Endocrine Disrupting Effects of Flame Retardants on Thyroid System

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SUMMARY

Accumulating scientific evidence shows that thyroid hormone synthesis and signaling are now recognized as one of the critical targets of environmental chemicals, especially of endocrine disruptors. Endocrine disrupting chemicals (EDCs) are artificial chemicals and consist of different types of molecules, for instance some pesticides, plasticizers, flame retardants (FRs), surfactants, many of which can interfere with thyroid hormone synthesis or their actions. FRs, essential members of endocrine disruptors, share similarities in their chemical structures when compared with thyroid hormones, and there are accumulating scientific findings pointing out that they may take part in dysfunction of thyroid hormone homeostasis. The primary aim of using FRs is to minimize the risk of fire and prevent its spreading. The potential effects of exposure to FRs on the thyroid and thyroid hormones have gained importance since they may easily migrate into the surrounding environment and are mainly found in house dust. Within the framework of the results of some experimental animal and in vitro studies, as well as limited human studies researching the consequences of FRs on the thyroid system, this paper aims to make a general assessment of whether these chemicals have a role in some thyroid diseases. Although the information that FRs with endocrine disrupting properties may have an effect on thyroid hormone levels and cause disruption in the thyroid system is still in its infancy, there is emerging evidence that some members of FRs may have thyroid disrupting properties.

Key Words: *Flame retardants, thyroid hormones, endocrine disruptors, thyroid toxicity.*

Alev Geciktiricilerin Tiroid Sistem Üzerindeki Endokrin Bozucu Etkileri

ÖZ

Sayısı giderek artan bilimsel bulgular çevreden maruz kalınan kimyasallar için, özellikle de endokrin bozucular olarak adlandırılan kimyasal grubu açısından, tiroid hormon sentezi ve sinyalizasyonunun önemli bir hedef haline geldiğini göstermektedir. Endokrin bozucu kimyasallar (EBK) insan yapımı kimyasallardır ve çok çeşitli moleküllerden oluşur. Bunlara bazı pestisitler, plastizerler, alev geciktiriciler (AG), surfaktanlar örnek verilebilir, bu kimyasalların çoğu tiroid hormon sentezine veya bu hormonların aktivitelerine müdahale etmektedir. AGler endokrin bozucuların önemli bir üyesidir, kimyasal yapıları tiroid hormonlarıyla benzerlik göstermektedir ve tiroid hormon homeostazının disfonksiyonunda rol oynayabileceğini gösteren bulguların sayısı artmaktadır. AGlerin kullanımının birincil amacı yangın riskini olabildiğince azaltmak ve yayılmasını önlemektir. Kolayca çevreye sızabilmeleri ve özellikle ev tozunda bulunabilmeleri nedeniyle AGlere maruziyetin tiroid ve tiroid hormonları üzerine potansiyel etkileri önem kazanmıştır. Tiroid sistem üzerine AGlerin etkilerini inceleyen bazı deneysel hayvan çalışmaları ve in vitro çalışmalar, bunun yanı sıra sınırlı sayıda insan çalışmasının sonuçları çerçevesinde, bu çalışmamızın amacı bu kimyasalların bazı tiroid hastalıklarında bir role sahip olup olamayacağı hakkında genel bir değerlendirme yapmaktır. Her ne kadar endokrin bozucu etkileri olan AGlerin tiroid hormon seviyelerini etkileyebileceği ve tiroid sistemde bozukluklara yol açabileceği bilgisi çok yeni olsa da, AGlerin bazı üyelerinin tiroid bozucu özelliklere sahip olduğuna dair bulgular ortaya çıkmaktadır.

Anahtar Kelimeler: *Alev geciktiriciler, tiroid hormonları, endokrin bozucular, tiroid toksisitesi.*

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INTRODUCTION

A significant number of synthetic chemical compounds have emerged; they have been produced and transferred into our surrounding environment since the mid-1930s till today (Yeung et al., 2011). Between 1950-2000, the production of chemical substances increased 60 times in mass, and global chemical sales increased over two times between 2004-2014 (Bolinius et al., 2018). The precise amount of chemicals on the global market is unknown; however, recently it is reported that the number of industrial chemicals and mixtures which have been registered for production are more than 350,000 (Brack et al., 2022). In 2018, total chemical consumption was 303 million tons in 27 member countries of the EU, and 221 million tons of this amount consisted of chemicals that are accepted to be hazardous to health. In addition, the use and production of chemical substances increased 16 times over the last 70 years in the USA (Sutton et al., 2012). It is calculated that this number refers to 13.000 kg for every individual living in the USA (Wang et al., 2016). In a research conducted by FDA, over 1800 chemicals were determined to interfere with one or more of three different pathways of endocrine system (androgen, eustrogen, and thyroid) (De Falco & Laforgia, 2021). Evidence is increasing day by day that exogenous chemicals, which have an effect on hormone production and hormone effects and are classified under the name of Endocrine Disrupting Chemicals (EDCs), can disrupt the established biological balance and cause significant changes in the protection of both our body and public health (Kahn et al., 2020). World Health Organisation (WHO) characterizes an endocrine disruptor as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations" (WHO, 2013). In light of this definition, ten critical characteristics of EDCs have now been identified. These characteristics include interaction or activation of hormone receptors, antagonizing these receptors,

altering hormone receptor expression, changing signal transduction among cells that respond to hormones, causing differences in synthesis, transport, distribution, or circulating levels, and finally, metabolism or clearance of hormones; and lastly altering the fate cells that function in the production of hormones or responding to hormones (La Merrill et al., 2020).

EDCs are a group of compounds with different chemical structures (Cok, 2021). There is a consensus today that acknowledged or potential EDCs might be present in industrial and consumer products. EDCs, which we might be exposed to intentionally or unintentionally in our daily life through different consumer products, are seen in a wide range of possible exposure sources from our food to the air we inhale.. In addition to regulatory health authorities such as WHO, the US Environmental Protection Agency (EPA), United Nations Environment Programme (UNEP) and European Union (EU); many scientific establishments, mainly Endocrine Society, accept EDCs as a global problem and work on developing programmes in order to decrease the number of EDCs and exposure to these compounds. Due to the accumulating scientific evidence regarding the role of EDCs, particularly in hormone-related diseases such as diabetes, reproductive diseases, neurodevelopmental diseases, breast cancer, prostate cancer, both the public and health authorities are concerned about exposure and potential adverse effects of these substances (Encarnação et al., 2019).

Thyroid hormones, which are among the most important hormones vital for a healthy life, are involved in various physiological processes. These include bone remodelling, mental status, cardiac function and regulation of metabolism. Therefore, normal functioning of the thyroid is substantial for maintaining psychological and physiological health. Furthermore, thyroid hormones have a crucial role in fetal development because levels of thyroid hormones need to be normal for the development

of the brain. In case of deficit in the levels of these hormones; neuronal growth and differentiation in the hippocampus, cerebral cortex, and cerebellum is reduced. Moreover, maternal thyroid homeostasis has a vital role in fetal development (Boas et al., 2012).

The synthesis and storage of thyroid hormones take place in the thyroid gland. Their transportation to target cells occurs through binding to thyroid hormone-distributing proteins facilitating the process; however, free hormones are the ones that can be transferred into the cell. The levels of thyroid hormones in our bloodstream are strictly controlled by the hypothalamus-pituitary-thyroid (HPT) axis which consists of the hypothalamus, the pituitary and thyroid gland; and it depends on a negative feedback mechanism. If the levels of T4 and T3 in the blood are perceived to be low, pituitary gland secretes thyroid stimulating hormone (TSH) and forms a stimuli promoting the thyroid gland. Consequently, additional thyroid hormones are synthesized and increasingly released to preserve the levels of hormones in a narrow range. The liver and kidney take part in the deactivation and clearance of these hormones. Deiodinating enzymes regulate the levels of thyroid hormones at the cellular level. In order to evaluate thyroid function clinically, levels of TSH/T4/T3 in serum or plasma are used. If a decrease in serum T4 without the combination of increased TSH is observed, it gives an idea of hypothyroxinemia; however, differing from this case, if both a reduction in T4 and increased TSH are observed, then overt hypothyroidism can be considered. Total T4 seems to be the main parameter in developmental toxicology guideline studies. The main purpose of thyroid hormones is to control gene transcription. The control of the thyroid signaling mechanism is essential for mammalian brain development because different degrees of thyroid hormones are needed for some specific brain subregions. Maternal T4 seems to be the only source of hormones for the developing fetus during the early stages of pregnancy; therefore, it is precisely controlled by transporters and deiodinases

in the placenta T3 concentrations in the brain only depend on deiodinase activity in the brain since only T4 is able to be transferred to the fetal brain. Functioning of the thyroid gland of human fetuses begins in mid pregnancy. In the later stages of the pregnancy, during the third trimester, majority of neural circuits are seen to appear and they continue developing beyond adolescence (Gilbert et al., 2020).

Major causes of thyroid-related dysfunctions include thyroid cancer, autoimmune thyroid diseases and deficiencies in iodine and some other micronutrients (Brent, 2010). It has been suggested that environmental iodine deficiency, some medical treatments including radiation therapy, autoimmune diseases and some genetic disorders may affect the development of these disorders. Moreover, recent researches have indicated that exposure to some EDCs originating from consumer products that are used in our daily lives, may have a role in the increase of thyroid-related diseases (Alsen et al., 2021). Since thyroid diseases are prevalent endocrine diseases and affect approximately more than 200 million people worldwide, there is an increasing awareness of thyroid-related diseases in societies (Keestra et al., 2021). Thyroid hormone system is very vulnerable since EDCs can affect thyroxine and its active metabolites throughout the whole process including precise feedback regulation, synthesis and distribution of this prohormone and metabolism, and action of these compounds. Most of the effects attributed to EDCs occur at the pre-receptor control of T3 ligand availability to T3 receptors, which results in thyroid hormone action due to mediation by ligands. All of the different components of this system; including thyroid hormone transporters, deiodinases, enzymes functioning in metabolism and T3-receptor forms, might play a role in mediation of adverse effects. Epidemiological results concerning EDC exposure and thyroid hormone related conditions point out that human development, specifically the maturing of the brain throughout the fetal and neonatal period, growth, differentiation, can be affected by EDCs.

When EDCs interfere with iodide or thyroid hormone transport, they may cause substantial and irreversible alterations on brain development and functions which can be seen from the parameters including cognition, behavior, or Intelligence quotient (IQ) deficits in later life. Also, metabolic processes in adult and aging humans may be open to adverse effects of EDCs (Köhrle & Frädrich, 2021). It is observed that bisphenol A, phthalates, perfluorinated chemicals, and brominated flame retardants (BFRs) may be among the substances with thyroid-disrupting properties (Boas et al., 2012). Some examples of possible thyroid disruptors are listed in Table 1 (Kabir et al., 2015).

Table 1. Examples of potential thyroid disruptors, the way they act, and the consequences on the thyroid system (Kabir et al., 2015)

Thyroid Disruptors	Mechanism of Action	Biological effect
Phthalates	-Preventing the entry of iodide into thyroid cell -Binding with thyroid transport protein competitively	-Reduced synthesis of T3 and T4 -Potential impact on fetal brain T4 production
Polychlorinated biphenyls (PCBs)	-Binding with thyroid transport protein competitively -Elevated metabolism in the liver -Inhibition of sulfation reaction -Inhibition of TSH receptor -Inhibiting the activity of the deiodinase enzyme - Changes in binding to thyroid receptor	- Potential impact on fetal brain T4 production -Enhanced biliary metabolism of T3 and T4 -Potential reduction of peripheral T3 synthesis due to reduced sulfation of thyroid hormones -Lower level of production of T3 and T4 -Reduced peripheral T3 synthesis - Changes in the gene transcription mediated by thyroid hormones
Triclosan	-Inhibition of sulfation reaction	-Potential reduction of peripheral T3 synthesis due to reduced sulfation of thyroid hormones
Chlordane	-Causing changes in the transport across the cell membrane	-A higher level of biliary elimination of T3 and T4
Flame Retardants	-Binding with thyroid transport protein competitively -Changes in binding to thyroid receptor	-Potential impact on fetal brain T4 production -Changes in the gene transcription mediated by thyroid hormones

FLAME RETARDANTS

Flame retardants (FRs) are compounds that are applied in order to lower flammability and prevent fires from starting and spreading (Yao et al., 2021). The idea of protection from fire appeared for the first time in Egypt thousands of years ago, later on alum solutions were applied to wooden battleships. However, the first FRs patent was registered in 1735. In 1820, J.L. Lussac played a major role in the history of FRs with his work on the resistance of curtains to flames in Parisian theaters. Afterwards progress of working on flame retardancy continued; emerge of halogenated, phosphorus and nitrogen based FRs in 1980 and organophosphate flame retardants (OPFRs) in 2003 can be named as critical events throughout this process (Vahabi et al., 2021). FRs are mainly applied to furniture such as upholstery, mattresses, carpets and curtains; electrical devices such as laptops, computers, phones and televisions; materials that are used in the construction process, for example, wires and cables that electricity runs through; materials that take part in insulation, such as polyurethane and polystyrene insulation foams; products like seats of the vehicle or the covers of these seats and overhead compartments and other materials in transportation such as cars, planes, and trains (Shaw et al., 2014).

FRs are categorized into two main groups which are additive FRs and reactive FRs. Additive FRs are added to combustibles, in contrast reactive FRs take part in chemical reactions to make that material more resistant to flame (Yao et al., 2021). The difference between additive and reactive FRs is that additives are applied after polimerization and no covalent bonds are formed between FRs and the material whereas reactive ones are applied during polimerization and have chemical bonds with the material (Dishaw et al.,

2014). General characteristics of FRs (Kozlowski et al., 2014) are described in Figure 1.

There are several advantages of FRs such as prevention of fires or keeping the fire growth slow, reduced loss of property, reduced injuries and death due to fires, reduced environmental contamination due to fires. At the same time, the critical disadvantage of FRs is that they may migrate out of the products and are released to the surroundings (Purser, 2014). FRs are found in the indoor air, dust and outdoor environment due to volatilization and leaching from the treated materials (Dishaw et al., 2014). In addition, the increasing amount of toxicity information due to exposure from the use of these substances has become a general concern.

Exposure of human beings to FRs take place in three ways which are diet, inhalation, and ingesting or dermally absorbing dust particles. Children's exposure is higher than adults because of ingesting more dust particles via hand-to-mouth and object-to-mouth activities (Dishaw et al., 2014). Most FRs share similarity with thyroid hormones in terms of chemical structure and are thought to take part in the disorder of thyroid hormone homeostasis (Mughal & Demeneix, 2017). The disrupting effects of FRs, that have been used from past to present or are used today, on thyroid functions and hormones of laboratory animals and humans are tried to be evaluated below in groups.

Figure 1. General characteristics of FRs (Kozlowski et al., 2014)

Polybrominated diphenyl ethers

Back in the 1970s after the application of polybrominated biphenyls were withdrawn, polybrominated diphenyl ethers (PBDEs) were preferred to be used due to flammability standards. PBDEs have no chemical bonds with the material that they are in; thus, they can be released from those products, contaminate the air, and become a component of dust. They may be released to the surrounding environment during the manufacturing process or due to wearing down of materials (Shaw et al., 2014). Due to such concerns, PBDEs were phased out and organophosphate esters (OPEs) appeared as alternatives (Doherty et al., 2019). Penta-PBDE was limited in Europe in 2002 and in the US in 2005 (Castorina et al., 2017).

When possible effects of PBDEs are considered, the thyroid system seems to be the primary target of PBDEs and their hydroxylated metabolites (Dishaw et al., 2014). Biotransformation of PBDEs results in hydroxylated-BDEs (OH-BDEs) and bromophenols. The structure of OH-BDEs has similarities with endogenous thyroid hormones; therefore, it might be the causing factor of part of PBDE toxicity. According to these toxicity results, effects on neurodevelopment can be seen as the prominent example of this toxicity. Thus, thyroid hormones are substantial components of cell migration and synaptogenesis in the brain and generally appropriate neurodevelopment. It is thought that behavioral/neurodevelopmental effects of PBDEs might happen due to impaired regulation of thyroid hormone throughout critical developmental windows (Dingemans et al., 2011; Dishaw et al., 2014).

In various studies, PBDEs have been chosen as the subject because of their risk of resulting in endocrine disruption and other adverse effects (Kim & Oh, 2014). In a study conducted on human serum, the disrupting mechanism of polychlorinated biphenyls (PCBs), PBDEs, and new flame retardants (NFRs) were evaluated by investigating TH-regulated proteins and gene expression. In this study, some of the compounds in these groups were observed to have a strong binding affinity towards thyroglobulin, TSH, gene expression of thyroid hormone receptor α-(TRα) and β- (TRβ), thyroxine-binding globulin (TBG), and iodothyronine deiodinase I (ID1). Levels of TSH, TBG and expression of TRα were lower among highly exposed group; however, higher expression of ID1 was observed (Guo et al., 2019). In a different study, serums from blood samples of 140 pregnant women were analyzed for PBDEs, phenolic metabolites, and thyroid hormones. A significant positive association was found between BDE47, 99 and 100 and free and total T4 levels, and also between these compounds and total T3 levels higher than normal range (Stapleton et al., 2011). In a different study concerning PBDEs, the association of 10 PBDE congeners and free and total T4 and TSH were investigated among 270 pregnant women. It was found that as the concentration of individual congeners increased 10-folds each time, it resulted in a decrease of TSH between 10.9% and 18.7%. There was a significant enhancement in the odds of subclinical hyperthyroidism among participants who were exposed the most to ΣPBDEs and BDEs 100 and 153. No significant relation was observed between PBDEs and free and total T4. Study's findings suggested that PBDEs are related to decreased TSH during pregnancy (Chevrier et al., 2010). As a different exposed group, office workers were seen as the subject of a study in which serum samples were used and whether an association exist between PBDE concentrations in serum and thyroid hormones was investigated. It was found that an inverse relationship existed between total T4 and each PBDE congener. On the other hand, total T3, free T4 or TSH and PBDEs in the serum did not present a strong relationship. The findings of the research pointed out that being exposed to PBDE may cause a decrease in the binding of T4 to serum T4 binding proteins (Makey et al., 2016). As another possible exposure group, adult male sport fish consumers were studied in order to observe whether an association exists between PBDE body burdens and several aspects concerning the thyroid

system. Serums were collected from 405 participants and analysed for different chemicals and hormones including PBDE congeners, thyroglobulin antibodies, T4, T3, TSH, and T4-binding protein. Measures of T4 and PBDEs were observed to be positively associated. In contrast PBDEs were negatively related with total T3 and TSH in 308 men who did not have conditions of diabetes or thyroid dysfunction. In addition, PBDEs had a positive association with percentage of T4 bound to albumin, on the contrary had an inverse association with the percentage of T4 bound to TBG. Study's findings suggested that PBDE exposure had a link with increased thyroglobulin antibodies and T4 (Turyk et al., 2008). In a research, in which the exposed population consisted of children, researchers investigated the relation of PBDEs and NFRs with thyroid hormone. The study was conducted on 174 school students who reside around a petrochemical complex with questionnaires and blood samples. It was found that there was a significant association between the sum of thirteen PBDE congeners and eight types of NFRs and T3 levels (Guo et al., 2018). In another study, researchers examined serum hormone levels in men recruited from an infertility clinic and determined 31 PBDE congeners and 6 alternate FRs in their house dust. Beside other findings of the study, when hormones related to the thyroid system was evaluated, considerable positive associations between serum levels of free T4 and total T3 and pentaBDEs were seen. In addition, octaBDEs were found to be positively related with serum free T4 and TSH (Johnson et al., 2013). In a study, which was conducted on female participants, whether PBDE concentrations in serum had a link with thyroid disease among women was investigated. The possibility of thyroid disease increased among those with the highest concentrations of BDE47, 99 and 100 in serum. Authors concluded that these compounds were related to thyroid disease and that the effects were observed to be greater in post-menopause (Allen et al., 2016). In a different study considering exposure of children, researchers collected serum

samples of children who attended to a school in town with an e-waste recycling area and of children from a school in a control area. Levels of PCBs and halogen FRs were determined to be much higher in the exposed group when compared with the control group. It was shown that internal exposure levels were closely related with responses of thyroid hormone related proteins and gene expression. An increase in the expression of ID1, a decrease in levels of TSH and expression of TRα- were observed due to more extensive exposure concentrations (Guo et al., 2020). On the contrary to studies mentioned above, Eggesbo and coworkers (2011) investigated the association of BFRs including six PBDEs with neonatal TSH via milk samples of 239 mothers. As a result, there was no significant association between important toxic PBDE congeners (BDE-47, 99, 153, 154, 209) and hexabromocyclododecane (HBCD) and TSH (Eggesbø et al., 2011).

When the effects of metabolites of PBDEs were considered, Li and coworkers (2010) found in their study that OH-PBDEs showed elevated thyroid hormone activities compared to PBDEs. Hydrogen bonding was seen between OH-PBDEs and TRβ (Li et al., 2010). 172 adults, who were not exposed because of occupation but lived in a FRs production region, provided serum samples for a study. When levels of PBDEs in serum and thyroid function parameters were evaluated, it was seen that a significant and positive association was seen between serum levels of some BDE congeners (BDE-47, 100, 99) and FT3, TT3, TT4 and thyroid peroxidase antibody (Zhao et al., 2021).

In a study conducted on adult male Sprague Dawley rats, the effects of a BFRs mixture on the reproductive system and thyroid function were examined. Beside other findings of the study, when the impact on thyroid system was examined, it was seen that the highest dose led to thyroid toxicity which was seen as hypertrophy of the thyroid gland epithelium and decreased levels of serum T4. Epithelium of thyroid

gland seemed thinner at lower doses; however, there were no alterations in the hormone levels (Ernest et al., 2012). In utero exposure of CD-1 mice in an in vivo study demonstrated that PBDE-209 resulted in reduced serum T3 in offspring; however, it did not reduce T4 (Tseng et al., 2008).

Tetrabromobisphenol A, Tetrachlorobisphenol A and Hexabromocyclododecane

Tetrabromobisphenol A (TBBPA) and tetrachlorobisphenol A (TCBPA) are applied as FRs in different products including plastic products, building materials, synthetic textiles and paints, their molecular formulas are shown in Figure 2. Approximately one third of total FRs use consists of TBBPA though TBBPA has the potential of being persistent in the environment and bioaccumulate (Kitamura et al., 2002). Due to phasing out of penta- and octa- BDE-based FRs, different BFRs including TBBPA and HBCDs have been seen as alternatives to be used instead of PBDEs. Besides human tissues, marine sediments and biota are among the environmental matrices in which these compounds are detected (Kim & Oh, 2014).

Kim and Oh (2014) examined the relationship between TBBPA and HBCDs and thyroid hormones and environmental factors using serum samples of infant-mother pairs (26 infants had congenital hypothyroidism and 12 infants were healthy). It is indicated that maternal transfer of these compounds are important and a weak correlation was seen between TBBPA and thyroid hormones, positively related to fT4 while negatively related to T3 (Kim & Oh, 2014). In another study focusing on TBBPA and TCBPA, TBBPA and TCBPA were evaluated according to their thyroid hormonal-disrupting activity, and a comparison was made between these compounds and bisphenol A. It was observed that TBBPA and TCBPA caused an inhibition in the binding of T3 to the thyroid hormone receptor. In rat pituitary cell line GH3 cells, these compounds caused an increase in proliferation and stimulated growth hormone production. According to the results of this study it is concluded that TBBPA and TCBPA may function as thyroid hormone agonists (Kitamura et al, 2002).
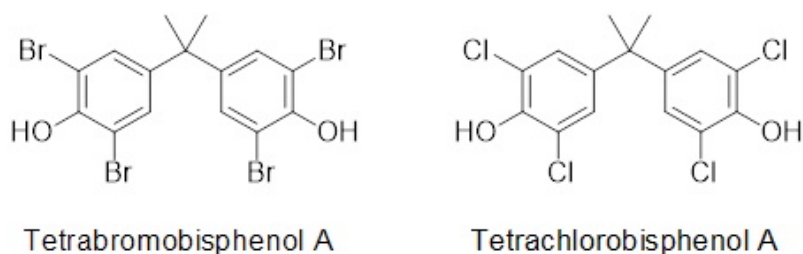

Figure 2. Structural formulas of TBBPA and TCBPA (Kitamura et al., 2002)

Phosphorus Flame Retardants

PBDEs are gradually being phased out because of their toxic effects, some of which are developmental toxicity, endocrine-disrupting effects, immunotoxicity, and neurotoxicity. Phosphorus flame retardants (PFRs) are seen as alternatives that are relatively efficient and safe (Zhang et al., 2016). PFRs consist of three main categories including organic, inorganic, and halogen-containing PFRs.

PFRs are mostly active in the solid phase of burning materials however some of them might show their action in the gas phase. Some PFRs are mixed into the polymer, while some have chemical bonds with the polymer. If the concentrations are compared, it is observed that the concentrations of PFRs in the environment seem to be higher than those of PBDEs. When exposure through indoor air is considered, exposure to concentrations of PFRs appears to be

higher than concentrations of PBDEs (Van der Veen & de Boer, 2012). Automobiles, offices, and homes are among the places in which PFRs have been found. In the US, Canadian, Asian, European, and Australian populations, detectable levels of PFR metabolites have been determined in urine. It is suggested that metabolite levels differ according to age, and higher exposures are seen in younger ages (Hoffman et al., 2017).

Organophosphate Flame Retardants

This group of FRs have taken place in the production for more than thirty years, and the application of these compounds have been increased as a result of the restriction of PBDEs, and some of the most well-known examples of OPFRs are listed in Table 2 (Castorina et al., 2017). OPFRs show their effect through increasing char formation, which results in a physical barrier between the material and the ignition source (Dishaw et al., 2014). OPFRs are classified as additive FRs (Doherty et al., 2019; Yao et al., 2021) and categorized as halogenated and non-halogenated aryl phosphates esters. They have primarily been used instead of PBDEs in the past twenty years (Wang et al., 2020). Textiles, glues, building materials, plastic products, chemicals, paints, furniture, baby products, electronic devices, and printed circuit boards are among the usage areas of OPFRs (Du et al., 2019; Ren et al., 2016; Yao et al., 2021). Therefore, they can easily leach into the environment (Ren et al., 2016; Yao et al., 2021) and have been detected in water, air, sediment, and dust (Yao et al., 2021). Preliminary data is suggesting direct human exposure to OPFRs through the measurement of dust samples and foam of baby products (Castorina et al., 2017).

Organophosphate esters (OPEs) are detected in office spaces, residential housing, and childcare environments. OPEs are particularly determined in indoor air and dust of indoor environments (Doherty et al., 2019). Routes of exposure to these compounds include inhaling dust in the indoor environment, ingesting dust or contaminated food, respiration of contaminated air, consumption of contaminated water, dermal absorption (Ding et al., 2019; Doherty et al., 2019). Metabolites of OPEs were detected in human biological matrices; placenta, urine, and breast milk can be given as examples. This may suggest that OPEs have the potential to accumulate in the human body (Ding et al., 2019). Urinary metabolites of some OPFRs are shown in Table 3.

An increasing number of studies have demonstrated that OPFRs may lead to carcinogenesis, neurotoxicity, and endocrine-disrupting activity (Yao et al., 2021). Also, it is demonstrated in experimental animal models that OPEs may lead to neurotoxicity, the disruption of the endocrine system, developmental toxicity, adverse reproductive issues, and other systemic effects (Ren et al., 2016).

As an example of OPFRs, when TDCPP is examined, it is seen that this compound is found in different environmental compartments such as indoor air, dust, and drinking water. It is mainly applied to polyurethane foams for the furniture. TDCPP is found to be relatively toxic when compared to other OPFRs according to acute toxicity results (Wang et al., 2013). TDCPP can induce different types of toxicities including developmental toxicity, nerve toxicity, hepatic toxicity, endocrine disrupting toxicity, nephron toxicity, acute toxicity and reproductive toxicity in animals (Wang et al., 2020). Also, it is suggested in an animal study that mRNA expression of thyroid hormone receptors and associated genes could be significantly upregulated due to TDCPP exposure (Wang et al., 2013).

Another example of OPFRs is TPHP, which is suggested in the literature to have the potential to interfere with thyroid function (Preston et al., 2017). According to present studies, several different toxicities are related to TPHP, including genotoxicity, reproductive toxicity, developmental toxicity, neurotoxicity, metabolic disruption, and endocrine effects (Castorina et al., 2017).

Table 2. Examples of OPFRs, their structural formula, chemical nomenclature, and abbreviated name (Doherty et al., 2019)

Structural Formula	Chemical Nomenclature	Abbreviation
	Tris (1,3-dichloro isopropyl) phosphate	TDCPP
	Tris (1-chloro-2-isopropyl) phosphate	TCIPP
	Tris (2-chloroethyl) phosphate	TCEP
	Triphenyl phosphate	TPHP

In the study by Ren and coworkers (2016) the activities of four OPEs including trimethylphosphate (TMP), TCEP, triethylphosphate (TEP), and TDCPP against thyroid hormone nuclear receptor were examined via in vitro methods. Results demonstrated that these compounds had agonistic activity towards TRβ, and TDCPP was found to be the most potent compound. In addition, it was found that these studied OPEs could fit into the ligand binding pocket of TRβ, and again TDCPP was bound more functionally. Overall, the authors suggested that disruption of the thyroid system by OPEs may occur through a mechanism involving the activation of TR (Ren et al., 2016). On the contrary to this study, in a study which took place in China, researchers used in silico, in vitro and in vivo methods in order to examine the thyroid hormone disrupting activity of nine phosphorus containing FRs. Their results suggested that some of

these compounds showed antagonistic activity on TRβ, including tributyl phosphate (TNBP), tricresyl phosphate (TMPP), TCIPP, and TDCPP. It is reported that this effect may be observed due to the direct binding of PFRs to TR. Due to the T3 antagonistic activity of TNBP and TMPP, the viability of GH3 cell lines significantly decreased in the presence of T3. The authors concluded that some PFRs have the possibility to disrupt thyroid hormones (Zhang et al., 2016).

In an *in vivo* study, domestic chicken eggs were exposed to TCPP and TDCPP and several aspects including thyroid hormone pathway and thyroid hormone levels were examined. Beside its other effects, TDCPP caused a reduction in plasma free T4 levels. The authors suggested that findings on phenotypic responses may be observed due to disruption of the thyroid hormone axis since it has a substantial role for normal growth and development of birds (Farhat

et al., 2013). In a different animal study, researchers exposed chicken embryos to OPFRs which are tris(2-butoxyethyl) phosphate (TBOEP), and TEP. Several aspects were evaluated, including thyroid hormone levels. Plasma T4 concentrations were observed to be decreased due to TEP doses (Egloff et al., 2014). An animal study conducted on fish demonstrated the possible effect of parental exposure to TDCPP on the thyroid endocrine system and the growth of zebrafish. The results showed that this compound was transferred to the offspring from adult zebrafish. In F1 larvae, a critical decrease was observed in T4 while there was a considerable increase in T3, also the transcription of some genes and expression of proteins that take part in the HPT axis were disrupted. These observations demonstrated that parental exposure to TDCPP could lead to the induction of thyroid disruption in the offspring (Ren et al., 2019). In a study using zebrafish embryos some aspects, such as whole-body concentrations of thyroid hormones and transcriptional profiles of genes that take part in the HPT axis, were evaluated. Due to TDCPP exposure, whole body T4 levels decreased and whole body T3 levels increased, which suggested the disruption of the thyroid endocrine system. Furthermore, being exposed to TDCPP led to an important increase in the transcription of genes that take part in thyroid development and thyroid hormone synthesis. According to the results of this study, it is reported that TDCPP caused endocrine disruption of the thyroid system (Wang et al., 2013). In another study, TDCPP exposure on adult zebrafish was examined, and when thyroid hormone homeostasis was evaluated, it was seen that plasma T4 and 3,5,3'-triiodothyronine levels considerably reduced in F0 females and F1 larvae/eggs. According to the results of the study, the authors concluded that TDCPP is capable of being passed on to the offspring due to the exposure of the parent and may result in the disruption of thyroid function and developmental neurotoxicity (Wang et al., 2015). In a study examining the transgenerational profile of TDCPP and polystyrene nanoplastics (PS-NPs) and

their impact on thyroid disruption in zebrafish, it was seen that when parent zebrafish were exposed to TDCPP either alone or combined with PS-NPs, it resulted in the induction of thyroid disruption in both adult zebrafish and offsprings. T4 and T3 levels decreased, and this seemed to affect the thyroid dysfunction of offspring due to transgenerational factors (Zhao et al., 2021).
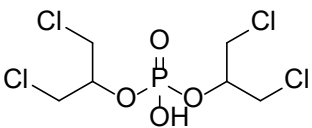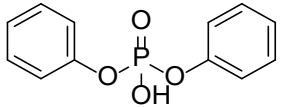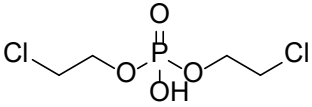
In a study which examined the effects of a different member of OPFRs, researchers used embryonic/larval zebrafish to examine the toxic effects of TPHP on thyroid endocrine system. In order to define the underlying mechanisms of such effects, rat pituitary (GH3) and thyroid follicular (FRTL-5) cell lines were used. According to the findings on the cell lines, it was suggested that TPHP stimulated thyroid hormone synthesis in the thyroid gland. Results with zebrafish larvae showed that TPHP caused important increases in T3 and T4 levels. Also, the expression of genes in thyroid hormone synthesis increased. In addition, the expression of genes that are linked with metabolism, elimination, and transport of thyroid hormones were significantly upregulated due to TPHP exposure. The authors indicated that in the early stages of zebrafish life, due to the disruption of central regulation and hormone synthesis pathways, TPHP could cause an increase in thyroid hormone levels (Kim et al., 2015).

Meeker and Stapleton (2010) investigated the association between TDCPP and TPHP and hormone levels and reproductive system parameters, and house dust was used in order to analyze the exposure. In addition to the findings about the reproductive system, the results showed that an increase in the TDCPP was related to a decrease in free T4 (Meeker & Stapleton, 2010). Prenatal urinary levels of OPE metabolites (mOPEs), concentrations of FT3, FT4, TSH, and some oxidative stress parameters in pregnant women and neonatal TSH heel blood were measured in newborns in a different study. A positive relation was seen between the concentrations of DBP and DPHP and either maternal or neonatal TSH levels; however,

no such relation was seen with maternal FT3 and FT4 levels. In addition, 8-OHdG was observed to mediate the association between neonatal TSH and DPHP, which led to the idea that DNA damage may take part in the disorder of fetal thyroid function (Y. Yao et al., 2021). Previous research has lead to the assumption that disruption of thyroid hormones caused by FRs may elevate cancer risk because increased TSH levels and chronic iodine deficiency are well-known factors on the risk of various types of cancer (Mughal & Demeneix, 2017). However, a study in which 100 females who were diagnosed with papillary thyroid cancer and 100 controls were recruited in order to determine the levels of six PFRs metabolites in urine, demonstrated a different perspective. The findings suggested that there are no associations between PFRs and papillary thyroid cancer risk (Deziel et al., 2018). Also, Hoffman and coworkers (2017) investigated whether higher exposure to FRs has an association

with an elevated risk of papillary thyroid cancer. It is reported that higher concentrations of FRs in household dust had a relationship with an increase in the risk of papillary thyroid cancer. This was observed especially for BDE-209 and TCEP. TCEP was linked with larger and more aggressive tumors, while BDE-209 was related to less aggressive tumors with smaller sizes. Overall, it was indicated that there may be an association between FRs in the home, BDE-209 and TCEP in particular, and papillary thyroid cancer (Hoffman et al., 2017b). In another study concerning the metabolites of OPFRs, the association between urinary DPHP concentrations and thyroid hormones was investigated in 51 adults. No significant link was seen between total T3, TSH, free T4 and DPHP, but it was found that particularly among women, being exposed to TPHP might be related to increased total T4 levels (Preston et al., 2017).

Table 3. Examples of urinary metabolites of several OPFRs (Doherty et al., 2019)

Structural Formula of Metabolite	Urinary Metabolite	Parent Compound
	Bis (1,3-dichloro isopropyl) phosphate (BDCIPP)	TDCPP
	Diphenyl phosphate (DPHP)	TPHP
	Bis (2-chloroethyl) phosphate (BCEP)	TCEP

CONCLUSION

Although legal regulations are made by health authorities and regulatory agencies try to prevent people from being exposed to FRs from various sources, the widespread use of these chemicals makes exposure inevitable. In this review, we focused on the effects of FRs on the thyroid system, but the potential health effects of FRs are not limited to

thyroid disruption. Exposure to FRs has been linked to various health risks, including neurological and developmental disorders, reproductive problems, and cancer. It should not be forgotten that the role of the dysfunction of hormones and hormone homeostasis, especially thyroid hormones, in the development of these diseases cannot be denied. As the use of FRs is in high amounts in all societies and new data are provided about their toxicity profiles over time, the use of some

members of these chemicals such as PBDEs has been restricted or prohibited. Moreover, although some of them were banned many years ago due to their toxic effects, they can still be found in the environment in high concentrations today. The best example of this can be given as BDE 209, which was added to Annex A of the Stockholm Convention on POPs (Persistent Organic Pollutants) in 2017. Results of experimental animal studies have shown that BDE 209 causes reductions in thyroid hormone levels and thyroid gland enlargement, and is an endocrine disruptor by causing a decrease in serum triiodothyronine.

As can be understood from this review, although there are enough scientific signals to draw our attention to the effects of FRs on the thyroid system, more human-sourced signals are needed to reach a complete conclusion. In fact, this review is intended to encourage further studies of human data on disorders of the thyroid system resulting from FRs exposure.

This review has been prepared to serve as a stimulus for further study of complex/controversial experimental animal results as well as human data. It is important to continue researching the potential hazards of FRs, and take measures to minimize exposure to these chemicals, especially for vulnerable populations such as infants, young children and pregnant women.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION STATEMENT

Determination of the Subject (İÇ), Literature Research (İİ, İÇ), Preparing the Study Text (İİ, İÇ), Reviewing the Text (İÇ,İİ)

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