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Plastic originated bisphenol A: A potential endocrine disruptor for fish reproduction

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Abstract
Bisphenol A (BPA) is an organic synthetic compound, abundantly used worldwide for the production of polycarbonate plastic and epoxy resins. It is an endocrine disruptor that can mimic estradiol by binding to and activating the same estrogen receptor as the natural hormone. It is not only hazardous to human population but also found to be acutely toxic to aquatic organisms in the range 1000–10,000µg/L for freshwater and marine species. In 2010, the U.S. Environmental Protection Agency reported that over one million pounds of BPA are released into the environment annually. BPA can enter the environment either directly from chemical, plastics, coat and staining manufacturers, from paper or material recycling companies, or indirectly leaching from plastic, paper and metal waste in landfills or ocean-borne plastic trash. BPA in anaerobic or semi aerobic sediment environments can persist for a prolonged period of time, leading to higher BPA levels in sediments than in surface water. Interestingly BPA can persist longer in seawater than in fresh water without any degradation (about 30 day) and the possibility of BPA contamination is higher marine than freshwater organisms. BPA possess endocrine disruption in different types of fishes by vitellogenin induction, upregulation of brain aromatase isoform mRNA, reduction of total sperm counts and induction of testis ova and poor somatic growth of male. It was also observed that environmentally relevant low level of BPA increased the expression of genes related to reproduction axis such as kiss1, kiss1r, Gnrh3, LH β, FSHβ, and ERα and dmrt1. BPA is also assumed to involve THR, in increasing the rate of early embryonic development in several fish species. Further, BPA exhibit very high estrogenic activity on the cyp19a1b gene, and increase concentration of vitellogenin in swim-up fry of freshwater fish species. Keeping in view of these, the present study is aimed to elucidate a baseline information about contamination routes of BPA in the aquatic environment and its endocrine-disruptive effects on aquatic organisms.

Keywords: Bisphenol A, endocrine disruption, reproduction, fish

1. Introduction
Bisphenol A (BPA) is an anthropogenic organic compound, tremendously used as a monomer for the production of polycarbonate plastic and epoxy resins (Staples *et al*., 1998) [37]. It is used for the production of transparent plastic bottles, plastic toys and a constituent of dental sealant (Suzuki *et al.*, 2000) [40]. With the constant demand for plastic products, the worldwide production of BPA has also increased in many folds. Out of all the xenobiotic compound registered for human use purpose by Environmental protection act, BPA (CAS Registry No. 80-05-7) has earned the highest amount of interest as well as controversy during the last decade (Crain *et al*., 2007) [6]. It is a xenoestrogen compound and mimics the structure of estrogen hence it is considered as a potential endocrine disrupter (Goodman *et al.*, 2006) [13]. BPA has increased human health concern to a large extent, due to its ubiquitous existence in the environment (Huang *et al*., 2012) [17]. This compound is detected in the urine of 95% of adults in the USA and Asia (Calafat *et al.*, 2005; Zhang *et al.*, 2011) [3, 48]. Discouraging the use of BPA, now-a-days some regulatory bodies such as the European Commission, the US Food and Drug Administration, have banned the use of BPA in baby bottles (Qiu, 2016) [32]. BPA is found to be acutely toxic to aquatic organisms in the range 1000–10,000µg/L for freshwater and marine species (Alexander *et al.*, 1988). In fishes, BPA exposure can lead to detrimental effect particularly during ontogenesis period (Crain *et al*., 2007) [6]. Its concentration is lower in stream water (max upto 21 mg/L) (Staples *et al.*, 2002) [38], but it can reach concentrations as high as 17,200 mg/L in landfill leachates (Alexander *et al.*, 1998).

2. Mode of contamination in aquatic ecosystem

Generally, the lower concentration of BPA found to be present in domestic sewage effluent than industrial sewage effluent (Fuerhacker *et al*., 2000) [11]. It has been observed that wastewaters from paper plants contain very high concentration of BPA, therefore, complete removal of BPA from the effluents of the plastic and paper production plant is not feasible (Rigol *et al.*, 2002; Quinn *et al*., 2003) [34, 32]. Furhacker *et al*. (2000) claimed that during wastewater treatment more than 90% of BPA concentration can be curtailed. However, several other studies suggested that the elimination rate of BPA in treatment plants varies from 37 to 94% (Lee and Peart, 2000; Fuerhacker *et al*., 2003) [29, 11].

Landfill leachates are the major point source of BPA contamination. By the hydrolysis of plastic in landfill leachates, BPA is released. Therefore, a very high concentration of BPA was reported from waste landfill leachates ranging from 1.3 to 17,200 µg/L with an average of 269 µg/L (Yamamoto *et al*., 2001) [46]. On note, the level of BPA in effluent is considerably lower than the leachates. As an instance, Yamada *et al*. (1999) [45] commented that the levels of BPA in four landfill leachates ranged from 15 to 5400 µg/L, whereas it ranged from 0.5 to 5.1 µg/L in the treated effluents. Its already proclaimed that marine debris washed ashore contain 60-80% plastic in volume, increasing the risk of further contamination of such anthropogenic chemicals into aquatic environment. Although in microbe-rich aerobic environment BPA degrades easily, it further creates a non-point source of contamination threat to the water body (Dorn *et al*., 1987) [7]. Crain *et al*, (2007) [6] stated that the comparatively lesser concentration of BPA found in stream waters (21µg/L) than that of the BPA concentration of landfill leachates (17 mg/ L). However, the river surface water contains very low concentration of BPA than that of the sediments (Kang, 2007) [22].

3. Fate of BPA in the aquatic environment

Photodegradation and biodegradation are two potential phenomena responsible for the degradation of this potential toxicant in the aquatic ecosystem. Photodegradation is the primary non-biological pathway responsible for the degradation of BPA in an aquatic environment. Chin *et al*., (2004) [5] reported that dry organic matter such as humic acid and fluvic acid found in the surface water helps in absorbing the irradiation thus generating reactive oxidant species (ROS) and some non-ROS intermediates. Since iron can yield ROS by reacting with hydrogen peroxides, complexes of iron with ROS or dry organic matter, for instance, Fe(III)-OH and Fe(III)-humic acid complexes, has found to impel further photodegradation of BPA (Zhou *et al*., 2004) [49]. However, biodegradation is a more potential phenomenon prevailing in the aquatic ecosystem for degradation of BPA. According to Kang and Kondo. (2002) [20], several bacteria species are responsible for degrading BPA in an aquatic environment and shortening its half-life to less than 5 days. Kang and Kondo, (2002) [20] stated that the efficiency of bacterial degradation can vary from (18-91%) depending on the bacterial species, however, two bacterial species such as (Pseudomonas strain and streptomyces species strain) has been isolated from river water with high BPA biodegradability (more than 90% over 10 days). The extent of biodegradation is mainly dependent upon bacterial population and abiotic factors such as temperature and oxygen. According to Kang and Kondo (2002a) [21]. BPA in river samples was found to be readily biodegraded under aerobic conditions (>90%), while in anaerobic conditions even after 10 days period no depreciation of BPA level was found. Along with the bacteria several planktons are reported for having the capacity for biodegradation and removal of estrogenic activity of BPA such as *Chlorellafuscavar vacuolate* (Hirooka *et al.*, 2005) [15].

Table 1: Endocrine disruption effect of BPA in different fish

Species	BPA exposure period	Endocrine-disrupting effect	Reference
Gold fish (*Carassius auratus*)	1 µmol for 8 day	Vitellogenin induction	Suzuki *et al.* (2003) [40]
Sword tail (*Xiphophorus helleri*)	2000 µg/l for 3 day 2000 µg/l for 60 days	Vitellogenin mRNA expression Induction of apoptosis in Fish testis cell	Kwak *et al.* (2001) [24]
Fathead minnow *(pimephales pomelas)*	119-205 µg/l for 71 days	Vitellogenin induction	Sohoni *et al.* (2001) [36]
Zebra fish (*Danio rerio)* Rainbow trout (*Onchorynchus mykiss*)	1000 µmol for 3 weeks	Vitellogenin induction	Van den Belt *et al.* (2003)
Guppies (*Poecilia reticulata*)	274 and 579 µg/l	Reduction of total sperm count	Haubruge *et al.* (2000) [14]
Brown trout	2.4 µg/l and 5 µg/l for two weeks	Delayed ovulation at 2.4 µg/l and elimination of ovulation at 5 microgram/l	Lahnsteiner *et al.* (2005) [27]
Medaka (*Oryzias latipes*)	1820 µg/l for 60 days	Induction of testis –ova and poor somatic growth of male	Yokota *et al.* (2000) [47]
Catla (*Catla catla)*	10, 100 and 1000 µg/l for 2 weeks	Increase in serum stress biomarker responses such as AST and ALT in all the concentrations. Concentration independent increase in serum creatinine level resulting kidney dysfunction Only 1000 µg/l induced significant vitellogenin expression	Faheem *et al*. (2019) [9]
Medaka	10 µg/l for 100 day after hatch	Induction of testes ova	Metcalfe *et al.* (2001) [10]
Sword tail	2 mg/l and 10 mg/l for short term (3 day) and long term (6 day)	Short term exposure induced vitellogenin mRNA expression And long-term exposure affected the growth	Kwak *et al*. (2001) [25]
Medaka	837-3120 µg/l for 3 weeks	Induction of testes ova	Kang *et al*. (2002) [21]
Medaka	1000 µg/l for 5 weeks	vitellogenin induction	Tabeta *et al*. (2004) [41]
zebrafish	5 and 50 µg/l for 21 days	Adverse effect on F1 generation GSI and egg production decreased	Ji *et al.* (2013) [18]

		Delayed hatching and decrease in hatching rate	
Medaka	10 µg/l	Reduction in number of eggs and hatching	Shioda *et al*. (2000) [35]
Turbot (*Scopthalmus maximus*)	59 µg/l for 3 weeks	Reduction of testosterone and 11-keto testo sterone,	Labadie and Budzinski, 2006 [26]
Zebra fish	10 µg/l for 72 hrs after fertilization	Brain aromatase isoform (p450 aromB) mRNA	Kishida *et al*. (2001) [23]

4. Mechanism of action

It was observed that environmentally relevant low level of BPA, affects the HPG axis and upregulates the expression of genes associated with reproduction axis such as kiss1, kiss1r, GnRH3, LHα, FSHβ and ERα (Qui *et al.,* 2015) and reduces expression of gene dmrt1 in male fish, which gene is responsible for male sex determination (Laing *et al.,* 2016) [28]. kiss1 is considered as the upstream regulator of GnRH neurons and it is observed that by exposure of BPA the kiss1 gene expression is upregulated along with the GnRH levels (Elizur, 2019) [8]. These cyp19a and cyp19b genes encode the cyt p-450 aromatase enzyme, which enzyme is responsible for the conversion of testosterone to estradiol and In various studies it has been reported that in BPA exposed fish, the upregulation of cyp19a (ovarian type) and cyp19b (brain type) genes has been seen (Sohoni *et al*., 2001; Lee *et al*., 2006) [36]. This synthetic xenoestrogen is further reported to interfere with the normal oestrogen signalling pathway by upregulating the expression of both ERα and ERβ in fishes (Qui *et al*., 2016). Along with that, it has been reported that BPA exposure also escalates FSH and LH hormone concentration in fish (Qui *et al.,* 2016). FSH and LH possess critical roles in Gonadal development of different teleost fishes (Prat *et al.,* 1996) [31]. Not only BPA interferes with the hormones of the Hypothalamic-Pituitary-Gonadal axis, but also it alters the thyroid hormone function during the period of ontogenesis. It is observed that BPA hasten up the embryonic development of fishes by acting as a thyroid hormone antagonistic (Castro *et al.,* 2013) [4]. It is also reported that even at environmentally relevant concentration BPA down-regulates the expression of the dmnt1 which is involved in DNA methylation during ontogenesis, indicating the epigenetic action of this chemical (Laing *et al*., 2016) [28]. So, there by upregulating and downregulating so many different genes, BPA causes the endocrine disruption of fishes.

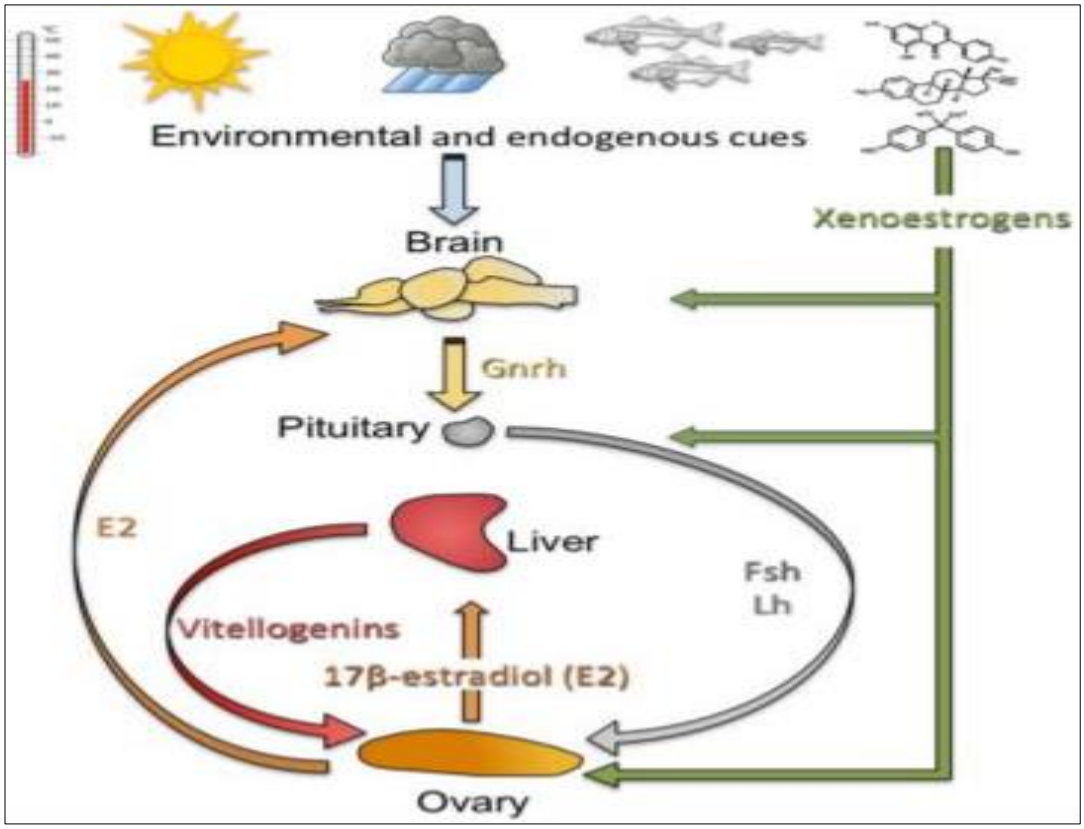

Fig 1: Model for the pathway of vitellogenesis regulation in teleost fish via the brain-pituitary-gonad (BPG) axis (Sullivan and yilmaz, 2018).

5. Metabolism and Bioaccumulation potential of BPA in fish

Detoxification of xenobiotic compounds in the fish body is dependent on UGT which a critical enzyme essential for this process (Tephly and Burchell, 1990) [42]. Basically in BPA exposed fishes, two types of BPA metabolites such as BPA sulfate and BPA glucuronide were identified, bt the later one is considered as a major metabolite as it the concentration of the later one in plasma is reported to be 100- 22600 times higher than the former one (Lindholst *et al*., 2003) [30]. Detoxification process is also linked with the bioaccumulation process. It is reported that when the detoxification pathway is saturated, excessive BPA leads to bioaccumulation (Upmeier *et al*., 2000) [43]. Kang (2007) [21] stated that the bioaccumulation factor in freshwater fish can range from 5 to 68. However, during the initial phases of the life cycle, the fishes are more prone to higher bioaccumulation threat (Honkanen *et al*., 2004) [16]. Although is reported that sea food

of supermarket is reported to be containing a potentially threatening amount of BPA with a range of (13-213 µg/ kg wet weight), indicating the higher bioaccumulation potential of BPA in the marine organisms (Basheer *et al*., 2004) [2]. This might be probably due to the reason that the persistence period of undegraded BPA in marine water can be as high as 30 days unlike the freshwater (Kang, 2007) [21].

6. Conclusion and future research prospects

The anthropogenic endocrine disruptive chemical BPA is used abundantly in the plastic production industry. Although a lot of different alternatives were tried and tested, nothing can be considered as the safe alternative of BPA as all the alternatives are having endocrine disruptive effect to various extents. Further, the bioaccumulation potential of BPA varies from species to species and this bioaccumulation elicits higher endocrine disruptive effect in fishes and organisms. Interestingly, very few existing literatures explained the effect of bioaccumulation in the endocrine system. Also, most of the studies have been conducted using BPA concentration not in relevance to the range of environmentally available concentration. Further, a research gap exists in regards to the effect of BPA in organisms of the marine environment, as most of the study models are based on freshwater organisms. Future studies can be directed keeping in view for the production of a safer alternative of BPA and more detailed study should take place for marine fishes keeping in view, the environmentally relevant concentration and the bioaccumulation effects.

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