Occurrence, fate and toxicity of Bisphenol A in the Aquatic Environment – A Short Review

E02 – Final Assignment

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Abstract

Bisphenol A (BPA) is an industrially widely used chemical and well known endocrine disruptor. Despite mostly of the studies are focused on its toxicology on humans, the aim of this short review has been to assess BPA major routes of contamination, occurrence, fate and toxicology in the water environment, especially on aquatic vertebrates.

Introduction

Production and Use

Bisphenol A (BPA) is a diphenylmethane derivative with two hydroxyphenyl groups and it is considered an hormonal system disruptor due to its similarity to natural hormones, which it is able to imitate. It behaves as an estrogen agonist and/or antagonist and as an androgen and thyroid hormone antagonist. Its endocrinological properties have been known since mid '30[1], but despite these evidences, BPA is a widely used chemical. According to the Global Bisphenol A (BPA) Market Report and Forecast 2021-2026 (https://www.researchandmarkets.com/), the worldwide value of BPA market is about 10.92 Billion USD in 2020 with an estimated production of 2-3 million tons per year. Almost 70% of BPA production is deputed for polycarbonate plastics which are largely used for habitual products (optical, media, automotive, electrical and electronics, housewares and appliances, construction, medical, packaging, etc.). 20% of BPA is produced as component of epoxy resins, which are used as coating on food and beverage metallic cans. The remaining is used as antioxidant or inhibitor of polymerization in some plasticizers, polyvinyl chloride, and thermal cash register paper[2]. As a consequence of this massive application, BPA has been detected both in terrestrial and marine environments, as well as in humans[3]. Therefore, in 2017, BPA was listed in the substances of very high concern list of the European Chemical Agency (ECHA)[4].

Environmental Presence

The presence of BPA in the environment is determined by anthropogenic activities, not being a native component of it. BPA contaminates the environment through different pathways, having measurable vapor pressure, water solubility and octanol-water partition coefficient. Therefore it is expected to partition to some level and it has been detected in various matrix as water, soil and sediments. It enters into the environment due to plastic products deposition or BPA manufacturers spillages[5], with an observed concentration, especially in sediments, higher in Asia[6]. Unless in ambient condition, BPA

is a solid, formed as crystals, it is released in the environment as particulates or dissolved in water with a reported water solubility of 300 mg/L[7].

In the aquatic environment, BPA is discharged through the BPA-based products transfer into rivers and marine waters and through the effluents from wastewater plants and landfill sites, leading to an exposure of the aquatic organisms (microorganisms, planktons, plants, invertebrates, and vertebrates) to the chemical[8]. Several ecotoxicological studies reported adverse effects on aquatic organisms exposed to low levels of BPA[3,8,9]. However, according to Canesi and Fabbri, 2015[10]. mostly of the studies are focused on aquatic vertebrates, specifically fishes, and they have been carried out in controlled settings in order to provide a better evaluation of the BPA mode of action, physiology effects and dose response. Thus, laboratory experiments make impossible to reproduce the drastic concentration variation, the complex chemical mixture in which BPA is present, and the various sensitivities of the different species to xenobiotics that occur in wildlife.

Physiochemical Properties

The chemical structure, molecular weight, CAS number and specific physicochemical properties of BPA are presented in **Table 1**. The octanol-water partition coefficient (log Kow) of BPA is 3.32, hence, with a log Kow ≤ 4, it is expected to be parted mostly in the water phase. Moreover, BPA presents a rapid metabolism[11].

Bioconcentration-Bioaccumulation

Considering the BPA bioconcentration factor (BCF), no tendency of the substance to significantly accumulate in biota has been reported. BCF mean is 71.85. This value is well below than the limit thresholds imposed from the regulatory agencies (EPA=1000, EU=2000)[12], therefore, BPA is not declared as a bioaccumulation concerning chemical.

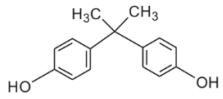
Compound	Chemical structure	Molecular formula	Molecular weight (g/mol)	CAS NO.	$logK_{ow}$	$logK_{oc}$	Half-life (day)				BCF
							Atmosphere	Water	Soil	Sediment	
BPA		$C_{15}H_{16}O_2$	228.29	080-05-7	3.32	4.88	0.13	37.5	75	337.5	71.85

Table 1 Physiochemical BPA properties evaluated through EPI-Suit Web 4.1

Contamination Route, occurrence and fate of BPA in aquatic environment

BPA can reach the aquatic environment migrating from BPA based products. Nevertheless, effluent from wastewater and landfill sites is considered the primary route of contamination[8].

Several investigation have been conducted to assess BPA biotreatability and biodegradation, using various approaches and endpoints. From available and collected data, BPA is expected to rapidly biodegrade and it is not persistent in surface waters and wastewater treatment plants equally operating acclimated and unacclimated microbial populations[7]. Analysing the BPA occurrence in water

environment (surface water, sewage and sludge), the concentrations were found averagely 1-10^2 ng/L, with levels in order of µg/L in heavily polluted areas[11].

Effluent from wastewater treatment plants

BPA has been detected in wastewater from paper and/or plastic production as well as domestic sewage treatment plants. It can be significantly removed through abiotic and biotic treatments (>90%), although not completely with a reported removal range from 37-94%[8]. In Japan wastewater containing BPA were analysed, reporting 72% COD and 57% BOD removal in 24 hours. More than 99% of BPA and 87.5% COD were removed using acclimated population in activated sludge treatment systems, in two weeks[12]. Furthermore Gassara et Al.[13] reported an increment of BPA maximum reaction rate for wastewater, using the oxidative action of extracellular fungal enzymes as lignin peroxidase. Commonly, domestic sewage effluents have lower levels of BPA than industrial ones. Mean concentration of BPA in effluent was found at the range of 1.1–696 ng/L[11]. J. Liu et Al 2021[11] reported a study case of BPA investigation in 52 water treatment plants located in 30 Chinese cities, suggesting a mean value of 4.69 ng/g in sludge after treatment.

Effluent from landfill sites

Elevate levels of BPA have been detected in leachates from waste landfill ranging from 1.3 to 17,200 μg/L (average 269 μg/L). However the effluent concentration is much lower considering the following treatment. According to J. Kang et Al.[8] , a monitoring of 4 landfill sites settled in Japan showed a BPA concentration ranging from 15 to 5400 μg/L in leachates, and from 0.5 to 5.1 μg/L in the effluents after treatment.

BPA migration from BPA-based products

Being a plastic additive, BPA can be leached into water from plastic materials. Leached concentrations have been detected in Japan coming from waster plastics, specifically Polyvinyl Chloride (PVC) products, ranging from 1.98 to 139 μg/L. Another possible source of high BPA levels, it is suggested to came from the inner surface-coating of tanks migration, detecting 0.061-1.11 μg/g dry weight in liquid manure samples[8].

BPA in Surface water

As reported in **Table 2** the concentration of BPA in surface waters has been evaluated in several countries. J. Liu et Al 2021 reported that in several Chinese locations, from 2013 to 2018, the BPs total concentration has drastically increased (average 380 ng/L), while the contribution rate of BPA decreased from 55% in 2013 to 9.5% in 2016, suggesting a proceeding replacement of BPA with alternative BPs[11]. In **Fig.1** the BPA concentration are reported for the Pearl River during the years. In other countries the concentration of BPA in rivers was not found higher then 8 μg/L[8]. While in a comprehensive study carried out in almost 19 years (1996-2014) on North America and European surface waters, the BPA concentrations were below detection limit in many cases. In North America and Europe the 95th percentile of BPA concentration in fresh water was 0.30 μg/L, while for marine water the 95th percentile in North America and Europe were 0.024 μg/L and 0.15 μg/L, respectively. The apparently lack of upwards trend, considering the increasing BPA based products production, may suggest that the BPA concentration in the water environment is not strictly correlated with the production amount of these materials[9], but with its presence itself in the product and it can decrease to not detected or low levels due to the biodegradation process and the dilution effect. In fact, in

surface water the BPA concentration rapidly decrease (<100µg/L) by 3-5 days, depending on the water system, estimating a 96% loss in the content. Whereas BPA half-lifes (on surface waters) calculated are 3 days, 2.5 days, and 4 days taking into account effluent, receiving stream and downstream channel respectively[7].

Fig 1 Concentrations of BPA detected in the Perl river (China), during 2013-2017 expressed in ng/L. The reduction of the BPA concentration suggests a partially replacement of the compound[11].

Country	Surface water (*µg*/L)	Period
Spain	< 0.05 – 1.51	2000 - 2006
Japan	0.01 – 1.4	2000 - 2006
Japan	0.02 – 0.15	2000 - 2006
Japan	< 0.2 – 1.9	2000 - 2006
Japan	< 0.09	2000 - 2006
Japan	< 0.5 – 0.9	2000 - 2006
The Netherlands	< 0.012 – 0.33	2000 - 2006
United States	< 1 – 8	2000 - 2006
China	0.03 – 0.083	2000 - 2006
Germany	0.0005 – 0.014	2000 - 2006
The Netherlands	< 0.0088 – 1	2000 - 2006
Japan	< 0.005 -0.08	2000 - 2006
Japan	0.02 – 0.03	2000 - 2006
Germany	< 0.05 – 0.272	2000 - 2006
Germany	0.004 – 0.092	2000 - 2006
Germany	0.009 – 0.776	2000 - 2006
Germany	0.0005 – 0.41	2000 - 2006
North America, 50th%ile concentration	0.003 – 0.008	1996 - 2014
North America, 95th%ile concentration	0.23 – 0.44	1996 - 2014
Europe, 50th%ile concentration	0.02 – 0.045	1996 - 2014
Europe, 95th%ile concentration	0.026 – 0.36	1996 - 2014

Table 2 Concentrations on surface waters detected globally. The values have been combined considering the 2000-2006 study reported in Kang JH et Al[8] and Staples C et Al[9]. The values are in the 10^{-6}-10^{-9} order depending on the geographic area, with averagely higher values in polluted areas of Japan and Us.

Acute and Chronic Toxicity of BPA on aquatic organisms

Considering aquatic invertebrates, the median lethal concentration LC50 ranges from 0.96 to 2.70 mg/L. While in fish, BPA LC50s suggest less toxicity, having more elevated values 6.8-17.9 mg/L. An acute exposition of 25 mg/L induces 100% mortality in Zebrafish embryos. Otherwise, rainbow trout oocytes exposed to 100 mg/L for 3 h, and developed in clean and fresh water, have manifested a 30% of mortality. Studies on BPA toxicity in amphibians were carried out at different developmental stages. Western clawed frog gastrulae does not present significant mortality after 72h exposure at 3 mg/L. A 96 h exposure at 4.6 mg/L and 6.8 mg/L results in 42% and 100% mortality respectively, for African clawed frog[14].

In chronic exposure experiments, African clawed frog did not manifest observable mortality at a BPA concentration of 0.497 mg/L. While Western clawed frog exposed to 1.4 mg/L until post-metamorphosis had developed a reduced survivor rate of 66.7% at juvenile stage. Increasingly, juvenile frogs life-cycle BPA exposed, resulted more sensitive to the chemical (LC50 ranging 0.50-1.4 mg/L) compared to the embryos (LC50 3.0 mg/L)[14]. Therefore, BPA is acutely toxic at concentrations ranging from 1.34 to 17.9 mg/L and chronically lethal from 0.50 to 0.78 mg/L range in aquatic species.

BPA Mechanisms of action and Effects on aquatic organisms

According La Merrill et al. (2020)[15], BPA has nine out ten Key characteristic of endocrine-disrupting chemicals. Mechanisms of action of BPA have been highlighted taking into account experimental studies led both in humans and animals. However, in comparison to mammals, a lack of information occurs for non-mammalian vertebrates and invertebrates, even though some evidences suggest a similar BPA interaction[10]. These studies have revealed that BPA binds to endocrine receptors (ER), ERα and ERβ, as well as GPER, membrane ER, thyroid hormone receptor and androgen receptor AR[15]. Specific receptors through which BPA acts, seem different in base on the tissue, because its activity depends on the levels of different ER variants expressed. Consequently, BPA can induce elevated alterations on sex hormone levels, thyroid hormone levels , and growth hormone levels.

Considering specifically aquatic organisms, the founded main route of exposure in fish is inhalation through gills and not the oral one which commonly occurs in Humans. Comparing to ingestion route of exposure, the inhalation is not as efficient in the liver. Hence, more relevant estrogenic effects have been evaluated in fish, dietary exposed to waterborne BPA, including the induction of vitellogenin (vtg) in males. Both the BPA agonism and antagonism on ERs has been detected in fish and frogs. In the Xenopus system, BPA has an antagonistic activity on ER (approx. 0.8% tamoxifene activity), possibly causing no evidence of the postranscriptional enhancement of vtg synthesis. At a concentration of 10 and 100μg/L, waterborne BPA reduces the masculinization effect of trembolone showing antagonism on ARs in fathead minnow. Additionally, BPA can act as Thyroid Hormones (THs) agonist/antagonist, resulting in a block of spontaneous and induced TH metamorphosis *in vivo*, for Xenopus in larval stage[10].

BPA can cause developmental and reproductive effects, in both male and female axis. In males, BPA induces male hormonal alterations, testicular cells death, a decrement of sperm mobility and density (1.75 μg/L in brown trout) , and spermatogenesis inhibition (12 μg/L in fathead minnows). Female species exposed to BPA presents alteration in egg production, resulting in delayed ovulation or no

ovulation (2 and 5 μg/L respectively in fish) and abnormal sex ratio (22.8 μg/L BPA induced approx. 62% to 70% of females in Xenopus). Moreover BPA interacts with metabolism and immune function inducing oxidative stress in fish exposed at concentration of 1.75-10 μg/L for 2 hours[10].

As a multifunctional endocrine disruptor, aquatic organisms are subjected to the various effects that the chemical can induce considering the whole developmental and physiological status widely different among species in water environments, resulting in a difficult assessment of the mechanism and the effects of action. In **Table 3** have been summarize some of the principal endocrine- distruptive effects reported in literature.

Species	BPA concentration and exposure period	Endocrine - disruptive effect
Vertebrates		
Fish		
Teleost fish (*Coris julis*)	80,000 μM/L for 2 weeks	Induction of binding levels of somatostatin receptor subtype$_2$, but decrease in levels of subtype$_5$
Goldfish (*Carrassius auratus*)	10 μM for 6 hours	Suppression of tartrate-resistant acid phosphatase and alkaline phosphatase
	1 μM 8 days	Reduction of plasma calcium level and calcitonin secretion/ Vitellogenin induction
Zebrafish (*Danio rerio*)	1000 μM/L for 3 weeks	Vitellogenin induction
	10 μM for 72 hours after fertilization	Upregulation of brain aromatase isoform (P450aromB) mRNA
	10 and 20 μM for 72 hours after fertilization	Induction of mortality
	20 μM for 72 hours after fertilization	Increase in the incidence of curved tails
Swordtail (*Xiphophorus helleri*)	2000 μg/L for 3 days	Vitellogenin mRNA expression
	2000 μg/L for 60 days	Induction of apoptosis in fish testis cells
Fathead minnow (*Pimephales promelas*)	119 – 205 μg/L for 2 weeks	Vitellogenin induction
	640 and 1280 μg/L for 43 days and 160 μg/L for 71 days	Vitellogenin induction
	640 and 1280 μg/L for 164 days	Inhibition of gonadal growth in male and female / reduction of egg production and hatchability in the F1 generation
	640 and 1280 μg/L for 71 and 164 days	Inhibition of somatic growth in male
	12 - 1280 μg/L for 164 days	Inhibition of spermatogenesis
Medaka (*Oryzias latipes*)	200 μg/L for 15 days	Embryonic deformity
	200 μg/L for 9 days	Induction of testis-ova
	1820 μg/L for 60 days	Induction of testis-ova
	10 μg/L for 100 days after hatch	Induction of testis-ova
	837 - 3120 μg/L for 3 weeks	Induction of testis-ova Vitellogenin induction
	10 μg/L for 4 weeks and 100 μg/L for 2 weeks	Induction of female specific proteins
	1000 μg/L for 5 weeks	Vitellogenin induction

	10 μg/L for 2 weeks	Reduction in the number of eggs and hatchings
	100 - 500 μg/L for 6 days	Induction of choriogenin L mRNA expression
	500 μg/L for 6 days	Induction of choriogenin H mRNA expression
Brown trout (*Salmo trutta f.fario*)	1.75 – 2.4 μg/L for 2 months	Reduction of sperm density, motility and swimming velocity
	5 μg/L for 2 months	Male: Reduction of semen mass Female: No ovulation
	1.75 – 5 μg/L for 2 months	Reduction of sperm motility rate and swimming velocity

Table 3 Sum of the principal BPA effects evaluated in laboratory experiments on vertebrates reported in literature[8,10,11,14]. The data have been divided for species, concentration/exposure and effects.

In **Fig 2**, it is reported a graphically representation of some BPA concentration/effects studied in laboratory conditions for aquatic vertebrates, compared of some notice concentrations found in water environments presented in litterature[8,10,11,12]. The concentrations in particular in polluted areas of Japan and US are highly above the estimated ranged concentration for the effects occurrence.

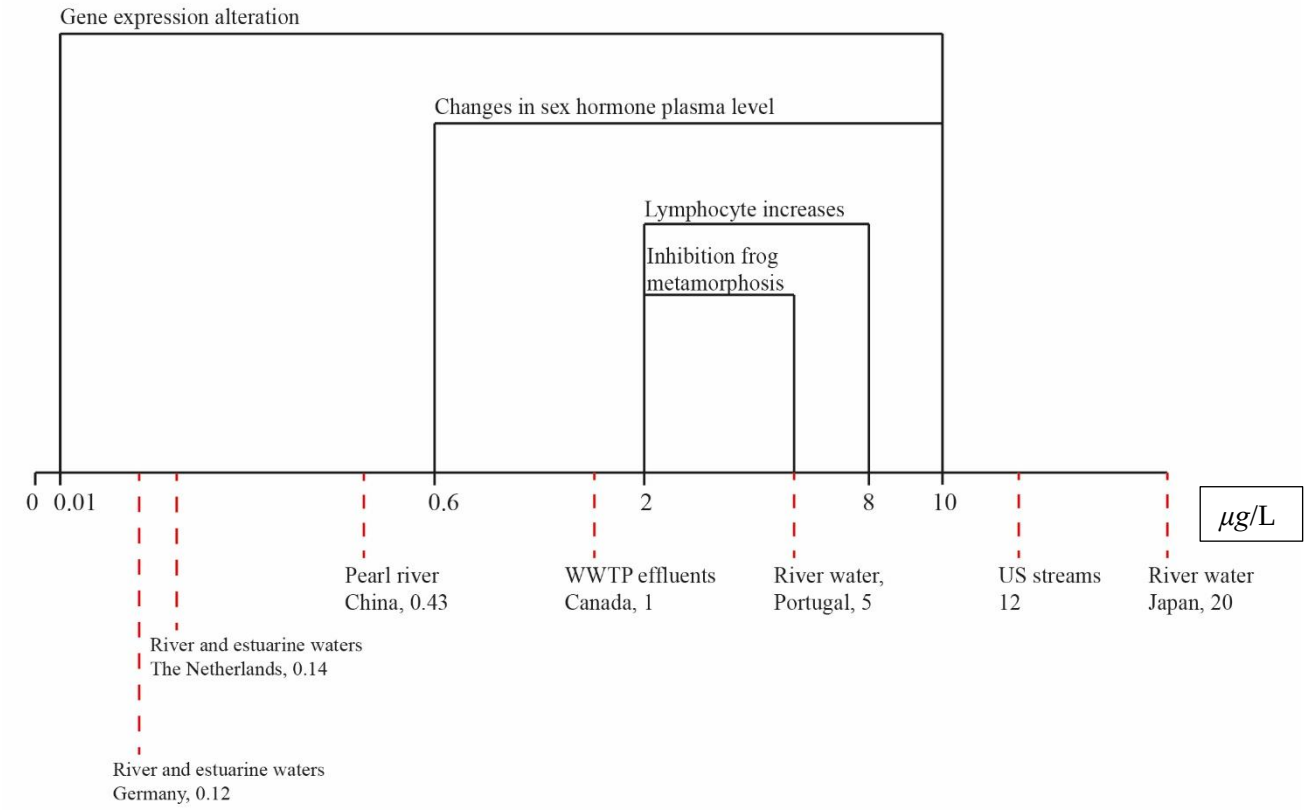


Fig. 2 Graphically partial representation of effects/concentrations. On the top are reported the ranged values for the appearance of effects in Laboratory studies on vertebrates, below the BPA concentration found in water environment globally reported. All the concentrations are expressed in µg/L.

Conclusions

In the present work, the contamination routes, and the water environmental fate of BPA have been discussed, as well as its endocrine-disruptive effects on aquatic organisms, specifically vertebrates.

Effluents from wastewater are the primary source of water contamination, however BPA can be biodegraded or metabolized by many aquatic organisms, resulting in a detoxification of the chemical.

Different studies reported endocrine-disruptive effects in both vertebrates and invertebrates. In fish the main effects are the vitellogenin induction and reproductive abnormalities, as well as feminization, and high mortality in several aquatic species.

Overall, BPA can be considered a chemical of potential concern for the aquatic ecosystem, considering that the concentration can exceed the limit for the effects occurrence. Additionally, laboratory studies cannot take into account the life-long exposure to BPA of species, being the chemical continually released in the environment. However the partially lack of information for the aquatic organisms and the experimental designs reported in literature are not sufficient to assess the capacity of the BPA impact in the environment.

Further more comprehensive studies can will certainly help to reach implemented regulatory implications, already started to be developed.

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