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Do Flame Retardant Chemicals Increase the Risk for Thyroid Dysregulation and Cancer?

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Abstract

Purpose of review: Flame retardant chemicals (FRs) are added to consumer products to reduce fire incidence and severity; approximately ~1.5 million tons of these chemical are used annually. However, their widespread has led to their ubiquitous presence in the environment and chronic accumulation in human tissues. We summarize current trends in human FR exposure, and review recent data highlighting concerns for thyroid dysregulation and cancer risk in human populations.

Recent findings: Polybrominated diphenyl ethers (PBDEs) were once commonly used FRs, but recently were phased-out. Exposure is associated with thyroid dysregulation (mainly T4 reductions) in animals, with new work focusing on specific mechanisms of action. PBDEs also impact human thyroid regulation and are related to clinical thyroid disease, but associations appear both dose and life-stage dependent. Emerging data suggest that common alternate FRs may be more potent thyroid disruptors than their predecessors, which is particularly concerning given increasing levels of exposure.

Summary: Potential health impacts of FR are only beginning to be understood for “legacy FRs” (i.e. PBDEs), and are largely unevaluated for newer-use chemicals. Cumulatively, current data suggest impact on thyroid regulation is likely, potentially implicating FRs in thyroid disease and cancers for which thyroid dysregulation impacts risk or prognosis.

Keywords

Flame retardant chemicals; thyroid regulation; thyroid cancer

Introduction to Flame Retardants

Every year new consumer products designed to improve our daily lives enter the market. There are new computers, tablets, and phones to help us more readily share information and be more efficient with our time, and new construction materials designed to meet improved

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building codes and make buildings and homes safer and more secure. However, these new products are often treated with synthetic chemicals, which can be emitted over time and lead to widespread exposure among the general population. Flame retardant chemicals (FRs) are a prime example of chemicals intended to improve our wellbeing, but which may have unintended health consequences.

Over the past decades, a number of mandatory and voluntary flammability standards have been implemented following an increase in the number of household fires [1]. To meet these standards, various industries use FRs in their products (e.g. foam insulation used in homes and buildings, electrical circuit boards, furniture and televisions). Although the past several years have seen increased awareness about the potential health hazards of FRs and changes to policies governing their use, global consumption is expected to increase by 50% between 2012 and 2019 [2].

Polybrominated diphenyl ethers (PBDEs), once among the most commonly used FRs, have received considerable attention due to their long environmental persistence, high bioaccumulation potential and likely toxicity. They share a similar chemical structure with thyroid hormones, particularly thyroxine (T4) and triiodothyronine (T3) (Figure 1), raising concerns about their potential to alter endocrine function, a hypothesis now supported by an extensive literature linking PBDEs with thyroid hormone regulation (detailed below). These concerns lead to PBDEs being largely phased out or banned beginning in the mid-2000s, but now alternative FRs, including other brominated flame retardants (BFRs) and organophosphate flame retardants (PFRs), have become popular replacements and are being used in higher volumes (Figure 1) [3, 4].

Given the increasing use of FRs and their known exposure pathways (discussed below), it is imperative that we understand their potential health effects. For example, FRs have been implicated in several types of cancer, and more research is ongoing to elucidate potential connections [5]. This review article summarizes recently published research on the effects of several types of FRs on thyroid regulation and cancer.

Human flame retardant exposure

Many FRs are used as chemical additives, meaning that they are not chemically bonded to the polymers and resins in which they are used, and are predisposed to migrate into the environment over time. The primary pathway of human exposure to FR depends both on the compound of interest and the geographic region of study. In the U.S., exposure to PBDEs occurs mainly though incidental ingestion of indoor dust, inhalation of indoor air, and to a lesser extent, via dietary sources; however, in Europe, where some PBDE mixtures were not used, and phased out earlier, exposure is primarily dietary [4, 6, 7]. Exposure to other FRs is thought to follow similar patterns, with the relative importance of each pathway differing based on physiochemical properties [8-11].

Although the vast majority of humans have measureable levels of exposure biomarkers in their bodies, FR exposure varies geographically. People living in North America tend to have serum and breastmilk PBDEs levels that are one to two orders of magnitude higher than

those in Europe and Asia [12]. Biomonitoring data indicate that PBDE exposure increased from the 1970s through the early 2000s [12]; however, new data show that PBDE exposure may be declining [13-15]. For example, Among California women, serum PBDE levels decreased by 40% from 2008-2009 to 2011-2012 [13], likely reflecting their phase-out.

Unlike PBDEs which persist in the human body for months to years, PFRs are rapidly metabolized and excreted in urine. The recent development of assays to measure urinary biomarkers of PFR exposure has led to numerous new studies investigating exposure [16]. Although this work indicates ubiquitous exposure, it also demonstrates considerably higher levels of exposure among young children (e.g. [17-20]). For example, the levels of a urinary biomarker of TDCIPP (a PFR) were 15 times higher in young children compared to their mothers [17]. To date, PFR exposure patterns have not been evaluated over a sufficient time period to provide insights on temporal trends; however, increasing levels of exposure over the last 15 years seem probable based on the changes in average urinary metabolite concentrations reported in research conducted over the past several years (Figure 2). While biomonitoring data are not available to evaluate trends in humans, environmental data indicate that levels of BFRs are increasing; Dodson et al. reported that levels of compounds found in Firemaster® 550 (FM550), a mixture of BFRs and PFRs used as a replacement for PBDEs, increased in household dust between 2006 and 2011 [36].

FR Thyroid Toxicity

PBDEs.

Given the similarities in chemical structure between PBDEs and thyroxine (Figure 1), a number of investigations using animal models have focused on thyroid dysregulation as an endpoint of interest. Earlier work in the late 1990s and 2000s demonstrated that exposure to PBDEs in rodents, fish, and avian species all led to significant reductions in circulating levels of T4, and sometimes T3 (reviewed in [37]); however, the mechanisms responsible were unclear. Further studies suggested that both competitive binding for serum transporters (e.g. transthyretin and thyroid binding globulin) and upregulation of clearance enzymes (e.g. glucuronidases) could lead to the decreases in circulating levels [38-40]. Recent in vitro and in vivo studies have investigated more specific mechanisms and consequences. For example, a study in adult male fathead minnows found that dietary exposure to low and high doses (300-fold difference) of BDE-209 (a commonly used PBDE in plastics) led to very similar decrements in circulating T3 and T4 levels, and similar inhibition of thyroid deiodinase Type 2 activity (~50%) in the brain [41]. And a study using rats found that gestational and lactational exposure to a commercial PBDE mixture led to significant decreases in T3 and T4 in both the exposed dams and their offspring, with more severe reductions observed in the offspring at postnatal day 21 [42]. Furthermore, they observed significant increases in hepatic ethoxyresorufin-O-deethylase (EROD), pentoxyresorufin-O-dealkylase (PROD) and benzyloxyrsorufin-O-dealkylase (BROD) activity in male and female offspring, suggesting that a number of metabolic pathways, including metabolism of thyroid hormones, could be affected. While accumulation has always been thought to be a passive process, one study demonstrated that PBDEs are substrates for organic anion transporting polypeptides (OATPs) which can then actively transport PBDEs, particularly in hepatic tissue [43].

OATPs also transport thyroid hormones in select tissues, indicating another mechanism by which thyroid dysregulation can occur. In cell culture, PBDEs also have been shown to inhibit sodium iodine symporter (NIS)-mediated iodide uptake in rat thyroid follicular FRTL-5 cells [*44]. Specifically, BDE-47 (a common PBDE congener) was found to be a non-competitive inhibitor of NIS, and to decrease the expression of thyroid peroxidase.

In human liver tissues, PBDEs can be metabolized, albeit at very slow rates, to oxidative metabolites known as hydroxylated PBDEs (OH-BDEs) [45]. OH-BDEs are often detected in human serum, but at levels which are much lower than PBDEs [46-48]. OH-BDEs are even more similar in structure to thyroid hormones than PBDEs due to the addition of a hydroxyl group on the aromatic ring (Figure 1), likely explaining why OH-BDEs are often more active and potent in eliciting adverse effects on thyroid endpoints (e.g. protein binding, deiodinase inhibition, etc) [49]. Therefore, it is possible that some effects observed in vivo are associated with these more active metabolites that are not often measured in epidemiological studies.

Other BFRs.

While PBDEs have now been phased-out of manufacturing, other BFRs are still used in furniture, insulation, and electronics. Although these compounds are not as well studied as PBDEs, their chemical structure suggests they may also interfere with thyroid regulation. One BFR, tetrabromobisphenol-A (TBBPA), has been used in high volumes for several decades and is a brominated analogue of the well-characterized endocrine disruptor, bisphenol-A (BPA) [37]. Studies conducted with TBBPA demonstrate that like PBDEs, TBBPA exposure in animals leads to decreases in circulating T4 levels. TBBPA also has been shown to inhibit thyroid deiodinase Type 1 activity and strongly bind and inhibit estrogen and thyroid sulfotransferases [40, 50, 51]. More recently, the National Toxicology Program conducted a two-year carcinogenicity study with Wistar Han rats and found that exposure was significantly tied with an increase in uterine carcinomas [*52]. Further characterization of the molecular and morphologic features of these tumors suggests that uterine tumors caused by exposure to TBBA are similar to type 1 endometrial carcinomas observed in women and warrant further investigation in epidemiological studies.

FM550 contains both BFRs and PFRs, and in an in vivo study with rats, was shown to result in significant increases in dam serum thyroxine levels as well as early puberty and metabolic dysfunction in offspring exposed gestationally and lactationally [53]. Furthermore, a metabolite of one of the BFRs in FM 550 (TBMEHP) was shown to significantly decrease serum T3 levels in rats and activate a nuclear receptor (PPARg) involved in adipogenesis [54].

PFRs.

Animal studies suggest that the PFRs may exert similar or even more potent endocrine disrupting effects as the PBDEs they replaced [*55, 56]. In chronic exposure studies in zebrafish, for example, TDCIPP was found to significantly reduce plasma T4 and T3 levels in females, but not males, and was similar whether exposure occurred during embryogenesis or in adults [*57, *58]. In an another study, pubertal Sprague Dawley rats

orally exposed to TDCIPP displayed elevated serum T3 levels, increased expression of deiodinase Type 1 activity, and downregulation of thyroid nuclear receptor beta [*59]. In addition, follicular hyperplasia was observed in the rat thyroid tissue, and several genes related to thyroid hormone biosynthesis were upregulated, including thyroid peroxidase and the sodium iodide symporter. The mechanism responsible for changes in circulating levels is not clear, but increased upregulation of clearance enzymes (e.g. Uridine 5'-diphospho-glucuronosyltransferase) has been observed in vivo and in vitro and has been hypothesized to play a role [*59, 60]. Alternatively, TDCIPP may elicit some effects through nuclear receptor binding, as a recent study demonstrated that TDCIPP can antagonize TRb [61].

Triphenyl phosphate (TPHP) is another PFR used both as a FR and as a plasticizer in a variety of applications (e.g. nail polish [28]). Aqueous exposure to TPHP in zebrafish led to significant increases in tissue levels of T3 and T4 at all doses tested. In a thyroid follicular cell line (FRTL-5), TPHP exposure led to increased expression of NIS and TPO genes, suggesting stimulation of thyroid hormone synthesis [*62].

FRs and Human Thyroid Regulation

Results from epidemiologic studies investigating relationships between PBDEs and circulating thyroid hormone concentrations are consistent with animal studies, in that they indicate that exposure is associated with altered thyroid regulation; however, the direction and magnitude of effect varies considerably between species and across studies. A recent meta-analysis reported that relationships between PBDEs and thyroid hormones follow U-shaped patterns, with low levels of exposure inversely associated with thyroid hormones and higher level associated with thyroid hormone increases (TSH and TT4) [**63]. These results suggest that differences in the range of exposure between studies may explain previously observed inconsistencies. Differences in the life-stage of participants (e.g. infants vs adults) included in past studies also could be driving conflicting findings related to thyroid hormone regulation and have yet to be formally considered. The effects of PFRs on human thyroid hormone regulation have been less explored, but data suggest that higher levels of TDCIPP in the home environment are inversely associated with fT4 and among adult men [64]. Two additional studies have reported positive associations between a urinary metabolite of TPHP (i.e. diphenyl phosphate) and fT4 and TT4, [*30, 65] with greater impact observed among women [*30].

Emerging evidence indicates that the impact of FR exposure on thyroid hormone regulation is leading to clinically-significant downstream heath impacts [**66, **67]. Among Canadian women, higher levels of exposure were associated with increased prevalence of hypothyroidism, with the relationship stronger among women aged 30-51years [**66]. A recent study of U.S. women demonstrated that those with the highest levels of exposure to PBDEs also were more likely to report a previous diagnosis of thyroid disease; however, in this study findings were stronger among postmenopausal women [**67]. While these studies are not entirely consistent with respect to higher risk groups, they strongly suggest that the mechanism by which PBDEs impact thyroid disease risk could be mediated through cross-talk with estrogen. Difference between studies could be explained by differences in the case definition, although one would expect significant overlap of case definitions given

the prevalence of hypothyroidism or by differences in the range of exposure which was higher on average in the U.S. cohort compared to the Canadian cohort. To our knowledge, relationships between clinically-significant thyroid disease and exposure to replacement flame retardants have yet to be evaluated.

Clinical hypothyroidism is associated with the growth of many cancers, and hyperthyroidism has been linked to the prevalence of several types of cancer, including thyroid, suggesting that chemicals that disrupt thyroid hormone homeostasis in a significant way may contribute to cancer risk and severity [68]. However, by in large, the potential of FRs to contribute to human cancer risk or prognosis has not been evaluated in epidemiologic studies. Thyroid cancer has been investigated in a single study among participants of the Prostate, Colorectal, Lung and Ovarian Cancer Screening Trial, which reported no association between exposure to the commercial PentaBDE mixture and the odds of developing thyroid cancer [69]. The literature linking FR exposure to other cancers is equally limited, although levels of several PBDEs in residential dust recently were associated with increased risk of childhood acute lymphoblastic leukemia [70]. To our knowledge, there have been no contemporary studies examining human cancer risk and exposure to currently-used FRs, potentially because capturing relevant exposure measures for these compounds is problematic due to their rapid metabolism in the human body or to the lack of exposure biomarkers.

Conclusions

Although the last several years have seen significant advances in research related to PBDEs and thyroid regulation and disease, our understanding of their health impacts remains limited. Even less is known about the alternative FRs (e.g. PFRs and alternative BFRs), compounds for which exposure levels appear to be increasing. Given their structural similarities to PBDEs and thyroid hormones (i.e. alternative BFRs), and the limited number of animal studies suggesting alterations in circulating levels of thyroid hormones following exposure, more research is needed to understand the full extent of endocrine disruption for these compounds, and most importantly, mixtures of FRs that most people are exposed to on a daily basis.

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Key Points:

- Exposure to flame retardant chemicals, particularly newer-use flame retardants, is likely increasing.
- Evidence demonstrates that exposure to several different classes of flame retardant chemicals impacts thyroid hormone regulation and function.
- It remains unclear whether flame retardant exposure increases the risk of thyroid cancer; however, additional data are urgently needed as current evidence supports the hypothesis that flame retardant chemicals may impact the risk or severity of thyroid and other cancers.

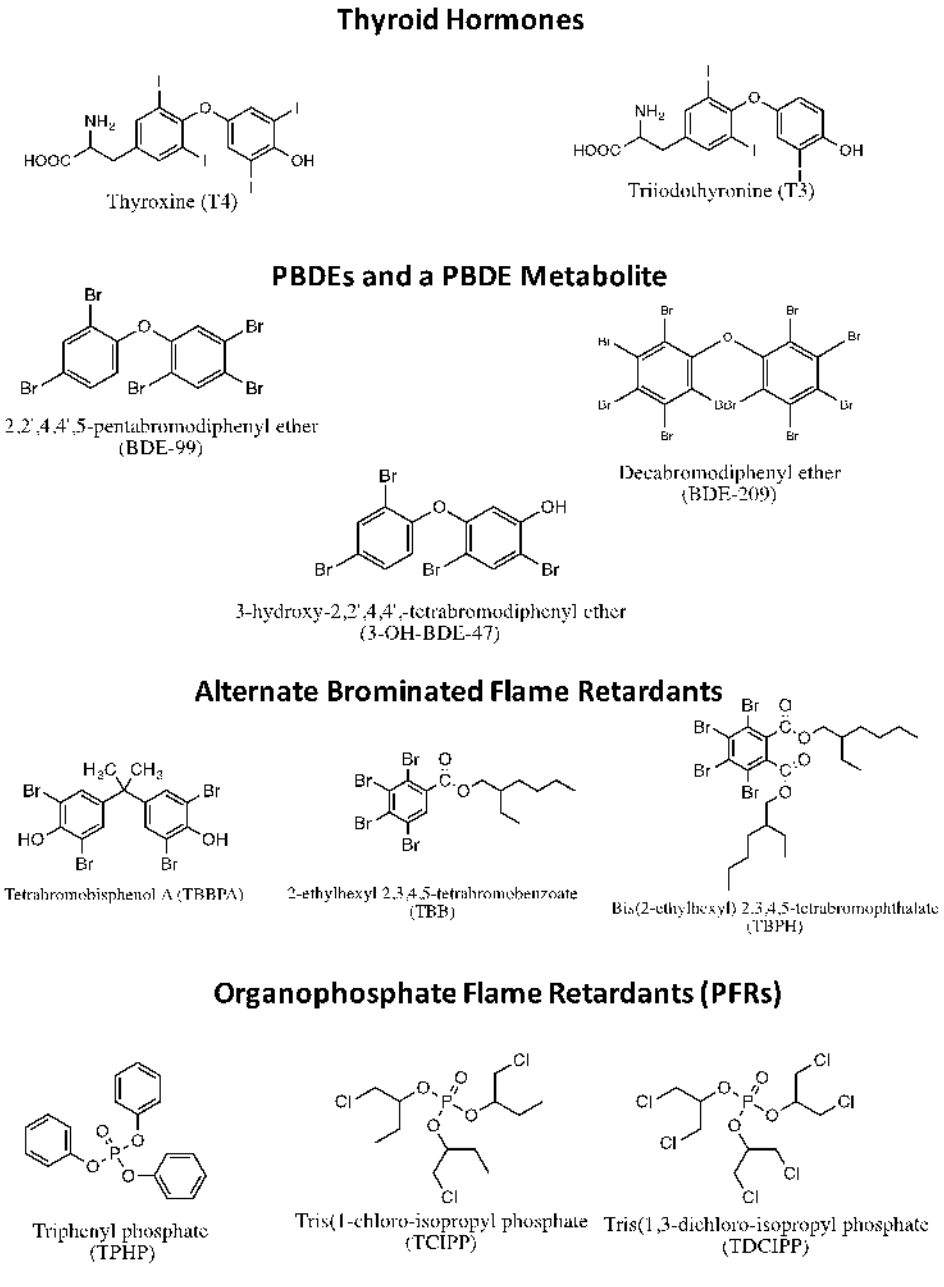

Figure 1.
Chemical structures of thyroid hormones and flame retardants.

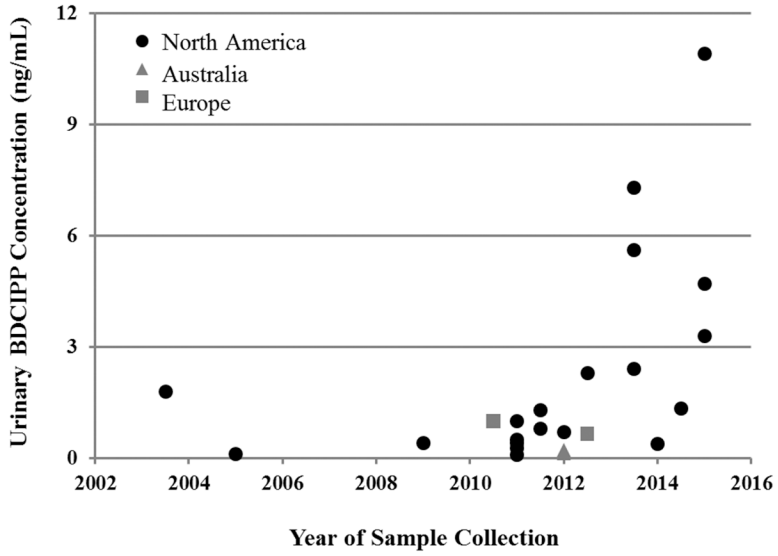

Figure 2.

PFR metabolite concentrations may be increasing over time. Temporal trends in geometric mean (or median where mean not reported) urinary BDCIPP (a PFR metabolite) concentrations in North America, Europe, and Australia [8, 16-35].