Insight Into The Aquatic Toxicity And Ecological Risk of Bisphenol B, And Comparison With That of Bisphenol A

Yue Wang
Nanjing University of Science and Technology
Tianyi Zhao
Nanjing University of Science and Technology
Xianhai Yang
Nanjing University of Science and Technology
Huihui Liu (hhliu@njust.edu.cn)
Nanjing University of Science and Technology https://orcid.org/0000-0003-2400-0286

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Abstract

As one of the alternatives of 2,2-bis(4-hydroxyphenyl)propane (bisphenol A, BPA), 2,2-bis(4-hydroxyphenyl)butane (bisphenol B, BPB) has not gained sufficient concerns so far, due to the limited concentration and toxicity data available. In this study, the acute toxicity of BPB to three aquatic organisms, i.e., *Tetradesmus obliquus*, *Daphnia magna* and *Danio rerio*, was investigated, and it showed that *Daphnia magna* was the most sensitive organism with the half effective concentration (EC_{50}) of 3.93 mg/L. Thereout, the screened *Daphnia magna* was exposed to BPB for 21 days to explore the chronic toxicity. Results indicated that BPB restricted the body length of parent *Daphnia magna* and reduced the total number of broods and neonates. The no-observed effect concentration of BPB to *Daphnia magna* was as low as 0.01 mg/L, which was two orders of magnitude lower than that reported 0.86–5.00 mg/L of BPA. Furthermore, the ecological risk of BPB was quantitatively assessed using the risk quotient (*RQ*) method. Obviously, although the environmental concentrations and detectable rate of BPB were much lower than that of BPA, its ecological risk was not necessarily lower. Hence, BPB should not be ignored in the future environmental monitoring and management.

Introduction

Over the years, BPA has been widely used in infant feeding bottles, cooking utensils, food cans, and medical devices (Pelch et al. 2019). Numerous studies have shown that BPA had obvious endocrine disrupting effect on human and animals, thus some governments have restricted its production and usage (Liu et al. 2021, Pelch et al. 2019, Usman &Ahmad 2016). As a result, some other bisphenol analogues, such as BPB, 4,4'-methylenediphenol (bisphenol F, BPF) and 4-hydroxyphenyl sulfone (bisphenol S, BPS), have been mass-produced for wide applications (Liu et al. 2021, Usman &Ahmad 2016). Among them, BPB had the most similar structure to BPA, and it was one of the most frequently studied chemical in the 2019 PubMed search (Pelch et al. 2019). Chang et al. (2014) and Zhou et al. (2020)) reported that BPB was less biodegradable than BPA in surface water and river sediment; Chen et al. (2002)) proved that BPB displayed a much higher acute toxicity to *Daphnia magna* than BPA. Moreover, BPB has stronger estrogen activity and anti-androgen activity than BPA, especially it was identified as a potent human pregnane X receptor agonist (Kitamura et al. 2005). Therefore, given the higher aquatic toxicity and endocrine disrupting property, BPB should have deserved more attention than BPA.

BPB has always been detected in human urine and serum (Asimakopoulos et al. 2016, Liang et al. 2020), and the main routes of BPB entering human body were diet and water drinking. Canned foodstuffs have the highest detection of BPB. For instance, BPB was reported to occur in the 66.7% of canned meat from Oporto Metropolitan Area (Cunha et al. 2020), the 21% of canned tomato from Italy (Grumetto et al. 2008), and the 50% of canned beverages from Portugal (Cunha et al. 2011). Through a survey for the samples from drinking water treatment plants across China, BPB was detected with 0–3.2 ng/L in drinking water and 0–14.3 ng/L in source water (Wang et al. 2020, Zhang et al. 2019). However, in the natural environment, BPB has rarely been reported. Especially in the surface waters, BPB was measured

in only five samples from China, and the concentrations ranged from 0.17–46 ng/L, which were much lower than that of BPA (Shan et al. 2014, Yan et al. 2017, Zhao et al. 2019). It was noted that BPB had high detection frequencies in wastewater. Even after a series of treatment processes, it can still be detected in the effluent, which would allow it to enter the natural waters (Cesen et al. 2019, Qian et al. 2021).

Due to the occurrence of BPB in natural waters, it is necessary to concern its potential hazard to aquatic organisms. *Daphnia magna* and *Danio rerio* are the common model organisms for the aquatic toxicity. BPB exhibited a higher acute toxicity to *Daphnia magna* than BPA, with an order of magnitude lower 50% effective concentration (EC_{50}) values (Chen et al. 2002). BPB could alter the gene expression on the HPG axis of zebrafish, and disrupt their hormone balance, and thereby impairing their reproduction (Yang et al. 2017). Furthermore, comparing with BPA, BPB has a larger octanol-water partition coefficient (*K*ow) based on EPI Suite 4.11, which makes BPB much easier to be adsorbed and accumulate in organisms. Moreover, Ike et al. (2006)) and Zhou et al. (2020)) have showed whether under the aerobic condition or anaerobic condition, BPB was more resistant to biodegrade than BPA and had longer half-life in surface water. In view of the occurrence of BPB in natural waters and its obvious toxicity to aquatic organisms, it is significant to get a full assessment for the ecologic risk of BPB, and then reconsider its safety as BPA replacement.

In the present study, the acute toxicity of BPB to three aquatic organisms, i.e., *Tetradesmus obliquus* (*T. obliquus*), *Daphnia magna* (*D. magna*) and *Danio rerio* were researched; thereout, the most sensitive organism (*D. magna*) was screened. Furthermore, the 21-day chronic toxicity of BPB to *Daphnia magna* was explored, by measuring a series of reproduction parameters. Finally, data on the concentrations of BPB in natural waters were collected from literatures, and then the ecological risk of BPB was evaluated using the risk quotient method. Meanwhile, the aquatic toxicity and ecological risk of BPB was compared with those of BPA, which emphasized the importance of paying attention to the BPB in aquatic environment.

Materials And Methods

Chemicals and reagents

Bisphenol B (BPB, > 98% purity) was purchased from Aladdin (Shanghai, China). Dimethyl sulfoxide (DMSO), used as the solvent of BPB, was obtained from J&K Scientific Ltd. (Shanghai, China). The culture medium for alga was purchased from Hope Bio-Technology Co., Ltd. (Qingdao, China), and its composition was presented in Table S1 (Supporting Information, SI). The culture medium for *D. magna* was prepared in our laboratory, and its composition was presented in Table S2. At the start and end of test, solutions were analyzed by HPLC (Agilent 1260 Infinity II, Agilent Technologic, China) and the measured concentrations were within ± 20% of nominal. Thus, all given concentrations in this paper were nominal concentrations. The three model organisms used in this study, i.e., *T. obliquus*, *D. magna* and

Danio rerio, were all obtained from Institute of Hydrobiology, Chinese Academy of Science (Wuhan, China).

Acute toxicity test of bisphenol B to T. obliquus

T. obliquus were incubated according to the standard protocols in OECD 201 (OECD 2011). All the flasks and culture medium (Table S1) were sterilized by autoclaving under 120°C for 15 min. The algae were maintained in an incubator at 23 ± 2°C and at 16h: 8h light: dark cycle (illumination 4000 lux). In the algal growth inhibition test, the initial cell density of algae was (2–5) × 10^3 cells/mL. Based on the results from pre-test, *T. obliquus* were exposed to different concentrations of BPB at the range of 2–15 mg/L. After 96 hours, the optical density (*OD*) of algal solution at the wavelength of 650 nm was measured using an ultraviolet spectrophotometer (Unico, model UV 2100). The cell numbers were calculated according to the relationship between *OD* values and the cell numbers. Comparing with the control group, the inhibition rate of algal growth for each group was obtained, and then the EC_{50} value was calculated.

Acute toxicity test of bisphenol B to D. magna

D. magna was cultured according to the standard protocols in OECD 202 (OECD 2004). The temperature, pH and hardness of culture medium (Table S2) were 20 ± 2°C, 7.2–7.8 and 140–250 mg/L (expressed as $CaCO_3$), respectively. The culture medium was aerated vigorously in advance and renewed every other day. *D. magna* were maintained at nature light–dark cycle and fed once daily with *T. obliquus* at a concentration of (1–5) × 10^5 cells/mL. Before acute toxicity test, $K_2Cr_2O_7$ was used to verify the sensitivity of *D. magna*. Based on pre-test, ten neonates (6–24 hours old) were exposed to the 50 mL BPB solutions with the concentrations of 1–12 mg/L. During the test, the *D. magna* was not fed and the test solution was not renewed since the BPB is stable. After 48 h, the *D. magna* those failed to swim within 15 s of agitation by slightly shaking tubes, were considered to be immobilized. The immobility of each group was recorded, and then the EC_{50} value was calculated.

Acute toxicity test of bisphenol B to Danio rerio

Danio rerio was cultured according to the standard protocols in OECD 203 (OECD 2019). The wild-type *Danio rerio* (AB strain; total length: 1.96 ± 0.135 cm; wet weight: 0.134 ± 0.0159 g) were acclimatized for two weeks in laboratory before experiments. The fish were cultured in a recirculating aquaculture system under 25 ± 1°C with nature light–dark cycle. The dissolved oxygen level was kept at 90 ± 10% of air saturation value by continuous aeration. About a half of culture medium was renewed once two days. The fish were fed twice daily with *Artemia saline* and three times per week with neonates of *D. magna*. The acute toxicity test for zebrafish was carried out in a semi-static system. Eight individuals were randomly transferred into 1.5 L BPB solution with the concentrations of 3.0–5.3 mg/L. During exposure, no food was added and the solution was not renewed. The dead fish were removed immediately, and the number of dead fish were recorded after 96 hours exposure. The mortality for each group were recorded, and then the 50% lethal concentration (LC_{50}) value was calculated.

Chronic toxicity test of bisphenol B to D. magna

The chronic toxicity of BPB to *D. magna* was performed according to the standard protocols in OECD 211 (OECD 2012). The BPB concentrations were set as 0.01, 0.02, 0.04, 0.08 and 0.10 mg/L, which ensured the *D. magna* did not die during the 21-day exposure, and evident toxic effect could be observed. Each group was performed in ten replicates. The neonatal *D. magna* (6–24 hours old) was transferred to 50 mL test solution and fed daily with *T. obliquus*. To keep the BPB concentrations stable, the test solutions were renewed every other day.

During 21-day exposure, the survival and fecundity of parent *D. magna* were monitored and the new neonates were counted and removed daily. The chronic toxicity of BPB on *D. magna* was determined by the following indicators: the time of the first brood, the number of neonates in the first brood, the number of broods and the total neonates for the whole period. Meanwhile, the body length of parent *D. magna* was measured using an optical microscope (OLYMPUS). Additionally, a comprehensive index, i.e., the intrinsic rate of population growth (r_m), was calculated using the above reproductive parameters by the Lotka's formula (Lotka 1913).

Risk characterization

The risk quotient (*RQ*) method, proposed by European technical guidance documents, was used to assess the impact of BPB and BPA to aquatic environment. The *RQ* could be calculated as follow:

$$RQ = \frac{MEC}{PNEC}$$

1

where *MEC* represents the measured environmental concentration; *PNEC* represents the predicted no-effect concentration, which was calculated by:

$$PNEC = \frac{NOEC}{AF}$$

2

where the *NOEC* is the no-observed effect concentration in chronic toxicity. *AF* is the assessment factor, which was taken as 100 in this study based on standard protocols (European Commission 2003).

Even though the original European technical guidance document classified the risk into two grades, which were high risk and low risk at the case of $RQ > 1$ and $RQ < 1$, respectively. In this study, in order to assess the potential hazard of BPB more strictly, the risk was divided as three grades. When $RQ > 1$, the risk was considered as high; When $0.1 < RQ < 1$, the risk was considered as medium; When $RQ < 0.1$, the risk was considered as low (Zhao et al. 2019).

Statistics

In this study, all the acute toxicity tests for three organisms were performed in triplicate, while the chronic toxicity test for *D. magna* was performed in decuplicate. Moreover, for each bioassay, a blank control and a solvent control were all included, and the concentration of solvent DMSO was limited within 0.05% (v/v). All data were expressed as mean ± standard deviation. The dose-response curves were fitted with GraphPad Prism 9, and then the EC_{50} or LC_{50} values with the 95% confidence intervals were obtained. Significance analysis was performed in OriginPro 8 software (OriginLab). Datasets obtained from chronic toxicity tests were analyzed by hypothesis testing. The normality of data was tested using the Shapiro–Wilk's test followed by homogeneity of variance tested using Bartlett's test, based on the results of which, suitable test (such as Dunnett's test and Kruskal–Wallis test) was chose to test the differences. The *p* value less than 0.05 was considered as statistically significant.

Results And Discussion

Acute toxicity of bisphenol B

In the test of acute toxicity, comparing with the control group, the solvent control groups did not cause significant effect on the growth or survival of organisms, indicating that 0.05% DMSO was negligible in the exposure groups. Significant dose-response relationships between BPB concentrations and the inhibition rate of algal growth, the immobilization of *D. magna* or the mortality of *Danio rerio* were observed (Fig. 1). The resulting EC_{50} (or LC_{50}) values with the 95% confidence intervals were listed in Table 1. For *T. obliquus*, the 96 h EC_{50} value was 12.3 mg/L. Czarny et al. (2021)) studied the toxic effect of BPB on two cyanobacteria, and found that the 7–14 d EC_{50} were 36.5–40.3 mg/L and 44.2–87.3 mg/L. Apparently, the green algae were more sensitive to BPB than cyanobacteria. For *D. magna*, the 48 h EC_{50} value was 3.93 mg/L. This was in good agreement with the result reported by Chen et al., who found that the 48 h EC_{50} value of BPB to *D. magna* was 5.50 mg/L (Chen et al. 2002). For *Danio rerio*, the 96 h LC_{50} value was 4.13 mg/L. Unfortunately, to our knowledge, there are no other studies on the acute toxicity of BPB to zebrafish.

Table 1
Half effective (or lethal) concentrations of BPB to three organisms in the acute toxicity.

Species	Endpoints	Effect value (mg/L)	95% Confidence interval (mg/L)
Tetradesmus obliquus	96 h EC_{50}	12.3	11.7–13.1
Daphnia magna	48 h EC_{50}	3.93	3.53–4.37
Danio rerio	96 h LC_{50}	4.13	4.07–4.19

According to the criteria from "the globally harmonized system of classification and labelling of chemicals (GHS)" (GHS 2019), chemicals with 10 mg/L < EC_{50} (or LC_{50}) < 100 mg/L were considered as class III toxic substances; while chemicals with EC_{50} (or LC_{50}) < 10 mg/L were considered as class II toxic

substances. Thereout, *D. magna* and *Danio rerio* seem to be more vulnerable to BPB than *T. obliquus*. Obviously, there was an order of magnitude difference in EC_{50} (or LC_{50}) value between *T. obliquus* and other two organisms, indicating that BPB posed little risk to the primary trophic organisms. Among the three species, *D. magna* was the most sensitive species to BPB, followed by *Danio rerio* and *T. obliquus*. *D. magna* naturally occurs in the lentic freshwater system, and it is often a standard test organism for the aquatic toxicity of chemicals (Nagato et al. 2016). In order to explore the environmental risk of BPB, it is crucial to further study the chronic toxicity of BPB to *D. magna*, under a low dose for a long-term exposure.

Due to the ubiquity in environment and the well-known endocrine disrupting effect of BPA, we collected the data on the aquatic toxicity of BPA from previous literatures. The acute toxicity data were presented in Table S3. As shown, the EC_{50} values of BPA to algae ranged from 8.65 to 63.5 mg/L (Li et al. 2009, Tišler et al. 2016, Zhang et al. 2014), and those to *D. magna* ranged from 7.30 to 14.4 mg/L (Alexander et al. 1988, Brennan et al. 2006, Hirano et al. 2004, Ike et al. 2002, Liu et al. 2019, Mansilha et al. 2013, Nagato et al. 2016). In the case of zebrafish, the range of LC_{50} values was 8.04–12.8 mg/L (Blanc et al. 2019, Chan &Chan 2012, Corrales et al. 2017, Moreman et al. 2017, Mu et al. 2018). By contrast, BPB was more hazardous to aquatic organisms than BPA, even though it has a lower detectable rate in the environment. In addition, BPB has a larger hydrophobicity than BPA, which means that it has higher bioaccumulation in the body of organisms (Chen et al. 2016). All of these further demonstrate that more attention should be paid to BPB in water in the future.

Chronic toxicity of bisphenol B to D. magna

Although the detectable rate and the concentration of BPB in environmental media are quite low, the aquatic organisms live in water for a long time and they are always inevitably exposed to BPB. In this study, the most sensitive organism, i.e., *D. magna*, was employed to evaluate the chronic toxicity of BPB, through a series of parameters relating to reproductive ability, which were the time of the first brood, the number of neonates in the first brood, the number of broods and the total neonates in the 21-day exposure.

As shown from Fig. 2A, almost all of females produced the first brood on the 7th–11th day. Relative to the control, no visible change in the first reproduction time was observed in all the treatments even at concentration up to 0.10 mg/L. The number of the first brood progeny exhibited a somewhat decreasing trend with increasing BPB concentration (Fig. 2B). However, no statistically significant differences between the treatments and the control were found. This may be because the exposure time was too short, and the slight changes in the two indicators were just a stress response, which was not enough to cause significant differences. The number of broods and the total neonates were measured during the whole 21 days period, and they showed a descending trend with the increase of BPB concentration (Fig. 2C and 2D). The decrease in the number of broods may be due to the delayed spawning time. In addition, a significantly negative correlation between the total neonates and the BPB concentrations was observed ($p < 0.01$). It further proved that BPB, as an endocrine disrupting compound, impeded the

process of oogenesis and limited the birth of offspring. Moreover, under the high BPB concentrations (> 0.04 mg/L), some ephippia were found at the bottom of test solution, which suggesting that *D. magna* shifted from parthenogenesis to sexual reproduction, in response to the adverse environment caused by BPB exposure.

In addition to the reproductive ability, the growth status of parent *D. magna* is also an important indicator of chronic toxicity. After 21 days exposure, the average body length of parent *D. magna* in each group was presented in Fig. 3A. As shown, even though no regular trend was observed, the *D. magna* in 0.04, 0.08 and 0.10 mg/L BPB groups has smaller body length than that in control group. Thus, BPB inhibited the growth of parent *D. magna*, which was unfavorable for their performance to produce offspring. As shown from Fig. 3B, comparing with the control group, exposure to 0.08 and 0.10 mg/L BPB could result in a significant reduction in r_m value. The reduction of r_m meant that BPB inhibited the growth and renewal of population. Hence, once *D. magna* was exposed to BPB for a long time, it would encounter a devastating damage, not only from the individual level but also from the population level.

Ecological risk assessment of BPB and BPA

According to the protocol of risk quotient method, the calculation of risk quotient required the no-observed effect concentration (*NOEC*) and the measured concentration in environment (*MEC*). Among multiple endpoints, the most sensitive endpoint was the number of broods and the corresponding 21 d-*NOEC* value was estimated at 0.01 mg/L. In this case, 0.01 mg/L, was employed as the *NOEC* value of BPB. In addition, we also collected the toxicity data of BPA from previous literatures (Table S3). Results indicated that *D. magna* was also the most sensitive organism to BPA, and the *NOEC* values of BPA in chronic toxicity were reported as 0.86–5.00 mg/L (Brennan et al. 2006, Jemec et al. 2012, Mansilha et al. 2013, Tišler et al. 2016). Obviously, the *NOEC* value of BPB was two orders of magnitude lower than that of BPA, while the EC_{50} value of BPB was just one order of magnitude lower than that of BPA (as shown in Section 3.1 and Table 1). Comparing the two compounds, the difference in *NOEC* from chronic toxicity was much larger than that in EC_{50} from acute toxicity. This difference further demonstrated that in the long run, BPB was much more hazardous to aquatic organisms than BPA.

The concentration data of BPB and BPA in surface waters around the world were collected from previous studies (Tables S4–S6). BPA, as a well-known endocrine disrupting compound, was one of the frequently detected compounds in environmental monitoring. There were a large number of studies about BPA, and nearly all of them had 100% detectable rate. The average concentrations of BPA were 5.56–930 ng/L, and China and India were the most detected area (Jin &Zhu 2016, Lalwani et al. 2020, Si et al. 2019, Yamazaki et al. 2015, Zhao et al. 2019). Comparing to the abundant data of BPA the available data of BPB was limited. Up to now, BPB was reported in only five samples from surface waters, which all located at China (Shan et al. 2014, Yan et al. 2017, Zhao et al. 2019). The mean of BPB concentrations ranged from 3.32 to 20 ng/L, and the highest concentration occurred in Taihu Lake with 46 ng/L (Yan et al. 2017). In most samples, BPB was often detected at trace levels or even couldn't reach a detectable level.

The low concentration and detectable rate of BPB should be accounted to its small consumption, because the main BPA alternatives were BPF and BPS, rather than BPB.

The ecological risk of BPA and BPB were calculated using the above *NOEC* values and concentration data (Fig. 4). Due to the limit of data for BPB, few of risk values of BPB were presented, and all of them occurred in China waters. As shown from Fig. 4A, the BPB in inland lakes, i.e., Taihu Lake, Luoma Lake and Chaohu Lake, behaved as higher ecological risks than that in open coastal water, i.e., Pearl River Estuary. This result implied that anthropogenic activities mainly contributed to the risk of BPB, and good hydrodynamic condition could mitigate the risk of BPB to the ecosystem to some extent. Nevertheless, BPA from the same waters all had lower risks than BPB, even though it had much higher concentrations than BPB. Additionally, the risk of BPA from the waters around the world were presented in Fig. 4A and 4B, and results indicated that except for Jialu River (Henan Province, China), nearly all of them had a low ecological risk with $RQ < 0.1$, whether in the rivers/lakes from China or from other countries. Overall, the risk of BPA may not be as serious as it has been thought, although it was well-known because of its high health risk to humans.

Conclusions

Due to the low concentration and detectable rate in environmental media, BPB was rarely concerned in previous studies. However, owing to the continuous discharge and the high hydrophobicity, BPB would maintain the concentration at a certain level, even increase gradually in the future. In this study, *D. magna* was found to be more sensitive to BPB than *T. obliquus* and *Danio rerio*; the chronic toxicity indicated that BPB could not only disrupt the fecundity of individual *D. magna*, but also inhibit their population growth. Ecological risk assessment highlighted that BPB may cause risk to the aquatic organisms. Moreover, a full-scale comparison between BPB and BPA indicated that although BPB was rarely detected and reported, it had larger acute toxicity and chronic toxicity than BPA, thereby causing higher risk to the ecological system. Thus, BPB should deserve more attention than BPA. Especially, when making the strategies of management and control for bisphenol analogues, concentrations were not the only criterion for identifying their hazard, while the toxic effect should also be taken into account.

Declarations

Authorship contributions

Yue Wang: Writing original draft, Experiment, Investigation. Tianyi Zhao: Experiment, Methodology. Xianhai Yang: Conceptualization, Language editing. Formal analysis. Huihui Liu: Supervision, Project administration, Funding acquisition.

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Data Availability

All data used during the study are available from the corresponding author on request.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests

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Figures

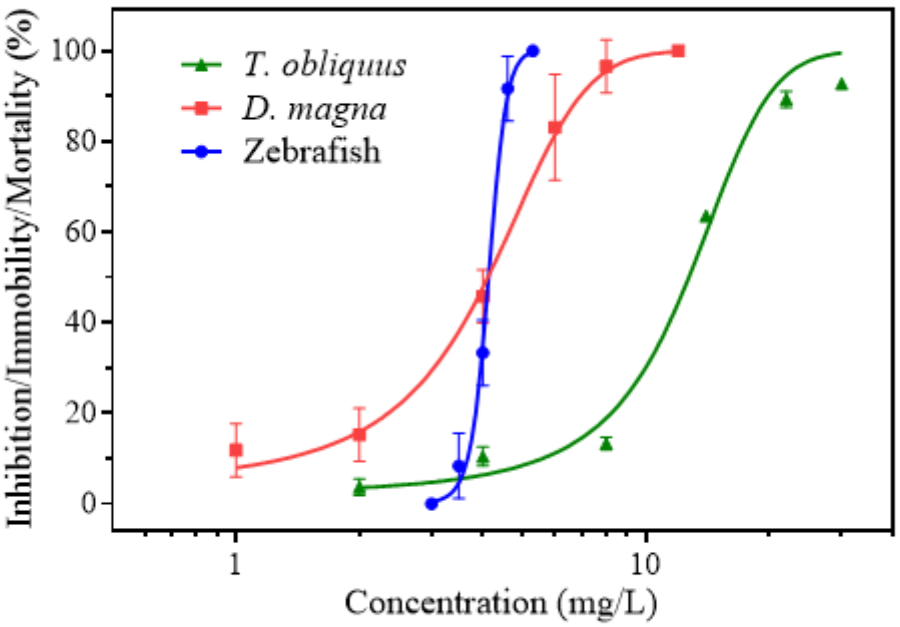

Figure 1

Dose-response relationships between BPB concentrations and the inhibition rate of algal growth, the immobilization of D. magna or the mortality of Danio rerio.

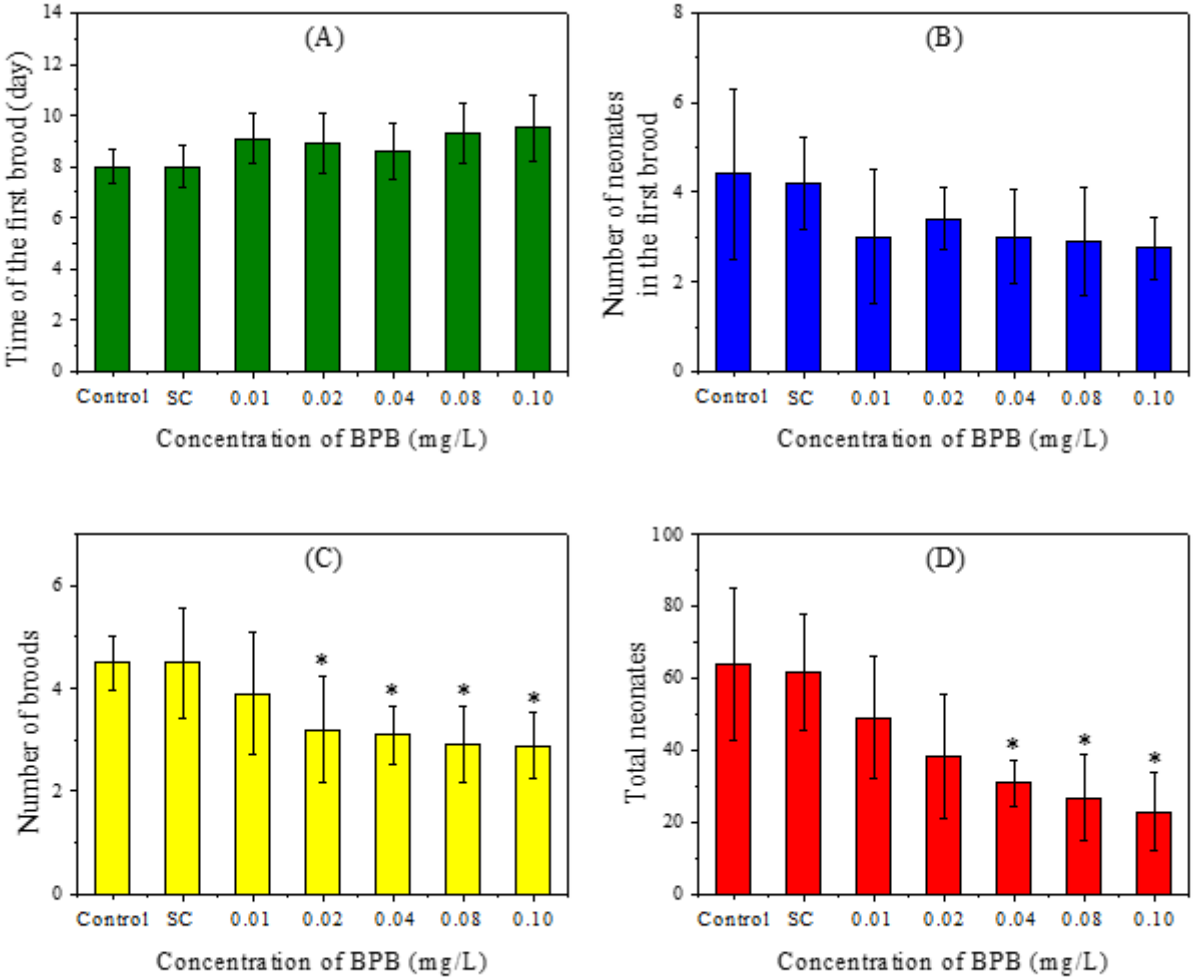

Figure 2

Chronic toxicity of BPB on the reproduction of D. magna after 21 days exposure. (A) Time of the first brood (days); (B) Number of neonates in the first brood; (C) Number of broods; (D) Total number of neonates. Asterisk (*) indicates a significant difference from the control group ($p < 0.05$).

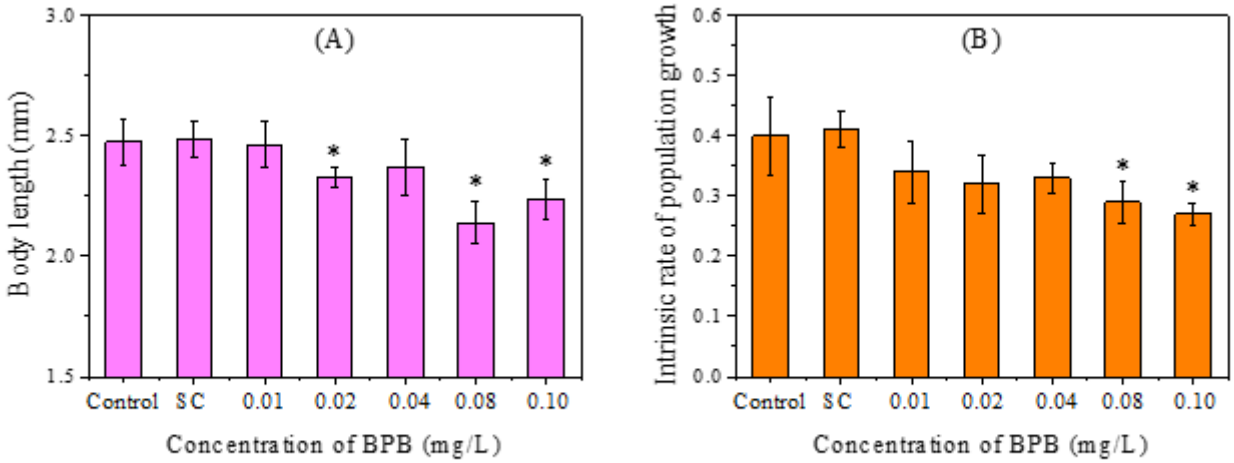

Figure 3

Effect of BPB on the body length of parent D. magna (A) and the intrinsic rate of population growth (B) after 21 days exposure. Asterisk (*) indicates a significant difference from the control group ($p < 0.05$).

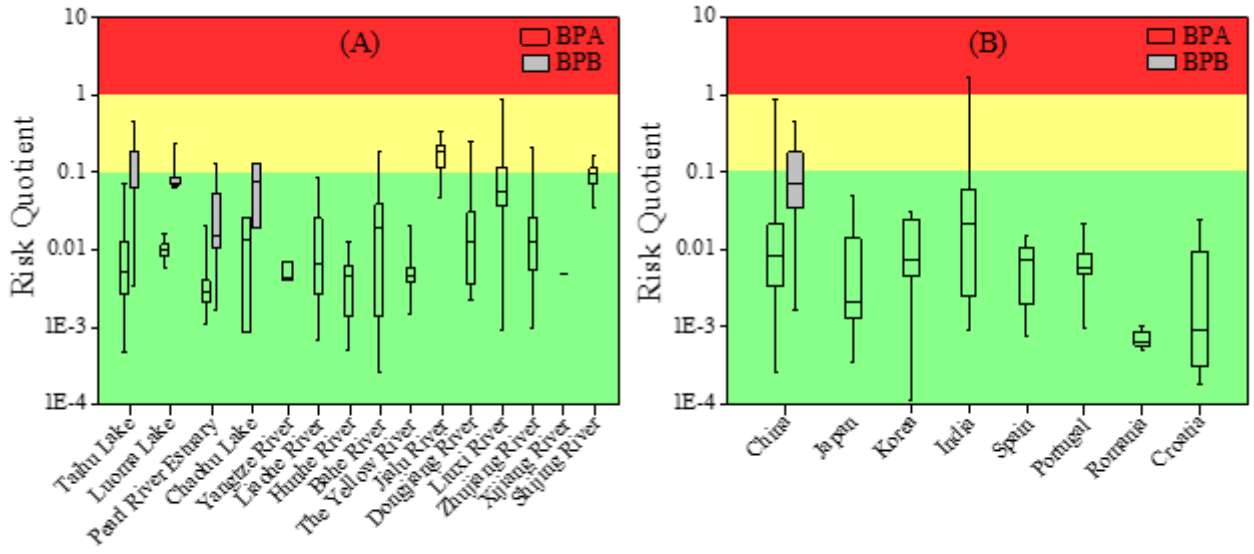

Figure 4

Box plots (minimum, maximum, 25th, 75th, and median) of the risk quotient of BPA and BPB from the surface waters from China (A) and other countries (B).

Supplementary Files

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