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Critical Review

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Bisphenol Analogues Other Than BPA: Environmental Occurrence, Human Exposure, and Toxicity—A Review

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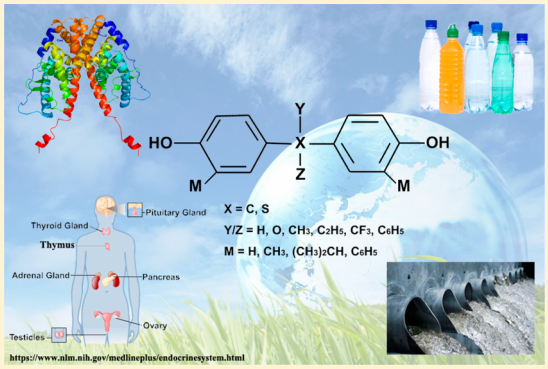
Supporting Information

ABSTRACT: Numerous studies have investigated the environmental occurrence, human exposure, and toxicity of bisphenol A (BPA). Following stringent regulations on the production and usage of BPA, several bisphenol analogues have been produced as a replacement for BPA in various applications. The present review outlines the current state of knowledge on the occurrence of bisphenol analogues (other than BPA) in the environment, consumer products and foodstuffs, human exposure and biomonitoring, and toxicity. Whereas BPA was still the major bisphenol analogue found in most environmental monitoring studies, BPF and BPS were also frequently detected. Elevated concentrations of BPAF, BPF, and BPS (i.e., similar to or greater than that of BPA) have been reported in the abiotic environment and human urine from some regions. Many analogues exhibit endocrine disrupting effects, cytotoxicity, genotoxicity, reproductive toxicity, dioxin-like effects, and neurotoxicity in laboratory studies. BPAF, BPB, BPF, and BPS have been shown to exhibit estrogenic and/or antiandrogenic activities similar to or even greater than that of BPA. Knowledge gaps and research needs have been identified, which include the elucidation of environmental occurrences, persistence, and fate of bisphenol analogues (other than BPA), sources and pathways for human exposure, effects on reproductive systems and the mammary gland, mechanisms of toxicity from coexposure to multiple analogues, metabolic pathways and products, and the impact of metabolic modification on toxicity.



INTRODUCTION

Bisphenol A (BPA; 2,2-bis(4-hydroxyphenyl)propane) is one of the highest production volume chemicals worldwide.[1] BPA is used in the production of polycarbonate plastics and epoxy resins, as well as in many consumer products including food containers, paper products (e.g., thermal receipts), water pipes, toys, medical equipment, and electronics.[1] BPA is ubiquitous in the environment; and humans are exposed to this chemical via dietary and nondietary sources.[1,2] Previous studies have reported the widespread occurrence of BPA in human serum, urine, placental tissue, umbilical cord blood, and breast milk, revealing a global exposure.[1−3] A large body of research has documented adverse effects of BPA on reproduction and development, neural networks, and cardiovascular, metabolic, and immune systems in in vitro assays and laboratory animal studies.[4−7] The concern over widespread human exposure and associated health effects has led to regulations on the production and usage of BPA in North America and the European Union. In 2010, the Canadian Government prohibited the import and sale of polycarbonate baby bottles containing BPA.[8] The European Union also prohibited the use of BPA in infant feeding bottles since 2011.[9] The public concern and governmental regulations on BPA stimulated the development and production of alternative substances to replace BPA in a myriad of applications. A number of chemicals that are structurally similar to BPA have already been used in the manufacture of polycarbonate plastics and epoxy resins. These chemicals share a common structure of two hydroxyphenyl functionalities and are collectively referred to as

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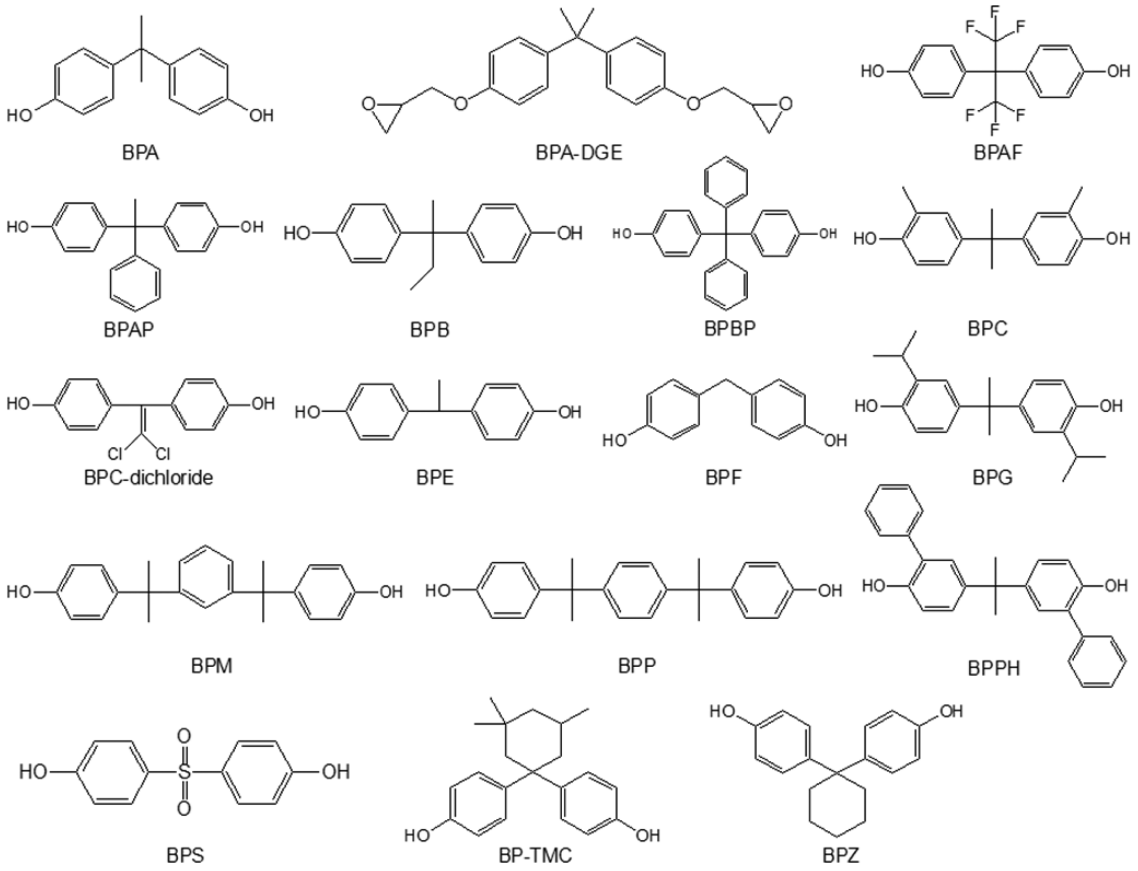

Figure 1. Chemical structures of bisphenol analogues reviewed in the present study. Full names of bisphenol analogues are given in Table S1 of Supporting Information.

bisphenol analogues (Figure 1). A total of 16 bisphenol analogues have been documented for industrial applications.

BPF (4,4′-methylenediphenol), BPS (4-hydroxyphenyl sulfone), and BPAF (4,4′-hexafluoroisopropylidene)diphenol) are among the main substitutes of BPA in the manufacturing of polycarbonate plastics and epoxy resins. BPF has a broad range of applications such as lacquers, varnishes, liners, adhesives plastics, and water pipes, as well as in dental sealants, oral prosthetic devices, tissue substitutes and coatings for food packaging.[10] BPS is commonly used in epoxy glues, can coatings and thermal receipt papers, as well as in sulfonated poly(ether ketone ether sulfone) (S-PEKES) and as an additive in dyes and tanning agents.[11] BPAF is used as a cross-linker in fluoroelastomers, electronics and optical fibers, and as a high-performance monomer for polyimides, polyamides, polyesters, polycarbonate copolymers and other specialty polymers.[12,13] BPAF is also used in specialty polymer applications, including plastic optical fibers and waveguides.[14] The domestic production of BPAF in the U.S. was reported to range from 10,000 to 500,000 pounds annually between 1986 and 2002.[15] There is a general lack of production or usage data for all other BPA analogues, but studies have suggested that the production and application of some bisphenol analogues are on the rise globally.[11,12,15]

The occurrence of bisphenol analogues in environmental compartments, foods or food containers, consumer products, and human specimens has been documented. Available studies, although limited in numbers, have reported a variety of toxic effects of bisphenol analogues such as BPF and BPS.[16] However, in comparison with numerous BPA studies, investigations on other bisphenol analogues are still limited. The goals of this review are to compile and analyze the current state of knowledge on the occurrence of bisphenol analogues in the environment, consumer products and foodstuffs, and on human exposure and toxicity; and to identify knowledge gaps and future research needs. The review is structured into six topics: (a) bioavailability and environmental persistence; (b) occurrence in the environment, consumer products and food; (c) human biomonitoring and exposures; (d) toxicity; (e) effects of metabolic modification on toxicity; and (f) knowledge gaps and research needs.

BIOAVAILABILITY AND ENVIRONMENTAL PERSISTENCE

Environmental behavior (e.g., transport and bioavailability) and fate of organic chemicals can be greatly influenced by their physicochemical properties.[17,18] However, data on experimentally determined physicochemical properties for bisphenol analogues are generally limited. In the present review, we used the U.S. Environmental Protection Agency (EPA) Estimation Program Interface (EPI) Suite Version 4.11 to calculate properties such as log K_{ow} (octanol−water partition coefficient), log K_{aw} (air−water partition coefficient), bioconcentration factor (BCF), bioaccumulation factor (BAF), and half-lives ($t_{1/2}$) in air, water, soil, and sediments for selected bisphenol analogues (Table S1; Supporting Information).[19] The EPI Suite employs quantitative structure−property relationship (QSPR) models to estimate physicochemical properties of chemicals for which experimental data are missing. This approach has been broadly applied in risk

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assessments, although it is not recommended to use whenever actual measurements from laboratory studies exist.[19] Estimated log K_{ow} values of bisphenol analogues range from 1.65 to 7.17, and a few analogues such as BPBP (bis(4-hydroxyphenyl)-diphenylmethane), BPG (2,2-bis(4-hydroxy-3-isopropylphenyl)propane), BPM (4,4′-(1,3-phenylenediisopropylidene)bisphenol), BPP (4,4′-(1,4-phenylenediisopropylidene)bisphenol), BPPH (2,2-bis(2-hydroxy-5-biphenylyl)propane) and BP-TMC (4,4′-(3,3,5-trimethylcyclohexylidene)bisphenol) have log K_{ow} values > 5, which suggests their tendency to adsorb into sediments and to accumulate in tissues.[17] However, similar to BPA, which is subject to rapid metabolism,[20] other analogues may be metabolized at similar rates, thus reducing their bioaccumulation potencies. Indeed, only BPM and BPP have a calculated BCF proximate to 2000 L/kg, a criterion for consideration to be bioaccumulative by the European Union Registration, Evaluation and Authorization of Chemicals (REACH) regulation,[17] whereas the other analogues have BCF values ranging from 3.5 to 640 L/kg.

BPA analogues undergo atmospheric oxidation with half-lives ($AO_{t1/2}$) of <0.4 day and log K_{aw} < −5 (Supporting Information Table S1; EPIWEB 4.1). BPAF has the highest overall environmental persistence over the other analogues. Laboratory studies have shown that some bisphenol analogues are subject to microbial and photochemical degradation. The biodegradability of bisphenol analogues in seawater was ranked as BPF ≫ BPA > BPP > BPE (4,4′-ethylidenebisphenol) > BPB (2,2-bis(4-hydroxyphenyl)butane) ≫ BPS.[21−23] Under anaerobic conditions in sediments, the rank of biodegradability was BPF > BPS, BPA > BPE > BPB.[22] BPF degrades at a faster rate than BPA, whereas BPS, BPB and BPP are more resistant to biodegradation than BPA in aquatic environments.[21,22] Bisphenol analogues are overall more persistent in sediments (half-life $t_{1/2}$ = 135−1621 days) than in soil ($t_{1/2}$ = 30−360 days) and water ($t_{1/2}$ = 15−180 days) (Supporting Information Table S1). However, the biodegradation can be enhanced in the rhizosphere of *Phragmites australis*.[24] Photodegradation of BPE and BPF was reported to occur in water with the formation of a hydrated electron-phenoxyl radical pair as the common main degradation pathway.[25,26] Hydroxylated BPF and *p*-hydroxybenzenesulfonic acid were the main products of BPF and BPS photoionization, respectively.[25,27] Photodegradation of BPE, BPP, and BPZ in water with coexistence of *β*-cyclodextrin was also reported, which formed a complex with bisphenol analogues and catalyzed the degradation by more readily producing hydroxyl radicals.[26,28,29] Overall, given that bioaccumulation and persistence greatly influence the environmental dynamics and fate, further studies are needed to elucidate the bioconcentration, bioaccumulation, degradation, volatilization, oxidation, and photolysis of bisphenol analogues under natural environmental conditions. Elucidation of potential environmental transformation products of bisphenol analogues is also warranted in future studies.

OCCURRENCE IN THE ENVIRONMENT, CONSUMER PRODUCTS, AND FOODSTUFFS

Environmental Compartments. This section is organized and discussed based on different environmental compartments where bisphenol analogues have been reported, including indoor dust, sediments, fresh and seawater, sewage effluent and sludge (Table 1). The analogues detected in the environment to date include BPAF, BPAP (4,4′-(1-phenylethylidene)-bisphenol), BPB, BPF, BPP, BPS, and BPZ (4,4′-cyclohexylidenebisphenol), as well as BPA (Table 1). These eight bisphenols were investigated in indoor dust collected from a number of countries from Asia, Europe, and the North America.[30,31] The median concentration of total bisphenols (∑BPs; a sum of all detectable analogues including BPA) by country ranged from 0.15 (Pakistan) to 4.48 μg/g (Greece). Bisphenol analogues were also detected in sediments from the U.S., Japan, and Korea, with a median ∑BP concentration by country ranging from 3.2 to 12.6 ng/g dw.[32] BPAF was found at concentrations (0.9−246 ng/L) similar to that of BPA (6.6−74.6 ng/L) in river water from a city moat in Beijing (China), whereas the former analogue was found to be more abundant than BPA (i.e., 0.18−2010 ng/g versus 1.37−42.8 ng/g) in surficial sediments from Hangzhou Bay (China).[33] Elevated BPAF concentrations were found in water (up to 15.3 μg/L), sediments (up to 2 μg/g dw), soil (up to 331 ng/g dw), and indoor dust (up to 739 ng/g dw) collected near a manufacturing plant in Jiaxing City, Zhejiang Province (China).[34] In river and seawater collected from Japan, Korea, and China, BPF concentrations exceeded 1000 ng/L in several study sites, e.g. ranging up to 2850 ng/L in the Tamagawa River in Tokyo.[35] Multiple sites had ∑BP concentrations exceeding a predicted no-effect concentration (PNEC) of 1500 ng/L for BPA recommended by the European Union.[35] Bisphenol analogues were also reported in sewage sludge. In sludge collected from 52 Chinese municipal wastewater treatment plants (WWTPs), the geometric mean concentrations of BPF, BPS, and BPA were 3.84, 3.02, and 4.69 ng/g dw, respectively, followed by BPAF (0.85 ng/g dw) and BPE (0.23 ng/g dw).[36] Median BPF concentration (249 ng/g dw) also approached that of BPA (275 ng/g dw) in Korean sewage sludge.[37] The composition of bisphenol analogues differed among three types of Korean WWTP that treated wastes originating from industrial, domestic, and mixed sources. The sludge from industrial WWTPs was dominated by BPA, whereas the sludge from domestic and mixed WWTPs was dominated by BPF.[37] Lee et al. suggested that BPF was increasingly applied in certain applications, including water pipes and structures used in treatment plants, and estimated the emission of bisphenols through discharges of sludge and wastewater effluent from Korean WWTPs to be 7.0−42.3 and 104.4−429 kg/y, respectively.[37] A U.S. study reported the ∑BP concentrations of 12.8−4730 ng/g dw (median: 265) in sewage sludge collected from 74 WWTPs.[38] The annual emission of bisphenols through sewage sludge and wastewater discharges was estimated to be 3390 and 45 900 kg/y, respectively, constituting <0.02% of the bisphenol production in the U.S.[38]

An analysis of the relative abundance of bisphenol analogues (i.e., concentration ratio of individual bisphenol analogue to ∑BPs) based on the literature data provides a direct demonstration of relative abundances of bisphenol analogues in environmental samples (Figure 2). While BPA was generally the dominant analogue, contributing to over 60% of the total bisphenol concentrations in most environmental compartments, BPF and BPS were also frequently detected as the second and third most abundant analogues (Figure 2). Elevated detection frequencies and concentrations of BPAF, BPF, and BPS have also been reported in the abiotic environment in some regions; for instance, BPF was the most abundant bisphenol analogue in surface water from some sites in Japan, Korea, and China, contributing to over 70% of the total concentrations on average.[35] This may indicate high usage of

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Table 1. Concentrations of Bisphenol Analogues in Environmental Compartments, Foods, Consumer Products, And Humans.[a]

matrix	region	Year	N	unit	BPA	BPAF	BPAP	BPB	BPE	BPF	BPP	BPS	BPZ	total	ref
Environment															
sediment	U.S.	1998–2012	82	ng/g	1.49	nd	nd	nd	nd	1.44	nd	nd	nd	3.24	32
	Japan	2012	56	ng/g	8.3	nd	nd	nd	nd	3.57	nd	nd	nd	12.6	
	Korea	2008	34	ng/g	6.02	nd	nd	nd	nd	nd	nd	nd	nd	8.84	
sediment	China	2012	5	ng/g	9.1	489		nd		0.6		0.07		498	33
sediment	China		13	ng/g		169									34
water	Japan	2013–2014	18	ng/L	12					215		3.4			35
	China		6	ng/L	22.2					277		nd			
	Korea		10	ng/L	63					nd		nd			
	India		14	ng/L	380					nd		26.5			
water	China		16	ng/L		3080									34
water	China	2012	5	ng/L	11.4	2.2		nd		nd		0.51		14.1	33
soil	China		68	ng/g		0.35									34
sludge	Korea	2011	40	ng/g	275	nd	nd	nd		249	nd	3.8	nd	769	37
sludge	China	2010–2011	52	ng/g	9.4	0.4			0.06	1.9		4.3		101	36
sludge	U.S.	2006–2007	76	ng/g	222	<1.8	<1.8	<1.8		8.2	<1.8	5.8	<1.8	265	38
indoor dust	China		17	ng/g		124									34
indoor dust	China	2012–2014	34	ng/g	330	1.9	<0.5	<1		<1	<2	<2	<0.5	350	31
	Colombia		42	ng/g	120	2.2	<0.5	<1		33	<2	2.4	<0.5	180	
	Greece		28	ng/g	1500	2.5	<0.5	<1		780	<2	860	<0.5	3900	
	India		35	ng/g	130	1.5	<0.5	<1		6.7	<2	4.2	<0.5	180	
	Japan		14	ng/g	1700	4.1	<0.5	<1		230	<2	160	<0.5	2600	
	South Korea		16	ng/g	720	3.0	<0.5	<1		1000	<2	3.6	<0.5	1600	
	Kuwait		17	ng/g	250	2.5	<0.5	<1		22	<2	20	<0.5	380	
	Pakistan		22	ng/g	66	1.3	<0.5	<1		50	<2	1.8	<0.5	150	
	Romania		23	ng/g	600	0.39	<0.5	<1		2.0	<2	82	<0.5	870	
	Saudi Arabia		19	ng/g	650	2.2	<0.5	<1		73	<2	28	<0.5	1200	
	US		22	ng/g	1500	1.4	<0.5	<1		200	<2	<2	<0.5	220	
	Vietnam		12	ng/g	230	1.1	<0.5	<1		57	<2	<2	<0.5	400	
	all		284	ng/g	440	1.8	<0.5	<1		36	<2	3.2	<0.5	610	
indoor dust	U.S.	2006, 2010	38	μg/g	1.6	<0.001	<0.001	<0.001		0.05	<0.001	0.63	0.001	2.54	30
	China	2010	55	μg/g	0.63	<0.001	<0.001	<0.001		0.04	<0.001	0.13	0.001	1.11	
	Japan	2012	22	μg/g	2.7	<0.001	<0.001	<0.001		0.06	<0.001	0.82	0.001	3.79	
	Korea	2012	41	μg/g	3.3	<0.001	<0.001	<0.001		0.45	<0.001	0.36	0.001	4.48	
	All		156	μg/g	1.6	<0.001	<0.001	<0.001		0.10	<0.001	0.36	0.001	2.66	
Food															
beverage	U.S.	2008–2012	31	ng/g	0.24	<0.01	<0.01	0.01		0.03	0.03	<0.01	0.03	0.34	49
dairy products	U.S.		29	ng/g	2.55	0.03	0.19	0.01		0.13	0.01	0.04	0.03	2.99	
fats and oils	U.S.		5	ng/g	1.9	<0.01	<0.01	0.01		0.26	0.01	<0.01	0.03	2.23	
fish and seafood	U.S.		23	ng/g	3.23	0.01	<0.01	0.01		4.63	0.01	0.02	0.03	7.95	
cereals	U.S.		48	ng/g	0.61	<0.01	0.01	0.02		0.08	0.13	0.01	0.03	0.89	
meat	U.S.		51	ng/g	0.85	0.01	0.05	0.01		1.34	0.35	0.61	0.03	3.25	
fruits	U.S.		20	ng/g	0.53	0.02	0.06	0.01		0.03	0.01	0.01	0.03	0.70	

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Table 1. continued

matrix	region	Year	N	unit	BPA	BPAF	BPAP	BPB	BPE	BPF	BPP	BPS	BPZ	total	ref
Food															
vegetables	U.S.		45	ng/g	8.99	0.01	0.12	0.01		1	0.47	0.02	0.08	10.7	
All			267	ng/g	3	0.01	0.06	0.01		0.93	0.21	0.13	0.03	4.38	
cereals	China	2012	39	ng/g	0.38	<0.01	<0.01	0.01		0.03	0.01	<0.01	0.03	0.51	50
meat	China		20	ng/g	0.10	<0.01	<0.01	0.01		0.03	0.01	<0.01	0.03	0.69	
fish and seafood	China		11	ng/g	4.46	<0.01	<0.01	0.01		0.03	0.01	0.15	0.03	7.85	
eggs	China		11	ng/g	0.97	<0.01	<0.01	0.01		0.03	0.01	<0.01	0.03	1.25	
milk products	China		17	ng/g	0.94	<0.01	<0.01	0.01		0.06	0.01	<0.01	0.03	1.29	
bean products	China		27	ng/g	0.15	<0.01	<0.01	0.01		0.03	0.01	<0.01	0.03	0.37	
fruits	China		20	ng/g	0.53	<0.01	<0.01	0.01		0.03	0.01	<0.01	0.03	1	
vegetables	China		42	ng/g	0.22	<0.01	<0.01	0.01		0.03	0.01	<0.01	0.03	2.02	
cookies	China		26	ng/g	0.67	<0.01	<0.01	0.01		0.03	0.01	<0.01	0.03	1.08	
beverages	China		4	ng/g	7.84	<0.01	<0.01	0.01		0.03	0.01	<0.01	0.03	7.93	
cooking oils	China		11	ng/g	0.72	<0.01	<0.01	0.01		0.03	0.01	<0.01	0.03	0.91	
condiments	China		48	ng/g	0.005	<0.01	<0.01	0.01		0.03	0.01	<0.01	0.03	0.10	
others	China		13	ng/g	0.10	<0.01	<0.01	0.01		0.03	0.01	<0.01	0.03	0.32	
All			289	ng/g	0.21	<0.01	<0.01	0.01		0.03	0.01	<0.01	0.03	0.79	
canned tomatoes	Italy		38	ng/g	nd-115			nd-85.7							51
soft drinks	Spain		10	μg/L	nd-0.68					nd-0.26			nd-0.09		54
filling liquids	Spain		10	μg/L	nd-14					nd-7.1			nd-0.92		54
beverages	Portugal		30	μg/L	nd-4.7			nd-0.17							56
infant formula	Portugal		7	μg/L	nd-0.4			nd							56
canned food_supernatant	Spain			ng/mL	11.7−317							nd-175			53
canned food	Spain			ng/g	nd-77.7							nd-36.1			53
soft drinks	Spain	2009	11	ng/L	nd-607					nd-218					55
food	Spain	2013		ng/g	nd-241			nd-40							52
mustard	Switzerland			μg/g						5−10					57
Consumer Products															
thermal receipt papers	Albany, U.S.	2010−2011	81	μg/g								440			40
	other cities, U.S.		10	μg/g								200			
	Japan		6	μg/g								620			
	Korea		11	μg/g								0.7			
	Vietnam		3	μg/g								0.3			
	All		111	μg/g								180			
various paper products	NY, U.S.	2010−2011	157	μg/g								7			40
source-segregated paper	Denmark	2013		μg/g	5			0.03	0.04	0.04		0.3			44
mixed paper	Denmark	2013		μg/g	5.6			0.03	0.04	0.04		0.4			
thermal paper	Denmark	2014		μg/g	16300			<3	<4	<4		7800			
personal care products	China	2012−2013	117	ng/g	0.51	0.2	0.47	0.75		0.82	0.72	0.45	0.74	5.95	39
	U.S.	2012−2013	114	ng/g	0.55	0.21	0.41	0.72		0.99	0.99	0.38	0.71	7.7	
Human															
urine	U.S.	2010−2011	31	ng/mL								0.299			58, 64
	China		89	ng/mL	1.1							0.226			

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Table 1. continued

matrix	region	Year	N	unit	BPA	BPAF	BPAP	BPB	BPE	BPF	BPP	BPS	BPZ	total	ref
Human															
	India		38	ng/mL	1.59							0.072			
	Japan		36	ng/mL	0.84							1.18			
	Korea		33	ng/mL	2							0.030			
	Kuwait		30	ng/mL	1.24							0.172			
	Malaysia		29	ng/mL	1							0.071			
	Vietnam		29	ng/mL	1.42							0.160			
	All		315	ng/mL	1.2					0.228		0.168			
urine	China	2013	94	ng/mL	0.886	0.018						0.029			59
urine	Saudi Arabia	2014	130	ng/mL	4.92	0.05	0.3	0.05		0.19	0.093	13.3	0.06	19.0	61
urine	India	2012−2013	76	ng/mL	5.08							0.04			60
serum	Italy		69	ng/mL	2.91			5.15							62

[a]Median, geometric mean, or mean values, whichever available, were summarized in this table. A range of concentrations was given if no mean or median data were reported. Blank cells indicate that the compound was not examined or the information was missing from original references. nd = nondetectable.

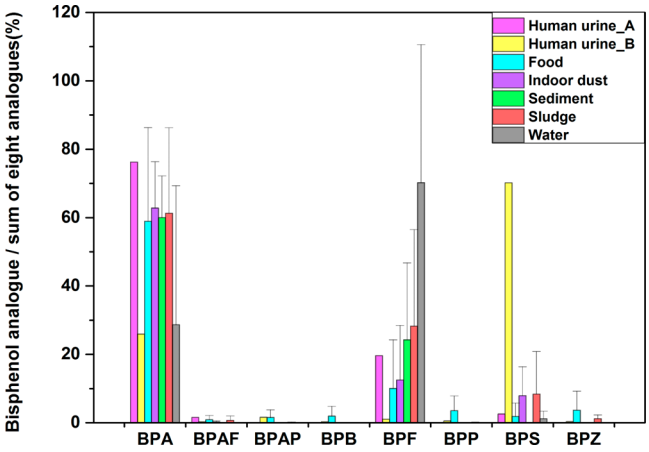

Figure 2. Concentration ratios of an individual bisphenol analogue to the sum of eight bisphenols in human urine,[59,61] food,[49] indoor dust,[30,31] sediment,[32] sludge,[36,37] and water.[35] Human urine A and B data are from Yang et al.[59] and Asimakopoulos et al.,[61] respectively.

BPF as a BPA replacement in southeastern Asian regions. Several analogues, such as BPB and BPZ, were sporadically found in the environment, likely suggesting their specialized applications and localized emissions. Available reports also revealed that the concentrations and composition profiles of bisphenol analogues varied widely among matrices and geographical locations. However, previous environmental studies are limited to countries including the U.S., China, Japan, Korea, and India, as well as a few countries from Europe and the middle-east; and data are missing from the rest of the world. Data are also scarce or completely lacking in environmental compartments, including air, drinking water, and wildlife. These data gaps greatly limit our capacity for assessing the sources, environmental distribution, and fate of bisphenol analogues regionally or globally, as well as the associated human and wildlife exposure pathways and risks.

Consumer Products. Bisphenol analogues were found in personal care products (PCPs), thermal receipt papers, currency bills, household waste papers, and recycled paper products (Table 1). Detection rates of BPA, BPAF, BPAP, BPB, BPF, BPP, BPS, and BPZ in PCPs (including body washes, hair care products, makeup, sanitary products, skin locations, toilet soaps, and toothpaste) from the U.S. and China ranged from 2.6% to 13.4% (GM of ∑BPs = 6.0 and 7.7 ng/g, respectively).[39] BPS was found in thermal receipt papers from the U.S., Japan, Korea, and Vietnam at a geometric mean concentration (0.181 mg/g) similar to that of BPA, and in 87% of currency bills from 21 countries (GM = 0.029 μg/g).[40] The major source of BPS in currency bills was attributed to thermal receipt papers, which come in contact with currency bills frequently. BPA has been used as a color developer in thermal papers, resulting in high concentrations (up to 3−22 g/kg) in thermal receipt papers.[41] A major U.S. thermal paper manufacturer reported a recent replacement of BPA with BPS, while several other producers have replaced BPA with other analogues including BPS.[40,42] As approximately 30% of thermal papers enter the paper recycling streams, thermal papers may become an important source of bisphenol analogues to wastepaper and recycled paper products (e.g., toilet paper); the latter may subsequently contribute bisphenols to wastewater.[43] Indeed, BPS was frequently detected in household waste paper from Denmark, with median concen-

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Table 2. Estimation of Daily Intake Rate of Bisphenol Analogues Based on Human Urine Biomonitoring Data[a]

country	population	N		BPA	BPA-DGE[b]	BPAMC[c]	BPATrC[d]	BPAF	BPAP	BPF	BPS	ref
China	adults	90	conc.[e]	0.886				0.018		0.228	0.029	59
			DIR[f,g]	0.021				0.0004		0.005	0.001	
India	children (age <14 y)	76	conc.	5.08	37.0						0.04	60
			DIR[g]	0.019	0.863						0.001	
Saudi Arabia	adults and children (median age: 37 y)	130	conc.	2.01					0.21	2.16	4.92	61
			DIR[g]	0.047					0.005	0.05	0.115	
U.S.	11−66 y	31	conc.	3.017		0.055	0.047					63
			DIR[h]	0.060		0.001	0.001					
seven Asian countries[i]	children and adolescents (age <20 y)	47	conc.	1.758								64
			DIR[j]	0.039								
	adults (age ≥20 y)	249	conc.	1.300								
			DIR[k]	0.037								
	male	153	conc.	1.613								
			DIR[l]	0.037								
	female	143	conc.	1.850								
			DIR[m]	0.037								
U.S. and seven Asian countries[i]	children and adolescents (age <20 y)	33	conc.								0.412	58
			DIR[j]								0.009	
	adults (age ≥20 y)	265	conc.								0.152	
			DIR[k]								0.004	
	male	152	conc.								0.226	
			DIR[l]								0.005	
	female	150	conc.								0.16	
			DIR[m]								0.003	

[a]The estimation of human intake rate follows the equation: urinary bisphenol concentration (μg/L) × urinary output (L/day)/body weight (kg) = μg bisphenol/kg/day.[65] [b]BPA-DGE = bisphenol A diglycidyl ether. [c]BPAMC = bisphenol A monochloride. [d]BPTrMC = bisphenol A trichloride. [e]Median or geometric mean concentration (μg/L). [f]DIR = Daily intake rate (μg bisphenol/kg/day). [g]Assuming 1.4 L/day urine and 60 kg body weight (bw). [h]Assuming 1.4 L/day urine and 70 kg bw. [i]Asian countries including China, India, Japan, Korea, Kuwait, Malaysia, and Vietnam. [j]Assuming 0.66 L/day urine and 30 kg bw. [k]Assuming 1.7 L/day urine and 60 kg bw. [l]Assuming 1.6 L/day urine and 70 kg bw. [m]Assuming 1.2 L/day urine and 60 kg bw.

trations of 0.4 and 0.3 μg/g in source-segregated and mixed household waste, respectively, approximately 15 times lower than that of BPA.[44] BPF was also detected at a lower frequency (<33%) and with a lower concentration (median 0.04 μg/g).[44] Humans may be exposed to bisphenols present in various consumer products via dermal exposure and hand-to-mouth transfer.[45−48] Additional factors, such as the usage of hand sanitizer, may facilitate the exposure via these routes.[48] The median estimated daily intakes (EDI) of BPS through dermal exposure via handling of papers were estimated to be 293 ng/day and 21.8 μg/day for the general population and occupationally exposed individuals, respectively.[40] The EDI of bisphenols via hand-to-mouth transfer from paper products is not known. Also lacking is the measurement of human exposure from bisphenol-containing consumer products other than paper products and PCPs. Thus, further investigations are critically needed to evaluate the migration of bisphenol analogues from various consumer products and the subsequent contribution to human exposure and environmental contamination.

Foodstuffs. Dietary sources have been suggested to contribute to BPA exposure greater than the nondietary sources by at least 1 order of magnitude.[2] Recent studies also reported non-BPA analogues in foodstuffs from different countries. BPF was found to be the second abundant analogue in a U.S. survey of various food items, including beverages, dairy products, fats and oils, fish and seafood, meat, cereals, fruits, and vegetables (Table 1; Figure 2).[49] The mean concentrations of BPA and BPF in the U.S. foods were reported to be 3 and 0.93 ng/g wet weight (ww), respectively.[49] Canned foods were found to contain higher concentrations of individual and total bisphenols than foods sold in glass, paper, or plastic containers.[49] A Chinese survey reported mean ∑BP concentration of 9.35 ng/g (median: 0.79 ng/g) in a variety of foodstuffs.[50] The mean EDI through foods were estimated to be 646 and 664 ng/kg bw/day for adult Chinese males and females, respectively.[50] By contrast, the EDI for the U.S. adults was estimated to be 54.6 ng/kg bw/day, less than the EDIs for infants (<1 year; 142 ng/kg bw/day), toddlers (1 − <6 years; 243 ng/kg bw/day), and children (6 − <11 years; 117 ng/kg bw/day).[49] BPB, BPF, or BPS, as well as BPA, were also reported in canned products and/or soft drinks and filling liquids from several European countries.[51−56] In addition to contamination from food can coatings and production, natural occurrence of BPF was also reported in mild mustard made of the seeds of *Sinapis alba*, where it was a reaction product from the breakdown of the glucosinolate glucosinalbin with 4-hydrobybenzyl alcohol.[57] The consumption of 20 g of mustard can lead to an intake of 100−200 μg of BPF, representing a significant human exposure. Diet is believed to be the major source of human BPA exposure.[2] For bisphenol analogues that are used in food can coatings, a similar pattern is expected. However, some analogues are used exclusively in specialized applications such as fluoroelastomer production and a major

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Table 3. Potency of Bisphenol Analogues in Comparison with That of BPA.[a]

receptor	assay	BPAF	BPAP	BPB	BPC	BPE	BPF	BPP	BPS	BPZ	reference
Estrogenic Activity											
ERα[b]	yeast 2-hybrid						0.79		0.10		16
ER	MVLN								0.0001		69
ERα	GFP-ERα:PRL-HeLa	6.67	0.0004	0.0001	25.35					1.70	70
ER	BG1Luc4E$_2$[f]			0.67		0.17	0.10		0.07		71
ERα	E-screen						4.83				72
ERα	MCF-7	12.6		9.0			0.63		0.57		73
ERα	E-screen						0.47		0.03		74
ERα	MELN						0.48		0.04		74
ERα	HELN						0.24		0.10		74
ERβ	HELN						0.36		0.30		74
ERα	MELN								0.55		16
ERα and ERβ[c]	BG1Luc4E$_2$								0.08		16
ERα	E-screen						0.89		0.67		16
ERα	yeast 2-hybrid						2.42		0.16		16
ERα	E-screen						0.99		0.90		16
ERα	Yeast 2-hybrid						2.67		0.20		16
ERα	MCF-7								0.62		16
ERα	E-screen						0.10				16
ERα	E-screen						0.64				16
ERα	yeast bioreporter						1.00		0.01		16
ERα	E-screen						0.27				16
ERα	E-screen						0.60				16
ERα	MVLN						0.50				16
ERα	HepG2	2.81							0.12		16
mER[d]	GH3/B6/F10 ERK[g]								0.43		16
mER	GH3/B6/F10 ERK								0.71		16
median		6.67	0.0004	0.67	25.35	0.17	0.62		0.16	1.70	
mean		7.36	0.0004	3.22	25.35	0.17	1.00		0.30	1.70	
Antiandrogenic Activity											
AR[e]	EcoScreen+DHT[h]						0.52				16
AR	CV-1[i]	1.81									16
AR	CHO[j]			1.12		2	1.27				71
AR	MDA-MB453+DHT						0.78				72
AR	NIH3T3	3.31		2.53			0.36		0.25		73
AR	PALM						0.132				74
AR	yeast						1.95				75
median		2.56		1.82		2	0.65				
mean		2.56		1.82		2	0.83				
Antiestrogenic Activity											
ERα	E-screen+tamoxifin						1.12				72
ERβ	GST-ERβ-LBD[k]	47.6									14
ERβ	GFP-ERβ:PRL-HeLa	25.16	9.05	4.55	10.32				0.29	5.46	70
Androgenic Activity											
AR	MCF-7								0.40		74
AR	PALM								0.79		74

[a]Determined by diving the effective or inhibitory concentrations for half-maximal receptor activation or competitive binding activity (EC_{50} or IC_{50}) of BPA to other analogues; a value >1 indicates a greater potency of a bisphenol analogue compared to that of BPA; a value <1 indicates a less potency of a bisphenol analogue than that of BPA. [b]ERα = estrogen receptor α. [c]ERβ = estrogen receptor β. [d]mER = membrane estrogen receptor. [e]AR = androgen receptor. [f]human ovarian adenocarcinoma cell line. [g]Clonal rat prolactinoma cell line; ERK = extracellular signal regulated kinase. [h]DHT = diethylstilbestrol. [i]African green monkey kidney cells. [j]Chinese hamster ovary cell line. [k]Glutathione S-transferase-fused NR ligand-binding domain protein

exposure route for such analogues can be through nondietary sources.

Overall, the studies on the occurrence of bisphenol analogues in environmental compartments, consumer products, and foodstuffs clearly demonstrate that analogues other than BPA are present in the environment and that humans are exposed via multiple routes. Although BPA is generally the most dominant bisphenol in different matrices, some analogues have approximated or surpassed BPA in concentrations in some environmental and food samples, likely reflecting a shift from BPA to other substitutes in some applications. The BPA replacements subject to increasing detection in the environment should be given more attentions in future environmental monitoring studies and food safety evaluations. Although the number of studies is increasing and data are being accumulated, current scientific knowledge is apparently insufficient to

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elucidate sources, environmental distribution, and the fate of bisphenol analogues regionally or globally. Comprehensive assessment of human exposure to bisphenol analogues (other than BPA) from dietary and nondietary sources is lacking and requires additional studies. As bisphenols differ in applications, more efforts are also needed to elucidate and weigh analogue-dependent dietary (e.g., food and drinks) and nondietary (e.g., inhalation, dermal contact, and hand-to-mouth transfer) human exposure routes.

HUMAN BIOMONITORING AND EXPOSURES

Since BPA is rapidly excreted as BPA-conjugates, urine has been commonly used as the matrix for biomonitoring.[2] Urinary concentrations of total (free and conjugated) BPA have been used to evaluate BPA exposure from all sources.[1] Recent studies have begun to assess urinary concentrations of bisphenol analogues, but available data remain very limited. A multinational study reported BPS in 81% of human urine samples from the U.S. and seven Asian countries, at concentrations of up to 21 ng/mL (GM = 0.168 ng/mL).[58] Median BPS concentrations in urine samples from the Asian countries were 1 order of magnitude lower than that of BPA in the same set of samples, with the exception of Japanese specimens. Japanese urine contained the highest BPS concentrations (GM = 1.18 ng/mL), followed by the U.S. (0.299 ng/mL), China (0.226 ng/mL), and other Asian countries. A further study by Yang et al. analyzed urine samples collected from residents living near a BPAF manufacturing plant in China, and detected a number of analogues, including BPA (GM = 0.886 ng/mL), BPF (GM = 0.228 ng/mL), BPAF (GM = 0.018 ng/mL), and BPS (GM = 0.029 ng/mL).[59] BPS was also detected in urine samples from obese and nonobese Indian children (0.05 ± 0.05 and 0.61 ± 2.34 ng/mL, respectively), much lower than BPA concentrations (6.84 ± 6.39 and 8.5 ± 8.05 ng/mL, respectively).[60] However, BPS concentrations (median 4.92 ng/mL) surpassed those of BPA (median 2.01 ng/mL) and BPF (2.16 ng/mL) and became the most dominant analogue in urine from a population in Jeddah, Saudi Arabia (Figure 2).[61] As BPS is relatively more heat and light stable than BPA due to its rigid O═S═O double bonds, the authors suspected that BPS is more widely used than BPA in tropical countries.[61] In addition to urine, human blood was also assessed for bisphenols. An Italian study reported the presence of BPB in human serum from healthy and endometriotic women at a mean concentration of 5.15 ng/mL, greater than BPA concentrations (mean: 2.91 ng/mL).[62]

Human intake rates for bisphenol analogues were estimated based on urinary biomonitoring data published previously,[58−61,63,64] following the method employed by Lakind et al.[65] (Table 2). Although single spot urine samples mainly reflect the exposure occurring shortly before urine collection, the intake rate estimation based on urinary concentrations may still be capable of interpreting the average population exposure once the sample size is sufficiently large.[2] The mean or median daily intake rates of individual analogues or derivatives ranged from 0.001 to 0.863 μg/kg/day in the U.S. and several Asian countries. The intake rates of bisphenol analogues were generally 1 order of magnitude lower than that of BPA in the same populations. As a comparison, the estimated median BPA exposures from international studies were in the range of 0.01−0.05 μg/kg/day for adults and 0.02−0.12 μg/kg/day for children.[2] The only exception was found in a Saudi Arabian population where BPS had a higher human intake rate than BPA (0.115 versus 0.047 μg/kg/day).[61] The intake rates of total bisphenols were below a temporary TDI (t-TDI; 4 μg/kg/day) determined for BPA by the European Food Safety Authority.[66] However, it should be noted that conjugates of main BPA substituents (e.g., BPF and BPS) have rarely been addressed in human biomonitoring studies, which may greatly underestimate real exposures. Limited studies have suggested that children may be subject to greater BPS exposure than adults,[58] a pattern that has been reported for BPA.[2] Children may be subject to enhanced exposure due to dust ingestion and frequent hand-to-mouth transfer.[2,67,68] Thus, age- or sex-dependent exposure should be given more attention in future biomonitoring studies.

TOXICITY OF BISPHENOL ANALOGUES

Available studies have reported various toxic effects, including endocrine disruption, cytotoxicity, genotoxicity, reproductive toxicity, dioxin-like effects, and neurotoxicity, of bisphenol analogues. A recent article by Rochester and Bolden has systematically reviewed hormonal activities of BPF and BPS and concluded that these two analogues have the potency similar to BPA for estrogenic, antiestrogenic, androgenic, and antiandrogenic activities.[16] BPS also has potencies similar to that of estradiol in membrane-mediated pathways, which are critical to cellular actions such as proliferation, differentiation, and apoptosis.[16] Our review will add to the information on the toxic potency of bisphenol analogues other than BPS and BPF which were reviewed by Rochester and Bolden.[16]

Endocrine Disruption. Estrogenic and antiandrogenic potencies of bisphenol analogues have been the subject of intense investigations. Besides BPF and BPS, BPAF, BPB, and BPC (2,2-bis(4-hydroxy-3-methylphenyl)propane) exhibit estrogenic potencies similar to or greater than that of BPA. Table 3 compares relative toxic potencies of bisphenol analogues with that of BPA, based on the effective concentration for half-maximal receptor activation activity (EC_{50}) in in vitro studies.[16,69−74] An analogue (BPX) has a greater estrogenic potency than BPA if the EC_{50} ratio of BPA to BPX is greater than 1, whereas a ratio <1 implies a lower potency. The ratios in different studies ranged from 2.81 to 12.6 for BPAF (median 6.67), 0.0001 to 9.0 for BPB (median 0.67), 0.10 to 4.83 for BPF (median 0.62), and 0.0001 to 0.90 for BPS (median 0.16) (Table 3). Antiandrogenic activities similar to or greater than that of BPA were also reported for BPAF, BPB, BPE, and BPF, based on the inhibitory concentration for half-maximal competitive binding with receptor (IC_{50}).[16,71−75] In the luciferase reporter gene assays with human breast cancer cell line (MCF-7), the EC_{50} values for estrogenic activity were 16.8 and 17.0 μg/L for BPAF and BPB, respectively, followed by BPA (143.8 μg/L), BPF (200.2 μg/L) and BPS (275.3 μg/L).[73] The inhibitory effects on the androgenic activity of 5α-dihydrotestosterone in mouse fibroblast cell line, NIH3T3, were also reported for BPAF (IC_{50} = 437 μg/L), BPB (412 μg/L), BPA (982 μg/L), BPF (2403 μg/L), and BPS (4255 μg/L).[73] Rosenmai et al. determined the effects of BPB, BPE, BPF, and BPS on estrogen and androgen receptor (ER and AR) activities and revealed that most analogues exhibited potencies within the same order of magnitude as that of BPA.[71] BPS was less estrogenic and antiandrogenic than BPA, but the former showed the largest efficacy on 17α-hydroxyprogesterone.[71] BPA, BPF, and BPS activated both human estrogen receptors (hERα and hERβ), but BPS was more active in the hERβ than hERα assay, whereas BPA and BPF were more active in the

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hERα assay.[74] BPA and BPF were strong human androgen receptor (hAR) antagonists (BPA > BPF). BPA, but not BPF or BPS, was a weak human pregnane X receptor (hPXR) agonist.[74] Sui et al. reported BPB (≥484.6 μg/L) to be a potent agonist for hPXR, but did not affect mouse PXR activity.[76] Eladak et al. reported that BPS (2.5 μg/L), BPF (2.0 μg/L) or BPA (2.3 μg/L) decreased basal testosterone secretion by human fetal testes, demonstrating antiandrogenic effects.[77] The H295R steroidogenesis assay revealed that BPF and BPA induced the production of 17β-estradiol at a lowest-observed-effect-concentration (LOEC) of 6007 and 6849 μg/L, respectively, whereas BPA and BPS inhibited the production of free testosterone production at a LOEC of 228 and 7508 μg/L, respectively.[78]

In addition to estrogenic and antiandrogenic effects, antiestrogenic and androgenic activities were also reported for bisphenol analogues. By using the multiparametric, high throughput microscopy-based platforms, Stossi et al. found that BPAF, BPAP, BPB, BPC, and BPZ exhibited higher affinity for ERβ than that for ERα and act as ERβ antagonists, and their log EC_{50} values were an order of magnitude lower than that of BPA.[70] By contrast, they mostly act as agonists or mixed agonists and antagonists on ERα.[70] Antiestrogenic effect was also reported for BPF which competed with 17β-estradiol for binding to the MCF-7 ER,[72] whereas BPS acted as a weak hAR agonist.[74] Matsushima et al. reported that BPAF was a full agonist for ERα and a highly specific antagonist for ERβ.[14] It acted as a strong antagonist of the activity of 17β-estradiol and the potency was 47.6 times higher that of BPA.

Cytotoxicity and Genotoxicity. Studies have reported cytotoxic and genotoxic effects of BPAF, BPAP, BPF, BPP, and BPS, which revealed that some of these analogues have genotoxic potencies greater than or similar to that of BPA. Unlike many endocrine disruption studies, studies on the cytotoxicity and genotoxicity of bisphenols rarely provided effective concentrations or doses such as EC_{50}. Thus, a quantitative comparison of relative toxic potencies of bisphenol analogues with that of BPA, similar to that outlined in Table 3, was not available for cytotoxicity and genotoxicity, as well as other toxic effects discussed below. Audebert et al. reported similar ranges of cytotoxicity for BPA and BPF, whereas the genotoxicity was only observed for BPF in human hepatoma cell line (HepG2) cells.[79] BPA, BPF, and BPAF decreased the viability of human peripheral blood mononuclear cells (PBMCs).[80] In comparison with BPA, BPF and BPAF also enhanced the formation of reactive oxygen species (ROS, including OH·), which damages the lipids and proteins in PBMCs. Cabaton et al. showed that BPF was effective on HepG2 cell DNA fragmentation at noncytotoxic concentrations.[10] At concentrations of 0.1 to 10 μmol/L, BPA and BPS, but not BPF, BPAF, or BPZ, induced significant DNA damage in HepG2 cells after 24 h exposure.[81] Fic et al. also evaluated genome-wide gene expression of BPA (2.3 μg/L), BPAF (3.4 μg/L), and BPS (2.5 μg/L) exposure by culturing estrogen-dependent osteosarcoma cells with each of these chemicals.[82] Significant effects on gene expression were observed for BPS, followed by BPAF and BPA. All tested bisphenols affected genes related to fetal development, but only BPA affected genes related to the immune system. Lee et al. also suggested that BPAP, BPM and BPP exhibited greater genotoxic potentials than that of BPA in mutant chicken DT40 cells.[83] An in vivo study in gestating Wistar rats revealed that BPA, BPF, and BPS affected differently the 5α-reductase expression and dopamine (DA)−serotonin (5-HT) systems in the prefrontal cortex of juvenile female rats.[84] BPA decreased 5α-R2 and 5α-R3 mRNA and protein levels, whereas BPF and BPS decreased 5α-R3 mRNA levels at postnatal day 21.[84]

Reproductive, Neurotoxic, and Dioxin-Like Effects. Exposure of female adult zebrafish (*Danio rerio*) to BPS (>0.5 μg/L) significantly decreased egg production and the gonadosomatic index.[85] Continuous exposure of F1 zebrafish embryos to BPS decreased hatchability and increased malformation. Exposure also affected the feedback regulatory circuits of hypothalamic-pituitary-gonad (HPG) axis and impaired the development of offspring.[85] Developmental exposure of zebrafish to BPS also impaired reproduction potential and hormonal balance in adults.[11] Exposure of embryonic zebrafish to BPA (1.6 μg/L) and BPS (1.7 μg/L) resulted in an 180% and 240% increase, respectively, in neurogenesis within the hypothalamus.[86] In addition, exposure to BPA or BPS during the neurogenic development in early life stages elicited hyperactive behaviors in later stages.[86] Héliès-Toussaint et al. reported a decrease in lipolysis after BPA or BPS treatment of mouse 3T3-L1 adipocytes, while only BPS increased glucose uptake and leptin production.[87] These findings suggested that both BPA and BPS are involved in obesity and steatosis, but through different metabolic pathways. Dioxin-like effects were demonstrated for BPS only at a high concentration (75 100 μg/L), which exhibited a significant effect on aryl hydrocarbon receptor (AhR)-mediated luciferase reporter gene activity in COS-7 cells.[88]

In summary, Supporting Information Table S2 lists the variety of toxic effects reported for bisphenol analogues (other than BPA) to date, including acute toxicities not discussed above.[89,90] Our review demonstrates that many bisphenol analogues exhibit a range of toxic effects similar to those observed for BPA and that similar modes of action may be expected between BPA and other analogues. Some analogues (i.e., BPAF, BPB, BPF, and BPS) exhibited toxic potencies similar to or even greater than that of BPA, raising safety concerns on their applications as BPA replacements. However, interpretation of toxicity data from available reports should be carried out with caution, as the effective or treatment doses of bisphenols during laboratory studies were greater than or even far beyond environmentally realistic concentrations in most cases. To date, toxicity studies remain remarkably limited in the determination of modes of action and quantitative toxic end points or benchmarks, both in vitro and in vivo, for a variety of analogues. Although toxic effects of individual analogues were assessed, the mechanisms of toxicity from exposure to a mixture of bisphenol analogues at environmentally relevant levels have rarely been studied. These knowledge gaps impede comprehensive assessments of the safety of bisphenol analogues to environmental quality and human health. Additional research is urgently needed to fill in knowledge gaps and deepen toxicity evaluations, given that the production and applications of bisphenol analogues are on the rise and that many of them have already been present in environmental compartments, foods, and humans.

EFFECTS OF METABOLIC MODIFICATION ON TOXICITY

Laboratory animal studies and in vitro bioassay have shown that BPA can be metabolized to glucuronidated (e.g., BPA glucuronide or BPAG), hydroxylated (e.g., 3-hydroxy BPA), sulfated (e.g., BPA monosulfate or BPAMS and BPA disulfate

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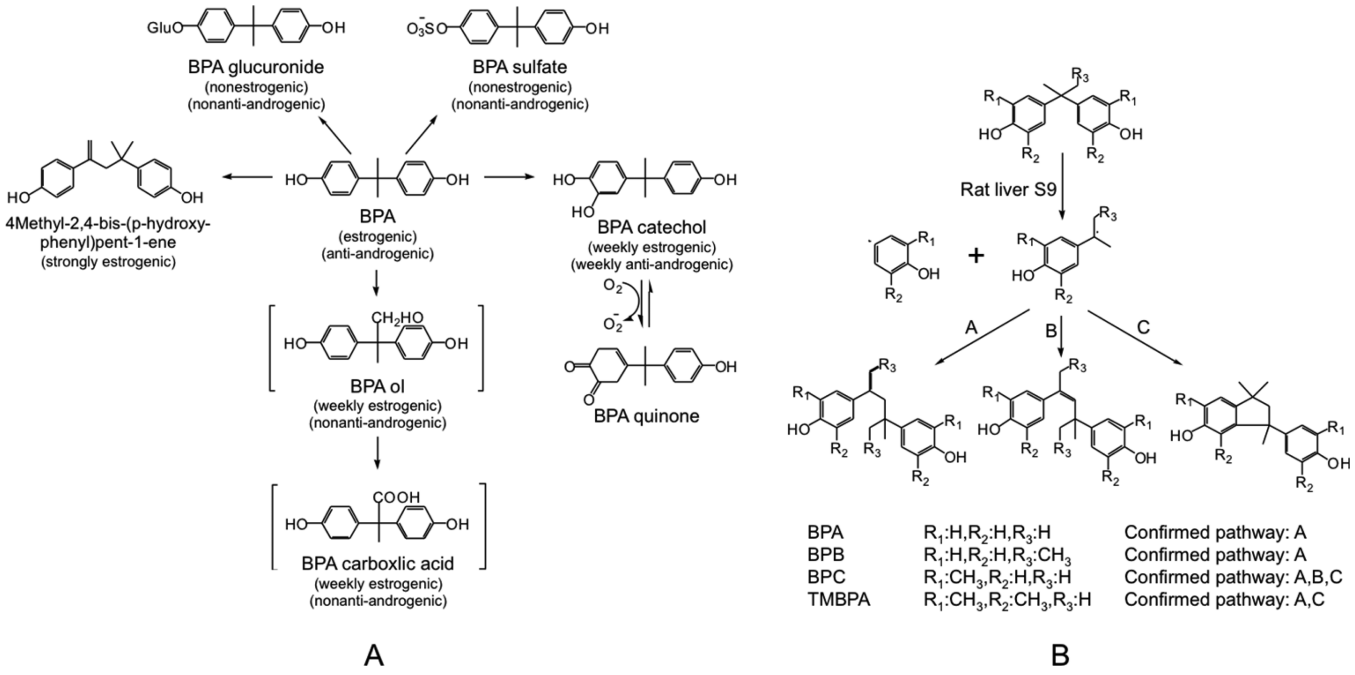

Figure 3. (A) Postulated metabolic pathways of bisphenol A; (B) Metabolic pathways of bisphenol analogues by rat liver S9 fraction leading to the formation of dimerized products. Data are from Kitamura et al. and Okuda et al., respectively.[73,91]

or BPADS) and dimerized forms. Both free and conjugated BPA have been reported in human urine.[63] Metabolism and excretion pathways of bisphenol analogues may resemble that of BPA. Figure 3A illustrates postulated metabolic pathways leading to the production of a variety of metabolites, as summarized by Kitamura et al.[73] Okuda et al. reported the detection of catechol metabolites of BPB, BPC, BPE, BPF, and BPZ after incubation with rat liver S9 fraction.[91] Cabaton et al. studied the metabolism of BPF in female Sprague−Dawley rats with a single dose of [^{3}H]BPF.[92] The excretion of BPF residues was mainly through urine and, to a lesser extent, in feces. The elimination rate of BPF was lower than that reported for BPA. At least six metabolites were detected in urine, with a sulfate conjugate as the major product. In human liver microsomes or with recombinant cytochrome P450 isoenzymes in the presence of triphosphopyridine nucleotide (NADPH) and reduced glutathione (GSH), BPA, BPAF, BPC, BPF, and BPZ were biotransformed into hydroxylated metabolites and their corresponding glutathione (GSH) conjugates.[93]

Metabolism largely affects the toxicity of bisphenols. The effects of metabolic modification on the estrogenic and antiandrogenic activities of BPA have been discussed and summarized by Kitamura et al. (Figure 3A).[73] Conjugation with β-glucuronide and sulfate represents the predominant metabolic pathway of BPA, which was generally believed to reduce biological activities of BPA and facilitate its excretion via urine (Figure 3A).[73,91] However, BPA-glucuronide was reported to induce adipocyte differentiation in human and murine preadipocytes.[94] Stowell et al. also reported that BPA is sulfated and desulfated by the same enzymes as estrone and that sulfated BPA conjugates stimulated the growth of breast tumor cells.[95] Treatment of MCF-7 cells with sulfated BPA increased the concentration of BPA inside the cells, likely through a coupled desulfation and uptake pathway. Therefore, sulfation may increase the estrogenic potential of BPA.[95] In addition, BPA conjugates may be subject to deconjugation in utero or in newborns. Glucuronidated BPA can be deconjugated in utero by β-glucuronidase, an enzyme present at high concentrations in placenta and other tissues, while BPA sulfates can be deconjugated in newborns by arylsulfatase C which develops in early life stages.[96] These studies questioned if rapid metabolism can ensure negligible risk from BPA and highlighted the importance of careful evaluation of metabolic modification on BPA toxicity. This argument also applies to other bisphenol analogues, given that glucuronidation and sulfation may represent the two main conjugation pathways for other analogues.

Additionally, a dimerized form of BPA metabolite, 4-methyl-2,4-bis(*p*-hydroxy-phenyl)pent-1-ene (MBP), has been demonstrated to be more estrogenic than BPA.[73,97] Metabolic activation to MBP may not be significant under normal circumstances. However, it can be more significant when glucuronidation becomes an inefficient detoxification pathway for BPA.[98] Given that rat and human fetal livers show little or no glucuronidation, metabolic activation to dimerized BPA such as MBP may occur *in vivo*, especially in the fetus.[91,99,100] Similar bioactivation may be expected for other analogues. Indeed, after incubation with rat liver S9 fraction, BPB and BPC, as well as tetramethyl BPA, were found to produce dimerized metabolites via multiple pathways (Figure 3B).[91] Other analogues, such as BPF and BPG, may also have the potency to produce dimerized products, following the postulated dimerized metabolic pathways (Figure 3B). Bioactivation was also found in in vitro biotransformation of BPA in human liver microsomes and cytochrome P450 isoenzymes with the addition of NADPH and GSH, which produced hydroxycumyl alcohol (HCA) in addition to monohydroxylated metabolites.[93] HCA was reported to exhibit greater ER-binding activity than BPA.[101] Metabolites structurally similar to HCA were also produced from BPF and BPZ via a similar biotransformation mechanism (i.e., *ipso*-substitution reaction).[93] Additionally, an in vitro assay revealed that the metabolites of BPS formed by the rat liver S9 fraction showed elevated estrogenic activity compared to BPS itself.[69] As a

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metabolite of BPF produced in rate in vivo, dihydroxybenzophenone (DHB) exhibited cytotoxic effect, although its potency was less than that of BPF.[79] Overall, the limited number of metabolism studies has indicated the effects of metabolic modification on the toxicities of bisphenol analogues. Elucidation of metabolic pathways and products should be emphasized during risk assessments of bisphenol analogues.

KNOWLEDGE GAPS AND RESEARCH NEEDS

The presence of many bisphenol analogues other than BPA in environmental media, foodstuffs, consumer products, and humans from many regions of the world, suggests a large scale and potentially a global contamination trend. Humans are exposed to bisphenol analogues via the same pathways that have been demonstrated for BPA, including oral, dermal, hand-to-mouth transfer, as well as other mechanisms. To date, TDI values are generally lacking for non-BPA analogues. The estimated daily intake rates of total bisphenols from existing studies were in general below the temporal TDI recommended for BPA. However, researchers warned that human exposure risk assessment based on TDI should be carefully considered.[2] This may be attributed to considerable uncertainty in the exposure estimates for nondietary sources, potential toxic interaction among analogues, or the effects of metabolic modification on toxicity, as well as other potential factors.[2,73,91] Available toxicity studies have suggested that BPF and BPS are not safe alternatives to BPA.[16] The present review also quantitatively demonstrated that some analogues (e.g., BPAF, BPB, BPF, and BPS) reveal toxic effects similar to or greater than that of BPA. However, existing data overall are not sufficient for the assessment of human exposure routes and risks for non-BPA analogues as well as bisphenols as a class of xenoestrogens. Future research is needed in a variety of fields, including environmental monitoring, toxicity evaluations, elucidation of the sources, fate and effects, and human exposure assessments. Below the knowledge gaps were identified and prioritized to the best of our knowledge for future research needs. It is noted that additional aspects not included hereinafter may exist and also require attentions and research efforts.

Gap 1. Research is needed to better elucidate the environmental occurrence of bisphenol analogues (other than BPA) regionally or globally. There is still a dearth of information on the production and usage as well as distributions of these analogues in the global environment, including transport to remote areas. Some environmental matrices, including air, drinking water, and wildlife, have received no or few investigations. The lack of environmental data impedes the evaluation of sources, environmental distribution, and fate of bisphenols. Regional or global monitoring studies are critically needed to establish baseline levels and track the spatial and temporal distributions of these emerging chemicals in the environment.

Gap 2. Monitoring the sources and pathways of human exposure is needed. Regional or continental human exposure and biomonitoring studies should include bisphenol analogues in addition to BPA as target analytes. Efforts are needed to elucidate analogue-dependent dietary and nondietary exposure pathways and associated daily intakes, particularly for sensitive subpopulations such as children and pregnant women. Epidemiological studies should include bisphenol analogues to assess any link between exposure and potential human health outcomes.

Gap 3. Research is needed to address the mechanisms of toxicity from coexposure to multiple bisphenol analogues along with other environmental toxicants. Most available toxicity studies evaluated effects from a single bisphenol analogue. Although the measured or estimated typical daily intake rates of bisphenols were generally below the TDI determined for BPA, some studies have argued that health risks can result from exposure to single or multiple chemicals with doses lower than the TDI.[102,103] Given that a number of bisphenol analogues coexist with BPA in environmental compartments, foods, and consumer products, it is important to understand the mechanisms and consequences of exposure to multiple analogues, ideally at environmentally relevant compositions. The potential additive or synergistic effects produced by a mixture of bisphenol analogues should also be considered in epidemiological studies or human health risk assessments. A new TDI for bisphenols based on the coexistence of multiple analogues and toxic interactions from a mixture should be pursued for a better assessment of human exposure risks.

Gap 4. Research is needed to better elucidate metabolic pathways and products of bisphenol analogues (including their derivatives) and the impacts of metabolic modification on toxicity. Previous metabolic studies are only limited to few selected bisphenol analogues, whereas metabolic pathways and products remain largely unidentified for most analogues. Metabolic studies are also scarce for the derivatives of bisphenol analogues. BPA derivatives such as chlorinated BPA were also found in environmental matrices and human samples.[55,63,104] Chlorinated BPA derivatives exhibited the potency to activate human ERs similar to that of BPA, displaying a full agonistic activity toward ERα.[105] BPA trichloride (BPATrC) also can activate human peroxisome proliferator-activated receptor γ (PPARγ), whereas BPA did not activate PPARγ.[105] A derivative of BPS, dimethyl BPS (DMBPS), was also reported to induce significant DNA damage in the comet assay.[81] Therefore, investigations into metabolic pathways and products of bisphenol analogues as well as their derivatives are critical to risk assessments.

Gap 5. Toxicity studies are needed to better elucidate the mechanisms and effects of bisphenol analogues on the reproductive systems. Maffini et al. reviewed the main organs and developmental stages that could be affected by prenatal exposure to BPA, including ovaries and the oocytes, puberty and cyclicity, mammary gland, female reproductive tract, and male reproductive organs.[106] These tissues and developmental stages can be the targets of many bisphenol analogues, particularly those exhibiting estrogenic and/or antiandrogenic activities similar to or greater than that of BPA. BPF has been shown to be efficiently absorbed and distributed to the reproductive tract in female rats and its residues (including metabolites) can pass the placental barrier at a later stage of gestation in rats, implying a potential effect on offspring.[92] To date, laboratory studies addressing the effects of bisphenol analogues on the reproductive systems and development of organs such as mammary gland have rarely been conducted.

Gap 6. Studies on environmental persistence and the fate of bisphenol analogues are lacking. Environmental persistence of organic contaminants, particularly the resistance to environmental and biological transformation, can determine the fate and exposure risks to humans and ecosystems.[107] Studies addressing photodegradation and microbial degradation are needed to understand environmental transformation products and fate of bisphenols. The transformation products can behave

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differently in terms of environmental persistence and toxicity compared to their parent compounds, which warrants close investigations. At present, there is a lack of experimental data on the half-lives of many analogues, as well as their potential transformation pathways, in various environmental compartments.

Gap 7. Robust analytical methodologies are needed for the identification of potential environmental and metabolic transformation products, speciation analysis and analysis of free and conjugated forms. Therefore, advancement of analytical techniques will boost bisphenol research in the fields of environmental investigation, human exposure, metabolic, and toxicity studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.5b05387.

Tables S1 and S2 (PDF)

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Notes

The authors declare no competing financial interest.

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