Current Topics in Analytical Chemistry
Vol. 13, 2021

Review

A review on the recent advances in the analyses of Bisphenol-A and its replacements in beverages and foods with commentary

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ABSTRACT

Because of Bisphenol-A's known human endocrine disrupting abilities and other possible health effects, different and evolving technologies are needed in continuing to improve the sample preparation, detection and analysis methods used to identify Bisphenol-A (BPA) and other bisphenols (BPs) in beverages and foods. Various reviews, Cao 2012, Caballero-Casero and Rubio, *et al*. 2016, Almeida, *et al*. 2018, Siracusa, *et al*. 2018, Vilarinho and Silva, *et al*. 2019, Schmid and Welle 2020 and Kaya, *et al*. 2021 have addressed these matters in diverse ways. This manuscript seeks to highlight these meaningful reviews, while providing commentary on the need to continue to provide information on the most current and effective methods towards identifying BPA and its possible by-products and replacements that may be leached from their containers into beverages and foods. The exciting development of instruments and related powerful software enables the un-targeted identification of as-yet, un-identified bisphenols and related compounds. These newer analytical tools, used in conjunction with carefully designed leaching studies, can provide important migration information, that along with newer toxicological data**,** would enable regulatory bodies to set effective limits to the potential exposures to consumers of unwanted chemicals coming from containers used in bottled waters, beers, energy drinks, sodas, and foods.

KEYWORDS: LC, GC, MS, Bisphenol-A, bisphenols, EDCs, beverage and food containers.

INTRODUCTION

For over seventy years, Bisphenol-A (BPA) (Fig. 1) has been widely used commercially as a monomer in the production of polycarbonate containers and as a reactant in the manufacturer of epoxy resins [1]. As the negative health effects of BPA and its replacements, such as Bisphenol-F (BPF), Bisphenol-AF (BPAF) and/or Bisphenol-S (BPS) (Fig. 1), have become harder and more complicated to detect, newer and more refined analytical methods are needed. BPA and certain of its known commercial replacements have been classified as confirmed or potential endocrine disrupting chemicals (EDCs). EDCs affect biological developmental processes, reduce basal testosterone levels in males, and could cause such adverse health effects as cardiovascular diseases, cancers, diabetes, and obesity, among others [2].

In 2018, Siracusa, *et al*. published an extensive review on the effects of BPA and its analogs on reproductive health with 204 citations [2]. This extensive review focused on the effect of BPA, and its more common replacements, BPF, BPAF, BPS

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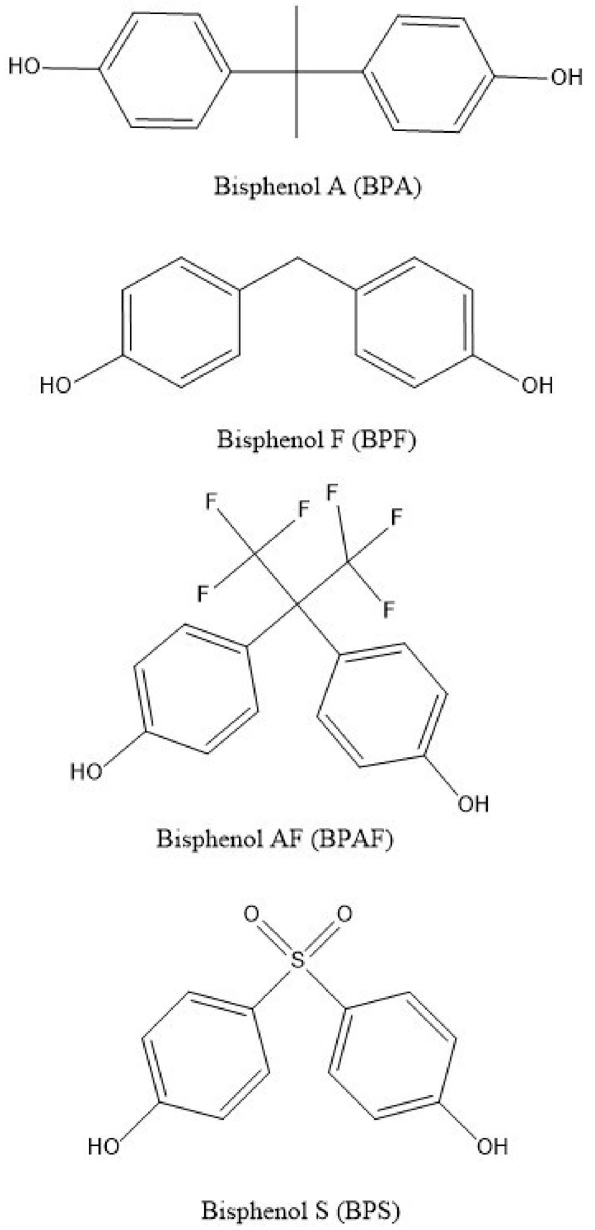

Fig. 1. Chemical structures, common names and abbreviations for: Bisphenol-A (BPA), Bisphenol-F (BPF), Bisphenol-AF (BPAF) and Bisphenol-S (BPS).

and Tetrabromobisphenol-A (TBBPA) (Fig. 1, 2), on their reported human exposure, toxicokinetics, endocrine activities and reproductive toxicity. Multiple studies have shown that these reported replacements have similar endocrine potencies when compared to BPA. Their review is organized into eleven tables and provides important summaries [2]. Russo, *et al*. in 2018, published an interesting study that showed, that in certain cases, the relative log of the capacity factors determined by immobilized artificial membrane liquid chromatography (IAM-LC) of BPA and seven of the bisphenol-analogs was linearly correlated to the log of their affinity indexes for phospholipids, which could further show a relationship with their *in vitro* toxicity. It was indicated that in general, BPF, BPS and BPE were estimated to be less toxic, BPB and BADGE (Fig. 2, 3) to have similar toxicity as BPA, while BPM and BPAF were estimated to be more toxic [3]. (Note it will be documented later in several reports that especially BPAF had been detected in beer samples stored in aluminun cans). Also in 2018, Sharma *et al*. used computer- generated programs to estimate the binding affinities of BPA along with 17 other bisphenols (BPs) and other recognized EDCs to human receptors. Of interest is that their computer modelling predicted that such analogs as BPAF, BPM and BPPH (Fig. 1, 2) showed higher binding efficiencies to certain human nuclear acceptors than BPA [4]. In 2018, Mokra *et al*. reported that even at such low concentrations as one ng/mL, BPA, BPF, BPAF and BPS produced oxidative DNA damage in human peripheral blood mononuclear cells, a key process to cancer initiation. Their results showed that BPS, which has been the most commonly used substitute for BPA, showed the least oxidative DNA cell damage [5].

The European Food Safety Authority (EFSA) in 2018 had adopted the Tolerable Daily Intake (TDI) of 4 µg of BPA per kg of body weight/day in foods with a Specific Migration Limit (SML) of 0.05 mg of BPA per kg in food [6]. The U.S. Food & Drug Administration (FDA) continues to review the scientific safety data except for issuing warnings on the harmful exposure of BPA to infants in food and milk products, while the U.S. FDA continues to assure the consumers of the safe use of BPA in food packaging. [7] (Note only the latest adopted or regulatory values for BPA and its analogues here are reported. This is because the reviews by Vilarinho and Silva *et al*. (2019) [1] and Schmid and Welle (2020) [8] effectively have documented the historical development of the various, especially the European Union's (EU's), regulations for the levels of BPA and certain of its replacements that have been

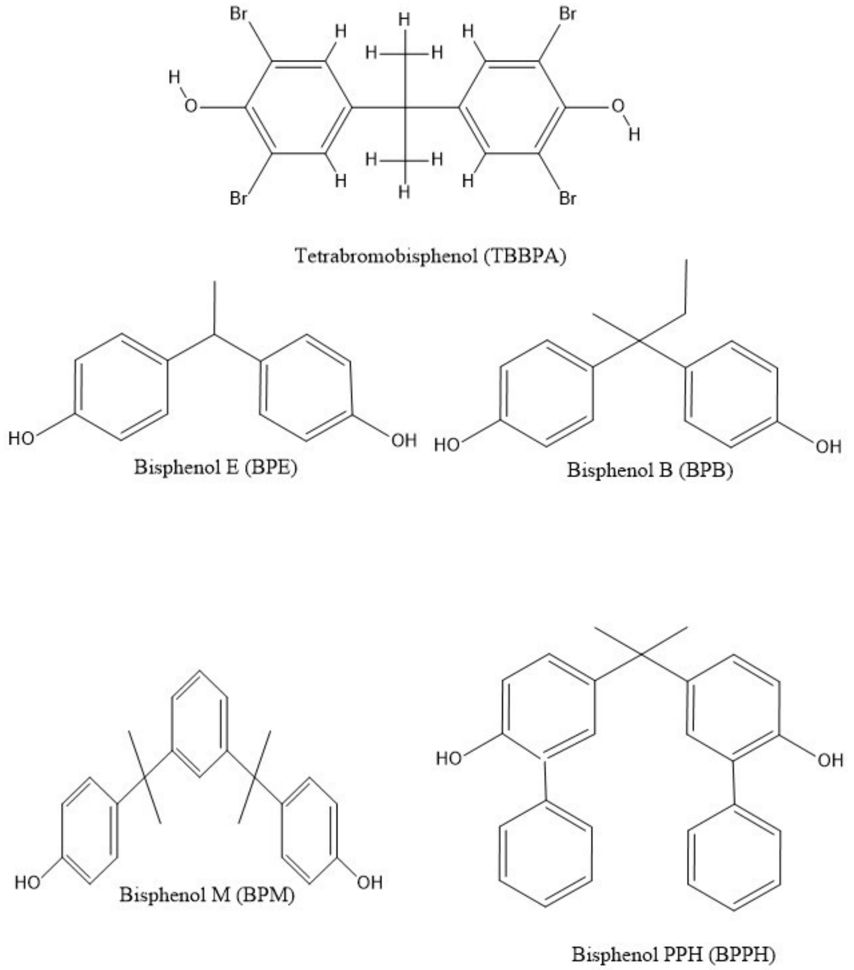

Fig. 2. Chemical structures, common names and abbreviations for: TetraBromoBisphenol (TBBPA), Bisphenol-E (BPE), Bisphenol-B (BPB), Bisphenol-M (BPM) and Bisphenol-PPH (BPPH).

shown to migrate from their containers' liners into beverages and foods.).

Reviews of the various analytical methods

In the process of preparing this manuscript, it was determined that at least five, recently published, interesting review articles had presented different and diverse views on the commercial uses, the potential harmful effects and the evolving analysis methods used in the detection and determination of BPA and other bisphenols as they may become exposed to beverages and foods. First in 2012, X.-L. Cao, long involved with research on the determination of BPA, summarized in Tabular form the various analytical methods used for the determination of BPA in food samples. His Table 1 which seems to have established the general format that has been followed by later updating reviews was organized with the following sub-headings: Sample, Extraction/Clean Up, Derivatization, Separation and Detection, Limit of Detection (LOD), Limit of Quantitation (LOQ), Recovery and Precision and Reference. Cao cited 93 references [9].

In 2016, Caballero-Casero, Lunar and Rubio published an extensive, updating review with 158 citations. Their first table included BPA and 18 other bisphenols with their chemical names, structures, Chemical Abstracts Service (CAS) number, octanol-water partition coefficients (log $K_{o/w}$) and ionization constants (pK_a). Their second table is unique as it documented the levels of BPA and BPS found in human exposure, biological and environmental samples, with 25 references cited. In their third table, which listed 78 citations, they summarized the analytical method used. Their Table 3 had the following sub-headings: Sample Type (size), Analytes, Sample Treatment, Separation/ Detection, RSD (%), R (for Recovery) in %, Detection Limits and Reference. The tables included very interesting and valuable commentary [10].

Soon after, in 2018, Almeida *et al*. provided a very different review which summarized the most recent *in vitro* and *in vivo* toxicity and recognized human health effects of BPA's [11]. They noted that historically, BPA had been used as a monomer or additive in the manufacture of polycarbonate plastics accounting for about 64% of BPA's world's demand. BPA also is used as a reactant in the manufacture of epoxy resins accounting for an additional about 34% of its world's demand. The remaining about 4% of it is used in flame retardants and other polymer formulations. Other commercial uses for BPA and other Bisphenol replacements are found in certain medical and dental devices, printing inks, thermal paper, and as components or residues of epoxy, resin-based paints and glues. It was detailed that in 2015, BPA was one of the world's most widely commercially used compounds. It was estimated that the worldwide BPA consumption, estimated at 7.7 million metric tons in 2015, should increase between 3 to 5% by 2022 [11]. It is noted that these production figures indicated a steady industrial increase in consumption, even though the U.S., E.U. and Canada have prohibited the use of BPA in infant feeding bottles. Nevertheless the potential migration of BPA from beverage and food containers into their contents remains a significant concern. This migration is amplified by heating, noteworthy when the containers are microwaved, or when exposed to either acidic or basic solutions. Because for certain applications, BPA has been replaced by BPF and BPS. (Fig. 1) Almeida *et al*. included the impact of those two bisphenols in their review. It is noted that very few studies have examined the hormonal actions of either BPF or BPS, but since they have similar structures to BPA, i.e.- having two phenol groups, both BPF and BPS also should have similar hormonal activity. Interestingly BPF has found considerable commercial use as a replacement for BPA due to BPF's lack of two-central methyl-groups, which allows BPF to form thicker and more durable polymeric products. In their review section, Almeida *et al*. detailed the E.U.'s legislation developments on the allowed limits for the migration of BPA from food contact materials. Besides the expected higher exposures levels of BPA and possibly other bisphenols to manufacturing workers, it is the long-term exposure of BPA from the migrations from food containers that remains the principal concern. It is the slow accumulating build-up of either BPA and/or BPs in blood and tissues in humans over long periods of time, -i.e., chronic exposure, that worries most. Several scientific studies have shown that when extracting solutions are exposed to elevated temperatures, especially due to food sterilization processes required for certain foods, significant elevated levels of BPs were found to migrate from the epoxy resins used in can coatings. Almeida *et al.* effectively summarized and provided commentary on the many endocrine- disrupting, carcinogenic, cardiovascular, immune, metabolic, reproductive, and toxicological studies attributed to BPA and certain other bisphenols. While no specific emphasis of which analysis methods was used in the 158 citations referenced, the authors' goal of reviewing the effect of BPA and certain of the BPs on food exposure and impact on human health contains important and interesting information [11].

In 2019, Russo *et al*. reported doing a risk assessment of 7 different bisphenols in 52 types of beverages that were extensively consumed in the European, especially in the Italian market. They asked the interesting question in their title: "Are canned beverages industries progressively switching to Bisphenol AF?"

This is an important question because as they reported in their Table 1, consistently high concentrations of Bisphenol-AF (BPAF) were found in many of the beer beverages. (Their Table 1 is included here in this review with permission of John Wiley & Sons Publishing Company). Bisphenol-AF (BPAF) hexafluoroisopropylidene diphenol has two fully fluorinated, central substitution groups. That would be the same fully-fluorinated substitution pattern of another important group of widely used commercial chemicals, namely per- and polyfluoroalkyl substances (PFAS). It should be

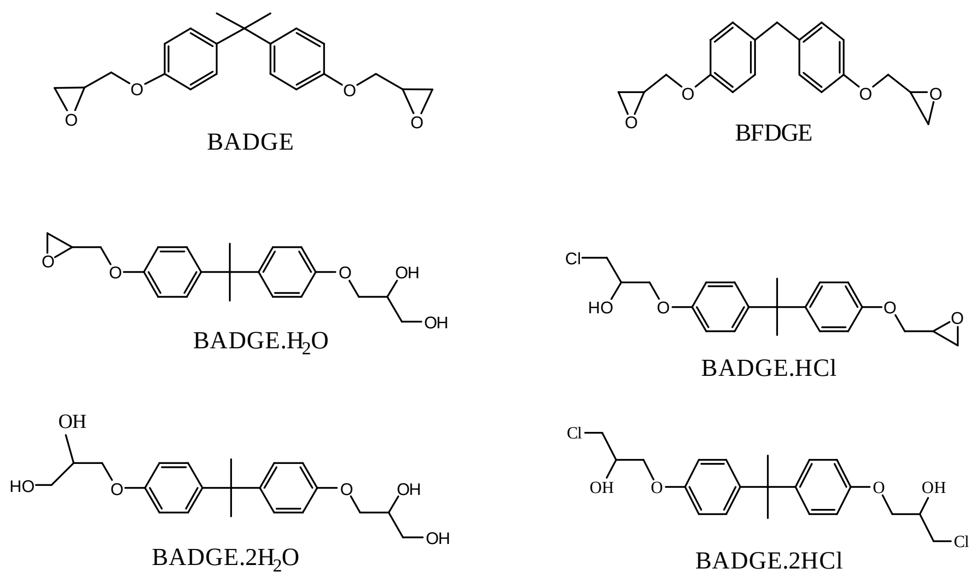

Fig. 3. Chemical structures, common names and abbreviations for: BADGE, BFDGE, BADGE.$H_2$0, BADGE.2$H_2$0, BADGE.HCL and BADGE.2HCL.

noted that the PFAS family of compounds, extensively used in many commercial products worldwide, is often referred to a "forever" or "legacy" chemicals and have been either banned commercially or restricted since 2009 by the Stockholm Convention. Documented reports have shown that the family of PFAS compounds bioaccumulate, persist and may be toxic. Hence, one should be concerned about the potential use of the fully-fluorinated, central tri-fluorinated groups in Bisphenol-AF (BPAF) in materials for consumption by humans, as reported in Table 1 [12].

Much as both Cao (2012) [9] and Caballero, Lunar and Rubio (2016) [10] had done, Vilarinho and Silva, *et al*. (2019) continued in reviewing the on-going literature with 140 citations [1]. As first referenced, this review provided the reaction scheme which shows how phenol, acetone and carbonyl chloride is reacted to form BPA. A second reaction scheme shows how BPA with two chlorohydrin in condensation polymerizations reactions produce bisphenol-a-diglycidyl ether (BADGE). Note BFDGE is the chlorohydrin adduct of BPF. BADGE is known to rapidly become hydrolysed in water solution or in the presence of acid due to acidic reaction conditions to form various hydrochloric adducts. Their structures are depicted in Fig. 3. As done in the earlier 2012 and 2016 reviews, Vilarinho's, and Silva's, *et al*. (2019) [1] review is organized into four tables as follows:

- Table 1. Methods to extract BPA and various BPs and levels of migration from plastics and cans in food simulants or foods (57 citations).
- Table 2. Conditions of the Gas Chromatographic methods used to determine BPA and BPs (29 citations, with most having used GC/MS, a few with MS/MS and most reporting the use of capillary columns packed with a 5%-phenylmethylsiloxane liquid phase).
- Table 3. Conditions of liquid chromatography methods used to determine BPA and BPs (46 citations), with many having used fluorescent detection (FLD), a few with ultraviolet absorption detection (UVD), while most, especially the more recent ones, using MS or MS/MS. An Octa-decyl siloxane (C-18) derivatized silica support packed column having a range, from 2.7 to 5 μm particle size, on a fully porous support being the most used column support).
- Table 4 details the historical evolutions of the European Union's (EU's) regulatory agencies in coming to a consensus and setting the Tolerable Daily Intact (TDI) and Specific Migration Limit (SML) related to BPA in plastic food contact material as listed earlier [6].

Table 1. Samples of beers and energy drinks (*Reprinted with permission from Russo *et al.*, 2019 [12]).

Sample	Country of origin	BPF	BPE	BPA	BPB	BPAF	BADGE	BPM
Beer #1	Italy	32.61 ± 2.0	Np	Np	13.99 ± 1.6	114.15 ± 3.0	24.17 ± 0.1	Np
Beer #2	Italy	Np	Np	11.60 ± 0.7	<LOQ	Np	113.74 ± 3.0	Np
Beer #3	USA	Np	Np	Np	Np	138.91 ± 2.0	32.60 ± 1.6	Np
Beer #4	Poland	139.26 ± 5.0	Np	Np	8.10 ± 0.7	272.27 ± 5.0	59.14 ± 2.0	Np
Beer #5	Italy	Np	Np	Np	Np	56.11 ± 2.0	<LOQ	Np
Beer #6	The Netherlands	Np	Np	Np	Np	Np	Np	Np
Beer #7	Slovenia	Np	Np	Np	Np	150.98 ± 5.6	Np	Np
Beer #8	Italy	31.33 ± 1.7	Np	Np	Np	85.80 ± 2.3	24.00 ± 1.7	Np
Beer #9	UK	Np	<LOQ	13.48 ± 0.8	<LOQ	160.67 ± 3.2	39.41 ± 1.8	68.68 ± 4.0
Beer #10	Germany	Np	Np	Np	<LOQ	136.79 ± 5.0	30.77 ± 2.0	Np
Beer #11	Germany	Np	Np	15.14 ± 1.2	<LOQ	126.04 ± 3.2	28.20 ± 1.2	536.64 ± 9.0
Beer #12	The Netherlands	Np	Np	<LOQ	<LOQ	116.45 ± 2.1	31.49 ± 0.8	644.20 ± 8.0
Beer #13	Slovenia	Np	Np	<LOQ	Np	Np	Np	120.32 ± 3.0
Beer #14	Italy	59.14 ± 2.0	Np	Np	9.19 ± 0.8	102.87 ± 2.0	Np	56.37 ± 2.3
Beer #15	Germany	Np	Np	9.58 ± 0.8	<LOQ	171.07 ± 2.3	41.17 ± 0.6	Np
Beer #16	Japan	Np	Np	Np	Np	55.73 ± 1.8	<LOQ	Np
Beer #17	Italy	Np	Np	<LOQ	7.66 ± 0.6	224.40 ± 3.2	52.96 ± 0.8	Np
Beer #18	Germany	Np	<LOQ	<LOQ	<LOQ	231.08 ± 5.3	58.81 ± 2.1	Np
Beer #19	Germany	Np	Np	9.95 ± 0.8	Np	Np	Np	Np
Beer #20	Italy	20.55 ± 1.7	Np	Np	Np	72.73 ± 3.2	<LOQ	Np
Beer #21	Denmark	Np	Np	Np	Np	145.05 ± 2.4	32.36 ± 2.2	Np
Beer #22	Germany	Np	Np	<LOQ	<LOQ	186.69 ± 3.2	38.18 ± 2.4	Np
Beer #23	Germany	Np	Np	Np	Np	112.11 ± 1.8	21.07 ± 1.4	Np
Beer #24	Italy	Np	Np	Np	Np	133.67 ± 4.0	26.81 ± 0.4	Np
Beer #25	The Netherlands	Np	Np	Np	Np	74.83 ± 2.0	<LOQ	Np
Beer #26	The Netherlands	Np	Np	<LOQ	Np	192.87 ± 3.0	45.96 ± 1.5	Np
Beer #27	Germany	Np	Np	<LOQ	Np	141.97 ± 3.7	37.17 ± 1.8	30.36 ± 2.0
Beer #28	Romania	Np	Np	Np	<LOQ	141.09 ± 3.8	40.21 ± 1.8	37.52 ± 2.0
Beer #29	Ukraine	34.41 ± 2.0	Np	Np	<LOQ	134.25 ± 2.8	29.61 ± 3.2	Np
Beer #30	Ukraine	Np	Np	Np	<LOQ	201.06 ± 3.0	37.20 ± 4.0	182.74 ± 5.0
Beer #31	Russia	26.65 ± 2.0	Np	Np	<LOQ	108.38 ± 4.0	22.41 ± 2.4	Np
Beer #32	Russia	44.48 ± 4.7	Np	<LOQ	47.8 ± 5.0	131.18 ± 4.0	28.09 ± 3.2	Np
Beer#33	Poland	83.88 ± 4.3	Np	Np	<LOQ	211.26 ± 2.0	52.78 ± 2.6	Np
Beer #34	Italy	110.40 ± 1.8	Np	Np	<LOQ	283.53 ± 1.8	53.64 ± 1.8	1,358.32 ± 3.0
Beer# 35	Italy	83.39 ± 4.9	Np	Np	<LOQ	208.47 ± 5.3	42.97 ± 2.0	219.94 ± 9.0
Beer #36	Belgium	44.70 ± 2.6	Np	Np	Np	141.59 ± 2.0	30.54 ± 2.0	Np
Beer #37	Poland	91.10 ± 0.8	Np	Np	Np	146.28 ± 5.3	36.07 ± 3.0	23.11 ± 1.1
Beer #38	Poland	83.18 ± 1.2	Np	Np	<LOQ	165.44 ± 4.2	39.16 ± 4.0	128.60 ± 2.4
Beer #39	Poland	41.71 ± 3.7	Np	Np	Np	122.48 ± 4.3	25.24 ± 2.0	Np
Energy drink #1	USA	25.28 ± 1.8	58.75 ± 2.0	76.46 ± 1.2	Np	Np	Np	Np
Energy drink #2	USA	Np	Np	25.45 ± 2.0	Np	Np	Np	Np
Energy drink #3	USA	Np	Np	<LOQ	Np	Np	27.82 ± 1.8	Np
Energy drink #4	USA	Np	Np	Np	183.2 ± 1.5	Np	Np	Np
Energy drink #5	USA	Np	Np	Np	Np	Np	Np	Np
Energy drink #6	USA	Np	Np	Np	Np	Np	Np	Np
Energy drink #7	USA	Np	Np	Np	Np	Np	Np	Np
Energy drink #8	USA	Np	Np	Np	Np	Np	Np	Np
Energy drink #9	USA	Np	Np	Np	Np	Np	Np	Np
Energy drink #10	Italy	Np	Np	Np	Np	Np	Np	Np
Energy drink #11	Italy	Np	Np	Np	Np	Np	Np	Np
Energy drink #12	Japan	Np	Np	Np	Np	Np	Np	Np
Energy drink #13	Austria	Np	Np	Np	Np	Np	Np	Np

Note: Concentration values are in ng/mL.
Np, not present.

*Reprinted with permission of John Wiley & Sons from Table 1 of Russo, G., Varriale, F., Barbato, F., Grumetto, L., Are canned beverages industries progressively switching to Bisphenol AF? J. Food Sci., 2019, 84, 3303-3311.

Recent review detailing the importance of migration studies

In 2020 Schmid and Welle authored a very different review, which focused more on the historical development of beverage packings [8]. This review provides an excellent explanation of the importance of the chemical migration studies of the various compounds from metal cans, cardboard multi-layers, glass and polyethylene terephthalate (PET) bottles into their contained beverages. Various European regulations were detailed concerning the chemical migration of both intentional and non-intentional substances that could be added to foods and beverages. A total of 70 citations were

Table 2. Recent gas chromatographic methods used to analyse for Bisphenol-A and related Bisphenols in beverage and food containers.

Sample (Matrix)	**Extraction/Clean up**	**Separation/Detection**	**LOD and LOQ**	**Compounds analyzed**	**Reference**
Various Beverages Water, Diet Cola, Ice Tea	SPE- C18 bonded cartridges, 500 mg/ 6 cc Large Sample Volume 50 to 200 mL, eluentwas collected, derivatized to diesters with acetic anhydride	GC/MS, DB-5MS capillary column of 30m x 0.25 mm x 0.25 micron dimensions, temp. program employed,MS in EI mode using SIM with internal standard and isotope dilution used for quantitation.	MDL for BPA varied with 50, 100, 200 volumes passed through the SPE cartridge. 1.2, 0.62, and 0.29 pg/g. But for other beverages MDLs were foundto be higher.	BPA, BPF, BPE, BPB, BPAF. For beverages in PET bottles, BPA levels ranged from 0.022-0.030 ng/g. But BPA levels in cans ranged from 0.085-0.32 ng/g, n = 3	[14] 2018 X.-L. Cao Results proved that large sample volumes improved the detection limits and accuracy of the results.
Examined the detection and performed studies on the migration of BPs from the liners of beverage cans and sport drinks	Studied the effectiveness of various extraction solutions for migration studies. The extracts prepared by SPE, derivatized with MSTFA. Used standardized migration/ leaching test, EU 10/2011	GC-MS/MS column 5%-phenylmethylsiloxane 30 m x 0.25 mm, 0.25 um for targeted work. In addition UHPLC-QTOF used for non-targeted work	Extensive LOD, LOQ and recovery studies reported for various extracting solutions used.	BPA and 11 other BPs tested for. Cans were found to leach 10X more than plastic bottles	[15] 2020 Kowačič BPA was detected at high concentrations and most frequently from cans and reusable steel bottles.
10 different canned beverages.	Used liquid-liquid Extaction. Attenuated Total Reflectance (ATR-FTIR) used to identify the type of can coatings.	Used Purge & Trap (PT)-GC/MS to identify potential volatiles from can coatings. Used HPLC-FLD to analyze bisphenols in empty beverage cans, with ACN extracts, HPLC column C-18 (150 mm X 3.2 mm, 3 microns) with a Water/ ACN/MeOH gradient. Bisphenol identity confirmed by HPLC-MS/MS.	LODs of 0.005 mg/L for most bisphenols, Used HPLC-FLD. Most often BADGE was detected along with Cyclo-di-Badge.	BPE, BPF, BADGE, BADGE. Water product Badge. HCl product in addition to Cyclo-di-Badge.	[16] 2021 Lestido-Cardama. Conclusion: No detectable amounts of bisphenols studied were deemed to exit at levels that might pose a risk to human health.

Table 3. Recent liquid chromatographic methods used to analyse for Bisphenol-A and related Bisphenols in beverage and food containers.

Sample (Matrix)	Extraction/Clean Up	Separation/Detection	LOD and LOQ	Compounds Analyzed	Reference
Canned Beers from various EU Markets	Solvent extractions followed by BPA-Molecular Imprinted Polymer SPE supports which allowed for the removal of most of the undesired beer matrix.	UHPLC-FLD Column, Reverse Phase- C-18/Amide Bonded (75 mm x 4.6 mm, 2.7 micron) gradient water/ACN	LODs of 0.15 ng/mL LOQs 0.50 ng/mL Recoveries for the 5 BPs ranged 76-103%	BPA, BPF, BPB, BADGE, BFDGE	[17] 2019 Cirillo, 14 of the 40 canned beers found to have BPA, BPF and BADGE at conc. 0.5 to 2.5 ng/mL
Beers, Energy Drinks	Solvent extraction followed by SPE, evaporated, extracted in ACN and then microfiltered	HPLC-FLD C18 column, 250 mm x 4.6 mm, 5 micron isocratic water/ACN. Confirmation by high-resolution HRMS to nth-power. (LTQ Orbitrap, Fourier Transform MS) Used with a C18, (150 mm x 2.1 mm, 3.5 micron) UHPLC column.	LOD of 3.75 ng/mL LOQ of 12.51 ng/mL	BPA and 6 other BPs in Beers and Energy Drinks	[12, 18] 2019, 2016 Russo *et al*. reported finding high concentrations of BPAF and BADGE, with lesser amounts of BPB, BPA, PBF, BPM in many European Beers (Refer to Table 1)
Migration of BPA from can coatings into beverages at end of shelf life	Used migration contact experiments according to EU standard- 20% ethanol/ 80% water, at 60 °C for 10 days	UHPLC-MS/MS column C18 (100 mm x 2.1 mm, 2.6 micron, (-) ESI MS/MS)	Not Specified	BPA	[19] 2019, Stäker, C. and Welle, F. Accelerated migration conditions found to overestimate migration of BPA into foods
Migration from metal cans used to store beverages and foods	Used various beverage and food extracting solutions for simulated migration studies, performed long-term, elevated temperature storage migration tests	UHPLC-MS/MS, column C18 100 mm x 2.1 mm, 1.8 micron, optimized water/ACN gradient 0.5% formic, ammonium formate added	LODs of 0.28 to 14.8 ug/L LOQs of 0.94 to 49.3 ug/L for the 10 compounds of interest. Recoveries from 89.5 to 109%	BADGE, Novolac Glycidyl Ether (or NOGE) and their derivatives	[20] 2020 Hwang Only BADGE and BADGE. 2H2O found but detected below the mandated Specific Migration Limit (SML)

Table 3 continued..

Canned Vegetables 27 in total	A reasonable quantity of the aqueous phase in contact with the food, filtered and exposed to one or more different SPME fibers: PDMS-DVB poly(dimethylsiloxane - divinylbenzene) or CW (Carbowax) phase	HPLC-FLD- C18 column 300 mm x 3 mm, 5 micron, particle size of 100 Angstrom silica pores. Gradient of water/ACN or MeOH FLD set at 225 nm excitation, 305 nm emission. For confirmation used LC-MS/MS (neg-APCI) and the same C18 HPLC column	LOD- 0.005 mg/kg LOQ- 0.01 mg/kg for BPA only. Recoveries of 90%, 77% and 72% at 0.01, 0.05, 0.25 mg/kg, respectively. But noted that LC-MS/MS gave higher LODs 0.1 mg/kg	BPA was not detected in any of the 19 canned vegetables	[21] 2020- Vilarinho Conclusion: Extracts of liquid from canned vegetables can be detected accurately by HPLC-FLD
Coffee Capsules or Pods 37 different brands	Used Liquid-liquid extraction, followed by vacuum evaporation and then micro-filtration	UPLC-MS/MS, Column-Phenyl-Hexyl (100 mm X 2.1 mm, 1.7 micron) using gradient water/methanol, (-) ESI-MS/MS	LOD BPA 0.4 ng/mL; recoveries 80-105% at 2 ng/mL; spiked MDLs BPA 0.34 ng/mL	BPA, BPF, BPS analyzed for but mostly Benzophenone detected. Also 4-nonylphenol (4-NP) Dimethyl Terephalate (DMTP), Dibutyl Phthalate (DBP), Di(2-ethylhexyl) Phthalate (DEHP) were searched for.	[22] 2020 Sakaki, Provatas Conclusion: Targeted contamination in U.S. capsule and French Coffees were found to be below the established guidelines
Canned Foods and Beverages on the Chinese market (total of 151 canned products)	Used solvent extraction for solids, liquid-liquid extraction for beverages. SPE clean-up, in addition migration studies performed.	UHPLC-MS/MS, Column C18 (100 mm x 2.1 mm, 0.7 micron), gradient conditions, water/MeOH, MS/MS (-) ESI	LODs of 0.3 to 1.1 ug/kg LOQs of 0.10 to 3.6 ug/kg	BPA, BPF, BPS	[23] 2021 P. Cao Calculated the estimate of dietary exposure, advised lowering the mandated SML of BPA to children and adults

Table 3 continued..

BPA exposure from 36 alcoholic and non-alcoholic beverages on the Greek market	Used special BPA-Molecularly Imprinted Polymers (MIP) SPE supports. Reported BPA imprinting factor of 3.63. Implication that MIP allows for greener and more selective method of extraction.	HPLC with UV (photo-diode array detector); column, C-18 (250 mm x 4 mm, 5 microns)	LOD 0.003 ng/uL for BPA LOQ 0.011 ng/uL for BPA Recovery 93-105%,	BPA, BPF and BPS	[24] 2021 Tsalbouris Noted that the MIP-SPE made the SPE sample work-up more selective. BPA was found to be leached into beverages packed in cans in comparison to packed in PET bottles
Metabolites identified from *in vitro* metabolism studies run in rat and human liver microsomes	Incubated in human and rat liver microsomes, broths, quenched in cold ACN, centrifuged, evaporated, filtered and then analyzed.	UHPLC-MS/MS, column Biphenyl (100 mm x 2.1 mm 2.6 micron). Water/ACN gradient, also a F5 column of similar dimensions, along with a Triple Quad-TOF and/or MS/MS and (-) ESI Ionization mode	Most reported in the ppm concentration range unless targeted ions	BPA, BPF, BPS, BPAF, cumylphenol tetramethylbisphenol F (TMBPF)	[25] 2021 Ousji Over 50 metabolites, some not previously reported, mostly due to oxidative metabolic reactions, different GSH adducts, glucuronides sulfate adducts and Dimers.

given. Comparison of levels of chemical contamination from all types of beverages stored in glass bottles compared to lined cans or carboard packages is presented. It was noted that recently updated EU regulation No10/2011 had been issued for such alcoholic beverages [6]. However, the authors suggested that alcoholic beverages such as beers, with alcoholic strength between 6 to 20% v/v, might better be compared to the food 'simulant' extracting solutions of 20% ethanol/water v/v. As one might expect, their review did not specify the analytical instruments that should be required (e.g. GC vs. LC) or how they may be coupled to detection systems (MS, FID, FLD or UV). Nonetheless, it is implied that the analytical methods and instrumentation should be required to meet the general requirements for the intended purpose and to comply with defined criteria in regulations [8].

Review of various sensor methods

In 2021 Kaya *et al*. published a very different, informative, but related review with a total of 128 citations. Their topic was the current uses, on-going research and the potential of electrochemical sensors, imprinted polymers and aptamer-based electrochemical sensors. These miniature, low-cost, rapid and adaptable sensors are or can be applied, especially to commercial processes. To date such sensors have been incorporated as monitors in the production of beverage and food containers, baby bottles, medical devices, and for on-site monitoring. To improve their performance and sensitivities, different nanomaterials, such as carbon nanotubes, graphene oxides and metal nanoparticles, have been layered or modified to the surface of the electrochemical sensors. Their Table 1 is organized with the following headings: the various BPs used, their IUPAC names, chemical structures, areas of use, and application to which each sensor had been used with 9 citations listed. With 58 citations Table 2 summarized the analytical performances, listing the use of the sensor (mostly designed to monitor BPA), the electrochemical method employed, linear range (often 2-orders of magnitude), LOD and LOQ, sensitivity, % recovery, and the type of sample used. In on-going efforts to improve especially the selectivity, Molecular Imprinted Polymers (MIPs) embedded into a suitable substrate or surface have found important uses. To prepare a MIP-based sensor, the targeted template is reacted with monomer, cross-linking and activating agents and then affixed or deposited onto a suitable surface. MIPs have found expanding applications, -i.e., incorporation into the silica support of Solid Phase Extraction (SPE) cartridges or onto metallic substrates. Table 3, listing 14 citations, details the use of such MIP impregnated sensors with generally the same headings and details as listed in Table 2. Very interesting is the novel use of Aptasensors, which have incorporated into their fabric such biorecognition elements as antibodies, enzymes, nucleic acids or special biological cells. Hence Aptasensors when coupled into a transducer can act as a biosensor for biorecognition. A final Table 4 lists 11 citations that have reported the development of Aptameter-based sensor for the determination of BPA and other specific bisphenols. In this Table the following sub-headings appeared: electrochemical method employed, linear range (often 1 to 2- orders of magnitude), LOD and LOQ, sensitivity, % recovery, and for which applications or samples they had been used [13].

CONCLUSION

The intent of this manuscript has been to continue the give note to published articles in the investigations of BPA and the many other BPs that have been identified to have the potential to migrate into beverages and foods. No one can argue that effective, initial sample preparation is required so that the lowest detection limits are achieved in the analysis step. Such pre-analysis clean-up steps as solid phase extraction (SPE) especially with the use of Molecular Impregnated Polymer (MIP)-modified supports, liquid-liquid extraction (LLE), extraction with derivatization, headspace solid phase microextraction (SPME), stir-bar extraction, ultrasound dispersive extraction, and 'Quick Easy Cheap Effective Rugged and Safe' (QuEChERS) have been proven effective.

There seems to be no general conclusion whether gas chromatography or liquid chromatography has a clear advantage as to which general chromatographic method would work best for the separation and detection of BPs. Various forms of Mass Spectrometry (MS) have become the general detector of choice. Which chromatographic method used is dependent on the investigator(s) choice and expertise. However, it is clear by the various reviews cited that literally hundreds of very different, but related published manuscripts have shown that there is a concerted, world-wide effort to scientifically study the use of BPA and the many different analogs and/or replacements that continue to be incorporated into the liners of beverage and food containers. The toxicological effects of BPA and the other BPs continue to be of concern to animal, humans and to the overall environments. There is concern that even more persistent, or toxic bisphenol substitutes, such as BPF, BPAF and/or BPS, pictured in (Fig. 1-3), are replacing BPA in the manufacturing processes. FTIR and other spectroscopic methods have been proven effective at identifying new reactant products, being formulated into the commercial processing when the liner coatings of the containers are monitored. Laboratories continue to employ GC-MS and GC- MS/MS due to the superior resolution capability of the capillary GC columns. Liquid chromatography, LC-FLD, LC-MS and UHPLC-MS/MS, especially with LCs' variety of bonded stationary phases having different modes of interactions create interesting but powerful challenges. This may be especially true in the applications of Hydrophilic Interaction Liquid Chromatography (HILIC) due to its ability to separate the more polar, water- soluble molecules. Newer developments and refinements of mass spectrometry, -i.e. its modes of ionization and the adoption of accurate mass time-of-flight mass spectrometers (LC/Q-TOF), no doubt need to be exploited. The continued commercial use of BPA and its replacements in all types of commercial products should be continually monitored so that their reduced migration into beverages and foods does not occur.

ACKNOWLEDGEMENTS

This work was generously supported by a grant from the Beatrice Fox Auerbach Foundation Fund at the Hartford Foundation for Public Giving, as well as by the Center for Environmental Sciences & Engineering and Institute of the Environment at the University of Connecticut.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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