

7-31-2023

## Brominated Flame Retardants: A Literature Review of The Toxicity Mechanisms, Clinical Manifestations, And Current Treatments

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### Recommended Citation

Prasetyo, Yacobus Christian and Sholikhah, Eti Nurwening (2023) "Brominated Flame Retardants: A Literature Review of The Toxicity Mechanisms, Clinical Manifestations, And Current Treatments," *Occupational and Environmental Medicine Journal of Indonesia*: Vol. 1: No. 2, Article 4.

DOI: <https://doi.org/10.7454/oemji.v1i2.1007>

Available at: <https://scholarhub.ui.ac.id/oemji/vol1/iss2/4>

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### **Cover Page Footnote**

We express gratitude to dr. Sudi Indra Jaya, M.Biomed and apt. Eustachia Diajeng Wandansari, S.Farm., M.Biomed. who facilitated communication access between us, as well as Dr. dr. Ronald Winardi Kartika, Sp.BTKV(K)-VE, FIHA, FICS, AIFO-K who provided us with early information on the call for paper session of the TRIGONOM FORKOM Webinar. We would also thank all colleagues, staff, and seniors from Pharmacology Class of the Master of Biomedical Sciences study program at Universitas Gadjah Mada for their moral support for the research, authorship, and publication of this article.

## Review

# Brominated Flame Retardants: A Literature Review of The Toxicity Mechanisms, Clinical Manifestations, And Current Treatments

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## ARTICLE INFO

### Article history

Received: 9 November 2022

Revised: 12 July 2023

Accepted: 22 July 2023

### Keywords

Endocrine Disruptors,  
Flame Retardants,  
Genotoxicity,  
Neurotoxicity,  
Polybrominated  
Compounds

## ABSTRACT

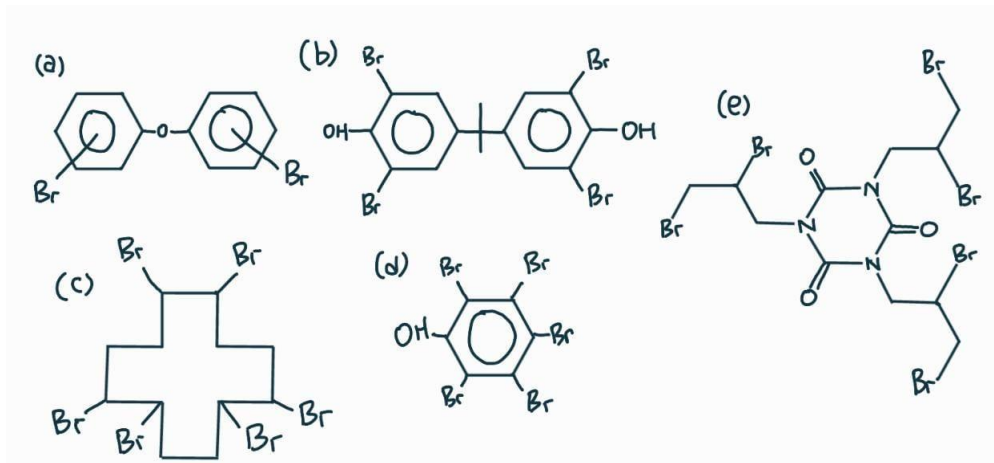
Brominated flame retardants (BFRs) are organohalogen compounds that can inhibit fire formation and delay its spread in manufacturing materials. BFRs are known to be toxic to the environment and humans. BFRs could persist for years prolonging potential exposure and toxicity to living beings. Indonesia had begun to reduce the use, even though some of toxic BFRs are still illegally circulating. This review aims to describe some aspects of BFRs toxicity including the mechanism, its clinical manifestations, and the current possible treatments. Toxicity after BFRs exposure includes endocrine, neurodevelopmental, and genotoxicity. The toxicity is manifested in some clinical conditions such as hypothyroidism, gonadal disturbance, or neurological disorders. Currently, no definitive specific treatment is available, so the treatment is focused on primary survey as well as surface decontamination with running water and gastrointestinal decontamination with activated charcoal of some dose if the ingestion is less than 1 hour.

## INTRODUCTION

Flame retardants are compounds that can inhibit the formation of fire and delay the spread of fire in manufacturing materials such as plastics, textiles<sup>1</sup>, and electronics<sup>2</sup>. Flame retardant compounds are usually used as surface polishers and coatings that are prone to ignition. The flame retardant can just be mixed with the base material and thus can be released into the environment (additive) or it can also be chemically bonded to the base material, so it is not easily released into the surroundings (reactive). Mineral flame retardants are usually additive, while organohalogen and organophosphate compounds can be reactive or additive.<sup>3</sup> Until 2020, it was recorded that around 2.19 million tons of flame retardants were used worldwide, the largest market (46%) being in Asia-Pacific, and brominated flame retardants (BFRs) were frequently used with a total demand of 28.4% in Asia.<sup>2</sup>

BFR belongs to the group of organohalogen compounds. The BFR group consists of up to 80 types of registered compounds with the most used BFRs being polybrominated-diphenyl ether (PBDE), hexabromocyclododecane (HBCD), and tetrabromobisphenol-A (TBBPA).<sup>4</sup> PBDEs were subdivided commercially based on the degree of bromination, into decaBDE, octaBDE, and pentaBDE, with decaBDE ever accounting for 90% of all PBDE use.<sup>5</sup> There are also new BFRs

(novel BFR/NBFR) such as pentabromotoluene (PBT) and Tris (2,3-dibromopropyl) isocyanurate (TBC), to replace the traditional BFR. NBFR is currently known to consist of about 30 types of compounds. The chemical structure of several BFRs can be seen in Figure 1.



**Figure 1.** Chemical structures of several BFRs (a) PBDE, (b) TBBPA, (c) HBCD, (d) PBT, and (e) TBC. Adapted from Dong et al<sup>6</sup> and Fonnum et al<sup>4</sup>.

Concerns for BFRs as an environmental toxicant emerged around the 1980s after it was found in environmental samples. In the following years, it was also found in human samples.<sup>7</sup> BFR like PBDEs tend to survive for years in the environment and easily transfer from basic materials to air, dust, soil, and water surfaces.<sup>8</sup> Ni et al<sup>9</sup> reported that even with the state of art waste incinerators equipped with pollution control technologies, BFRs such as PBDE and HCBDE are still released on a small scale to the environment. Human exposure to BFR is known to trigger toxic effects on the endocrine system, disrupt the development of the nervous system<sup>10</sup>, and induce genotoxicity<sup>11</sup> as well. Table 1 shows several BFRs with their 50% lethal concentration/dose (LC50/LD50) in experimental animals.

**Table 1.** Examples of BFRs with their LC50/LD50 in experimental animals<sup>6,12</sup>

Type of BFR	Subjects	LC50/LD50
PBDE	Zebrafish larvae	96 hrs LC50 5,37mg/L
TBBPA	Zebrafish larvae	96 hrs LC50 5,27mg/L
DBDPE	Rat Rabbit	LD50 single oral dose >5000mg/kg LD50 dermal >2g/kg
BTBPE	Rat	4 hrs LC50 inhalation >36,68 g/m <sup>3</sup>
PBT	Fish	LC50 >5mg/L
PBEB	Rabbit	LD50 dermal >8g/kg
TBC	Rat	LD50 oral >15g/kg

LC50: lethal concentration for 50% animals in samples; LD50: lethal dose for 50% animals in samples; PBDE: polybrominated diphenyl ether; TBBPA: tetrabromobisphenol-A; DBDPE: decabromodiphenyl ethane; BTBPE: bis (2,4,6-tribromophenoxy) ethane; PBT: 2,3,4,5,6-pentabromotoluene; PBEB: 2,3,4,5,6-pentabromoethyl benzene; TBC: tris (2,3-dibromopropyl) isocyanurate; hrs: hours; mg/L: milligram per liter; mg/kg: milligram per kilograms; g/kg: gram per kilograms; g/m<sup>3</sup>: gram per cubic meter.

Due to their toxicity, some BFRs such as PentaBDE and octaBDE are currently banned in almost all European countries, including Japan. In the United States, the developers even have voluntarily withdrawn both PDBEs.<sup>4</sup> Indonesia commits to reducing toxic industrial wastes including

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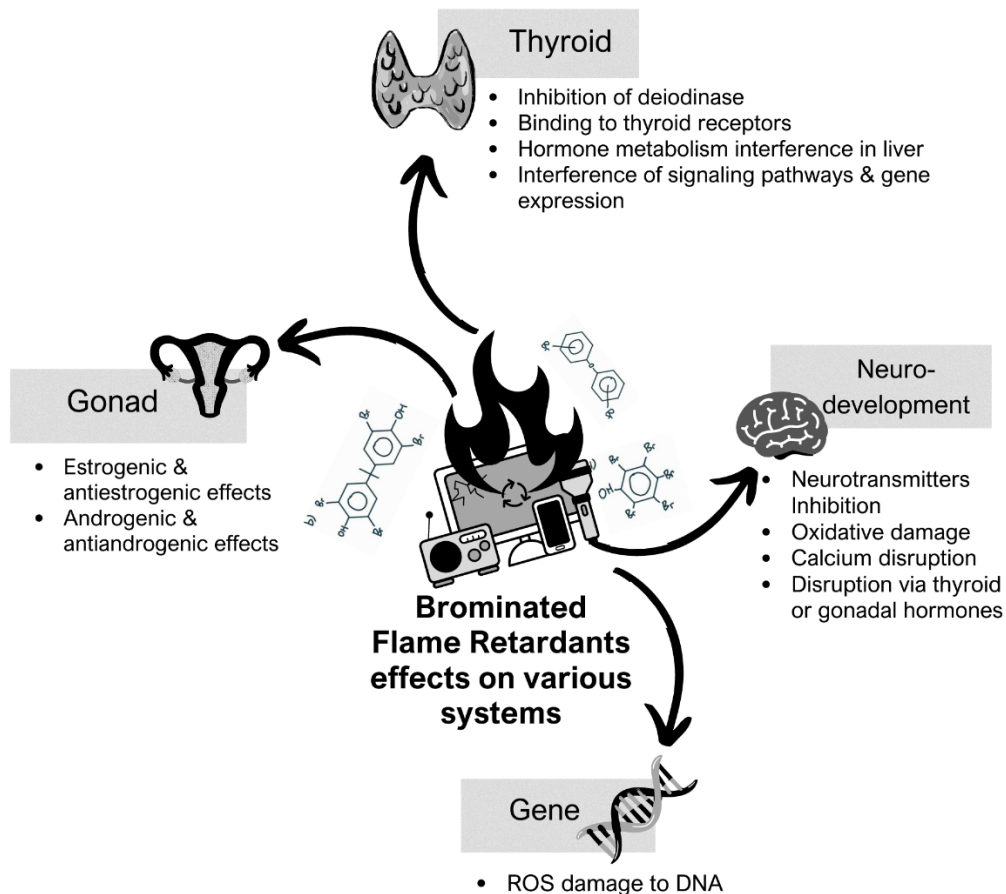
PDBE, starting in 2009 after the ratification of the Stockholm Convention. In 2018, the Indonesian Ministry of Industry collaborated with United Nations Development Program (UNDP) to limit and eliminate the use of PBDE. However, according to the ministry, PBDE is still circulating illegally in Indonesia.<sup>13</sup> Other BFRs such as TBBPA are also still widely produced so they may be exposed to humans and elicit their toxic effect.<sup>14</sup> NBFR which is used as a substitute for traditional BFR also has similar properties like volatility and lipophilicity as PBDEs, thereby increasing awareness of the toxicity of this flame-retardant group<sup>8</sup>, and therefore, human exposure to BFRs may continue. This review aims to briefly describe the mechanism of BFR toxicity, its clinical manifestations, and the possible treatments currently known.

## **METHODS**

This literature review is based on literature searching from the Pubmed database, Google search engine, and hand-searching from the library of the Faculty of Medicine, Universitas Kristen Duta Wacana. Keywords used include but are not limited to, brominated flame retardants and the types (BFR, NBFR, PDBE, TBBPA, HBCD, and so on), mechanism of toxicity, management, treatment, workups, and synonyms. Articles are limited by language with articles in English included. No limitation from the year published. The article included must be on the topic of BFR and its toxicity, articles about the management of BFR toxicity in the form of experimental and observational research, reviews, and grey literature such as guidelines, government publications, and websites, as well as medical textbooks and electronic books. Exclusion criteria consist of the unavailability of abstract or full text, comparing BFR toxicity with other forms of flame retardants, or articles about BFR toxicity in perspective on environmental toxicity alone without effect on humans or experimental animals.

## **MECHANISM OF BFR TOXICITY**

The main routes of exposure to BFRs in humans are through ingestion of dust-contaminated food, inhalation, or dermal contact. It is estimated that the highest exposure in younger children is due to the habit of putting their hands in their mouths.<sup>8</sup> Toxicokinetic data indicate that PDBE is well absorbed from oral, intratracheal, intraperitoneal (>80%), and dermal (>60%)<sup>15</sup>, and has the potential to accumulate in adipose tissue including breast milk in living beings because it is lipophilic.<sup>8</sup> It has a relatively long half-life, about 15-91 days in humans.<sup>16</sup> The higher the bromination level the easier it is to eliminate.<sup>17</sup> This section will explain the mechanism of toxicity of BFRs while Figure 2 contains a summary of the mechanism.



**Figure 2.** BFRs mechanism of toxicity in thyroid<sup>12,18 - 20</sup>, gonad<sup>10,21 - 25</sup>, neurodevelopment<sup>6,10,26,27</sup>, and gene<sup>11</sup>.

### 1. Disruption of Endocrine System – Thyroid

BFRs disrupt the endocrine system, with the thyroid hormone system as one of the main targets. Some of the mechanisms are by inhibiting deiodinase (ID) enzymes<sup>12</sup>, interacting with thyroid receptors (TR)<sup>18</sup>, interfering with thyroid hormone metabolism in the liver<sup>19</sup>, and interfering with signaling pathways and gene expression in cells<sup>20</sup>.

The thyroid gland produces 2 hormones called thyroxine (T4) and triiodothyronine (T3). Both hormones are produced in thyroid epithelial cells that are assembled in functional units called follicles. The follicle surrounds a colloidal nucleus in the form of a glycoprotein called thyroid-binding globulin (TBG). TBG serves as a storage site for thyroid hormones and is also involved in thyroid hormone synthesis. T4 and T3 are regulators of all metabolisms, and their effects are regulated in the long term. All tissues are targets for thyroid hormone, and the main target organs include the liver, kidneys, heart, brain, pituitary gland, sex glands/gonads, and spleen. The thyroid gland synthesizes and secretes T4 and T3, but about 90% of what is secreted is in the form of T4. Once secreted into the blood, thyroid hormone is immediately bound to serum proteins, and very little T4 (0.1%) and T3 (1%) are in free form. Circulating thyroid-binding proteins include TBG (binding 80% of thyroid hormone), thyroxine-binding prealbumin/transthyretin (TBPA/TTP), and albumin (both binding the remaining 20%).<sup>28</sup> Under normal conditions of the thyroid system, these proteins will carry plasma T4 to the tissues. T4 will be activated to become active T3 and become a signal molecule to the cell nucleus to then carry out its function and be inactivated again (inactive T3) when the function has been achieved.<sup>6</sup>

Deiodinization is a process mediated by the enzyme deiodinase for thyroid hormone regulation. On exposure to NBFR (DBDPE), deiodinase is inhibited (or induced) so that T4 regulation is disturbed which triggers hypothyroidism.<sup>6</sup> Several deiodinases were triggered by TBBPA and PBDE in zebrafish studies, which continued to cause systemic hypothyroidism due to T4 overuse.<sup>12</sup> T4 levels are known to decrease with exposure to HCB. This is also thought to be due to increased



uptake of the tissue. HCB is known to increase the expression of anion-transporting peptide (OATP) mRNA that introduces thyroid hormone to tissues<sup>10</sup>.

BFRs are able to interact with thyroid hormone receptors (TR, with 2 variants TR $\alpha$  and TR $\beta$ ). TBBPA is known to bind to TR stronger than T<sub>3</sub><sup>22</sup>, and causes antagonism.<sup>18</sup> TBBPA and PBDE have also been studied causing tissue-specific changes in TR.<sup>12</sup> Some NBFRs have similarities to T<sub>4</sub> and thus interfere with the transport of T<sub>4</sub> by TTR to the central nervous system or from the placenta to the fetus during pregnancy. TBBPA and its hydroxylated metabolite PBDE are known to bind to TTR and interfere with T<sub>4</sub> transport. The binding of NBFR to TBG also interferes with thyroid hormone transport and function to other tissues.<sup>6</sup>

BFRs also interfere with thyroid hormone metabolism in the liver. BFR chemical structure has a benzene ring or a structure like it. The structure could trigger binding to aryl-hydrocarbon receptors in the liver and induces CYP450 enzymes and UDP-glucuronosyltransferase (UDPGT) to increase thyroid hormone metabolism in the liver.<sup>19</sup> It was observed that serum T<sub>4</sub> levels were markedly reduced in rats exposed to both low and high concentrations of PBDE (PBDE 3-60mg/kg/day), whereas T<sub>4</sub> biotransformation in the liver was found to be increased upon exposure to high doses of PBDE.<sup>29</sup>

Impaired cell signaling and gene expression can be impaired by BFR exposure. PBDE antagonizes T<sub>3</sub>-mediated proliferation, whereas coadministration of HCB actually increases T<sub>3</sub>-mediated proliferation.<sup>10</sup> TBBPA is known to be a thyroid hormone agonist and it induces proliferation in GH3 cells. PBDE is known to decrease the expression of thyroid system-related genes, namely thyroglobulin (TG), TR $\beta$ , thyroid stimulating hormone (TSH), and TTR, but increase the expression of the sodium-iodine symporter (NIS), thyroid peroxidase (TPO), and TR $\alpha$ . TG is a protein synthesis material for thyroid hormones. TSH is a regulator of thyroid hormone synthesis. As stated before, TTR is a T<sub>4</sub> carrier in serum and cerebrospinal fluid. Disturbances in TR $\beta$ , TR $\alpha$ , and TTR may indicate impaired function of circulating thyroid hormones. Meanwhile, disturbances in TSH and TG as well as abnormal levels of T<sub>4</sub> and T<sub>3</sub> indicate a disturbance in the thyroid synthesis. Both disturbances could ultimately disrupt signaling at the cellular level.<sup>20</sup>

## 2. Disruption of Endocrine System – Gonad

BFR is able to cause disturbances in gonadal hormones in the form of estrogenic and anti-estrogen effects as well as androgenic and anti-androgenic effects<sup>10</sup>. Gonads are organs that function to produce gametes (sperm in males and oocytes in females) and secrete sex hormones. The gonadal system functions as an active reproductive system starting at puberty. Gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the anterior pituitary to secrete FSH and LH. FSH and LH then go to the gonads to then stimulate their function.<sup>30</sup>

In women, ovaries produce steroid hormones estrogen (including estradiol, estriol, and estrone) and progesterone. FSH and LH stimulate the development of follicles in the ovaries and trigger the secretion of estrogen from these follicles. LH then also stimulates ovulation, the formation of the corpus luteum, and the secretion of progesterone and estrogen from the corpus luteum. Estrogen will stimulate the growth, development, and maintenance of female reproductive organs, stimulate, and maintain secondary sexual characteristics (including breast enlargement and pelvic dilation), and stimulate protein synthesis. Progesterone prepares the endometrium for implantation as well as the mammary glands for milk synthesis. These two hormones, together with follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary regulate the menstrual cycle, maintain pregnancy, and prepare for lactation. The ovaries also produce inhibin and relaxin. Inhibin functions as an inhibitor of FSH while relaxin relaxes the myometrium at the time of implantation.<sup>30</sup>

The menstrual cycle in women serves to prepare the endometrium each month to receive a fertilized ovary. The menstrual cycle consists of the ovarian cycle and the endometrial/uterine cycle, and can be divided into the menstrual phase, the preovulatory phase, the ovulatory phase, and the post-ovulatory phase. Control of GnRH stimulates both cycles via FSH and LH. In the menstrual phase, the ovaries produce primordial follicles under the influence of FSH, which then develop into secondary follicles; In the endometrium, there is sloughing, consisting of 50-150mL of blood, tissue, mucus, and endometrial epithelial cells due to the decrease in progesterone and estrogen, resulting in an increase in prostaglandins, which triggers uterine arteriole constriction which leads to the death of endometrial cells. In the preovulatory phase, some of the secondary follicles begin to secrete inhibin and one of the follicles in both ovaries has grown larger than the other and becomes the dominant follicle which develops continuously into a deGraaf follicle which continues to produce estrogen, increasing blood estrogen levels; In the uterus, high blood estrogen stimulates endometrial repair and cells begin to undergo mitosis and thicken the endometrium to grow secretory glands which are then called the stratum functionalis. In the ovulation phase, the deGraaf follicle ruptures and releases a secondary oocyte due to high LH secretion (LH surge); In the endometrium,

proliferation continues. The post-ovulatory phase is about 14 days after ovulation, in the ovaries, the mature follicles collapse and the formation of a hemorrhagic corpus occurs, theca cells and granulosa cells mix to form the corpus luteum which secretes progesterone, estrogen, relaxin, and inhibin, and absorbs the remaining blood clots; In the uterus, progesterone and estrogen produced by the corpus luteum maintain the growth of the endometrial glands, which also begin to secrete glycogen. If fertilization does not occur, the corpus luteum, which is a maximum of 2 weeks old, experiences a decrease in hormone secretion and degrades to a corpus albicans, there is a decrease in estrogen, progesterone, inhibin, a re-release of GnRH, FSH, and LH, and the cycle returns to the menstrual phase. When fertilization occurs, the oocyte will begin to divide and the corpus luteum can live for more than 2 weeks because of the human chorionic gonadotropin (hCG) hormone which is secreted by the chorion from the embryo about a week after fertilization.<sup>30</sup>

In males, LH stimulates the production of the male sex hormone testosterone in the testes which then triggers spermatogenesis while Sertoli cells in the testes secrete androgen binding protein (ABP) which binds to testosterone and maintains high concentrations in seminiferous tubules of the testes. Testosterone stimulates the descent of the testes before birth, regulates sperm production, controls sexual organs, stimulates bone growth and protein anabolism, and stimulates the development of secondary male sexual characteristics including the development of a beard and deep voice. Like the ovaries, the testes also produce inhibin which can inhibit FSH.<sup>30</sup>

In addition to the testes in males, there are androgens produced by other endocrine glands, namely the adrenal cortex in males and females. The androgen synthesized from the adrenal glands is dehydroepiandrosterone (DHEA). In men after puberty, DHEA levels can be said to be insignificant, because other androgens, namely testosterone, play a more role and have higher levels. In women, DHEA has the important function of promoting libido and can be converted to estrogen. After menopause, all female estrogen comes from the adrenal glands.<sup>30</sup>

Some BFRs have been reported to have an estrogenic effect in experimental animals and an anti-estrogen effect from their metabolites. Mice exposed to PBDE showed elevated calbindin-D9k (CaBP-9K), a marker of estrogen action. CaBP-9K expression in rat uterus increases with estrogen and decreases with progesterone in estrus and early gestation. PBDE injection increased CaBP-9k mRNA expression which also provided a uterotrophic response, which was reversed when anti-estrogens were administered.<sup>21</sup> Female rats given PBDE injection at 10-18 days of gestation reported giving birth to pups with higher ovarian weight, although there was no difference in uterine weight. There was downregulation of progesterone receptor mRNA while upregulation occurred in estrogen receptors (ER)- $\alpha$ , ER $\beta$ , and insulin-like growth factor-1 (IGF-1).<sup>24</sup> Another study found reduced estradiol and testosterone in childhood, whereas in adulthood, reduced anogenital distance and feminization of sexually dimorphic behavior were found.<sup>25</sup> Estrogenic effects were not demonstrated by HBCD and TBBPA either in vivo in fish or in vitro on human T47D cells. Exposure of TBBPA, HBCD, and PBDE to estrogen-responsive transgenic zebrafish through food and water did not increase estrogen receptor expression. The metabolites of hydroxylated PBDE are known to have anti-estrogen effects. This metabolite inhibits estradiol-mediated induction in zebrafish. However, it seems that this inhibition is related to the uncoupling that occurs in oxidative phosphorylation from experimental animals, so the anti-estrogen effect is doubtful.<sup>10</sup>

BFR can disrupt androgen homeostasis and reproductive system development. TBBPA exposure in rat broodstock can increase gonadal organ weight in first-generation male rats. TBBPA also influences circulating testosterone, aromatase in the ovaries, and the weight of the pituitary gland in male rats. In female adrenals, some PBDEs induce androgen synthesis, whereas exposure to PBDEs in male rats reduces the growth of accessory reproductive organs so it seems that PBDEs also have anti-androgen effects. This is consistent with a study in mice that exposed a PBDE for 31 days and showed delayed separation of the foreskin as a marker of puberty and reduced ventral prostate and seminal vesicle growth.<sup>23</sup> In adult males, exposure to PBDE increased LH hormone significantly and increased testosterone, androstenedione, and estrone insignificantly.<sup>10</sup>

The anti-androgen effect shown by PBDE is due to their inhibition of dihydrotestosterone (DHT)-mediated transcription at the androgen receptor (AR). From 27 BFR, it is known that all have antagonistic effects on AR. This antagonist effect is even 100 times stronger than flutamide, a prostate therapeutic agent and a quantitative structure-activity relationship (QSAR) model has been carried out with the result that the most potent PBDEs are those that have bromine down in the ortho- or meta-position but do not have bromine in para- position.<sup>31</sup>

In addition to the direct effect on AR, there are other mechanisms that are thought to cause its antagonistic or agonistic effect. Several BFRs and their metabolites are thought to trigger or inhibit steroidogenic enzymes important in the conversion of testosterone to estradiol, namely aromatase/CYP19, and in the biosynthesis of DHEA and androstenedione in the adrenal glands, and testosterone in the testes (CYP17). Hydroxylated or methoxylated PBDE metabolites are known to



inhibit CYP19 at low concentrations, whereas tribromophenol induces this enzyme. Hydroxylated PBDE and tribromophenol are also known to inhibit CYP17 mRNA expression. Tribromophenol exposure increased the expression of genes that function in the biosynthesis of androgens and estrogens as well as mineralocorticoids and glucocorticoids, namely 3 $\beta$ -hydroxysteroid dehydrogenase isomerase (3 $\beta$ -HSD).<sup>10</sup>

### 3. Neurodevelopmental Disruption

Neurodevelopmental toxicity by BFR remains related to its toxic nature to the endocrine system.<sup>10</sup> Because of its importance in early human development, several investigators have attempted to describe the neurodevelopmental toxicity of BFR in more detail. The nervous system develops from the ectoderm, which is one of the layers of the gastrula, the development of the embryo. The process of developing the nervous system begins after gastrulation. The ectoderm fuses with a portion of the mesoderm called the notochord to become the neural ectoderm. The most lateral part of the neural plate will become the neural crest while the middle part begins to form the neural groove. The neural grooves then fuse, closing to form the neural tube, while the neural crest cells separate to the periphery. This neural tube will become the central nervous system. Disruption in this process will lead to failure of the formation of the nervous system.<sup>32</sup>

PBDE was investigated to cause changes in the levels of post-synaptic protein in the mouse hippocampus which are involved in the ability of the synapse to deliver signals/synaptic plasticity. Mice aged 10 days after birth given high doses of BDE orally experienced decreased long-term potentiation and low levels of NR2B and GluR1 proteins, namely the subunit of the glutamate receptor, and Ca<sup>2+</sup>/calmodulin-dependent protein kinase II activation via autophosphorylation<sup>27</sup>. Other BFRs are known to inhibit neurotransmitter uptake, HCBd inhibits dopamine uptake, while TBBPA inhibits dopamine, glutamate, and GABA uptake.<sup>26</sup>

NBFR can cause neurodevelopmental toxicity through 2 mechanisms, namely direct (on nerve cells) and indirect (against the hypothalamic-pituitary-thyroid/HPT and hypothalamic-pituitary-gonadal/HPG axis). The direct mechanism stems from oxidative damage and disruption of calcium homeostasis. Damage to the antioxidant system is known to be triggered by NBFR and causes the accumulation of reactive oxygen species (ROS) which can damage nerve cells and tissues. NBFR interferes with the work of 2 main antioxidant enzymes, namely superoxide dismutase (SOD) and catalase (CAT). Glutathione supplies are also reduced due to having to take NBFR. Then, NBFR also interferes with genes that play a role in oxidative stress such as *sod1*, *sod2*, *cyc1*, *mt-co2*, *mgst1*, *cat*, and *gpx-1*, thereby triggering the release of ROS. It is also known that calcium hemostasis is impaired upon exposure to NBFR. An increase in the intracellular calcium concentration triggers a response that damages the cell cytoskeleton and function, which ultimately leads to cell damage and apoptosis.<sup>6</sup>

Indirect mechanisms for neurodevelopmental toxicity are related to thyroid and gonadal hormone disruptions. The disruptions of the thyroid system include inhibition of ID activity, interaction with TR, interference with thyroid hormone metabolism, and impair cell signaling as explained before. Disturbances in gonadal hormones are caused by NBFR being able to activate/inhibit AR or ER, trigger changes in sex hormone levels, and interfere with the transcription of target genes on the HPG axis. NBFR binding to AR/ER in the form of agonism or antagonism can affect sexual reproduction, development, and behavior, interfering with gender differentiation in the brain which further affects hormone levels, or brain morphology and function. In addition, NBFR can also interfere with GnRH activation and inhibit enzymes that produce steroid hormones such as CYP17, CYP19, and 3 $\beta$ -HSD.<sup>6</sup>

### 4. Genotoxicity

Genotoxicity is a deleterious effect that affects the integrity of the genetic material of a cell. Hydroxylated PBDEs and PBDEs have been reported to have genotoxicity through double-strand breaks in DNA. The mechanism of genotoxicity is thought to be through the accumulation of ROS. PBDE increases the accumulation of ROS that trigger base damage to DNA, resulting in blockade of the replication process leading to chromosomal damage.<sup>11</sup>

## CLINICAL MANIFESTATION & WORKUPS OF BFR TOXICITY

Exposure to BFR in patients can manifest as certain pathological conditions. NTP<sup>33</sup> reported an occurrence of cancer in mice and rats exposed to PBDE. A cross-sectional study of 745 women in Canada reported that exposure to PBDEs was associated with the incidence of hypothyroidism (prevalence ratio 1.7, 95% CI 1-3).<sup>34</sup> Endocrine effects in the form of inhibition of thyroxine receptors were also found in TBBPA and HBCD exposure, while HBCD exposure inhibited progesterone

receptors and disrupt normal gonadal cycle and signaling.<sup>22</sup> A meta-analysis of 7 studies found an association between PBDE levels and a reduction in infant weight of about 50.1 grams (95% CI - 95.9 - -5.3).<sup>35</sup>

Regarding nervous system manifestations, it was found that PBDE was predisposed in the neonate brain of mice and interfered with the development of the nervous system until adult mice. Adult mice experienced behavioral changes that worsened with age when at 3 days of gestation the mice were exposed to PBDE<sup>36</sup>. The behavioral changes observed included disturbances in the daily behavior of mice and hyperactivity which were also found in postnatal PBDE exposure to newborn mice.<sup>37</sup> In addition, learning and memory disorders were also found<sup>38</sup> as well as disturbances in the cholinergic system of mice<sup>39</sup>. In humans, a meta-analysis of 4 studies comparing prenatal and childhood PBDE exposure with neurodevelopmental outcomes reported a 3.7-point decrease in IQ (95% CI -6.56- -0.83) for a 10-fold increase in PBDE exposure.<sup>40</sup>

BFR laboratory tests for everyday clinical purposes are still not yet available currently when this article is written<sup>8</sup> so history taking and physical examination are the mainstay to confirm the diagnosis of the disorder. Manifestations of hypothyroidism in BFR are not very obvious because thyroid function decreases gradually. Manifestations of reduced thyroid hormone can be in the form of general symptoms related to the slowing of metabolic processes and accumulation of matrix glycosaminoglycans in the interstitial tissue. Metabolic processes slow down in hypothyroid conditions which can cause fatigue, slow movement, and speech, intolerance to cold temperatures, constipation, weight gain even though not to severe obesity, and bradycardia. Manifestations of accumulation of matrix glycosaminoglycans can be seen from the hair and skin that tends to be rough, the face looks fat (puffy facies), an enlarged tongue, and a rough voice. These signs are easier to recognize in younger patients because they are physiologically present in older patients.<sup>41</sup>

The skin in hypothyroid patients tends to be cold and pale. This is due to reduced blood flow to this area. There is hyperkeratosis and atrophy of the epidermal cell layer resulting in dry and rough skin. Sweat is usually reduced on the patient's skin due to a lack of sweat gland secretion. The patient's hair is usually dry and falls out easily, the nails also become brittle. If severe, there may be non-pitting edema called myxedema as a result of glycosaminoglycan infiltration in the skin associated with water retention. Other manifestations include periorbital edema in the eyes and weakness of the muscles around the eyes. The coagulation system in hypothyroid patients tends to be hypercoagulable, making it prone to bleeding. Hypometabolism that occurs in hypothyroidism causes a decrease in heart rate and contractility leading to decreases of cardiac output. As a result, hypothyroid patients get tired easily when doing activities. Patients may also experience sleep apnea due to an enlarged tongue. Constipation is caused by reduced intestinal motility in the gastrointestinal tract. In women, menstrual disorders are mostly oligo-amenorrhea and a small proportion are hypermenorrhea and menorrhagia. This menstrual disorder results in reduced fertility, and if pregnancy occurs, usually an abortion will occur in the early days of pregnancy. In men, reduced libido, erectile dysfunction, delayed ejaculation, and abnormalities in sperm morphology occur. Hypothyroid patients also experience muscle weakness, myopathy, cramps, joint pain, and stiffness. Some laboratory tests may show hyponatremia due to reduced water excretion, increased serum creatinine, and hyperlipidemia. Drug clearance also decreases in hypothyroid patients so they are susceptible to toxicity.<sup>41</sup>

## CURRENT AVAILABLE TREATMENTS FOR BFR TOXICITY

The principle of poisoning treatments consists of supportive and specific management. Supportive management should be carried out for all poisoned patients, including cases with BFRs. A primary ABCDE survey should be performed on all patients regarding exposure chronicity and treatment must be provided immediately if there was interference from one of the components. Point A (airway and c-spine control) ensures that the airway is free from obstruction and that the neck vertebrae are unobstructed; Point B (breathing and oxygenation) ensures the patient can breathe well and get enough oxygen; Point C (circulation and hemorrhage control) ensures the patient's circulation is good and stops bleeding; Point D (disability) in the form of a rapid assessment of the patient's neurological condition, using the AVPU (alert, verbal response, pain response, or unresponsive) method or the Glasgow Coma Scale; and Point E (exposure or environmental control) which is to keep patients (and helper) away from exposure to BFRs.<sup>42</sup>

Specific management includes reducing/inhibiting further absorption of the poison, increasing the elimination of the poison, and stopping the effect of the poison with a specific antidote. However, until this article is written, there is currently no definitive specific treatment for BFR exposure. Exposure usually comes from food contaminated with dust so the amount is relatively small.<sup>8</sup> The long final elimination of some BFRs and their lipophilicity<sup>15</sup> make it possible for BFRs to accumulate

in the body making specific management difficult. Several attempts can be made, such as decontaminating the surface exposed to BFRs. Affected clothing should be removed immediately and washed with soap and water. The hands should then also be washed immediately after touching any objects, considering that BFRs can be found in many everyday items and are easily released into the environment. In case of eye exposure to suspected BFR-contaminated materials, irrigation should be done immediately with running water for at least 15 minutes before referral to the hospital.<sup>43</sup> For a rare case of ingesting a large amount of BFR, absorption could be inhibited by using activated charcoal. The adult dose of activated charcoal is 50-100 g, for children of less than 1 year old the dose is 0,5-1 g/kg or 10-25 g maximum, and for children of 1 to 12 years old could be administered 25-50g maximum dose of activated charcoal. The use of activated charcoal is not recommended for BFR ingestions longer than 1 hour<sup>42</sup>, given the good absorption of BFRs.<sup>15</sup>

## CONCLUSION

BFR toxicity remains an important problem because of the possible prolonged exposures in the environment and humans. The effect of BFRs on the endocrine and nervous systems as well as cellular to DNA levels can be manifested in various symptoms such as hypothyroidism, behavioral disorders, decreased IQ, gonadal disorders, and low birth weight babies. Specific treatment is still not available other than the administration of activated charcoal. It is important to observe personal hygiene to avoid exposure as well as surface and gastrointestinal decontamination if exposed to BFR in large doses. At the level of policymakers, support to the government in reducing and eliminating the use of toxic BFRs and other hazardous materials is very much needed. Experimental, observational, and literature studies on hazardous materials need to be continued as a form of this support.

## DECLARATION

**Acknowledgments:** We express gratitude to dr. Sudi Indra Jaya, M.Biomed and apt. Eustachia Diajeng Wandansari, S.Farm., M.Biomed. who facilitated communication access between us, as well as Dr. dr. Ronald Winardi Kartika, Sp.BTKV(K)-VE, FIHA, FICS, AIFO-K who provided us with early information on the call for a paper session of the TRIGONOM FORKOM Webinar. We would also thank all colleagues, staff, and seniors from the Pharmacology Class of the Master of Biomedical Sciences study program at Universitas Gadjah Mada for their moral support for the research, authorship, and publication of this article.

**Financial Disclosure:** The authors received no financial support for the publication of this article.

**Conflict of Interests:** The authors have no conflicts of interest to declare.

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