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Do Polybrominated Diphenyl Ethers (PBDEs) Increase the Risk of Thyroid Cancer?

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Abstract

An increased incidence of thyroid cancer has been reported in many parts of the world including the United States during the past several decades. Recently emerging evidence has demonstrated that polyhalogenated aromatic hydrocarbons (PHAHs), particularly polybrominated diphenyl ethers (PBDEs), alter thyroid hormone homeostasis and cause thyroid dysfunction. However, few studies have been conducted to test whether exposure to PBDEs and other PHAHs increases the risk of thyroid cancer. Here, we hypothesize that elevated exposure to PHAHs, particularly PBDEs, increases the risk of thyroid cancer and may explain part of the increase in incidence of thyroid cancer during the past several decades. In addition, genetic and epigenetic variations in metabolic pathway genes may alter the expression and function of metabolic enzymes which are involved in the metabolism of endogenous thyroid hormones and the detoxification of PBDEs and other PHAHs. Such variation may result in different individual susceptibilities to PBDEs and other PHAHs and the subsequent development of thyroid cancer. The investigation of this hypothesis will lead to an improved understanding of the role of PBDEs and other PHAHs in thyroid tumorigenesis and may provide a real means to prevent this deadly disease.

Introduction

Thyroid cancer is the most common endocrine malignancy and is one of few cancers which show a female predominance, with a fairly consistent female to male ratio of three-to-one (1). An increasing incidence of thyroid cancer has been observed in several countries and especially in the United States during the past several decades (2–6). A recent report by Davies and Welch (7) further confirmed the rapid increase in thyroid cancer incidence using SEER data.

It is possible that part of the increase could be due to changes in diagnostic procedures or increased medical attention to thyroid nodules. However, it is also possible that part of the increase in thyroid cancer incidence is real. In fact, recent animal and human studies strongly

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suggest that the emergence or change in exposure to environmental or lifestyle factors during the last 20–30 years may be responsible for the observed increase. Such environmental factors are polyhalogenated aromatic hydrocarbons (PHAHs), particularly polybrominated diphenyl ethers (PBDEs). In the following, we present evidence to support the hypothesis that exposure to polyhalogenated aromatic hydrocarbons (PHAHs), particularly polybrominated diphenyl ethers (PBDEs), is associated with an increased risk of thyroid cancer.

Human Exposure to PBDEs

Since 1965, PBDEs have been widely used as flame retardants in the United States in a variety of commercial and household products such as paints, plastics, foam furniture padding, textiles, rugs, curtains, televisions, building materials, airplanes and automobiles. The use of PBDEs has increased rapidly during the last three decades in the U.S. and other parts of the world. The production of PentaBDE, a type of PBDE that is easily absorbed by animals and human beings, almost doubled between 1992 and 2001 (8). The global demand for PBDEs reached 200,000 tons in 2003 (9). Today, half of the PBDEs and 95% of the PentaBDE used worldwide are consumed by the U.S. and Canada (10). Studies show that the PBDE body levels in the U.S. population were at least 10 times higher than in Europe and other industrialized areas (11). Furthermore, there is evidence that the body levels are continuously increasing (11). Inhalation and ingestion of PBDEs in air and food products are the major routes of human exposure (12).

The European Union banned the use of two PBDEs (Penta- and OctaBDE) in 2004 due to increasing evidence that PBDEs may result in thyroid toxicity, liver toxicity, and neurodevelopmental toxicity, and because PBDEs accumulate in human breast milk (13). The State of Washington also passed a bill banning the use of PBDEs in 2007 (14). However, these compounds, like other previously banned PHAHs (such as PCBs and organochlorine insecticides), will remain ubiquitous in the environment due to their stability, persistence, and their ability to bioaccumulate. In other words, despite increased regulation, humans will continue to be exposed to these chemicals.

PBDEs and Thyroid Function

Both animal and human studies have reported a relationship between PBDEs and thyroid hormones. Several animal studies have shown that exposure to commercial PBDE mixtures, such as penta-BDE, tetra-BDE, and octa-BDE, causes a significant decrease in serum thyroxine (T4) concentration in rodents (15–20). A Swedish study (21) reported a positive correlation between triiodothyronine (T3) and PBDE183, between T4 and both PBDE28 and PBDE100 in plasma. In addition to PBDEs, other PHAHs, such as PCBs, DDE, and HCB, have also been reported to alter thyroid hormone levels in both animal (18,22–26) and human (27–31) studies.

Although the underlying mechanism of thyroid hormone disruption by PBDEs and other PHAHs has not been fully characterized, two possible mechanisms have been suggested. First, the chemical structure of PHAHs closely resembles that of the thyroid hormones T3 and T4 (Figure 1). Thus, the hydroxylated metabolites of PHAHs may competitively bind to thyroid transport proteins and thyroid hormone receptors (32). Meerts et al. (33) showed that hydroxylated metabolites of PBDEs bind with high affinity to thyroid hormone transport protein transthyretin (TTR) in an in vitro competitive binding assay. Marsh et al. (34) found that synthesized dihydroxy-PBDEs bind to thyroid receptor proteins TR- α 1 and TR- β . Brouwer et al. (35) found a hydroxylated metabolite of PCB competitively displaces T4 from TTR in rats. Specific and competitive interactions of hydroxylated PCBs with TTR in rats and with human TTR in vitro have also been reported (36,37). Second, PBDEs can induce thyroid hormone metabolic enzyme activity, including cytochrome P450 isozymes (CYPs), uridine-5-diphosphate-glucuronyltransferases (UDPGTs), deiodinases (IDs), and sulfotransferases

(SULTs). Zhou et al. (19) showed that the reduction in circulating T3 and T4 due to exposure to PBDEs was coincident with increased activities of ethoxyresorufin-O-deethylase (EROD, a marker for CYP1A1 activity) and pentoxyresorufin-O-deethylase (PROD, a marker for CYP2B activity) in rats. The study also found that PBDEs induced hepatic UDPGTs activity, suggesting that T4 glucuronidation was one factor contributing to the reduction in serum T4 (19). Recent evidence by Pacyniak et al. (38) shows that PBDEs are activators for pregnane X receptor (PXR). The activation of PXR can induce phase I and phase II drug metabolizing enzymes resulting in enhanced elimination of thyroid hormones (39). In addition to PBDEs, PCB mixtures and certain PCB congeners, including 77, 169, 126, 156, and 153, were also found to be capable of accelerating T4 glucuronidation by inducing liver UDPGTs (19,40–46). PCB 77 and the hydroxylated metabolites of PCBs were found to be inhibitors of ID-1 (41), as well as SULTs (47), and enhancers of ID-2 (42).

In addition to altering thyroid hormone activity, PHAHs could also cause thyroid dysfunction by interfering with the hypothalamus-pituitary-thyroid (HPT) axis. It has been shown that normal thyroid function depends on a finely tuned HPT system, which is in turn supported by, and responsive to, thyroid hormone levels. Thus, as PHAHs cause a disturbance in circulating levels of thyroid hormones, it could produce a negative effect on the HPT system leading to thyroid dysfunction (48). *In vitro* and *in vivo* studies showed that exposure to PHAHs at high concentrations causes a decreased T4 concentration and a hypothyroid state (49). Exposure to congener-specific PHAHs causes a decrease in circulating thyroid hormone levels that results in an increased secretion of pituitary thyroid stimulating hormone (TSH). Furthermore, increases in TSH levels in the thyroid gland leads to hyperthyroidism (49,50).

PHAHs and Thyroid Cancer

Experimental studies show that TSH stimulation of the thyroid gland can lead to proliferative changes of follicular cell including hypertrophy and hyperplasia, as well as neoplasia in rodents (51). A 2-year feeding study with BDE209 in B6C3F1 mice showed a significant increase in the combined incidence of follicular-cell hyperplasia of the thyroid gland in both groups of treated male and female mice (52). Thus, it is biologically plausible that exposure to PBDEs and other PHAHs increases thyroid cancer risk.

Several animal studies have provided evidence linking PHAHs and thyroid cancer risk. In a hamster study on HCB carcinogenic activity (53), the male hamsters fed with HCB experienced a significantly increased risk of thyroid alveolar adenomas. A chronic toxicity and carcinogenicity study on rats showed that thyroid follicular cell adenoma was significantly increased with various commercial PCB mixtures in a non-dose-related manner, suggesting that PCBs act as indirect, nongenotoxic carcinogens (54). Vansell et al. (55) further investigated the role of PCBs as tumor promoters in the formation of thyroid tumors in rats, and found that after initiating thyroid tumors with diisopropanolnitrosamine and treating the rats with PCB mixtures as tumor promoters, thyroid carcinomas were increased among the treated animals..

Thus far, very few human studies have been conducted to evaluate the relationship between PHAHs and risk of thyroid cancer. A study by Grimalt et al. (56) investigated the association between HCB and thyroid cancer risk in an area where high levels of HCB pollution was reported from an organochlorinated-compounds factory in Catalonia, Spain. Based on data from a population-based cancer registry, the study found a significantly increased incidence rate of thyroid cancer (SIR=6.7, 95% CI,1.6–28). This result provided first evidence of a possible relationship between PHAHs, particularly HCB, and thyroid cancer risk.

Hypothesis

Based on the evidence presented above, we hypothesize that human exposure to PBDEs and other PHAHs increases the risk of thyroid cancer and that the increasing human exposure to PHAHs may be partially responsible for the increase thyroid cancer incidence during the past decade in the U.S. and around the world. Although the underline mechanisms are currently unclear, it is possible that PBDEs and other PHAHs induce abnormal proliferation in the thyroid, resulting in cells to an initial and pre-cancerous state that is vulnerable for thyroid cancer transition. In addition, genetic and epigenetic variation in metabolic pathway genes may alter the expression and function of metabolic enzymes that are involved in metabolizing endogenous thyroid hormones and detoxifying PBDEs and other PHAHs. Genetic polymorphisms in these metabolic pathway genes in the population may result in individual differences in susceptibility to thyroid cancer from exposure to PBDEs and other PHAHs.

Testing the Hypothesis

As a first step, a well-designed, population-based case-control study with a sufficient sample size would provide evidence of the potential role of PBDEs and other PHAHs in impacting the risk of thyroid cancer. A nested case-control study with a prospective design would provide further evidence of a potential causal relationship between thyroid cancer and PBDEs and other PHAHs. Genetic and epigenetic analyses of metabolic pathway genes will help to identify high risk individuals.

Conclusion

The incidence of thyroid cancer has been increasing in the U.S. and recent studies strongly suggest that part of the observed increase in thyroid cancer rates may be due to the increase in population exposure to PHAHs, particularly PBDEs. Considering the ubiquitous exposure of these compounds, and the rapid increase in thyroid cancer, there exists a need for a well-designed epidemiologic investigation to determine whether these compounds are associated with thyroid cancer risk.

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Figure 1.
Chemical structures of thyroid hormones and PHAHs