Review

A targeted review on fate, occurrence, risk and health implications of bisphenol analogues

Cyrene J. Catenza, Amna Farooq, Noor S. Shubear, Kingsley K. Donkor[*]

Department of Physical Sciences, Thompson Rivers University, 805 TRU Way, Kamloops, BC, V2C 0C8, Canada

HIGHLIGHTS

- BPA and its alternatives are now ubiquitously detected worldwide.
- Bisphenols are prevalent in numerous food and environmental matrices.
- Positive correlations observed between urinary BPA levels and various diseases.
- BPA alternatives pose equal or greater harmful effects to human health.
- Activated carbon, chitosan, enzymes and microorganisms can remove bisphenols.

GRAPHICAL ABSTRACT
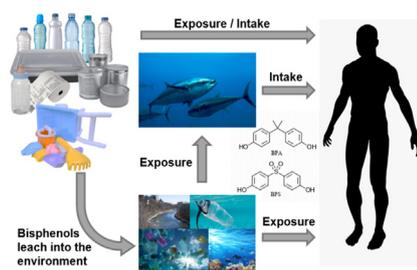
ARTICLE INFO

ABSTRACT

Due to its widespread applications and its ubiquitous occurrence in the environment, bisphenol A (BPA) and its alternatives have gained increasing attention, especially in terms of human safety. Like BPA, alternatives such as bisphenol S (BPS), bisphenol F (BPF), and bisphenol AF (BPAF) have also been identified to be endocrine-disrupting chemicals (EDCs). Hence, in this study, we reviewed the literature of BPA and its alternatives mainly published between the period 2018–2020, including their occurrences in the environment, human exposure, and adverse health effects. The review shows that bisphenols are prevalent in the environment with BPA, BPS, and BPF being the most ubiquitous in the environment worldwide, though BPA remains the most abundant bisphenol. However, the levels of BPS and BPF in different environmental media have been constantly increasing and their fates and health risks are being evaluated. The studies show that humans and animals are exposed to bisphenols in many different ways through inhalation and ingestion and the exposure can have serious health effects. Urinary bisphenols (BPs) levels were frequently reported to be positively associated with different health problems such as cancer, infertility, cardiovascular diseases, diabetes and neurodegenerative diseases. Our literature study also shows that BPs generate reactive oxygen species and disrupt various signalling pathways, which could lead to the development of chronic diseases. Activated carbon-based and chitosan-based sorbents have been widely utilized in the removal of BPA in aqueous solutions. In addition, enzymes and microorganisms have also been getting much attention due to their high removal efficiencies.

© 2020 Elsevier Ltd. All rights reserved.

---

* Corresponding author.
  E-mail address: kdonkor@tru.ca (K.K. Donkor).

Contents

1. Introduction

Bisphenols (BPs) are one of the most common phenols in the environment that are characterized by the presence of two phenols connected by an alkyl group (Roark, 2020). BPs are one of the main components of polycarbonate plastics, which are used in consumer goods and containers that store foods and beverages (Barboza et al., 2020; Roark, 2020; Rochester and Bolden, 2015). They are also used in the production of epoxy resin linings of metal-based food and beverage cans, as well as other consumer products such as thermal paper, medical equipment, toys, electronics, and water pipes (Chen et al., 2016; Lehmler et al., 2018; Rosenfeld and Feng, 2011). Bisphenol A (BPA), the representative of BPs, was first synthesized in 1981 and has been utilized in the production of plastics since the 1950s (Rubin, 2011; Vogel, 2009). To date, it is the most highly produced BP globally, with worldwide consumption of about 7.7 million metric tons in 2015 and is expected to increase by 3.1 million metric tons by 2022 (Lehmler et al., 2018). However, since BPA is one of the building blocks of many plastic products, it could leach into the environment; hence, it has been identified as an environmental contaminant, showing its occurrence in environmental compartments such as air, water, soil, sediment, indoor dust, and human tissues (Hanaoka et al., 2002; Kang et al., 2006; Roark, 2020). In addition, BPA was also reported as an endocrine disruptor chemical (EDC) (Krishnan et al., 1993), which is potentially associated with numerous diseases such as breast cancer (Ayyanan et al., 2011; Betancourt et al., 2010; Kass et al., 2012; Yang et al., 2009), infertility (Bloom et al., 2011; Caserta et al., 2013; Ehrlich et al., 2012), cognitive dysfunction (Tian et al, 2010, 2011), diabetes (Melzer et al., 2010; Shankar and Teppala, 2011; T. Wang et al., 2012), cardiovascular diseases (Lang et al., 2008; Melzer et al., 2010; Shankar et al., 2012), and obesity (Carwile and Michels, 2011; H. Wang et al., 2012). As a response to these concerns, several countries have banned the use of BPA in various consumer products (Almeida et al., 2018; Jalal et al., 2018). In turn, the search for safe alternatives has since gained increasing attention in the research community (Tables 1–6).
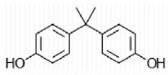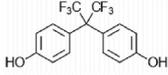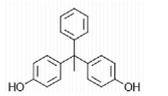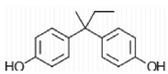
Keeping in mind the harmful health effects of BPA, countries like Japan, Canada, and the European Union have banned the use of BPA in some consumer products (Adeyemi et al., 2020). In addition, several companies have also voluntarily taken BPA out of their plasticware and canned food packaging. However, they generally replaced it with other BPs such as bisphenol S (BPS), bisphenol P (BPP), bisphenol Z (BPZ), bisphenol AP (BPAP), bisphenol AF (BPAF), bisphenol E (BPE), and bisphenol F (BPF). Among the BPA alternatives, BPS and BPF are the most commonly used in commercial and consumer products. Like BPA, BPF is also used in the production of epoxy resins and coatings. Few of the consumer products that utilize epoxy resins made of BPF include varnishes, liners, adhesives, plastic, water pipes, and food packaging (Rochester and Bolden, 2015). Meanwhile, BPS is widely used for different industrial applications, such as a constituent of phenolic resins and as an electroplating solvent (Rochester and Bolden, 2015). Both BPS and BPF have also been detected in various everyday products, including personal care products (PCPs), thermal paper, and foods (Rochester and Bolden, 2015). However, since BPS and BPF are structurally similar to BPA, numerous studies have also identified them to be EDCs; hence, they might also pose the same toxic effect as BPA (Rochester and Bolden, 2015).

Another BPA alternative that has been getting more attention lately is BPAF. It is a fluorinated compound related to bisphenol A in which the two methyl groups are replaced with trifluoromethyl groups. It is mostly used as a BPA alternative in industries manufacturing plastics and epoxy resins. It is also used in the hoses and linings of food processing machines. However, recent studies have also identified BPAF as an EDC due to its a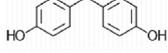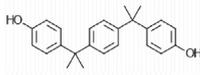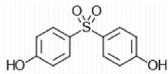bility to bind to estrogen receptors such as ERα, ERβ, and GPER (Okazaki et al., 2018; Q. Zhao et al., 2019). In addition, it has also been reported that BPAF might have a more potent estrogenic activity than BPA, especially in breast cancer cells (Q. Zhao et al., 2019).

In this present paper, we will review the literature on bisphenols (BPs) mainly published after 2018, including their occurrence and fate in the environment, human exposure, and health implications. The review covers the potential sources and levels of bisphenols in environmental, food matrices and numerous consumer products across the world. In all these matrices, bisphenols were found to be

Table 1
Physical and chemical properties of bisphenol analogues.

Compound (Abbreviation)	Chemical name	Molecular formula	Molecular weight	Boiling point	Melting point	pKa	log K_{OW}	Structure[a]
BPA	2,2-bis (4 hydroxyphenyl) propane	$C_{15}H_{16}O_2$	228.29	220 °C	150 −157 °C	10.1	3.43	
BPAF	4,4'-(hexafluoro-isopropylidene) diphenol	$C_{15}H_{10}F_6O$	336.23	400 °C	125 −126 °C	9.2	4.47	
BPAP	4,4'-(1-phenylethylidene) bisphenol	$C_{20}H_{18}O$	290.4	473 −475 °C	182 −183 °C	9.66−10.27	4.86	
BPB	2,2-bis (4-hydroxyphenyl) butane	$C_{16}H_{18}O$	242.31	412 −414 °C	138 −140 °C	10.1	4.13	
BPC	4,4'-(2,2-dichloroethene-1,1-diyl) diphenol	$C_{14}H_{10}Cl_2O_2$	281.1	405 °C	213 −217 °C	9.86	−	
BPE	4,4'-Ethylidenebisphenol	$C_{14}H_{14}O_2$	214.26	−	−	−	−	
BPF	4,4'-dihydroxydiphenyl methane	$C_{13}H_{12}O_2$	200.23	389 −390 °C	128 −130 °C	pKa$_1$ = 7.55 pKa$_2$ = 10.80	2.91	
BPP	4,4'-(1,4-phenylenediisopropylidene) bisphenol	$C_{24}H_{26}O_2$	346.46	514 −515 °C	199 −200 °C	9.78−10.38	6.25	
BPS	4,4'-sulfonyldiphenol	$C_{12}H_{10}O_4S$	250.27	240 −241 °C	240.5 °C	8.2	1.65	
BPZ	4,4'-cyclohexylidenebisphenol	$C_{18}H_{20}O_2$	268.35	440 −441 °C	165 −166 °C	9.76−10.37	5.00	
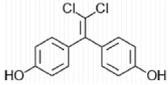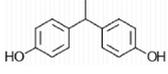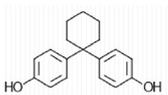
[a] Structures were drawn using ChemDoodle software (iChemLabs, LLC, Virginia, USA).

prevalent in the world and detected to differing extents. BPs were found to impact human health and linked to fertility, cancer, cardiovascular diseases, obesity, allergy diseases, and neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. The review identifies which bisphenol is dominantly related to the particular disease. Furthermore, potential methods using activated carbon, chitosan, enzymes and microorganisms to remove BPs in the environment are also discussed. Overall, this review paper aims to give a thorough distribution of BPs in the environment and understand the toxicities of BPA and its alternatives.

2. Occurrence and fate of bisphenols

Bisphenols do not occur naturally; however, they have become ubiquitous in the environment due to their high production, consumption, and consequent introduction into the environment (Corrales et al., 2015). They are released as fugitive dust from closed systems during processing, handling, and transportation of plastic materials (Cousins et al., 2002). The elevated temperature used in the manufacturing process results in the release of molten BPs into the environment. In addition, BPs have also been found to leach

into the environment from plastics and thermographic papers found in landfills, and polyvinyl chloride (PVC) pipelines used for transporting water (Asakura et al., 2004; Huang et al., 2012). The occurrences of BPs were frequently reported in indoor dust (Caban and Stepnowski, 2020a; W. J. Deng et al., 2018), surface water (Huang et al., 2020; Lalwani et al., 2020), wastewater (Česen et al., 2018), sewage sludge (Pang et al., 2019), and sediments (Mukhopadhyay et al., 2020; Staples et al., 2018).

2.1. Bisphenols in indoor dust

One of the potential sources of human exposure to bisphenols (BPs) is indoor dust, as people typically spend most of their time indoors (H. Zhang et al., 2020). BPs can enter the human body through inhalation and dermal exposure to dust (Corrales et al., 2015). BPs were found in 33 paired indoor house dust and urine in Singapore (M. Liu et al., 2019). Among the investigated BPs, BPA was the most abundant in both house dust and urine samples, with a geometric means (GMs) of 3420 and 2.61 ng g^{-1}, respectively. BPS was also well detected in all dust and urine samples with GMs of 714 and 0.077 ng g^{-1}, respectively. Furthermore, BPA

Table 2
Concentrations (ng g^{-1}) and detection rate of bisphenols in indoor dust worldwide.

Country	Sampling Sites	Compound(s)	n[a]	Concentration Range	Concentration (mean or median)	DR[b] %	Reference
Singapore	houses	BPA, BPS	33	BPA: <1972-22516 BPS: 153-6491	BPA: 3420 BPS: 714	BPA: 93 BPS: 100	Liu et al. (2019)
Poland	house rooms, chemistry laboratory, changing room of a clothes shop	BPA	13	561−9504	2726	100	Caban and Stepnowski (2020a)
Spain	bedrooms, living rooms, cars, offices	BPA, BPS, BPF	47	BPA: 3803-13486 BPS: 282-736 BPF: 57-659	–	BPA: 100 BPS: 70-100 BPF: 73-100	Dueñas-Mas et al. (2019)
Spain	Public places: museums, public libraries, high schools Private places: cars, houses	BPA	58	32571-48647 (public) 350-6001 (private)	–	100	Velázquez-Gómez et al. (2019)
Hong Kong	kindergartens, primary schools	BPA	11	10−200	79	–	Deng et al. (2018a,b)
China	university dormitories	BPA, BPS, BPF, BPAF, BPAP, BPZ	40	BPA: ND[c]−32500 BPS: ND-810 BPF: ND-770 BPAF: ND-30 BPAP: ND-480 BPZ: ND-910	BPA: 2980 BPS: 220 BPF: 150 BPAF: 10 BPAP: 210 BPZ: 160	BPA: 80 BPS: 77 BPF: 57 BPAF: 70 BPAP: 75 BPZ: 70	(H. Zhang et al., 2020)
China	houses	BPA	39	<50-5200	610	95	(J. Zhang et al., 2020)
Columbia			45	<50-5100	750	93	
Greece			26	2100−22000	5700	100	
India			33	<50-7100	310	82	
Japan			5	3300−36000	6400	100	
Kuwait			18	130−9000	1300	100	
Pakistan			25	<50-3100	260	76	
Romania			21	900−12000	2600	100	
Saudi Arabia			30	570−17000	3900	100	
South Korea			16	1800−17000	7500	100	
USA			10	950−8200	2800	100	
Vietnam			18	<50-13000	770	100	
China	houses	BPA	34	37−4400	330	100	Wang et al. (2015)
Columbia			42	9.6−2000	120	100	
Greece			28	27−4400	1500	100	
India			35	20−6200	130	100	
Japan			14	250−10000	1700	100	
Kuwait			17	39−1200	250	100	
Pakistan			22	9.7−710	66	100	
Romania			23	18−1700	600	100	
Saudi Arabia			19	110−3200	650	100	
South Korea			16	270−3600	720	100	
USA			22	260−32000	1500	100	
Vietnam			12	27−1400	230	100	

[a] n: sample size.
[b] DR: detection rate.
[c] ND: not detected.

concentrations in dust and urine samples were found to be positively correlated using Pearson correlation analysis (n = 32; r = 0.491; p < 0.01). In addition, BPA concentration and the elevated oxidative stress indicated by high levels of 8-OHdG were also found to have a positive correlation using Spearman correlation analysis (r = 0.353; p < 0.05). These findings offer evidence of the significance of the indoor environment to human exposure and suggest that BPA induces oxidative stress (M. Liu et al., 2019).

In a study conducted by Caban and Stepnowski (2020), BPA contamination was assessed in different microenvironments in Poland. These include a laboratory, office, house, and clothes shop. Among the samples collected in these microenvironments, the dust in the laboratory has the highest concentration of BPA (9504 ± 465 ng g^{-1}), which is contributed mostly from the floor

made from epoxy resins (Caban and Stepnowski, 2020a). In addition, the detection rate (DR) of BPA in dust samples from different microenvironments was reported to be 100%, with concentrations ranging from 561 to 9504 ng g^{-1} in all microenvironments. In a similar study done by Dueñas-Mas et al. (2019), higher concentrations of BPA (3803−13486 ng g^{-1}) were detected in indoor dust samples taken from private microenvironments (living rooms, bedrooms, offices, and cars) in Spain (n = 47). In addition, BPS and BPF, which are common BPA substitutes, were also detected in the samples with concentrations ranging from 282 to 736 ng g^{-1} and 57−659 ng g^{-1}, respectively. In a different research in Spain, BPA was found in multiple communal places such as museums, public libraries, and high schools (Velázquez-Gómez et al., 2019). Higher BPA levels (32571-48647 ng g^{-1}) were reported in these public

Table 3
Concentrations of bisphenols in wastewater (ng L^{-1}), both influent and effluent, and sewage sludge (ng g^{-1}) worldwide.

Sample	Country	WWTP Location	Compound(s)	n[a]	Concentration (mean or median)	Reference
wastewater	Slovenia	Ljubljana, Domžale-Kamnik. Novo mesto, Velenje, Golnik	BPAF, BPAP, BPB, BPC, BPE, BPF, BPS, BPZ	18	BPAF: 16.5 (inf[b]), 7.74 (eff[c]) BPAP: 74.9, 4.91 BPB: 8.46, 0.755 BPC: 5.66, 1.45 BPE: 84.4, 1.94 BPF: 16.4, <0.470 BPS: 21.3, <0.317 BPZ: 151, 44.2	Česen et al. (2018)
	USA	Albany area of New York State	BPA, BPS, BPF	16	BPA: 90.0 (inf), 42.9 (eff) BPS: 31.2, 23.6 BPF: 90.2, 64.9	Xue and Kannan (2019)
	China	Dalian	BPA, BPS, BPF, BPE, BPB, BPAP, BPAF, BPZ	—	BPA: 412 (inf), 30.0 (eff) BPS: 109, 11.9 BPF: 66.4, <4.97 BPE: 9.39, ND[d] BPB: <6.79, ND BPAP: 1.16, ND BPAF: 1.03, 0.48 BPZ: ND, ND	Sun et al. (2018)
sludge	China	15 cities of Henan Province	BPA, BPS, BPF, BPAF, BPAP, BPB, BPZ	30	BPA: 43.0 BPS: 1.50 BPF: 4.73 BPAF: 0.93 BPAP: 0.51 BPB: 0.25 BPZ: 0.44	Pang et al. (2019)
	USA	Albany area of New York State	BPA, BPS, BPF	28	BPA: 238−961 (GM[e] range) BPS: 7.76−15.8 BPF: 140	Xue and Kannan (2019)

[a] n: sample size.
[b] inf: influent.
[c] eff: effluent.
[d] ND: not detected.
[e] GM: geometric mean.

places compared to houses, cars, and offices. These values were also much higher than those from other communal places such as kindergartens and primary schools in Hong Kong (79 ng g^{-1} dw, mean, n = 11) (W. J. Deng et al., 2018) and Chinese university dormitories (2980 ng g^{-1}, median, n = 40) (H. Zhang et al., 2020).

In another study, the occurrence of microplastics containing BPA was assessed in 286 indoor house dust samples. These samples were collected from 12 countries (China, Colombia, Greece, India, Japan, Kuwait, Pakistan, Romania, Saudi Arabia, South Korea, the USA, and Vietnam) from 2010 to 2014 (J. Zhang et al., 2020). A DR of 100% of free BPA was reported in dust samples from most countries except for China (95%), Colombia (93%), India (82%), and Pakistan (76%). The highest BPA concentration in house dust was found in samples from South Korea (7500 ng g^{-1}, median), followed by Japan (6400 ng g^{-1}), Greece (5700 ng g^{-1}), Saudi Arabia (3900 ng g^{-1}), and the USA (2800 ng g^{-1}) (J. Zhang et al., 2020). However, these results do not agree with the previous study done by Wang et al. (2015), where they also did a comparative assessment of human exposure to BPs, including BPA from 2012 to 2014. The BPA concentration values reported in the 2015 study were lower. In addition, Wang et al. (2015) have reported the highest BPA concentration was found in Japan (1700 ng g^{-1}, median), followed by Greece (1500 ng g^{-1}), the U.S. (1500 ng g^{-1}), South Korea (720 ng g^{-1}), and Saudi Arabia (650 ng g^{-1}). Nevertheless, the results from both studies have indicated that BPA consumption is highest in these five countries.

2.2. Bisphenols in wastewater and sludge

Wastewater treatment plants (WWTPs) are one of the most common pollution controls used globally. Organic pollutants, such as BPs in wastewaters that are released from homes, businesses, and many industries, are collected in sewers and are delivered into WWTPs for removal. However, previous studies have shown that BPA and other BPs are not completely eradicated from the wastewater, with removal efficiencies of 62.5−99.6%, before they are released into the environment (Luo et al., 2014). Hence, WWTPs are considered as one of the major sources of BPs in the environment. Česen et al. (2018) investigated the presence of 8 BPs (BPAF, BPAP, BPB, BPC, BPE, BPF, BPS, and BPZ) in wastewater (WW) influent and effluent samples collected from 5 Slovene WWTPs. BPZ was found to be dominant among the 8 BPs in both influent (151 ng L^{-1}, mean) and effluent (44.2 ng L^{-1}) samples, followed by BPE (inf: 84.4 ng L^{-1}, eff: 1.94 ng L^{-1}) and BPAP (74.9 ng L^{-1}, 4.91 ng L^{-1}). Since effluents are discharged after wastewater treatment processes, it is expected for the BP concentrations to be considerably lower. However, these effluents that contain BPs after treatment are known to be the direct source of BPA contamination in the aquatic environment. On contrary, instead of BPZ, Xue and Kannan (2019) have reported BPA (inf: 90.8 ng L^{-1}, eff: 42.9 ng L^{-1}, GM, n = 16), BPF (90.2 ng L^{-1}, 64.9 ng L^{-1}), and BPS (31.2 ng L^{-1}, 23.6 ng L^{-1}) to be the most abundant BPs in influent and effluent samples collected from WWTPs in New York State, USA. These results were in accordance with the distribution profiles of BPs observed in indoor dust (Xue and Kannan, 2019). In a similar study, BPA (inf: 412 ng L^{-1}, eff: 30.0 ng L^{-1}), BPS (109 ng L^{-1}, 11.9 ng L^{-1}), and BPF (66.4 ng L^{-1}, <MLOQ) were also found to be dominant in WWTPs in Dalian, China (Sun et al., 2018).

Sewage sludge was identified as an important reservoir for nutrition; therefore, a land application was deemed to be an

Table 4
Concentrations of bisphenols in water (ng L^{-1}) worldwide.

Sample	Country	Sampling Site	Compound(s)	n[a]	Concentration range	Reference
freshwater	India	Delhi-National Capital Territory, Jammu & Kashmir, Uttar Pradesh, Bihar, West Bengal, Odisha, Andhra Pradesh, Tamil Nadu, Kerala, Maharashtra, Gujarat, Rajasthan, Punjab states	BPA, BPS, BPF	74	BPA: <16.7−14800 BPS: <16.7−341 BPF: <16.7−209	Lalwani et al. (2020)
	China	Liuxi River	BPA, BPS, BPF	28	BPA: 75.6−7480 BPS: 19.9−65600 BPF: ND[b] - 474	Huang et al. (2018)
	China	Donjiang and Zhujiang rivers	BPA, BPS, BPF, BPAF, BPE, BPBP, BPG, BPP, BPPH, BPZ, BPTMC	26	BPA: 19.0−2180 BPS: 0.07−133 BPF: 0.24−255 BPAF: ND-6.59 BPE: ND-2.69 BPBP: ND-0.43 BPG: ND-2.47 BPP: ND-1.93 BPPH: ND-1.03 BPZ: ND-1.09 BPTMC: ND-101	Huang et al. (2020)
	Turkey	Danube, Dniepr, and Dniestr rivers	BPA		4620−29920	Ozhan and Kocaman (2019)
	Canada	Saint-Zéphirin River	BPA	−	3.9−17	Goeury et al. (2019)
	Brazil	Sinos River Hydrographic Basin	BPA	−	ND-517	Peteffi et al. (2019)
	Philippines	Laguna Lake	BPA	9	0.71−47.40	Sta. Ana and Espino (2020)
	Malaysia	Langat River	BPA	10	1.18−8.34	Wee et al. (2019)
	Czech Republic	Elbe River	BPAF, BPM, BPP, BPF, BPS	−	BPAF: <LOQ[c] - 205 BPM, BPP: <LOQ-60 BPF: <LOQ-75 BPS: <LOQ-27	
	Poland	Gdansk streams and reservoir	BPS	4	<MDL[d] - 1584	Caban and Stepnowski (2020b)
	Slovenia and Croatia	Sava River	BPS, BPP, BPZ, BPAP	−	BPS: 1.68−35.2 BPP: 6.45 BPZ: 0.250−9.11 BPAP: 0.540−0.903	Marjeta et al. (2019)
seawater	China	Pearl River Estuary	BPA, BPS, BPF, BPAF, BPB, DHBP, BPP, BPFL	25	BPA: 12.5−176 BPS: 3.14−121 BPF: 9.58−399 BPAF: 3.55−30.6 BPB: 0.36−18.1 DHBP: 4.78−209 BPP: 0.31−93.7 BPFL: ND-3.65	Zhao et al. (2019a,b)
	Turkey	Mediterranean Sea, Black Sea, Sea of Marmara	BPA		13800-15340	Ozhan and Kocaman (2019)

[a] n: sample size.
[b] ND: not detected.
[c] LOQ: limit of quantification.
[d] MDL: method detection limit.

Table 5
Concentrations of bisphenols in sediments (ng g^{-1}) worldwide.

Country	Sampling Site	Compound(s)	n[a]	Concentration range	Reference
India	Adyar and Cooum rivers	BPA	18[c]	10.70−2026 (Adyar) 7.58−1398 (Cooum)	Mukhopadhyay et al. (2020)
China	Liuxi River, Guangzhou	BPA, BPS, BPF	20	BPA: 0.11−359 BPS: 0.06−45.4 BPF: 0.02−36.4	Huang et al. (2018)
China	Donjiang and Zhujiang rivers	BPA, BPS, BPF, BPAF, BPE, BPBP, BPG, BPP, BPPH, BPZ, BPTMC	26	BPA: 26.6−1860 BPS: ND[c] −5.60 BPF: 16.0−1390 BPAF: ND-4.40 BPE: ND-2.55 BPBP: ND-0.35 BPG: ND-210 BPP: ND-2.78 BPPH: ND-<1.18 BPZ: ND-2.32 BPTMC: ND-20.95	Huang et al. (2020)
Croatia	Kaštela Bay	BPA	−	1.84−81.39 (suspended matter) 1.05−46.31 (sediment)	Anđelić et al. (2020)
Norway	Lake Mjøsa and Oslo Fjord	BPTMC	−	380−730	Pavel et al. (2021)

[b]18 samples from each site.

[a] n: sample size.

[c] ND: not detected.

effective disposal method (Pang et al., 2019). However, it is also one of the reservoirs for contaminants. BPs are adsorbed onto the solid particles or sludge during the removal processes (Sun et al., 2017). Therefore, sewage sludge is also considered as a potential source of BPs in the environment. The occurrence of BPs in sewage sludge from WWTPs in Central China was investigated by Pang et al. (2019). Thirty sewage sludge samples were collected from different WWTPs in 15 cities of Henan province. The authors found that BPA, BPS, BPAF, and BPF were the most frequently found BPs in sewage sludge with DRs of 96.7−100% while BPB and BPZ were only found in 11 and 9 sewage samples with low DRs of 33.3% and 30.0%, respectively. Although BPA was found to be the most efficiently removed BP during the wastewater treatment process (Sun et al., 2017), it was still found to be the most abundant among the seven BPs in sewage sludge with a GM of 43.0 ng g^{-1} dw (10.5−1539 ng g^{-1} dw, range), followed by BPF and BPS with GMs of 4.61 ng g^{-1} dw (nd-39.8 ng g^{-1} dw) and 1.50 ng g^{-1} dw (0.50−649 ng g^{-1} dw), respectively. Xue and Kannan (2019) have also evaluated the contamination of BPs in two different WWTPs in New York State, USA. Compared to the previous study, though at the same magnitude, the authors found higher concentrations of BPA (238−961 ng g^{-1} dw, GM range) and BPF (140 ng g^{-1} dw, GM for average concentration).

2.3. Bisphenols in waters and sediments

Water and sediment are also one of the most important reservoirs for environmental contaminants; hence, it is also crucial to monitor BP contaminations to evaluate their effects on the surrounding environment. For the past years, multiple studies have determined BP concentrations in waters and sediments worldwide.

A recent study done by Lalwani et al. (2020) determined the levels of eight BPs (BPA, BPS, BPF, BPB, BPP, BPAF, BPZ, and BPAP) in 74 samples of surface waters in Indian waters. For those waters, 43 were collected from river water, 6 were from canal water, 2 were from lake water, and 2 were from pond water. Among the eight BPs, only BPA, BPS and BPF were detected in the samples, while the remaining BPs were not found in any sample. In river water samples, BPs were detected with concentrations ranging from <16.7−14800 ng L^{-1} for BPA, <16.7−341 ng L^{-1} for BPS, and <16.7−84.8 ng L^{-1} for BPF. Among the river water samples, the

highest concentrations of BPA (14800 ng L^{-1}) and BPF (84.8 ng L^{-1}) were found in Yamuna River, while the highest BPS (341 ng L^{-1}) was found in Adyar River. On the other hand, BP concentrations ranging from <16.7−3450 ng L^{-1} (BPA), <16.7−266 ng L^{-1} (BPS), and <16.7−209 ng L^{-1} (BPF) were reported in canal water samples. The BPA concentrations in the pond and lake waters ranged from <16.7 to 289 ng L^{-1}, but BPS and BPF were not detected. BPA was also detected in the riverine sediments of Adyar and Cooum rivers with concentration range of 10.70−2026 ng g^{-1} and 7.58−1398 ng g^{-1}, respectively (Mukhopadhyay et al., 2020).

Multiple studies were also conducted to assess the occurrences of BPs in Chinese waters. In an older study, the BPA, BPS, and BPF were also detected in urban river water, as well as in sediments in Guangzhou, South China (Huang et al., 2018). BPA and BPS were detected in all river water samples, while BPF showed a lower DR of 89%. Among the three BPs, BPA was found to be the most abundant with a median concentration of 572 ng L^{-1}, followed by BPS (173 ng L^{-1}) and BPF (33.5 ng L^{-1}). All three BPs were also detected in all sediment samples, but lower concentrations were obtained for BPA (77 ng g^{-1}, median), BPF (7.5 ng g^{-1}), and BPS (2.42 ng g^{-1}). Eleven BPs were also detected in the surface water and sediments of Dongjiang River and Zhujiang River in the study conducted by Huang et al. (2020). Like the previous studies, BPA had the highest level in surface water and sediments among the detected BPs, with concentrations up to 2180 ng L^{-1} and 1970 ng L^{-1}, respectively. In another study, the occurrence of BPs was also investigated in seawater samples collected in 25 sites in the estuary of Pearl River, the largest river in South China (X. Zhao et al., 2019). BPF (46.7 ng L^{-1}, median) was found to be dominant among the BPs, followed by BPA (30.8 ng L^{-1}), DHBP (25.0 ng L^{-1}), and BPS (12.3 ng L^{-1}). However, these values, except for BPF, were lower than those in river water (freshwater) samples.

Despite the ban of BPA use, it remains to be the most frequently detected BP in the aquatic environment around the world. In a study done in Turkey, Ozhan and Kocaman (2019) investigated the contamination of BPA in both seawater and freshwater samples. The authors found that BPA concentrations in freshwater (4620−29920 ng L^{-1}) has a broader range than in seawater (13800-15340 ng L^{-1}). They also estimated that 223.7 kg of BPA is released yearly into the rivers in their study. In addition, high concentrations were observed in the sampling area where WW discharge occurs,

Table 6
Concentrations and estimated daily intake/dermal exposure dose of bisphenols in consumer products (ng g^{-1}), foods (ng g^{-1}) and beverages (ng L^{-1}).

Sample	Country	Compound(s)	n[a]	Concentration range	Estimated daily intake	Reference
thermal paper receipts	Nigeria	BPA	80	1.50×10^6 - 3.16×10^6	0.20 µg/day (general population) 9.89 µg/day (workers)	Adeyemi et al. (2020)
	Spain & UK	BPA	17	6.0×10^4 – 6.3×10^7	–	Castro et al. (2019)
	Brazil	BPA, BPS	22	BPA: $<1.7 \times 10^5$ - 1.69×10^7 BPS: $<3.0 \times 10^4$ - 8.93×10^6	–	Molina-Molina et al. (2019)
	France		47	BPA: $<1.7 \times 10^5$ - 2.03×10^7 BPS: $<3.0 \times 10^4$ - 1.26×10^7	–	
	Spain		43	BPA: $<1.7 \times 10^5$ - 1.93×10^7 BPS: $<3.0 \times 10^4$ - 1.33×10^7	–	
	China	BPA, BPS	120	BPA: ND[b] -1.87×10^7 BPS: ND- 1.68×10^7	ΣBP: 1.77 µg/day	Yang et al. (2019)
infant socks	Spain	BPA	96	44.4–3736	19.6 pg/kg/day	Freire et al. (2019)
childcare items and jewelleries	Israel	BPA	70	0.04–9.9 ppm[c]	–	Negev et al. (2018)
pantyhose	China, Japan, South Korea, Portugal, Chile, US	BPA, BPS, BPF, BPB, BPP, BPZ, BPAF	74	BPA: <1.3–504 BPS: <0.3 -2.19×10^6 BPF: <12.5 -1.28×10^6 BPB: <1.3–7230 BPP: <1.3–34.5 BPZ: <0.5 BPAF: <0.1–0.8	ΣBP: 0.82–58000 pg/kg bw/day	Li and Kannan (2018)
canned & non-canned foods	Spain	BPA, BPB, BPE	40	BPA: <0.17 –88.66 BPB: <0.17–4.19 BPE: <0.17 –12.35	BPA: 0.23 µg/kg bw/day (canned), 0.03 µg/kg bw/day (non-canned) BPB: 0.004 µg/kg bw/day, 0.005 µg/kg bw/day BPE: 0.002 µg/kg bw/day, 0.01	González et al. (2020)
meat	Egypt	BPA		31.02 –724.06 ppb[d]	–	Osman et al. (2018)
fish				57.68 –168.52 ppb	–	
vegetables and fruits				5.57–233.78 ppb	–	
milk				30.89 –312.08 ppb		
beverages				13.96 –154.34 ppb	–	
feed additives				2.87–937.49 ppb	–	
canned foods and beverages	China	BPA, BPS, BPF	151	BPA: ND-837 BPS: ND-1.6 BPF: ND-75.4	BPA: 28.1–73.4 ng/kg bw/day BPS: 0.2–0.4 ng/kg bw/day BPF: 4.3–11.1 ng/kg bw/day	Cao et al. (2020)

[a] n: sample size.
[b] ND: not detected.
[c] ppm: parts per million.
[d] ppb: parts per billion.

providing evidence that WWTP is one of the major sources of BPA in the environment (Ozhan and Kocaman, 2019). In a similar study, the distribution of BPA in sediments and suspended matter in Croatia was also examined (Andelić et al., 2020). The results obtained showed that BPA concentrations were higher in the suspended matter (1.84–81.39 ng g^{-1}) than in sediments (1.05–46.31 ng g^{-1}), which could be due to the affinity of BPA for small organic particles, which are higher in the suspended matter (Andelić et al., 2020). Similar studies were also conducted in Canada, Brazil, Philippines, and Malaysia to evaluate the concentration of BPA in freshwaters (Goeury et al., 2019; Peteffi et al., 2019; Sta. Ana and Espino, 2020; Wee et al., 2019). The highest level of BPA was found in water samples from Brazil, with concentrations ranging from not detected (ND) to 517 ng L^{-1} (Peteffi et al., 2019),

followed by the samples from the Philippines (0.71–47.40 ng L^{-1}) (Sta. Ana and Espino, 2020). However, lower levels of BPA were detected in Canada and Malaysia, with concentrations ranging from 3.9 to 17 ng L^{-1} and 1.18–8.34 ng L^{-1}, respectively (Goeury et al., 2019; Wee et al., 2019).

Meanwhile, there were only few studies done to report the occurrences of BPA alternatives in the aquatic environment worldwide. In a study done by Pavel et al. (2021), the occurrences of BPA alternatives in Norwegian aquatic sediments and Czech surface waters were investigated. The authors found that only bisphenol TMC (BPTMC) was detected in Norwegian aquatic sediments, with a mean concentration of 600 ng g^{-1} dw. On the other hand, Czech surface waters were found to be contaminated with BPAF (91 ng L^{-1}, mean), BPM and BPP (25 ng L^{-1}), BPF (21 ng L^{-1}), and

BPS (6.2 ng L^{-1}). The occurrence of BPS in Polish surface waters was also reported in a recent study done by Caban and Stepnowski (2020b). The authors have reported BPS concentrations of 122 ng L^{-1} and 1584 ng L^{-1} in the samples taken from Oruński stream and the outflow from Świętokrzyska I retention tank, respectively. In a different study, multiple BPA alternatives were detected in surface water samples from Slovenia and Croatia along the Sava River (Marjeta et al., 2019). Among the BPA alternatives, BPS was found to be dominant, with a mean concentration of 9.00 ng L^{-1}, followed by BPP (6.45 ng L^{-1}, mean) and BPZ (4.68 ng L^{-1}).

2.4. Bisphenols in consumer products and foodstuffs

BPs were also detected in different consumer products such as paper products, baby bottles, and toys. In the study conducted by Adeyemi et al. (2020), BPA levels ranging from 1.50 to 3.16 mg g^{-1} were detected in 80 thermal receipts obtained from different locations in Nigeria such as banks, gas stations, supermarkets, and lottery outlets. Likewise, BPA was also found in paper products from other countries such as Brazil, China, France, Spain, and United Kingdom (Castro et al., 2019; Molina-Molina et al., 2019; Yang et al., 2019). The highest BPA concentration in paper products was found in France (<0.17−20.27 mg g^{-1}, range) (Molina-Molina et al., 2019). In addition to BPA, BPS was also detected in paper products with concentrations ranging from not detected (ND) to 16.8 mg g^{-1} (Yang et al., 2019). Freire et al. (2019) have also reported the occurrence of BPA in socks for infants and young children in Spain. BPA was detected in 90.6% samples, with concentrations ranging from 4.44 to 3736 ng g^{-1}. However, 35.6% of the samples have exceeded the European Union (EU) standards of 0.1 ppm for toys (Freire et al., 2019). Likewise, Negev et al. (2018) also found traces of BPA in childcare items and jewelry items purchased in retail chains in Israel and international low-cost online retailers. Concentrations ranging from 0.04 ppm to 9.9 ppm were detected in 22% of childcare item samples, with 17% exceeding the EU migration standard. In another study, Li and Kannan (2018) have also reported elevated concentrations of BPs, including BPA, BPS, BPF, BPB, BPP, BPZ, and BPAF in pantyhose collected from China, Japan, South Korea, Portugal, Chile, and the U.S. Among the seven BPs, BPS and BPF were found to be the most abundant with concentration ranges of <0.3−2190000 ng g^{-1} and <12.5−1280000 ng g^{-1}, respectively, followed by BPB (<1.3−7230 ng g^{-1}, range) and BPA (<1.3−504 ng g^{-1}). These results suggest that paper products, socks, childcare items, and pantyhose are noteworthy sources of BPs, which draws attention to the potential health risk from dermal exposure to BPs present in these products.

Since epoxy resins are used as inner coatings for food cans and containers, BPs may leach from these packaging materials, contaminating specific foods during storage. Hence, numerous studies have documented the presence of BPs in foods. In addition, dietary sources have been reported to be the highest contributor to BP exposure (Chen et al., 2016). In a study conducted by González et al. (2020), the occurrence of nine BPs in canned and non-canned foods purchased in Spain was assessed. Among the nine BPs, BPA, BPE, and BPB were detected in food samples. BPA was detected in 93% and 36% of canned and non-canned foods, respectively, with mean concentrations of 22.49 ng g^{-1} and 4.73 ng g^{-1}, respectively. Meanwhile, BPE was detected in non-canned mushroom (2.40 ng g^{-1}, mean) and nuts (12.35 ng g^{-1}). Lastly, BPB was found in canned and non-canned chicken and olive oil samples. Osman et al. (2018) have also reported BPA contaminations in canned foods, feed, beverages, and drinks in baby bottles from Egyptian Markets. Canned chicken cocktail sausage samples were found to have the highest BPA contamination with a mean concentration of 710.59 ppb. The authors also found that the leaching of BPA from baby bottles to milk contributes to the highest contamination (123.53 ppb) compared to other infant drinks. Similarly, dietary exposures to BPA, BPS, and BPF from canned foods and beverages in China were also estimated by analyzing 151 canned product samples collected from major Chinese cities (Cao et al., 2020). Among the three BPs, BPA has the highest DR (92.1%), followed by BPS (49.7%) and BPF (45%). Highest BPA residue level was found in canned fruit (837 ng g^{-1}), canned meat (300 ng g^{-1}), and canned corns and/or beans (275 ng g^{-1}). On the other hand, canned meat (75.4 ng g^{-1}), canned mushrooms (31.8 ng g^{-1}), and canned seafood were found to have the highest BPF residue level. Lastly, other canned foods (1.6 ng g^{-1}), canned corns and/or beans (1.5 ng g^{-1}), and canned meat (1.3 ng g^{-1}) have the highest BPS residue levels.

3. Health implications of bisphenols

3.1. Fertility

Bisphenols are one of the potential factors affecting human reproductive health. Several prospective cohort studies investigated individuals undergoing *in vitro* fertilization (IVF) and examined the associations of urinary BPA concentration with various reproductive endpoints, such as fertilization success, implantation success, ovarian response, and embryo quality. Shen et al. (2020) evaluated the relationship between urinary BPA concentration and the primary outcomes of IVF. Single-spot urine samples were collected from 351 women undergoing IVF treatments on the same day their oocytes were retrieved. Their results showed inverse relationships between urinary BPA concentration and the number of retrieved oocytes, clinical pregnancy, and implantation (Shen et al., 2020). Radwan et al. (2020) also found a significant decrease in the number of oocytes retrieved and implantation rate in patients with high urinary BPA concentration (n = 450 women). However, both studies did not find a correlation between urinary BPA concentration and embryo quality and fertilization rate (Radwan et al., 2020; Shen et al., 2020). In a different prospective cohort study with 700 Chinese couples attempting pregnancy, Wang et al. (2018) observed a decrease in fecundability − the probability of getting pregnant within one menstrual cycle − and an increase in the chances of infertility in women with high urinary BPA concentration. In addition, they also reported that associations of BPA concentration in urine with fecundability and infertility are more prevalent among women over 30 years of age (Wang et al., 2018).

The correlation between BPA concentration and male fertility was also examined in several studies. In their older study, Radwan et al. (2018) evaluated the relationship between urine BPA level and semen quality, sperm DNA damage, and sperm aneuploidy − abnormal number of chromosomes in a haploid set. In this study, a total of 315 men under 45 years of age were recruited from infertility clinics. High urinary BPA levels were reported to increase the percentage of immature sperm and sperm chromosome disomy and decrease the motility of the sperm. These findings provided evidence that BPA exposure is an essential factor for declining male semen quality. The associations of urinary BPA levels with semen quality and reproductive hormone levels were also assessed in a cross-sectional study with 215 healthy university male students (Adoamnei et al., 2018). From their results, a significant inverse correlation was observed between the urinary BPA and sperm concentrations. In addition, a positive association was observed between urinary BPA concentration and serum luteinizing hormone, suggesting that BPA has a direct negative effect on the function of Leydig cell − cells that produce and secrete testosterone

and androgens, which are hormones that are critical in the development of reproductive function in males (Adoamnei et al., 2018).

Animal studies also show the harmful effects of BPA on reproduction. Park et al. (2020) identified the adverse effect pubertal exposure to BPA during the maturation of spermatozoa in the epididymis and resulting effects on male mice fertility. Following BPA exposure, pERK 1/2 was found to be significantly increased in the caput (head) epididymis. Consequently, an increase in luminal pH was observed, resulting in premature capacitation of spermatozoa. In addition, fertility-related proteins also exhibited abnormal expression following BPA exposure. As a result of these changes, male fertility declined in both *in vitro* and *in vivo* (Park et al., 2020). In a different study, BPA exposure was also reported to disrupt spermatogenesis leading to a decrease in total sperm count (Rahman et al., 2020). High BPA exposure was also found to reduce sperm motility by inducing overproduction of reactive oxygen species (ROS) and decreasing spermatozoa's intracellular ATP. In addition, in line with the previously mentioned study, their findings showed that BPA compromised sperm fertility in mice.

3.2. Cancer

Numerous studies have linked BPs to different types of cancer. Indeed, exposure to BPA was reported to enhance the migration and invasiveness of ovarian cancer cells and induce the metastasis of cancer cells by activating the canonical Wnt signalling pathway (Hui et al., 2018). Consistently, Guo et al. (2020) have discovered that a low dose of BPA via the same pathway could upregulate the expression of stem cell-specific markers at mRNA and protein levels. This upregulation results in the promotion of ovarian cancer cell differentiation into cancer stem cells, which are cells that increase the probability of tumour survival and invasion to other tissues (Guo et al., 2020). In a study done by Castillo-Sanchez et al. (2020), BPA was reported to mediate the migration of human breast cancer cells by inducing the activation of signal transduction pathways via G-protein coupled receptor (GPCR) and/or epidermal growth factor receptor (EGFR) transactivation. Also, BPA activates integrin β1 to stimulate the migration of triple-negative breast cancer cells (TNBC) (Jia et al., 2019).

Meanwhile, BPS was indicated to play a role in the development of breast cancer by changing the DNA methylation level of the promoter region of breast cancer-related genes such as *CDH1, SFN, TNFRSF10C* (Huang et al., 2019). Abnormal methylation of a gene's promoter region could lead to gene silencing, which contributes to the initiation or malignant progression of tumours (Huang et al., 2019). In addition, low levels of BPS trigger the progression of TNBC by promoting its migration and invasion (Q. Deng et al., 2018). In a different study, Song et al. (2019) investigated the effect of BPS to non-small cell lung cancer (NSCLC). Their results showed that low concentrations of BPS induce migration of NSCLC cells via ERK1/2 mediated activation of TGF-β/Smad2/3 signals, which are involved in the regulation of NSCLC development by promoting cell mobility, invasiveness, and metastasis (Song et al., 2019). Other BPs that have been frequently linked to breast cancer are BPF and BPAF. In the study conducted by Lei et al. (2019, 2018), low levels of BPF and BPAF were reported to activate GPCR-mediated PI3K/Akt and Erk signals-facilitates the proliferation of and other biological effects of breast cancer cells. These BPF- and BPAF-induced activations stimulate the generation of ROS and elevate intracellular calcium ion (Ca^{2+}) levels, which ultimately led to the increase of DNA damage and promotion of cell proliferation of human breast cancer cells. Overall, these studies provide evidence that the potential harm of these BPA derivatives to human health is also of concern.

3.3. Diabetes

According to the World Health Organization (WHO), more than 422 million people are diagnosed with diabetes, and, in 2016, more than 1.6 million deaths were directly caused by diabetes. Over the years, BPs have also been linked to diabetes, with numerous studies suggesting that BPs influence glucose metabolism through various mechanisms (Rezg et al., 2014). Indeed, BPA exposure was reported to be positively associated with type-2 diabetes mellitus (T2DM) risk in humans (Hwang et al., 2018). Both urinary and serum BPA concentrations were found to have a positive association with the risk of T2DM. Additionally, urinary BPAF and BPS levels were shown to be significantly positively correlated with T2DM (Duan et al., 2018). These results are consistent with other studies, which also suggested that BPs, including BPA, BPS, and BPAF, are positively associated with T2DM (Duan et al., 2018; Haq et al., 2020).

Furthermore, BPA substitutes, such as BPAF, BPS, and BPF, were also investigated for their association with gestational diabetes mellitus (GDM) (Zhang et al., 2019). Among the three substitutes, BPAF was reported to be correlated with the increased risk of GDM among pregnant women, while BPS was found to have a disrupting effect on the plasma glucose levels. However, the authors have also indicated that the effect of BPS depends on fetal sex. Women carrying a male fetus might be less sensitive and vulnerable to BPS exposure than those with female fetuses (Zhang et al., 2019).

On the contrary, although slightly higher urinary BPA concentrations were obtained from children with type-1 diabetes mellitus (T1DM), no significant correlation was observed between urinary BPA levels and the risk of T1DM (İnce et al., 2018). However, an inverse relationship was found between urinary BPA levels and birth weight, which could be due to prenatal exposure (İnce et al., 2018). In a more recent study done by Chang et al. (2020), the relationship between urinary BPA levels and risk of diabetes among 276 adults in the Cheyenne River Sioux Tribe was investigated. Similarly, the authors did not find any statistically significant differences in BPA levels between cases and controls. In summary, the results of epidemiological studies reporting the relationships between BP concentrations and the risk of diabetes have been inconsistent.

3.4. Cardiovascular diseases

Although BPs were frequently linked to cardiovascular diseases (CVD), not many studies have been done to investigate the relationship between BP concentrations and CVD. In addition, most of the studies done in this area were derived from the United States National Health and Nutrition Examination Survey (NHANES) data. Cai et al. (2020) have reported significant correlations between BPA exposure (indicated by urinary BPA levels) and several CVD outcomes, including congestive heart failure, angina pectoris, myocardial infarction, and coronary heart disease. They also obtained a positive correlation between BPA exposure and stroke in the U.S. population. Furthermore, a gender difference in the association of BPA exposure and CVD outcomes was observed. Their results have shown that these associations are more prevalent in males than in females. In a prospective birth cohort study, the relationship between maternal prenatal BPA exposure and cardiometabolic risk factors in children at the age of 2 years was also examined by Ouyang et al. (2020). High prenatal urinary BPA levels were found to be linked with higher systolic and diastolic blood pressure in girls, but not in boys. Instead, higher plasma glucose was obtained in boys with medium maternal prenatal BPA concentration. However, no associations were found between child urinary BPA concentration and cardio-metabolic risk factors. Both

studies have shown sex-specific findings and positive associations between BPA exposure and CVD risks and factors; however, more well-coordinated and prospective studies are needed to confirm these results.

3.5. Other health implications

BPs were also linked to other health problems such as obesity and childhood asthma. In a recent study, B. Liu et al. (2019) used the data from U.S. NHANES 2013 to 2014 to evaluate the associations of BPA, BPS, and BPF with obesity in children and adolescents. Positive correlations of BPF and BPA with general and abdominal obesity were found, especially in boys. However, no correlation was observed between BPS exposure and obesity. The authors also suggested that since children and adolescents are rapidly growing, the adverse effects of BPA and its substitutes might amplify (B. Liu et al., 2019). Amin et al. (2018) have also reported in their study with 132 children and adolescents that urinary BPA concentration is positively associated with increased body mass index (BMI) and waist circumference (WC). Furthermore, the authors have also observed that urinary BPA concentration was significantly affected by age and other demographic parameters such as using cosmetics, plastic packaging, water and beverage plastic containers and passive smoking (Amin et al., 2018). BPs were also suggested to disrupt the immune function and promote the development of allergy-related diseases, such as asthma (Ma et al., 2019). Mendy et al. (2020) found that BPA is positively correlated with current asthma in children aged 6−11 years old. Meanwhile, a positive correlation between urinary BPF and asthma was mainly observed in adults, while the association of asthma with BPS was only found in men (Mendy et al., 2020). In addition, numerous studies have also reported BPA to be significantly associated with the development of neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases (Di Pietro et al., 2020; Musachio et al., 2020; Sukjamnong et al., 2020; Wang et al., 2019; Xue et al., 2020).

4. Removal of bisphenols

The concern of BPs as environmental pollutants has triggered research in finding efficient and environmentally friendly methods to remove BPs in the environment. Nevertheless, companies are using "BPA-free" labelling to differentiate their products as environmentally friendly when they may be just as harmful or worse. Several studies have investigated the use of activated carbon (AC), chitosan, enzymes, and microorganisms for the removal of BPs.

4.1. Activated carbon

The adsorption on AC is one of the most efficient and commonly used methods for the removal of BPs in aqueous environments. It is widely used in water treatment to remove organic pollutants. The efficiency of removal by AC is determined by the octanol/water partition coefficient (K_{OW}) of the compound. In general, compounds with log K_{OW} >2 are efficiently removed by adsorption onto AC (Javed et al., 2018). Since the log K_{OW} of BPs ranges from 1.25 to 7.17, AC-based materials could be used for their removal. Javed et al. (2018) synthesized and investigated an ultra-high surface area asphalt-derived activated carbon (AS) for the removal of BPA in an aqueous environment. AS was found to be highly efficient for the adsorption of BPA. In addition, the maximum adsorption capacity of AS (1113 mg g^{-1}) was found to be four times higher than the commercially purchased AC (271 mg g^{-1}) (Javed et al., 2018). Zbair et al. (2018) evaluated the use of an argan nutshell as a precursor for producing AC. In addition, the efficiency of phosphoric acid (H$_3$PO$_4$) and sodium hydroxide (NaOH) as chemical activators were also

investigated. The activated carbon (AC-HP) prepared from an argan nutshell using H$_3$PO$_4$ was found to be an effective adsorbent for the removal of BPA. AC-HP was found to have high adsorption capacity (1250 mg g^{-1}) at 293 K, which is higher than the previous study (Zbair et al., 2018). In a different paper, Wirasnita et al. (2018) studied the adsorptive removal of BPA, BPS, and BPF from water using AC-amended constructed wetlands (AC-CWs). Removal efficiencies of the BPs by AC-CW were found to be between 98% and 100%. The authors also found that the efficient and stable removal of BPs by AC-CW was a two-step process: initially, BPs are adsorbed on the AC and are subsequently degraded by bacteria on the AC (Wirasnita et al., 2018). The removal of BPA and BPS from water using activated carbon clothes (ACCs) was enhanced by the presence of the bacteria *Escherichia coli* (López-Ramón et al., 2019). The presence of bacteria during the adsorption process increases the surface hydrophobicity of the sorbent, hence, increasing its adsorption capacity by 33% for BPA and 24% for BPS.

4.2. Chitosan

Chitosan, a natural product derived from natural substances, is gaining attention as an effective biosorbent due to its high contents of hydroxyl and amino functional groups on its surface, which helps it to interact with different chemicals and polymers (Nurunnabi et al., 2017). A magnetic dodecyl chitosan/silica composite was synthesized and characterized by Hu et al. (2018) for the enrichment of emerging BPs, including BPS, BPF, BPAF, and BPA from aqueous solutions. Excellent adsorption was observed for each BPs on the resulting composite with adsorption rates ranging from 87 to 99% within 15 min. In addition, maximum enrichment efficiencies of 94−99% were also achieved for the four BPs. The authors have reported that hydrophobic interaction was the principal mechanism for the adsorption of BPs onto the magnetic dodecyl chitosan/silica composite. Furthermore, the composite can be easily recycled by solvent washing and magnetic separation technologies (Hu et al., 2018). Therefore, the magnetic dodecyl chitosan/silica composite has the potential to be used as a recyclable sorbent for the removal of BPs from aqueous solutions. In another study, aluminum-based metal-organic framework/sodium alginate composite beads with chitosan (Al-MOF/SA-CS) and without chitosan (Al-MOF/SA) were prepared and applied by Luo et al. (2019) in the removal of BPA from aqueous solutions. Al-MOF/SA-CS composite was found to have a maximum adsorption capacity of 139.9 mg g^{-1} at 298 K, which is higher than the maximum adsorption capacity of Al-MOF/SA (100.8 mg g^{-1}), suggesting the significance of the incorporation of chitosan. In addition, Al-MOF/SA-CS have exhibited good reusability; hence, it can be a promising adsorbent for BPA removal from wastewaters (Luo et al., 2019).

4.3. Enzyme

Another commonly used method to remove BPs is biological degradation catalyzed by the enzyme laccase − a lignin-degrading enzyme mainly used to cause BPA biodegradation (Nejad et al., 2018a). The major sources of laccases are the white-rot basidiomycetes fungi, plants, insects, and bacteria (Nejad et al., 2018b). In the study done by Nejad et al. (2018a), the use of laccase from the fungi *Phanerochaete chrysosporium* in the biocatalytic elimination of BPA from aqueous solutions was optimized and evaluated. The maximum elimination of BPA was achieved at a pH value of 8, initial laccase concentration of 3 U mL^{-1}, initial BPA concentration of 2 mM, and 180 min of incubation at 40 °C.

However, one of the limitations of using enzymes in the removal of organic pollutants in wastewaters is the loss of enzyme activity

during treatment. For example, laccase was reported to be highly susceptible to loss of enzyme activity when it interacts with BPA polymerization products (Nejad et al., 2018b). Hence, in order to preserve the enzyme activity, surface active additives were used to protect the enzymes from inhibitory components. Alshabib and Onaizi (2020) assessed the effectiveness of different surfactants, including rhamnolipid biosurfactant (RL), polyethylene glycol (PEG), and Triton X-100, in enhancing the removal of BPA by laccase. At 1 ppm, RL has displayed the highest removal rate and removal extent of BPA. It increases the activity of laccase from 46.06 $U\,L^{-1}$ (control, no additive) to 52.08 $U\,L^{-1}$ (with RL), achieving more than 13% enhancement of enzyme activity. Furthermore, the treatment of BPA in the presence of RL for 2 h led to about 23% enhancement of the removal efficiency of BPA. Likewise, the addition of 1 ppm PEG and Triton X-100 have also increased the activity of laccase by 8% and 5%, respectively (Alshabib and Onaizi, 2020). In an older study, Nejad et al. (2018b) also investigated the effect of PEG and Triton X-100 on the enzymatic treatment of BPA with laccase from *P. chrysosporium*. Like the previously discussed paper, the addition of PEG and Triton X-100 increased the activity of laccase and protecting it from inactivation, with PEG having the greater effect. However, the authors have observed that despite the increase of laccase activity, there was no significant increase in the removal efficiency of BPA (Nejad et al., 2018b).

4.4. Microorganisms

Degrading organisms such as bacteria were also effectively used to remove BPA from the environment. Many BPA-degrading bacteria have been isolated from water, soil, and plants. Louati et al. (2019) investigated the biodegradation activities of 340 bacterial strains isolated from the desert and arid soils from southern Tunisia. Among these strains, ten bacterial strains showed high potential for removing BPA in mineral salt medium containing 1 mM BPA. They were able to assimilate BPA as a sole carbon source (Louati et al., 2019). These strains belong to genera *Pseudomonas, Enterobacter, Klebsiella,* and *Pantoea.* The BPA removal rate of these strains varied from 36 to 97%. Among the ten strains, *Pseudomonas putida* showed the highest BPA-degrading ability. *P. putida* was able to degrade half of the initial BPA concentration within two days and remove all BPA within eight days of incubation (Louati et al., 2019). Six bacterial strains were also isolated from the sediment in the Rio Grande River and were tested for their BPA-degrading ability (Sarma et al., 2019). However, only three strains, which are closely related to *Bacillus subtilis, Citrobacter freundii,* and *Citrobacter* sp., showed outstanding BPA-degrading ability. The formation of a bacterial consortium — a combination of all three bacterial strains — achieved 100% degradation of BPA after 72 h of incubation. The efficiency of *B. subtilis* HV-3 coupled with bio-electrochemical systems in the removal of BPA from contaminated soil was investigated by Mohan et al. (2020). About 98% bio-electrodegradation was achieved under optimized conditions (initial BPA concentration of 100 mg L^{-1}; pH 7; and applied voltage of 1.0 V).

5. Conclusions

In this review, we examined over 100 peer-reviewed articles, mainly published from 2018 to 2020, to summarize the occurrence of BPA and its alternatives in various environmental compartments, such as indoor dust, wastewater, sludge, water, and sediments. Herein, we found that BPs have now become ubiquitous worldwide, and although countries have banned the use of BPA, it remains the most abundant among BPs in all environmental media. At the same time, BPS and BPF have been frequently detected alongside BPA, and their levels are continuously increasing as

reflected by the comparable concentrations of BPS, BPF, and BPA in various environmental compartments. Another aim of this review was to understand the potential risks of BPs to human health. We found that BPA and its alternatives, especially BPS, BPAF, and BPF, can induce the generation of ROS, which could cause infertility and lead to the onset of cancer. Furthermore, exposure to BPA was also found to disrupt various signalling pathways and lead to the development of chronic diseases such as CVD and diabetes. However, most studies only focused on the adverse effect of BPA and more studies are needed to investigate the potential risk of BPA alternatives to human health. Nevertheless, though our findings might not be considered as definitive proof, the data we collected from numerous studies is enough to raise concerns on the harmful effects of BPA and its alternatives to human health. Lastly, possible methods for the removal of BPA in aqueous solutions were also discussed in this review. The use of AC- and chitosan-based materials are still being utilized to this day. However, the use of enzymes and microorganisms and their incorporation into AC-based methods are gaining increased attention due to their high/enhanced removal efficiencies. As a result, methods based on AC with enzymes and/or microorganisms will likely continue to be researched, synthesized, and developed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

References

Adeyemi, J.A., Gallimberti, M., Olise, C.C., Rocha, B.A., Adedire, C.O., Barbosa, F.J., 2020. Evaluation of bisphenol A levels in Nigerian thermal receipts and estimation of daily dermal exposure. Environ. Sci. Pollut. Res. 27, 37645−37649.

Adoamnei, E., Mendiola, J., Vela-Soria, F., Fernández, M.F., Olea, N., Jørgensen, N., Swan, S.H., Torres-Cantero, A.M., 2018. Urinary bisphenol A concentrations are associated with reproductive parameters in young men. Environ. Res. 161, 122−128.

Almeida, S., Raposo, A., Almeida-González, M., Carrascosa, C., 2018. Bisphenol A: food exposure and impact on human health. Compr. Rev. Food Sci. Food Saf. 17, 1503−1517.

Alshabib, M., Onaizi, S.A., 2020. Enzymatic remediation of bisphenol A from wastewaters: effects of biosurfactant, anionic, cationic, nonionic, and polymeric additives. Water, Air, Soil Pollut. 231, 428.

Amin, M.M., Ebrahim, K., Hashemi, M., Shoshtari-Yeganeh, B., Rafiei, N., Mansourian, M., Kelishadi, R., 2018. Association of exposure to bisphenol A with obesity and cardiometabolic risk factors in children and adolescents. Int. J. Environ. Health Res. 29, 94−106.

Andelić, I., Roje-Busatto, R., Ujević, I., Vuletić, N., Matijević, S., 2020. Distribution of bisphenol a in sediment and suspended matter and its possible impact on marine life in Kastela Bay, Adriatic Sea, Croatia. J. Mar. Sci. Eng. 8, 480.

Asakura, H., Matsuto, T., Tanaka, N., 2004. Behavior of endocrine-disrupting chemicals in leachate from MSW landfill sites in Japan. Waste Manag. 24, 613−622.

Ayyanan, A., Laribi, O., Schuepbach-Mallepell, S., Schrick, C., Gutierrez, M., Tanos, T., Lefebvre, G., Rougemont, J., Yalcin-Ozuysal, Ö., Brisken, C., 2011. Perinatal exposure to bisphenol A increases adult mammary gland progesterone response and cell number. Mol. Endocrinol. 25, 1915−1923.

Barboza, L.G.A., Cunha, S.C., Monteiro, C., Fernandes, J.O., Guilhermino, L., 2020. Bisphenol A and its analogs in muscle and liver of fish from the North East Atlantic Ocean in relation to microplastic contamination. Exposure and risk to human consumers. J. Hazard Mater. 393, 122419.

Betancourt, A.M., Eltoum, I.A., Desmond, R.A., Russo, J., Lamartiniere, C.A., 2010. *In utero* exposure to bisphenol A shifts the window of susceptibility for mammary carcinogenesis in the rat. Environ. Health Perspect. 118, 1614−1619.

Bloom, M.S., vom Saal, F.S., Kim, D., Taylor, J.A., Lamb, J.D., Fujimoto, V.Y., 2011. Serum unconjugated bisphenol A concentrations in men may influence embryo

quality indicators during *in vitro* fertilization. Environ. Toxicol. Pharmacol. 32, 319–323.

Caban, M., Stepnowski, P., 2020a. Determination of bisphenol A in size fractions of indoor dust from several microenvironments. Microchem. J. 153, 104392.

Caban, M., Stepnowski, P., 2020b. The quantification of bisphenols and their analogues in wastewaters and surface water by an improved solid-phase extraction gas chromatography/mass spectrometry method. Environ. Sci. Pollut. Res. 27, 28829–28839.

Cai, S., Rao, X., Ye, J., Ling, Y., Mi, S., Chen, H., Fan, C., Li, Y., 2020. Relationship between urinary bisphenol a levels and cardiovascular diseases in the U.S. adult population, 2003-2014. Ecotoxicol. Environ. Saf. 192, 110300.

Cao, P., Zhong, H., Qiu, K., Li, D., Wu, G., Sui, H., Song, Y., 2020. Exposure to bisphenol A and its substitutes, bisphenol F and bisphenol S from canned foods and beverages on Chinese market. Food Contr. 120, 107502.

Carwile, J.L., Michels, K.B., 2011. Urinary bisphenol A and obesity: NHANES 2003-2006. Environ. Res. 111, 825–830.

Caserta, D., Bordi, G., Ciardo, F., Marci, R., La Rocca, C., Tait, S., Bergamasco, B., Stecca, L., Mantovani, A., Guerranti, C., Fanello, E.L., Perra, G., Borghini, F., Focardi, S.E., Moscarini, M., 2013. The influence of endocrine disruptors in a selected population of infertile women. Gynecol. Endocrinol. 29, 444–447.

Castillo-Sanchez, R., Ramirez-Ricardo, J., Martinez-Baeza, E., Cortes-Reynosa, P., Candanedo-Gonzales, F., Gomez, R., Salazar, E.P., 2020. Bisphenol A induces focal adhesions assembly and activation of FAK, Src and ERK2 via GPER in MDA-MB-231 breast cancer cells. Toxicol. Vitro 66, 104871.

Castro, G., Rodríguez, I., Ramil, M., Cela, R., 2019. Direct analysis in real time accurate mass spectrometry determination of bisphenol A in thermal printing paper. Talanta 205, 120086.

Česen, M., Lenarčič, K., Mislej, V., Levstek, M., Kovačič, A., Cimrmančič, B., Uranjek, N., Kosjek, T., Heath, D., Dolenc, M.S., Heath, E., 2018. The occurrence and source identification of bisphenol compounds in wastewaters. Sci. Total Environ. 616–617, 744–752.

Chang, A., Ridpath, A., Carpenter, J., Kieszak, S., Sircar, K., Espinosa-Bode, A., Nelson, D., Martin, C., 2020. Urine bisphenol A and arsenic levels in residents of the Cheyenne River Sioux Tribe, South Dakota, with and without diabetes. J. Med. Toxicol. 16, 276–283.

Chen, D., Kannan, K., Tan, H., Zheng, Z., Feng, Y.L., Wu, Y., Widelka, M., 2016. Bisphenol analogues other than BPA: environmental occurrence, human exposure, and toxicity - a review. Environ. Sci. Technol. 50, 5438–5453.

Corrales, J., Kristofco, L.A., Baylor Steele, W., Yates, B.S., Breed, C.S., Spencer Williams, E., Brooks, B.W., 2015. Global assessment of bisphenol A in the environment: review and analysis of its occurrence and bioaccumulation. Dose-Response 13, 1–29.

Cousins, I.T., Staples, C.A., Kle, G.M., Mackay, D., 2002. A multimedia assessment of the environmental fate of bisphenol A. Hum. Ecol. Risk Assess. 8, 1107–1135.

Deng, Q., Jiang, G., Wu, Y., Li, J., Liang, W., Chen, L., Su, Q., Li, W., Du, J., Wong, C.K.C., Chen, Z., Wang, H., 2018a. GPER/Hippo-YAP signal is involved in bisphenol S induced migration of triple negative breast cancer (TNBC) cells. J. Hazard Mater. 355, 1–9.

Deng, W.J., Li, N., Wu, R., Richard, W.K.S., Wang, Z., Ho, W., 2018b. Phosphorus flame retardants and bisphenol A in indoor dust and PM2.5 in kindergartens and primary schools in Hong Kong. Environ. Pollut. 235, 365–371.

Di Pietro, P., D'Auria, R., Viggiano, A., Ciaglia, E., Meccariello, R., Dello Russo, R., Alessandro, A.A., Vecchione, C., Nori, S.L., Santoro, A., 2020. Bisphenol A induces DNA damage in cells exerting immune surveillance functions at peripheral and central level. Chemosphere 254, 126819.

Duan, Y., Yao, Y., Wang, B., Han, L., Wang, L., Sun, H., Chen, L., 2018. Association of urinary concentrations of bisphenols with type 2 diabetes mellitus: a case-control study. Environ. Pollut. 243, 1719–1726.

Dueñas-Mas, M.J., Ballesteros-Gómez, A., Rubio, S., 2019. Emerging bisphenol A replacements (colour developers) in indoor dust from Spain. Emerg. Contam. 5, 168–172.

Ehrlich, S., Williams, P.L., Missmer, S.A., Flaws, J.A., Ye, X., Calafat, A.M., Petrozza, J.C., Wright, D., Hauser, R., 2012. Urinary bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF. Hum. Reprod. 27, 3583–3592.

Freire, C., Molina-Molina, J.M., Iribarne-Durán, L.M., Jiménez-Díaz, I., Vela-Soria, F., Mustieles, V., Arrebola, J.P., Fernández, M.F., Artacho-Cordón, F., Olea, N., 2019. Concentrations of bisphenol A and parabens in socks for infants and young children in Spain and their hormone-like activities. Environ. Int. 127, 592–600.

Goeury, K., Vo Duy, S., Munoz, G., Prévost, M., Sauvé, S., 2019. Analysis of Environmental Protection Agency priority endocrine disruptor hormones and bisphenol A in tap, surface and wastewater by online concentration liquid chromatography tandem mass spectrometry. J. Chromatogr. A 1591, 87–98.

González, N., Cunha, S.C., Ferreira, R., Fernandes, J.O., Marquès, M., Nadal, M., Domingo, J.L., 2020. Concentrations of nine bisphenol analogues in food purchased from Catalonia (Spain): comparison of canned and non-canned foodstuffs. Food Chem. Toxicol. 136, 110992.

Guo, Y., Li, B., Yan, X., Shen, X., Ma, J., Liu, S., Zhang, D., 2020. Bisphenol A and polychlorinated biphenyls enhance the cancer stem cell properties of human ovarian cancer cells by activating the WNT signaling pathway. Chemosphere 246, 125775.

Hanaoka, T., Kawamura, N., Hara, K., Tsugane, S., 2002. Urinary bisphenol A and plasma hormone concentrations in male workers exposed to bisphenol A diglycidyl ether and mixed organic solvents. Occup. Enviromental Med. 59, 625–629.

Haq, M.E.U., Akash, M.S.H., Sabir, S., Mahmood, M.H., Rehman, K., 2020. Human exposure to bisphenol A through dietary sources and development of diabetes mellitus: a cross-sectional study in Pakistani population. Environ. Sci. Pollut. Res. 27, 26262–26275.

Hu, J., Liu, W., Liu, H., Wu, L., Zhang, H., 2018. Preparation and enrichment properties of magnetic dodecyl chitosan/silica composite for emerging bisphenol contaminants. Marterials 11, 1881.

Huang, Y.Q., Wong, C.K.C., Zheng, J.S., Bouwman, H., Barra, R., Wahlström, B., Neretin, L., Wong, M.H., 2012. Bisphenol A (BPA) in China : a review of sources , environmental levels, and potential human health impacts. Environ. Int. 42, 91–99.

Huang, C., Wu, L.H., Liu, G.Q., Shi, L., Guo, Y., 2018. Occurence and ecological risk assessment of eight endocrine-disrupting chemicals in urban river water and sediments of South China. Arch. Environ. Contam. Toxicol. 75, 224–235.

Huang, W., Zhao, C., Zhong, H., Zhang, S., Xia, Y., Cai, Z., 2019. Bisphenol S induced epigenetic and transcriptional changes in human breast cancer cell line MCF-7. Environ. Pollut. 246, 697–703.

Huang, Z., Zhao, J.L., Yang, Y.Y., Jia, Y.W., Zhang, Q.Q., Chen, C.E., Liu, Y.S., Yang, B., Xie, L., Ying, G.G., 2020. Occurrence, mass loads and risks of bisphenol analogues in the Pearl River Delta region, South China: urban rainfall runoff as a potential source for receiving rivers. Environ. Pollut. 263, 114361.

Hui, L., Li, H., Lu, G., Chen, Z., Sun, W., Shi, Y., Fu, Z., Huang, B., Zhu, X., Lu, W., Xia, D., Wu, Y., 2018. Low dose of bisphenol A modulates ovarian cancer gene expression profile and promotes epithelial to mesenchymal transition via canonical Wnt pathway. Toxixological Sci 164, 527–538.

Hwang, S., Lim, J., Choi, Y., Jee, S.H., 2018. Bisphenol A exposure and type 2 diabetes mellitus risk: a meta-analysis. BMC Endocr. Disord. 18, 81.

İnce, T., Balcı, A., Yalçın, S.S., Özkemahlı, G., Erkekoglu, P., Kocer-Gumusel, B., Yurdakök, K., 2018. Urinary bisphenol-A levels in children with type 1 diabetes mellitus. J. Pediatr. Endocrinol. Metab. 31, 829–836.

Jalal, N., Surendranath, A.R., Pathak, J.L., Yu, S., Chung, C.Y., 2018. Bisphenol A (BPA) the mighty and the mutagenic. Toxicol. Reports 5, 76–84.

Javed, H., Luong, D.X., Lee, C., Zhang, D., Tour, J.M., Alvarez, P.J.J., 2018. Efficient removal of bisphenol-A by ultra-high surface area porous activated carbon derived from asphalt. Carbon N. Y. 140, 441–448.

Jia, B., Shi, T., Li, Zongwei, Shan, S., Ji, P., Li, Zhuoyu, 2019. Toxicological effects of bisphenol A exposure-induced cancer cells migration via activating directly integrin ß1. Chemosphere 220, 783–792.

Kang, J., Kondo, F., Katayama, Y., 2006. Human exposure to bisphenol A. Toxicology 226, 79–89.

Kass, L., Altamirano, G.A., Bosquiazzo, V.L., Luque, E.H., Muñoz-de-Toro, M., 2012. Perinatal exposure to xenoestrogens impairs mammary gland differentiation and modifies milk composition in Wistar rats. Reprod. Toxicol. 33, 390–400.

Krishnan, A.V., Stathis, P., Permuth, S.F., Tokes, L., Feldman, D., 1993. Bisphenol-A: an estrogenic substance is released from polycarbonate flasks during autoclaving. Endocrinology 132, 2279–2286.

Lalwani, D., Ruan, Y., Taniyasu, S., Yamazaki, E., Kumar, N.J.I., Lam, P.K.S., Wang, X., Yamashita, N., 2020. Nationwide distribution and potential risk of bisphenol analogues in Indian waters. Ecotoxicol. Environ. Saf. 200, 110718.

Lang, I.A., Galloway, T.S., Scarlett, A., Henley, W.E., Depledge, M., Wallace, R.B., Melzer, D., 2008. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. JAMA, J. Am. Med. Assoc. 300, 1303–1310.

Lehmler, H.J., Liu, B., Gadogbe, M., Bao, W., 2018. Exposure to bisphenol A, bisphenol F, and bisphenol S in U.S. Adults and children: the national health and nutrition examination Survey 2013-2014. ACS Omega 3, 6523–6532.

Lei, B., Sun, S., Xu, J., Feng, C., Yu, Y., Xu, G., Wu, M., Peng, W., 2018. Low-concentration BPAF- and BPF-induced cell biological effects are mediated by ROS in MCF-7 breast cancer cells. Environ. Sci. Pollut. Res. 25, 3200–3208.

Lei, B., Sun, S., Zhang, X., Feng, C., Xu, J., Wen, Y., Huang, Y., Wu, M., Xu, Y., 2019. Bisphenol AF exerts estrogenic activity in MCF-7 cells through activation of Erk and PI3K/Akt signals via GPER signaling pathway. Chemosphere 220, 362–370.

Li, A.J., Kannan, K., 2018. Elevated concentrations of bisphenols, benzophenones, and antimicrobial in pantyhose collected from six countries. Environ. Sci. Technol. 52, 10812–10819.

Liu, B., Lehmler, H.-J., Sun, Y., Xu, G., Sun, Q., Snetselaar, L.G., Wallace, R.B., Bao, W., 2019. Associations of bisphenol A and its substitutes, bisphenol F and bisphenol S, with obesity in United States children and adolescents. Epidemiology 43, 59–67.

Liu, M., Jia, S., Dong, T., Han, Y., Xue, J., Wanjaya, E.R., Fang, M., 2019. The occurrence of bisphenol plasticizers in paired dust and urine samples and its association with oxidative stress. Chemosphere 216, 472–478.

López-Ramón, M.V., Ocampo-Pérez, R., Bautista-Toledo, M.I., Rivera-Utrilla, J., Moreno-Castilla, C., Sánchez-Polo, M., 2019. Removal of bisphenols A and S by adsorption on activated carbon clothes enhanced by the presence of bacteria. Sci. Total Environ. 669, 767–776.

Louati, I., Dammak, M., Nasri, R., Belbahri, L., Nasri, M., Abdelkafi, S., Mechichi, T., 2019. Biodegradation and detoxification of bisphenol A by bacteria isolated from desert soils. 3 Biotech 9, 228.

Luo, Y., Guo, W., Ngo, H.H., Nghiem, L.D., Hai, F.I., Zhang, J., Liang, S., Wang, X.C., 2014. A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment. Sci. Total Environ. 473–474, 619–641.

Luo, Z., Chen, H., Wu, S., Yang, C., Cheng, J., 2019. Enhanced removal of bisphenol A from aqueous solution by aluminum-based MOF/sodium alginate-chitosan

composite beads. Chemosphere 237, 124493.

Ma, Y., Liu, H., Wu, J., Yuan, L., Wang, Y., Du, X., Wang, R., Marwa, P.W., Petlulu, P., Chen, X., Zhang, H., 2019. The adverse health effects of bisphenol A and related toxicity mechanisms. Environ. Res. 176, 108575.

Marjeta, C., Ahel, M., Terzi, S., John, D., Heath, E., 2019. The occurrence of contaminants of emerging concern in Slovenian and Croatian wastewaters and receiving Sava river. Sci. Total Environ. 650, 2446–2453.

Melzer, D., Rice, N.E., Lewis, C., Henley, W.E., Galloway, T.S., 2010. Association of urinary bisphenol A concentration with heart disease: evidence from NHANES 2003/06. PloS One 5.

Mendy, A., Salo, P.M., Wilkerson, J., Feinstein, L., Ferguson, K.K., Fessler, M.B., Thorne, P.S., Zeldin, D.C., 2020. Association of urinary levels of bisphenols F and S used as bisphenol A substitutes with asthma and hay fever outcomes. Environ. Res. 183, 108944.

Mohan, H., Lim, J.-M., Lee, S.-W., Cho, M., Park, Y.-J., Seralathan, K.-K., Oh, B.-T., 2020. Enhanced removal of bisphenol A from contaminated soil by coupling *Bacillus subtilis* HV-3 with electrochemical system. Chemosphere 249, 126083.

Molina-Molina, J.M., Jiménez-Díaz, I., Fernández, M.F., Rodriguez-Carrillo, A., Peinado, F.M., Mustieles, V., Barouki, R., Piccoli, C., Olea, N., Freire, C., 2019. Determination of bisphenol A and bisphenol S concentrations and assessment of estrogen- and anti-androgen-like activities in thermal paper receipts from Brazil, France, and Spain. Environ. Res. 170, 406–415.

Mukhopadhyay, M., Sampath, S., Muñoz-Arnanz, J., Jiménez, B., Chakraborty, P., 2020. Plasticizers and bisphenol A in Adyar and Cooum riverine sediments, India: occurrences, sources and risk assessment. Environ. Geochem. Health 42, 2789–2802.

Musachio, E.A.S., Araujo, S.M., Bortolotto, V.C., Couto, S. de F., Dahleh, M.M.M., Poetini, M.R., Jardim, E.F., Meichtry, L.B., Ramborger, B.P., Roehrs, R., Guerra, G.P., Prigol, M., 2020. Bisphenol A exposure is involved in the development of Parkinson like disease in *Drosophila melanogaster*. Food Chem. Toxicol. 137, 111128.

Negev, M., Berman, T., Reicher, S., Sadeh, M., Ardi, R., Shammai, Y., 2018. Concentrations of trace metals, phthalates, bisphenol A and flame-retardants in toys and other children's products in Israel. Chemosphere 192, 217–224.

Nejad, Z.G., Borghei, S.M., Yaghmaei, S., 2018a. Kinetic studies of bisphenol A in aqueous solutions by enzymatic treatment. Int. J. Environ. Sci. Technol. 16, 821–832.

Nejad, Z.G., Borghei, S.M., Yaghmaei, S., 2018b. Effect of polyethylene glycol and Triton X-100 on the enzymatic treatment of bisphenol A. Int. J. Eng. 31, 1816–1823.

Nurunnabi, M., Revuri, V., Huh, K.M., Lee, Y., 2017. Polysaccharide Based Nano/microformulation: an Effective and Versatile Oral Drug Delivery System, Nanostructures for Oral Medicine. Elsevier Inc. https://doi.org/10.1016/B978-0-323-47720-8/00015-8.

Okazaki, H., Hirao-Suzuki, M., Takeda, S., Takemoto, Y., Mizunoe, R., Haraguchi, K., Watanabe, K., Takiguchi, M., Aramaki, H., 2018. Bisphenol AF as an activator of human estrogen receptor β1 (ERβ1) in breast cancer cell lines. J. Toxicol. Sci. 43, 321–327.

Osman, M.A., Mahmoud, G.I., Elgammal, M.H., Hasan, R.S., 2018. Studying of bisphenol A levels in some canned food, feed and baby bottles in Egyptian markets. Fresenius Environ. Bull. 27, 9374–9381.

Ouyang, F., Zhang, G.H., Du, K., Shen, L., Ma, R., Wang, Xia, Wang, Xiaobin, Zhang, J., 2020. Maternal prenatal urinary bisphenol A level and child cardio-metabolic risk factors: a prospective cohort study. Environ. Pollut. 265, 115008.

Ozhan, K., Kocaman, E., 2019. Temporal and spatial distributions of bisphenol A in marine and freshwaters in Turkey. Arch. Environ. Contam. Toxicol. 76, 246–254.

Pang, L., Yang, H., Lv, L., Liu, S., Gu, W., Zhou, Y., Wang, Y., Yang, P., Zhao, H., Guo, L., Dong, J., 2019. Occurrence and estrogenic potency of bisphenol analogues in sewage sludge from wastewater treatment plants in Central China. Arch. Environ. Contam. Toxicol. 77, 461–470.

Park, Y.-J., Rahman, S., Pang, W.-K., Ryu, D.-Y., Kim, B., Pang, M.-G., 2020. Bisphenol A affects the maturation and fertilization competence of spermatozoa. Ecotoxicol. Environ. Saf. 196, 110512.

Pavel, Š., Helena, Š., Gönül, F., Kode, V., Diana, L., Bruås, L., Grabic, R., Kocour, H., 2021. Bisphenols emerging in Norwegian and Czech aquatic environments show transthyretin binding potency and other less-studied endocrine-disrupting activities. Sci. Total Environ. 751, 141801.

Peteffi, G.P., Fleck, J.D., Kael, I.M., Rosa, D.C., Antunes, M.V., Linden, R., 2019. Ecotoxicological risk assessment due to the presence of bisphenol A and caffeine in surface waters in the Sinos River Basin - Rio Grande do Sul - Brazil. Braz. J. Biol. 79, 712–721.

Radwan, M., Wielgomas, B., Dziewirska, E., Radwan, P., Kałużny, P., Klimowska, A., Hanke, W., Jurewicz, J., 2018. Urinary bisphenol A levels and male fertility. Am. J. Men's Health 12, 2144–2151.

Radwan, P., Wielgomas, B., Radwan, M., Krasiński, R., Klimowska, A., Kaleta, D., Jurewicz, J., 2020. Urinary bisphenol A concentrations and *in vitro* fertilization outcomes among women from a fertility clinic. Reprod. Toxicol. 96, 216–220.

Rahman, M.S., Pang, W.-K., Ryu, D.-Y., Park, Y., Pang, M.-G., 2020. Multigenerational and transgenerational impact of paternal bisphenol A exposure on male fertility in a mouse model. Hum. Reprod. 35, 1740–1752.

Rezg, R., El-Fazaa, S., Gharbi, N., Mornagui, B., 2014. Bisphenol A and human chronic diseases: current evidences, possible mechanisms, and future perspectives. Environ. Int. 64, 83–90.

Roark, A.M., 2020. Endocrine Disruptors and Marine Systems, Encyclopedia of the World's Biomes. Elsevier. https://doi.org/10.1016/b978-0-12-409548-9.12426-1.

Rochester, J.R., Bolden, A.L., 2015. Bisphenol S and F: a systematic review and comparison of the hormonal activity of bisphenol a substitutes. Environ. Health Perspect. 123, 643–650.

Rosenfeld, P.E., Feng, L.G.H., 2011. Mercury, BPA, and pesticides in food. In: Risks of Hazardous Wastes, pp. 223–235.

Rubin, B.S., 2011. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. J. Steroid Biochem. Mol. Biol. 127, 27–34.

Sarma, H., Nava, A.R., Encerrado Manriquez, A.M., Dominguez, D.C., Lee, W.-Y., 2019. Biodegradation of bisphenol A by bacterial consortia isolated directly from river sediments. Environ. Technol. Innov. 14, 100314.

Shankar, A., Teppala, S., 2011. Relationship between urinary bisphenol A levels and diabetes mellitus. J. Clin. Endocrinol. Metab. 96, 3822–3826.

Shankar, A., Teppala, S., Sabanayagam, C., 2012. Bisphenol A and peripheral arterial disease: results from the NHANES. Environ. Health Perspect. 120, 1297–1300.

Shen, J., Kang, Q., Mao, Y., Yuan, M., Le, F., Yang, X., Xu, X., Jin, F., 2020. Urinary bisphenol A concentration is correlated with poorer oocyte retrieval and embryo implantation outcomes in patients with tubal factor infertility undergoing *in vitro* fertilisation. Ecotoxicol. Environ. Saf. 187, 109816.

Song, P., Fan, K., Tian, X., Wen, J., 2019. Bisphenol S (BPS) triggers the migration of human non-small cell lung cancer cells via upregulation of TGF-β. Toxicol. Vitro 54, 224–231.

Sta Ana, K.M., Espino, M.P., 2020. Occurrence and distribution of hormones and bisphenol A in laguna lake, Philippines. Chemosphere 256, 127122.

Staples, C., van der Hoeven, N., Clark, K., Mihaich, E., Woelz, J., Hentges, S., 2018. Distributions of concentrations of bisphenol A in North American and European surface waters and sediments determined from 19 years of monitoring data. Chemosphere 201, 448–458.

Sukjamnong, S., Thongkorn, S., Kanlayaprasit, S., Saeliw, T., Hussem, K., Warayanon, W., Hu, V.W., Tencomnao, T., Sarachana, T., 2020. Prenatal exposure to bisphenol A alters the transcriptome-interactome profiles of genes associated with Alzheimer's disease in the offspring hippocampus. Sci. Rep. 10, 9487.

Sun, Q., Wang, Y., Li, Y., Ashfaq, M., Dai, L., Xie, X., Yu, C.P., 2017. Fate and mass balance of bisphenol analogues in wastewater treatment plants in Xiamen City, China. Environ. Pollut. 225, 542–549.

Sun, X., Peng, J., Wang, M., Wang, J., Tang, C., Yang, L., Lei, H., Li, F., Wang, X., Chen, J., 2018. Determination of nine bisphenols in sewage and sludge using dummy molecularly imprinted solid-phase extraction coupled with liquid chromatography tandem mass spectrometry. J. Chromatogr. A 1552, 10–16.

Tian, Y.H., Baek, J.H., Lee, S.Y., Jang, C.G., 2010. Prenatal and postnatal exposure to bisphenol A induces anxiolytic behaviors and cognitive deficits in mice. Synapse 64, 432–439.

Tian, Y.H., Hwan Kim, S., Lee, S.Y., Jang, C.G., 2011. Lactational and postnatal exposure to polychlorinated biphenyls induces sex-specific anxiolytic behavior and cognitive deficit in mice offspring. Synapse 65, 1032–1041.

Velázquez-Gómez, M., Hurtado-Fernández, E., Lacorte, S., 2019. Differential occurrence, profiles and uptake of dust contaminants in the Barcelona urban area. Sci. Total Environ. 648, 1354–1370.

Vogel, S.A., 2009. The politics of plastics: the making and unmaking of bisphenol A '"safety. Am. J. Publ. Health. https://doi.org/10.2105/AJPH.2008.159228.

Wang, H., Li, Z., Kang, L., Li, X., 2012a. Synthesis and field emission of β-SiC nanowires on silicon nanoporous pillar array. Appl. Surf. Sci. 259, 79–82.

Wang, T., Li, M., Chen, B., Xu, M., Xu, Y., Huang, Y., Lu, J., Chen, Y., Wang, W., Li, X., Liu, Y., Bi, Y., Lai, S., Ning, G., 2012b. Urinary bisphenol A (BPA) concentration associates with obesity and insulin resistance. J. Clin. Endocrinol. Metabol. https://doi.org/10.1210/jc.2011-1989.

Wang, W., Abualnaja, K.O., Asimakopoulos, A.G., Covaci, A., Gevao, B., Johnson-Restrepo, B., Kumosani, T.A., Malarvannan, G., Minh, T.B., Moon, H.-B., Nakata, H., Sinha, R.K., Kannan, K., 2015. A comparative assessment of human exposure to tetrabromobisphenol A and eight bisphenols including bisphenol A via indoor dust ingestion in twelve countries. Environ. Int. 83, 183–191.

Wang, B., Zhou, W., Zhu, W., Chen, L., Wang, W., Tian, Y., Shen, L., Zhang, J., 2018. Associations of female exposure to bisphenol A with fecundability: evidence from a preconception cohort study. Environ. Int. 117, 139–145.

Wang, H., Zhao, P., Huang, Q., Chi, Y., Dong, S., Fan, J., 2019. Bisphenol-A induces neurodegeneration through disturbance of intracellular calcium homeostasis in human embryonic stem cells-derived cortical neurons. Chemosphere 229, 618–630.

Wee, S.Y., Aris, A.Z., Yusoff, F.M., Praveena, S.M., 2019. Occurrence and risk assessment of multiclass endocrine disrupting compounds in an urban tropical river and a proposed risk management and monitoring framework. Sci. Total Environ. 671, 431–442.

Wirasnita, R., Mori, K., Toyama, T., 2018. Effect of activated carbon on removal of four phenolic endocrine-disrupting compounds, bisphenol A, bisphenol F, bisphenol S, and 4-tert-butylphenol in constructed wetlands. Chemosphere 210, 717–725.

Xue, J., Kannan, K., 2019. Mass flows and removal of eight bisphenol analogs, bisphenol A diglycidyl ether and its derivatives in two wastewater treatment plants in New York State, USA. Sci. Total Environ. 648, 442–449.

Xue, J., Zhang, L., Xie, X., Gao, Y., Jiang, L., Wang, J., Wang, Y., Gao, R., Yu, J., Xiao, H., Xiao, H., 2020. Prenatal bisphenol A exposure contributes to Tau pathology: potential roles of CDK5/GSK3β/PP2A axis in BPA-induced neurotoxicity. Toxicology 438, 152442.

Yang, M., Ryu, J.H., Jeon, R., Kang, D., Yoo, K.Y., 2009. Effects of bisphenol A on breast cancer and its risk factors. Arch. Toxicol. 83, 281–285.

Yang, Yunjia, Yang, Yi, Zhang, J., Shao, B., Yin, J., 2019. Assessment of bisphenol A alternatives in paper products from the Chinese market and their dermal

exposure in the general population. Environ. Pollut. 244, 238–246.

Zbair, M., Ainassaari, K., Drif, A., Ojala, S., Bottlinger, M., Pirilä, M., Keiski, R.L., Bensitel, M., Brahmi, R., 2018. Toward new benchmark adsorbents: preparation and characterization of activated carbon from argan nut shell for bisphenol A removal. Environ. Sci. Pollut. Res. 25, 1869–1882.

Zhang, W., Xia, W., Liu, W., Li, X., Hu, J., Zhang, B., Xu, S., Zhou, Y., Li, J., Cai, Z., Li, Y., 2019. Exposure to bisphenol A substitutes and gestational diabetes mellitus: a prospective cohort study in China. Front. Endocrinol. 10, 262.

Zhang, H., Quan, Q., Zhang, M., Zhang, N., Zhang, W., Zhan, M., Xu, W., Lu, L., Fan, J., Wang, Q., 2020. Occurrence of bisphenol A and its alternatives in paired urine and indoor dust from Chinese university students: implications for human exposure. Chemosphere 247, 125987.

Zhang, J., Wang, L., Kannan, K., 2020. Microplastics in house dust from 12 countries and associated human exposure. Environ. Int. 134, 105314.

Zhao, Q., Howard, E.W., Parris, A.B., Ma, Z., Xing, Y., Yang, X., 2019a. Bisphenol AF promotes estrogen receptor-positive breast cancer cell proliferation through amphiregulin-mediated crosstalk with receptor tyrosine kinase signaling. PloS One 14, e0216469.

Zhao, X., Qiu, W., Zheng, Y., Xiong, J., Gao, C., Hu, S., 2019b. Occurrence, distribution, bioaccumulation, and ecological risk of bisphenol analogues, parabens and their metabolites in the Pearl River Estuary, South China. Ecotoxicol. Environ. Saf. 180, 43–52.