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RESEARCH ARTICLE ARAŞTIRMA MAKALESİ

Are potential bisphenol-A substitutes really safe for aquatic life? Impact on primary producers

Potansiyel bisphenol-A ikameleri sucul yaşam için gerçekten güvenli mi? Birincil üreticiler üzerindeki etkisi

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Abstract: Bisphenol A threat to environmental health and human health and has been added to the Candidate List as Very High Concern Substances by the European Chemicals Agency. This led to the replacement of bisphenol A (BPA) with bisphenol analogues, which were considered "safer". However, there are very few scientific studies on the impact of BPA analogues on the environment. In this study, three analogues bisphenol B (BPB), bisphenol A diglycidyl ether (BADGE) and bisphenol F diglycidyl ether (BFDGE) were selected to investigate their ecotoxicological effects on the marine phytoplankton species *Phaeodactylum tricornutum*, which is representative of primary producers. *Phaeodactylum tricornutum* was exposed to different concentrations (0.5, 0.8, 1.0, 1.5, 2.0 mg/L) of BPB, BADGE and BFDGE analogues for 72 hours and the toxicity values of three BPA analogues were calculated by OECD 201 algal growth inhibition assay (IC_{50}/EC_{50}). In the light of the data obtained, algal growth inhibition (IC_{50}/EC_{50}) values for marine phytoplankton *Phaeodactylum tricornutum* were determined as 3.91 mg-BPA/L, 7.83 mg-BPB/L, 5.69 mg-BFDGE/L, 11.71 mg-BADGE/L. The results revealed that BPB, BFDGE and BADGE showed lower toxicity to *Phaeodactylum tricornutum* compared to BPA algal growth inhibition (3.91 mg-BPA/L). Therefore, it is necessary to share the results of the adverse effects of BPA analogues on aquatic organisms and to conduct ecotoxicological risk assessments.

Keywords: Bisphenol analogues, marine phytoplankton, algal growth inhibition test, toxicity, *Phaeodactylum tricornutum*

Öz: Bisfenol A çevre sağlığı ve insan sağlığı için tehdit oluşturmaktadır ve "Avrupa Kimyasallar Ajansı" tarafından "Çok Yüksek Önem Arz Eden Maddeler" olarak aday listeye eklenmiştir. Bu durum, bisfenol A'nın (BPA) "daha güvenli" olduğu düşünülen bisfenol analogları ile değiştirilmesine yol açmıştır. Bununla birlikte, BPA analoglarının çevre üzerindeki etkisine ilişkin çok az bilimsel çalışma bulunmaktadır. Bu çalışmada, birincil üreticileri temsil eden deniz fitoplankton türü *Phaeodactylum tricornutum* üzerindeki ekotoksikolojik etkilerini araştırmak için üç analog bisfenol B (BPB), bisfenol A diglisidil eter (BADGE) ve bisfenol F diglisidil eter (BFDGE) seçilmiştir. *Phaeodactylum tricornutum* BPB, BADGE ve BFDGE analoglarının farklı konsantrasyonlarına (0.5, 0.8, 1.0, 1.5, 2.0 mg/L) 72 saat boyunca maruz bırakılmış ve üç BPA analoğunun toksisite değerleri OECD 201 alg büyüme inhibisyonu deneyi (IC50/EC50) ile hesaplanmıştır. Elde edilen veriler ışığında, deniz fitoplanktonu *Phaeodactylum tricornutum* için alg büyüme inhibisyonu (IC50/EC50) değerleri 3.91 mg-BPA/L, 7.83 mg-BPB/L, 5.69 mg-BFDGE/L, 11.71 mg-BADGE/L olarak belirlenmiştir. Sonuçlar BPB, BFDGE ve BADGE'nin *Phaeodactylum tricornutum* için BPA alg büyüme inhibisyonuna (3.91 mg-BPA/L) kıyasla daha düşük toksisite gösterdiğini ortaya koymuştur. Bu nedenle, BPA analoglarının sucul organizmalar üzerindeki olumsuz etkilerinin sonuçlarının paylaşılması ve ekotoksikolojik risk değerlendirmelerinin yapılması gerekmektedir.

Anahtar Kelime: Bisfenol analogları, deniz fitoplanktonu, alg büyüme inhibisyon testi, toksisite, *Phaeodactylum tricornutum*

INTRODUCTION

In the plastics industry over the last century, monomeric components have been transformed into plastic polymers in the final product and to improve end-use performance (Deanin, 1975). BPA is an important synthetic chemical widely used in the industrial production of polycarbonate plastics and phenolic resins (Ballesteros-Gómez, 2014; Ou et al., 2006). BPA cause a hazardous effect on both human and environmental health due to its toxicity (Diler et al., 2022; Minaz et al., 2022a; Muhamad et al., 2016). The use of BPA, which has become a global concern, has been restricted by the "European Chemicals Agency and European Food Safety Authority" due to its adverse effects by being placed on the "Candidate List of Substances of Very High Concern" (Andersson, et al., 2018). As a result of these restrictions, manufacturers have developed more than 200 BPA analogues that are structurally similar (Lucarini et al., 2020; Xie et al., 2022).

BPB is used in Europe for the coating of beverage cans and production of polycarbonate resins (Grumetto et al., 2008). In a study conducted in Italy, BPB was detected in canned peeled tomatoes samples between 27.1-85.7 µg/kg (Grumetto et al., 2008). A study by Cunha et al. (2011) in canned beverages in Portugal found BPB levels as 0.06- 0.16 µg/L. In the same study, BPB was found in all cola samples tested and was detected as 0.03-4.70 µg/L (Cunha et al., 2011). Due to their lipophilic properties (logKoc>3), bisphenol analogues have a tendency to accumulate in sediment. In Beibu Bay, South China Sea, BPB was detected in both water (14%) and sediment samples (18%) (Gao et al., 2023). In a study conducted in the Persian Gulf, bisphenol A and its analogues accumulated in 5 different marine organisms and the highest levels were found in Epinephelus coioides as 13.58 µg-BPA/kg.dw and 10.30 µg-BPB/kg.dw on a dry weight basis (dw) (Akhbarizadeh et al., 2020).

BADGE (bisphenol A diglycidyl-ether) and BFDGE (bisphenol F diglycidyl-ether) are used as a monomer in epoxy resin production during the reaction of BPA or BPF (Bello et al., 2021; Poole et al., 2004; Szczepańska et al., 2018). In 2015, annual BADGE production was estimated 9072 tons in the US (Wang et al., 2021). BADGE/BFDGE is also used in the production of dental restorative products (Olea et al., 1996). Organosol polyvinylchloride (PVC) is used as an additive as an initiator in food contact applications (Coulier et al., 2010). BADGE can be easily converted to chlorinated or hydrolysis products and most of the products resulting from this conversion are toxic (Marqueno et al., 2019). Studies have identified that presence of BADGE and BFDGE in the environment (Wang et al., 2012). Due to concerns of mutagenicity, antiandrogenicity and genotoxicity (Poole et al., 2004) the European Union has set the limit for BADGE and their hydrolysis products to enter foods at 9 mg/kg (Lane et al., 2015). Biles et al. (1999) tested liquid concentrates of diet cola, canned fish products and infant formula liquid concentrates from Washington D.C. grocery stores and reported the presence of BADGE in sardine, tuna, anchovy and herring fish samples. According to study by Simoneau et al. (1999) BADGE were found tested 382 canned fish oil samples collected from 15 members of the European Union and Swiss national supermarket. When the literature is examined, there is a lack of data on in vitro toxicological studies on cell types of BADGE and BFDGE chemicals. On the one hand, BADGE has been reported to be able to induce apoptosis or cell death in cell lines (Bishop-Bailey et al., 2000).

Bisphenol A and its analogues are known to cause bioaccumulation in aquatic organisms and are prone to biomagnification at trophic levels (Guo et al., 2017; Kim et al., 2020; Wu and Seebacher, 2020). Despite the increasing number of ecotoxicology studies (Chen et al., 2002; Czarny et al., 2021; Diler et. al., 2022; Guo et al., 2017; Kovalakova et al., 2020; Liu vd., 2010; Mihaich et al., 2009; Minaz et al., 2022a, b; Minaz and Kurtoglu, 2024; Paerl and Justic, 2011; Pascoe et al., 2002; Seoane et al., 2021; Tato et al., 2018; Xiang et al., 2018), data on BPA's environmental risk and its analogues on aquatic organisms and primary producer marine phytoplankton species are extremely scarce.

Phytoplankton are photosynthetic microorganisms mediate the biogeochemical cycles of carbon, nutrients (nitrogen and phosphorus) and oxygen in aquatic ecosystems, while also playing an important role as primary producers of the food web (Cakal Arslan et al., 2024). The presence of BPA and its analogues not only negatively affects the reproduction and biodiversity of phytoplankton, but these can also cause hazard on other organisms by accumulating at higher trophic levels (Kovalakova et al., 2020). Therefore, there is a need to assess the impacts of BPA and its analogues on marine ecosystems in terms of environmental control and management.

In this study, it is aimed to reveal the ecotoxicological effects of BPA and three BPA analogues (BPB, BADGE and BFDGE) on the marine phytoplankton species *Phaeodactylum tricornutum* and to present preliminary data for a better understanding of their effects on aquatic organisms.

MATERIALS AND METHODS

Chemicals

The chemicals that formed the basis of our study in the experiments were purchased from Sigma-Aldrich (St. Louis, MO, USA) bisphenol A (BPA), bisphenol B (BPB), bisphenol A diglycidyl ether (BADGE), bisphenol F diglycidyl ether (BFDGE). Chemicals were dissolved in dimethyl sulfoxide (DMSO), determined to be non-toxic by preliminary experiments, and prepared before starting 100 ppm stock biotests.

Microalgae media and trial culture conditions

The test organism *Phaeodactylum tricornutum* was cultured in F/2 medium (Guillard, 1975) in the Ecotoxicology laboratory of the Faculty of Fisheries, Ege University.

A pre-culture was established before the test and incubated at 20±1°C. The initial cell concentration in the test cultures was approximately 4-5x10^{-4} cells/ml for *Phaeodactylum tricornutum*. The experiments were performed in 20 ml sterile glass tubes with 3 replicates. Samples were illuminated at a photoperiod of 14:10 (light:dark) hours under constant illumination at approximately 2000 lux and kept on a 100 rpm shaker. Cell density was confirmed using a Neubauer hemocytometer counting chamber at 24, 48 and 72-hour time points (Anonymous, 1984).

Algal growth inhibition test

The algal growth inhibition test was performed according to the OECD 201 standard (OECD; 2011). Cell count data at 0 and 72 h were evaluated based on growth rate as described in standard protocols. IC_{50} values were calculated as 50% growth inhibition of the test population compared to the control based on growth rate.

Statistical analysis

Data were analysed by One-Way ANOVA using the IBM software package SPSS v26 for Windows. Growth rate data were compared with controls using the Tukey test. Differences between groups were considered significant ($P<0.05$) (Özdamar, 1999).

RESULTS

Due to the importance of primary production for the aquatic ecosystem, the marine diatom *P. tricornutum* was exposed to increasing concentrations (0.5, 0.8, 1.0, 1.5, 2.0 mg/L) of BPA and its analogues (BPB, BADGE and BFDGE) to determine its algal growth inhibition value. A limiting effect was observed in the cell numbers from the lowest concentration due to toxicants compared to the control (Control=0.74-1.15; 0.5 mg/L=0.57-0.93). As a result of the study, it was determined that there were statistically significant differences between the

experimental groups (P<0.05) (Figure 1). At the lowest concentration (0.5 mg/L), a limiting effect between 15-22% was observed in all chemicals, while the limiting effect increased in parallel with the increase in concentration. It was observed that all chemicals had a limiting effect on the growth rate depending on the concentration, and the inhibition percentages calculated by the dose-response curve also increased. (Figure 2). According to the EC_{50} values calculated for BPA and its analogues depending on different concentrations, the toxicity of bisphenols were sequenced as BPA>BFDGE>BPB>BADGE, respectively. EC_{50} values for all chemicals were calculated as 3.91, 5.69, 7.83, and 11.71 mg/L for BPA, BFDGE, BPB, and BADGE, respectively (Figure 3).

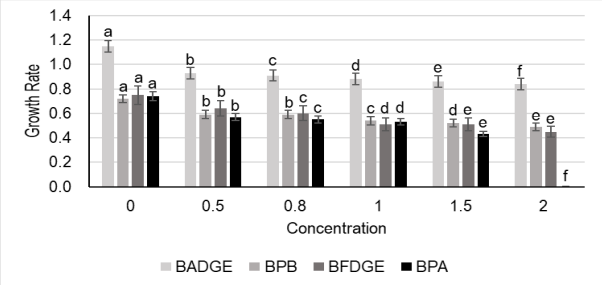

Figure 1. Growth rates of chemicals according to the results of applied concentrations (Different letters (a; b; c; d; e; f) indicate statistical difference. A represents the group with the highest mean and f represents the group with the lowest mean (P<0.05) (± standard error) (n=3))

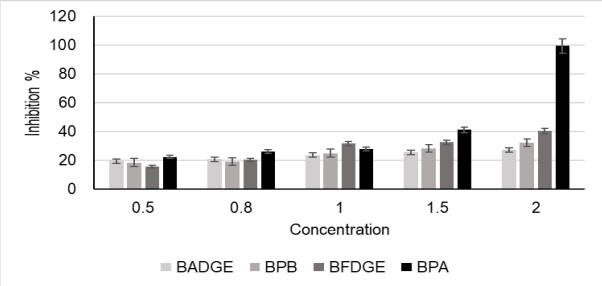

Figure 2. Inhibition percentages of chemicals according to the results of applied concentrations (There is no significant difference between groups sharing the same letter. Different letters (a; b; c; d) indicate that there is a significant difference between the groups (P<0.05) (± standard error) (n=3))

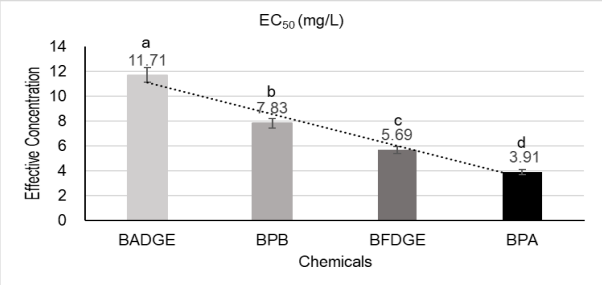

Figure 3. EC_{50} values calculated according to the results of the applied concentrations (Each group (a; b; c; d) is significantly different from the others groups (P<0.05) (± standard error) (n=3))

DISCUSSION

Bisphenol A and its analogues are global concern due to their ubiquity in the environment, their endocrine disrupting activity and their negative impact on the aquatic ecosystem (Xing et al., 2022). Many analogues have been confirmed to exert similar or stronger negative effects on aquatic organisms (Liu et al., 2021). Therefore, our study provides an overview of the toxicity of bisphenol A and its analogues BPB, BADGE and BFDGE and their impact on the growth rate of primary producers.

Much less is known about endocrine disruption chemicals (EDCs) such as BPs in terms of their harmful effects on food web organisms compared to organisms at higher trophic levels. Czarny et al. (2021) reported that many BPs penetrate the phytoplankton cell membrane due to their lipophilic properties (log Kow) and negatively affect many physiological processes such as photosynthesis, growth rate. Our study supports the thesis of Czarny et al. (2021) by showing that BPs have a constraining effect on the growth rate of *P. tricornutum* species. Since prokaryotic and eukaryotic primary producers lack endocrine systems, the mechanisms of action of chemicals differ from organisms at higher trophic levels.

Liu et al. (2010) reported that EC_{50} values for BPA as 3.73 and 8.65 mg/L for *Navicula incerta* and *Stephanodiscus hantzschii* respectively. In our study, this value for *P. tricornutum* was determined as 3.91 mg/L. When our study was compared with the 96-hour BPA exposure of Liu et al. (2010), our species was found to be more sensitive than the diatom *Stephanodiscus hantzschii*. The EC_{50} value we determined for *P. tricornutum* is similar to that of *Navicula incerta*. Liu et al. (2010) obtained the EC_{50} value for this species as 7.96 mg/L. Accordingly, it was determined that BPA had a more toxic and limiting effect on *P. tricornutum* than *Cyclotella caspia*.

In a study with the cyanobacterium *Cylindrospermopsis raciborskii* exposed to BPA, Xiang et al. (2018) found that the EC_{50} value is 9.66 mg/L. Also, BPA caused changes in cell morphology. Compared to our study, BPA was more toxic to *P. tricornutum* species.

Czarny et al. (2021) examined the effects of individual and mixed bisphenol analogues on cyanobacteria. Accordingly, BPAF, BPB and BPC were more toxic than BPA on *Anabaena variabilis* and *Microcystis aeruginosa*. The growth and EC_{50} data in our study are similar to this study.

When the data in the current study were compared with previous studies, it was determined that EC_{50} values varied according to the species. There are no studies conducted with *P. tricornutum* species with BPA and its analogues. When the EC_{50} values obtained from studies with different species exposed to several BPA analogues are compared with our study, it is thought that this species (*P. tricornutum*) is more resistant than other species, and the reason for this is thought to be due to the chitin structure of the cell wall of *P. tricornutum* species.

CONCLUSION

Due to the importance of primary production to the aquatic ecosystem, this study evaluated the effects of increasing concentrations of BPA, BADGE, BPB and BFDGE compounds on the marine diatom *P. tricurnitum*. According to the data obtained, it was observed that the toxicants had a limiting effect on cell numbers from the first concentration compared to the control. It was observed that all chemicals had a limiting effect on the growth rate depending on the concentration, and there was an increase in the inhibition percentages calculated by the dose-response curve. According to the EC_{50} values calculated for bisphenol A and its analogues depending on the concentrations applied, the most toxic bisphenols were determined as BPA>BFDGE>BPB>BADGE, respectively.

BPA and its analogues are widely used in our country and in the world. Analogues produced to replace BPA show similar toxicity and estrogenic activity to BPA. Therefore, they may not be as safe as thought and legal regulations should be introduced for their use. The determination of estrogenic toxicity of these chemicals and the development of ecotoxicological tests necessary for environmental and human health should continue. The levels of bisphenolic compounds in Türkiye's rivers, lakes and waste discharge points and in the organisms found there should be determined. The levels of these compounds in drinking water and food should be determined and safety limits should be set. In order to take these measures, previous studies should be examined and new toxicological procedures should be developed in line with these literatures.

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AUTHORSHIP CONTRIBUTIONS

Koray Benas: Conceptualization, resources, investigation, methodology, writing-reviewing and editing. Özlem Çakal Arslan: Conceptualization, resources, methodology, formal analysis, investigation, project administration.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest or competing interests.

ETHICS APPROVAL

No specific ethical approval was necessary for the study.

DATA AVAILABILITY

All relevant data is inside the article.

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