Toxicology International, *29(1) : 47-63; 2022. DOI: 10.18311/ti/2022/v29i1/27859*

Online ISSN : 0976-5131; Print ISSN : 0971-6580

Toxicology International

Contents available at: www.informaticsjournals.com/index.php/toxi



Environmental Fate, Exposure and Toxicity of New Emerging Pollutant: Tetrabromobisphenol A.

Prince Sharma[1]*, Khushboo Sharma[1], Mandeep Singh[1] and Pooja Chadha[2]

[1]Cytogenetics Lab, Department of Zoology, Guru Nanak Dev University, Amritsar, Punjab – 143005, India; princeranyal@gmail.com, skhushboo200@gmail.com, mandeepdhimnman15@gmail.com
[2]Department of Zoology, Guru Nanak Dev University, Amritsar, Punjab – 143005, India; poojachadha77@yahoo.co.in

ARTICLE INFO

KEYWORDS: Brominated Flame Retardants (BFRs), E-Waste, Tetra-Bromo-Bis-Phenol A (TBBPA), Toxicity

ARTICLE HISTORY
Received: 01-06-2021
Revised: 10-11-2021
Accepted: 13-11-2021

Abstract

Brominated Flame Retardants (BFRs) are being utilized to reduce the flammability of plastics, textiles, and electronics. They differ in their chemical properties and structures, and it is conventional that these distinctions alter their biological interactions as well as toxicity. Tetra-Bromo-Bis-Phenol A (TBBPA) is a pervasive environmental contaminant that is seen in both abiotic and biotic matrices. This review discusses the occurrence, distribution, and fate of TBBPA from source to the environment. Recent studies have raised worry over the potentially harmful implications of TBBPA exposure in humans and wildlife, prompting its characterization under group 2A "Probably carcinogenic to humans" by the International Agency for Research on Cancer. Worldwide there are no present confinements on its production and usage. On the other hand, very little information is accessible with respect to its toxicity to humans and aquatic animals. More research is required to characterize human exposure to TBBPA in and around production facilities, as well as in e-waste recycling regions. So as to safeguard the environment and human health, detailed investigations are urgently needed, especially on tracking the exposure pathways which may affect the workers and local residents around the exposure sites.

1. Introduction

Brominated Flame Retardants (BFRs) are commonly used as additives to reduce flammability[1] in many consumer goods like plastics, textiles, and electronic equipments. Tetra-Bromo-Bis-Phenol A (TBBPA), poly-Brominated Diphenyl Ethers (PBDEs), and Hexa-Bromo-Cyclo-

*Author for correspondence

Dodecanes (HBCD) are three profoundly produced and normally utilized BFRs. Among these, TBBPA is one of the most prevalent and commonly used brominated flame retardant (BFR) which is being manufactured at high volumes in the world[2–5]. Recently, it has become the highest selling and hazardous omnipresent environmental contaminant[6,7].

The increasing concentration of TBBPA in the environment might be because of its discharge from industries producing or utilizing this compound and additionally from items containing TBBPA. TBBPA being lipophilic shows high persistence in the environment, equivalent to poly-Chlorinated Biphenyls (PCBs) and dioxins[8]. Because of that persistence, it can bioaccumulate and can be a potential danger for the environment as well as human beings.

TBBPA appeared to be present in several environmental compartments, for example, sewage sludges in Sweden[9] and Canada[10], in several fish species along North sea coasts[11] and harbor porpoise along UK coasts[11]. It was additionally detected in human blood and breast milk samples[12,13].

Although TBBPA is anticipated to have low acute toxicity to humans as it is quickly excreted in mammals[14], it is reported to be toxic to aquatic organisms[15,16], and it additionally can disrupt the endocrine system, thyroid hormones, and neurobehavioral functions after long-term exposure[17]. The EU risk assessment, published in 2006, concluded that there is no hazard for humans concerning TBBPA exposure yet the International Agency for Research on Cancer (IARC) has upgraded this flame retardant to cluster 2A (probably carcinogenic to humans)[18].

2. Literature Search Process

This review was completed by exploring important research and review papers published in journals, books and other online materials. References from some of the identified studies were also reviewed for additional relevant information. The articles for literature search were mainly collected from Google Scholar, PubMed, Science Direct, Springer, Research Gate and Taylor and Francis. The papers published in the past 20 years were mainly considered for the study. The main keywords that were used to search articles include "sources", "occurence", "exposure" and "toxicity" of TBBPA. Most of the papers used for this review were found by searching only the keyword "Tetrabromobisphenol A". The papers were checked manually and then filtered based on title, abstract and the paper contents. Mendeley software was used to store the bibliography data and add citations.

3. TBBPA Structure and Physico-Chemical Properties

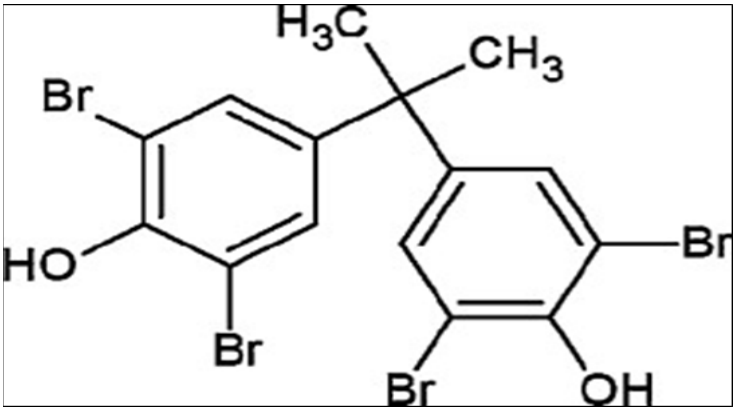
The basic structure of 3,3',5,5'-TBBPA consists of two hydroxyphenyl rings linked by a carbon bridge with bromine substitution at the 3, 3',5, and 5'-position. It is manufactured by bromination of bisphenol A leading to the formation of primarily the tetrabrominated form of bisphenol A.

TBBPA is described by low water solubility, low Henry's law constant and vapor pressure, moderate to high octanol-water partition coefficient, and high organic carbon-water partition coefficient[19]. It is a phenolic compound and can exist in molecular and ionic forms depending on pH. Both forms coexist when the solution pH is between dissociation coefficients, pKa1, and pKa2[20] Ionic forms of TBBPA can be monoprotic and diprotic depending on whether one or both hydrogen atoms on the hydroxyl groups of the molecule are lost amid ionization[19] (Table 1).

4. Occurrence and Environmental Fate

TBBPA, a pervasive environmental contaminant is found in both abiotic and biotic matrices. The first report of the presence of TBBPA at 20 ng/g dw in the sediment from the Meya River in Japan was reported by Watanabe *et al.*,[21]. Afterward number of reports has been published showing its presence in the air. It has also been detected in soil[22–24], sediments[25–29], sludge[11,30,31], surface water[25,28,32], dust[27,33–35], and air[6,34,36]. Recently, the contamination level, distribution, and ecotoxicity of TBBPA in water and sediment from the Weihe river basin have been reported by Wang *et al.*[37].

In additive applications, there is potential for TBBPA to escape from the product and enter the air and dust of the indoor environment[38]. The highest additive use of TBBPA is found in TV/computer casings[39]. For instance, old electronic/electrical appliances, especially TV/



$C_{15}H_{12}Br_4O_2$

Table 1. Physico-chemical properties of TBBPA

Molecular formula	**$C_{15}H_{12}Br_4O_2$**
Molecular weight	543.875 g/mol
Density	2.12 gcm^{-3} (20 °C)
Melting point	178 °C
Boiling point	250 °C
Solubility in H_2O	Insoluble
Vapour pressure	1.37×10^{-8} mm Hg at 25 °C

computers were observed to be the primary sources of TBBPA in indoor air and dust[40,41]. Also, the dust from inside of TV sets when analyzed analytically showed the presence of TBBPA, HBCD, and Poly-Brominated Dibenzo-p-dioxins/Dibenzo-furans (PBDD/Dfs)[41]. Abb *et al*.,[42] analyzed the brominated flame retardants in house dust while estimating the degree of contamination of the indoor environment with flame retardant.

Main emission sources of TBBPA into the environment are through various waste streams that are generated during manufacturing and processing and upon disposal[43], but it also reported to be leaked out from a variety of commercial products being used in houses[42,44]. Other sources that have been recognized are TBBPA manufacturing sites[6], sites manufacturing TBBPA-based products[45], electronic waste (e-waste) recycling and disposal sites[6,33], and Waste-Water Treatment Plants (WWTPs)[30].

Israel, China, the United States, Jordan, and Japan are the leading global producers of TBBPA[46]. The biggest BFR manufacturing companies include Great Lakes Chemical in Indiana, USA, Albemarle Chemical in Virginia, USA, and the Dead Sea Chemical in Beer-Sheva, Israel[47].

TBBPA is most prevalent in e-waste plastics and scraps PCBs, which represent roughly 30% and 3.6% of absolute domestic waste by weight[48]. These materials are considered hazardous and likely to end up at informal recyclers without environmental management[48]. Elevated levels of TBBPA have been found close to TBBPA-containing product manufacturing facilities, including electronics manufacturing[26,29,49] and general industrial sites[50]. The domestic generation of e-waste is increasing in many countries and developing countries such as China; e-waste import contributes to a growing e-waste problem. Although the volume of e-waste entering China is unknown, it receives shipments from the US,

Europe, South Korea, Japan, and other neighboring Asian countries and is likely the biggest e-waste dumping site in the world. Different nations in Asia and Africa, including Vietnam and Nigeria, are also importing e-waste[22,51]. The prevalence of TBBPA in dust samples obtained from residential homes in an e-waste recycling region in southeast China has been reported by Wu *et al.,*[33]. In municipal sewage sludge in China, TBBPA was the most frequently observed bisphenol analog in 52 municipal sewage sludge samples collected from 30 sites[30]. Geens *et al.,*[44] also detected TBBPA in indoor dust samples from 18 houses and 2 offices in Flanders, Belgium. Feng *et al.,*[26] detected TBBPA and HBCD in sediments of the major rivers and estuary in the Pearl River delta, a highly urbanized and industrial region of China.

TBBPA is discharged into the aquatic environment, not just from the migration from TBBPA-based items but also through effluent from wastewater treatment plants and landfill sites. Morris *et al.,*[11] investigated the distribution and fate of TBBPA and HBCD in waste water treatment plants, landfills leachates, sediments, and food web species in the North Sea basin. Also, brominated flame retardants have been detected in Korean river sediments[49]. Several reports have been published regarding the occurrence of TBBPA in the aquatic ecosystem[39]. Also sub-urban rivers near Paris, France have been reported to contain trace levels of PBDEs and TBBPA[52]. Sindiku *et al.,*[51] analyzed the presence of PBDD/DFs in e-waste plastics from Cathode Ray Tube (CRT) casings in Nigeria. The PBDD/Fs in CRT casings containing TBBPA was found at a concentration of around 0.1µg/g of TBBPA levels.

The elevated concentration of polybrominated biphenyls has been observed in whales and dolphins demonstrating the bioavailability of these chemicals[53]. Harrad *et al.,*[54] reported TBBPA concentration in water, sediments, and fish from English Lake and found concentrations of TBBPA ranging from 140 to 3200 pg L^{-1} (in water), 330 to 3800 pg g^{-1} dry weight (in sediments), and <0.29 to 1.7ng g^{-1} lipid weight (in fish). Concentrations of TBBPA and HBCD were also determined in human adipose tissues in New York City and 3 marine organisms collected from coastal waters of Florida, USA (bottlenose dolphins, bull shark, and Atlantic sharpnose shark)[55].

Xu *et al.,*[32] investigated the occurrence and distribution characteristics of TBBPA and HBCD in water and sediments from Taihu Lake, China, and found that the TBBPA levels in water were below the detection limit of 1.12ng/l while in sediments the levels were between 0.056 ng/g dry weight and 2.15 ng/g dry weights.

Once discharged to the environment, TBBPA has a moderately short half-life, with concentrations decreasing with increasing distance from point sources[32,49,54]. The distribution and fate of TBBPA in environmental media are impacted by numerous processes including adsorption, photolysis, and biological degradation. In neutral environments, TBBPA is predominantly molecular and tends to be absorbed by suspended particles in water and air. Subsequent transportation and deposition in sediment and soil could pose a risk to aquatic ecosystems and create human exposure pathways by contaminating drinking water sources or food stocks[56].

TBBPA may undergo degradation by photolysis and biological processes resulting in the formation of intermediates. The photodegradation half-life of TBBPA in water is 6.6 to 80.7 days and it varies with the season[57]. Debromination and mineralization of TBBPA could be achieved by its photolytic degradation[58]. The photochemical transformation of TBBPA in an aqueous solution under UV light has been examined by Eriksson *et al.,*[59]. Complete debromination and degradation by alkaline TiO_2 under UV light radiation were observed by Horikoshi *et al.,*[60]. Photolysis is plagued by humic substance concentration and hydrogen ion concentration, where debromination and breakage of the C=C bond were the main reaction pathways[61]. Reaction product embodies bisphenol A (BPA), an alternative intermediates that may be more persistent and deadly than TBBPA. Voordeckers *et al.,*[62] studied the biotransformation of TBBPA, tetrachlorobisphenol A, and their ultimate biodehalogenation product, bisphenol A, in anoxic estuarine sediments and highlighted the potential for accumulation of bisphenol A in anoxic sediments. O-methylation and debromination affect TBBPA occurrence in sediment and soil, where oxic and anoxic conditions may also lead to the formation of BPA and mono- and dimethyl ethers[63].

5. Exposure

Major TBBPA exposure pathways for humans are through breast milk, diet, and indoor air and dust[64]. In Toulouse, France TBBPA was detected in breast milk samples at 0.062 to 37.34 ng/g lw[65] and in Norway at 0.067 ng/g lw[13]. Humans are primarily exposed through a

combination of ingestion, inhalation, and dermal contact with contaminated media, such as dust, or consumer products containing TBBPA[6]. The daily average intake of TBBPA is estimated to be in the range of 0.018 and 0.97 ng/kg bw for dust inhalation and dust ingestion respectively[35], 1.34 ng/kg bw through food consumption[66] and particularly for infants, 6.62-10.1 ng/kg bw[67]α, β, γ-hexabromocyclododecane (HBCDD.

Human umbilical cord exchange was believed to be another essential source of TBBPA consumption for infants[65,68,69]. TBBPA absorption by the dermal route is observed to be poor due to its physicochemical properties and based upon knowledge from a penetration study conducted with human skin *in vitro,* it was reported that under 1% of the applied dose of TBBPA was retained dermally[70].

Fundamental bioavailability of TBBPA is low (F < 0.05) because of broad hepatic first pass biotransformation to glucuronides and sulfates, which are dominatingly discharged with bile from the liver because of their high sub-atomic weight. A postponed elimination was only observed after oral administration of a single dose of 1000 mg/kg bw, apparently due to the saturation of conjugation reactions[71]. At lower doses, over 95% of orally administered TBBPA is excreted, partially as the parent compound and in the form of metabolites in feces within 72h after a single dose with associated very little tissue retention or bioaccumulation[71–73]. The half-life of TBBPA in humans was calculated to be just about 2 days[74]. On the other hand, toxicokinetics studies in human subjects, rats, and mice demonstrated low systemic bioavailability of TBBPA to humans and rats[14], and mice[75].

6. Toxicology Studies

Knowledge of the toxicity attributed by TBBPA comes mainly from experiments on mammalian models which depicted its role as an endocrine disruptor[76,77], an oxidative stress inducer[78], promote adipocyte differentiation[79] and a possible carcinogen[76]. Although there is little evidence of the toxic effects of TBBPA on non-model organisms (wildlife)[1], recent studies have shown that TBBPA can cause growth impairment in sea bivalves[80].

In vivo, toxicokinetic studies on humans and rats have indicated low levels of TBBPA and metabolites in the blood after oral exposure[14,81]. Although the bioavailability and toxicity of TBBPA are thought to be low[14,72], there is still concern about toxicological effects especially in areas where exposure levels are high[6]. In the present section, various studies reporting endocrine-disrupting activity, reproductive toxicity, and other effects like neurotoxicity, immunotoxicity, and genotoxicity caused due to TBBPA exposure have been summarized.

6.1 Endocrine-Disrupting Activity

Several studies demonstrated endocrine-disrupting effects of TBBPA in both *in vitro* and *in vivo* tests[17,77,82–86]. There is accumulating evidence demonstrating that TBBPA can interact with and alter estrogen homeostasis. TBBPA has been shown to inhibit estradiol sulfurylation *in vitro*[87], and crystallographic studies demonstrated that it can bind to estrogen sulfotransferase SULT1E1 with high affinity[88]. TBBPA can also stimulate ovarian cancer cell proliferation through the G Protein-coupled estrogen Receptor 30 (GPR30) pathways[89]. A two-year oral exposure assessment conducted by the National Toxicology Program (NTP) reported an increased incidence of epithelial atypical hyperplasia in uterine tissue of Wistar Han rats exposed to 250 mg/kg/ day of TBBPA and tumor formation in the uterus at higher doses[3]. A follow-up study provided evidence of altered estrogen signaling, biosynthesis, and metabolism in the liver and uterus of rats exposed to 250 mg/kg/ day TBBPA.[3] As sex steroids are critical for many aspects of brain organization, especially sexual differentiation[90,91], neurodevelopment is found to be impacted by TBBPA exposure.

Thyroid Hormones (THs) play a key role in a wide range of vertebrate physiological functions both during early development and in adult life stages, influencing the maturation of bones[92] gonads[93] and the central nervous system[94]. Because of the structural resemblance to the thyroid hormone thyroxin (T4) and BPA, a suspected endocrine disruptor, the thyroid hormone signaling pathways were found to be susceptible to TBBPA exposure[39,95]. In the wake of entering the body, TBBPA can upset typical cell work by going about as a thyroid hormone[96], eventually affecting health. The thyroid secretion activity of TBBPA was examined by[82] using rat pituitary GH3 cell lines, in which the release of growth hormone was reported to be thyroid hormone-dependent. In those experiments, TBBPA stimulated the production of growth hormone and enhanced the proliferation

of GH3 cells. Parsons *et al.,*[97] showed that TBBPA can disrupt the thyroid axis of zebrafish embryo-larvae at multiple levels by altering mRNA transcript levels of genes encoding deiodinases, thyroid synthesis proteins, transport proteins, and glucuronidation enzymes.

TBBPA competed with thyroxine (T4) for Transport by Transthy-Retin (TTR), inhibited receptor binding of triiodothyronine (T3), and altered the expression of Thyroid hormone Receptors (TR) *in vitro*[82,86,87]. TBBPA has also been shown to alter serum T4 and the expression of TR *in vivo*[3]. Disruption of thyroid hormone signaling is well known to result in adverse neuro developmental outcomes including cognitive deficits[98].

Numerous *in vivo* studies have shown that both TBBPA and PBDEs can alter the circulating levels of both T4 and T3 in a range of vertebrate species, including fish[15,99]. The thyroidal system is centrally driven by the Hypothalamic-Pituitary-Thyroid (HPT) axis and under peripheral control in all vertebrates. The HPT axis is regulated as a negative feedback mechanism in which the level of Thyroid-Stimulating Hormone (TSH) secreted by the pituitary controls the production and release of T4 by the thyroid follicles. In the peripheral system, TH activity is tightly regulated by the metabolizing enzymes iodothyronine deiodinases, type I, II, and III (D1, D2, and D3), which can modulate TH signaling in individual tissues as well as controlling serum TH concentrations. D2 catalyzes the Outer Ring Deiodination (ORD) of T4 to produce the bioactive T3. In contrast, D3 catalyzes the Inner Ring Deiodination (IRD) of T4 and T3 producing the inactive metabolites reverse T3 (rT3) and 3, 3′-diiodo-L-thyronine (T2), respectively. D1 is a kinetically inefficient enzyme that is capable of catalyzing both IRD and ORD[100,101].

Several studies have demonstrated that BFRs can elicit localized effects on the expression of thyroid-related genes in adult fathead minnows (*Pimephales promelas*) and Chinese rare minnows (*Gobiocypris rarus*)[99,102].

6.1.1 Reproductive Toxicity

Negative reproductive impacts and physiological developments have been observed in aquatic species, such as zebrafish (≥0.023 µM or 0.013 mg/L)[16,103] and frogs (≥10−8 M or 0.05 mg/L)[83,104,105] and earthbound species such as earthworms (≥0.31 mg/kg dw) and a few kinds of plants (≥0.5 mg/kg dw)[106].

Due to its estrogen-like property, TBBPA has been demonstrated to diminish reproductive accomplishments by impacting the reproductive system[16]. In a study performed by Kester *et al.,*[107] TBBPA turned out to be a genuinely strong inhibitor of the sulfation of estradiol by estrogen sulfotransferase, an important inactivation pathway of estradiol. The inhibition of this enzyme may prompt enhanced bioavailability of estradiol *in vivo*. The subsequent weak estrogen-like properties have been affirmed by several other studies[108–110]. Cultured MCF-7 breast cancer cells demonstrated a fragile estrogenic response to TBBPA[109,111] and TBBPA has been shown to repress *in vitro* estrogen sulfonation[87], demonstrating the potential for both direct and indirect estrogenic activity. Increased female internal reproductive organ weights in ovariectomized mice exposed to TBBPA for three days (20 mg/kg/day, intraperitoneal) confirmed *in vivo* estrogenicity[83].

Sperm count, motility, and deformity are the basic indicators of sperm quality in males `reproductive toxicology. The male sex steroid testosterone (T) acts as a significant factor in spermatogenesis and ensures the normal phenotype of the male reproductive system[112] . Estradiol (E2) is also essential for the formation of sperm. Studies reported that TBBPA has some properties similar to estrogen[82,108], and later its anti-estrogenic activity was confirmed[83].

In one study, TBBPA exposure resulted in reduced sperm counts and increased abnormal sperm in Sterlet[113]. Moreover, TBBPA was found to induce testicular cell apoptosis[15,114] and reduction in sperm quality[115]. Linhartova *et al.*[113] suggested that TBBPA exposure caused epididymal sperm DNA damage and protein distribution anomalies.

Zhang *et al.,*[116] demonstrated that TBBPA and TCBPA caused a decrease in sperm number and activity and an increase in sperm deformities in male *Rana nigromaculata*. Sanders *et al.,*[3] reported that chronic oral treatment of TBBPA to female Wistar Han rats resulted in an increased incidence of cell proliferation and tumor formation in the uterus. Von Krogh *et al.,*[117] reported that TBBPA displayed endocrine disruptive properties and directly interfered with reproductive function-related gene expression in Atlantic cod. TBBPA also induced apoptosis in spermatogenic cells by increasing Mitochondrial Membrane Potential (MMP) and generation of reactive oxygen species[118].

The mechanism of the neurotoxicity of TBBPA is complex. Pullen *et al.,*[119] observed that TBBPA could act on the nervous system through the inhibition of neurotransmitter take-up into synaptosomes and dopamine take-up into synaptic vesicles. Evidence of TBBPA developmental neurotoxicity in rodent models included abnormal development of the dentate hilus, greater numbers of reelin-expressing interneurons during post-natal development, and excess neurons in adulthood[120]. Neurobehavioral effects of TBBPA in mice that caused behavioral alteration due to the accumulation of a small amount of TBBPA in the brain regions including the striatum were reported[75]. Cho *et al.,*[121] reported TBBPA induced apoptosis of neural stem cell and also increased reactive oxygen species generation and mitochondrial dysfunction. Recent studies demonstrated that TBBPA has neurotoxic effects in mice[122,123] and zebrafish[124,125].

TBBPA is additionally known to be immunotoxic, as exhibited by *in vitro* inhibition of the expression of CD25, a receptor essential for the proliferation of activated T-cells[126]. Exposure to TBBPA induced immunotoxicity in murine macrophages[127]. The effect of TBBPA was studied on mice through treatment and it was observed that TBBPA treatment affected the host immunity causing mild immune injury in lung tissues with the wound aggravated to severe pneumonia by Respiratory Syncytial Virus (RSV) infection in mice. Besides, irregular changes in cytokine production and immune cell populations were observed[128].

Toxicological effects, such as severe disorientation, lethargy, decreased egg production and decreased reproductive success were observed in a partial life-cycle test with zebrafish (*Danio rerio*) exposed to environmentally relevant water-borne concentrations of TBBPA[15]. *In vitro* assay for determining Reactive Oxygen Species (ROS) by fluorescence Di-Chloro-Fluorescein (DCF) demonstrated that TBBPA could induce a dose-dependent formation of ROS and decrease calcium levels in human neutrophils[129]. However, some recent investigations have additionally demonstrated that dose-dependent ROS formation is just the effect of the chemical reaction of TBBPA with substrate used for ROS measurement, which could be affirmed in cell-free models[130,131].

Findings of *in vitro* and *in vivo* studies have shown that TBBPA can upset signal transduction pathways[82,132–135]. For instance, TBBPA repressed binding of T3 to the plasma carrier protein, Trans-Thy-Retin (TTR) at concentrations ranging about 1×10^{-6} to 1×10^{-4} M, enhanced proliferation of rat pituitary GH3 cells and MtT/E-2 cells, and triggered the production of growth hormone[82]. In a recent study, Yin *et al.,*[136] reported TBBPA exposure in mouse embryonic stem cells at early-stage neural development interfered with Notch and wingless/Int-1 pathways. TBBPA can alter circulating concentrations of TH and influence Thyroid hormone Receptors (ThRs) and go about as agonist or antagonist bringing about modulation of transcription in TH transduction pathways in fluorescent transgenic *Xenopus laevis* embryos[137].

6.1.2 Genotoxicity

The genotoxic impact of TBBPA is still hazy because the data for genotoxic studies is inadequate. Very few investigations have been done to reveal the genotoxic potential of TBBPA. The results of the studies done so far are also contradictory. No increase in DNA damage in the alkaline comet assay was observed in the testicular cells of CD-1 mice given tetrabromobisphenol A in corn oil twice (24 hours apart) at doses of 500, 1000, or 2000 mg/kg bw[138]. TBBPA was found to have no effect on the frequency of micronucleated erythrocytes in the peripheral blood of male and female B6C3F1 mice exposed by gavage (10–1000 mg/kg bw in corn oil on five days per week for fourteen weeks). In scallops (*Chlamys farreri*), tetrabromobisphenol A (0.2, 0.4, and 0.8 mg/L for up to 10 days) induced DNA damage in the gills and digestive gland tissues in a time- and dose-dependent manner[139]. In a study, Wang *et al.,*[140] exposed THP-1 cell lines to BDE-47, HBCD, and TBBPA and observed a significant increase in % tail DNA with increasing exposure concentration.

7. Conclusion

TBBPA is a brominated flame retardant applied in a wide variety of consumer products. While earlier risk assessment studies concluded that there is no risk to human health associated with exposure to TBBPA, recent studies identified this chemical as "probably carcinogenic to humans". Therefore, it is important to accurately

characterize human exposure to this flame retardant in different domestic and occupational environmental settings worldwide and also to evaluate its genotoxic and carcinogenic effects in mammals and aquatic organisms. More research is required to evaluate the risk associated with potential degradation/debromination of TBBPA to produce the hazardous chemical Bis-Phenol A (BPA) under various environmental conditions. As robust and recent toxicological data for emerging flame retardant is insufficient so there is dire need to do scientific studies so that the general public can be sensitized regarding its exposure and toxicity.

8. Conflict of interest

The authors declare no conflict of interest.

9. Acknowledgements

The authors are thankful to The Council of Scientific and Industrial Research CSIR New Delhi for providing financial assistance to Prince Sharma and Special Assistance Programme (SAP) of UGC for providing necessary facilities.

10. References

1. Pittinger CA, Pecquet AM. Review of historical aquatic toxicity and bioconcentration data for the brominated flame retardant tetrabromobisphenol A (TBBPA): Effects to fish, invertebrates, algae, and microbial communities. Environ Sci Pollut Res. 2018; 25(15):14361-14372. https://doi.org/10.1007/s11356-018-1998-y. PMid:29671227.
2. de Wit CA, Herzke D, Vorkamp K. Brominated flame retardants in the Arctic environment - trends and new candidates. Sci Total Environ. 2010; 408(15):2885-2918. https://doi.org/10.1016/j.scitotenv.2009.08.037. PMid:19815253.
3. Sanders JM, Coulter SJ, Knudsen GA, Dunnick JK, Kissling GE, Birnbaum LS. Disruption of estrogen homeostasis as a mechanism for uterine toxicity in Wistar Han rats treated with tetrabromobisphenol A. Toxicol Appl Pharmacol. 2016; 298:31-39. https://doi.org/10.1016/j.taap.2016.03.007. PMid:26988606 PMCid:PMC4825186.
4. Usenko CY, Abel EL, Hopkins A, Martinez G, Tijerina J, Kudela M, Norris N, Joudeh L, Bruce ED. Evaluation of common use Brominated Flame Retardant (BFR) toxicity using a Zebrafish embryo model. Toxics. 2016; 4(3):21. https://doi.org/10.3390/toxics4030021. PMid:29051424 PMCid:PMC5606660.
5. Zhou H, Yin N, Faiola F. Tetrabromobisphenol A (TBBPA): A controversial environmental pollutant. J Environ Sci. 2020; 97:54-66. https://doi.org/10.1016/j.jes.2020.04.039. PMid:32933740.
6. Liu K, Li J, Yan S, Zhang W, Li Y, Han D. A review of status of tetrabromobisphenol A (TBBPA) in China. Chemosphere. 2016; 148:8-20. https://doi.org/10.1016/j.chemosphere.2016.01.023. PMid:26800486.
7. Kefeni KK, Okonkwo JO, Olukunle OI, Botha BM. Brominated flame retardants: Sources, distribution, exposure pathways, and toxicity. Environ Rev. 2011; 19(1):238-253. https://doi.org/10.1139/a11-010.
8. De Boer J, Wester PG, Klamer HJC, Lewis WE, Boon JP. Do flame retardants threaten ocean life? Nature. 1998; 394(6688):28-29. https://doi.org/10.1038/27798. PMid:9665124.
9. Alaee M, Arias P, Sjödin A, Bergman Å. 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; 29(6):683-689. https://doi.org/10.1016/S0160-4120(03)00121-1.
10. Lee HB, Peart TE. Organic contaminants in Canadian municipal sewage sludge. Part I. Toxic or endocrine-disrupting phenolic compounds. Water Qual Res J Canada. 2002; 37(4):681-696. https://doi.org/10.2166/wqrj.2002.046.
11. Morris S, Allchin CR, Zegers BN, Haftka JJH, Boon JP, Belpaire C, Leonards PE, Van Leeuwen SP, De Boer J. Distribution and fate of HBCD and TBBPA brominated flame retardants in North Sea estuaries and aquatic food webs. Environ Sci Technol. 2004; 38(21):5497-5504. https://doi.org/10.1021/es049640i. PMid:15575264.
12. Jakobsson K, Thuresson K, Rylander L, Sjödin A, Hagmar L, Bergman Å. Exposure to polybrominated diphenyl ethers and tetrabromobisphenol A among computer technicians. Chemosphere. 2002; 46(5):709-716. https://doi.org/10.1016/S0045-6535(01)00235-1.

13. Thomsen C, Lundanes E, Becher G. Brominated flame retardants in archived serum samples from Norway: A study on temporal trends and the role of age. Environ Sci Technol. 2002; 36(7):1414-1418. https://doi.org/10.1021/es0102282. PMid:11999045.
14. Schauer UMD, Völkel W, Dekant W. Toxicokinetics of tetrabromobisphenol A in humans and rats after oral administration. Toxicol Sci. 2006; 91(1):49-58. https://doi.org/10.1093/toxsci/kfj132. PMid:16481339.
15. Kuiper RV, Van Den Brandhof EJ, Leonards PEG, Van Der Ven LTM, Wester PW, Vos JG. Toxicity of tetrabromobisphenol A (TBBPA) in zebrafish (*Danio rerio*) in a partial life-cycle test. Arch Toxicol. 2007; 81(1):1-9. https://doi.org/10.1007/s00204-006-0117-x. PMid:16738895.
16. Kuiper R V., Cantón RF, Leonards PEG, Jenssen BM, Dubbeldam M, Wester PW, Van den Berg M, Vos JG, Vethaak AD. Long-term exposure of European flounder (*Platichthys flesus*) to the flame-retardants tetrabromobisphenol A (TBBPA) and hexabromocyclododecane (HBCD). Ecotoxicol Environ Saf. 2007; 67(3):349-360. https://doi.org/10.1016/j.ecoenv.2006.12.001. PMid:17258806.
17. Van der Ven LTM, Van de Kuil T, Verhoef A, Verwer CM, Lilienthal H, Leonards PEG, Schauer UM, Cantón RF, Litens S, De Jong FH, Visser TJ. Endocrine effects of tetrabromobisphenol-A (TBBPA) in Wistar rats as tested in a one-generation reproduction study and a subacute toxicity study. Toxicology. 2008; 245(1-2):76-89. https://doi.org/10.1016/j.tox.2007.12.009. PMid:18255212.
18. Grosse Y, Loomis D, Guyton KZ, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Mattock H, Straif K. Carcinogenicity of some industrial chemicals. Lancet Oncol. 2016; 17(4):419-420. https://doi.org/10.1016/S1470-2045(16)00137-6.
19. Environment Canada. Screening Assessment Report TBBPA. En14-110/2013E-PDF. Government of Canada, Ottawa, Ontario; 2013.
20. Kuramochi H, Kawamoto K, Miyasaki K, Nagahama K, Maeda K, Li XW, Shibata E, Nakamura T, Sakai SI. Determination of physicochemical properties of tetrabromobisphenol A. Environ Toxicol Chem. 2008; 27(12):2413-2418. https://doi.org/10.1897/07-472.1. PMid:18613742.
21. Watanabe I, Kashimoto T, Tatsukawa R. Identification of the flame retardant tetrabromobisphenol-a in the river sediment and the mussel collected in Osaka. Bull Environ Contam Toxicol. 1983; 31(1):48-52. https://doi.org/10.1007/BF01608765. PMid:6309291.
22. Matsukami H, Tue NM, Suzuki G, Someya M, Tuyen LH, Viet PH, Takahashi S, Tanabe S, Takigami H. Flame retardant emission from e-waste recycling operation in northern Vietnam: Environmental occurrence of emerging organophosphorus esters used as alternatives for PBDEs. Sci Total Environ. 2015; 514:492-499. https://doi.org/10.1016/j.scitotenv.2015.02.008. PMid:25701386.
23. Qu G, Liu A, Wang T, Zhang C, Fu J, Yu M, Sun J, Zhu N, Li Z, Wei G, Du Y. Identification of tetrabromobisphenol A allyl ether and tetrabromobisphenol A 2,3-dibromopropyl ether in the ambient environment near a manufacturing site and in mollusks at a coastal region. Environ Sci Technol. 2013; 47(9):4760-4767. https://doi.org/10.1021/es3049916. PMid:23550727.
24. Zhu ZC, Chen SJ, Zheng J, Tian M, Feng AH, Luo XJ, Mai BX. Occurrence of brominated flame retardants (BFRs), organochlorine pesticides (OCPs), and polychlorinated biphenyls (PCBs) in agricultural soils in a BFR-manufacturing region of North China. Sci Total Environ. 2014; 481(1):47-54. https://doi.org/10.1016/j.scitotenv.2014.02.023. PMid:24576782.
25. Xiong J, An T, Zhang C, Li G. Pollution profiles and risk assessment of PBDEs and phenolic brominated flame retardants in water environments within a typical electronic waste dismantling region. Environ Geochem Health. 2015; 37(3):457-473. https://doi.org/10.1007/s10653-014-9658-8. PMid:25503846.
26. Feng AH, Chen SJ, Chen MY, He MJ, Luo XJ, Mai BX. Hexabromocyclododecane (HBCD) and tetrabromobisphenol A (TBBPA) in riverine and estuarine sediments of the Pearl River Delta in southern China, with emphasis on spatial variability in diastereoisomer- and enantiomer-specific distribution of HBCD. Mar Pollut Bull. 2012; 64(5):919-925. https://doi.org/10.1016/j.marpolbul.2012.03.008. PMid:22475420.
27. Wang J, Liu L, Wang J, Pan B, Fu X, Zhang G, Zhang L, Lin K. Distribution of metals and brominated flame retardants (BFRs) in sediments, soils and plants from an informal e-waste dismantling site, South

China. Environ Sci Pollut Res. 2015; 22(2):1020-1033. https://doi.org/10.1007/s11356-014-3399-1. PMid:25106518.
28. Yang S, Wang S, Liu H, Yan Z. Tetrabromobisphenol A: Tissue distribution in fish, and seasonal variation in water and sediment of Lake Chaohu, China. Environ Sci Pollut Res. 2012; 19(9):4090-4096. https://doi.org/10.1007/s11356-012-1023-9. PMid:22825637.
29. He MJ, Luo XJ, Yu LH, Wu JP, Chen SJ, Mai BX. Diasteroisomer and enantiomer-specific profiles of hexabromocyclododecane and tetrabromobisphenol A in an aquatic environment in a highly industrialized area, South China: Vertical profile, phase partition, and bioaccumulation. Environ Pollut. 2013; 179:105-110. https://doi.org/10.1016/j.envpol.2013.04.016. PMid:23665846.
30. Song S, Song M, Zeng L, Wang T, Liu R, Ruan T, Jiang G. Occurrence and profiles of bisphenol analogues in municipal sewage sludge in China. Environ Pollut. 2014; 186:14-19. https://doi.org/10.1016/j.envpol.2013.11.023. PMid:24355443.
31. Gorga M, Martínez E, Ginebreda A, Eljarrat E, Barceló D. Determination of PBDEs, HBB, PBEB, DBDPE, HBCD, TBBPA and related compounds in sewage sludge from Catalonia (Spain). Sci Total Environ. 2013; 444:51-59. https://doi.org/10.1016/j.scitotenv.2012.11.066. PMid:23262324.
32. Xu J, Zhang Y, Guo C, He Y, Li L, Meng W. Levels and distribution of tetrabromobisphenol a and hexabromocyclododecane in Taihu Lake, China. Environ Toxicol Chem. 2013; 32(10):2249-2255. https://doi.org/10.1002/etc.2318. PMid:23804316.
33. Wu Y, Li Y, Kang D, Wang J, Zhang Y, Du D, Pan B, Lin Z, Huang C, Dong Q. Tetrabromobisphenol A and heavy metal exposure via dust ingestion in an e-waste recycling region in Southeast China. Sci Total Environ. 2016; 541:356-364. https://doi.org/10.1016/j.scitotenv.2015.09.038. PMid:26410710.
34. Zhou X, Guo J, Zhang W, Zhou P, Deng J, Lin K. Tetrabromobisphenol A contamination and emission in printed circuit board production and implications for human exposure. J Hazard Mater. 2014; 273:27-35. https://doi.org/10.1016/j.jhazmat.2014.03.003. PMid:24709479.
35. Ni HG, Zeng H. HBCD and TBBPA in particulate phase of indoor air in Shenzhen, China. Sci Total Environ. 2013; 458-460:15-19. https://doi.org/10.1016/j.scitotenv.2013.04.003. PMid:23639907.
36. Schlabach M. Brominated Flame Retardants (BFR) in the Nordic Environment. In: Nordic Council of Ministers; 2011.
37. Wang X, Li C, Yuan X, Yang S. Contamination level, distribution characteristics, and ecotoxicity of tetrabromobisphenol a in water and sediment from Weihe River Basin, China. Int. J. Environ. Res. Public Health. 2020; 17(11):1-13. https://doi.org/10.3390/ijerph17113750. PMid:32466414 PMCid:PMC7312569.
38. Birnbaum LS, Staskal DF. Brominated flame retardants: Cause for concern? Environ Health Perspect. 2004; 112(1):9-17. https://doi.org/10.1289/ehp.6559. PMid:14698924 PMCid:PMC1241790.
39. Covaci A, Voorspoels S, Abdallah MAE, Geens T, Harrad S, Law RJ. Analytical and environmental aspects of the flame retardant tetrabromobisphenol-A and its derivatives. J. Chromatogr. A. 2009; 1216(3):346-363. https://doi.org/10.1016/j.chroma.2008.08.035. PMid:18760795.
40. Sellström U, Jansson B. Analysis of tetrabromobisphenol A in a product and environmental samples. Chemosphere. 1995; 31(4):3085-3092. https://doi.org/10.1016/0045-6535(95)00167-7.
41. Takigami H, Suzuki G, Hirai Y, Sakai Sichi. Transfer of brominated flame retardants from components into dust inside television cabinets. Chemosphere. 2008; 73(2):161-169. https://doi.org/10.1016/j.chemosphere.2008.06.032. PMid:18657291.
42. Abb M, Stahl B, Lorenz W. Analysis of brominated flame retardants in house dust. Chemosphere. 2011; 85(11):1657-1663. https://doi.org/10.1016/j.chemosphere.2011.06.022. PMid:21724229.
43. Watanabe I, Sakai SI. Environmental release and behavior of brominated flame retardants. Environ Int. 2003; 29(6):665-682. https://doi.org/10.1016/S0160-4120(03)00123-5.
44. Geens T, Roosens L, Neels H, Covaci A. Assessment of human exposure to Bisphenol-A, Triclosan and Tetrabromobisphenol-A through indoor dust intake in Belgium. Chemosphere. 2009; 76(6):755-760. https://doi.org/10.1016/j.chemosphere.2009.05.024. PMid:19535125.
45. Zhou X, Guo J, Zhang W, Zhou P, Deng J, Lin K. Occurrences and inventories of heavy metals and

brominated flame retardants in wastes from printed circuit board production. Environ Sci Pollut Res. 2014; 21(17):10294-10306. https://doi.org/10.1007/s11356-014-2927-3. PMid:24777328.
46. BSEF. TBBPA factsheet: tetrabromobisphenol A for printed circuit boards and ABS plastics; 2012.
47. Ma J, Qiu X, Zhang J, Duan X, Zhu T. State of polybrominated diphenyl ethers in China: An overview. Chemosphere. 2012; 88(7):769-778. https://doi.org/10.1016/j.chemosphere.2012.03.093. PMid:22546636.
48. Duan H, Hu J, Tan Q, Liu L, Wang Y, Li J. Systematic characterization of generation and management of e-waste in China. Environ Sci Pollut Res. 2016; 23(2):1929-1943. https://doi.org/10.1007/s11356-015-5428-0. PMid:26408118.
49. Lee IS, Kang HH, Kim UJ, Oh JE. Brominated flame retardants in Korean river sediments, including changes in polybrominated diphenyl ether concentrations between 2006 and 2009. Chemosphere. 2015; 126:18-24. https://doi.org/10.1016/j.chemosphere.2015.01.004. PMid:25655576.
50. Sánchez-Brunete C, Miguel E, Tadeo JL. Determination of tetrabromobisphenol-A, tetrachlorobisphenol-A and bisphenol-A in soil by ultrasonic assisted extraction and gas chromatography-mass spectrometry. J Chromatogr A. 2009; 1216(29):5497-5503. https://doi.org/10.1016/j.chroma.2009.05.065. PMid:19524246.
51. Sindiku O, Babayemi JO, Tysklind M, Osibanjo O, Weber R, Watson A, Schlummer M, Lundstedt S. Polybrominated dibenzo-p-dioxins and dibenzofurans (PBDD/Fs) in e-waste plastic in Nigeria. Environ Sci Pollut Res. 2015; 22(19):14515-14529. https://doi.org/10.1007/s11356-015-5260-6. PMid:26347415.
52. Labadie P, Tlili K, Alliot F, Bourges C, Desportes A, Chevreuil M. Development of analytical procedures for trace-level determination of polybrominated diphenyl ethers and tetrabromobisphenol A in river water and sediment. Anal Bioanal Chem. 2010; 396(2):865-875. https://doi.org/10.1007/s00216-009-3267-x. PMid:19921511.
53. Law RJ, Alaee M, Allchin CR, Boon JP, Lebeuf M, Lepom P, Stern GA. Levels and trends of polybrominated diphenylethers and other brominated flame retardants in wildlife. Environ Int. 2003; 29(6):757-770. https://doi.org/10.1016/S0160-4120(03)00110-7.
54. Harrad S, Abdallah MAE, Rose NL, Turner SD, Davidson TA. Current-use brominated flame retardants in water, sediment, and fish from english lakes. Environ Sci Technol. 2010; 44(13):5318. https://doi.org/10.1021/es101746s.
55. Johnson-Restrepo B, Adams DH, Kannan K. Tetrabromobisphenol A (TBBPA) and hexabromocyclododecanes (HBCDs) in tissues of humans, dolphins, and sharks from the United States. Chemosphere. 2008; 70(11):1935-1944. https://doi.org/10.1016/j.chemosphere.2007.10.002. PMid:18037156.
56. Malkoske T, Tang Y, Xu W, Yu S, Wang H. A review of the environmental distribution, fate, and control of tetrabromobisphenol A released from sources. Sci Total Environ. 2016; 569-570:1608-1617. https://doi.org/10.1016/j.scitotenv.2016.06.062. PMid:27325014.
57. WHO. Tetrabromobisphenol A and Derivatives. Environmental Health Criteria 172. International Programme on Chemical Safety. World Health Organization, Geneva, Switzerland; 1995.
58. Han SK, Bilski P, Karriker B, Sik RH, Chignell CF. Oxidation of flame retardant tetrabromobisphenol A by singlet oxygen. Environ Sci Technol. 2008; 42(1):166-172. https://doi.org/10.1021/es071800d. PMid:18350892 PMCid:PMC2376276.
59. Eriksson J, Rahm S, Green N, Bergman Å, Jakobsson E. Photochemical transformations of tetrabromobisphenol A and related phenols in water. Chemosphere. 2004; 54(1):117-126. https://doi.org/10.1016/S0045-6535(03)00704-5.
60. Horikoshi S, Miura T, Kajitani M, Horikoshi N, Serpone N. Photodegradation of tetrahalobisphenol-A (X = Cl, Br) flame retardants and delineation of factors affecting the process. Appl. Catal. B. 2008; 84(3-4):797-802. https://doi.org/10.1016/j.apcatb.2008.06.023.
61. Bao Y, Niu J. Photochemical transformation of tetrabromobisphenol A under simulated sunlight irradiation: Kinetics, mechanism and influencing factors. Chemosphere. 2015; 134:550-556. https://doi.org/10.1016/j.chemosphere.2014.12.016. PMid:25559172.
62. Voordeckers JW, Fennell DE, Jones K, Häggblom MM. Anaerobic biotransformation of tetrabromobisphenol A, tetrachlorobisphenol A, and bisphenol A in estuarine sediments. Environ Sci Technol. 2002;

36(4):696-701. https://doi.org/10.1021/es011081h. PMid:11878385.

63. Li F, Wang J, Jiang B, Yang X, Nastold P, Kolvenbach B, Wang L, Ma Y, Corvini PF, Ji R. Fate of Tetrabromobisphenol A (TBBPA) and Formation of Ester- and Ether-Linked Bound Residues in an Oxic Sandy Soil. Environ Sci Technol. 2015; 49(21):12758-12765. https://doi.org/10.1021/acs.est.5b01900. PMid:26444952.
64. Shi ZX, Wu YN, Li JG, Zhao YF, Feng JF. Dietary exposure assessment of Chinese adults and nursing infants to tetrabromobisphenol-A and hexabromocyclododecanes: Occurrence measurements in foods and human milk. Environ Sci Technol. 2009; 43(12):4314-4319. https://doi.org/10.1021/es8035626. PMid:19603640.
65. Cariou R, Antignac JP, Zalko D, Berrebi A, Cravedi JP, Maume D, Marchand P, Monteau F, Riu A, Andre F. Exposure assessment of French women and their newborns to tetrabromobisphenol-A: Occurrence measurements in maternal adipose tissue, serum, breast milk and cord serum. Chemosphere. 2008; 73(7):1036-1041. https://doi.org/10.1016/j.chemosphere.2008.07.084. PMid:18790516.
66. Shi Z, Zhang L, Zhao Y, Sun Z, Zhou X, Li J, Wu Y. Dietary exposure assessment of Chinese population to tetrabromobisphenol-A, hexabromocyclododecane and decabrominated diphenyl ether: Results of the 5th Chinese Total Diet Study. Environ Pollut. 2017; 229:539-547. https://doi.org/10.1016/j.envpol.2017.06.093. PMid:28688304.
67. Huang M, Li J, Xiao Z, Shi Z. Tetrabromobisphenol A and hexabromocyclododecane isomers in breast milk from the general population in Beijing, China: Contamination levels, temporal trends, nursing infant's daily intake, and risk assessment. Chemosphere. 2020; 244:125524-125524. https://doi.org/10.1016/j.chemosphere.2019.125524. PMid:31812044.
68. Kim UJ, Oh JE. Tetrabromobisphenol A and hexabromocyclododecane flame retardants in infant-mother paired serum samples, and their relationships with thyroid hormones and environmental factors. Environ Pollut. 2014; 184:193-200. https://doi.org/10.1016/j.envpol.2013.08.034. PMid:24060738.
69. Antignac JP, Cariou R, Maume D, Marchand P, Monteau F, Zalko D, Berrebi A, Cravedi JP, Andre F, Le Bizec B. Exposure assessment of fetus and newborn to brominated flame retardants in France: Preliminary data. Mol Nutr Food Res. 2008; 52(2):258-265. https://doi.org/10.1002/mnfr.200700077. PMid:18186099.
70. ECB. European Union Risk Assessment Report - 2,2', 6,6'-tetrabromo-4,4'- isopropylidenediphenol (tetrabromobisphenol-A or TBBP-A) (CAS: 79-94-7) Part II - Human Health. Institute for Health and Consumer Protection, European Chemicals Bureau, European Commission; 2006.
71. Knudsen GA, Sanders JM, Sadik AM, Birnbaum LS. Disposition and kinetics of tetrabromobisphenol A in female Wistar Han rats. Toxicol Rep. 2014; 1:214-223. https://doi.org/10.1016/j.toxrep.2014.03.005. PMid:24977115 PMCid:PMC4071299.
72. Colnot T, Kacew S, Dekant W. Mammalian toxicology and human exposures to the flame retardant 2,2′ ,6,6′ -tetrabromo-4,4′ -isopropylidenediphenol (TBBPA): Implications for risk assessment. Arch Toxicol. 2014; 88(3):553-573. https://doi.org/10.1007/s00204-013-1180-8. PMid:24352537.
73. Kuester RK, Sólyom AM, Rodriguez VP, Sipes IG. The effects of dose, route, and repeated dosing on the disposition and kinetics of tetrabromobisphenol A in male F-344 rats. Toxicol Sci. 2007; 96(2):237-245. https://doi.org/10.1093/toxsci/kfm006. PMid:17234645.
74. Sjödin A, Patterson DG, Bergman Åke Å. A review on human exposure to brominated flame retardants - Particularly polybrominated diphenyl ethers. Environ Int. 2003; 29(6):829-839. https://doi.org/10.1016/S0160-4120(03)00108-9.
75. Nakajima A, Saigusa D, Tetsu N, Yamakuni T, Tomioka Y, Hishinuma T. Neurobehavioral effects of tetrabromobisphenol A, a brominated flame retardant, in mice. Toxicol Lett. 2009; 189(1):78-83. https://doi.org/10.1016/j.toxlet.2009.05.003. PMid:19463927.
76. Lai DY, Kacew S, Dekant W. Tetrabromobisphenol A (TBBPA): Possible modes of action of toxicity and carcinogenicity in rodents. Food Chem Toxicol. 2015; 80:206-214. https://doi.org/10.1016/j.fct.2015.03.023. PMid:25818463.
77. Liang S, Zhou H, Yin N, Lu Y, Faiola F. Embryoid body-based RNA-seq analyses reveal a potential

TBBPA multifaceted developmental toxicity. J Hazard Mater. 2019; 376:223-232. https://doi.org/10.1016/j.jhazmat.2019.05.030. PMid:31129320.

78. Jarosiewicz M, Krokosz A, Marczak A, Bukowska B. Changes in the activities of antioxidant enzymes and reduced glutathione level in human erythrocytes exposed to selected brominated flame retardants. Chemosphere. 2019; 227:93-99. https://doi.org/10.1016/j.chemosphere.2019.04.008. PMid:30986606.
79. Akiyama E, Kakutani H, Nakao T, Motomura Y, Takano Y, Sorakubo R, Mizuno A, Aozasa O, Tachibana K, Doi T, Ohta S. Facilitation of adipocyte differentiation of 3T3-L1 cells by debrominated tetrabromobisphenol A compounds detected in Japanese breast milk. Environ Res. 2015; 140:157-164. https://doi.org/10.1016/j.envres.2015.03.035. PMid:25863188.
80. Jiang S, Miao J, Wang X, Liu P, Pan L. Inhibition of growth in juvenile manila clam Ruditapes philippinarum: Potential adverse outcome pathway of TBBPA. Chemosphere. 2019; 224:588-596. https://doi.org/10.1016/j.chemosphere.2019.02.157. PMid:30844590.
81. Cope RB, Kacew S, Dourson M. A reproductive, developmental and neurobehavioral study following oral exposure of tetrabromobisphenol A on Sprague-Dawley rats. Toxicology. 2015; 329:49-59. https://doi.org/10.1016/j.tox.2014.12.013. PMid:25523853.
82. Kitamura S, Jinno N, Ohta S, Kuroki H, Fujimoto N. Thyroid hormonal activity of the flame retardants tetrabromobisphenol A and tetrachlorobisphenol A. Biochem Biophys Res Commun. 2002; 293(1):554-559. https://doi.org/10.1016/S0006-291X(02)00262-0.
83. Kitamura S, Kato T, Iida M, Jinno N, Suzuki T, Ohta S, Fujimoto N, Hanada H, Kashiwagi K, Kashiwagi A. Anti-thyroid hormonal activity of tetrabromobisphenol A, a flame retardant, and related compounds: Affinity to the mammalian thyroid hormone receptor, and effect on tadpole metamorphosis. Life Sciences. 2005; 76(14):1589-1601. https://doi.org/10.1016/j.lfs.2004.08.030. PMid:15680168.
84. Lilienthal H, Verwer CM, van der Ven LTM, Piersma AH, Vos JG. Exposure to tetrabromobisphenol A (TBBPA) in Wistar rats: Neurobehavioral effects in offspring from a one-generation reproduction study. Toxicology. 2008; 246(1):45-54. https://doi.org/10.1016/j.tox.2008.01.007. PMid:18295390.
85. Williams AL, Desesso JM. The potential of selected brominated flame retardants to affect neurological development. J Toxicol Environ Health B Crit Rev. 2010; 13(5):411-448. https://doi.org/10.1080/10937401003751630. PMid:20582854.
86. Meerts IATM, Van Zanden JJ, Luijks EAC, Van Leeuwen-Bol I, Marsh G, Jakobsson E, Bergman Å, Brouwer A. Potent competitive interactions of some brominated flame retardants and related compounds with human transthyretin in Vitro. Toxicol Sci. 2000; 56(1):95-104. https://doi.org/10.1093/toxsci/56.1.95. PMid:10869457.
87. Hamers T, Kamstra JH, Sonneveld E, Murk AJ, Zegers BN. In vitro screening of the endocrine disrupting potency of brominated flame retardants and their metabolites. 2004; 66:3016-3020.
88. Gosavi RA, Knudsen GA, Birnbaum LS, Pedersen LC. Mimicking of estradiol binding by flame retardants and their metabolites: A crystallographic analysis. Environ Health Perspect. 2013; 121(10):1194-1199. https://doi.org/10.1289/ehp.1306902. PMid:23959441 PMCid:PMC3801471.
89. Hoffmann M, Gogola J, Kotula-Balak M, Ptak A. Stimulation of ovarian cell proliferation by tetrabromobisphenol A but not tetrachlorobisphenol A through G protein-coupled receptor 30. Toxicol in Vitro. 2017; 45:54-59. https://doi.org/10.1016/j.tiv.2017.08.009. PMid:28811233.
90. McCarthy MM, Wright CL, Schwarz JM. New tricks by an old dogma: mechanisms of the Organizational/Activational Hypothesis of steroid-mediated sexual differentiation of brain and behavior. Horm behav. 2009; 55(5):655-665. https://doi.org/10.1016/j.yhbeh.2009.02.012. PMid:19682425 PMCid:PMC2742630.
91. Simerly RB. Wired for reproduction: Organization and development of sexually dimorphic circuits in the mammalian forebrain. Annu Rev Neurosci. 2002; 25:507-536. https://doi.org/10.1146/annurev.neuro.25.112701.142745. PMid:12052919.
92. Williams GR. Thyroid hormone actions in cartilage and bone. Eur Thyroid J. 2012; 3-13. https://doi.org/10.1159/000345548.

93. Wagner MS, Wajner SM, Maia AL. The role of thyroid hormone in testicular development and function. J Endocrinol. 2008; 199(3):351-365. https://doi.org/10.1677/JOE-08-0218. PMid:18728126 PMCid:PMC2799043
94. Chan S, Kilby MD. Thyroid hormone and central nervous system development. J Endocrinol. 2000; 165(1):1-8. https://doi.org/10.1677/joe.0.0500001.
95. Boas M, Feldt-Rasmussen U, Main KM. Thyroid effects of endocrine disrupting chemicals. Mol Cell Endocrinol. 2012; 355(2):240-248. https://doi.org/10.1016/j.mce.2011.09.005. PMid:21939731.
96. Guyot R, Chatonnet F, Gillet B, Hughes S, Flamant F. Toxicogenomic analysis of the ability of brominated flame retardants TBBPA and BDE-209 to disrupt thyroid hormone signaling in neural cells. Toxicology. 2014; 325:125-132. https://doi.org/10.1016/j.tox.2014.08.007. PMid:25172293.
97. Parsons A, Lange A, Hutchinson TH, Miyagawa S, Iguchi T, Kudoh T, Tyler CR. Molecular mechanisms and tissue targets of brominated flame retardants, BDE-47 and TBBPA, in embryo-larval life stages of zebrafish (*Danio rerio*). Aquat Toxicol. 2019; 209:99-112. https://doi.org/10.1016/j.aquatox.2019.01.022. PMid:30763833.
98. Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C. Influence of maternal thyroid hormones during gestation on fetal brain development. Neuroscience. 2017; 342:68-100. https://doi.org/10.1016/j.neuroscience.2015.09.070. PMid:26434624 PMCid:PMC4819012.
99. Lema SC, Dickey JT, Schultz IR, Swanson P. Dietary exposure to 2,2′,4,4′-tetrabromodiphenyl ether (PBDE-47) alters thyroid status and thyroid hormone-regulated gene transcription in the pituitary and brain. Environ Health Perspect. 2008; 116(12):1694-1699. https://doi.org/10.1289/ehp.11570. PMid:19079722 PMCid:PMC2599765.
100. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev. 2002;23(1):38-89. https://doi.org/10.1210/edrv.23.1.0455. PMid:11844744.
101. Bianco AC, Kim BW. Deiodinases: Implications of the local control of thyroid hormone action. J Clin Investig. 2006; 116(10):2571-2579. https://doi.org/10.1172/JCI29812. PMid:17016550 PMCid:PMC1578599.
102. Li Y, Zhou Q, Wang Y, Xie X. Fate of tetrabromobisphenol A and hexabromocyclododecane brominated flame retardants in soil and uptake by plants. Chemosphere. 2011; 82(2):204-209. https://doi.org/10.1016/j.chemosphere.2010.10.021. PMid:21051070.
103. Hu J, Liang Y, Chen M, Wang X. Assessing the toxicity of TBBPA and HBCD by zebrafish embryo toxicity assay and biomarker analysis. Environ Toxicol. 2009; 24(4):334-342. https://doi.org/10.1002/tox.20436. PMid:18767142.
104. Veldhoen N, Boggs A, Walzak K, Helbing CC. Exposure to tetrabromobisphenol-A alters TH-associated gene expression and tadpole metamorphosis in the Pacific tree frog *Pseudacris regilla*. Aquat Toxicol. 2006; 78(3):292-302. https://doi.org/10.1016/j.aquatox.2006.04.002. PMid:16678281.
105. Shi H, Qian L, Guo S, Zhang X, Liu J, Cao Q. Teratogenic effects of tetrabromobisphenol A on Xenopus tropicalis embryos. Comp Biochem Physiol C Toxicol Pharmacol. 2010; 152(1):62-68. https://doi.org/10.1016/j.cbpc.2010.02.013. PMid:20188212.
106. Shi YJ, Xu XB, Zheng XQ, Lu YL. Responses of growth inhibition and antioxidant gene expression in earthworms (*Eisenia fetida*) exposed to tetrabromobisphenol A, hexabromocyclododecane and decabromodiphenyl ether. Comp Biochem Physiol C Toxicol Pharmacol. 2015; 174-175:32-38. https://doi.org/10.1016/j.cbpc.2015.06.005. PMid:26117064.
107. Kester MHA, Bulduk S, Van Toor H, Tibboel D, Meinl W, Glatt H, Falany CN, Coughtrie MW, Schuur AG, Brouwer A, Visser TJ. Potent inhibition of estrogen sulfotransferase by hydroxylated metabolites of polyhalogenated aromatic hydrocarbons reveals alternative mechanism for estrogenic activity of endocrine disrupters. Journal of Clinical Endocrinol Metab. 2002; 87(3):1142-1150. https://doi.org/10.1210/jcem.87.3.8311. PMid:11889178.
108. Samuelsen M, Olsen C, Holme JA, Meussen-Elholm E, Bergmann A, Hongslo JK. Estrogen-like properties of brominated analogs of bisphenol A in the MCF-7 human breast cancer cell line.

Cell Bio Toxicol. 2001; 17(3):139-151. https://doi.org/10.1023/A:1011974012602. PMid:11693576.

109. Olsen CM, Meussen-Elholm ETM, Samuelsen M, Holme JA, Hongslo JK. Effects of the environmental oestrogens bisphenol A, tetrachlorobisphenol A, tetrabromobisphenol A, 4-hydroxybiphenyl and 4,4′-dihydroxybiphenyl on oestrogen receptor binding, cell proliferation and regulation of oestrogen sensitive proteins in the human. Pharmacol Toxicol. 2003; 92(4):180-188. https://doi.org/10.1034/j.1600-0773.2003.920408.x. PMid:12753421.
110. Meerts IATM, Letcher RJ, Hoving S, Marsh G, Bergman Å, Lemmen JG, van der Burg B, Brouwer A. In vitro estrogenicity of polybrominated diphenyl ethers, hydroxylated PBDEs, and polybrominated bisphenol A compounds. Environ Health Perspect. 2001; 109(4):399-407. https://doi.org/10.1289/ehp.01109399. PMid:11335189 PMCid:PMC1240281.
111. Körner W, Hanf V, Schulter W, Bartsch H, Zwirner M, Hagenmaier H. Validation and application of a rapid in vitro assay for assessing the estrogenic potency of halogenated phenolic chemicals. Chemosphere. 1998; 37(9-12):2395-2407. https://doi.org/10.1016/S0045-6535(98)00297-5.
112. Scott HM, Mason JI, Sharpe RM. Steroidogenesis in the fetal testis and its susceptibility to disruption by exogenous compounds. Endocr Rev. 2009; 30(7):883-925. https://doi.org/10.1210/er.2009-0016. PMid:19887492.
113. Linhartova P, Gazo I, Shaliutina-Kolesova A, Hulak M, Kaspar V. Effects of tetrabrombisphenol A on DNA integrity, oxidative stress, and sterlet (*Acipenser ruthenus*) spermatozoa quality variables. Environ Toxicol. 2015; 30(7):735-745. https://doi.org/10.1002/tox.21953. PMid:24459015.
114. Zatecka E, Ded L, Elzeinova F, Kubatova A, Dorosh A, Margaryan H, Dostalova P, Peknicova J. Effect of tetrabrombisphenol A on induction of apoptosis in the testes and changes in expression of selected testicular genes in CD1 mice. Repro Toxicol. 2013; 35(1):32-39. https://doi.org/10.1016/j.reprotox.2012.05.095. PMid:22677475.
115. Ogunbayo OA, Lai PF, Connolly TJ, Michelangeli F. Tetrabromobisphenol A (TBBPA), induces cell death in TM4 Sertoli cells by modulating Ca2+ transport proteins and causing dysregulation of Ca2+ homeostasis. Toxicol in Vitro. 2008; 22(4):943-952. https://doi.org/10.1016/j.tiv.2008.01.015. PMid:18329244.
116. Zhang H, Liu W, Chen B, He J, Chen F, Shan X, Du Q, Li N, Jia X, Tang J. Differences in reproductive toxicity of TBBPA and TCBPA exposure in male *Rana nigromaculata*. Environ Pollut. 2018; 243:394-403. https://doi.org/10.1016/j.envpol.2018.08.086. PMid:30199813.
117. von Krogh K, Ropstad E, Nourizadeh-Lillabadi R, Haug TM, Weltzien FA. In vitro effects of bisphenol a and tetrabromobisphenol a on cell viability and reproduction-related gene expression in pituitaries from sexually maturing atlantic cod (*Gadus morhua* L.). Fishes. 2019; 4(3):1-16. https://doi.org/10.3390/fishes4030048.
118. Steves AN, Bradner JM, Fowler KL, Clarkson-Townsend D, Gill BJ, Turry AC, Caudle WM, Miller GW, Chan AW, Easley IV CA. Ubiquitous Flame-Retardant Toxicants Impair Spermatogenesis in a Human Stem Cell Model. Science. 2018; 3:161-176. https://doi.org/10.1016/j.isci.2018.04.014. PMid:29901031 PMCid:PMC5994764.
119. Pullen S, Boecker R, Tiegs G. The flame retardants tetrabromobisphenol A and tetrabromobisphenol A-bisallylether suppress the induction of interleukin-2 receptor α chain (CD25) in murine splenocytes. Toxicology. 2003; 184(1):11-22. https://doi.org/10.1016/S0300-483X(02)00442-0.
120. Saegusa Y, Fujimoto H, Woo GH, Ohishi T, Wang L, Mitsumori K, Nishikawa A, Shibutani M. Transient aberration of neuronal development in the hippocampal dentate gyrus after developmental exposure to brominated flame retardants in rats. Arch Toxicol. 2012; 86(9):1431-1442. https://doi.org/10.1007/s00204-012-0824-4. PMid:22415764.
121. Cho JH, Lee S, Jeon H, Kim AH, Lee W, Lee Y, Yang S, Yun J, Jung YS, Lee J. Tetrabromobisphenol A-Induced Apoptosis in Neural Stem Cells Through Oxidative Stress and Mitochondrial Dysfunction. Neurotox Res. 2020; 38(1):74-85. https://doi.org/10.1007/s12640-020-00179-z. PMid:32108298.
122. Viberg H, Eriksson P. Differences in neonatal neurotoxicity of brominated flame retardants, PBDE 99 and TBBPA, in mice. Toxicology. 2011; 289(1):59-

65. https://doi.org/10.1016/j.tox.2011.07.010. PMid:21820030.
123. Kim AH, Chun HJ, Lee S, Kim HS, Lee J. High dose tetrabromobisphenol A impairs hippocampal neurogenesis and memory retention. Food Chem Toxicol. 2017; 106:223-231. https://doi.org/10.1016/j.fct.2017.05.053. PMid:28564613.
124. Chen J, Tanguay RL, Xiao Y, Haggard DE, Ge X, Jia Y, Zheng Y, Dong Q, Huang C, Lin K. TBBPA exposure during a sensitive developmental window produces neurobehavioral changes in larval zebrafish. Environ Pollut. 2016; 216:53-63. https://doi.org/10.1016/j.envpol.2016.05.059. PMid:27239688.
125. Zhu B, Zhao G, Yang L, Zhou B. Tetrabromobisphenol A caused neurodevelopmental toxicity via disrupting thyroid hormones in zebrafish larvae. Chemosphere. 2018; 197:353-361. https://doi.org/10.1016/j.chemosphere.2018.01.080. PMid:29407805.
126. Mariussen E, Fonnum F. The effect of brominated flame retardants on neurotransmitter uptake into rat brain synaptosomes and vesicles. Neurochem Int. 2003; 43(4-5):533-542. https://doi.org/10.1016/S0197-0186(03)00044-5.
127. Wang X, Wei L, Zhu J, He B, Kong B, Xue Z, Jin X, Fu Z. Environmentally relevant doses of tetrabromobisphenol A (TBBPA) cause immunotoxicity in murine macrophages. Chemosphere. 2019; 236:124413. https://doi.org/10.1016/j.chemosphere.2019.124413. PMid:31545206.
128. Watanabe W, Shimizu T, Sawamura R, Hino A, Konno K, Hirose A, Kurokawa M. Effects of tetrabromobisphenol A, a brominated flame retardant, on the immune response to respiratory syncytial virus infection in mice. Int Immunopharmacol. 2010; 10(4):393-397. https://doi.org/10.1016/j.intimp.2009.12.014. PMid:20074668.
129. Reistad T, Mariussen E, Fonnum F. The effect of a brominated flame retardant, tetrabromobisphenol-A, on free radical formation in human neutrophil granulocytes: The involvement of the MAP kinase pathway and protein kinase C. Toxicol Sci. 2005; 83(1):89-100. https://doi.org/10.1093/toxsci/kfh298. PMid:15456914.
130. Szychowski KA, Wójtowicz AK. TBBPA causes neurotoxic and the apoptotic responses in cultured mouse hippocampal neurons in vitro. Pharmacol Rep. 2016; 68(1):20-26. https://doi.org/10.1016/j.pharep.2015.06.005. PMid:26721346.
131. Tetz LM, Kamau PW, Cheng AA, Meeker JD, Loch-Caruso R. Troubleshooting the dichlorofluorescein assay to avoid artifacts in measurement of toxicant-stimulated cellular production of reactive oxidant species. J Pharmacol Toxicol Methods. 2013; 67(2):56-60. https://doi.org/10.1016/j.vascn.2013.01.195. PMid:23380227 PMCid:PMC3795613.
132. Strack S, Detzel T, Wahl M, Kuch B, Krug HF. Cytotoxicity of TBBPA and effects on proliferation, cell cycle and MAPK pathways in mammalian cells. Chemosphere. 2007; 67(9):405-411. https://doi.org/10.1016/j.chemosphere.2006.05.136. PMid:17254629.
133. Fini JB, Riu A, Debrauwer L, Hillenweck A, Le mével S, Chevolleau S, Boulahtouf A, Palmier K, Balaguer P, Cravedi JP, Demeneix BA. Parallel biotransformation of tetrabromobisphenol A in *Xenopus laevis* and mammals: Xenopus as a model for endocrine perturbation studies. Toxicol Sci. 2012; 125(2):359-367. https://doi.org/10.1093/toxsci/kfr312. PMid:22086976.
134. Zhang KS, Chen HQ, Chen YS, Qiu KF, Zheng X Bin, Li GC, Yang HD, Wen CJ. Bisphenol A stimulates human lung cancer cell migration via upregulation of matrix metalloproteinases by GPER/EGFR/ERK1/2 signal pathway. Biomed Pharmacother. 2014; 68(8):1037-1043. https://doi.org/10.1016/j.biopha.2014.09.003. PMid:25312822.
135. Baumann L, Ros A, Rehberger K, Neuhauss SCF, Segner H. Thyroid disruption in zebrafish (*Danio rerio*) larvae: Different molecular response patterns lead to impaired eye development and visual functions. Aquat Toxicol. 2016; 172:44-55. https://doi.org/10.1016/j.aquatox.2015.12.015. PMid:26765085.
136. Yin N, Liang S, Liang S, Yang R, Hu B, Qin Z, Liu A, Faiola F. TBBPA and Its Alternatives Disturb the Early Stages of Neural Development by Interfering with the NOTCH and WNT Pathways. Environ Sci Technol. 2018; 52(9):5459-5468. https://doi.org/10.1021/acs.est.8b00414. PMid:29608295.
137. Jugan ML, Levi Y, Blondeau JP. Endocrine disruptors and thyroid hormone physiology. Biochem Pharmacol. 2010; 79(7):939-947. https://doi.org/10.1016/j.bcp.2009.11.006. PMid:19913515.

138. Hansen MK, Sharma AK, Dybdahl M, Boberg J, Kulahci M. In vivo Comet assay - statistical analysis and power calculations of mice testicular cells. Mutat Res Genet Toxicol Environ Mutagen. 2014; 774:29-40. https://doi.org/10.1016/j.mrgentox.2014.08.006. PMid:25440908.
139. Hu F, Pan L, Xiu M, Liu D. Dietary accumulation of tetrabromobisphenol A and its effects on the scallop *Chlamys farreri*. Comp Biochem Physiol Part - C: Toxicol Pharmacol. 2015; 167:7-14. https://doi.org/10.1016/j.cbpc.2014.08.002. PMid:25183548.
140. Wang B, Wang H, Han D, Chen J, Yin Y. Studying the mixture effects of brominated flame retardants and metal ions by comet assay. Environ Pollut. 2020; 267:115677. https://doi.org/10.1016/j.envpol.2020.115677. PMid:33254668.