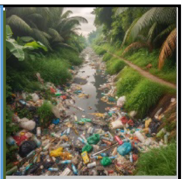
JEMAT 2023, Vol 11, No 2, 1-7
https://doi.org/10.54987/jemat.v11i2.846

HIBISCUS PUBLISHER

JOURNAL OF ENVIRONMENTAL MICROBIOLOGY AND TOXICOLOGY

Website: http://journal.hibiscuspublisher.com/index.php/JEMAT/index



JEMAT VOL 11 NO 2 2023
Plastics-polluted river

Exposure and Toxicity of Polybrominated Diphenyl Ethers: A Mini Review

Raneesha Navaretnam[1], Izazy' Nur Mohd Jaafar[1], Mohd Yunus Shukor[1] and Nur Adeela Yasid[1]*

[1]Department of Biochemistry, Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.

*Corresponding author:
Dr. Nur Adeela Yasid,
Department of Biochemistry,
Faculty of Biotechnology and Biomolecular Sciences,
Universiti Putra Malaysia,
43400 UPM Serdang,
Selangor,
Malaysia.
Email: adeela@upm.edu.my

HISTORY

Received: 15th Oct 2023
Received in revised form: 15th Dec 2023
Accepted: 28th Dec 2023

KEYWORDS

Polybrominated Flame Retardant
Uses
Toxic effects
Monitoring
Exposure

ABSTRACT

Polybrominated Diphenyl Ethers (PBDEs), recognized as persistent organic pollutants by the United Nations Environment Programme, are a class of brominated flame retardants that pose significant environmental and health risks. These compounds, consisting of two aromatic rings with up to 10 bromine atom substitutions, are categorized into penta-BDE, octa-BDE, and deca-BDE based on their bromine content, each exhibiting distinct environmental behaviors. PBDEs with fewer bromine atoms are more volatile and prone to bioaccumulation, raising significant health concerns. These compounds, often added physically to products, can leach into the environment, leading to pollution during production and after the parent polymer degrades. The transformation of higher brominated diphenyl ethers into less brominated forms in the environment further complicates their impact, with mono-brominated BDE-3 being particularly concerning due to its extended atmospheric photolysis lifetime and increased bioavailability. The management of PBDEs is challenging due to their persistence and transformation in the environment. As endocrine disruptors, they are linked to various acute and chronic toxicological effects, including neurodevelopmental toxicity, teratogenicity, and potential carcinogenicity. Their structural similarity to thyroid hormones allows them to disrupt thyroid hormone balance, leading to further health complications. The subject of this review is to summarize the current body of knowledge that is essential to understand their long-term effects on ecosystems and human health and to develop strategies to mitigate their adverse impacts.

INTRODUCTION

Polybrominated diphenyl ethers (PBDEs) are a class of brominated flame retardants that have gained notoriety as significant environmental contaminants. Recognized by the United Nations Environment Programme (UNEP) in 2009 as a new category of persistent organic pollutants (POPs), PBDEs have raised global environmental and health concerns [1]. Structurally, PBDEs are characterized by two aromatic rings, offering 1 to 10 positions for bromine atom substitutions on the diphenyl ether framework. This structure is crucial for their flame-retardant properties [1].

There are 209 possible congeners of PBDEs, each is identified by a specific number, similar to the nomenclature used for polychlorinated biphenyls (PCBs). However, the actual number of congeners present in the environment is somehow limited, and is influenced by the chemical properties and composition of commercial PBDE mixtures [2]. These mixtures are typically categorized into three main types based on their bromine content, which are penta-BDE, octa-BDE, and deca-BDE. Each type has distinct uses and environmental behaviors [2], however, the numbers of congeners formed are limited due to their chemical properties and composition of the PBDE commercial mixtures. Penta-BDE, primarily used in polyurethane foam for furniture cushioning, has been the focus of environmental studies due to its high potential for bioaccumulation and toxicity. Octa-BDE, commonly added to acrylonitrile butadiene styrene (ABS) plastics, is used in various office equipment and electronic housings. Deca-BDE, the most brominated form, is used in high-impact polystyrene, polyolefin, and polypropylene plastics. These materials are prevalent in a wide range of products, including electronics, automobiles, airplanes, and construction and building materials [2,3].

Polybrominated diphenyl ethers (PBDEs) were a major contributor to environmental and health problems until their supposedly worldwide phase-out in 2004. Problems with PBDE

https://doi.org/10.54987/jemat.v11i2.846

bioaccumulation and biomagnification in the food chain persist due to the chemicals' persistent nature [4]. Remaining traces of penta- and octa-BDE in recyclable trash are anticipated to persist until around 2030, even with the phase-out process. Deca-BDE is expected to continue being used until 2036 in certain aviation and automotive applications. [5].

PBDEs with fewer bromine atoms are more volatile and have a greater tendency to bioaccumulate in the environment [6,7]. This feature raises significant health concerns since these PBDEs with lower bromination levels are physically added to products instead of being chemically bound. Because of this, they are able to dissolve in water and cause environmental pollution both during production and after the parent polymer evaporates, since they are able to escape the matrix.

Higher bromination diphenyl ethers can decompose into less bromine atom-containing PBDEs when exposed into the environment. The mono-brominated diphenyl ethers (BDEs) are a significant class among these compounds because BDE-3 has an exceptionally extended atmospheric photolysis lifetime in comparison to the other mono-BDEs [8]. The increased bioavailability of BDE-3, the most basic form of mono-BDE and a common degradation product of higher polybrominated diphenyl ethers, makes it a very dangerous substance [9–12]. Because of the increased toxicity and health concerns it may cause, its presence in the environment is worrisome.

Managing the legacy of persistent organic pollutants like PBDEs is complicated because of their continuous existence and transformation in the environment. To learn how they will affect ecosystems and people in the long run, and to come up with solutions to lessen or eliminate their negative effects, ongoing research and monitoring are required. As a group, PBDEs are considered endocrine disruptors [13,14] besides causing various acute and chronic toxicological effects on organisms such as neurodevelopment toxicity, teratogenicity and potential carcinogenicity [15,16].

Since the chemical structure of PBDE is almost identical to the thyroid hormones (TH), 3,3′,5-triiodothyronine (T_3) and 3,3′,5,5′-tetraiodothyronine (T_4), they may bind efficiently to thyroid hormone receptors and the transport protein transthyretin, which can upset the equilibrium of thyroid hormones [17]. There are also reports on DNA damage, alterations in gene expression and oxidative stress in earthworms [18]. Additionally, PBDEs have been linked to problems in the reproductive system of male rats [14] and in fishes [19,20].

Brominated flame retardants

There are three types of brominated flame retardants: reactive, additive, and brominated monomers, which are classified according to the method of compound integration. According to [21], In order to make brominated polymers, nonhalogenated polymers are mixed with brominated monomers such as brominated styrene or brominated butadiene. Reactive flame retardants, on the other hand, include tetrabromobisphenol A (TBBPA). The chemical incorporation of hexabromocylododecane (HBCDD) and polybrominated diphenyl ethers (PBDEs) into polymers increases the likelihood of these chemicals seeping out into the environment, which has recently sparked concerns. [22] found that in 2019, brominated flame retardants generated an estimated 37.2% of total revenue.

In addition to being one of the most widely used families of brominated flame retardants, polybrominated diphenyl ethers (PBDEs) are additive flame retardants [21] it was found that PBDEs are made by brominating diphenyl ether using a Friedel-Craft catalyst in a solvent like dibromomethane. There are 209 potential congeners since diphenyl ether molecules can hold up to 10 hydrogen atoms, any of which can be swapped out for bromine atoms. Given that PBDEs and PCBs have a structural similarity, the nomenclature founded by [1] is also applied in naming PBDEs. CCommercially, PBDEs are categorized according to their average bromine concentration and are produced at three different bromination degrees: pentabromodiphenyl ether (Penta-BDE), octabromodiphenyl ether (Octa-BDE), and decabromodiphenyl ether (Deca-BDE) [23–25]. Plastics for commercial equipment and upholstery foams for cushioning are two main uses for octa- and penta-BDE, whilst deca-BDEs were mostly utilized in electronic enclosures like television cabinets [26].

Before 1995, the United States and Israel were the top two countries producing PBDEs. China started producing PBDEs in the 1980s, with Deca-BDE being the main ingredient. Around the year 2000, China became a major player in the Deca-BDE market. In contrast, Deca-BDE was subject to bans and limitations in 2013, following the end of 2004 for Penta-BDE and Octa-BDE [27,28]. In the years that followed, Europe and Japan reduced their PBDE production to the point that it contributed less than 10% of the global total [30].

The phase out of flame retardants was accompanied by an increase in the use of organophosphate flame retardants such as TDCIPP and TCIPP, and the commercial FR mixture Firemaster 550 (FM550), which comprises TPHP, isopropylated triaryl phosphates (ITPs), 2-ethylhexyl-2,3,4,5- tetrabromobenzoate (EH-TBB) and bis(2-ethylhexyl)-tetrabromophthalate (BEH-TEBP) [29,30]. Using NBFR or other flame retardants poses a risk, though, that additional additives will be added, removed, or substituted, leading to an endless loop of chemical additives that are difficult to remove and could be even more harmful than their original congeners [5].

PBDE characteristics, application and routes of exposure

PBDEs bind readily to soil or sediments but have little solubility in water because they are hydrophobic and fat-soluble. This allows them to float through the air by clinging to particles in the air, but they are unable to travel freely through underground water sources [23]. Noncovalent bonding to plastics and textiles allows PBDEs to selectively release them into the environment over the products' lifespan, unlike PCBs [31]. These chemicals seep into the environment via waste disposal leachates, recycling facilities, emissions from manufacturing processes, and the volatilization of many PBDE-containing items [23,32,33]. In addition to that, the number of bromine atoms influences the volatilization of PBDEs from the soil surfaces in which higher brominated PBDEs demonstrates lower volatilities [26]. [23] suggests that lower brominated congeners lacked the binding capacity of higher brominated congeners to soil and sediment particles.

Household dust is a common place to find higher-brominated PBDEs because of their lengthy half-lives, sorption characteristics, and high persistence [34]. Sediments, soil, and sewage sludge are likely to retain PBDEs to a high degree since these contaminants are less soluble in water, which limits their redistribution. Manufacturing locations and e-waste recycling centers had the highest concentrations of PBDEs, while less developed places and rural areas had lower concentrations [26].
The routes of exposure of PBDEs include inhalation, oral exposure, or dermal contact with contaminated products [35]. [26] mentioned that PBDE deposits in soil and water expose fish

and benthic organisms to these pollutants, making the food chain the primary source of environmental exposures. To support this statement, [36] reported that fish consumption was the primary pathway for PBDE exposure for the people of Hong Kong compared to dust ingestion while another study showed that humans were likely exposed to PBDE through seafood [37,38]. [38] also brought attention to comparable results, where the PBDE level in food consumption was 931 ng/kg bw/day, which was greater than the 18.1 and 1.2 ng/kg bw/day levels in adults and children, respectively, due to dust ingestion. Biomagnification happens when higher-ranking predators consume their prey's accumulated PBDE concentrations [39,40]. PBDEs are expelled from the human bodies primarily through blood and sweat and no data was obtained for excretion of PBDEs through urine [41]. Therefore, blood and sweat can be efficient biomonitoring tools to evaluate the mode of elimination of this persistent organic pollutant. A mindmap of PBDE's application and routes of exposure is summarized below (**Fig. 1**).

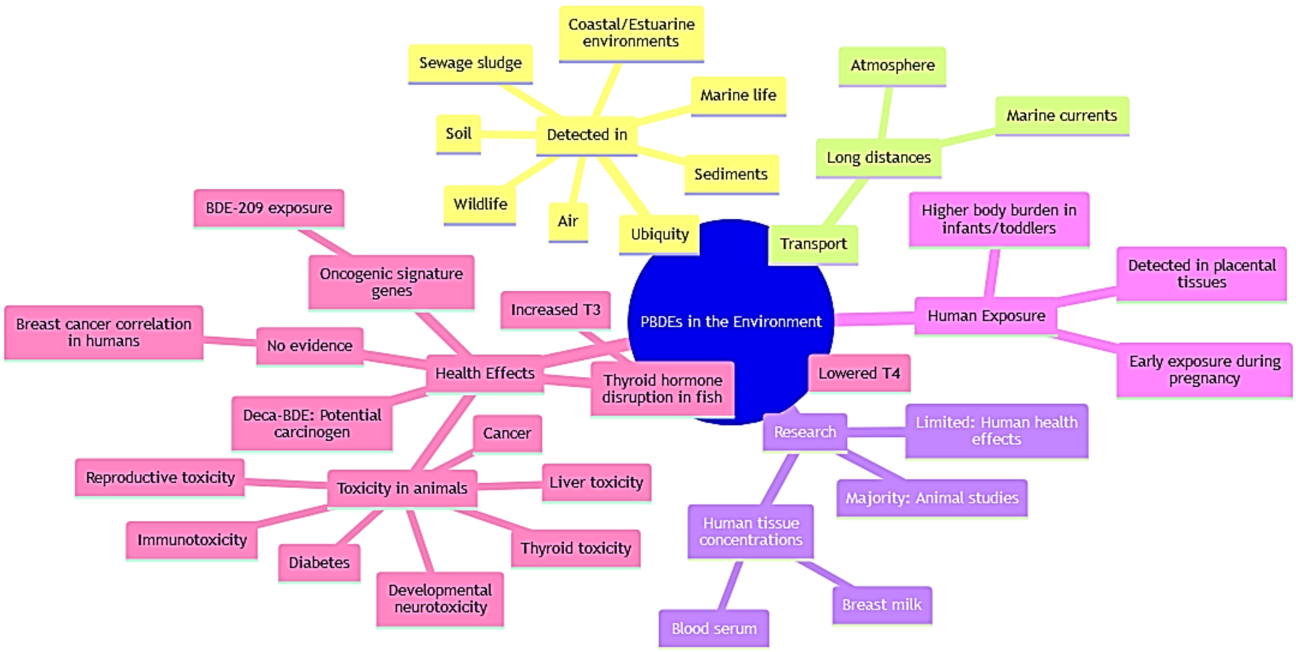


Fig. 1. A mind map of PBDE's impact on the environment through route of exposure visualized and summarized using the Mermaid Chart software (v 10.6.1).

PBDE toxicity in humans and animals

PBDEs have been found in many different parts of the environment, including sewage sludge, air, soil, sediments, estuaries, wildlife, and other marine life [23,26,42]. The environmental persistence of PBDEs is explained by the fact that they can be carried quite large distances (> 1,000 km) by air and ocean currents. Little is known about the impact of PBDEs on human health, and the vast majority of study on the topic has been conducted on animals as summarized in **Table 1**. Nevertheless, a fair number of articles were published in relation to PBDE levels in human tissues, such as blood serum and breast milk [29,43,44].

The body burden of PBDEs in infants 9 and toddlers are three to ninefold higher compared to adults [45]. Furthermore, it has been found that PBDEs can be found in human placental tissues, which implies that children may be exposed to brominated flame retardants during pregnancy [46]. Deca-BDE is a potential carcinogen as suggested by [26]. Conclusive data on the carcinogenic potential of PBDEs is still an active area of research, suggested by [47], Regardless, the study succeeded in drawing attention to the link between BDE-209 exposure and the enrichment of oncogenic hallmark genes in human embryonic kidney cells. Changes in expression were found to be strongly associated with different types of cancers. Animal studies have linked PBDE toxicity to a variety of health problems, including neurotoxicity during development, reproductive issues, immunotoxicity, thyroid issues, diabetes, liver problems, and cancer [48–52].

Besides that, PBDEs have also interrupted thyroid hormone homeostasis by lowering thyroxine (T4) levels while increasing triiodothyronine (T3) levels in fish [53]. In contrary to animal studies, serum levels of BDE-47, BDE-100 or BDE-153 provided no evidence with regards to its correlation with breast cancer in humans [44].

4-bromodiphenyl ether (BDE-3) is the photodegraded product of higher brominated polybrominated diphenyl ethers (PBDE) which is collectively known as brominated flame retardants additive [60]. The utmost safe level for protecting aquatic organisms in freshwater environments that was recommended by the United States Environmental Protection Agency (USEPA) was 6.2 µg/L [61].

Toxicity studies on BDE-3 is scant and past studies on BDE-3 were mostly performed on rats, mice, roundworm, and seedlings as outlined in **Table 2**. BDE-3 was used to evaluate the reproductive toxicity in mice treated intragastrically. As a result of the experiment, the sperm count of mice was dose-dependently reduced while increase in the number of abnormal sperm production was recorded [60]. The previous study also proposed that the tyrosine, purine and riboflavin metabolism might be able to provide explanation for the toxicity metabolism of BDE-3.

https://doi.org/10.54987/jemat.v11i2.846

Table 1. The effect of PBDEs on morphological and metabolic activity of different human test specimen.

Specimen/life stage	PBDE	Findings	Reference
Psetta maxima/ embryo-larval stages	BDE-47 and BDE-99	Embryonic abnormalities, pericardial edema, skeletal deformities, and decreased hatching success (larvae). It was shown that BDE-47 was more hazardous than BDE-99.	[49,54]
Danio rerio/adult	6-OH-BDE-47 and 6,6′-diOH-BDE-47	T3 and T4 levels throughout the body rose, causing severe delays in development and morphological abnormalities.	[55]
Male Harlan Sprague Dawley rat	BDE-47, BDE-209, *HBCD, TBB, TBPH, TBBPA-DBPE, BTBPE, DBDPE, HCDBCO	While PBDE-47 upregulated transcripts from the Nrf2 antioxidant pathway, total thyroxine (TT4) concentrations decreased and hepatocellular toxic endpoints were disrupted.	[56]
Male and female Wistar Han rats/ utero/postnatal/adult	DE-71 (PBDE-99 (41.7%), PBDE-47 (35.7%), PBDE-100 (10.4%),	Researchers observed carcinogenic effects in male rats' thyroid and pituitary gland tumors, as well as in female rats' uterus (stromal polyps/stromal sarcomas).	[57]
Male and female B6C3F1 mice/ adult	PBDE-154 (3.6%), PBDE-153 (3.3%), and PBDE85 (2%)	It is possible that hormone balance disruption, oxidative damage, and molecular and epigenetic alterations in target tissues contribute to PBDE carcinogenic activity.	[57]
Long-Evans rats/ pregnant adults	DE-71	The developmental neurotoxicity of PBDEs may be due to changes in energy metabolism and processes associated with neuroplasticity and growth	[58]
Human fibroblast cell line HS68	BDE-209, BDE-47 and BDE-99,	Chemicals increased the likelihood of DNA damage, cellular cycle protein modifications, oxidative stress, apoptosis regulation, energy imbalance, and cell proliferation/transformation risk.	[59]

*1,3,5,7,9,11-Hexabromocyclododecane (HBCD), 2-ethylhexyl-2,3,4,5-Tetrabromobenzoate (TBB), Bis(2-ethylhexyl) tetrabromophthalate (TBPH), Tetrabromobisphenol A-bis(2,3-dibromopropyl ether) (TBBPA-DBPE), 1,2-bis(tribromophenoxy)ethane (BTBPE) (Firemaster 680), Decabromodiphenylethane (DBDPE), Hexachlorocyclopentadienyl-dibromocyclooctane (HCDBCO).

Table 2. The toxicity effect of BDE-3 on various test specimens according to previous studies.

Specimen	Dosage of BDE-3	Duration	Findings	Reference
Populus tomentosa Carr seedlings	0 mg/L, 3 mg/L and 30 mg/L	23, 47 and 58 days	Damage to and changes in the anatomy of leaves, stunted growth, chlorosis, and necrosis; caused disruption of photosynthesis and developmental processes in plants.	[63]
Triarrhena sacchariflora seedlings	0.3 mg/L, 3.0 mg/L, 30.0 mg/L and 300.0 mg/L	28 days	The seedlings suffered damage and did not develop adventitious roots. At higher dosages, browning or withering of the leaves was noted.	[64]
*Caenorhabditis elegans r*oundworm	Multiple dosages	24 hours and long-term exposure from L4 stage until death 21 days	Life expectancy reduced, fertility reduced, and egg laying delayed.	[18]
Male Sprague Dawley rats	0, 50, 100, and 200 mg/kg body weight/day		Less testosterone in the blood, halting the formation of Leydig cells via inhibiting activation of AKT, ERK1/2, and AMPK, and then producing reactive oxygen species (ROS).	[62]
Mice	0.0015, 1.5, 10 and 30 mg/kg	42 days	Changes in the epididymides and seminiferous tubules, a drop in sperm count and an increase in the percentage of aberrant sperm	[48]

Other than that, BDE-3 was also said to induce programmed cell death in *Caenorhabditis elegans* as a result of elevation in the reactive oxygen species that ultimately damaged DNA [18], implying the possibilities of developing reproductive dysfunction. In addition to that, BDE-3 was also associated with lowered life spans, hampered fecundity, and delayed egg laying. Not only was BDE-3 tested in mice and worms, but it was also used to study effects in plants. [62] investigated the effects of BDE-3 on adventitious root differentiation and biomass at concentrations of 3.0 mg/L; however, seedlings of *Triarrhena sacchariflora* exhibited inhibitory effects and damage symptoms at a higher dose of 30.0 mg/L.

In addition, BDE-3 was found to have detrimental effects on the microscopic structure of the roots, stems, and leaves in an experiment with *Populus tomentosa* Carr seedlings. Additionally, at low concentrations of BDE-3 treatments, the leaf color became shallow, and at higher concentrations, albinism was visible. When exposed to quantities lower than 30 mg/L, BDE-3 had a beneficial effect on adventitious root differentiation and biomass, just as it has in earlier studies [63]. A mindmap of PBDE’s toxicity is summarized below (**Fig. 2**).

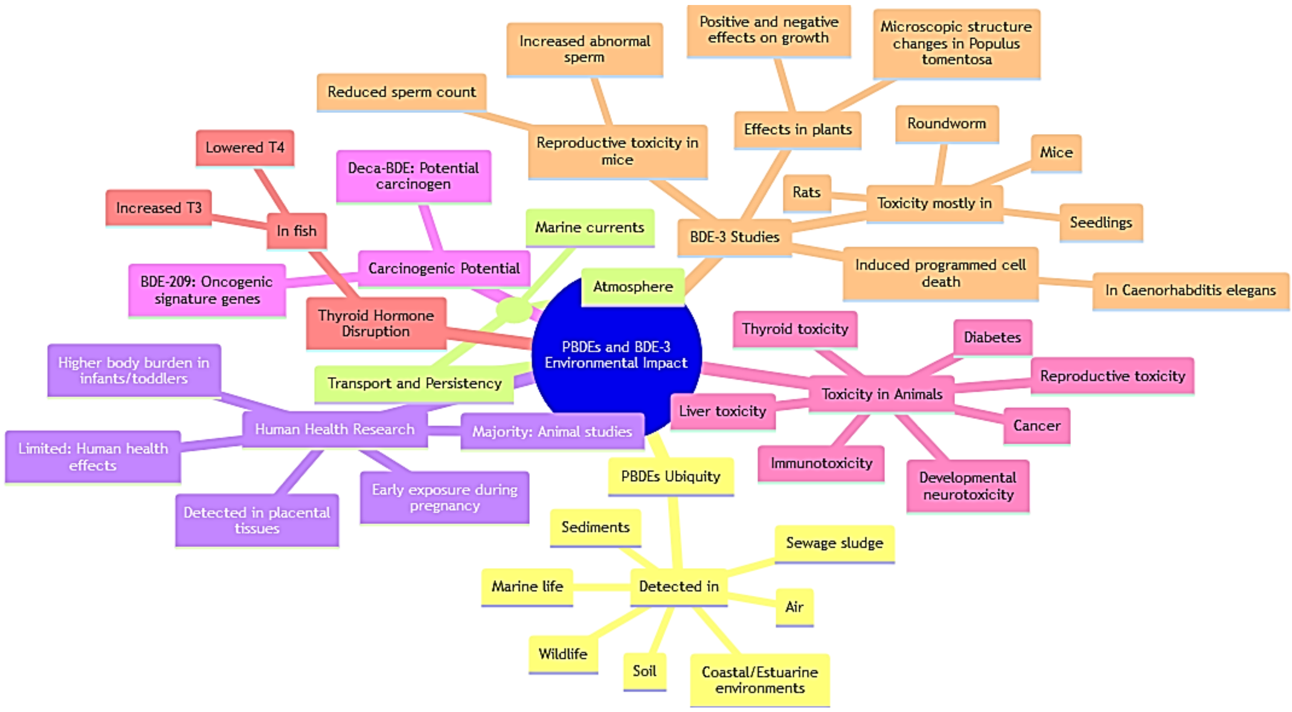


Fig. 2. A mind map of PBDE's toxicity to humans and other organisms visualized and summarized using the Mermaid Chart software (v 10.6.1).

CONCLUSION

In conclusion, Polybrominated Diphenyl Ethers (PBDEs), a class of brominated flame retardants, present significant environmental and health challenges. Identified as persistent organic pollutants, their environmental persistence and bioaccumulation potential, especially those with fewer bromine atoms, raise major concerns. PBDEs' affinity for fat and soil, and their ability to bioaccumulate and biomagnify through the food chain, expose humans and wildlife to various health risks. Despite efforts to phase out certain PBDEs, their legacy persists, with continuous environmental and biological impacts. Their interference with thyroid hormone functions and potential carcinogenic effects underscores the urgent need for ongoing research and effective management strategies to mitigate their long-term consequences on ecosystems and human health.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Ballschmiter K, Zell M. Analysis of polychlorinated biphenyls (PCB) by glass capillary gas chromatography: Composition of technical aroclor- and Clophen-PCB mixtures. Fresenius Z Für Anal Chem. 1980 Jan;302(1):20–31.
2. U.S. Environmental Protection Agency. An exposure assessment of polybrominated diphenyl ethers. 2010.
3. Shaw SD, Blum A, Weber R, Kannan K, Rich D, Lucas D, et al. Halogenated flame retardants: do the fire safety benefits justify the risks? Rev Environ Health. 2010;25(4):261–305.
4. Hull TR, Law RJ, Bergman Å. Environmental Drivers for Replacement of Halogenated Flame Retardants. In: Polymer Green Flame Retardants [Internet]. Elsevier; 2014 [cited 2023 Dec 29]. p. 119–79. Available from: https://linkinghub.elsevier.com/retrieve/pii/B978044453808600004 4
5. Sharkey M, Harrad S, Abou-Elwafa Abdallah M, Drage DS, Berresheim H. Phasing-out of legacy brominated flame retardants: The UNEP Stockholm Convention and other legislative action worldwide. Environ Int. 2020 Nov;144:106041.
6. Gill S, Hou Y, Li N, Pulido O, Bowers W. Developmental neurotoxicity of polybrominated diphenyl ethers mixture de71 in Sprague-Dawley rats. J Toxicol Environ Health A. 2016;79(12):482–93.
7. Yogui GT, Sericano JL. Polybrominated diphenyl ether flame retardants in the U.S. marine environment: A review. Environ Int. 2009 Apr;35(3):655–66.
8. Raff JD, Hites RA. Deposition versus Photochemical Removal of PBDEs from Lake Superior Air. Environ Sci Technol. 2007 Oct 1;41(19):6725–31.
9. Li X, Huang J, Fang L, Yu G, Lin H, Wang L. Photodegradation of 2,2′,4,4′-tetrabromodiphenyl ether in nonionic surfactant solutions. Chemosphere. 2008 Nov;73(10):1594–601.
10. Zhuang Y, Ahn S, Luthy RG. Debromination of Polybrominated Diphenyl Ethers by Nanoscale Zerovalent Iron: Pathways, Kinetics, and Reactivity. Environ Sci Technol. 2010 Nov 1;44(21):8236–42.
11. Zhuang Y, Jin L, Luthy RG. Kinetics and pathways for the debromination of polybrominated diphenyl ethers by bimetallic and nanoscale zerovalent iron: Effects of particle properties and catalyst. Chemosphere. 2012 Oct;89(4):426–32.
12. Huang K, Lu G, Lian W, Xu Y, Wang R, Tang T, et al. Photodegradation of 4,4′-dibrominated diphenyl ether in Triton X-100 micellar solution. Chemosphere. 2017 Aug;180:423–9.
13. Sutha J, Anila PA, Umamaheswari S, Ramesh M, Narayanasamy A, Poopal RK, et al. Biochemical responses of a freshwater fish Cirrhinus mrigala exposed to tris(2-chloroethyl) phosphate (TCEP). Environ Sci Pollut Res. 2020 Sep;27(27):34369–87.
14. Zhang M, Zhao F, Zhang J, Shi J, Tao H, Ge H, et al. Toxicity and accumulation of 6-OH-BDE-47 and newly synthesized 6,6′-diOH-BDE-47 in early life-stages of Zebrafish (Danio rerio). Sci Total Environ. 2021 Apr;763:143036.
15. Ding G, Yu J, Cui C, Chen L, Gao Y, Wang C, et al. Association between prenatal exposure to polybrominated diphenyl ethers and young children's neurodevelopment in China. Environ Res. 2015 Oct;142:104–11.
16. Poston RG, Saha RN. Epigenetic Effects of Polybrominated Diphenyl Ethers on Human Health. Int J Environ Res Public Health. 2019 Jul 29;16(15):2703.
17. Siddiqi MA, Laessig RH, Reed KD. Polybrominated diphenyl ethers (PBDEs): new pollutants-old diseases. Clin Med Res. 2003 Oct;1(4):281–90.

18. You X, Xi J, Cao Y, Zhang J, Luan Y. 4-Bromodiphenyl Ether Induces Germ Cell Apoptosis by Induction of ROS and DNA Damage in Caenorhabditis elegans. Toxicol Sci. 2017 Jun;157(2):510–8.
19. Yu L, Han Z, Liu C. A review on the effects of PBDEs on thyroid and reproduction systems in fish. Gen Comp Endocrinol. 2015 Aug;219:64–73.
20. Yu L, Liu C, Chen Q, Zhou B. Endocrine disruption and reproduction impairment in zebrafish after long-term exposure to DE-71. Environ Toxicol Chem. 2014 Jun;33(6):1354–62.
21. Alaee M. An overview of commercially used brominated flame retardants, their applications, their use patterns in different countries/regions and possible modes of release. Environ Int. 2003 Sep;29(6):683–9.
22. Grand View Research. Flame Retardant Market Size, Share & Trends Analysis Report By Product (Halogenated, Non-halogenated), By Application, By End Use, By Region, And Segment Forecasts. 2020.
23. ATSDR (Agency for Toxic Substance and Disease Registry). Toxicological profile for polybrominated biphenyl and polybrominated diphenyl ethers. 2017.
24. European Chemicals Bureau. European Union risk assessment report: Diphenyl ether, octabromo derivative. 2003.
25. Gill U, Chu I, Ryan JJ, Feeley M. Polybrominated Diphenyl Ethers: Human Tissue Levels and Toxicology. In: Ware GW, editor. Reviews of Environmental Contamination and Toxicology [Internet]. New York, NY: Springer New York; 2004 [cited 2023 Dec 29]. p. 55–97. (Reviews of Environmental Contamination and Toxicology; vol. 183). Available from: http://link.springer.com/10.1007/978-1-4419-9100-3_3
26. EPA. Polybrominated diphenyl ethers (PBDEs) action plan. In United States Environmental Protection Agency. 2009.
27. Gorini F, Iervasi G, Coi A, Pitto L, Bianchi F. The Role of Polybrominated Diphenyl Ethers in Thyroid Carcinogenesis: Is It a Weak Hypothesis or a Hidden Reality? From Facts to New Perspectives. Int J Environ Res Public Health. 2018 Aug 24;15(9):1834.
28. Venier M, Salamova A, Hites RA. Halogenated Flame Retardants in the Great Lakes Environment. Acc Chem Res. 2015 Jul 21;48(7):1853–61.
29. Hammel SC, Hoffman K, Lorenzo AM, Chen A, Phillips AL, Butt CM, et al. Associations between flame retardant applications in furniture foam, house dust levels, and residents' serum levels. Environ Int. 2017 Oct;107:181–9.
30. Ekpe OD, Choo G, Barceló D, Oh JE. Introduction of emerging halogenated flame retardants in the environment. In: Comprehensive Analytical Chemistry [Internet]. Elsevier; 2020 [cited 2023 Dec 29]. p. 1–39. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0166526X19301060
31. Hooper K, McDonald TA. The PBDEs: an emerging environmental challenge and another reason for breast-milk monitoring programs. Environ Health Perspect. 2000 May;108(5):387–92.
32. Abbasi G, Li L, Breivik K. Global Historical Stocks and Emissions of PBDEs. Environ Sci Technol. 2019 Jun 4;53(11):6330–40.
33. Li WL, Ma WL, Jia HL, Hong WJ, Moon HB, Nakata H, et al. Polybrominated Diphenyl Ethers (PBDEs) in Surface Soils across Five Asian Countries: Levels, Spatial Distribution, and Source Contribution. Environ Sci Technol. 2016 Dec 6;50(23):12779–88.
34. Maddela NR, Venkateswarlu K, Kakarla D, Megharaj M. Inevitable human exposure to emissions of polybrominated diphenyl ethers: A perspective on potential health risks. Environ Pollut. 2020 Nov;266:115240.
35. Bocio A, Llobet JM, Domingo JL, Corbella J, Teixidó A, Casas C. Polybrominated Diphenyl Ethers (PBDEs) in Foodstuffs: Human Exposure through the Diet. J Agric Food Chem. 2003 May 1;51(10):3191–5.
36. Wang HS, Jiang GM, Chen ZJ, Du J, Man YB, Giesy JP, et al. Concentrations and congener profiles of polybrominated diphenyl ethers (PBDEs) in blood plasma from Hong Kong: Implications for sources and exposure route. J Hazard Mater. 2013 Oct;261:253–9.
37. Ma X, Zhang H, Yao Z, Zhao X, Wang L, Wang Z, et al. Bioaccumulation and trophic transfer of polybrominated diphenyl ethers (PBDEs) in a marine food web from Liaodong Bay, North China. Mar Pollut Bull. 2013 Sep;74(1):110–5.
38. Bedi M, Von Goetz N, Ng C. Estimating polybrominated diphenyl ether (PBDE) exposure through seafood consumption in Switzerland using international food trade data. Environ Int. 2020 May;138:105652.
39. Shaw SD, Kannan K. Polybrominated Diphenyl Ethers in Marine Ecosystems of the American Continents: Foresight from Current Knowledge. Rev Environ Health [Internet]. 2009 Jan [cited 2023 Dec 29];24(3). Available from: https://www.degruyter.com/document/doi/10.1515/REVEH.2009.24.3.157/html
40. Hu G cheng, Dai J yin, Xu Z cheng, Luo X jun, Cao H, Wang J she, et al. Bioaccumulation behavior of polybrominated diphenyl ethers (PBDEs) in the freshwater food chain of Baiyangdian Lake, North China. Environ Int. 2010 May;36(4):309–15.
41. Genuis SK, Birkholz D, Genuis SJ. Human Excretion of Polybrominated Diphenyl Ether Flame Retardants: Blood, Urine, and Sweat Study. BioMed Res Int. 2017;2017:1–14.
42. Jiang Y, Yuan L, Lin Q, Ma S, Yu Y. Polybrominated diphenyl ethers in the environment and human external and internal exposure in China: A review. Sci Total Environ. 2019 Dec;696:133902.
43. Wu Z, He C, Han W, Song J, Li H, Zhang Y, et al. Exposure pathways, levels and toxicity of polybrominated diphenyl ethers in humans: A review. Environ Res. 2020 Aug;187:109531.
44. Hurley S, Goldberg D, Park JS, Petreas M, Bernstein L, Anton-Culver H, et al. A breast cancer case-control study of polybrominated diphenyl ether (PBDE) serum levels among California women. Environ Int. 2019 Jun;127:412–9.
45. Linares V, Bellés M, Domingo JL. Human exposure to PBDE and critical evaluation of health hazards. Arch Toxicol. 2015 Mar;89(3):335–56.
46. Leonetti C, Butt CM, Hoffman K, Miranda ML, Stapleton HM. Concentrations of polybrominated diphenyl ethers (PBDEs) and 2,4,6-tribromophenol in human placental tissues. Environ Int. 2016 Mar;88:23–9.
47. Li M, Liu Z, Gu L, Yin R, Li H, Zhang X, et al. Toxic effects of decabromodiphenyl ether (BDE-209) on human embryonic kidney cells. Front Genet [Internet]. 2014 May 6 [cited 2023 Dec 29];5. Available from: http://journal.frontiersin.org/article/10.3389/fgene.2014.00118/abstract
48. Wei Z, Xi J, Gao S, You X, Li N, Cao Y, et al. Metabolomics coupled with pathway analysis characterizes metabolic changes in response to BDE-3 induced reproductive toxicity in mice. Sci Rep. 2018;
49. Noyes PD, Stapleton HM. PBDE flame retardants: Toxicokinetics and thyroid hormone endocrine disruption in fish. Endocr Disruptors. 2014 Jan;2(1):e29430.
50. Zhang Z, Li S, Liu L, Wang L, Xiao X, Sun Z, et al. Environmental exposure to BDE47 is associated with increased diabetes prevalence: Evidence from community-based case-control studies and an animal experiment. Sci Rep. 2016 Jun 13;6(1):27854.
51. Zhang Z, Sun ZZ, Xiao X, Zhou S, Wang XC, Gu J, et al. Mechanism of BDE209-induced impaired glucose homeostasis based on gene microarray analysis of adult rat liver. Arch Toxicol. 2013 Aug;87(8):1557–67.
52. Kozlova EV, Chinthirla BD, Pérez PA, DiPatrizio NV, Argueta DA, Phillips AL, et al. Maternal transfer of environmentally relevant polybrominated diphenyl ethers (PBDEs) produces a diabetic phenotype and disrupts glucoregulatory hormones and hepatic endocannabinoids in adult mouse female offspring. Sci Rep. 2020 Oct 22;10(1):18102.
53. Wu L, Li Y, Ru H, Xie H, Yao F, Ni Z, et al. Parental exposure to 2,2′,4,4′5 - pentain polybrominated diphenyl ethers (BDE-99) causes thyroid disruption and developmental toxicity in zebrafish. Toxicol Appl Pharmacol. 2019 Jun;372:11–8.
54. Mhadhbi L, Fumega J, Boumaiza M, Beiras R. Acute toxicity of polybrominated diphenyl ethers (PBDEs) for turbot (Psetta maxima) early life stages (ELS). Environ Sci Pollut Res. 2012;
55. Zhang T, Zhou X, Xu A, Tian Y, Wang Y, Zhang Y, et al. Toxicity of polybrominated diphenyl ethers (PBDEs) on rodent male reproductive system: A systematic review and meta-analysis of randomized control studies. Sci Total Environ. 2020 Jun;720:137419.
56. Shockley KR, Cora MC, Malarkey DE, Jackson-Humbles D, Vallant M, Collins BJ, et al. Comparative toxicity and liver

transcriptomics of legacy and emerging brominated flame retardants following 5-day exposure in the rat. Toxicol Lett. 2020 Oct;332:222–34.

57. Dunnick JK, Pandiri AR, Merrick BA, Kissling GE, Cunny H, Mutlu E, et al. Carcinogenic activity of pentabrominated diphenyl ether mixture (DE-71) in rats and mice. Toxicol Rep. 2018;5:615–24.
58. Kodavanti PRS, Royland JE, Osorio C, Winnik WM, Ortiz P, Lei L, et al. Developmental Exposure to a Commercial PBDE Mixture: Effects on Protein Networks in the Cerebellum and Hippocampus of Rats. Environ Health Perspect. 2015 May;123(5):428–36.
59. Manuguerra S, Espinosa Ruiz C, Santulli A, Messina C. Sub-lethal Doses of Polybrominated Diphenyl Ethers, in Vitro, Promote Oxidative Stress and Modulate Molecular Markers Related to Cell Cycle, Antioxidant Balance and Cellular Energy Management. Int J Environ Res Public Health. 2019 Feb 18;16(4):588.
60. Bjurlid F, Dam M, Hoydal K, Hagberg J. Occurrence of polybrominated dibenzo-p-dioxins, dibenzofurans (PBDD/Fs) and polybrominated diphenyl ethers (PBDEs) in pilot whales (Globicephala melas) caught around the Faroe Islands. Chemosphere. 2018 Mar;195:11–20.
61. Hartinie Marbawi, Ahmad Razi Othman, Mohd Izuan Effendi, Halmi, Jualang Azlan Gansau and Nur Adeela Yasid, Muhammad Arif Mukhriz Ros Saidon Khudri. Kinetic Analysis of the Adsorption of Glyphosate onto Palm Oil Fronds Activated Carbon. Hibiscus Publ. 7(1):29033.
62. Chen X, Dong Y, Tian E, Xie L, Wang G, Li X, et al. 4-Bromodiphenyl ether delays pubertal Leydig cell development in rats. Chemosphere. 2018 Nov;211:986–97.
63. Cai M, Li Y, Li Y, Du K. Physiological and biochemical responses and microscopic structure changes of Populus tomentosa Carr seedlings to 4-BDE exposure. Environ Sci Pollut Res. 2015 Sep;22(18):14258–68.
64. Ran S, Du C, Du KJ. Effects of 4-bromodiphenyl ether on the adventitious root differentiation of tissue culture seedlings of *Triarrhena sacchariflora*. Bioremediation J. 2020 Oct 1;24(4):283–92.