



Absence of neurotoxicity and lack of neurobehavioral consequences due to exposure to tetrabromobisphenol A (TBBPA) exposure in humans, animals and zebrafish

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Abstract

Tetrabromobisphenol A (2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol, CAS no. 79-94-7) (TBBPA) is an effective brominated flame retardant present in many consumer products whose effectiveness is attributable to its ability to retard flames and consequently save human lives. Toxicokinetic studies revealed that TBBPA when absorbed via the gastrointestinal tract is rapidly metabolized to glucuronide or sulfate metabolites which are rapidly eliminated by the kidney. TBBPA does not accumulate in the body and there is no evidence that the parent compound is present in the brain. Although this brominated flame retardant was detected in human breast milk and serum, there was no evidence that TBBPA reached the brain in in vivo animal studies as reflected by the absence of neuropathological, neurotoxic, or behavioral alterations indicating that the central nervous system is not a target tissue. These animal investigations were further supported by use of the larval/embryo observations that TBBPA did not produce behavioral changes in a larval/embryo zebrafish a model of chemical-induced neurotoxicity. Although some protein expressions were increased, decreased or not affected in the blood–brain barrier indicating no evidence that TBBPA entered the brain, the changes were contradictory, or gender related, and behavior was not affected supporting that this compound was not neurotoxic. Taken together, TBBPA does not appear to target the brain and is not considered as a neurotoxicant.

Keywords Brominated flame retardants · TBBPA · No CNS effects · Human · Animal · Zebrafish

Introduction

Tetrabromobisphenol A (2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol, CAS no. 79-94-7) (TBBPA), due to its low hazard profile in mammals and its effectiveness in providing fire safety (BSEF 2012), is the most widely produced brominated flame retardant. When TBBPA is employed as a flame retardant in epoxy resins in a variety of consumer products including printed circuit boards, communication and electronic equipment, appliances, transportation

devices (Birnbaum and Staskal 2004; BSEF 2012), TBBPA is chemically bound to constituents of the resin which is not released into the environment. In general, once in the environment TBBPA or TBBPA-containing products distribute to the soil and sediment (Rothenbacher and Pecquet 2018). The European Union (EU) has concluded that there was no terrestrial risk except in the case of heavily contaminated soil near TBBPA manufacturing sites but only if the predicted no-effect concentration (PNEC) exceeded 0.012 mg/kg (EU 2008). Liu et al. (2016a) indicated that the concentrations of TBBPA found in air ranged from 66,010 to 95,040 pg/m³; 1.6 to 7758 ng/g in soil and 850 to 4870 ng/L in water. China is one of the most polluted regions as compared with other countries. To place in perspective, the concentrations of TBBPA required to initiate effects in mammals are in the milligram to gram level that equals a margin of exposure (MOE) > than 200,000. For a chemical substance with health thresholds, i.e., not genotoxic and not carcinogenic, an MOE value > than 100 is considered protective. The MOE approach was developed by the European

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Food Safety Administration (EFSA 2011). It is important to note that TBBPA exhibits physicochemical properties such as low to moderate aqueous solubility, a low vapor pressure and a moderately high high/octanol/water partition coefficient that greatly diminished the ability of this compound to dissolve in media required to enter humans and wildlife (de Wit 2002; Environment Canada 2013).

Toxicokinetics

Human exposure to TBBPA and TBBPA-containing products from all sources is estimated to be low, even in the case of specific occupational exposure scenarios. The risk of adverse health effects remains low due to the physicochemical properties of TBBPA which act as a deterrent to absorption (Schauer et al. 2006). In essence, systemic bioavailability of TBBPA from all environmental sources in humans is low (Colnot et al. 2014; Yu et al. 2019).

The presence of TBBPA has been detected in human tissues. Cariou et al. (2008) reported in a study of 93 women that TBBPA was detected in 44% of the breast milk samples, at levels varying from 0.06 to 37.34 ng/g lipid weight, but was not detected in adipose tissue. This compound was also detected in 30% of the serum samples, with average values in maternal and cord serum of 154 pg/g fresh weight versus 199 pg/g fresh weight, respectively. In a recent investigation, Knudsen et al. (2018) demonstrated that oral administration of TBBPA to pregnant or nursing Wistar Han rats resulted in rapid metabolism such that, within 30 min, only TBBPA conjugates were detected through 8 h demonstrating that the nursing infant was not exposed to the free form of TBBPA. It is also important to note that Knudsen et al. (2018) reported the presence of the brominated flame retardant or its conjugate in the liver, uterus and mammary tissue of lactating animals but not in the central nervous system, which was claimed by Cannon et al. (2019) *in vitro* but not supported *in vivo* to be a target for neurotoxicity (NAS 2019). It is not clear why Knudsen et al. (2018) did not determine TBBPA levels in the central nervous system to affirm their own *in vitro* data (Cannon et al. 2019). Indeed, Cannon et al. (2019) administered a single oral dose (250 mg/kg) of TBBPA to Sprague–Dawley rats, excised brain tissue but reported no evidence of the presence of TBBPA or the TBBPA conjugate in this tissue, indicating that this brominated flame retardant did not traverse the blood–brain barrier to initiate a neurotoxic response.

Distribution and accumulation

This flame retardant was not present in maternal adipose tissue supporting the conclusion that TBBPA does not accumulate in human fat tissue. Further, in a large biomonitoring study of approximately of 50,000 serum samples in Canada the concentration of this flame retardant was below the limit of detection (LOD) of 0.03 ng/g serum in all samples (Environment Canada 2013). It is noteworthy that in other Canadian investigations, TBBPA was detected in only 5% of approximately 750 Inuit serum samples at 480 ng/L (Alberta 2008; Dallaire et al. 2009). Shi et al. (2013) reported in a population of 103 in Beijing that the concentration of TBBPA ranged from LOD to 12.5 ng/g lipid weight with a mean of 0.1 ng/g reaffirming that, if present, the presence of this brominated flame retardant in humans is very low. Thomsen et al. (2002) detected a concentration of < 1 ng/g lipid in serum of TBBPA in a Norwegian population. Evidence thus indicates that TBBPA is present in human breast milk and serum; however, these compound levels do not pose any significant adverse effects to human health (Kang et al. 2009; Liu et al. 2018).

To assess the ability of the concentration of a chemical to reach levels that are required to produce potential adverse effects either in *in vitro* models or *in vivo* in humans or animals, it is essential to establish the toxicokinetics (TK) of the compound of concern. In the case of TBBPA, several investigators have characterized the absorption, distribution, metabolism and excretion (ADME) of this flame retardant, the key components which constitute the sites where the compound travels after entry into the body to initiate a response (Yu et al. 2019). This factor is essential when one considers whether TBBPA exerts neurologic actions which are not supported by scientific observations (NAS 2019) as claimed by Cannon et al. (2019) since the active parent compound might not be bioavailable for transport into the central nervous system. In humans, oral administration of 0.1 mg/kg TBBPA resulted in extensive metabolism of the parent compound within 4 h with the unchanged compound in serum and urine below the LOD of 0.3 nmol/L and 4 µmol/L, respectively, in humans (Schauer et al. 2006).

The metabolism of TBBPA in the gastrointestinal tract and the formation of glucuronic or sulfate metabolites noted in humans are indicative of low bioavailability *in vivo*; these findings were confirmed in rats. Several investigators examined the toxicokinetics of TBBPA following single or repeated oral administration (Kuester et al. 2007; Knudsen et al. 2018; Kang et al. 2009; Haak and Lechter 2003; Schauer et al. 2006). Following gastrointestinal absorption in rats regardless of the dose (single or repeat dosing) over 95% of TBBPA is excreted as a glucuronide or sulfate conjugate indicating that the compound exhibits low bioavailability associated with limited or no retention (Colnot et al.

2014; Lai et al. 2015; Kuester et al. 2007; Knudsen et al. 2014; Yu et al. 2019).

Blood–brain barrier

Although TBBPA is absorbed from the gastrointestinal tract, this compound needs to traverse a significant blood–brain barrier (BBB) to enter the brain. The BBB is located at the brain capillary wall and constitutes the first line of defense against entry of xenobiotics. The BBB is a component of the neurovascular system which is composed of endothelial cells, pericytes and astrocytes. The entry or exit of toxicants from the brain is regulated by the BBB. The capillary endothelial cells form tight joints consequently leaving few or no pores between cells and thus the ability of a neurotoxicant to travel between the brain and peripheral blood is tightly controlled (Bradbury 1984). Toxicant entry into the brain thus must first reach the BBB and then traverse the capillary endothelium.

Several mechanisms exist for toxicants or endogenous compounds to permeate the BBB. One possible mechanism for permeating systemic organs is by binding to proteins in the serum. Compounds, like TBBPA, may bind to proteins if they are present in sufficient levels to enable binding and subsequently entry into organs such as heart, liver, kidneys. However, the protein level in the interstitial brain fluid is extremely low and thus such binding of toxicants as a mechanism for transfer from peripheral blood to brain is not feasible. This is especially true in the case for TBBPA as its bioavailability is low. Schauer et al. (2006) in their toxicokinetic investigation demonstrated that parent TBBPA bioavailability in blood was less than 5% of the parent compound being available for potential protein binding. Thus, transfer to the brain past the BBB via protein binding also does not seem feasible. It is well known that the permeability of toxicants into the brain is dependent on lipid solubility (Kim 2018). Kuester et al. (2007) administered TBBPA to F-344 rats and reported an absence of TBBPA parent compound in adipose tissue, and fat from kidney, mesentery, testes, thoracic cavity and total fat showing that this brominated flame retardant does not accumulate indicating that lipid solubility also was not a mechanism to cross the BBB.

The most prominent defense mechanisms involved in preventing or removing unwanted molecules from the brain are the active transport systems which play a role in limiting the distribution of neurotoxicants in the brain. The BBB is composed of various members of the adenosine triphosphate (ATP)-binding cassette transporter (ABC) and solute transporter (SLC) families, which remove or limit entry of foreign molecules from the brain. In addition to the apical plasma membrane, there are a number of efflux transporters including P-glycoprotein (P-gp), multidrug-resistant protein

(MDR), breast cancer-resistant protein (BCRP), and multidrug resistance-associated protein (MRP) 1, 2, 4 and 5 which act to pump any xenobiotics that were absorbed from the brain into the capillary endothelial cells and subsequently into the blood. It needs to be emphasized that the determination of the action of a xenobiotic on the BBB transport system does not equate to a neurotoxic, behavioral or neuropathologic response but is simply an observation that a compound interacted with a BBB transport protein. Bearing this in mind, Cannon et al. (2019) administered a single oral dose of 250 mg/kg TPPPA to Sprague–Dawley rats of both genders. After 6 h, the brain was extracted for measurement of P-gp, BCRP, and MRP2. However, the authors did not measure TBBPA or TBBPA conjugates in the brain and no evidence of any neurotoxic signs as proposed by the US EPA guidelines for neurotoxicity (US EPA 1998) including parasympathetic functions (lacrimation, salivation, frequency of urination), the presence or absence of piloerection, pupillary light reflex, palpebral reflex, evidence of ptosis, presence or absence of convulsions, abnormal movement gait or posture, muscle tone, unusual/abnormal behaviors, presence or absence of stereotypes, abnormal secretions and abnormal grip strength as described by Meyer et al. (1979) was reported. Further, neurobehavioral parameters as outlined by the Functional Observation Battery (FOB) according to the US EPA (1998) were not determined. Cannon et al. (2019) found that TBBPA increased P-gp and decreased BCRP accompanied by no change in MRP2 in males. In females, P-gp and BCRP were reduced with no accompanying alteration in MRP2. It appears that TBBPA might modulate a BBB transporter in opposite directions in males compared to females in the case of the protein expression P-gp while diminished protein expression of BCRP occurred in both genders and no marked change in the protein expression of MRP2 occurred in either gender but was not associated with any evidence of an effect on the central nervous system confirming the overall observations that the brain is not a target for TBBPA-mediated responses (NAS 2019; Kicinski et al. 2012; Cope et al. 2015; Williams and DeSesso 2010; Lai et al. 2015). At present, it is difficult to reconcile the suggestion that TBBPA exhibits a neurotoxic action (Cannon et al. 2019) as these authors failed to provide any scientific findings to support their claim. The fact that a compound at a real-world, non-environmental concentration of TBBPA produced alterations in protein expression of BBB transporters which were sex dependent cannot be equated with a neurotoxic response, especially as the brominated flame retardant was not detected in brain tissue.

Central nervous system as a target tissue

Human studies

Limited data are available on the consequences of human exposure attributed to TBBPA on the central nervous system. In our search of the peer reviewed literature, only a single study was found. In a cross-sectional investigation of 515 adolescents in Belgium, TBBPA did not show any significant decline in performance in several neurobehavioral tests based upon neurobehavioral evaluation system (NES) results (Kicinski et al. 2012). The NES is a computerized battery of tests developed to screen for neurological effects of an exposure to environmental agents (Baker et al. 1985). NES has been employed in numerous investigations to determine the impact of neurotoxins (White et al. 2003). In the four tests utilized by Kicinski et al. (2012), continuous performance, digit symbol, digit span and finger tapping (Letz 2000), there was no significant difference between TBBPA-exposed and control individuals indicating that neurobehavioral performance did not markedly decline.

Animal investigations

In rats, there are several investigations demonstrating that TBBPA did not exert adverse effects on the central nervous system using experimental models including the absence of a developed blood–brain barrier (BBB) in the fetus where the compound readily crossed from the blood into the brain without any interference on the ability to remove TBBPA as reported in a two generation investigation. As presented below neonatal, infant, and adult exposure to TBBPA were also examined with respect to TBBPA action on the central nervous system. Indeed, Cope et al. (2015) noted that in this animal model of TBBPA administration to pregnant and lactating mothers in a two generation study, that the brominated flame retardant did not produce any behavioral, neurological or neuropathologic alterations in newborns. In particular, TBBPA was administered orally at doses of 300 or 1000 mg/kg day to offspring over the course of two generations as well as in a separate experiment on TBBPA treatment of pregnant rats from gestation days 0–19. The neurological parameters measured were not markedly affected by TBBPA (Meyer et al. 1998) and included assessment of parasympathetic function (lacrimation, salivation, frequency of urination), the presence or absence of piloerection, pupillary light reflex, palpebral reflex, evidence of ptosis, the presence or absence of convulsions, abnormal movement, gait or posture, muscle tone, unusual/abnormal behaviors, presence or absence of abnormal secretions and abnormal grip strength. Further, TBBPA did not significantly affect neurobehavioral parameters as outlined by the functional observation

battery (FOB) according to the US EPA guidelines (1998). In addition, a lack of effect of TBBPA was noted following a neuropathological examination of all major brain regions including olfactory bulbs, cerebral cortices, hippocampus, basal ganglia, thalamus, hypothalamus, tectum, tegmentum, cerebral peduncles, brainstem, and cerebellum (Cope et al. 2015).

Lilienthal et al. (2008) administered TBBPA in doses as high as 3000 mg/kg to parental rats at mating and this dosage was continued throughout mating, gestation, and lactation. This brominated flame retardant produced no behavioral effects as evidenced by measurement of context conditioned fear, cue conditioned fear or sweet preference. Lilienthal et al. (2008) further reported that TBBPA-associated brainstem auditory evoked potentials were increased in females but not in males; however, the relevance of this observation, especially for human risk assessment, is questionable. Administration of 0.1 mg/kg TBBPA showed more freezing behavior in mice and significantly increased spontaneous alternation behavior in the Y-maze test, suggesting that TBBPA induced behavioral changes in the mouse (Nakajima et al. 2009). Although it is difficult to extrapolate the observed freezing or alternation in Y maze test to humans, there are factors to consider. The dosage of 0.1 mg is excessively greater than the nanogram range to which a human is exposed; and secondly there were no FOB determinations made as required by the EPA to establish that a chemical is a neurotoxin. The relevance of freezing or alternation in Y maze test to characterize neurotoxicity remains questionable.

In a comprehensive review of the literature, Williams and DeSesso (2010) reported that their analysis showed that although studies suggest that perinatal exposure affects motor activity, the effects observed were not consistent. This lack of consistency included the type of motor activity (locomotion, rearing, or total activity) affected, the direction (increase or decrease) and the pattern of change associated with exposure, the existence of a dose response, the permanency of findings, and the possibility of gender differences in response. The lack of consistency across studies precludes establishment of a causal relationship between perinatal exposure to TBBPA and alterations in motor activity.

Importantly, Good Laboratory Practices (GLP)-compliant studies that followed US Environmental Protection Agency (EPA)/Organization for Economic Cooperation and Development (OECD) guidelines for developmental neurotoxicity testing found no adverse effects associated with exposure to TBBPA at doses that were orders of magnitude higher and administered over longer durations than those used in the other studies reviewed. It is also important to note that a panel of experts convened by the National Academy of Sciences (NAS 2019) is in agreement with the numerous studies showing that the central nervous system is not a target for TBBPA and that this brominated flame retardant in vivo

Table 1 TBBPA target tissues following in vivo administration

Study design	Target tissue	References
Human	Thyroid	Kim and Oh (2014)
Human	Thyroid hormones	Kicinski et al. (2012)
Rat	Thyroid	Cope et al. (2015); Yu et al. (2019); Colnot et al. (2014)
Rat	Liver	Yu et al. (2019); NTP (2014); Dunnick et al. (2015)
Rat	Uterus	Sanders et al. (2016); Lai et al. (2016); Wikoff et al. (2015)

does not exhibit neurologic actions as erroneously suggested by Cannon et al. (2019). These observations reaffirm those of Knudsen et al. (2018) that the central nervous system is not a target for neurologic change. Even though TBBPA conjugates, the inactive bound form of TBBPA, may enter the brain in relatively low amounts, it is without any adverse consequences.

Zebrafish

It has been reported that TBBPA affects thyroid hormone levels in zebrafish with consequent alterations in behavior suggesting that this organism may be utilized as a novel model to identify neurotoxic compounds (Fraser et al. 2017; Zhu et al. 2018; DeWit et al. 2008). Alzualde et al. (2018) reported no marked change in behavior and neurotoxic effects in larval zebrafish exposed to 1–100 μM TBBPA. Godfrey et al. (2017) found no significant alterations in locomotor activity in zebrafish larva exposed to 13 μL TBBPA. Similarly, an absence of behavioral changes in zebrafish embryos or larvae exposed to TBBPA was reported by several other investigators (Noyes et al. 2015; Dach et al. 2019; Jarema et al. 2015; Truong et al. 2014). In contrast, Chen et al. (2016) found that zebrafish embryos exposure to 5 μM TBBPA altered larval behavior as evidenced by diminished activity bursts, lower speed of movement, motor deficits, delayed cranial motor neuron development, and inhibited primary motor neuron development. However, Fraser et al. (2017) demonstrated that larval zebrafish behavioral responses to TBBPA were dependent on the photo-regime, larval age and arena size. It is of interest to note that the TBBPA-induced alteration in zebrafish behavior was associated with photomotor differences (Reif et al. 2016) confirming that change in light and not TBBPA may be responsible for the observed behavioral alterations. Taken together, the evidence indicates that zebrafish exposure to TBBPA does not result in behavioral changes attributed to the flame retardant which is in agreement with the in vivo animal observations that have shown that TBBPA is not a neurotoxicant.

In vitro cell lines

The use of in vitro cell lines has been implemented to infer that TBBPA is neurotoxic. It needs to be emphasized that a cell line does not function in the same manner as an in vivo animal. The physicochemical characteristics of absorption, distribution, metabolism and excretion (ADME) are absent. In essence, the use of in vitro systems is simply a screening method to determine whether a chemical produces an effect on a target tissue. However, in order to state that a chemical is a neurotoxin in vivo experiments are needed. Liu et al. (2016b) incubated rat pheochromocytoma cells with TBBPA at 5 μM concentrations produced reduced cell viability, disturbed dopamine secretion and altered acetylcholinesterase activity. It is important to note that the concentration of TBBPA was excessive considering that humans are exposed to picogram to nanogram quantities of this chemical and there were no measures of neurotoxic parameters such as neurobehavior or function provided. Similarly, Lenart et al. (2017) found that an excessive concentration of 25 μM incubated with rat cerebellar granule cells stimulated genes involved in programmed neuronal death suggesting early suppression of autophagy and anti-apoptotic genes followed by delayed activation of genes associated with apoptosis. Although data obtained with TBBPA in cell lines are of academic interest, these findings are difficult to extrapolate to humans, especially due to the use of very high quantities of this flame retardant which are not environmentally relevant.

Concern regarding the potential adverse effects associated with flame retardants including TBBPA resulted in the National Academy of Sciences convening a panel of experts to examine the available data on the potential consequences of exposure to this brominated flame retardant. The targets for TBBPA where effects were documented as concluded by the panel are presented in Table 1. It is noteworthy that the central nervous system is not listed in Table 1 and was concluded not to be affected by this brominated flame retardant (NAS 2019). A summary of studies in Table 2 illustrates that TBBPA did not exert any significant effects on the central nervous system, affirming that this brominated flame retardant is not a neurotoxicant (NAS 2019; Kacew and Hayes 2018).

Table 2 Summary of absence of TBBPA-initiated neurotoxicity

Reference	Study design	Findings
Kicinski et al. (2012)	Human adolescent	No effect on attention, working memory and motor function
Lilienthal et al. (2008)	Rat	No effect on context conditioned fear- or cue-conditioned fear and sweet preference brain-stem auditory evoked potential increased in female but no effect in male
Williams and DeSesso (2010)	Rat	No neurobehavioral or neurodevelopmental
Cope et al. (2015)	Rat	No neurobehavioral, neurodevelopmental, or neuropathological effects
Cannon et al. (2019)	Rat	No evidence of neurotoxicity, inconsistent alterations in BBB protein expression dependent on gender
Kacew and Hayes (2018)	Rat	No effect on neural development

Conclusions

Evidence indicates that TBBPA in excessive biologically non-relevant concentrations affects the thyroid, uterus and liver. In agreement with a panel of experts convened by the National Academy of Sciences (NAS 2019), the central nervous system and consequent neurotoxicity were not considered as targets for TBBPA. These findings were borne out in numerous in vivo peer reviewed published papers. Data demonstrated a lack of effect of TBBPA on neurodevelopment, behavior and neuropathologic examinations. The suggestive observation that protein expression was altered in the BBB was conflicting and failed to confirm a neurotoxic action with no conclusive evidence of behavior, function or pathology presented. The zebrafish further confirmed that TBBPA did not affect behavioral or motor functions in this species. It is thus concluded that TBBPA is not a neurotoxicant and the brain is not a target for this compound.

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Compliance with ethical standards

Conflict of interest The authors received financial support in preparing this manuscript from American Chemistry Council's North American Flame Retardant Alliance.

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