery and the use of surrogate standards to monitor the extent of the deconjugation reaction.

Different strategies have been proposed for the extraction of mixtures of BPA + BPA chlorinated derivatives. They include extraction with an organic solvent such as methanol [41,45,58], mixtures of hexane-acetonitrile [47] or ethylacetate [46], salting-out assisted liquid–liquid extraction (SALLE) using acetonitrile as an extractant and 10 M ammonium formate as a salting-out reagent [43], DLLE with acetone as a dispersive solvent and trichloromethane as an extractant [57], and SPME on a fiber of polyacrylate, after removal of proteins with zinc sulphate in a basic medium [130]. One advantage of using acetonitrile as the extraction solvent is the simultaneous precipitation of endogenous proteins in the matrix. The use of hexane is particularly useful for lipid removal. Sample cleanup, as required, is carried out by SPE on C18 sorbents [47,58]. On the whole, reported recoveries were good, except for SALLE (33–45%) [43].

The methods reported for the determination of mixtures of BPA free, BPA conjugates (i.e. glucuronide, BPAG, and sulphate, BPADS) and BPA chlorinated derivatives are a bit more complicated [44]. Their determination in urine requires the use of three SPE sorbents; BPA and chlorinated derivatives are retained on OASIS HLB and eluted with methanol while BPAG and BPADS are subjected to extraction with Strata NH_2 and C18 in series. Elution of BPADS from Strata NH_2 is carried out with ammonia in methanol while BPAG is eluted from C18 with methanol. The determination of the same mixture of bisphenols in serum uses two SPE cartridges in series (i.e. Strata NH_2 and OASIS MCX). Similarly to urine, elution of BPADS from Strata NH_2 is carried out with ammonia in methanol while BPA, BPAG and BPA chlorinated derivatives are eluted from OASIS MCX with methanol. Recoveries in both urine and serum were in the range 76–129% [44].

Determination of mixtures of diglycidyl ethers has mainly involved urine [12,38,39,131] and the procedures reported for sample treatment are quite similar (i.e. repetitive extraction with ethylacetate, washing of the extract with water, evaporation and reconstitution in methanol [12,38,39]). Extraction with mixtures of ethylacetate-hexane gave poor recoveries for some diglycidyl ethers (e.g. 51% for BADGE.$2H_2O$) [131].

Scarce attention has been paid so far to the biomonitoring of mixtures of bisphenols [28,40,42,131]. Among the methods reported, it is worth mentioning the one described for the simultaneous determination of 18 bisphenols in human breast milk [40]. After protein precipitation with acetone, the sample is subjected to SPE with CHROMABOND HR-X followed by cleanup with SPE BPA-MIP and solvent evaporation. Recoveries for all bisphenols were in the range 90–109%.

2.3. Analysis

LC-MS/MS has become the first choice for separation and quantitation of mixtures of bisphenols, diglycidyl ethers and chlorinated derivatives (Table 3). GC–MS continues as a valuable alternative for determination of mixtures of bisphenols but application to mixtures of diglycidyl ethers and chlorinated derivatives

has been occasional. LC-MS/MS is generally preferred to analyze these compounds, because generic and fast methods for screening purposes can be developed, and the derivatization steps needed for a proper GC–MS analysis can be omitted [132]. A more simple technique, LC-FD, has found interesting applications related to the determination of mixtures of bisphenols and/or diglycidyl ethers in food, environmental and biological samples. Detailed information about chromatographic and detection conditions for the determination of mixtures of bisphenols and derivatives is summarized in Table 3.

2.3.1. Liquid chromatography tandem mass spectrometry

LC-MS/MS analysis of bisphenols and derivatives usually involves the use of reversed-phase C_{18} columns, atmospheric pressure ionization (API) interfaces and triple quadrupole analyzers operating in the multiple reaction monitoring (MRM) mode. Among API interfaces, electrospray ionization (ESI) is usually preferred because it provides better sensitivity for bisphenols and derivatives than atmospheric pressure chemical ionization (APCI). However, APCI has been successfully applied to the determination of chlorinated derivatives in sewage sludge [72,127] and biological samples [46,131].

Regarding bisphenols, their LC-MS/MS analysis is carried out using ESI in the negative mode and methanol–water as the mobile phase. Responses for bisphenols decrease in the presence of acetonitrile, probably because the lower surface tension of methanol that favors the desolvation of the electrospray droplets [132]. The addition of buffers or additives (e.g. acetic acid, ammonium acetate) to the mobile phase causes ion suppression and should be avoided [125]. Derivatization of bisphenols with pyridine-3-sulfonyl chloride has been proposed to enhance the detection capability of these compounds by ESI-MS/MS [132]. This derivatization reagent gives MS/MS transitions involving analyte-specific product ions rather than reagent-specific product ions. In this way, interferences arising from matrix components are reduced.

The ESI(−) full-scan MS spectrum of bisphenols only show the isotopic cluster corresponding to the deprotonated molecule $[M-H]^-$ [133]. For those bisphenols containing an alkyl chain in the central carbon (BPA, BPE, BPB, Table 1), their MS/MS spectra show the fragment $[M-H-CH_3]^-$ for BPA and BPE and $[M-H-C_2H_5]^-$ for BPB, as a base peak. Additionally, the MS/MS spectra of bisphenols show the product ion resulting from the cleavage of the hydroxylbenzyl group, $[M-H-C_6H_6O]^-$ for BPA, BPF, BPE and BPB and $[M-H-C_6H_5O]^-$ for BPS [24]. Other product ions are due to the cleavage of the hydroxyphenyl-alkyl bond that yields the ion at *m/z* 93 $[C_6H_5O]^-$ for BPF and BPB and the ion at *m/z* 92 $[C_6H_4O]^-$ for BPS [24].

The behavior of BPA chlorinated derivatives in ESI(−) depends on the chlorination degree [125]. In mobile phases consisting of methanol and water, the corresponding full-scan MS spectrum of MCBPA shows only the isotopic cluster corresponding to the deprotonated molecule $[M-H]^-$, however, the spectra of DCBPA, TCBPA and TeCBPA show a double-charged ion that corresponds to the deprotonation of both hydroxyl groups $[M-2H]^{2-}$. The relative abundance between the mono-charged and double-charged ions increases with the number of chlorine atoms, probably favored by the lower pKa values of the highly chlorinated derivatives of BPA. Addition of acetonitrile to the mobile phase causes double-charged ion suppression and, although the response for MCBPA decreases, acetonitrile-water [25] and ternary mixtures of water–acetonitrile–methanol [125] have been successfully used for determination of BPA chlorinated derivatives. The two most abundant product ions in the MS/MS spectra of these compounds are $[M-H-CH_3-HCl]^-$ and $[M-H-C_2H_4OCl]^-$, which have been used as quantifier and qualifier ions for their determination [125,133].

Quantification of BPA chlorinated derivatives by APCI, in negative mode, is better suited in mobile phases containing basic additives (e.g. aqueous ammonia–methanol [46,71,72]) in order to get improved ionization. In APCI(−), even under mild conditions, BPA chlorinated derivatives undergo in-source fragmentation to yield ions in agreement with those obtained in MS/MS. This behavior is more pronounced for the highly halogenated BPAs [132]. Nevertheless, as APCI(−) is selected as the ionization source, mixtures of BPA chlorinated derivatives are commonly fragmented under MS/MS [46,71,72,127].

Bisphenol diglydicyl ethers show a high tendency to form clusters of $[M+Na]^+$, $[M+K]^+$, $[M + NH_4]^+$and $[M + ACN]^+$ ions under electrospray conditions [134]. Some of these clusters (e.g. $[M+Na]^+$) are very stable and do not produce fragmentation in MS/MS, but efficient fragmentation can be obtained from $[M + NH_4]^+$ adducts. In order to enable the formation of ammonium adducts and ensure signal reproducibility, formic acid/ammonium formate buffer is generally used as an additive in the mobile phase (usually water–methanol) for analysis of bisphenol diglycidyl ethers in the ESI(+) [12,20,29,30,39,131]. Concentrations above 0.1% of formic acid are necessary to help the ionization process, but concentrations exceeding 0.3% have been known to produce ionization suppression [135]. Responses decrease for mobile phases consisting of acetonitrile-water, probably due to the fact that quasi-moleculars ions clusters between analytes and acetonitrile are not properly formed [29]. The fragmentation of $[M + NH_4]^+$ adducts starts with the cleavage of the phenyl-alkyl bond, which is followed by the α-cleavage of the ether group to generate the characteristic product ions at *m/z* 135, $[C_9H_{11}O]^+$, and *m/z* 107, $[C_7H_7O]^+$ [136].

Ion suppression due to sample-matrix components is a general problem in the analysis of bisphenols and derivatives by LC-(ESI) MS/MS and that requires the use of proper sample cleanup strategies to get accurate results, as it has been discussed in section 2.2. Efficient removal of interferences is achieved in about 65% of the methods reported so far after thorough sample cleanup, so external calibration can be used for quantification of bisphenols and derivatives. Otherwise, matrix-matched calibration [24,29,41–43,50,57,58,71,72] or the standard addition method [46,75,76,126] should be used. Single stable isotope-labelled standards such as BPA-d14, BPA-d16, BPA-$13C_{12}$, DCBPA-d12, TCBPA-$13C_{12}$, BADGE-d6 or BPS-$13C_{12}$ are frequently added to samples for correction of recoveries. Ion suppression due to buffer additives hinders the sensitive simultaneous determination of bisphenols and their diglycidyl ethers because the ammonium salts required to form the $[M + NH_4]^+$ adducts with diglycidyl ethers reduce drastically the signal for bisphenols [39,133,136–138].

Method quantitation limits for bisphenols and derivatives in canned food are usually within the range 0.01–10 ng g^{-1}, which is sensitive enough to study their occurrence in this type of exposure sources [15,23,24,29,30,49,50,112]. Regarding environmental samples, low MQLs are obtained for analysis of dust (e.g. 0.07–2 ng g^{-1} [18,20,60], sediments (e.g. 0.06–2.83 ng g^{-1} [48,126]) or sludge (e.g. 0.014–103 ng g^{-1} [61,71,72,75]). However, the most sensitive methods are related to the determination of bisphenols and derivatives in environmental waters owing to both the sensitivity of the technique and the high preconcentration factors achieved (e.g. MQLs of 2×10^{-5} ng mL^{-1} in drinking water [25] or 1×10^{-4} ng mL^{-1} in river water [76]). LC-MS/MS is the technique of selection for quantification of bisphenols and derivatives in biological samples; MQLs are usually in the range 0.01–1 ng mL^{-1} [42,43,57,131]. The analytical error of these methods, expressed as relative standard deviation of intra-day measurements, is below 20%.

2.3.2. Gas chromatography-mass spectrometry

GC–MS analysis of bisphenols involves their derivatization by acetylation or silylation, ionization with electron impact (EI) and ion separation in single quadrupole analyzers operating in the single ion monitoring (SIM) mode (Table 3). For years, this approach has been the most popular due to its high capabilities and sensitivity [132].

Derivatization of the free hydroxyl functional groups of bisphenols leads to sharp peaks, thus improving their separation, and enhanced sensitivity and accuracy. Acetylation with acetic anhydride has been the most frequent procedure to obtain bisphenol derivatives for GC–MS [26,27,33,35,37,42,54,55]. Silylation is also very common because the reaction is fast and quantitative and yields thermally stable and highly volatile derivatives [132]. The most popular silylation reagents for this application have been N,O-bis(trimethylsily)trifluoroacetamide, BSTFA [130], N,N-methyl-(trimethylsilyl)trifluoroacetamide, MSTFA [40] and BSTFA containing trimethylchlorosilane, TMCS [47]. The addition of TMCS favors the formation of single derivatives, since the reaction of BSTFA with analytes having different hydroxyl groups, such as bisphenols, can generate several derivatives, that reducing the sensitivity and selectivity of the analysis. Electron ionization spectra of bisphenols after silylation show as the base peak the loss of a methyl group from the cleavage of the isopropyl group. The molecular ion, with a relatively low intensity, is used for confirmation purposes [132].

Derivatization of deuterated internal standards has been found essential to maintain its isotopic purity during chromatographic separation on a fused-silica capillary column [139] since it degrades owing to the deuteron-proton (^{2}H–H) exchange in the aromatic portion of the molecule. This phenomenon has been attributed to the aromatic electrophilic exchange of deuterium atoms with active hydrogen atoms located on the internal surface of the column.

Linear quadrupoles have been the most used analyzers for GC–MS analysis of bisphenols [26,27,33,35,37,42,54,55]. They feature low cost, compactness and simplicity of operation. The last developments, related to the stability of mass calibration and higher scan-speed and sensitivity, continue to make these analyzers attractive.

Accurate quantification of bisphenols by GC–MS usually requires the use of matrix-matched calibration [26,27,37,42,54] or the standard addition method [47,55,130], however efficient removal of interferences can be achieved after some sample cleanup strategies, that allowing the use of external calibration [33,35,52,66,118]. In most of the reported methods, a single stable isotope-labelled standard (e.g. BPA-d14, BPA-d16 or BPA-^{13}C12) is used to correct for recoveries.

Sensitivity for the determination of bisphenols by GC–MS is highly variable and it mainly depends on the level of analyte preconcentration during sample treatment. Method quantitation limits for bisphenols in solid matrices range from 45 to 200 pg g^{-1} [37,54,55] to 1–10 ng g^{-1} [26,27,33] in canned food, from 26.7 to 29.2 ng g^{-1} in cosmetics and personal hygiene products [66] and 1.3–1.4 μg g^{-1} in paper [122]. Regarding liquid matrices, the highest sensitivity has been reported for bisphenols in canned drinks (e.g. MQLs are in the range 3.2–10 pg ml^{-1} [35,37,118]) although methods featuring lower sensitivity for these matrices have been also reported (e.g. MQLs of 2–10 ng ml^{-1} [33]). Bisphenols in biological fluids can be quantified at the low ng mL^{-1} level by GC–MS (e.g. MQLs of 0.1 ng mL^{-1} in urine [42], 0.15–0.36 ng mL^{-1} in milk [52] and 0.8–5 ng mL^{-1} in plasma [130] have been reported). The precision of these methods is acceptable; the analytical error, expressed as relative standard deviation of intra-day measurements, is below 20%.

2.3.3. Liquid chromatography-fluorescence detection

Both bisphenols and their respective diglycidyl ethers show native fluorescence in the solvents more frequently used in LC mobile phases, namely water, acetonitrile and methanol. LC-FD is well suited for the determination of mixtures of bisphenols and/or diglycidyl ethers in packed food [31,32,34,36,51,56,59,119,120] and environmental samples [123,124].

Reversed-phase LC is always used for the analysis of bisphenols and/or diglycidyl ethers. The composition of the mobile phase has an important effect on the elution order of diglycidyl ethers. Thus, the order of elution of BADGE.H_2O and BADGE.HCl.H_2O changes in methanol compared to acetonitrile due to the different hydrophobicity of both solvents [140,141].

Quantification of bisphenols and/or diglycidyl ethers by LC-FD is mostly carried out by using external calibration [28,32,34,36,51,56,59,123,124,128], sometimes after a thorough sample cleanup [32,34,36,51,56]. Matrix matched calibration [31,119] and the standard addition method [120] have been also proposed to correct for matrix effects. The identification of bisphenols and diglycidyl ethers in the sample is only based on retention times, so the possibility of false positives should be always considered.

The sensitivity of the LC-FD methods for bisphenols and/or diglycidyl ethers is good for their determination in food (e.g. MQLs between 0.3 and 50 ng g^{-1} in canned food [31,32,34,36,51,59] and from 1 to 14 ng mL^{-1} [119,120] in beverages), and because of the high preconcentration factors achieved, the sensitivity is very high for quantification of these analytes in environmental waters (e.g. 2.5–35 pg mL^{-1} [123,124,128]. The analytical error, expressed as relative standard deviations of intra-day measurements are mostly below 10%.

3. Assessing human and environmental risk to mixtures of bisphenols and derivatives

Risk assessment has long been the tool for science-based decision-making and has become an integral part of EU policy development. Common applied approaches for risk assessment of chemical mixtures are based on the combination of chemical target analysis and toxicity assessment, which is carried out by either whole-mixture or component-based methods. In whole-mixture methods, the mixture is considered as a single entity and toxicity is assessed by bioassays. Component-based methods rely on toxicological data and exposure information for individual mixture constituents. The mixture toxicity is then assessed in terms of expectable additive or interactive actions of mixture components [142]. Effect-directed analysis (EDA) and toxicity identification evaluation (TIE), widely used for identifying anthropogenic contaminants causing toxicological effects on environmental samples, are two examples of approaches that combine chemical target analysis and toxicity assessment [143].

Regarding bisphenols and derivatives, risk assessment is difficult at present due to major knowledge gaps related to their occurrence (e.g. where, how often and to what extent humans and the environment are exposed to mixtures of bisphenols and how exposure may change overtime) and mode of action (the molecular basis behind the deleterious effects of bisphenols and derivatives is poorly understood, especially at low doses).

Considering that the harmful effects caused by bisphenols mainly stem from their endocrine disruptors properties, a factor to have in mind is that other non-bisphenols EDCs will be almost always present in the target samples. So, risk assessment to bisphenols and derivatives will be only possible after determining their concentration in the target samples. Then, biotesting of standard solutions of these compounds, at the same composition found in

samples, or risk estimation by component-based methods, may be applied.

Because assessment of human and environmental risk to a mixture of bisphenols and derivatives is at an early stage, below some of the tools available for this assessment are briefly discussed with the aim of fostering research in this field. In addition to the estimation of risk, expected benefits from this research are estimation of safe levels and margins of exposure, ways to prioritize the mixtures of bisphenols and derivatives of major concern and guidelines to decrease the negative impact of plastic industry in both human health and the environment [142].

3.1. Bioassays

Among mechanisms reported to account for the deleterious effects of bisphenols and derivatives on human health and the environment, cellular response through nuclear-associated estrogen receptors (ERs), ERα and ERβ, has been considered the most important. Other nuclear-associated receptors have been also known to be activated (e.g. pregnane X receptor, estrogen-related receptor γ (ERRγ), the peroxisome proliferator activated receptor γ) or inhibited [e.g. androgen receptor (AR), thyroid hormone receptor (TR)] by bisphenol A or its halogenated derivatives [144]. Another important mechanism, proven for low BPA concentrations, is the stimulation of cellular responses through membrane-associated estrogen receptors (G protein-coupled ER) [145].

Assays based on receptor signaling are usually defined in terms of receptor activation using recombinant yeast or mammalian systems; cell proliferation in receptor-competent cells; and physiological responses (e.g. proliferation of uterine tissue in rodents and induction of vitellogenin in fish for the estrogen receptor, and the Hershberger assay for the androgen receptor) [78]. Most of these assays have been widely applied to the identification of endocrine disrupters in environmental samples [146,147].

Reporter gene systems based on yeast have been mainly used for the identification of estrogens (yeast estrogen screen, YES) and androgens (yeast androgen screen, YAS). In YES, genetically modified yeast cells (*Saccharomyces cerevisiae*), which contain the gene for the human estrogen receptor coupled with a so-called reporter gene (LacZ), indicate estrogenic effects. If an estrogenically active substance binds to the estrogen receptor in the cell, the corresponding gene and then the reporter gene are read. The latter gene encodes for an enzyme (beta-galactosidase), which converts chlorophenol red b-D-galactopyranoside and thus induces a color reaction, which is directly correlated to the existence of estrogenically active substances. After 3-day exposure to chemicals or environmental samples, the estrogenicity of the analyzed samples can be measured based on color induction. The same assay principle applies to the detection of anti-estrogenic substances in YES, as well as androgenic and anti-androgenic substances in YAS [148]. As microtiter plate-based test systems they meet the criteria of high-throughput applications and require small amounts of samples [149]. The specific mixture related problems that can be encountered during the application of such assays have been discussed by Frische et al. [150].

Reporter gene systems based on mammalian cells, mainly breast cancer cell lines (e.g. MCF-7), are available, among others, for estrogen, androgen and thyroid hormone receptors [78]. Mammalian reporter-gene assays include the CALUX (Chemically Activated LUciferase gene eXpression) type assays [151]. In these assays, when the EDC binds to the receptor, the receptor complex migrates toward the nucleus of the cell where it binds to a responsive element in the DNA. After transcription and translation of the reporter gene, an enzyme is formed that induces luminescence.

Cell proliferation-based assays have been reported for ER (E-screen), AR (A-screen) and TR (T-screen) [78]. The E-screen assay compares the cell number achieved by similar inocula of MCF-7 human breast cancer cells in the absence of estrogens (negative control) and in the presence of 17β-estradiol (E2, positive control) and a range of concentrations of chemicals suspected to be estrogenic. A-Screen assay is dependent on a suppressive effect of AR on ER signaling which requires co-exposure to estrogen and therefore the assay does not indicate AR activity in isolation. Because these assays are not engineered, the expressed receptor and subtypes depends on the endogenous expression of the cell. This can complicate interpretation of results since the cell may not have been exhaustively characterized for expression of receptor types other than the one of interest, and indeed could potentially alter expression in response to chemical stimuli.

In general, similar responses are observed as different bioassays are applied on the same sample, however notable differences are obtained in some cases. Thus, the E-screen gave higher estrogenicity (~6.51 ng g^{-1} fat) than the YES (<LOQ = 1.08 ng g^{-1} fat) for adipose tissues from fish with ovotestis [152]. Possible reasons may be the different extraction methods which did not remove all agents that may inhibit the bioassays or the fact that the E-screen also allows for stimulation of cell proliferation via cell signaling pathways not present in the YES. Anyway, the major difficulty with these simplified models is the extrapolation from effects in a cell culture to potential risks to human health.

Different studies based on *in vitro* assays have been recently conducted to assess the human and environmental risk to mixtures of bisphenols. Thus, the estrogenic potencies of eight BPs have been evaluated using a bioluminescence YES assay [153]. Although all BPs exhibited estrogenic activity, there were significant differences between the potency of individual chemicals. BPAF had the highest activity, followed by TCBPA, BPF, BPA, BPE and BPS.

The ER-CALUX assay has been applied to the evaluation of the estrogenic activity of drinking water after BPA removal by chlorination [154]. Targeted measurements first evidenced a fast removal of BPA (>99%) by chlorination with sodium hypochlorite (0.8 mg L^{-1}) within 10 min. Twenty one chlorination products of BPA were detected. The estrogenic activity of water samples, evaluated by the ER-CALUX assay, was found to significantly decrease after 10 min of chlorination, thus confirming that chlorination was effective at removing BPA in drinking water and that the generated compounds had significantly lower estrogenic activity.

The E-screen assay has been used to help in the design of non-estrogen active BPA analogs [155]. It was proved that the actions of the environmental hormones BPA analogs stemmed from two chemical properties; (i) 'stereo structure-controlled' and (ii) 'electronic structure-controlled' estrogen-like chemical activities. The results obtained constitute a valuable guide for the design and synthesis of BPA analogs without estrogen activity.

The effects of BPA, BPF and BPS on several major endocrine factors involved in testicular functioning have been examined [156]. Results from recombinant yeast cells expressing the AR or glucocorticoid receptor (GR) clearly showed that BPA and BPF were GR and AR antagonists with IC_{50} values of 67 and 60 mM for GR, and 39 and 20 mM, for AR, respectively, whereas BPS did not affect receptor activity. In addition, murine MA-10 Leydig cells exposed to BPF and BPS showed altered testicular steroidogenesis. Because of the fetal-like characteristics of MA-10 Leydig cells, the assay covered fetal steroidogenesis, which is highly relevant for studies of masculinization of male fetuses.

In vivo assays are considered to reflect receptor activity relatively directly. In mammals, there are well established *in vivo* assays for estrogen (rat uterotrophic bioassay) and androgen (Hershberger assay) receptor activity. In fish, the induction of vitellogenin (an egg yolk precursor protein) is controlled by ER, and this response can be

used to monitor exposure to estrogenic chemicals in juvenile or male fish [101]. Using vitellogenin induction in fish, the potential estrogenic effects of several bisphenols on medaka and common carp have been studied [157]. The order of *in vivo* estrogenic potencies of BPs was as follows: BPC ~ BPAF > BPB > BPA⋙BPP. Likewise, *in vivo* vitellogenin assay on zebrafish embryos/larvae proved that BPAF showed a stronger estrogenic activity than BPA [158].

3.2. Component-based methods

The studies reported so far have shown that endocrine disruptors, as present in mixtures, produce combined effects that can be described by the dose addition (DA) concept [101]. DA applies to mixtures where components interact with a specific molecule target through an identical mechanism of action. In this way, one chemical can be replaced totally or in part by an equal fraction of an equi-effective concentration (e.g. an EC_{50}) of another, while keeping the overall combined effect.

All the methods currently in use for the assessment of the risk to the exposure of mixtures of chemicals derive from the DA concept. Among them, the Hazard Index (HI), the Point of Departure Index (PODI) and the toxic equivalence factor (TEF), are the preferred ones [142]. Application of these methods requires the previous knowledge of the identity and concentration of the components making up the mixture, as well as their concentration effect on a biological system.

The HI is the summation of the ratios between the actual level of exposure and the reference dose, for each of the chemicals making up the mixture. Values of HI above 1 means that the total concentration of mixture components exceeds the level considered to be safe. In PODI, exposure levels of chemicals in a mixture are expressed as fractions of their respective points of departure (PODs), such as no observed adverse effect level (NOAELs) or Benchmark concentrations or doses (BMD). Extrapolation from animal to human are then dealt with by using one overall uncertainty factor. In this respect, PODI surpasses HI, since the reference doses for each mixture component in HI can be reached by using different uncertainty factors. The TEF is defined as the relative toxicity of an individual chemical to the most toxic chemical (which is assigned a toxic equivalent factor -TEF- value of 1.0). Then, the total equivalent quantity (TEQ) is estimated by summation of the concentrations of mixture components multiplied by the respective TEF. This method is only applicable when the underlying dose-effect relationships are linear. Otherwise, TEFs vary as a function of the effect level that is considered for analysis.

The total estradiol equivalent quantities (EEQs) of eight bisphenol (BPA, BPAF, BPAP, BPB, BPF, BPP, BPS, BPZ) in sludge from US [61] and China [153] have been recently reported. Values for EEQs in sludge from US wastewater treatment plants (WWTPs) were in the range 0.26–90.5 pg g^{-1} dw, with BPA accounting for 81% of the total estrogen equivalents, followed by BPAF (13%), BPS (3.5%) and BPF (1.9%). EEQs for bisphenols were 1000 times lower than the estrogenic activity contributed by natural estrogens present in the sewage sludge samples [61]. Similar EEQs were obtained in sludge from China WWTPs (2.16–49.13 pg g^{-1}dw), that accounting for 0.05–1.47% of the total EEQs in sewage sludge samples [153]. These results indicated that BPs made a minor contribution to the total estrogenic activity of the investigated sewage sludge. However, non-genomic mechanisms should be also taken into account in further experiments.

4. Conclusion

Because of their endocrine disruptor properties, low-dose effects and non-monotonic dose–response curves, understanding the effects of the mixtures of bisphenols to which humans and wildlife are exposed is increasingly important. A great deal of information exists about the concentrations of BPA in human biological samples and the environment, but data concerning the levels of multiple bisphenols and derivatives in the same samples are still scarce and more information on typical exposure situations needs to be compiled and systematized. Regarding human biomonitoring, comprehensive measurements of all exposure events during a lifetime, particularly during critical life stages such as fetal development, early childhood and the reproductive years, should be considered for a reliable assessment of human risk to mixtures of bisphenols.

Collecting such huge volume of human and environmental exposure data will require dedicated, targeted monitoring strategies and LC-MS/MS seems to be, at present, the most versatile technique for this purpose. Given the breadth and complexity of this task, monitoring methods involving simpler, generalized sample treatments, able to simultaneously quantify all the bisphenols and derivatives of interest in a range of matrices, are still lacking.

Other knowledge gaps hinder, at present, a reliable assessment of human and environmental risk to mixtures of bisphenols. They include the poor understanding of the mechanisms of low dose actions (including epigenetics and non-genomic pathways) and pharmacokinetics for the different components of the mixture. This knowledge would offer the possibility of strictly regulating, or even eliminating those bisphenols that are shown to have the greatest impact on a combination effect. It would also provide information about the feasibility of using certain index chemicals as surrogates for exposure measurements. And, last but not least, regulation on bisphenol-based plastic materials and other consumer products would be made in a more reliable way.

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