JOURNAL OF ENVIRONMENTAL SCIENCES 97 (2020) 54–66

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/jes

JES JOURNAL OF ENVIRONMENTAL SCIENCES

www.jesc.ac.cn

Tetrabromobisphenol A (TBBPA): A controversial environmental pollutant

Hui Zhou[1,2], *Nuoya Yin*[1,2], *Francesco Faiola*[1,2,*]

[1] *State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China*

[2] *College of Resources and Environment, University of Chinese Academy of Sciences, Beijing 100049, China*

ARTICLE INFO

Article history:
Received 24 November 2019
Revised 23 April 2020
Accepted 23 April 2020
Available online 7 June 2020

Keywords:
Tetrabromobisphenol A (TBBPA)
Developmental toxicity
Endocrine disrupting chemicals (EDC)
Hepatotoxicity
Neurotoxicity

ABSTRACT

Tetrabromobisphenol A (TBBPA) is one of the most widely used brominated flame retardants and is extensively used in electronic equipment, furniture, plastics, and textiles. It is frequently detected in water, soil, air, and organisms, including humans, and has raised concerns in the scientific community regarding its potential adverse health effects. Human exposure to TBBPA is mainly via diet, respiration, and skin contact. Various *in vivo* and *in vitro* studies based on animal and cell models have demonstrated that TBBPA can induce multifaceted effects in cells and animals, and potentially exert hepatic, renal, neural, cardiac, and reproductive toxicities. Nevertheless, other reports have claimed that TBBPA might be a safe chemical. In this review, we re-evaluated most of the published TBBPA toxicological assessments with the goal of reaching a conclusion about its potential toxicity. We concluded that, although low TBBPA exposure levels and rapid metabolism in humans may signify that TBBPA is a safe chemical for the general population, particular attention should be paid to the potential effects of TBBPA on early developmental stages.

Introduction

Tetrabromobisphenol A (2,2′6,6′-Tetrabromo-4,4′-isopropylidenediphenol, TBBPA (CAS 79-94-7)) is currently the most widely used brominated flame retardant (BFR). The three major production areas of TBBPA in the world include China, the USA, and the Middle East. The total production of TBBPA in these three regions was approximately 241,352 tons in 2016 (WorldAnalytics, 2019), while the annual production of TBBPA in China is around 180,000 tons (LM, 2019). Moreover, the global market for TBBPA is expected to increase at a compounded annual growth rate of approximately 3.8% over the next five years (WorldAnalytics, 2019). The main utilization of TBBPA is as a reagent in the production of epoxy and polycarbonate resins employed in electronic devices, furniture, and other equipment (Covaci et al., 2009).

Environmental surveys have shown that TBBPA can be released into the environment during production, processing, and final product usage and disposal (ECHA, 2008). Although there is no report describing the exact time when its production began, TBBPA was detected as early as Watanabe et al., 1983 in sediments from the Neya River in Japan (Watanabe et al., 1983). Currently, TBBPA is widespread in many kinds of abiotic and biotic matrices (Covaci et al., 2009). It can be found in air, water, soil, indoor dust, sediments, and sewage sludge from different locations (Covaci et al., 2009; Guerra et al., 2010; Huang et al., 2014; Kowalski and Mazur, 2014; Ni and Zeng, 2013; Takigami et al., 2009). It can also accumulate in the food chain (Shi et al., 2017).

The main exposure pathways to TBBPA for the general population include diet, ingestion of, and dermal contact with dust (Abdallah et al., 2015). As a consequence, TBBPA can be detected in human bodily fluid samples, such as breast milk and maternal/cord sera. In fact, several studies have reported TBBPA levels in blood serum up to 93.22 ng/g lipid weight (lw) in adults and 457.4 ng/g lw in infants (Cariou et al., 2008; Kim and Oh, 2014), and in cord blood serum up to 649.45 ng/g lw

* Corresponding author.
E-mail: faiola@rcees.ac.cn (F. Faiola).

https://doi.org/10.1016/j.jes.2020.04.039
1001-0742/

(Cariou et al., 2008). Similarly, TBBPA levels in breast milk could reach 37.34 ng/g lw (Cariou et al., 2008). Although with regional differences, these findings suggest that TBBPA equivalent concentrations in the body are generally much lower than 1–10 nmol/L, but in extreme cases can be as high as 1–2 μmol/L in cord serum lipids (nmol/L levels in serum when adjusted for lipid percentage). As far as the daily average TBBPA intake is concerned, studies have estimated it to be in the range of 0.018 and 0.97 ng/kg body weight (bw) for dust inhalation and dust ingestion respectively (Ni and Zeng, 2013), 1.34 ng/kg bw through food consumption (Shi et al., 2017), and particularly for infants, 6.62–10.1 ng/kg bw (Huang et al., 2020).

To date, few epidemiological analyses linking TBBPA to diseases or medical conditions are available. For example, one study showed that there was no consistent association between TBBPA blood levels and performance in neurobehavioral tests (Kicinski et al., 2012). Conversely, many toxicological evaluations of the potential toxicity of TBBPA have been conducted. Thus, in this review, most of the toxicological studies published so far were analyzed and an attempt was made to assess the TBBPA doses of exposure that may affect human health.

1. Studies addressing the potential toxicity of TBBPA

The widespread detection of TBBPA in abiotic and biotic matrices, as well as in human bodily fluid samples, has raised concerns among toxicologists about the potential health risks of TBBPA. The potential adverse effects of TBBPA on humans were investigated as early as 1979 (Inouye et al., 1979). Since then, various toxicological models have been employed to investigate TBBPA toxicity.

1.1. *Animal-based evaluations*

1.1.1. *Zebrafish*

Zebrafish is a classic model organism, which has been widely utilized to assess TBBPA toxicity and define human health risks. Table 1 lists the major toxicological findings in TBBPA-exposed zebrafish, with details on the treatments exerting the specific toxic effects.

In several studies, TBBPA caused obvious effects on growth and development (Table 1) (Baumann et al., 2016; Chen et al., 2016a, 2016b; Parsons et al., 2019; Usenko et al., 2016; Wu et al., 2016). In addition, TBBPA could increase oxidative stress, induce reactive oxygen species (ROS) production, and influence the antioxidant defense systems (Wu et al., 2016). Furthermore, TBBPA altered the expression of matrix metalloproteinases, which are important for the remodeling of the extracellular matrix during several processes, including wound healing, cell migration, and tissue morphogenesis (McCormick et al., 2010). All the above effects were generally observed at μmol/L levels or higher, except for effects on development, which started in the nmol/L range.

As far as the endocrine system is concerned, TBBPA has been shown to affect it (Table 1). For example, many studies have illustrated the effects of TBBPA on the thyroid hormone (TH) system. In fact, TBBPA affects the hypothalamic–pituitary–thyroid (HPT) axis-related gene expression, thus influencing thyroid functions (Parsons et al., 2019; Zhu et al., 2018). In addition, it could act as a TH antagonist (Zhang et al., 2015). TBBPA can disrupt TH-induced cell signaling pathways (Kudo et al., 2006) and can interfere with a series of TH-dependent processes during development (Parsons et al., 2019). Moreover, it could interfere with eye development (Baumann et al., 2016); have estrogenic activity (Chow et al., 2013); decrease hatching rate/delays hatching (Kuiper et al., 2007; Wu et al., 2016); and activate zebrafish peroxisome proliferator-activated receptor γ (PPARγ) to induce lipid accumulation at the larval stage and thus act as an obesogen (Riu et al., 2014). In some cases, these endocrine-disrupting effects could be elicited by low concentrations of TBBPA.

Additionally, TBBPA could exert neurodevelopmental toxicity, alter behavior (Chen et al., 2016a, 2016b; Usenko et al., 2016; Zhu et al., 2018), and elicit cardiac developmental toxicity (Wu et al., 2016). TBBPA could exert most of the above developmental effects at nmol/L levels.

Although many studies have demonstrated that TBBPA may be quite harmful, there are still reports claiming TBBPA as a safe chemical (Table 1). For example, up to 10 μmol/L TBBPA did not affect zebrafish development when the treatment was administered 48–96 hr post-fertilization (hpf), whereas it did so if administered at 8–48 hpf (Chen et al., 2016b; Jarema et al., 2015). Similarly, a 3-day exposure at equivalent TBBPA concentrations, from 24 hpf followed by a 3-day recovery period did not cause significant adverse effects (Chen et al., 2016b; Jarema et al., 2015). These data suggest that exposure at very early stages during development is critical for the potential toxic effects of TBBPA to be realized, and that organisms can recover if exposure is not continuous.

1.1.2. *Rodents*

Many studies have evaluated the effects of TBBPA in mouse/rat models including hepatotoxicity, nephrotoxicity, reproductive toxicity, neurotoxicity, and endocrine disruption (Tables 2 and 3).

TBBPA can induce liver damage by triggering inflammation responses and focal necrosis in hepatocytes not only in adults, but also in offspring during gestational and lactation stages (Dunnick et al., 2017; Tada et al., 2006), and also by disrupting heme metabolism (Szymanska et al., 2000). Moreover, TBBPA triggers an increase in dilation or atrophy of renal tubules and cysts in the kidneys (Tada et al., 2006), it induced polycystic kidneys in newborn rats (Fukuda et al., 2004), and overall, exerted kidney toxicity by inducing ROS through metabolism (Choi et al., 2011). All these effects were observed at doses higher than 250 mg/kg bw.

Reproductive organs were potential targets of TBBPA effects for exposures in the range of mg/kg bw. In fact, TBBPA can induce changes in seminiferous tubule morphology (Zatecka et al., 2013), testicular cell apoptosis, and cause damage to sperm DNA (Zatecka et al., 2014). Moreover, it could trigger uterine cancer in rats (Dunnick et al., 2015), potentially as a consequence of endocrine disruption (Sanders et al., 2016) or immunosuppression (Hall et al., 2017). Additional endocrine effects of high-dose TBBPA on the levels of circulating thyroxin (T4) and triiodothyronine (T3) have been reported (Van der Ven et al., 2008).

Neurotoxic effects of TBBPA include influence on hippocampal neurogenesis/memory retention (Kim et al., 2017), neuronal development in the brain (Saegusa et al., 2012), neurobehavior (Nakajima et al., 2009), and sensory neurons (Lilienthal et al., 2008). These effects also manifested at high doses (in the order of mg/kg bw). However, studies with single-dose exposure of TBBPA up to 115 mg/kg bw did not reveal any adverse effects on neural development and behavior (Hendriks et al., 2015; Viberg and Eriksson, 2011). Nevertheless, single dose studies may not reflect the real exposure conditions in humans, considering that TBBPA is quickly metabolized and eliminated.

Many other studies have reported that TBBPA is safe. For example, two studies exposed CD® rats and Wistar Han IGS rats, at doses up to 1000 mg/kg bw daily for several weeks (Dunnick et al., 2017; Osimitz et al., 2016). No significant effects were found in all tested indexes, including mortality, clinical signs, and histopathology. However, dysregulation of 132 genes with activation of metabolic networks, occurred in the livers of Wistar Han IGS rats (Dunnick et al., 2017; Osimitz et al., 2016). All results may be dependent on which parameters were measured. In fact, in two studies with the same TBBPA exposure to the same species of rats, one study observed no effects on what was tested (hepatic cytochrome P450 (CYP) gene expression) (Germer et al., 2006), while the other test showed changes in the levels of circulating T4 and T3 in males (Van der Ven et al., 2008). Interestingly, a two-generational study examined the effects of TBBPA on reproduction, development, and neurobehavior. Those results showed

Table 1 – Summary of key TBBPA (Tetrabromobisphenol A) toxicity studies with zebrafish models.

Test organism	Sex	Exposure doses and time	Main effects	Reference
Zebrafish (embryos/larvae)	-	0.1–1.0 mg/L, for 1–8 days.	Influence on hatching, survival, malformations, and growth rates (0.4–1.0 mg/L, 8 days); brain, heart, and tail cell apoptosis (1.0 mg/L, 8 days); oxidative stress and decrease in antioxidant enzyme activities (1.0 mg/L, 8 days).	Wu et al., 2016
Zebrafish (embryos/larvae)	-	0.04–2.7 μmol/L, for 48–120 hr.	Developmental retardation and deformities, such as edemas in the pericardial region and tail, small heads, swollen yolk sac extension (from 0.92 μmol/L, 96 hr); slight disruption of the TH system, with increased TH conjugation and clearance, abnormal thyroid follicle development and altered TH transport (from 0.04 μmol/L, 48 hr).	Parsons et al., 2019
Zebrafish	Male and female.	5, and 50 nmol/L, for 120 days post fertilization (dpf).	Reduction in body weight and length (5 nmol/L); for males: increase in swim speed and higher speed swim time, hyperactivity, and aggression (5 nmol/L, evaluated at 9 months after 4 months of detoxification).	Chen et al., 2016a
Zebrafish (embryos/larvae)	-	1.25–20 mg/L, for 6–168 hpf.	Induction of pericardial edema and fin malformations (2.5–5 mg/L, 168 hpf); decrease in spontaneous movement rate (5 mg/L, 24 hpf); increased acetylcholinesterase and glutathione-S-transferase (GST) activities (0.625–1.25 mg/L, 120 hpf); it may activate an antioxidant response and alter behavior during early development (1.25 mg/L, 120 hpf).	Usenko et al., 2016
Zebrafish (embryos/larvae)	-	50–400 μg/L, for 142 hpf.	Down-regulation of central nervous system development-related genes, decreased locomotor activity/average swimming speed, thyroid disruption (100 μg/L).	Zhu et al., 2018
Zebrafish (embryos/larvae)	-	5–10 μmol/L, for 8–96 hpf.	For 48–96 hpf exposure, no abnormal phenotypes; for 8–48 hpf exposure: morphological malformations and mortality, lower average activity and speed of movements, and neurobehavioral deficits (5–10 μmol/L).	Chen et al., 2016b
Zebrafish (embryos/larvae)	-	1.2–12 μmol/L, for 3 days (from 24 hpf) and evaluation at day 6.	No effects on locomotion.	Jarema et al., 2015
Zebrafish	Male and female.	0.023–1.5 μmol/L, for 30 days (adults) and 0-47 days post hatching (dph) (offspring).	Decreased egg production and hatching of larvae (from 0.047 μmol/L); high (81%) early post hatching mortality of larvae (1.5 μmol/L); surviving juveniles show female phenotype predominance.	Kuiper et al., 2007
Zebrafish (embryos/larvae)	Male and female.	0.11–0.82 (embryos) and 0.53–3.95 (larvae) mg/L, for 96 hr.	Estrogenic activity (from 0.82 (embryos) and 3.95 (larvae) mg/L).	Chow et al., 2013
Zebrafish (adults/embryos)	Male.	0.5-1.5 mg/L, for 72 hpf or 21 days.	No estrogenic activity; induction of developmental lesions, including yolk sac and pericardial edema, and hemorrhage (1–1.5 mg/mL, 72 hpf).	Song et al., 2014
Zebrafish (embryos/larvae)	-	10–1000 nmol/L, for 5–29 hpf and 3–11 dpf.	Activation of zebrafish PPARγ to induce lipid accumulation at the larval stage (100 nmol/L, 5–29 hpf); may act as an obesogen (10 nmol/L, 3–11 dpf).	Riu et al., 2014

-: not mentioned.

Table 2 – Summary of key TBBPA toxicity studies in rats.

Test organism	Animals status (age or body weight, bw)	Sex	Exposure pathway	Exposure doses and time	Main effects	Reference
Sprague-Dawley male rats	Postnatal day (PND) 18.	Male.	Oral gavage.	0, 125, 250 or 500 mg/kg bw for 30 days.	Increased absolute and relative liver weights, induced expression of CYP2B1 and constitutive androstane receptor in the liver, reduced serum T4 concentration, ROS induction and generation of 8-hydroxy-2′-deoxyguanosine (a biomarker of DNA oxidative damage) in testes and kidneys (200–500 mg/kg bw, 18–30 days).	Choi et al., 2011
Wistar rats	8 weeks.	Male and female.	Via diet.	30–300 mg/kg bw, for 28 days.	No effects on CYP gene expression.	Germer et al., 2006
Specific-pathogen-free male Sprague-Dawley rats	7 weeks.	Male.	Oral gavage administration in corn oil.	200–1000 mg/kg bw, for 14 days.	No toxicity to kidneys.	Kang et al., 2009
Wistar rats	For parental animals: 8 weeks.	Male and female.	Administer in food.	3–3000 mg/kg bw, with paternal and maternal exposure started 10 and 2 weeks before mating, respectively, and continued until measurement; 30–300 mg/kg bw for 28 days.	Increased testis and male pituitary weight in males (from 3 mg/kg bw); decrease in the levels of circulating T4 and increase in T3 levels in males (100 mg/kg bw, 28 days).	Van der Ven et al., 2008
Male and female CD® rats	8 weeks.	Male and female.	By gavage.	100–1000 mg/kg bw, for 90 days.	No significant effects in all tested indexes, including mortality, clinical signs, histopathology, neurobehavior, motor activity, and serum chemistry.	Osimitz et al., 2016
Sprague–Dawley rats	Various.	Male and female.	Through diet.	100–10000 mg/L, from gestational day 10 until day 20 after delivery.	For F1, no significant effects on thyroid function; not enough evidence for developmental brain effects.	Saegusa et al., 2009
Sprague-Dawley rats	8–10 weeks.	Male and female.	Oral gavage administration in corn oil.	10–1000 mg/kg bw (parental males and females were treated prior to and during mating; females through gestation, followed by treatment of pups; longest exposure, day 60 for F_2 pups).	No significant developmental and reproductive effects; no neurodevelopment, neurofunctional or neurobehavioral deficits; decrease in serum T4 (for parental and F1 generations), with no changes in serum T3 and thyroid stimulating hormone (TSH).	Cope et al., 2015
Wistar Han rats	12-week old and weighed (197 ± 17) g.	Female.	Oral gavage.	250 mg/kg, for 5 days.	Down-regulation of immune response pathways in uterus, and alteration in the expression of genes related to estrogen receptors, biosynthesis and metabolism in liver and uterus, as well as genes involved in cell division and growth, and thyroid homeostasis.	Hall et al., 2017; Sanders et al., 2016

(*continued on next page*)

Table 2 (*continued*)

Test organism	Animals status (age or body weight, bw)	Sex	Exposure pathway	Exposure doses and time	Main effects	Reference
Wistar Han rats	5–6 weeks.	Female.	Oral gavage administration in corn oil.	25–1000 mg/kg bw, for 13 weeks or 2 years (5 days a week).	Induction of uterine epithelial tumors (including adenomas, adenocarcinomas, and malignant mixed Müllerian tumors), endometrial epithelial atypical hyperplasia (250–500 mg/kg bw, 2 years); liver transcriptomes showed expression changes in 132 genes, with activation of IFN and metabolic networks (1000 mg/kg bw, 13 weeks).	Dunnick et al., 2015; Dunnick et al., 2017
Wistar rats	Body weight 180–220 g.	Male and female.	Oral gavage.	10–1125 mg/kg bw, for 7–28 days.	Levels of GSH lower in females and MDA higher in males (1125 mg/kg bw, 7 days).	Szymanska et al., 2000

that there were no remarkable effects on development, growth, and reproduction, even at the highest concentration tested (1000 mg/kg bw). The only histopathological change was a thinner brain parietal cortex in F2 pups at post-natal day 11 in the 1000 mg/kg bw exposure group, but without clear biological relevance (Cope et al., 2015).

1.1.3. *Concluding remarks*

In summary, numerous animal studies reveal that TBBPA is toxic to development, primarily affecting the specification and function(s) of the liver, kidneys, and the reproductive, nervous, and endocrine systems. It is worth noting that animals of different species and strains as well as animals of the same species but in different exposure stages, showed different degrees of sensitivity to TBBPA. Furthermore, zebrafish seemed more sensitive than mammals, while mice and Wistar rats were more sensitive than Sprague-Dawley (SD) rats. Interestingly, and as expected, early developmental stages were the most critically affected by TBBPA exposure.

1.2. In vitro *cell-based assessments*

1.2.1. *Toxicity data*

Many different cell models have been utilized to assess the adverse effects of TBBPA *in vitro* (Tables 4 and 5). TBBPA can induce oxidative stress in different cell types, such as hepatocytes and human airway epithelial cells. It triggered the accumulation of intracellular ROS/malondialdehyde (MDA), increased the ratio of oxidized-to-reduced glutathione (GSSG/GSH), decreased the cell mitochondrial membrane potential (MMP), and consequently increased the levels of apoptosis (Nakagawa et al., 2007; Wu et al., 2018; Zhang et al., 2019). TBBPA could also cause oxidative damage in human erythrocytes (Jarosiewicz et al., 2019) as well as trigger mitochondrial dysfunction in other cell types (Choi et al., 2017; Suh et al., 2017). Moreover, it could exert effects on basic cellular processes in various cell lines (Strack et al., 2007). All these effects were manifested at TBBPA μmol/L concentrations.

In reproductive toxicity evaluations, TBBPA induced apoptosis in spermatogenic cells by decreasing MMP and increasing ROS generation (Steves et al., 2018). It also lead to dysregulation of Ca^{2+} ion homeostasis to induce testicular mouse Sertoli cell death (Ogunbayo et al., 2008), and affected the cell cycle/cytoskeleton in spermatogonial cells (Liang et al., 2017). Moreover, TBBPA treatment altered placental estradiol levels (Honkisz and Wojtowicz, 2015a) and increased inflammation (Arita et al., 2018). TBBPA showed other endocrine-disrupting abilities (Honkisz and Wojtowicz, 2015b). For instance, it exerted estrogenic/anti-estrogenic activity (Hamers et al., 2006; Kitamura et al., 2002; Krivoshiev et al., 2016) and glucocorticoid receptor (GR)/androgen receptor (AR) antagonism (Christen et al., 2010; Roelofs et al., 2015). TBBPA is also a thyroid system disrupter (Grasselli et al., 2014) and can act as either a thyroid hormone receptor (TR) antagonist (Sun et al., 2009), or agonist (Kitamura et al., 2002). It can also induce testosterone synthesis (Roelofs et al., 2015). For some of these TBBPA-dependent endocrine disrupting activities, low nmol/L concentrations were sufficient (Tables 4 and 5).

For potential neurotoxicity, TBBPA induced intracellular Ca^{2+} imbalance, oxidative stress, depolarization of mitochondria, and activation of caspase-3 to promote nerve cell apoptosis (Al-Mousa and Michelangeli, 2012; Szychowski and Wojtowicz, 2016; Zieminska et al., 2017). TBBPA could significantly inhibit the activity of O-GlcNAcase, which is very important for controlling neuronal functions and eventually inducing cell apoptosis (Gu et al., 2019). Moreover, TBBPA had deleterious effects on functional neurotransmission endpoints (Hendriks et al., 2012), and decreased the uptake of neurotransmitters in brain synaptosomes/synaptic vesicles (Mariussen and Fonnum, 2003). Interestingly, TBBPA altered mouse and human embryonic stem cell (ESC) neural differentiation (Yin et al., 2018), promoted rat neural stem cell (NSC) differentiation into glial cells, and restrained the formation of neuronal phenotype (Slotkin et al., 2017); it could also impair the growth and development of neurites in human neural stem cells (hNSCs) (Gu et al., 2019). These findings suggest a potential disruption of the early stages of embryonic development. In most cell types, potential neurotoxic effects were observed at μM TBBPA concentrations. Nevertheless, when stem cell-based systems were employed, low nmol/L TBBPA levels altered neural differentiation.

TBBPA treatments influenced the expression of a variety of cytokines, including tumor necrosis factor alpha (TNFα), interleukins (IL)-1β, IL-4, IL-6, IL-8, interferon-gamma (IFNγ) as well as macrophage functions, thus affecting immune responses (Almughamsi and Whalen, 2016; Koike et al., 2013; Park et al., 2014; Wang et al., 2019). TBBPA disturbed proinflammatory responses (Park et al., 2014) as well as immune functions

Table 3 – Summary of key TBBPA toxicity studies in mice.

Test organism	Animals status (age or body weight)	Sex	Exposure pathway	Exposure doses and time	Main effects	Reference
Crlj:CD1 (ICR) mice	8 weeks.	Male and female.	Administered in food to parent mice.	15.7–1639.7 mg/kg bw, for gestational day (GD) 0–17; 42.1–4155.9 mg/kg bw, for lactational period, PND 0–27.	Increase in the serum concentration of total-cholesterol and in liver weights (from 1639.7 mg/kg bw, various time points); histopathological analyses showed inflammatory cells infiltration, focal necrosis in hepatocytes, and dilated or atrophied renal tubules and cysts (from 1639.7 mg/kg bw, various time points).	Tada et al., 2006
C57BL/6 mice	6 weeks.	Male.	Oral gavage.	20–500 mg/kg bw, for 2 weeks.	Reduction in new cell survival and neuronal differentiation in hippocampus (100 mg/kg bw).	Kim et al., 2017
Male closed colony ddY mice	3 weeks old and (12 ± 2.0) g body weight.	Male.	Oral gavage administration in corn oil.	0.1–250 mg/kg bw, for 3 hr.	Increased horizontal movement activities and TBBPA accumulation in the striatum (5 mg/kg bw); freezing behavior and spontaneous alternation behavior (0.1 mg/kg bw).	Nakajima et al., 2009
Neonatal male NMRI mice	PND 10.	Male.	By gavage.	Single dose exposure of 11.5 mg/kg bw and evaluation 24 hr later.	No effects on the levels of four proteins involved in maturation of the brain, neuronal growth and synaptogenesis, and both muscarinic and nicotinic cholinergic receptors.	Viberg and Eriksson, 2011
Neonatal male C57Bl/6 mice	PND 10.	Male.	By gavage.	Single dose exposure of 115 mg/kg bw, for evaluation on PND 17–19.	Induction of limited and insignificant effects on neurodevelopment and synaptic plasticity.	Hendriks et al., 2015
CD1 outbred mice	Various.	Male and female.	In drinking water.	35 μg/kg bw, from gestation to age of 70 days.	Potential to alter the epigenetic marking of sperm chromatin through generation of an anomalous content and distribution of protamine.	Zatecka et al., 2013

Table 4 – Summary of key TBBPA toxicity studies *in vitro* (primary cells).

Cell type	Exposure doses and time	Main effects	Reference
Human primary placenta cells	0.001–50 μmol/L, for 16 hr.	Increased levels of testosterone (2 nmol/L, 16 hr); increased oxidative stress (5 nmol/L, 16 hr); increase placental inflammation (5 nmol/L, 16 hr).	Arita et al., 2018
Human hepatocytes (L02 cells)	5–40 μmol/L, for 12–48 hr.	Increased intracellular ROS, MDA, and GSSG/GSH levels (10–40 μmol/L, 12 hr); induced mitochondrial apoptosis, and activation of the NRF2 pathway (5– 40 μmol/L, 48 hr).	Zhang et al., 2019
Male F344/Jcl rat hepatocytes	0.25–1.0 mmol/L, for 0.5–3 hr.	Dose- and time-dependent cell death, loss of cellular ATP/adenine nucleotide pools/GSH/protein thiols, and accumulation of GSSG and MDA (0.25–1 mmol/L, 0.5–3 hr).	Nakagawa et al., 2007
Human erythrocytes	1–25 μg/mL, for 48 hr.	Decrease in antioxidant enzyme activities (including superoxide dismutase, catalase, glutathione peroxidase, and the level of GSH), and augmentation of the externalization of phosphatidylserine (10–25 μg/mL, 48 hr).	Jarosiewicz et al., 2019
Testicular mouse sertoli (TM4) cells	Various.	Increased intracellular Ca^{2+} levels (5-60 μmol/L); induced mitochondrial depolarization (5 and 30 μmol/L, 1 min); inhibition of sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPases (SERCA) (0.4-1.2 μmol/L); activation of the Ryanodine receptor Ca^{2+} channel (0.4-4 μmol/L).	Ogunbayo et al., 2008
Human neutrophil granulocytes	0.1–20 μmol/L, for 2–60 min.	Enhanced ROS production (2–12 μmol/L, 1 hr), and intracellular [Ca^{2+}] levels (5–20 μmol/L); activation of protein kinase C (PKC) and MAP kinase pathways (12 μmol/L, 2–20 min).	Reistad et al., 2005
Mouse embryonic hippocampal neurons	0.001–100 μmol/L, for 0.5–24 hr.	Activated caspase-3 and generation of apoptotic bodies (0.1–1 μmol/L, 6 hr).	Szychowski and Wojtowicz, 2016
Rat cerebellar granule cells	7.5–25 μmol/L, for 30 min.	Induced intracellular Ca^{2+} imbalance, oxidative stress, depolarization of mitochondria, and cytotoxicity (7.5–25 μmol/L).	Zieminska et al., 2017
Mouse primary neocortical cells	0.001–100 μmol/L, for 6–24 hr.	Enhanced caspase-3 activity (100 nmol/L, 24 hr); lactate dehydrogenase (LDH) release, formation of apoptotic bodies, and decrease in the expression of PPARγ (10 μmol/L, 24 hr).	Wojtowicz et al., 2014
Rat embryonic NSCs and neuronotypic PC12 cells	0.2–5 μmol/L, for 6 days.	For NSCs, promotion of glial cell differentiation and restrain of the formation of neuronal phenotypes (1–2 μmol/L, 6 days); for PC12 cells, no significant effects.	Slotkin et al., 2017
Bone marrow isolated from 9-wk old male C57BL/6J mice	10–20 μmol/L, for 7–11 days.	Increased adipogenesis and suppressed osteogenesis (10–20 μmol/L, 7–11 days).	Watt and Schlezinger, 2015
Zebrafish and Xenopus oocytes, B35 rat neuroblastoma cells, and rat PC12 cells	0.01–10 μmol/L, for 20 min.	For Xenopus oocytes: action as agonist on human $GABA_A$ receptors, and as antagonist on human $\alpha_4\beta_2$ nicotinic acetylcholine (nACh) receptors (0.1–10 μmol/L); for B35 cells: inhibition of acetylcholine (ACh) receptors' expression, and increase of basal intracellular Ca^{2+}(1–10 μmol/L, 20 min); for PC12 cells: increased basal intracellular Ca^{2+}, and decreased levels of intracellular Ca^{2+} caused by depolarization (1–10 μmol/L, 20 min).	Hendriks et al., 2012
Rat brain synaptosomes, and male Wistar rat synaptic vesicles	0–50 μmol/L, for 15 min.	Inhibited uptake of the neurotransmitters dopamine (IC_{50} = 9 μmol/L), glutamate (IC_{50} = 6 μmol/L) and γ-amino-n-butyric acid (GABA) (IC_{50} = 16 μmol/L).	Mariussen and Fonnum, 2003
NK cells, monocyte-depleted peripheral blood mononuclear cells, and PBMCs	0.05–5 μmol/L, for 24 hr–6 days.	Decrease secretion of IFNγ (0.05 μmol/L, 24 hr).	Almughamsi and Whalen, 2016
Mouse splenocytes, bone marrow cells and BM-derived dendritic cells	0.001–10 μg/mL, for 24 hr–6 days.	Increased expression of major histocompatibility complex (MHC) class II molecules, CD86, IL-4, and T cell receptor in splenocytes (0.1–1 μg/mL, 24 hr).	Koike et al., 2013
Human NK cells	0.05–10 μmol/L, for 1 hr–6 days.	Decreased lytic function, tumor-target-binding-function, and ATP levels (0.05–1 μmol/L, 6 days).	Kibakaya et al., 2009

Table 5 – Summary of key TBBPA toxicity studies *in vitro* (cell lines).

Cell type	Exposure doses and time	Main effects	Reference
Human choriocarcinoma-derived placental JEG-3 cells	0.001–100 μmol/L, for 24–72 hr.	Increased levels of estradiol, progesterone, and aromatase (10–100 nmol/L, 24 hr); increased expression of PPARγ and decreased secretion of β-hCG (10 nmol/L, 24 hr); increased caspase-3 activity (1–5 nmol/L, 16–24 hr).	Honkisz and Wojtowicz, 2015a, Honkisz and Wojtowicz, 2015b
Human non-small cell lung cancer A549 cell line	8–64 μg/mL, for 12–48 hr.	Increased caspase-3 activity, ROS and MDA levels (8–16 μg/mL, 24–48 hr); influence on the expression of proteins involved in signaling transduction, energy metabolism, transcriptional regulation, and detoxifying system (8–32 μg/mL, 48 hr).	Wu et al., 2018
Rat pancreatic β-cells (RIN-m5F cell line)	0.1–40 μmol/L, for 48 hr.	Increased levels of inflammatory cytokines, nitric oxide, intracellular ROS, mitochondrial superoxide, cardiolipin peroxidation, and release of cytochrome c (20–40 μmol/L, 48 hr).	Suh et al., 2017
Osteoblastic MC3T3-E1 cells	0.1–50 μmol/L, for 48 hr–3 weeks.	Induced production of ROS, mitochondrial superoxide, cardiolipin peroxidation and cytochrome c release, and decreased ATP levels (1–40 μmol/L, 48 hr); decreased differentiation marker expression, collagen synthesis, alkaline phosphatase activity, and calcium deposition (1–20 μmol/L, 1–3 weeks).	Choi et al., 2017
Mouse C18-4 spermatogonial cells	0–100 μmol/L, for 24–72 hr.	Alteration in nuclear morphology (25 μmol/L, 72 hr), cell cycle (25 μmol/L, 48 hr; 10 μmol/L, 72 hr), cytoskeleton (25 μmol/L, 72 hr); trigger of DNA damage (25 μmol/L, 24 hr).	Liang et al., 2017
SH–SY5Y neuroblastoma cells	1–30 μmol/L, for 12–24 hr.	Activation of caspases increase in intracellular Ca^{2+} (20 μmol/L) and ROS, induction of depolarization of mitochondria, and increase of cytochrome c release (1–10 μmol/L, 12–24 hr).	Al-Mousa and Michelangeli, 2012
Spermatogenic cells	1–200 μmol/L, for 0.5–24 hr.	Decrease of spermatogonia and primary spermatocyte viability (100 and 200 μmol/L, 24 hr); induction of spermatogenic cells apoptosis, influence on the cell cycle in spermatogenic cells, increased ROS and reduced GSH/GSSG ratios in spermatogenesis, decreased mitochondrial membrane potential (10–100 μmol/L, 12–24 hr).	Steves et al., 2018
Neural progenitor cells derived from J1 mESCs	0.001–200 μmol/L, for 2 hr–12 days.	Perturbation of intracellular calcium levels and stimulation of ROS formation in mESCs (100 μmol/L, 2–4 hr); stimulate of ESC neural differentiation (1–500 nmol/L, 9–12 days).	Yin et al., 2018
Mouse 3T3-L1 fibroblast cells	10 μmol/L for 14 days.	Promoted adipocyte differentiation and lipid accumulation, and expression of adipocyte-specific proteins (10 μmol/L, 14 days).	Akiyama et al., 2015
Human mesenchymal stem cells (hMSCs)	1–10 μmol/L, for 14–21 days.	Increased lipid droplet numbers and adipocyte-related gene expression, stimulation of adipocyte differentiation (3.3 μmol/L, 21 days); no effects on osteoblast differentiation.	Kakutani et al., 2018
RAW264.7 mouse macrophage cell line	10–20 μmol/L, for 3 days.	Promoted osteoclast differentiation and activity, decreased levels of MMPs, and increased production of mitochondrial superoxide (20 μmol/L, 3 days).	Park et al., 2019
Mouse ESCs	1–100 nmol/L, for 2–28 days.	Effects on the nervous and cardiac/skeletal muscle systems' differentiation, and probable endocrine disrupting activities in part via prolactin signaling (1–100 nmol/L, 9–28 days).	Liang et al., 2019
PC12 cells and human NSCs	0–100 μmol/L, for 24 hr–3 days.	Inhibition of the activity of O-GlcNAcase in PC12 cells (25–100, 24 hr); impairment of the growth and development of NSCs (10 μmol/L, 3 days).	Gu et al., 2019
Human metastatic granulosa COV434 and KGN cell lines	1–50 nmol/L, for 24–72 hr.	Stimulated cell proliferation (10–50 nmol/L, 48–72 hr).	Hoffmann et al., 2017
Human breast carcinoma MCF-7 cell line	1–10 μmol/L, for 24 hr.	Induction of matrix metalloproteinase-9 (MMP-9) expression to induce cancer cell metastasis (5 μmol/L, 24 hr).	Lee et al., 2019
Cal-62 human thyroid anaplastic carcinoma cells, normal rat kidney epithelial cells (NRK), and human epithelial alveolar type II-like lung cells	5–200 μmol/L, for 24–120 hr.	In Cal-62 cells: influence on cell cycle regulation, and activation of extracellular-signal regulated kinase (ERK) (50–100 μmol/L, 24 hr); in NRK and A549 cells: ERK deactivation (50–200 μmol/L, 24 hr).	Strack et al., 2007

(*continued on next page*)

Table 5 (*continued*)

Cell type	Exposure doses and time	Main effects	Reference
Human first trimester extravillous trophoblast cell line HTR-8/SVneo	5–20 μmol/L, for 4–24 hr.	Increased secretion of IL-6, IL-8, and prostaglandin E2 (PGE2) (20 μmol/L, 2–24 hr); decreased secretion of transforming growth factor-beta (TGF-β), and increased expression of genes related to inflammatory pathways (10–20 μmol/L, 24 hr).	Park et al., 2014
Human bronchial epithelial BEAS-2B cell line	8–64 μg/mL, for 12–48 hr.	Influence on NF-κB, TNF, toll-like receptor (TLR), mitogen activated protein kinases (MAPK), and B-cell receptor signaling (32 μg/mL, 24–48 hr).	Wu et al., 2019
Murine macrophages RAW 264.7 cells	1–100 nmol/L, for 48 hr.	Upregulation of the expression of pro-inflammatory cytokines (including IL-1β, IL-6, and TNFα), downregulation of the expression of anti-inflammatory cytokines (including IL-4, IL-10, and IL-13), reduction of antigen-presenting-related genes' mRNA levels, influence on the phagocytic activity of macrophages, and induction of ROS (1–100 nmol/L, 48 hr).	Wang et al., 2019
Rat hepatoma, human osteoblast, human breast cancer, and Chinese hamster cells	0–12.5 μmol/L, for 24 hr.	Inhibited sulfation of estradiol (IC_{50} = 0.016 μmol/L, 24 hr); T4 competition (IC_{50} = 0.031 μmol/L, 24 hr); estrogenic effects (IC_{50} = 8.3 μmol/L, 24 hr).	Hamers et al., 2006
Human mammary carcinoma MDA-kb2cell line	0–100 μmol/L, for 24 hr.	Manifestation of weak antiandrogenic activity (10–50 μmol/L, 24 hr).	Christen et al., 2010
Recombinant yeasts stably expressing human AR or GR, and mouse Leydig tumorigenic cells	10 pmol/L–100 μmol/L, for 6–48 hr.	Display of GR (IC_{50} = 22 nmol/L) and AR (IC_{50} = 982 nmol/L) antagonism; induced testosterone synthesis (3–100 μmol/L, 48 hr).	Roelofs et al., 2015
African green monkey kidney CV-1 cell line	1–100 μmol/L, for 24 hr.	Action as TR antagonist (50–100 μmol/L, 24 hr).	Sun et al., 2009
Thyroid hormone-responsive GH3, and estrogen-responsive MtT/E-2 pituitary cell lines	0–10^{-2} mol/L, for 40 min–7 days.	Inhibited binding of T3 to thyroid hormone receptor (1×10^{-6}–1×10^{-4} mol/L, 40 min); TH-dependent induced proliferation of GH3 cells and production of GH (1×10^{-6}–1×10^{-4} mol/L, 2 days); estrogen-dependent induced proliferation of MtT/E-2 cells (1×10^{-5}–1×10^{-4} mol/L, 7 days).	Kitamura et al., 2002
Zebrafish liver ZFL cell line	0.2–2 μmol/L, for 24 hr.	No zebrafish thyroid hormone receptor β (zfTRβ) agonistic or antagonistic activity.	Yang and Chan, 2015
Human breast adenocarcinoma cell line (MCF-7)	10-1000 μmol/L, for 24 hr.	Exhibition of estrogenic and anti-estrogenic activities (100 and 1000 μmol/L, 24 hr).	Krivoshiev et al., 2016
Estrogen-responsive cells	1–50 μmol/L, for 48 hr.	No estrogenic activity.	Song et al., 2014
MCF-7 cells	0.02–20 μmol/L, for 36 hr–6 days.	No estrogenic effects observed.	Dorosh et al., 2011
MELN cell line, HELN-hERα and -hERβ reporter cell lines, PALM cells, HG5LN-hPXR cell line	0.01–10 μmol/L, for 3 hr–6 days.	No estrogenic activities; no androgenic and anti-androgenic activities; hPXR agonism (10 μmol/L, 16 hr) but not antagonism.	Molina-Molina et al., 2013
Steatotic FaO rat hepatoma cells	10^{-8}–10^{-5} mol/L, for 24 hr.	Decreased triglyceride content (10^{-8} mol/L, 24 hr) and lipid droplet size (10^{-6} mol/L, 24 hr); similar activity as equimolar T_3 (10^{-6} mol/L) on transcription of lipid homeostasis genes.	Grasselli et al., 2014

(Koike et al., 2013; Wu et al., 2019), and inflammatory response signaling (Wu et al., 2019). In addition, TBBPA decreased the natural killer (NK) cell lytic function (Kibakaya et al., 2009). Taken together, inflammatory and immune responses, although cell type-dependent, could manifest at TBBPA concentrations as low as 10–100 nmol/L (Tables 4 and 5).

Other *in vitro* studies suggest that TBBPA can stimulate cancer cell proliferation (Hoffmann et al., 2017)/metastasis, influence metabolism (Wu et al., 2018), facilitate adipocyte differentiation (Akiyama et al., 2015; Kakutani et al., 2018; Watt and Schlezinger, 2015), suppress osteogenesis/osteoblast functions (Choi et al., 2017; Watt and Schlezinger, 2015), promote osteoclast differentiation/activity (Park et al., 2019), and affect the early stages of embryonic development (Liang et al., 2019). Furthermore, some cellular processes, such as cancer cell proliferation and embryonic stem cell differentiation, were disrupted by 1–100 nmol/L TBBPA concentrations; others were not (Tables 4 and 5).

Interestingly, some studies have demonstrated that TBBPA exerts no endocrine disrupting effects, even at high concentrations. For example, up to 20 μmol/L TBBPA concentrations did not exert estrogenic activities in MCF-7 cells (Dorosh et al., 2011; Krivoshiev et al., 2016). Another study found that 10 μmol/L

TBBPA had no estrogenic, androgenic, or anti-androgenic activities (Molina-Molina et al., 2013). Similar conclusions were reached in a report using the zebrafish liver cell line ZFL, where 2 μmol/L TBBPA had no thyroid hormone receptor β agonistic or antagonistic activity, although TBBPA might disrupt TH circulation (Yang and Chan, 2015).

1.2.2. *Concluding remarks*

Scientists have utilized diverse cell models to deeply explore the effects of TBBPA and its modes of action. Different cell lines caused various degrees of effects. TBBPA mainly causes cell damage through oxidative stress, which affects the functions of various tissues and organs. It also affected basic life cycle, metabolism, stem cell differentiation, placenta development, immune/inflammatory responses, and endocrine disrupting effects. Most of these effects were observed at the μmol/L level.

2. explanations for the inconsistencies in TBBPA toxicity assays

The question of whether TBBPA has adverse health effects in humans has been addressed in many *in vivo* and *in vitro* studies, with diverse systems. However, the results were not always convincing one way or the other, even in very well-designed and executed experimental settings. Based on the studies reported in Tables 1–5, most of the TBBPA concentrations employed in those studies significantly exceeded the levels detected in the environment (up to 7758 ng/g in soil (Zhu et al., 2014), 6.26 to 511 pg/m^3 in indoor air (Ni and Zeng, 2013), up to 59,140 ng/g in dust (Ni and Zeng, 2013), and 4870 ng/L in water (Yang et al., 2012)), human bodily fluid/tissue samples (up to 688 ng/g lw in breast milk (Lankova et al., 2013), and 713 ng/g lw in serum (Kim and Oh, 2014)), as well as daily average TBBPA intake in humans (0.018–0.97 ng/kg bw from dust inhalation/ingestion (Ni and Zeng, 2013), 1.34 ng/kg bw through diet (Shi et al., 2017), and particularly for infants 6.62–10.1 ng/kg bw (Huang et al., 2020)). Moreover, specifically in early studies, toxicologists were using increasing concentrations of TBBPA until they measured an adverse effect no matter what it was, without taking into consideration relevant exposure doses. However, those studies were useful to dissect the potential mechanisms of toxicity, if any.

Some organisms or cell models may be more sensitive than others. Additionally, developmental stage, exposure timing, sex, and, of course, the choice of the targeted tissue(s) or organ(s) may have influenced whether a particular study concluded that TBBPA was safe. For example, a two-generational study evaluated the trans-generational effects of TBBPA exposure in CD1 outbred mice at a dosage of 35 μg/ (kg bw•day). Parent animals were exposed from gestation, while the F1 and F2 generations continued until the age of 70 days. TBBPA could induce testicular cell apoptosis and changes in seminiferous tubule morphology, although there was no evidence of sperm damage (Zatecka et al., 2013). Nevertheless, another study exposed C57BL/6J inbred mice to the same TBBPA dose and found damage in sperm DNA (Zatecka et al., 2014). These findings confirmed strain-specific effects in response to chemical exposure (Kacew et al., 1995).

For developmental stage and exposure timing response variations, in one study, both newborn (postnatal day (PND) 4) and young SD rats (5 weeks) were exposed to TBBPA for 18 days. Histopathology results revealed polycystic kidneys in newborn rats but no histopathological changes in young rats, even when treated at higher doses (Fukuda et al., 2004). Two other studies exposed SD rats to similar TBBPA doses as above, but at later stages (PND18 and 7-week), for 30 days. No exposure-related histopathological changes were observed in the liver, kidneys, testes, and thyroid (Choi et al., 2011), and no toxicity to kidneys was observed (Kang et al., 2009). Moreover, a study exposed zebrafish embryos/larvae to the same TBBPA concentrations for similar durations but at different developmental stages (8–48 hpf and 48–96 hpf). No abnormal phenotypes were measured after 48–96 hpf exposure. However, morphological malformations and mortality, lower average activity and speed of movements, as well as neurobehavioral deficits in the 8–48 hpf exposed group were measured (Chen et al., 2016b). Overall, these results indicate that early developmental stages may be critical for the potential toxicity of TBBPA.

Sex-specific adverse effects of TBBPA were also reported. In fact, in one study, TBBPA exposure from GD 9 to PND 90 yielded heightened anxiety-like behavior in the male offspring but not in the female offspring (Rock et al., 2019). Another study showed that TBBPA exposure lowered GSH levels only in female rats and elevated MDA levels only in male rats (Szymanska et al., 2000). Similarly, Lilienthal and colleagues observed a cochlear effect in females and neural effects in males after TBBPA exposure (Lilienthal et al., 2008). In addition, one study found sex-specific neurobehavioral and social interaction changes after chronic TBBPA exposure in adult zebrafish (Chen et al., 2016a).

In vitro studies evaluated TBBPA effects from different perspectives, as compared to live animal assays, and most of them concluded that TBBPA might be very harmful to humans. However, in addition to concentration issues (many of the studies employed too high TBBPA concentrations, in the μmol/L range), these studies may have neglected TBBPA metabolism, including the *in vivo* processes of absorption, distribution, modification, and excretion. A study investigated TBBPA toxico-kinetics in humans and rats after oral administration (Schauer et al., 2006); five human subjects were given 0.1 mg/kg bw TBBPA, while rats were given 300 mg/kg bw, in single doses. The concentrations of TBBPA and its metabolites in urine and blood were detected. The main metabolites identified included TBBPA-glucuronide and TBBPA-sulfate. In humans, the parental form of TBBPA was not detectable in plasma samples, whereas the concentrations of TBBPA-glucuronide and TBBPA-sulfate in plasma quickly declined to reach the LOD after 124 and 8 hr, respectively. In rats, the half-life of parent TBBPA was 13 hr. Another study in rats indicated that TBBPA had a half-life of approximately 7–9 hr and it could be eliminated in two days (Kang et al., 2009). Similarly, more than 94% of the administered TBBPA was eliminated predominantly through feces after 72 hr (Knudsen et al., 2014). Collectively, these results suggest that TBBPA is rapidly metabolized by conjugation and elimination, with a consequent low bio-availability (Kuester et al., 2007), especially in humans. However, although TBBPA is metabolized rapidly *in vivo*, it may still exert some adverse effects very quickly after exposure. In fact, one study exposed mice to TBBPA 3 hr before measurement and revealed increased horizontal movement activities, freezing behavior, spontaneous alternation behavior, and TBBPA accumulation in the striatum (Nakajima et al., 2009). Thus, although high doses were used (0.1 mg/kg bw), the data imply that rapid TBBPA metabolism may not protect humans from adverse effects, particularly in cases of continuous exposure.

For studies demonstrating TBBPA safety, there may still be controversy. Some studies only employed short-term TBBPA treatments (Song et al., 2014; Yang and Chan, 2015). Others only utilized adult animals that seem to have a better tolerance for TBBPA (Germer et al., 2006; Kang et al., 2009; Osimitz et al., 2016; Song et al., 2014), or just one single exposure dose, and evaluated the effects after a period of recovery, which may not be sufficient to conclude in favor of TBBPA safety (Hendriks et al., 2015; Jarema et al., 2015; Viberg and Eriksson, 2011). Furthermore, in MCF-7 cells TBBPA did not show any estrogenic activity at concentrations of 10 or 20 μmol/L (Dorosh et al., 2011; Molina-Molina et al., 2013), whereas it did so at 1,000 μmol/L (Krivoshiev et al., 2016). Interestingly, in the initial study of Saegusa et al. (2009) enough evidence was not collected to prove TBBPA effects in the developing brain of SD rats exposed from gestational day 10 to day 20 after delivery. However, several years later, deeper analyses by the same authors demonstrated that TBBPA affects neuronal development in the brain (Saegusa et al., 2012).

3. Conclusions

Based on the evidence collected thus far, it cannot yet be concluded whether TBBPA has adverse health effects on humans. The authors believe several issues need to be addressed before answering the question without reasonable doubt. For example, what are the actual TBBPA human exposure doses at present? Are those doses in the nmol/L range? Did the studies measuring these concentrations look only at the parental form of the chemical or also its metabolic products? Are these metabolic forms as toxic as TBBPA?

For risk assessments, TBBPA parental form concentrations in humans must be understood or must include its metabolic products in all the toxicological evaluations *in vitro*. It is also important that chemicals that have similar structures and thus behave similarly to TBBPA must be documented. In fact, TBBPA is used to produce derivatives, including TBBPA-BHEE, -BGE, -BAE, and -BDBPE. These derivatives can be detected in different environmental media (Ali et al., 2011; Qu et al., 2013; Tian et al., 2014) and have been demonstrated to be potentially harmful (Liu et al., 2016, 2018). In addition, in the daily life of humans, that exposure is not limited to one harmful substance; many substances may act together to increase individual effects. Moreover, subtle physiological changes caused by non-toxic chemicals (TBBPA may be one of them (Cope et al., 2015)) might be amplified and become significant after much longer exposure (years in humans) or in combination with other chemicals.

Perhaps TBBPA should be considered safe as many studies reporting TBBPA-dependent toxicity used very high concentrations that humans are never exposed to, and based on the evidence that TBBPA is metabolized to apparently innocuous metabolites (Knudsen et al., 2014; Kuester et al., 2007; Schauer et al., 2006) in the body. Nevertheless, studies with mouse and human embryonic stem cells indicate that TBBPA, at doses as low as 1 nmol/L, could interfere with very early stages of embryonic development, particularly neural development. These stages may be particularly sensitive to chemical offenses. Additionally, the general population, which is exposed to TBBPA low levels, even for a long time, may not experience any deleterious effects. However, occupational exposure in the population is not known. They are continuously exposed to relatively high doses. For instance, the concentration of TBBPA in air from the dismantling hall at a recycling plant was approximately 30 ng/m^3 (Sjodin et al., 2001). Another study evaluated the occurrence of TBBPA in an e-waste recycling area in South China. TBBPA levels in dust samples collected from e-waste recycling workshops and local residential homes were up to 19,600 and 1870 ng/g dust weight, respectively (Shen et al., 2019). Moreover, the concentration of TBBPA in environmental dust samples around a factory producing printed circuit boards was up to 9010 ng/g (Zhou et al., 2014). They also found workers' exposure to TBBPA via dust ingestion, dust dermal absorption, and PM10 inhalation in the raw material warehouse was approximately 2.41 ng/kg bw per day (Zhou et al., 2014), whereas the average estimated daily intake for a "standard Chinese man" was 1.34 ng/kg bw per day (Shi et al., 2017). Although the doses utilized in animal experiments, which supported TBBPA were not safe and far exceeded estimated human daily intakes, if the animals were exposed to much lower concentrations for much longer durations, years if possible, would they be still healthy?

Thus, to protect embryos and occupationally exposed populations, the potential toxicity of TBBPA should not be neglected, even if the general population may not experience any effects. Species variations imply that human-based systems should be preferred in the future to further evaluate TBBPA exposure risks to human health, particularly as many live animal models and assays have already been utilized. However, detailed knowledge of TBBPA metabolic products, organ/tissue targets, and endocrine abilities is critical for reliable *in vitro* toxicological assessments. Moreover, for *in vitro* studies utilizing very simple medium conditions, it should be considered whether physiological levels of molecules, such as hormones and cytokines, would counteract or amplify any detected effect of TBBPA, before concluding on its potential toxicity.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Nos. 21707160 and 21876197); the Chinese Academy of Sciences (No. QYZDJ-SSW-DQC017); and the K. C. Wong Education Foundation. We would like to thank Editage (www.editage.com) for English language editing.

REFERENCES

Abdallah, M.A.E., Pawar, G., Harrad, S., 2015. Evaluation of in vitro vs. in vivo methods for assessment of dermal absorption of organic flame retardants: a review. Environ. Int. 74, 13–22.

Akiyama, E., Kakutani, H., Nakao, T., Motomura, Y., Takano, Y., Sorakubo, R., et al., 2015. Facilitation of adipocyte differentiation of 3T3-L1 cells by debrominated Tetrabromobisphenol A compounds detected in Japanese breast milk. Environ. Res. 140, 157–164.

Al-Mousa, F., Michelangeli, F., 2012. Some commonly used brominated flame retardants cause Ca^{2+}-ATPase inhibition, beta-amyloid peptide release and apoptosis in SH-SY5Y neuronal cells. PLoS ONE 7, e33059.

Ali, N., Harrad, S., Goosey, E., Neels, H., Covaci, A., 2011. "Novel" brominated flame retardants in Belgian and UK indoor dust: implications for human exposure. Chemosphere 83, 1360–1365.

Almughamsi, H., Whalen, M.M., 2016. Hexabromocyclododecane and Tetrabromobisphenol A alter secretion of interferon gamma (IFN-gamma) from human immune cells. Arch. Toxicol. 90, 1695–1707.

Arita, Y., Pressman, M., Getahun, D., Menon, R., Peltier, M.R., 2018. Effect of Tetrabromobisphenol A on expression of biomarkers for inflammation and neurodevelopment by the placenta. Placenta 68, 33–39.

Baumann, L., Ros, A., Rehberger, K., Neuhauss, S.C., Segner, H., 2016. Thyroid disruption in zebrafish (Danio rerio) larvae: different molecular response patterns lead to impaired eye development and visual functions. Aquat. Toxicol. 172, 44–55.

Cariou, R., Antignac, J.P., Zalko, D., Berrebi, A., Cravedi, J.P., Maume, D., et al., 2008. Exposure assessment of French women and their newborns to tetrabromobisphenol-A: occurrence measurements in maternal adipose tissue, serum, breast milk and cord serum. Chemosphere 73, 1036–1041.

Chen, J., Tanguay, R.L., Simonich, M., Nie, S., Zhao, Y., Li, L., et al., 2016a. TBBPA chronic exposure produces sex-specific neurobehavioral and social interaction changes in adult zebrafish. Neurotoxicol. Teratol. 56, 9–15.

Chen, J., Tanguay, R.L., Xiao, Y., Haggard, D.E., Ge, X., Jia, Y., et al., 2016b. TBBPA exposure during a sensitive developmental window produces neurobehavioral changes in larval zebrafish. Environ. Pollut. 216, 53–63.

Choi, E.M., Suh, K.S., Rhee, S.Y., Oh, S., Kim, S.W., Pak, Y.K., et al., 2017. Exposure to Tetrabromobisphenol A induces cellular dysfunction in osteoblastic MC3T3-E1 cells. J. Environ. Sci. Health A 52, 561–570.

Choi, J.S., Lee, Y.J., Kim, T.H., Lim, H.J., Ahn, M.Y., Kwack, S.J., et al., 2011. Molecular mechanism of Tetrabromobisphenol A (TBBPA)-induced target organ toxicity in Sprague-Dawley male rats. Toxicol. Res. 27, 61–70.

Chow, W.S., Chan, W.K., Chan, K.M., 2013. Toxicity assessment and vitellogenin expression in zebrafish (Danio rerio) embryos and larvae acutely exposed to bisphenol A, endosulfan, heptachlor, methoxychlor and Tetrabromobisphenol A. J. Appl. Toxicol. 33, 670–678.

Christen, V., Crettaz, P., Oberli-Schrammli, A., Fent, K., 2010. Some flame retardants and the antimicrobials triclosan and triclocarban enhance the androgenic activity in vitro. Chemosphere 81, 1245–1252.

Cope, R.B., Kacew, S., Dourson, M., 2015. A reproductive, developmental and neurobehavioral study following oral exposure of Tetrabromobisphenol A on Sprague-Dawley rats. Toxicology 329, 49–59.

Covaci, A., Voorspoels, S., Abdallah, M.A., Geens, T., Harrad, S., Law, R.J., 2009. Analytical and environmental aspects of the flame retardant Tetrabromobisphenol-A and its derivatives. J. Chromatogr. A 1216, 346–363.

Dorosh, A., Ded, L., Elzeinova, F., Peknicova, J., 2011. Assessing oestrogenic effects of brominated flame retardants hexabromocyclododecane and Tetrabromobisphenol A on MCF-7 cells. Folia Biol. (Praha) 57, 35–39.

Dunnick, J.K., Morgan, D.L., Elmore, S.A., Gerrish, K., Pandiri, A., Ton, T.V., et al., 2017. Tetrabromobisphenol A activates the hepatic interferon pathway in rats. Toxicol. Lett. 266, 32–41.
Dunnick, J.K., Sanders, J.M., Kissling, G.E., Johnson, C.L., Boyle, M.H., Elmore, S.A., 2015. Environmental chemical exposure may contribute to uterine cancer development: studies with Tetrabromobisphenol A. Toxicol. Pathol. 43, 464–473.
ECHA, 2008. Risk assessment of 2,2',6,6'-Tetrabromo-4,4'-isopropylidene diphenol (Tetrabromobisphenol-A). https://echa.europa.eu/documents/10162/17c7379e-f47b-4a76-aa43-060da5830c07 (accessed November 13, 2019).
Fukuda, N., Ito, Y., Yamaguchi, M., Mitumori, K., Koizumi, M., Hasegawa, R., 2004. Unexpected nephrotoxicity induced by tetrabromobisphenol A in newborn rats. Toxicol. Lett. 150, 145–155.
Germer, S., Piersma, A.H., van der Ven, L., Kamyschnikow, A., Fery, Y., Schmitz, H.J., et al., 2006. Subacute effects of the brominated flame retardants hexabromocyclododecane and Tetrabromobisphenol A on hepatic cytochrome P450 levels in rats. Toxicology 218, 229–236.
Grasselli, E., Cortese, K., Fabbri, R., Smerilli, A., Vergani, L., Voci, A., et al., 2014. Thyromimetic actions of Tetrabromobisphenol A (TBBPA) in steatotic FaO rat hepatoma cells. Chemosphere 112, 511–518.
Gu, Y.X., Liang, X.X., Yin, N.Y., Yang, Y., Wan, B., Guo, L.H., et al., 2019. New insights into mechanism of bisphenol analogue neurotoxicity: implications of inhibition of O-GlcNAcase activity in PC12 cells. Arch. Toxicol. 93, 2661–2671.
Guerra, P., Eljarrat, E., Barcelo, D., 2010. Simultaneous determination of hexabromocyclododecane, Tetrabromobisphenol A, and related compounds in sewage sludge and sediment samples from Ebro River basin (Spain). Anal. Bioanal. Chem. 397, 2817–2824.
Hall, S.M., Coulter, S.J., Knudsen, G.A., Sanders, J.M., Birnbaum, L.S., 2017. Gene expression changes in immune response pathways following oral administration of Tetrabromobisphenol A (TBBPA) in female Wistar Han rats. Toxicol. Lett. 272, 68–74.
Hamers, T., Kamstra, J.H., Sonneveld, E., Murk, A.J., Kester, M.H.A., Andersson, P.L., et al., 2006. In vitro profiling of the endocrine-disrupting potency of brominated flame retardants. Toxicol. Sci. 92, 157–173.
Hendriks, H.S., Koolen, L.A., Dingemans, M.M., Viberg, H., Lee, I., Leonards, P.E., et al., 2015. Effects of neonatal exposure to the flame retardant Tetrabromobisphenol-A, aluminum diethylphosphinate or zinc stannate on long-term potentiation and synaptic protein levels in mice. Arch. Toxicol. 89, 2345–2354.
Hendriks, H.S., van Kleef, R.G., van den Berg, M., Westerink, R.H., 2012. Multiple novel modes of action involved in the in vitro neurotoxic effects of Tetrabromobisphenol-A. Toxicol. Sci. 128, 235–246.
Hoffmann, M., Gogola, J., Kotula-Balak, M., Ptak, A., 2017. Stimulation of ovarian cell proliferation by Tetrabromobisphenol A but not Tetrachlorobisphenol A through G protein-coupled receptor 30. Toxicol In Vitro 45, 54–59.
Honkisz, E., Wojtowicz, A.K., 2015a. Modulation of estradiol synthesis and aromatase activity in human choriocarcinoma JEG-3 cells exposed to Tetrabromobisphenol A. Toxicol In Vitro 29, 44–50.
Honkisz, E., Wojtowicz, A.K., 2015b. The role of Ppargamma in TBBPA-mediated endocrine disrupting effects in human choriocarcinoma JEG-3 cells. Mol. Cell. Biochem. 409, 81–91.
Huang, D.Y., Zhao, H.Q., Liu, C.P., Sun, C.X., 2014. Characteristics, sources, and transport of Tetrabromobisphenol A and bisphenol A in soils from a typical e-waste recycling area in South China. Environ. Sci. Pollut. Res. 21, 5818–5826.
Huang, M., Li, J., Xiao, Z., Shi, Z., 2020. 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 244, 125524.
Inouye, B., Katayama, Y., Ishida, T., Ogata, M., Utsumi, K., 1979. Effects of aromatic bromine compounds on the function of biological-membranes. Toxicol. Appl. Pharmacol. 48, 467–477.
Jarema, K.A., Hunter, D.L., Shaffer, R.M., Behl, M., Padilla, S., 2015. Acute and developmental behavioral effects of flame retardants and related chemicals in zebrafish. Neurotoxicol. Teratol. 52, 194–209.
Jarosiewicz, M., Krokosz, A., Marczak, A., Bukowska, B., 2019. Changes in the activities of antioxidant enzymes and reduced glutathione level in human erythrocytes exposed to selected brominated flame retardants. Chemosphere 227, 93–99.
Kacew, S., Ruben, Z., McConnell, R.F., 1995. Strain as a determinant factor in the differential responsiveness of rats to chemicals. Toxicol. Pathol. 23, 701–714.
Kakutani, H., Yuzuriha, T., Akiyama, E., Nakao, T., Ohta, S., 2018. Complex toxicity as disruption of adipocyte or osteoblast differentiation in human mesenchymal stem cells under the mixed condition of TBBPA and TCDD. Toxicol. Rep. 5, 737–743.
Kang, M.J., Kim, J.H., Shin, S., Choi, J.H., Lee, S.K., Kim, H.S., et al., 2009. Nephrotoxic potential and toxicokinetics of Tetrabromobisphenol A in rat for risk assessment. J. Toxicol. Environ. Health Part A 72, 1439–1445.
Kibakaya, E.C., Stephen, K., Whalen, M.M., 2009. Tetrabromobisphenol A has immunosuppressive effects on human natural killer cells. J. Immunotoxicol. 6, 285–292.
Kicinski, M., Viaene, M.K., Hond, Den, E., Schoeters, G., Covaci, A., Dirtu, A., C., et al., 2012. Neurobehavioral function and low-level exposure to brominated flame retardants in adolescents: a cross-sectional study. Environ. Health 11, 86.
Kim, A.H., Chun, H.J., Lee, S., Kim, H.S., Lee, J., 2017. High dose Tetrabromobisphenol A impairs hippocampal neurogenesis and memory retention. Food Chem. Toxicol. 106, 223–231.
Kim, U.J., Oh, J.E., 2014. Tetrabromobisphenol A and hexabromocyclododecane flame retardants in infant-mother paired serum samples, and their relationships with thyroid hormones and environmental factors. Environ. Pollut. 184, 193–200.
Kitamura, S., Jinno, N., Ohta, S., Kuroki, H., Fujimoto, N., 2002. Thyroid hormonal activity of the flame retardants Tetrabromobisphenol A and Tetrachlorobisphenol A. Biochem. Biophys. Res. Commun. 293, 554–559.
Knudsen, G.A., Sanders, J.M., Sadik, A.M., Birnbaum, L.S., 2014. Disposition and kinetics of Tetrabromobisphenol A in female Wistar Han rats. Toxicol. Rep. 1, 214–223.
Koike, E., Yanagisawa, R., Takigami, H., Takano, H., 2013. Brominated flame retardants stimulate mouse immune cells in vitro. J. Appl. Toxicol. 33, 1451–1459.
Kowalski, B., Mazur, M., 2014. The simultaneous determination of six flame retardants in water samples using SPE pre-concentration and UHPLC-UV method. Water Air Soil pollut. 225, 1866.
Krivoshiev, B.V., Dardenne, F., Covaci, A., Blust, R., Husson, S.J., 2016. Assessing in-vitro estrogenic effects of currently-used flame retardants. Toxicol In Vitro 33, 153–162.
Kudo, Y., Yamauchi, K., Fukazawa, H., Terao, Y., 2006. In vitro and in vivo analysis of the thyroid system-disrupting activities of brominated phenolic and phenol compounds in Xenopus laevis. Toxicol. Sci. 92, 87–95.
Kuester, R.K., Solyom, A.M., Rodriguez, V.P., Sipes, I.G., 2007. The effects of dose, route, and repeated dosing on the disposition and kinetics of Tetrabromobisphenol A in male F-344 rats. Toxicol. Sci. 96, 237–245.
Kuiper, R.V., van den Brandhof, E.J., Leonards, P.E., van der Ven, L.T., Wester, P.W., Vos, J.G., 2007. Toxicity of Tetrabromobisphenol A (TBBPA) in zebrafish (Danio rerio) in a partial life-cycle test. Arch. Toxicol. 81, 1–9.
Lankova, D., Lacina, O., Pulkrabova, J., Hajslova, J., 2013. The determination of perfluoroalkyl substances, brominated flame retardants and their metabolites in human breast milk and infant formula. Talanta 117, 318–325.
Lee, G.H., Jin, S.W., Kim, S.J., Pham, T.H., Choi, J.H., Jeong, H.G., 2019. Tetrabromobisphenol A induces MMP-9 expression via NADPH oxidase and the activation of ROS, MAPK, and Akt pathways in human breast cancer MCF-7 Cells. Toxicol. Res. 35, 93–101.
Liang, S., Yin, L., Yu, Shengyang, K., Hofmann, M.C., Yu X., 2017. High-content analysis provides mechanistic insights into the testicular toxicity of bisphenol A and selected analogues in mouse spermatogonial cells. Toxicol. Sci. 155, 43–60.
Liang, S., Zhou, H., Yin, N., Lu, Y., Faiola, F., 2019. Embryoid body-based RNA-seq analyses reveal a potential TBBPA multifaceted developmental toxicity. J. Hazard. Mater. 376, 223–232.
Lilienthal, H., Verwer, C.M., van der Ven, L.T., Piersma, A.H., Vos, J.G., 2008. Exposure to Tetrabromobisphenol A (TBBPA) in Wistar rats: neurobehavioral effects in offspring from a one-generation reproduction study. Toxicology 246, 45–54.
Liu, Q., Ren, X.M., Long, Y.M., Hu, L.G., Qu, G.B., Zhou, Q.F., et al., 2016. The potential neurotoxicity of emerging Tetrabromobisphenol A derivatives based on rat pheochromocytoma cells. Chemosphere 154, 194–203.
Liu, Q.S., Liu, N., Sun, Z.D., Zhou, Q.F., Jiang, G.B., 2018. Intranasal administration of Tetrabromobisphenol A bis(2-hydroxyethyl ether) induces neurobehavioral changes in neonatal Sprague Dawley rats. J. Environ. Sci. 63, 76–86.
LM, 2019. Market research and investment strategy report on Tetrabromobisphenol A in China. http://www.lmcmr.com/huaxuegongye/yuanyouchanpin/2019-01-28/13361.html (accessed November 12, 2019).
Mariussen, E., Fonnum, F., 2003. The effect of brominated flame retardants on neurotransmitter uptake into rat brain synaptosomes and vesicles. Neurochem. Int. 43, 533–542.
McCormick, J.M., Paiva, M.S., Haggblom, M.M., Cooper, K.R., White, L.A., 2010. Embryonic exposure to Tetrabromobisphenol A and its metabolites, bisphenol A and Tetrabromobisphenol A dimethyl ether disrupts normal zebrafish (Danio rerio) development and matrix metalloproteinase expression. Aquat. Toxicol. 100, 255–262.
Molina-Molina, J.M., Amaya, E., Grimaldi, M., Saenz, J.M., Real, M., Fernandez, M.F., et al., 2013. In vitro study on the agonistic and antagonistic activities of bisphenol-S and other bisphenol-A congeners and derivatives via nuclear receptors. Toxicol. Appl. Pharmacol. 272, 127–136.
Nakagawa, Y., Suzuki, T., Ishii, H., Ogata, A., 2007. Biotransformation and cytotoxicity of a brominated flame retardant, Tetrabromobisphenol A, and its analogues in rat hepatocytes. Xenobiotica 37, 693–708.
Nakajima, A., Saigusa, D., Tetsu, N., Yamakuni, T., Tomioka, Y., Hishinuma, T., 2009. Neurobehavioral effects of Tetrabromobisphenol A, a brominated flame retardant, in mice. Toxicol. Lett. 189, 78–83.
Ni, H.G., Zeng, H., 2013. HBCD and TBBPA in particulate phase of indoor air in Shenzhen. Chin. Sci. Total Environ. 458-460, 15–19.
Ogunbayo, O.A., Lai, P.F., Connolly, T.J., Michelangeli, F., 2008. Tetrabromobisphenol A (TBBPA), induces cell death in TM4 Sertoli cells by modulating Ca^{2+} transport proteins and causing dysregulation of Ca^{2+} homeostasis. Toxicol In Vitro 22, 943–952.
Osimitz, T.G., Droege, W., Hayes, A.W., 2016. Subchronic toxicology of Tetrabromobisphenol A in rats. Hum. Exp. Toxicol. 35, 1214–1226.

Park, H.R., Kamau, P.W., Korte, C., Loch-Caruso, R., 2014. Tetrabromobisphenol A activates inflammatory pathways in human first trimester extravillous trophoblasts in vitro. Reprod. Toxicol. 50, 154–162.
Park, S.Y., Choi, E.M., Suh, K.S., Kim, H.S., Chin, S.O., Rhee, S.Y., et al., 2019. . Tetrabromobisphenol A promotes the osteoclastogenesis of RAW264.7 cells induced by receptor activator of NF-kappa B ligand in vitro. J. Korean Med. Sci. 34, e267.
Parsons, A., Lange, A., Hutchinson, T.H., Miyagawa, S., Iguchi, T., Kudoh, T., et al., 2019. Molecular mechanisms and tissue targets of brominated flame retardants, BDE-47 and TBBPA, in embryo-larval life stages of zebrafish(Danio rerio). Aquat. Toxicol. 209, 99–112.
Qu, G., Liu, A., Wang, T., Zhang, C., Fu, J., Yu, M., et al., 2013. 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. 47, 4760–4767.
Reistad, T., Mariussen, E., Fonnum, F., 2005. 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. 83, 89–100.
Riu, A., McCollum, C.W., Pinto, C.L., Grimaldi, M., Hillenweck, A., Perdu, E., et al., 2014. Halogenated bisphenol-A analogs act as obesogens in zebrafish larvae (Danio rerio). Toxicol. Sci. 139, 48–58.
Rock, K.D., Gillera, S.E.A., Devarasetty, P., Horman, B., Knudsen, G., Birnbaum, L.S., et al., 2019. Sex-specific behavioral effects following developmental exposure to tetrabromobisphenol A (TBBPA) in Wistar rats. Neurotoxicology 75, 136–147.
Roelofs, M.J., van den Berg, M., Bovee, T.F., Piersma, A.H., van Duursen, M.B., 2015. Structural bisphenol analogues differentially target steroidogenesis in murine MA-10 Leydig cells as well as the glucocorticoid receptor. Toxicology 329, 10–20.
Saegusa, Y., Fujimoto, H., Woo, G.H., Inoue, K., Takahashi, M., Mitsumori, K., et al., 2009. Developmental toxicity of brominated flame retardants, Tetrabromobisphenol A and 1,2,5,6,9,10-hexabromocyclododecane, in rat offspring after maternal exposure from mid-gestation through lactation. Reprod. Toxicol. 28, 456–467.
Saegusa, Y., Fujimoto, H., Woo, G.H., Ohishi, T., Wang, L., Mitsumori, K., et al., 2012. Transient aberration of neuronal development in the hippocampal dentate gyrus after developmental exposure to brominated flame retardants in rats. Arch. Toxicol. 86, 1431–1442.
Sanders, J.M., Coulter, S.J., Knudsen, G.A., Dunnick, J.K., Kissling, G.E., Birnbaum, L.S., 2016. Disruption of estrogen homeostasis as a mechanism for uterine toxicity in Wistar Han rats treated with Tetrabromobisphenol A. Toxicol. Appl. Pharmacol. 298, 31–39.
Schauer, U.M., Volkel, W., Dekant, W., 2006. Toxicokinetics of tetrabromobisphenol a in humans and rats after oral administration. Toxicol. Sci. 91, 49–58.
Shen, M., Ge, J., Lam, J.C.W., Zhu, M., Li, J., Zeng, L., 2019. Occurrence of two novel triazine-based flame retardants in an E-waste recycling area in South China: implication for human exposure. Sci. Total Environ. 683, 249–257.
Shi, Z., Zhang, L., Zhao, Y., Sun, Z., Zhou, X., Li, J., et al., 2017. Dietary exposure assessment of Chinese population to Tetrabromobisphenol-A, hexabromocyclododecane and decabrominated diphenyl ether: results of the 5th Chinese Total Diet Study. Environ. Pollut. 229, 539–547.
Sjodin, A., Carlsson, H., Thuresson, K., Sjolin, S., Bergman, A., Ostman, C., 2001. Flame retardants in indoor air at an electronics recycling plant and at other work environments. Environ. Sci. Technol. 35, 448–454.
Slotkin, T.A., Skavicus, S., Stapleton, H.M., Seidler, F.J., 2017. Brominated and organophosphate flame retardants target different neurodevelopmental stages, characterized with embryonic neural stem cells and neuronotypic PC12 cells. Toxicology 390, 32–42.
Song, M., Liang, D., Liang, Y., Chen, M., Wang, F., Wang, H., et al., 2014. Assessing developmental toxicity and estrogenic activity of halogenated bisphenol A on zebrafish (Danio rerio). Chemosphere 112, 275–281.
Steves, A.N., Bradner, J.M., Fowler, K.L., Clarkson-Townsend, D., Gill, B.J., Turry, A.C., et al., 2018. Ubiquitous flame-retardant toxicants impair spermatogenesis in a human stem cell model. I. Science 3, 161–176.
Strack, S., Detzel, T., Wahl, M., Kuch, B., Krug, H.F., 2007. Cytotoxicity of TBBPA and effects on proliferation, cell cycle and MAPK pathways in mammalian cells. Chemosphere 67, S405–S411.
Suh, K.S., Choi, E.M., Rhee, S.Y., Oh, S., Kim, S.W., Pak, Y.K., et al., 2017. Tetrabromobisphenol A induces cellular damages in pancreatic beta-cells in vitro. J. Environ. Sci. Health A 52, 624–631.
Sun, H., Shen, O.X., Wang, X.R., Zhou, L., Zhen, S.Q., Chen, X.D., 2009. Anti-thyroid hormone activity of bisphenol A, Tetrabromobisphenol A and Tetrachlorobisphenol A in an improved reporter gene assay. Toxicol In Vitro 23, 950–954.
Szychowski, K.A., Wojtowicz, A.K., 2016. TBBPA causes neurotoxic and the apoptotic responses in cultured mouse hippocampal neurons in vitro. Pharmacol. Rep. 68, 20–26.
Szymanska, J.A., Piotrowski, J.K., Frydrych, B., 2000. Hepatotoxicity of Tetrabromobisphenol-A: effects of repeated dosage in rats. Toxicology 142, 87–95.
Tada, Y., Fujitani, T., Yano, N., Takahashi, H., Yuzawa, K., Ando, H., et al., 2006. Effects of Tetrabromobisphenol A, brominated flame retardant, in ICR mice after prenatal and postnatal exposure. Food Chem. Toxicol. 44, 1408–1413.
Takigami, H., Suzuki, G., Hirai, Y., Sakai, S., 2009. Brominated flame retardants and other polyhalogenated compounds in indoor air and dust from two houses in Japan. Chemosphere 76, 270–277.
Tian, Y., Chen, J., Ouyang, Y.Z., Qu, G.B., Liu, A.F., Wang, X.M., et al., 2014. Reactive extractive electrospray ionization tandem mass spectrometry for sensitive detection of Tetrabromobisphenol A derivatives. Anal. Chim. Acta 814, 49–54.
Usenko, C.Y., Abel, E.L., Hopkins, A., Martinez, G., Tijerina, J., Kudela, M., et al., 2016. Evaluation of common use brominated flame retardant (BFR) toxicity using a zebrafish embryo model. Toxics 4 (3), 21.
Van der Ven, L.T.M., de Kuil, T.V., Verhoef, A., Verwer, C.M., Lilienthal, H., Leonards, P.E.G., et al., 2008. Endocrine effects of Tetrabromobisphenol-A (TBBPA) in Wistar rats as tested in a one-generation reproduction study and a subacute toxicity study. Toxicology 245, 76–89.
Viberg, H., Eriksson, P., 2011. Differences in neonatal neurotoxicity of brominated flame retardants, PBDE 99 and TBBPA, in mice. Toxicology 289, 59–65.
Wang, X., Wei, L., Zhu, J., He, B., Kong, B., Xue, Z., et al., 2019. Environmentally relevant doses of Tetrabromobisphenol A (TBBPA) cause immunotoxicity in murine macrophages. Chemosphere 236, 124413.
Watanabe, I., Kashimoto, T., Tatsukawa, R., 1983. Identification of the flame-retardant Tetrabromobisphenol-A in the river sediment and the mussel collected in Osaka. B Environ. Contam. Tox. 31, 48–52.
Watt, J., Schlezinger, J.J., 2015. Structurally-diverse, PPARgamma-activating environmental toxicants induce adipogenesis and suppress osteogenesis in bone marrow mesenchymal stromal cells. Toxicology 331, 66–77.
Wojtowicz, A.K., Szychowski, K.A., Kajta, M., 2014. PPAR-gamma agonist GW1929 but not antagonist GW9662 reduces TBBPA-induced neurotoxicity in primary neocortical cells. Neurotox. Res. 25, 311–322.
WorldAnalytics, 2019. Global Tetrabromobisphenol-A (TBBA) (CAS 79-94-7) Market Competitive Analysis, Market Size, Share, Consumption, Production Forecast 2019-2023. https://worldanalytics24.com/global-tetrabromobisphenol-a-tbba-cas-79-94-7-market/236248/ (accessed November 12, 2019).
Wu, S., Ji, G., Liu, J., Zhang, S., Gong, Y., Shi, L., 2016. TBBPA induces developmental toxicity, oxidative stress, and apoptosis in embryos and zebrafish larvae (Danio rerio). Environ. Toxicol. 31, 1241–1249.
Wu, S., Zhu, Z., Chen, J., Wu, M., Qiu, L., 2019. Transcriptomic analyses of human bronchial epithelial cells BEAS-2B exposed to brominated flame retardant (Tetrabromobisphenol A). Environ. Toxicol. 34, 742–752.
Wu, S.J., Wu, M., Qi, M.T., Zhong, L., Qiu, L.Q., 2018. Effects of novel brominated flame retardant TBBPA on human airway epithelial cell (A549) in vitro and proteome profiling. Environ. Toxicol. 33, 1245–1253.
Yang, J., Chan, K.M., 2015. Evaluation of the toxic effects of brominated compounds (BDE-47, 99, 209, TBBPA) and bisphenol A (BPA) using a zebrafish liver cell line. ZFL. Aquat. Toxicol. 159, 138–147.
Yang, S.W., Wang, S.R., Wu, F.C., Yan, Z.G., Liu, H.L., 2012. Tetrabromobisphenol A: tissue distribution in fish, and seasonal variation in water and sediment of Lake Chaohu, China. Environ. Sci. Pollut. Res. 19, 4090–4096.
Yin, N., Liang, S., Liang, S., Yang, R., Hu, B., Qin, Z., et al., 2018. TBBPA and its alternatives disturb the early stages of neural development by interfering with the NOTCH and WNT pathways. Environ. Sci. Technol. 52, 5459–5468.
Zatecka, E., Castillo, J., Elzeinova, F., Kubatova, A., Ded, L., Peknicova, J., et al., 2014. The effect of Tetrabromobisphenol A on protamine content and DNA integrity in mouse spermatozoa. Andrology 2, 910–917.
Zatecka, E., Ded, L., Elzeinova, F., Kubatova, A., Dorosh, A., Margaryan, H., et al., 2013. . Effect of Tetrabrombisphenol A on induction of apoptosis in the testes and changes in expression of selected testicular genes in CD1 mice. Reprod. Toxicol. 35, 32–39.
Zhang, Y., Li, Y., Qin, Z., Wang, H., Li, J., 2015. A screening assay for thyroid hormone signaling disruption based on thyroid hormone-response gene expression analysis in the frog Pelophylax nigromaculatus. J. Environ. Sci. 34, 143–154.
Zhang, Y., Wang, X., Chen, C., An, J., Shang, Y., Li, H., et al., 2019. Regulation of TBBPA-induced oxidative stress on mitochondrial apoptosis in L02cells through the Nrf2 signaling pathway. Chemosphere 226, 463–471.
Zhou, X.Y., Guo, J., Zhang, W., Zhou, P., Deng, J.J., Lin, K.F., 2014. Tetrabromobisphenol A contamination and emission in printed circuit board production and implications for human exposure. J. Hazard. Mater. 273, 27–35.
Zhu, B.R., Zhao, G., Yang, L.H., Zhou, B.S., 2018. Tetrabromobisphenol A caused neurodevelopmental toxicity via disrupting thyroid hormones in zebrafish larvae. Chemosphere 197, 353–361.
Zhu, Z.C., Chen, S.J., Zheng, J., Tian, M., Feng, A.H., Luo, X.J., et al., 2014. 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. 481, 47–54.
Zieminska, E., Lenart, J., Diamandakis, D., Lazarewicz, J.W., 2017. The role of Ca(2+) imbalance in the induction of acute oxidative stress and cytotoxicity in cultured rat cerebellar granule cells challenged with Tetrabromobisphenol A. Neurochem. Res. 42, 777–787.