Indian Journal of Experimental Biology
Vol. 64, January 2026, pp. 78-86
DOI: 10.56042/ijeb.v64i01.18600

Structural binding interaction of polybrominated diphenyl ethers (PBDEs) with thyroxine binding globulin: Insights into thyroid signaling disruption

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Received 06 April 2025; revised 15 June 2025

Polybrominated diphenyl ethers (PBDEs) represent an important class of halogenated flame retardants incorporated into a variety of consumer products to slowdown the spread of fire and mitigate the damage to property and human life.They have widespread environmental presence attributed to their leach out from consumer products and persistent nature making them resistant to degradation. Multiple studies have highlighted the structural resemblance between PBDEs and thyroid hormones, allowing them to mimic thyroid hormone activity and potentially disrupt its function. Therefore, it becomes pertinent to investigate and gather more data on PBDE induced thyroid dysregulation and associated toxicological effects in humans. Thyroxine-binding globulin (TBG) regulates thyroid hormone metabolism and its distribution in body making it vital for controlling thyroid hormone homeostasis. The objective of this study was to investigate the molecular interactions of commonly detected PBDEs, BDE-100 and BDE-209 with in the TBG ligand binding pocket. These ligands underwent Schrodinger's induced fit docking (IFD) along with structural binding analysis, which included molecular interaction evaluation and binding energy calculation. The analysis demonstrated that all the ligands were strongly bound within the TBG pocket, with a high degree of similarity in the TBG interacting residues between the specified PBDE ligands and the native TBG ligand, thyroxine. The calculated binding energy values for BDE-209 were higher than that of TBG native ligand, while BDE-100 values were somewhat lower but not significantly so.In conclusion, the results indicated that BDE-209 is more effective than BDE-100 in inhibiting the binding of thyroid hormones to TBG, though both PBDEs possess this ability. As a result, this could disrupt the circulatory transport of thyroid hormones and their availability at target sites, potentially causing thyroid dysregulation.

Keywords: Endocrine disruption, Polybrominated diphenyl ethers, Thyroid dysregulation, Structural characterisation

Fire poses a major threat to property and human life, and significantly increases public costs[1,2]. To mitigate these risks, flame retardants are incorporated into various materials, providing an essential safety measure that guarantees adherence to fire safety regulations and assists in delaying the progression of flames[3,4]. They minimize the damage on property and save human lives by offering extra escape time to the vulnerable section of population including senior citizens, children, and low-income population. According to a recent report, the global flame-retardant market reached US$ 9.2 billion in 2022 with projection of US$ 13.5 billion by the year 2028[5]. Polybrominated diphenyl ethers (PBDEs) are synthetic flame retardants historically used in electronics, textiles, and furniture[6,7]. The PBDEs exposure is associated with cancer, neurotoxicity, and other metabolic dysfunction, primarily through endocrine disruption and interference with hormonal signaling[8] .Generally, the majority of the PBDEs are resistant to degradation[9] and their breakdown potential diminishes with an increase in halogenation levels[10,11]. Their widespread presence in the environment can be attributed to their propensity to leach from consumer products. Additionally, their persistent and bioaccumulative characteristics further enhance their extensive environmental distribution. Numerous studies have confirmed the presence of these substances in various environmental settings, with particularly higher concentrations observed in industrialised and urban areas[12]. They can enter the human body through multiple pathways, including dermal contact, inhalation of contaminated dust or soil, and ingestion of polluted food or water. However, PBDEs have garnered considerable attention because of their potential to cause negative health impacts in both humans and wildlife[13,14].

The three commonly used commercial PBDE mixtures containing penta, octa and deca-BDE were

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listed among persistent organic pollutants (POPs) in the last two decades under Stockholm Convention in 2009 and 2017 due to their inherent high persistence, bioaccumulation, long-range transport, and toxic nature[15-17]. While PBDEs have been restricted, banned, or phased out in countries like the United States, Japan, India, and those within the European Union[18,19], but they are still reported from indoor environments in high concentrations due to leach out from the buildings and furnishing products[20,21], resulting in continuous human exposure and bioaccumulation[22]. Moreover, their gradual migration from consumer products into the environment probably will continue for numerous years in future too[23]. In China, the use and production of penta and octa-BDE commercial mixtures were banned in year 2014 which reduced the lower brominated PBDE contamination levels in food and human milk samples[24-26], however, the industrial synthesis and application of deca-BDE is still permitted with an annual output of nearly 24,000 metric tons[17,27,28]. Also the exposure from indoor contamination is more concerning as majority of the people spend more than 90% of their life in indoor environment[29,30]. Specifically, children usually are at increased risk of exposure to PBDEs due to an increased hand-to-mouth activity, different breathing zone, faster metabolism, and increased inhalation rate[31-33]. Additionally, toddlers are exposed to PBDEs through dust via hand-to-mouth contact at levels nine times higher than adults, with median daily exposure estimates of 1380 ng for toddlers compared to 154 ng for adults[34]. Furthermore, daily exposure to PBDEs from all sources for children aged 1–5 years was estimated at 13.3 ng/kg-bw/day, with approximately 77% of this exposure coming from dust[35]. Among the various PBDEs, BDE-209 is among the most prevalent in environmental compartments[36], with median concentrations in dust samples in the USA of 4.5 μg/g in homes and 4.2 μg/g in offices[37]. High levels of BDE-209, especially in homes, schools, and cars, indicate a growing trend of contamination[38]. BDE-209's unique physicochemical properties include its high stability, hydrophobicity, and ability to persist in the environment. These characteristics allow it to accumulate in various environmental compartments and resist degradation, contributing to its widespread presence and potential toxicity[39]. Likewise, BDE-100 is another PBDE compound produced on a large scale, but toxicological data remain scarce, raising scientific concern. As key regulators of cellular energy and function, mitochondria were used to assess the effects of BDE-100 at concentrations ranging from 0.1 to 50 μM, with high concentrations inducing notable mitochondrial alterations[40].

The PBDEs have widespread environmental presence sharing their structural similarity with thyroid hormones[41]. Therefore, it becomes pertinent to investigate and gather more data on thyroid dysregulation and associated toxicological effects in humans. Thyroxine-binding globulin (TBG) is vital for controlling thyroid hormone homeostasis. The regulation of thyroid hormone metabolism and distribution in the body primarily relies on TBG. TBG binds a substantial portion of thyroid hormones, thereby regulating their distribution and availability to target tissues, which makes it highly important for controlling the availability of free, physiologically active thyroid hormones. The levels of free thyroid hormones provide a more accurate reflection of the relevant physiological status than total hormone levels, which can be influenced by variations in binding protein levels. In conclusion, TBG is an essential component of the intricate regulatory system that controls thyroid hormone balance. Its dynamic interactions with thyroid hormones, along with its role in various physiological and pathological processes, underscore the importance of understanding its contribution to overall thyroid health[42-45]. This study is aimed to characterise the structural binding of the commonly found PBDEs, BDE-100 and BDE-209 to the ligand binding pocket of the thyroxine transport protein, TBG, using molecular docking simulations. The objectives were to describe the structural interactions between indicated PBDEs and TBG, and to investigate the potential disruption of thyroid hormone transport by these frequently identified compounds. While previous research has highlighted the possibility of thyroid dysfunction due to various PBDE congeners, studies examining their impact on thyroid hormone transport, particularly concerning these two PBDEs, BDE-100 and BDE-209 are limited. Moreover, despite previous studies on other congeners, it is essential to prioritise further research on BDE-209 and BDE-100 due to their widespread use and potential risks. BDE-209, commonly produced in deca-formulation products, remains a significant environmental and health concern because of its stability and persistence. Similarly, BDE-100, though less studied, shares similar properties and is also produced at large scale. Given their enduring presence in the environment and their possible long-term impacts, studying these two compounds is

crucial to fully understanding their effects, even in light of prior research on other congeners. Furthermore, no structural studies have been published on the interactions of these two PBDE ligands with the TBG ligand binding pocket. Thus, this study fills this gap by focusing on the structural interactions of BDE-100 and BDE-209 with TBG.

Materials and Methods

For this study, two frequently detected PBDE ligands, BDE-100 and BDE-209 were used. The PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/) was used to retrieve their three-dimensional structural coordinates. Additionally, the Schrodinger 2017 suite was used to perform the structural binding study of these PBDE ligands, with Maestro 11.4 acting as the graphical user interface (Schrodinger, LLC, New York, NY, 2017). The specific methodology is explained in our earlier research[46,47].

Protein preparation

The Protein Data Bank (PDB; http://www.rcsb.org/) was used to obtain the three-dimensional structural coordinates for the TBG crystal structure in complex with the natural ligand, thyroxine (T4), solved at 1.55 Å resolution (PDB code: 4X30). Processing came next, in which the protein complex was ready for subsequent stages using Schrodinger Glide's protein preparation wizard methodology for molecular simulation investigations (Schrodinger suite 2017-4; Schrodinger, LLC) as described previously[46,47]. The TBG crystal complex was initially imported into the Glide docking program as part of the protein preparation process. Moreover, water molecules were eliminated, and hydrogen atoms and charges were added. Finally, energy minimisation was carried out after the hydrogen bond networks were optimised.

Ligand preparation

The structures of PBDEs (BDE-100 and BDE-209) were obtained from the PubChem database, with chemical IDs 154083 and 14410, respectively. Their two-dimensional structures are shown in Fig. 1. For simulation investigations, the indicated ligands were prepared using Schrodinger's LigPrep module (Schrodinger 2017: LigPrep, Schrodinger, LLC) as described in our earlier research research[46,47].

Induced Fit Docking

Both PBDE ligands, BDE-100 and BDE-209, as well as T4, were docked into the TBG ligand binding pocket utilizing Schrodinger′s Induced Fit Docking (IFD) module, as previously outlined in our studies[46,47]. Unlike conventional rigid docking, IFD allows for flexibility in both the protein's ligand binding site as well as ligand. To develop and validate protocols for accurately predicting the poses of receptor-ligand interactions and the corresponding alterations in the ligand binding pocket of the protein receptor, we utilised Schrodinger′s Glide and Refinement module in Prime. In summary, the initial phase of the IFD process involved generating a grid at the binding site of the native ligand, T4, within TBG. The protein preparation phase utilised an RMSD cutoff of 0.18 Å to conduct constrained minimisation of the protein receptor. Subsequently, initial Glide docking was executed with a softened potential and optional removal of side chains for both the PBDE ligands, resulting in the retention of twenty docking poses by default. Following this, side chain predictions were made for amino acids within a 5 Å radius of each receptor-ligand complex for any given pose, and minimisation was carried out. Additionally,

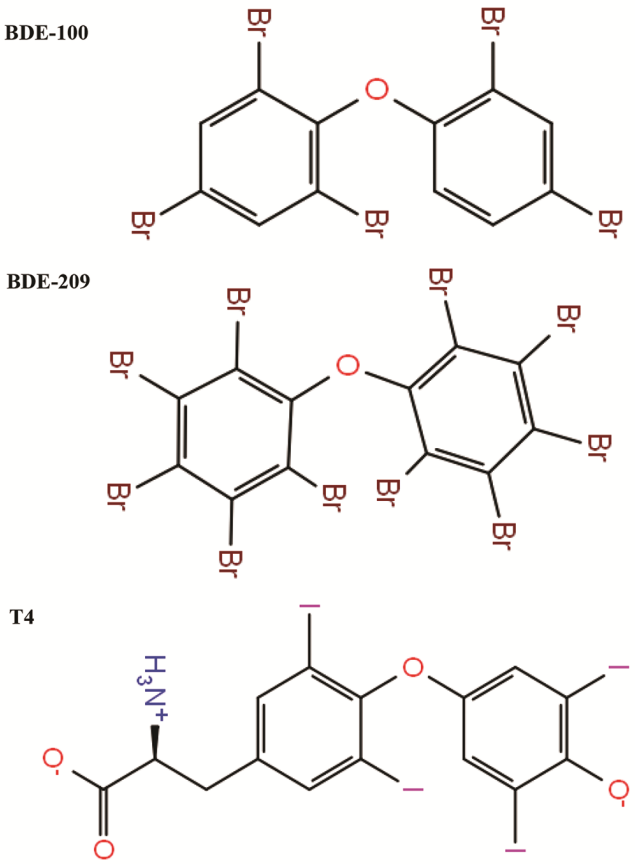

Fig.1 — Two-dimensional structure of BDE-100, BDE-209 and TBG native ligand, T4.

ligand minimisation was conducted for each receptor-ligand complex pose. We also performed Glide re-docking and estimated the IFD score. An extended sampling protocol was implemented as well. Furthermore, IFD was conducted for the native ligand of TBG, T4 too.

Binding energy estimation

The binding affinity of both the PBDE ligands, BDE-100 and BDE-209 for the TBG binding pocket was calculated using the molecular mechanics generalised born surface area (MMGB-SA) function from the Prime module of Schrodinger 2017, as detailed in our previous studies[46,47].

Results

The two frequently detected PBDEs congeners, BDE-100, and BDE-209, successfully docked in the TBG ligand binding pocket. The stability of the indicated PBDE ligands in the TBG ligand binding pocket was suggested by the tight placement of each ligand in the ligand binding pocket utilising the IFD technique. Only the top-ranking pose was ultimately selected and proceeded with for structural binding investigation and characterisation, even though several display poses were generated for every protein-ligand docking complex. Similarly, TBG native ligand T4 docked successfully and was firmly positioned in the ligand binding pocket after IFD. Again, the top-ranking display pose was chosen and proceeded with for additional examination. The Fig. 2 displays the top ranked docking display poses that reveal interactions between the TBG amino acid residue and each of the indicated PBDE ligands. Moreover, Fig. 3 shows the optimal docking pose that displays interactions between TBG amino acid residues and its native ligand, T4. The indicated PBDE ligands, BDE-100 and BDE-209 interacted with 15 and 17 respectively amino acid residues in the TBG ligand binding pocket (Fig. 2A & 2B).

IFD of BDE-100 ligand with TBG

The IFD docking display complex TBG-BDE100 demonstrated an array of interactions with a multitude of amino acid residues of TBG. In total, 15 amino acid residues were identified, each engaging in a variety of molecular interactions such as hydrophobic interactions, hydrogen bonding, and van der Waals forces with BDE-100. The amino acid residues within the TBG ligand binding pocket that participated in various interactions included Ser-24, Ala-27, Gln-238, Leu-246, Leu-248, Ser-266, Leu-269, Lys-270, Trp-272, Asn-273, Leu-276, Leu-376, Arg-378, Arg-381, and Ile-383 (Fig. 2A). Additionally, one hydrogen bonding interaction between BDE-100 and Arg-381 was also observed.

Likewise, the native ligand docking display complex, TBG-T4, displayed several molecular contacts with many TBG amino acid residues (Fig. 3). Fifteen amino acid residues in total were shown to exhibit various molecular interactions with T4, such as hydrophobic, hydrogen bonding, van der Waals, salt bridge, etc. The amino acids in question were Ser-23, Ala-27, Gln-238, Leu-246, Leu-248, Leu-269, Lys-270, Trp-272, Asn-273, Leu-276, Leu-376, Arg-378, Arg-381, Ser-382 and Ile-383. Additionally, T4 demonstrated two interactions with Asn-273 through

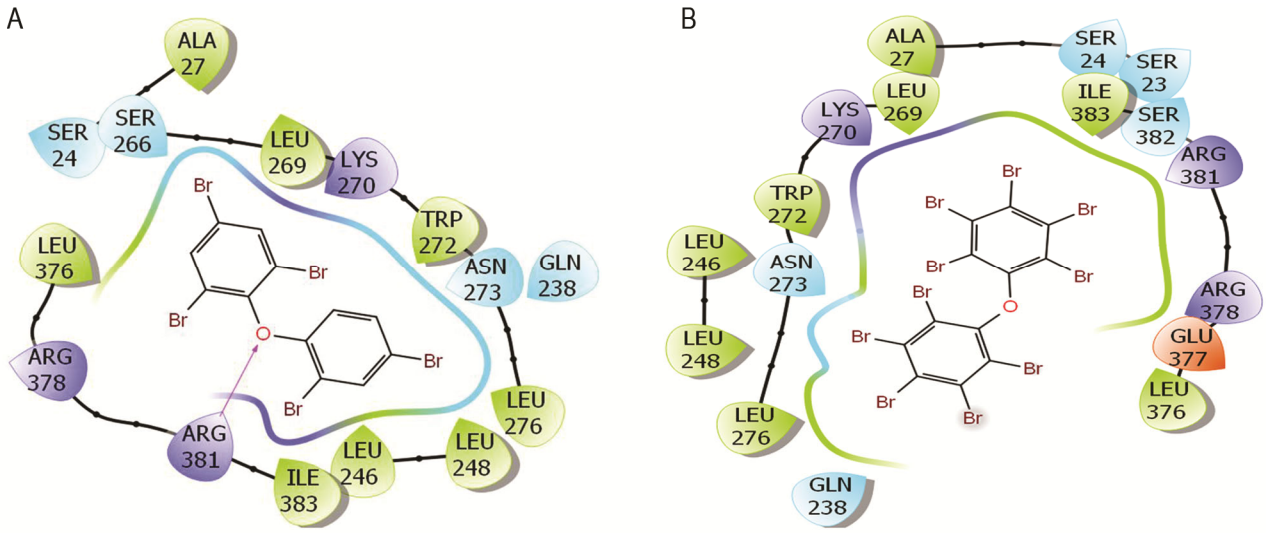

Fig. 2— Molecular interactions of PBDEs (A) BDE-100, (B) BDE-209 with amino acid residues lining TBG ligand binding pocket.

hydrogen bonds. Furthermore, T4 established two additional hydrogen bonding interactions with Arg-381 and Arg-378, respectively. Additionally, two salt bridge interactions with Lys-270 and Arg-381 were also observed (Fig. 3). Moreover, Table 1 lists additional crucial structural binding characterization parameters for BDE-100 and the TBG native ligand, T4, such as IFD, Dock score, Glide score, binding energy, etc. Furthermore, it was calculated that BDE-100 and T4 shared about 87% of their TBG-interacting amino acid residues. Besides, two additional amino acid residues Ser-24 and Ser-266 were also observed interacting with BDE-100. In contrast to TBG native ligand T4, the calculated binding energy for BDE-100 was low, which is crucial for structural binding characterisation.

IFD of BDE-209 ligand with TBG

The congener BDE-209 showed a variety of molecular interactions with TBG amino acid residues. Seventeen amino acid residues were seen in the docking display pose of BDE-209 interacting with TBG in different molecular ways (Fig. 2B). The amino acid residues within the TBG ligand binding pocket that participated in various interactions included Ser-23, Ser-24, Ala-27, Gln-238, Leu-246, Leu-248, Leu-269, Lys-270, Trp-272, Asn-273, Leu-276, Leu-376, Glu-377, Arg-378, Arg-381, Ser-382 and Ile-383. Additionally, a 100% match in amino acid interactions was found when the docking poses of the native ligands T4 and BDE-209 were compared. However, because of extra amino acid residues, such as Ser-24 and Glu-377, other molecular interactions were also seen in the TBG-BDE209 complex (Fig. 2B).

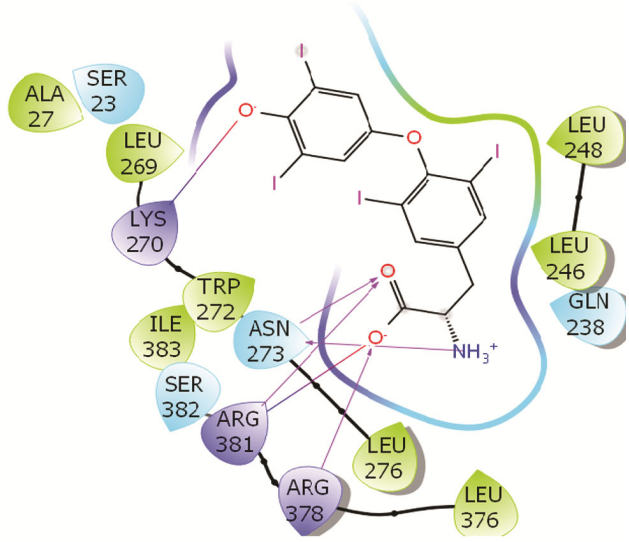

Fig. 3— Molecular interactions of a TBG native ligand, T4 with amino acid residues lining TBG ligand binding pocket.

Discussion

The objective of this study was to gain structural understanding of the possible interruption of circulatory thyroid hormone transport by PBDEs, BDE-100, and BDE-209, as well as to predict the resulting implications in thyroid dysregulation. Our analysis of the structural binding data showed that both PBDE ligands, BDE-100 and BDE-209, successfully bound within the ligand-binding pocket of TBG. The results also indicated that the docked complexes, TBG-BDE100 and TBG-BDE209 were stable. This stability and the overall quality of the TBG-PBDE complexes were further confirmed by the calculated binding energy values and various structural binding parameters, such as the Dock score, IFD score, and glide score. Numerous molecular interactions, including salt bridges, hydrophobic interactions, van der Waals forces and hydrogen bonding observed in the docked complexes of TBG and PBDEs, significantly contributed to the stability of these complexes. A comparative analysis of the selected docking displays of TBG-PBDE complexes in relation to the native ligand configuration of the TBG-T4 complex, showed 87–100% similarity in the interactions of amino acid residues within the ligand binding pocket of TBG. The binding energy values determined for BDE-100 were less than that estimated for the native ligand of TBG, T4, while the values calculated for BDE-209 exceeded those estimated for T4. Therefore, our findings indicate that the PBDE ligands, BDE-100, and BDE-209, may interfere with the transport of thyroid hormones by TBG. This disruption could lead to thyroid dysfunction,

Table 1 — Structural binding indices of plasticizers (BDE-100, BDE-209) and a TBG native ligand, T4

Ligand	Number of interacting residues	Percentage of interacting residues common with native ligand (%)	IFD score	Docking score (Kcal/mol)	Glide score (Kcal/mol)	MMGB-SA (Kcal/mol)
BDE-100	15	86.6%	-828.74	-6.91	-6.91	-108.52
BDE-209	17	100%	-831.12	-8.16	-8.16	-146.14
T4	15	100%	-833.29	-8.37	-8.37	-124.31

potentially resulting in several health problems including developmental issues. The binding energy estimation results indicate that the TBG-BDE209 complex exhibits greater stability compared to the TBG-BDE100 complex, suggesting that BDE-209 has a higher binding affinity for the TBG binding pocket than BDE-100. The enhanced stability of the TBG-BDE209 complex indicates a stronger association, which may lead to a more significant disruption of TBG's physiological functions compared to the TBG-BDE100 complex. This observed difference is likely to have a substantial effect on their thyroid dysfunction activities.

As per a literature review, few studies are documented on structural binding characterisation of PBDEs ligands with proteins including TBG[48-50]. However, there are no known structural investigations reported on molecular interactions of BDE-100 and BDE-209 with TBG. Nevertheless, we recently published the structural characterisation and molecular interactions of TBG with BDE-28, BDE-85, BDE-154 and BDE-183[51]. In another study, we performed structural binding characterisation of BDE-153 against TBG ligand binding pocket[52]. Additionally, we reported the binding of both hydroxy and methoxy metabolites of PBDE's to TBG[53]. Furthermore, *in vitro* binding experiments utilising fluorescent probes have demonstrated that several hydroxylated PBDEs effectively bind to TBG with some of the analogues exhibiting greater binding compared to T4[54]. Findings from a fluorescence displacement assay indicated that hydroxylated PBDEscould potentially displace thyroid hormones from their binding sites on TBG[55]. Additionally, a Surface Plasmon Resonance investigation revealed that certain hydroxylated metabolites of PBDEs exhibited strong binding affinity to TBG[56]. Several contemporary investigations have revealed that PBDE sulphate metabolites bind with TBG, which may indicate a disruption in normal thyroid function[57].

Numerous epidemiological studies have explored the relationship between circulating thyroid hormone (TH) levels and exposure to polybrominated diphenyl ethers (PBDEs) in human tissues. However, the findings remain indecisive, and no conclusive outcomes have been established. The relationship between PBDE exposure and serum T4 levels has been the subject of conflicting research. Some investigations have reported positive correlations[58-60], while others have observed negative relationships[61-63], and certain studies have found no significant associations in both pregnant women and adult men[64,65]. The observed positive correlations between PBDEs and total thyroxine (TT4) and free thyroxine (FT4) contrast with the typical outcomes of animal research conducted in laboratories. These discrepancies may arise from several factors, including elevated exposure levels and the younger developmental stages of the animals at the time of exposure, variations between acute and chronic exposure, and the distinct impacts of different congeners[55]. A study highlighted that prenatal exposure to polybrominated diphenyl ethers (PBDEs) may increase thyroid-stimulating hormone (TSH) levels in the umbilical cord blood of infants delivered vaginally[66]. Another study revealed negative correlation between serum TSH levels and PBDE exposure at median concentrations below 30 ng/g lipid. In contrast, a positive association was observed when median levels exceeded 100 ng/g lipid, with no significant correlation found in the 30-100 ng/g lipid range[67]. A similar trend was seen in the relationship between PBDE exposure and TT4 serum levels[68].

Likewise, laboratory animal studies have similarly demonstrated changes in thyroid hormone concentrations due to exposure to PBDEs[69]. Specifically, variations in T4 levels have been observed in rodents, felines, and avian species subjected to PBDEs exposure[70-72]. Numerous studies involving rodents have indicated that exposure to PBDEs is associated with decreased serum levels of T4, ultimately resulting in hypothyroidism. Studies on rats have shown that TBG binding with PBDEs[73], is inversely correlated with thyroid hormone levels and PBDE exposure[74]. A study on rodents found a notable reduction in T4 levels on exposure to PBDEs both before and after birth[75-76]. Reduced T4 levels were observed in rat offspring exposed to PBDEs during pregnancy[77]. A zebrafish study investigating the transgenerational effects of BDE-209 exposure revealed lower T4 levels and decreased expression of the thyroid hormone receptor gene in F1 individuals[78].

Conclusion

The findings from our research indicated that the two PBDE ligands, BDE-100 and BDE-209 showed considerable overlap in the amino acid residues interacting within the TBG ligand binding pocket, akin to those of the native ligand T4. Importantly, the binding energy of BDE-209 exceeded that of T4, while BDE-100 displayed lower values without significant difference. As a result, our initial findings

suggest that BDE-209, along with BDE-100 to a lesser extent, may engage in competitive binding with TBG, potentially displacing the native ligand T4. This competitive interaction could interfere with the transport of thyroid hormones in the bloodstream, potentially leading to thyroid hormone dysfunction and related health issues.

Acknowledgement

The Deanship of Scientific Research (DSR) at King Abdulaziz University (KAU), Jeddah, Saudi Arabia has funded this Project under grant no (G: 299-141-1443).

Conflict of interest

The authors acknowledge that there is no conflict to declare.

References

1 Global Fire Statistics Centre. (2022). Global fire mortality statistics. *GFSCPublications.*
2 United Nations Economic and Social Council. (2021). Economic impact of global fire incidents. *United Nations Publication*.
3 Xue J, Xiao Q, Zhang M, Li D & Wang X. Toxic Effects and Mechanisms of Polybrominated Diphenyl Ethers. *Int J Mol Sci,* 24 (2023) 13487.
4 National Institute of Environmental Health Sciences. *Flame Retardants*. 14 April 2023.
5 IMARC group report, 2023. Flame Retardants Market: Global Industry Trends, Share, Size, Growth, *Opportunity and Forecast* 2023-2028.
6 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*, 696 (2019) 133902.
7 Klinčić D, Dvoršćak M, Jagić K, Mendaš G & Romanić SH. Levels and distribution of polybrominated diphenyl ethers in humans and environmental compartments: a comprehensive review of the last five years of research. *Environ Sci Pollut Res Int*, 27 (2020) 5744.
8 García-Suastegui WA, Navarro-Mabarak C, Silva-Adaya D, Dolores-Raymundo HG, Alvarez-Gonzalez MY, León-Olea M & Ramos-Chávez LA. Neurotransmitter Systems Affected by PBDE Exposure: Insights from In Vivo and In Vitro Neurotoxicity Studies. *Toxics,* 13(2025) 316.
9 Besis A & Samara C. Polybrominated diphenyl ethers (PBDEs) in the indoor and outdoor environments–a review on occurrence and human exposure. *Environ Pollut*, 169 (2012) 217.
10 Loganathan BG & Kannan K. Global organochlorine contamination trends: an overview. *AMBIO A J Hum Environ*, 23 (1994) 187.
11 Nouira T, Risso C, Chouba L, Budzinski H & Boussetta H. Polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) in surface sediments fromMonastir Bay (Tunisia, CentralMediterranean): occurrence, distribution and seasonal variations. *Chemosphere*, 93 (2013) 487.
12 Jiang L, Yang J, Yang H, Kong L, Ma H, Zhu Y, Zhao X, Yang T &Liu W. Advanced understanding of the polybrominated diphenyl ethers (PBDEs): Insights from total environment to intoxication. *Toxicology.* 509 (2024)153959.
13 Johnson-Restrepo B & Kannan K. An assessment of sources and pathways of human exposure to polybrominated diphenyl ethers in the United States. *Chemosphere*, 76 (2009) 542.
14 Trudel D, Scheringer M, Von Goetz N & Hungerbühler K. Total consumer exposure to polybrominated diphenyl ethers in north america and europe. *Environ Sci Technol.* 45 (2011) 2391.
15 UNEP/POPs (2009a) HexaBDE and heptaBDE. (http://chrn. pops.int/lmplementation/Alternatives/ AlternativestoPOPs/ChemicalslistedinAnnexA/HexaBDEandh eptaBDE/tabid/5862/Default.aspx.
16 UNEP/POPs(2009b)TetraBDEandpentaBDE.(http://chm.pops. int/lmplementation/Alternatives/AlternativestoPOPs/Chemical slistedinAnnexA/TetraBDEandpentaBDE/ta bid/5868/Default.aspx).
17 UNEP/POPs (2017) Decabromodiphenyl Ether (Commercial Mixture, c-decaBDE). (http:/ /chm.pops. int/lmplemen tation/ Alternatives/ AlternativestoPO Ps/Chemicalsliste dinAnnexA/cdecaBDE/tabid/5985/Default.aspx).
18 Olisah C, Okoh OO & Okoh AI. A bibliometric analysis of investigations of polybrominated diphenyl ethers (PBDEs) in biological and environmental matrices from 1992–2018. *Heliyon*, 4 (2018) e00964.
19 Sharkey M, Harrad S, Abdallah MA, Drage DS & Berresheim H. Phasing-out of legacy brominated flame retardants: The UNEP Stockholm Convention and other legislative action worldwide. *Environ Int*, 144 (2020) 106041.
20 Li X, Liu Y, Yin Y, Wang P & Su X. Occurrence of some legacy and emerging contaminants in feed and food and their ranking priorities for human exposure. *Chemosphere*, 321 (2023)138117.
21 Yu X, Liu B, Yu Y, Li H, Li Q, Cui Y & Ma Y. Polybrominated diphenyl ethers (PBDEs) in household dust: A systematic review on spatio-temporal distribution, sources, and health risk assessment. *Chemosphere*, 314 (2023) 137641.
22 Kanaya N, Bernal L, Chang G, Yamamoto T, Nguyen D, Wang YZ, Park JS, Warden C, Wang J, Wu X, Synold T, Rakoff M, Neuhausen SL & Chen S. Molecular Mechanisms of Polybrominated Diphenyl Ethers (BDE-47, BDE-100, and BDE-153) in Human Breast Cancer Cells and Patient-Derived Xenografts. *Toxicol Sci*, 169 (2019) 380.
23 Andrade, NA, McConnell LL, Anderson MO, Torrents A & Ramirez M. Polybrominated diphenyl ethers: Residence time in soils receiving biosolids application. *Environ Pollut*, 222 (2017) 412.
24 Luo Q, Shan Y, Muhammad A, Wang S, Sun L & Wang H. Levels, distribution, and sources of organophosphate flame retardants and plasticizers in urban soils of Shenyang, China. *Environ Sci Pollut Res Int*, 25 (2018) 31752.
25 Wang J, Zhao X, Wang Y & Shi Z. Tetrabromobisphenol A, hexabromocyclododecane isomers and polybrominated diphenyl ethers in foodstuffs from Beijing, China: Contamination levels, dietary exposure and risk assessment. *Sci Total Environ*, 666 (2019) 812.
26 Zhao X & Shi Z. Legacy brominated flame retardants in human milk from the general population in Beijing, China: Biomonitoring, temporal trends from 2011 to 2018, and

nursing infant's exposure assessment. *Chemosphere*, 285 (2021) 131533.
27 Shi Z, Zhang L, Li J & Wu Y. Legacy and emerging brominated flame retardants in China: a review on food and human milk contamination, human dietary exposure and risk assessment. *Chemosphere*, 198 (2018) 522.
28 UNEP/POPs (2019) http://chm.pops.int/TheConvention/ThePOPs/tabid/673/Default. Aspx.
29 Lucattini L, Poma G, Covaci A, de Boer J, Lamoree MH &Leonards PEG. A review of semi-volatile organic compounds (SVOCs) in the indoor environment: occurrence in consumer products, indoor air and dust. *Chemosphere*, 201 (2018) 466.
30 Melymuk L, Demirtepe H & Jílková SR. Indoor dust and associated chemical exposures. *Curr Opin Environ Sci Health*, 15 (2020) 1.
31 van den Eede N, Heffernan AL, Aylward LL, Hobson P, Neels H, Mueller JF & Covaci A. Age as a determinant of phosphate flame retardant exposure of the Australian population and identification of novel urinary PFR metabolites. *Environ Int,* 74 (2015)1.
32 Gibson EA, Stapleton HM, Calero L, Holmes D, Burke K, Martinez R, Cortes B, Nematollahi A, Evans D, Anderson KA & Herbstman JB. Differential exposure to organophosphate flame retardants in mother-child pairs. *Chemosphere*, 219 (2019)567.
33 Koppen G, Govarts E, Vanermen G, Voorspoels S, Govindan M, Dewolf MC, den Hond E, Biot P, Casteleyn L, Kolossa-Gehring M, Schwedler G, Angerer J, Koch HM, Schindler BK, Casta˜no A, L´opez ME, Sepai O, Exley K, Bloemen L, Knudsen LE, Joas R, Joas A, Schoeters G & Covaci A. Mothers and children are related, even in exposure to chemicals present in common consumer products. *Environ Res*, 175 (2019) 297.
34 Stapleton HM, Kelly SM, Allen JG, Mcclean MD & Webster TF. Measurement of polybrominated diphenyl ethers on hand wipes: estimating exposure from hand-to-mouth contact. *Environ Sci Technol*, 42 (2008) 3329.
35 Johnson-Restrepo B & Kannan K. An assessment of sources and pathways of human exposure to polybrominated diphenyl ethers in the United States. *Chemosphere*, 76 (2009) 542.
36 Noyes PD & Stapleton HM. Toxicokinetics and thyroid hormone endocrine disruption in fish. *Endocr Disruptors*, 2 (2014) e29430.
37 Allen JG, Stapleton HM, Vallarino J, McNeely E, McClean MD, Harrad SJ, Rauert CB & Spengler JD. Exposure to flame retardant chemicals on commercial airplanes. *Environ Health*, 12 (2013) 17.
38 Zheng K, Zeng Z, Lin Y, Wang Q, Tian Q & Huo X. Current status of indoor dust PBDE pollution and its physical burden and health effects on children. *Environ Sci Pollut Res Int*, 30 (2023) 19642.
39 Sun Y, Xu Y, Wu H & Hou J. A critical review on BDE-209: Source, distribution, influencing factors, toxicity, and degradation. *Environ. Int*, 183 (2024) 108410.
40 Pereira LC, de Souza AO & Dorta DJ, Polybrominated diphenyl ether congener (BDE-100) induces mitochondrial impairment. *Basic Clin Pharmacol Toxicol*, 112(2023) 418.
41 Hoffman K, Lorenzo A, Butt CM, Hammel SC, Henderson BB, Roman SA, Scheri RP, Stapleton HM & Sosa JA. Exposure to flame retardant chemicals and occurrence and severity of papillary thyroid cancer: A case-control study. *Environ Int*, 107 (2017) 235.
42 Chakravarthy V & Ejaz S. Thyroxine-Binding Globulin Deficiency. *StatPearls Publishing*. (2025)
43 Heo J, Kim SM, Ryu HJ, Park H, Kim TH, Chung JH, Park HD & Kim SW. Identification of Mutations in the Thyroxine-Binding Globulin (TBG) Gene in Patients with TBG Deficiency in Korea*. Endocrinol Metab (Seoul),* 37 (2022) 870.
44 Werner SC, Braverman LE & Ingbar SH. Chapter 6, Hormone transport in blood. *5th ed. Philadelphia: Lippincott*, (1986) 116.
45 Oppenheimer JH. Role of plasma proteins in the binding, distribution and metabolism of the thyroid hormones. *N Engl J Med*, 278 (1968) 1153.
46 Sheikh IA. Stereoselectivity and potential endocrine disrupting activity of Bis-(2-ethylhexyl) phthalate (DEHP) against human progesterone receptor: A computational perspective. *J Appl Toxicol*, 36 (2016) 741.
47 Zughaibi TA, Sheikh IA & Beg MA. Insights into the Endocrine Disrupting Activity of Emerging Non-Phthalate Alternate Plasticizers against Thyroid Hormone Receptor: A Structural Perspective. *Toxics*, 10 (2022) 263.
48 Cao J, Lin Y, Guo LH, Zhang AQ, Wei Y & Yang Y. Structure-based investigation on the binding interaction of hydroxylated polybrominated diphenyl ethers with thyroxine transport proteins. *Toxicology*, 277(2010) 20.
49 Yang W, Shen S, Mu L & Yu H. Structure-activity relationship study on the binding of PBDEs with thyroxine transport proteins. *Environ Toxicol Chem*, 30 (2011) 2431.
50 Li F, Xie Q, Li X, Li N, Chi P, Chen J, Wang Z & Hao C. Hormone activity of hydroxylated polybrominated diphenyl ethers on human thyroid receptor-beta: in vitro and *in silico* investigations. *Environ Health Perspect*, 118 (2010) 602.
51 Sheikh IA, Zughaibi TA, Beg MA, Macha MA & Alharthy SA. Role of polybrominated diphenyl ethers in thyroid hormone transport disruption. *Ind J Exp Biol*, 63 (2025) 18.
52 Sheikh IA & Beg MA. Structural binding perspectives of common plasticizers and a flame retardant BDE-153 against thyroxine binding globulin: potential for endocrine disruption. *J Appl Toxicol*, 42 (2022) 841.
53 Sheikh IA & Beg MA. Structural studies on the endocrine-disrupting role of polybrominated diphenyl ethers (PBDEs) in thyroid diseases. *Environ Sci Pollut Res Int*, 27 (2020) 37866.
54 Ren XM & Guo LH. Assessment of the Binding of Hydroxylated Polybrominated Diphenyl Ethers to Thyroid Hormone Transport Proteins Using a Site-Specific Fluorescence Probe. *Environ Sci Technol*, 46 (2012) 4633.
55 Cao J, Lin Y, Guo LH, Zhang AQ, Wei Y & Yang Y. Structure-Based Investigation on the Binding Interaction of Hydroxylated Polybrominated Diphenyl Ethers with Thyroxine Transport Proteins. *Toxicology*, 277 (2010) 20.
56 Marchesini GR, Meimaridou A, Haasnoot W, Meulenberg E, Albertus F, Mizuguchi M, Takeuchi M, Irth H & Murk AJ. Biosensor discovery of thyroxine transport disrupting chemicals. *Toxicol Appl Pharmacol*, 232 (2008) 150.
57 Qin WP, Li CH, Guo LH, Ren XM & Zhang JQ. Binding and activity of polybrominated diphenyl ether sulfates to thyroid hormone transport proteins and nuclear receptors. *Environ Sci Process Impacts*, 21 (2019) 950.
58 Turyk ME, Persky VW, Imm P, Knobeloch L, Chatterton R & Anderson HA. Hormone disruption by PBDEs in adult male sport fish consumers. *Environ Health Perspect*, 116 (2008)1635.

59 Stapleton HM, Eagle S, Anthopolos R, Wolkin A & Miranda ML. Associations between polybrominated diphenyl ether (PBDE) flame retardants, phenolic metabolites, and thyroid hormones during pregnancy. *Environ Health Perspect*, 119 (2011)1454.
60 Meeker JD, Johnson PI, Camann D & Hauser R. Polybrominated diphenyl ether (PBDE) concentrations in house dust are related to hormone levels in men. *Sci Total Environ*, 407 (2009) 3425.
61 Zota AR, Park JS, Wang Y, Petreas M, Zoeller RT &Woodruff TJ. Polybrominated diphenyl ethers, hydroxylated polybrominated diphenyl ethers, and measures of thyroid function in second trimester pregnant women in California. *Environ Sci Technol*, 45 (2011) 7896.
62 Abdelouahab N, Langlois MF, Lavoie L, Corbin F, Pasquier JC & Takser L. Maternal and cord-blood thyroid hormone levels and exposure to polybrominated diphenyl ethers and polychlorinated biphenyls during early pregnancy. *Am J Epidemiol*, 178 (2013) 701.
63 Makey CM, McClean MD, Braverman LE, Pearce EN, He XM, Sjödin A, Weinberg JM& Webster TF. Polybrominated Diphenyl Ether Exposure and Thyroid Function Tests in North American Adults. *Environ Health Perspect*, 124 (2016) 420.
64 Bloom M, Spliethoff H, Vena J, Shaver S, Addink R & Eadon G. Environmental exposure to PBDEs and thyroid function among New York anglers. *Environ Toxicol Pharmacol*, 25 (2008) 386.
65 Chevrier J, Harley KG, Bradman A, Gharbi M, Sjödin A & Eskenazi B. Polybrominated diphenyl ether (PBDE) flame retardants and thyroid hormone during pregnancy. *Environ Health Perspect*, 118 (2010) 1444.
66 Herbstman JB, Sjödin A, Apelberg BJ, Witter FR, Halden RU, Patterson DG, Panny SR, Needham LL & Goldman LR. Birth delivery mode modifies the associations between prenatal polychlorinated biphenyl (PCB) and polybrominated diphenyl ether (PBDE) and neonatal thyroid hormone levels. *Environ Health Perspect*, 116 (2008) 1376.
67 Zhao X, Wang H, Li J, Shan Z, Teng W & Teng X. The Correlation between Polybrominated Diphenyl Ethers (PBDEs) and Thyroid Hormones in the General Population: A Meta-Analysis. *PLoS ONE*, 10 (2015) e0126989.
68 Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S &Wiersinga W. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. T*hyroid*, 21 (2011) 1081.
69 Darnerud PO.Brominated flame retardants as possible endocrine disrupters. *Int J Androl*, 31 (2008) 152.
70 Czerska M, Zieli´nski M, Kami´nska J & Ligocka D. Effects of polybrominated diphenyl ethers on thyroid hormone, neurodevelopment and fertility in rodents and humans. *Int J Occup Med Environ Health*, 26 (2013) 498.
71 Walter KM, Lin YP, Kass PH & Puschner B. Association of Polybrominated Diphenyl Ethers (PBDEs) and Polychlorinated Biphenyls (PCBs) with Hyperthyroidism in Domestic Felines, Sentinels for Thyroid Hormone Disruption. *BMC Vet Res*, 13 (2017) 120.
72 Guigueno MF & Fernie KJ. Birds and flame retardants: A review of the toxic effects on birds of historical and novel flame retardants. *Environ Res*, 154 (2017) 398.
73 Szabo DT, Richardson VM, Ross DG, Diliberto JJ, Kodavanti PR & Birnbaum LS. Effects of perinatal PBDE exposure on hepatic phase I, phase II, phase III, and deiodinase 1 gene expression involved in thyroid hormone metabolism in male rat pups. *Toxicol Sci*, 107 (2009) 27.
74 Lee E, Kim TH, Choi JS, Nabanata P, Kim Y, Ahn MY, Jung KK, Kang IH, Kim TS, Kwack SJ, Park KL, Kim SH, Kang TS, Lee J, Lee BM & Kim HS. Evaluation of liver and thyroid toxicity in SpragueDawley rats after exposure to polybrominated diphenyl ether BDE209. *J Toxicol Sci*, 35 (2010) 535.
75 Hamers T, Kamstra JH, Sonneveld E, Murk AJ, Kester MH, Andersson PL, Legler J & Brouwer A. In vitro profiling of the endocrine-disrupting potency of brominated flame retardants. *Toxicol Sci*, 92 (2006) 157.
76 Kim TH, Lee YJ, Lee E, Kim MS, Kwack SJ, Kim KB, Chung KK, Kang TS, Han SY, Lee J, Lee BM & Kim HS. Effects of gestational exposure to decabromodiphenyl ether on reproductive parameters, thyroid hormone levels, and neuronal development in Sprague-Dawley rats offspring. *J Toxicol Environ Health A*, 72 (2009) 1296.
77 Kuriyama SN, Wanner A, Fidalgo-Neto AA, Talsness CE, Koerner W & Chahoud I. Developmental exposure to low-dose PBDE-99: Tissue distribution and thyroid hormone levels. *Toxicology*, 242 (2007) 80.
78 Han Z, Li Y, Zhang S, Song N, Xu H, Dang Y, Liu C, Giesy JP & Yu H. Prenatal transfer of decabromodiphenyl ether (BDE209) results in disruption of the thyroid system and developmental toxicity in zebrafish offspring. *Aquat Toxicol*, 190 (2017) 46