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Review

Bisphenol Analogs in Aquatic Environments and Their Effects on Marine Species—A Review

Jacopo Fabrello and Valerio Matozzo *

Department of Biology, University of Padova, Via Ugo Bassi 58/B, 35121 Padova, Italy
* Correspondence: valerio.matozzo@unipd.it; Tel.: +39-049-8276201

Abstract: Bisphenol A analogs are currently used in manufacturing and as plasticizers as a substitute for bisphenol A. This replacement is taking place because bisphenol A is recognized as an endocrine disruptor chemical (EDC) that can also cause oxidative stress and genotoxic effects in aquatic species. Bisphenol A analogs have a similar chemical structure to BPA, raising doubts about their use as safer substitutes. This review intends to summarize the concentrations of BPA analogs found in aquatic environments and the effects of these emerging compounds on marine species. Generally, studies indicate that BPA analogs have similar effects to their precursor, altering the neuroendocrine system in several marine species. Furthermore, BPA analogs can cause oxidative stress and developmental alterations. The available information on the biological effects of BPA analogs suggests that more effort should be performed to assess the effects of these compounds in marine organisms.

Keywords: BPA; bisphenol analogs; marine environment; emerging contaminants

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1. Introduction

Bisphenols are synthetic and widely used compounds characterized by the presence of two hydroxyphenyl functionalities [1]. The most important bisphenol is bisphenol A (BPA), which was firstly synthesized in 1891 [2]. Its importance mainly derives from the discovery of its polymerization in the middle of the 20th century to make polycarbonate plastic. Indeed, it is a common plasticizer used in the production of polycarbonate plastics, epoxy resins used to line metal cans, and in many plastic consumer products including toys, water pipes, drinking containers, eyeglass lenses, sports safety equipment, dental monomers, medical equipment, and consumer electronics [3]. The BPA world production in 2002 was 2.8 million metric tons [2], rose to a consumption of 7.7 million metric tons in 2015, and is expected to reach 10.6 million metric tons in 2022 [4], and more than 100 tons of BPA are annually released into the atmosphere [5]. BPA is used also as a color developer in thermal paper and its usage in thermal paper manufactured in the EU and placed on the EU market was 2776 tons in 2017 [6]. BPA is considered as a chemical compound of very high concern due to its toxicity on reproduction and its endocrine disrupting effects both in humans and other animals [7–9], leading to BPA restrictions whereby it was removed from many industries and banned in the manufacture of baby bottles by many governments such as USA, Canada, and the EU. Furthermore, the EU has limited the BPA usage to less than 0.02% by weight in thermal paper since January 2020 [10].

1.1. Bisphenol A Analogs Production and Usage

Recently, BPA has been replaced by other similar compounds named bisphenol A analogs (BPA analogs) (Table 1). Currently, at least 148 different substances show the presence of the "bisphenol" moiety [11]. This group includes 17 bisphenols with the generic "bisphenol" structure, and "bisphenol derivatives" that have constituents with structural features common to bisphenols [11]. Bisphenols differ in both the chemical group between the two hydroxyphenyls and the presence of other chemical groups, such as brominated and chlorinated compounds.

Table 1. Main bisphenol A analogs and their chemical characteristics.

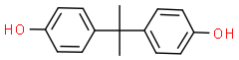
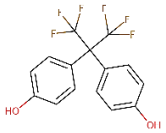
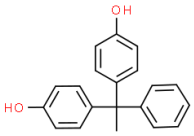
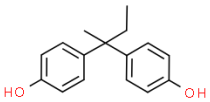
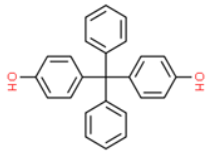
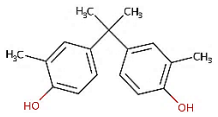
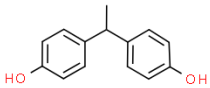
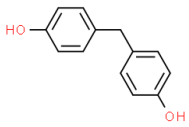
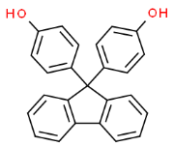
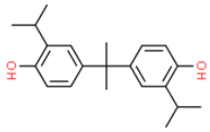
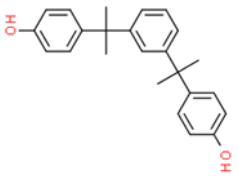
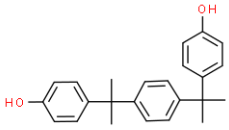
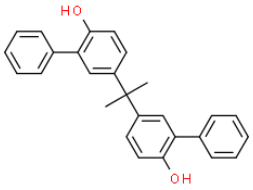
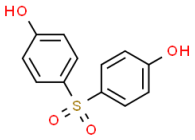
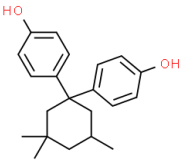
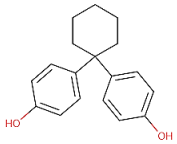
Name (Abbreviation)	CAS Number	Structural Formula	Log Kow	Molecular Weight (g/mol)
Bisphenol A (BPA)	80-05-7		3.32	228.29
Bisphenol AF (BPAF)	1478-61-1		3.69	336.23
Bisphenol AP (BPAP)	1571-75-1		4.38	290.36
Bisphenol B (BPB)	77-40-7		3.95	242.31
Bisphenol BP (BPBP)	1844-01-5		4.96	352.43
Bisphenol C (BPC)	79-97-0		4.32	256.34
Bisphenol E (BPE)	2081-08-5		3.12	214.26
Bisphenol F (BPF)	620-92-8		2.91	200.23
Bisphenol FL (BPFL)	3236-71-3		4.90	350.42
Bisphenol G (BPG)	127-54-8		6.04	312.45
Bisphenol M (BPM)	13595-25-0		6.10	346.46
Bisphenol P (BPP)	2167-51-3		6.10	346.46

Table 1. *Cont.*

Name (Abbreviation)	CAS Number	Structural Formula	Log Kow	Molecular Weight (g/mol)
Bisphenol PH (BPPH)	24038-68-4		6.59	380.48
Bisphenol S (BPS)	80-09-1		1.29	250.27
Bisphenol TMC (BPTMC)	129188-99-4		5.87	310.43
Bisphenol Z (BPZ)	843-55-0		4.44	268.35

Note: The reported Log Kow value is the experimental or predicted average.

The main BPA analogs recently used in the production of polycarbonate plastics and epoxy resins are bisphenol F (BPF), bisphenol S (BPS), and bisphenol AF (BPAF). Moreover, BPF is also used in food packaging, liners, water pipes, dental sealants, industrial floors, grouts, electrical varnishes, coatings, lacquers, plastics, adhesives, and tissue substitutes [1,12]. In addition, BPS has also several uses, such as epoxy glues, thermal receipt papers, sulfonated poly (ether ketone ether sulfone), and as an additive in dyes agents [1]. Another bisphenol A analog, namely, BPAF, is used in common polymer applications, such as a cross-linker in fluoroelastomers, electronics, and optical fibers, as a high-performance monomer for polyimides, polyamides, polyesters, polycarbonate copolymers and in specialty polymer applications such as plastic optical fibers and waveguides [1]. Similarly, bisphenol AP (BPAP), is used as a plasticizer and flame retardant in synthesizing plastic, rubber, polymer materials, the chemical industry, and in the medical industry [13]. Furthermore, brominated bisphenols have been produced, such as tetrabromobisphenol A (TBBPA) and tetrabromobisphenol S (TBBPS) and their analogs/derivates, which are used as flame retardants [14].

The production amount of BPA analogs is usually not available, but it is considered increasing [1,15]. Indeed, BPS usage has increased twice from 200 tons in 2016 to 397 tons in 2017 (98% increase) [9], and the European Food Safety Authority (EFSA) reports that the annual production of BPS is 1000–10,000 tons [16]. Regarding BPAF, its annual production in the USA was in the range of approximately 4.5–220 tons from 1986 to 2002, while its manufacture/import in the EU is 100–1000 tons per year [17,18]. In the case of brominated bisphenols, the most used is TBBPA with a global production of over 170,000 metric tons/year [19].

Despite their new usage, BPA analogs are considered hormonally active due to their similar chemical structure to BPA. Indeed, these substances can cause endocrine-disrupting effects acting as estrogenic, progesteronic, and anti-androgenic compounds [12,15]. For instance, BPS, which was first synthesized in 1869 and used as a dye, was introduced into cash-register receipts in 2006 as a speculatively safer compound instead of BPA [20]. However, it has been recently reported that it has genotoxic and estrogenic activities,

similarly to BPA, being able to bind to estrogen receptors in vitro [20]. Moreover, in the case of bisphenol F diglycidyl ether (BPF-DGE), the EU banned its use as a food packaging material and settled a Tolerably Daily Intake (TDI) for the sum of bisphenol A diglycidyl ether (BPADGE) and its metabolites (BADGE·H_2O and BADGE·$2H_2O$) at 0.15 mg kg^{-1} bw per day, while for BADGE chlorohydrins, the restriction was settled at 1 mg kg^{-1} of food [21].

1.2. Biodegradation of Bisphenols

Bisphenols reach the aquatic environment not only from wastewater treatment plants (WWTPs) and discharge from urban and industrial areas, but they can also be continuously released and adsorbed by microplastics [22]. After their release, bisphenols can be degraded in several ways in the environment including photodegradation, oxidation, and biodegradation. However, bisphenols are mainly biodegraded. Indeed, several organisms including bacteria, fungi, algae, and plants can degrade bisphenols [23]. In the case of BPA, it can be degraded in other organic compounds by more than ninety bacterial strains throughout many pathways [23–25]. In addition, some microorganisms can degrade several bisphenol analogs. For example, the *Sphingomonas* species can biodegrade up to six bisphenol analogs, including BPS, BPF, BPB, BPE, BPZ, and BPC. Likewise, *Cupriavidus* and *Sphingobium* can biodegrade six different bisphenols, while *Bacillus* and *Pseudomonas* can degrade at least five or four bisphenols, respectively [23].

However, the persistence in the water of bisphenols is highly variable. Indeed, some bisphenols can be rapidly degraded in river water such as BPF, which was completely biodegraded in 37 days [26]. On the contrary, the biodegradation of BPAF, BPE, and BPB was minimal, while the biodegradation of BPS appeared to be higher than that of BPA, but lower than that of BPF in rivers [26]. In addition, BPAF has a half-life that ranges from 15 to 180 days in water [1]. BPA in seawater persists longer than in rivers, with a BPA degradation that started from 40 to 60 days, posing a risk for marine organisms [27]. Moreover, bisphenols biodegradability in seawater was ranked as BPF $\gg$ BPA > BPP > BPE > BPB $\gg$ BPS [1]. Lastly, in marine sediment under aerobic conditions, the half-life of BPA is 14.5 days [28].

1.3. Occurrence of Bisphenols in Aquatic Environments

In aquatic environments, the mostly detected bisphenol is BPA with a concentration that is usually in the range of ng/L in both surface waters (wastewater treatment plants, streams, rivers, and lakes) and seawaters, as reported in Table 2. However, some reports reveal that its concentrations can reach hundreds of ng/L to tens of µg/L, exceeding in some cases the predicted no-effect concentration for water (PNEC), set at 1500 ng/L by the EU [29]. In addition, the EU established a PNEC value of 150 ng/L for BPA in marine water [29]. Bisphenol A analogs are often found at lower concentrations than BPA, in the range of a few ng/L [30–32]. However, it has been reported that their concentrations can reach hundreds and thousands of ng/L. Indeed, BPAF was recorded at a mean concentration of 140 ng/L in surface water in China [33], while BPF reached 2850 ng/L and BPS reached 65,600 ng/L in surface water of Japan and China, respectively [34,35].

In the marine environment, bisphenol analogs have a common concentration from very few ng/L up to tens of ng/L [30,36,37], even if their concentrations can reach upper concentrations, as in the case of BPF that had a maximum concentration of 282 ng/L and 1470 ng/L in seawater in South China and in the Tokyo Bay, respectively [30,34]. These values are close to the PNEC value and could be passed due to the higher use and environmental release of BPA analogs. Moreover, bisphenol A analogs, such as BPA, can also be bioaccumulated by marine animals, as observed in shrimps, crabs, mollusks, and fishes [30,37], and can be transferred through the food web and cross-generation as observed in the humpback Dolphins (*Sousa chinensis*), in which six bisphenols (BPA, BPAF, BPB, BPF, BPP, and BPS) have been detected even in fetuses [38].

Table 2. Bisphenol analogs concentrations in WWTPs, surface waters, and seawaters around the world.

Compound	Body Water, (Country)	Min–Max Concentration (Mean) (ng/L)	Reference
BPA	WWTP influent (China)	3–62,010 (mean = 2031)	[39]
	Surface water (Japan)	3.1–120	[34]
	Surface water (Korea)	1.0–272	[34]
	Surface water (China)	ND–98	[34]
	Surface water (Brazil)	ND–517	[40]
	Surface water (India)	ND–1950	[34]
	Surface water (China)	22.9–3360	[33]
	Surface water (China)	ND–34.9 (mean = 12.8)	[41]
	Surface water (China)	4.2–141	[31]
	Surface water (China)	28–560	[42]
	Surface water (China)	78.9–310	[43]
	Surface water (Turkey)	4620–29,920	[44]
	Surface water (China)	75.6–7480 (mean = 922)	[35]
	Seawater (Italy)	ND–145	[45]
	Seawater (China)	9.48–173	[30]
	Seawater (Turkey)	4160–16,920	[44]
	Seawater (East China Sea)	2.3–49 (mean = 18)	[37]
	Seawater (Tokyo Bay)	ND–431 (mean = 325)	[34]
	Seawater (Greece)	10.6–52.3 (mean = 25)	[46]
	Seawater (Singapore)	ND–2470	[47]
	Seawater (Singapore)	ND–694	[48]
	Seawater (Singapore)	6–1493	[49]
	Seawater (Baltic Sea)	ND–5.7	[50]
	Seawater (East China Sea)	2.7–52 (mean = 23)	[36]
BPAF	WWTP influent (China)	ND–9 (mean = 2)	[39]
	WWTP (China)	6.6–160 (mean = 17)	[51]
	WWTP (Slovenia–Croatia)	0.0367–3.4 (mean = 1.47)	[52]
	WWTP (China)	ND–18.5	[53]
	Surface water (China)	ND–2.58 (mean = 1.01)	[53]
	Surface water (China)	mean=140 ng/L	[33]
	Surface water (China)	ND–10.8 (mean = 3)	[41]
	Surface water (China)	0.13–11	[31]
	Surface water (China)	0.7–84	[42]
	Seawater (South China)	0.40–3.59	[30]
	Seawater (East China Sea)	0.12–0.91 (mean = 0.21)	[36]
	Seawater (East China Sea)	ND–0.57 (mean = 0.24)	[37]
BPAP	WWTP influent (China)	1.1–75 (mean = 26)	[39]
	WWTP (China)	ND–21	[51]
	Surface water (Slovenia–Croatia)	0.54–0.903 (mean = 0.704)	[52]

Table 2. *Cont.*

Compound	Body Water, (Country)	Min–Max Concentration (Mean) (ng/L)	Reference
	Surface water (China)	ND–0.39	[31]
	Surface water (China)	1–56	[42]
BPB	WWTP (Slovenia–Croatia)	27.1	[52]
	WWTP influent (China)	1–8 (mean = 4)	[39]
	WWTP (China)	ND–8 (mean = 2.2)	[51]
	WWTP (Poland)	29.29–62.49	[54]
	Surface water (China)	ND–14.3 (mean = 1.0)	[41]
	Surface water (China)	ND–28	[42]
	Surface water (China)	ND–7.9	[43]
	Surface water (China)	ND–5.7	[32]
	Seawater (South China)	0.17–13.1	[30]
BPBP	WWTP (China)	ND–0.21	[53]
	Surface water (China)	ND–0.43	[53]
BPC	WWTP (Poland)	ND–7.57	[54]
	WWTP influent (China)	6	[39]
	WWTP (China)	ND–360 (mean = 68)	[51]
	WWTP (China)	ND–0.38	[53]
BPE	WWTP (Slovenia–Croatia)	476	[52]
	WWTP influent (China)	2–84 (mean = 16)	[39]
	WWTP (Poland)	25.16–58.71	[54]
	WWTP (China)	ND–31 (mean = 16)	[51]
	WWTP (China)	ND–7.71	[53]
	Surface water (China)	ND–2.69	[53]
	Surface water (China)	ND–6.18 (mean = 0.98)	[41]
	Surface water (China)	ND–20.3	[55]
BPF	WWTP (Slovenia–Croatia)	2.54–117 (mean = 44.3)	[52]
	WWTP influent (China)	3–90 (mean = 39)	[39]
	Wastewater (India)	ND–333	[56]
	WWTP (China)	ND–180 (mean = 26)	[51]
	WWTP (China)	0.52–271	[53]
	Surface water (Japan)	76–2850	[34]
	Surface water (China)	0.24–34.4	[53]
	Surface water (Korea)	ND–1300	[34]
	Surface water (China)	ND–1110	[34]
	Surface water (India)	ND–289	[34]
	Surface water (India)	ND–209	[56]
	Surface water (China)	21.3–230	[43]
	Surface water (China)	ND–12.56 (mean = 2.18)	[41]
	Surface water (China)	ND–474 (mean = 82.8)	[35]
	Surface water (China)	ND–5.6 (mean = 0.83)	[31]

Table 2. *Cont.*

Compound	Body Water, (Country)	Min–Max Concentration (Mean) (ng/L)	Reference
	Surface water (China)	ND–1600	[42]
	Seawater (East China Sea)	ND–0.65 (mean = 0.31)	[37]
	Seawater (South China)	2.37–282 ng/L	[30]
	Seawater (East China Sea)	ND–0.91	[36]
	Seawater (Tokyo Bay)	ND–1470 (mean = 373)	[34]
BPFL	Surface water (China)	ND–0.069	[31]
	Surface water (China)	ND–2.21	[30]
BPG	WWTP (Poland)	ND–33.08	[54]
	WWTP (China)	ND–1.76	[53]
	Surface water (China)	ND–2.47	[53]
BPM	Seawater (East China Sea)	ND–0.74	[36]
BPP	WWTP influent (China)	1.5–27 (mean = 8)	[39]
	WWTP (China)	2.7–300 (mean = 17)	[51]
	Surface water (China)	ND–1.93	[53]
	Surface water (Slovenia–Croatia)	6.45	[52]
	Surface water (China)	0.27–1.53	[30]
BPPH	WWTP (China)	ND–0.38	[53]
	Surface water (China)	ND–0.68	[53]
BPTMC	WWTP (China)	0.09–5.3	[53]
	Surface water (China)	ND–101 (mean=8.8)	[53]
BPS	WWTP (Slovenia–Croatia)	108–435 (mean = 316)	[52]
	WWTP (India)	ND–438	[56]
	WWTP influent (China)	7–318 (mean = 54)	[39]
	WWTP (China)	90–1100 (mean = 290)	[51]
	WWTP (China)	0.10–932	[53]
	Surface water (Japan)	ND–8.7	[34]
	Surface water (China)	0.07–133 (mean = 12.7)	[53]
	Surface water (Korea)	ND–42	[34]
	Surface water (China)	ND–135	[34]
	Surface water (China)	19.9–65,600 (mean = 3720)	[35]
	Surface water (India)	ND–7200	[34]
	Surface water (Slovenia–Croatia)	1.68–35.2 (mean = 9)	[52]
	Surface water (China)	mean= 27.6 ng/L	[33]
	Surface water (India)	ND–341	[56]
	Surface water (Poland)	ND–1584	[57]
	Surface water (Romania)	6.15–8.23	[58]
	Surface water (England)	ND–306	[59]
	Surface water (China)	ND–5.2 (mean = 1.1)	[41]
	Surface water (China)	0.22–67	[31]

Table 2. *Cont.*

Compound	Body Water, (Country)	Min–Max Concentration (Mean) (ng/L)	Reference
	Surface water (China)	ND–1600	[42]
	Surface water (China)	3.2–7.8	[32]
	Seawater (East China Sea)	0.15–12 (mean = 2.2)	[36]
	Seawater (South China)	1.6–59.8	[30]
	Seawater (East China Sea)	0.12–11 (mean = 3.7)	[37]
	Seawater (Tokyo Bay)	ND–15 (mean = 8.5)	[34]
BPZ	WWTP (China)	ND–540 (mean=7)	[51]
	WWTP (Poland)	24.64–66.62	[54]
	WWTP influent (China)	3–151 (mean = 77)	[39]
	WWTP (China)	ND–1.15	[53]
	Surface water (Slovenia–Croatia)	0.25–9.11 (mean = 4.68)	[52]
	Surface water (China)	ND–1.09	[53]
	Surface water (China)	ND–0.70 (mean = 0.054)	[31]
	Surface water (China)	ND–45	[42]
	Surface water (China)	ND–2.8	[32]
TBBPA	Surface water (China)	23.9–224	[55]
	Surface water (China)	ND–4870	[60]
	Surface water (England)	0.14–3.2	[61]
	Seawater (East China Sea)	0.25–25 (mean = 2.3)	[36]

2. Effects of Bisphenols on Marine Species

2.1. Effects of Bisphenol A

The effects of bisphenols have been evaluated on some marine species, such as microalgae, mollusks, rotifers, sea urchins, polychaetae, crustaceans, fishes, and mammals. However, BPA is still the most studied bisphenol, while the effects of the other compounds are substantially unknown. BPA is considered as an EDC, being able to mimic the natural estrogens causing impairment in hormonal sensitivity and responsiveness. It is well known that BPA can also affect the immune system, antioxidant enzymes, neuroendocrine system, and embryo development in humans [62]. Similarly, several studies demonstrated that BPA could cause detrimental effects on marine species. BPA can alter the reproductive system of marine species, as demonstrated in *Mytilus edulis* specimens exposed for 3 weeks to 50 µg/L of bisphenol A [63]. The authors also observed a slight increase in phosphoproteins in the mantle gonadal tissue of females, and after histological investigations, they observed atretic oocytes in half of the BPA-exposed mantles, while on the other half there were post-spawning stage gonads [63]. Effects on the reproductive system were also reported in the mud crab *Macrophthalmus japonicus* where a significant upregulation of the vitellogenin (VTG) gene was observed in the ovaries after 96 h of exposure to the tested concentration (1, 10, and 30 µg/L) and a significant upregulation of VTG gene was also observed in hepatopancreas at 30 µg/L. Moreover, a significantly higher VTG gene expression was observed after 7 days of exposure at 1 µg/L in hepatopancreas and under all the tested concentrations in ovaries [64]. The same authors investigated the effect of BPA on the molting process. After one day of exposure, there was an ecdysone receptor gene up-regulation (EcR) in the hepatopancreas at 1, 10, and 30 µg/L, while in gills only 1 and 10 µg/L caused a significant up-regulation. However, the EcR gene expression in hepatopancreas was downregulated at 1 and 30 µg/L after 4 days. Interestingly, after

one week of exposure, an opposite trend between the two tissues was observed, with the 10 µg/L treatment that caused a significant decrease in expression in gills and a significant increase in hepatopancreas [65].

In another crustacean species, namely, the whiteleg shrimp *Litopenaeus vannamei*, exposure to 2 µg/L of BPA induced a significantly smaller gonad-somatic index with a consequent delay in the gonad development stage with respect to the controls. Moreover, exposed shrimps had a lower oxygen consumption rate, an increased ammonia extraction rate, and a downregulation of metabolism-related gene expression. In addition, the authors observed an upregulation of gonadal development-related hormones and the expression of gene-encoding regulatory hormones [66]. It was also highlighted that BPA can cause embryotoxic effects [67–69]. For instance, in the mussel *Mytilus galloprovincialis*, BPA interfered with shell formation at different larval stages with spatial alteration of the expression of genes involved in shell formation and in serotoninergic system development [70]. In the same species, Balbi et al. [71] observed several gene expression alterations in embryos hatched from eggs previously exposed to 10 µg/L of BPA. In a similar study, in which fertilized eggs of *Haliotis diversicolor supertexta* were exposed to four BPA concentrations (0.05, 0.2, 2, and 10 µg/mL), it was demonstrated that BPA can affect embryonic development. Moreover, the authors concluded that BPA could markedly reduce embryo hatchability, increase developmental malformation, and suppress the metamorphosis behavior of larvae [72]. Larvae malformations were also recorded in the two ascidian species *Ciona robusta* and *Ciona intestinalis* after exposure to concentrations higher than 10 µM [69]. Furthermore, most of the embryos of the sea urchin *Hemicentrotus pulcherrimus* exposed to 10 µM of BPA for 24 or 48 h after fertilization showed a suppressed development by the hatching stage [67]. In addition, juveniles of *H. pulcherrimus* exposed for 80 days to 0.5 µM of BPA showed a reduction in the relative test diameter [67]. However, the authors reported that BPA effects on early development were less remarkable than that of ethynyl estradiol [67]. An analog study reported that BPA can affect the development of embryos of the sea urchin *Paracentrotus lividus*. Indeed, animals exposed to 300 µg/L of BPA showed spermiotoxic and embryotoxic effects and skeleton malformation was observed in plutei [68]. Moreover, larvae skeletal malformations were also observed in the embryos of sea urchin *Arbacia lixula* after BPA exposure [73]. Lastly, fertilized eggs of the sea urchin *Lytechinus pictus* exposed to BPA showed failed cytokinesis leading to multipolar spindles in a dose-dependent manner [74].

BPA can also affect the immune system in bivalves. Indeed, BPA injected in *M. galloprovincialis* (25 nM nominal concentration in the hemolymph) caused a significant lysosomal membrane destabilization in hemocytes at all the post-injection times (6, 12, and 24 h). Moreover, BPA changed the phosphorylation state of mitogen-activated protein kinases (MAPKs) and signal transducers and activators of transcription (STAT), indicating that BPA can affect kinase-mediated cell signaling in mussel hemocytes in vivo [75]. Furthermore, in the bivalve *Tegillarca granosa* total hemocyte count (THC) was reduced after 2 weeks of exposure to 10 ng/L and 100 ng/L of BPA and a decrease in red granulocyte percentage and an increase in both basophil granulocyte and hyalinocyte was reported [76]. In addition, the phagocytic activities of hemocytes were significantly reduced and the content of γ-aminobutyric acid, dopamine, and acetylcholine in hemolymph was increased [76]. On the contrary, the expression of four immune-related genes and genes encoding modulatory enzymes and receptors for neurotransmitters was significantly suppressed [76]. An impairment of the neuro system was also observed in the claw muscles of the artic spider crab *Hyas araneus* in which there was a significant reduction in acetylcholinesterase activity (AChE) after 3 weeks of exposure to 50 µg/L of BPA [77]. In another study, the crab *Charybdis japonica* was exposed for 1, 3, 6, 9, and 15 days to 0.125, 0.25, 0.5, and 1 mg/L, respectively. The authors reported a reduction in THC values in crabs exposed to 1 mg/L for 1, 3, and 6 days; 6 days of exposure to 0.5 mg/L of BPA also caused a THC reduction [78]. They also observed that superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), lysozyme (LSZ), and phenoloxidase (PO) activities reached the highest values during the

first week and then decreased during the second week of exposure in both hemolymph and hepatopancreas, while malondialdehyde content (MDA) gradually increased over time following the exposure [78]. Histological analysis revealed that the rough endoplasmic reticulum of hepatopancreas cells appeared swollen and reduced in number [78]. Moreover, vacuoles, lysosomes, and myeloid bodies were observed in the hepatopancreas cells [78]. In addition, in the same crab species, there was a significantly increased expression of the heat shock protein gene HSP90 under all the tested concentrations (0.05, 0.5, 1 mg/L) after 12, 24, 48, and 96 h of exposure [79].

BPA can cause detrimental effects on the antioxidant system also in bivalves. Indeed, in specimens of *M. galloprovincialis* injected with 50 µL of BPA solutions (from a 10 mM stock solution in ethanol diluted in artificial seawater), containing respectively, 3, 15, and 60 ng BPA, corresponding to a nominal concentration of BPA 3, 15, and 60 ng/g dry weight or per mussel, BPA caused an increased gene expression of the estrogen receptor MeER2 and induced downregulation of antioxidant genes, catalase, and metallothioneins 24 h post injection [80]. In addition, BPA altered the activity of CAT, glutathione S-transferase (GST), glutathione reductase (GR), and the total glutathione amount [80]. Moreover, exposure for 7 days of *Perna viridis* to 98, 996, and 10,111 ng/L of BPA had immunomodulatory, genotoxic, and endocrine-disruptive effects [81].

The effects of BPA were also evaluated in polychaetae. In *Ophryotrocha diadema* BPA caused a significant reduction in the number of laid eggs only after five weeks of exposure at the highest concentration tested (1.4611 mg/L) [82]. Furthermore, in the polychaete *Perinereis aibuhitensis* exposed for 4, 7, and 14 days to 10, 50, and 100 µg/L, respectively, BPA caused the increase in G protein alpha subunit gene expression in both the body wall and in the head, on which there was the higher induced expression [83]. Lastly, recent studies have shown that some degradation products and metabolites of BPA have much higher estrogenicity or toxicity than BPA. For instance, 4-methyl-2,4-bis(4-hydroxyphenyl)pent-1-ene (MBP), a metabolite of bisphenol A, has shown an estrogenic activity approximately 1000-fold higher than BPA [84,85].

2.2. Effects of Bisphenol A Analogs

The effects of BPA analogs are poorly studied in marine species. However, in a recent study, BPF, BPS, and BPA were tested in the marine rotifer *Brachionus koreanus* for 24 h [86]. The authors reported that both BPA and BPF caused a reduction in cumulative offspring. In addition, 10 mg/L of BPA, 10 mg/L of BPF, and 15 mg/L of BPF caused a significant reduction in life span. Moreover, the three bisphenols increased the reactive oxygen species level (ROS), with BPS and BPF increasing the ROS and GST levels at almost all the tested concentrations (1, 5, and 10 mg/L) [86]. BPF as well as BPA significantly altered the expression level of cytochrome P450 (*CYP*) and *GST* genes [86].

Furthermore, in the brackish water flea *Diaphanosoma celebensis,* the gene expression of seven ecdysteroid pathway-related genes (*cyp314a1*, *EcRA*, *EcRB*, *USP, nvd, HR3,* and *E75*) were altered after exposure for 48 h at high concentrations of BPA (0.12, 0.6, and 3.0 mg/L), BPS (0.92, 4.6, and 23.0 mg/L), and BPF (0.6, 1.0, and 5.0 mg/L), suggesting an ecdysteroid signaling pathway disruption and an alteration of the endocrine system. However, the expression patterns of BPS and BPF were different from those of BPA [87,88]. In the same species exposed to the same concentrations, BPA, BPS, and BPF differently modulated the gene expression of the estrogen-related receptors, vitellogenin and vitellogenin receptors, indicating that these compounds can also affect the normal reproduction-related pathway [89]. Moreover, an in silico study on the Pacific oyster *Magallana gigas* revealed that BPF has a high affinity for the estrogen receptor (ER) and that BPA has a higher binding energy for ER than the estrogen hormone itself [90]. In a recent in vitro study, TBBPA, BPA-E (Bisphenol A BIS (2,3-dihydroxy propyl) ether), and BPAF tested at 50 µM caused the reduction in residual carboxylesterase activity in the digestive gland extracts of both *Octopus vulgaris* and *Sepia officinalis* [91]. Similarly, the three BPA analogs caused an inhibition effect also in the hemolymph of *O. vulgaris* [91]. Recently, the effects of several

bisphenol A analogs on β-esterases were also tested in the sea turtle *Caretta caretta*. The results showed that only TBBPA (at 50 μM) significantly inhibit the plasmatic carboxyl esterase activity, however, TBBPA did not inhibit acetylcholinesterase [92]. Furthermore, in the marine amphipod *Gammarus aequicauda* exposed to 0.25, 0.5, and 1 mg/L of BPA, BPF, or BPS for 24 h, there was a general increase in DNA damage in both hemocytes and spermatozoa. In detail, BPF caused a significant increase in DNA damage at all the tested concentrations in hemocytes and in spermatozoa at 1 mg/L, while the BPS exposure increased the mean DNA damage level with respect to the controls in both somatic and germ cells, but not significantly. The authors concluded that both BPF and BPS caused lower DNA damage than BPA [93].

In a recent study, juveniles of the brown trout *Salmo trutta* were exposed for 2 or 8 weeks to 2 or 20 mg/kg fish. After 2 weeks, the level of the thyroid hormone triiodothyronine (T3) in plasma was elevated after Bisphenol S exposure at the high concentration and paralleled by an increase in micronucleated cells. BPS did not cause statistical differences in the hematocrit, hemoglobin levels, or glucose levels in comparison with the control. However, there was a significantly higher hematocrit level in fish exposed to the high dose of BPS compared to fish exposed to the low dose of BPS after 2 weeks of exposure. On the contrary, the vitellogenin levels in blood were not altered by BPS, and only the higher dose of BPA increased the level. After 2 weeks, T3 levels were significantly higher in fish treated with the high dose of BPS compared with controls, but thyroxin T4 levels were not altered. At the same time as the exposure, the high dose of BPS increased the micronuclei percentage in the erythrocytes, while after 8 weeks, the same treatment decreased the percentage of binucleated erythrocytes [94]. Furthermore, the hepatocytes of the rainbow trout *Oncorhyncus mykiss* treated for 24 h with BPS (0, 15.63, 31.25, 62.50, 125, 250, and 500 μM) showed that cytotoxicity increased in a concentration-dependent manner. Moreover, all the tested BPS concentrations caused a reduction in SOD activity, while CAT and GPX activity was generally increased at higher concentrations. GST activity was significantly increased at a concentration of 31.25 μM or higher, while GST Theta 1-1 activity and the reduced glutathione content (GSH) were decreased at these concentrations. Moreover, the oxidative damage measured as malondialdehyde content increased at 125, 250, and 500 μM of BPS [95]. In an analog study, the hepatocytes of rainbow trout were exposed to BPF using the same experimental design. As in the case of BPS, BPF increased dose-dependently its cytotoxic effects. The malondialdehyde content was increased at BPF concentrations between 15.63 and 250 μM, whereas it remained unchanged at 500 μM. Interestingly, SOD and CAT activities were increased and decreased, respectively, in all treatment concentrations. Moreover, the GSH level increased with concentrations of BPF between 15.63 and 250 μM but decreased significantly at 500 μM. In addition, GPX and GST were significantly increased at a BPF concentration from 31.25 μM, and at 125 μM, respectively. The authors concluded that the toxic mechanism of BPF was mainly based on cell membrane damage and oxidative stress, influencing the antioxidant defenses [96]. The effect of BPS was also tested on the juveniles of olive flounders (*Paralichthys olivaceus*) that were injected with a concentration of 50 mg/kg. Treatment caused a transcriptome alteration in the liver. In particular, BPS significantly increased the transcription of egg process and vitellogenesis-related genes, including zona pellucida sperm-binding proteins, and estrogen receptors, with increases in plasma 17β-estradiol (E2) and VTG concentrations. In addition, there was an increased gene expression of genes involved in antioxidant defense systems, while genes involved in innate immunity were decreased [97]. Moreover, there was an increased activity of both CAT and GST in the liver [97].

Recently, specimens of medaka (*Oryzias melastigma*) were exposed for 70 days to 200 μg/L of BPA, BPF, BPAF, or their mixture [98]. After 70 days of exposure to BPAF, males showed a higher body weight and body length. On the other side, the condition factor of males was significantly reduced by the mixture and increased in females owing to BPF exposure [98]. In addition, the BPAF-exposed fishes had a survival rate significantly lower than controls. Moreover, the histological analysis indicated that bisphenol exposure led

to vacuolization and local lesions in the liver, especially in the BPAF group. These results are like those observed by Peng et al. [78] in crabs exposed to BPA. In addition, medaka fishes showed an altered antioxidant enzyme activity, with a reduction in both SOD and CAT activity in the liver of males exposed to BPAF or MIX. In females, both BPF and BPAF caused a reduction in the total swimming distance, while in males this reduction was observed only in the mixed treatment. All the bisphenols caused an up-regulation of genes involved in lipid synthesis and metabolism in the liver of female fish and, interestingly, all genes involved in eukaryotic ribosome biogenesis were downregulated in females exposed to BPAF [98]. In males, the differentially expressed genes were mainly involved in steroid biosynthesis, arachidonic acid metabolism, nicotinate, and nicotinamide metabolism [98]. Moreover, BPAF appeared to cause an estrogenic effect with an increased coriogenins and vitellogenins gene expression in the liver of male fishes [98].

Bisphenol A analogs can alter the microbiome of the mussel *M. galloprovincialis* larvae, as demonstrated after exposure to BPA and BPF (10 μg/L). The results indicated that after 24 h post fertilization, BPF altered the microbiome, with an alteration in the abundance of six genera, such as potential pathogens (*Vibrio*, *Arcobacter*, and *Tenacibaculum*) and genera involved in xenobiotic biotransformation (*Oleispira*). Similarly, after 48 h post fertilization, BPF induced changes in five genera. Interestingly, BPF caused similar effects to BPA, but lower than those caused by 17β-estradiol [99].

Very few studies have been conducted on microalgae. A recent study demonstrated an alteration of the antioxidant system in the microalgae *Chlorella pyrenoidosa* exposed for 6 days to BPS (5.0, 10.0, 15.0, 20.0, and 40.0 mg/L), BPA, and their mixture [100]. On the 6th day, BPA was 3.7 times more toxic than BPS and the bisphenol mixture and showed higher inhibition effects with respect to the single bisphenols, indicating a synergistic effect. BPF caused an alteration in chlorophyll A content; in particular, the concentration of 5 mg/L increased the chlorophyll content, while the other concentrations decreased the chlorophyll content in a dose-dependent manner. Similarly, the higher doses of the mixture caused a chlorophyll A level decrease, even if, at the initial exposure times, the low doses had a stimulation effect [100]. Furthermore, 6 days of exposure at 15, 20, and 40 mg/L of BPS increased ROS levels, and peroxidase activity, while the SOD activity was enhanced by all the tested concentrations [100]. In the case of the mixture, only the two lowest concentrations increased the ROS levels and the activities of SOD and peroxidase increased gradually with the increase in the combined concentration of BPA and BPS [100]. Lastly, the malondialdehyde amount was increased by all the BPF concentrations and by most mixture concentrations [100].

As a concluding remark, it can be highlighted that BPA analogs can act as EDCs and can also affect the immune system, antioxidant system, genetics, and behavior in aquatic species. BPA is going to be replaced with structurally similar compounds that are speculatively considered safer compounds. In the context of higher BPA analog usage and release into aquatic environments, recent studies have highlighted that the marine concentrations can already pose environmental risks to non-target species. However, the effects of BPA analogs and their mixtures on marine organisms are still mainly unknown and need to be deeply investigated.

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