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# Exposures, Mechanisms, and Impacts of Endocrine-Active Flame Retardants

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## Abstract

This review summarizes the endocrine and neurodevelopmental effects of two current-use additive flame retardants (FRs), tris (1,3-dichloro-isopropyl) phosphate (TDCPP) and Firemaster® 550 (FM 550), and the recently phased-out polybrominated diphenyl ethers (PBDEs), all of which were historically or are currently used in polyurethane foam applications. Use of these chemicals in consumer products has led to widespread exposure in indoor environments. PBDEs and their hydroxylated metabolites appear to primarily target the thyroid system, likely due to their structural similarity to endogenous thyroid hormones. In contrast, much less is known about the toxicity of TDCPP and FM550. However, recent *in vitro* and *in vivo* studies suggest that both should be considered endocrine disruptors as studies have linked TDCPP exposure with changes in circulating hormone levels, and FM 550 exposure with changes in adipogenic and osteogenic pathways.

### Keywords

flame retardant; PBDE; endocrine disruption; thyroid; metabolite; OH-BDE; neurodevelopment; organophosphate

## Introduction

Flame retardants (FRs) are chemicals applied to a variety of consumer products, including upholstered furniture, electronic casings, building materials, and baby products, to meet flammability standards [1,2]. California technical bulletin 117 (TB 117) is flammability standard for residential furniture that requires products to meet an open flame test. Although TB117 applies only to items sold in California, it has led to the widespread use of FRs in residential furniture sold throughout the US.



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This review will focus on halogenated and organophosphate FRs (OPFRs), which interrupt the fire propagation cycle through two mechanisms (for physicochemical properties and structural information see Figure 1). Halogenated FRs, (i.e., those containing bromine and chlorine), are particularly effective at trapping free radicals and slowing fire spread in the gas phase. In contrast, the phosphate backbone in OPFRs increases char formation, creating a physical barrier between the ignition source and the material [3]. Additive FRs are applied after polymerization and are not covalently bound while reactive FRs are added during polymerization and are chemically bound to the material. Most FRs associated with human health concerns are additive and can be released from treated products over time, accumulating in indoor environments.

Halogenated FRs, such as polybrominated diphenyl ethers (PBDEs) were a dominant class of FRs in North America for several decades. PBDEs were sold as three commercial mixtures, referred to as PentaBDE, OctaBDE, and DecaBDE, in reference to the degree of bromination of the major BDE congener in each mixture. In the United States, the Penta- and OctaBDE mixtures were voluntarily phased out starting in 2005 after reports of persistence, bioaccumulation, and toxicity. The DecaBDE mixture was phased out at the end of 2013. While the use of PBDEs in products has ceased, human exposure will continue for decades due to the reservoir of existing products containing PBDEs.

Tris (1,3 dichloro-2-propyl) phosphate (TDCPP), was applied to children's pajamas during the late 1970s. Although TDCPP use in children's sleepwear was discontinued in the 1970s due to concerns of potential carcinogenicity, it became the primary FR replacement in polyurethane foam (PUF) following the phase-out of PBDEs. Firemaster® 550 (FM 550), a mixture of brominated and organophosphate flame retardants, was marketed as a less toxic and less bioaccumulative alternative to PentaBDE and was intended to be used in polyurethane foam [4]. The brominated components of FM 550 have been identified as 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB or TBB) and bis(2-ethylhexyl)-2,3,4,5-tetrabromophthalate (BEH-TEBP or TBPH), the latter of which is a brominated analog of the phthalate plasticizer di-2-ethylhexylphthalate (DEHP) [5]. The organophosphate components of FM 550 include triphenylphosphate (TPP) and numerous TPP analogs with various degrees of aryl isopropylation (referred to collectively as iTPP) [3]. Figure 1 contains a summary of these chemicals, their properties, and their structures.

## Exposure to Flame Retardants

Over the past few decades, increasing attention has focused on FR additives used in polyurethane foam (PUF) found in furniture (e.g., sofas, chairs, mattresses, etc.) and electronics (e.g., televisions) [1,2,6]. The typical application rates for FRs in PUF in furniture are approximately 4-5% by weight of the foam, and FR application in plastic casings of TVs has been measured at around 10-15% by weight [7,8]. Over the product lifetime, FRs slowly volatilize or escape from the treated materials and accumulate in indoor air and dust particles or escape to the outdoor environment (for dust measurements, see Figure 1).

Human exposure to FRs occurs through three pathways: inhalation, diet, and exposure to dust particles either through inadvertent ingestion or dermal absorption [9**,10]. Exposure to FRs is typically greater in children compared with adults [11]. FRs accumulate in indoor dust, and children, particularly toddlers, ingest more dust particles on a daily basis due to higher hand-to-mouth and object-to-mouth activities [9**,12]. In a children's exposure study, Stapleton et al. (2012b) found that PBDE residues measured on handwipes and indoor dust were the strongest predictor of PBDE levels measured in blood, supporting dust ingestion as a pathway of exposure [9**]. In contrast, studies conducted in Europe have found that diet is a primary route of exposure to PBDEs among the general population [13,14]. These regional differences in exposure pathways are likely driven by differences in flammability standards. The concentrations of the FRs most commonly used in PUF are higher in dust samples collected in the US compared with the concentrations measured in dust from some European countries that do not have residential flammability standards [15]. This likely explains why body burdens of PBDEs commonly used in PUF are higher in the US compared with European countries [16].

A few recent studies have focused on potential human exposure to TDCPP and FM 550. Similar to PBDEs, TDCPP and FM550 components (e.g. TPP), are nearly ubiquitous in dust samples, however concentrations vary widely [3]. Based on measurements of TDCPP and EH-TBB in dust collected from several European countries [17,18] it appears that exposure levels of both flame retardants would be lower in Europe relative to the US, similar to trends observed for PBDEs. This again may be a reflection of the higher use of these FRs in PUF containing furniture in the US to meet residential flammability standards. However, more studies are really needed to understand regional differences in exposure. For biomonitoring of TDCPP exposure, most studies rely on measurements of a urinary metabolite, bis (1,3-dichloro-isopropyl) phosphate (BDCPP). A few recent studies have observed some weak but significant associations between TDCPP levels in indoor dust with urinary BDCPP levels in the US populations; however, the relationships are not as strong as those observed for PBDEs, suggesting that exposure to indoor dust may not be the leading source of exposure [19**,20]. As FM 550 is a mixture of several types of FRs, some of which are used separately as FRs, measuring exposure is a bit more challenging. A recent study measured tetrabromobenzoic acid (TBBA), a metabolite of EH-TBB, in urine and suggested it would be a good biomarker of exposure to FM 550 [21]. TBBA was detected in >70% of urine samples and levels were significantly associated with EH-TBB levels measured in handwipes. These studies demonstrate that use of FRs in PUF leads to widespread exposure, particularly for children, highlighting a need to understand potential health impacts.

## Endocrine Related Effects of FRs

### 1. PBDEs

Epidemiology studies have shown that children of mothers with higher pregnancy PBDE burdens had greater risk for IQ deficits and impaired learning behaviors later in life [22-24*]. Additionally, in a series of rodent studies Viberg *et al*. found that exposure to PBDEs impaired spatial memory, learning, and altered spontaneous behavior in adult and developing rats [25-30], supporting the human observations. In addition, in a series of *in*

*vitro* experiments using a rat neuronal cell line (PC12 cells), PBDEs and their metabolites caused increased calcium release and altered neurotransmitter release suggesting disrupted neurodevelopment [31,32].

Potential mechanisms of PBDE-induced neurotoxicity have been reviewed previously [33,34], and one hypothesized mechanism for the behavioral/neurodevelopmental effects is disruption of thyroid hormone regulation during critical developmental windows. PBDEs are biotransformed into hydroxylated polybrominated diphenyl ethers (OH-BDEs) and bromophenols through oxidative metabolism in mammals [35,36]. OH-BDEs are structurally more similar to endogenous thyroid hormones, and may be responsible for some of the observed PBDE toxicity [32]. Thyroid hormones (TH) are essential for cell migration and synaptogenesis in the brain, and proper neurodevelopment overall [37,38]. Multiple studies have documented the ability of OH-BDEs to bind to thyroid transporter proteins, the thyroid nuclear receptor, and even the estrogen receptor [39*-43]. PBDE/OH-BDE receptor binding differs by the congener and by the species/assay used [39*,43-46], and PBDE effects on other nuclear hormone receptors have been recently reviewed by Ren *et al*. [47]. In rodent studies, PBDE exposure often causes a reduction in serum thyroxine (T4) or triiodothyronine (T3) [48,52], which is attributed to increased clearance of TH by metabolizing enzymes [53]. Multiple proteins, including deiodinase (DI), sulfotransferase (SULT), and uridine diphosphate-glucuronosyltransferases (UGT) enzymes, along with membrane transporters mediate the activation, metabolism, and uptake of thyroid hormones in peripheral tissues. In support of this hypothesis, rodent studies have reported enhanced expression of UGTs in animals exposed to PBDEs [53,54]. Other *in vitro* studies have reported that PBDEs and OH-BDEs alter DI and SULT activity, suggesting that there are multiple endpoints by which thyroid hormone regulation may be impacted by PBDE exposure [55,56]. Similar thyroid disruption has also been observed in fish species exposed to PBDEs, which has been recently reviewed by Noyes *et al* [57]. Human studies have observed conflicting associations between PBDE exposure and TH status, with some reporting increases in T4 and TSH, and others finding no significant associations [58,60].

In addition to PBDE effects on neurodevelopment and thyroid hormone regulation, there have also been studies observing effects between PBDE exposure and reproductive endpoints. Serum PBDE levels in US women were associated with longer time to pregnancy and reduced fecundability [61]. Dust PBDE concentrations were inversely associated with levels of free androgen, luteinizing hormone (LH), and follicle stimulating hormone (FSH), and positively associated with inhibin B and sex hormone binding globulin (SHBG) in a study of US men [62]. The summarized effects suggest that PBDEs are endocrine active (Table 1).

## 2. TDCPP

TDCPP has a much shorter half-life in tissues compared with PBDEs. In human and rodents, it is rapidly metabolized to the dialkyl phosphate, BDCPP and excreted in urine [19**, 20,63]. Until recently, few studies have evaluated the potential adverse effects of TDCPP, however, there is mounting evidence to suggest that OPFRs also affect endocrine systems (Table 1). Several studies have reported sex-dependent effects of TDCPP exposure on the

hypothalamic-pituitary-gonad (HPG) axis. Adult zebrafish exposed to TDCPP for 14 days showed elevated serum levels of estradiol (E2) and testosterone (T) in both males and females. In males, the E2/T ratio was slightly elevated, while females showed an E2/T ratio decrease. Similarly, mRNA expression of vitellogenin (VTG) was increased in males and decreased in females. Changes in serum hormone levels corresponded with increased mRNA expression of CYP17 and CYP19A, enzymes involved in sex steroid synthesis. Nearly identical results were observed in two human cell lines, MVLN and H295R, suggesting that these results are likely to be conserved across vertebrate species [64**,65]. In a similar study, a 21 day exposure in adult zebrafish decreased fecundity, egg production, the number of spawning events, fertilization, and hatching success in addition to altering serum hormone levels and mRNA expression of numerous HPG axis genes [65]. The mechanisms driving these HPG axis effects have yet to be fully elucidated, however one study reported that TDCPP and other OPFRs acted as ER antagonists, decreasing the binding of E2 to the ER in a human cell line (MVLN) [64**].

In addition to reproductive end points, TDCPP has also been implicated in dysregulation of the thyroid hormone system. In one human epidemiological study, high concentrations of TDCPP in house dust were associated with decreased T4 levels in a cohort of men [66]. Similarly, thyroid hormone levels were altered in TDCPP exposed zebrafish and chicken embryos: T3 levels increased in exposed zebrafish while T4 levels decreased in zebrafish and chicken embryos [67,68]. Early life TDCPP exposure in zebrafish was also found to alter mRNA expression of several genes that regulate thyroid function [67,69]. However, the current mechanisms responsible for these changes in circulating thyroid hormone levels are unknown.

In PC12 cells, TDCPP altered several neurodevelopmental processes, including cell replication, growth, and phenotypic differentiation [70]. These effects were similar to the effects of chlorpyrifos, an organophosphate pesticide and established developmental neurotoxicant. Importantly, TDCPP effects were equivalent to or greater than chlorpyrifos at equimolar concentrations [70]. A more recent study in PC12 cells found that TDCPP exposure altered expression (mRMA and protein) of several genes that regulate several important neurodevelopmental processes, including apoptosis, synaptogenesis, and neurite outgrowth [71*]. Notably, due to the importance of the HPT axis in neurodevelopment these two endpoints may be causally linked.

## 3. FM 550

Because FM 550 is a more recently introduced chemical product, little is known about the potential toxicity of this mixture. However, several recent studies have examined the specific toxicity of TPP, one of the organophosphates in FM 550. For example, TPP appears to elicit effects very similar to that of TDCPP. Adult zebrafish exposed to TPP for 14 or 21 days exhibited reduced fecundity, altered sex steroid levels (E2, T, and VTG) and changes in mRNA expression of HPG axis related genes [65]. *In vitro* studies reported similar effects in human cell lines [64**]. Importantly, TPP and iTPPs interact with several nuclear receptors, including the androgen receptor (AR), *in vitro*. TPP inhibited AR activity, while the effects of iTPP congeners varied [72]. In one epidemiological study, high levels of TPP in indoor

dust were associated with decreased sperm counts in men, but had no effects on T4 serum levels [66]. Although less pronounced than those for TDCPP, increased expression of thyroid receptors have also been reported with TPP exposure in zebrafish [69]. FM 550 elicited severe cardiotoxicity and heart deformities in embryonic zebrafish. These phenotypes were found to be driven by TPP and mono-iTPPs acting as arylhydrocarbon receptor 2 (AHR2) agonists [73].

Less is known about the potential toxicity of the brominated components of FM 550, EH-TBB and BEH-TEBP. BEH-TEBP is the brominated analog of bis (2-ethylhexyl) phthalate (DEHP), which is considered a known reproductive toxicant and also impairs fatty acid metabolism and thyroid hormone levels [74]. In addition, EH-TBB exhibits a similar structure to the toxic metabolite of DEHP, mono-2-ethylhexyl phthalate (MEHP). Several studies have shown that EH-TBB and BEH-TEBP can be absorbed and elicit various toxicological effects, including behavioral and endocrine-disrupting effects. In a laboratory study, fish accumulated EH-TBB and EH-TBPH via dietary exposure and demonstrated increased DNA damage in blood and liver tissue [75]. Perinatal exposure to FM 550 in rats led to accumulation of EH-TBB and BEH-TEBP in both maternal and pup tissues. Male pups in this study exhibited a significant weight increase, increased thickness of the left ventricular wall, and decreased performance in several behavioral tests compared with pups born from unexposed dams [76**]. Female pups also exhibited a significant weight increase and entered puberty earlier than pups from unexposed dams. While limited to only one study, this perinatal exposure suggests that exposure to FM 550 can alter adipogenic and developmental pathways. As a follow-up to this study, researchers also investigated the effects of FM 550 and its individual components on nuclear receptor activation [77*] and adipogenic and osteogenic pathways in cell culture [78*]. Combined results from these studies suggest that FM 550, and particularly TPP, may be eliciting an obesogenic phenotype due to activation of the nuclear receptor PPARγ and upregulation of adipogenesis, which may occur at the expense of osteogenesis. Further studies are warranted to determine if the phenotype observed in rodents is due to effects from TPP alone or from the mixture of chemicals present in FM 550.

*In vitro*, EH-TBB and BEH-TEBP have been shown to alter the production of sex hormones in human testicular cells and in a mammalian steroidogenesis assay [79,80]. While the mechanism of toxicity has not been fully elucidated, evidence indicates that EH-TBB and BEH-TEBP may affect the reproductive and thyroid systems in a manner similar to DEHP. It is important to note that EH-TBB and BEH-TEBP are likely rapidly biotransformed following absorption. Metabolism studies are limited, but in fish, rats, and human tissue preparations, EH-TBB was metabolized to form 2,3,4,5-tetrabromobenzoic acid (TBBA) and its methyl-ester analog (2,3,4,5-tetrabromomethyl benzoate) [76**,81,82]. Less is known about the potential toxicity of these metabolites, but they may be useful urinary biomarkers of exposure [83]. BEH-TEBP can be metabolized to form mono (2-ethylhexyl)-2,3,4,5-tetrabromophthalate (TBMEHP), but it appears to occur at a much slower rate than EH-TBB [81,84]. Due to biotransformation, EH-TBB will be less persistent and exhibit shorter half-lives in humans than PBDEs. However, chronic exposure to the

components of FM 550 is occurring in the indoor environment, particularly to children, and the potential health implications should be further investigated.

## Conclusions

Through increased biomonitoring research, it is quite clear that the most common flame retardants used in polyurethane foam are now ubiquitous in indoor environments, leading to chronic exposure to large populations, particularly children. With PBDEs, inadvertent ingestion of dust particles in the home environment has been established as the primary exposure pathway in the US population; however, the differences in vapor pressure and partitioning behavior of these new FRs may lead to differences in the exposure pathways, which requires further investigation. For example, given the higher vapor pressure of TDCPP relative to PBDEs, inhalation may be a more important exposure pathway than dust ingestion, yet no studies have investigated the relative contributions of each to total exposure. While PBDEs have been primarily phased out of use in consumer products, exposures to new types of FRs are increasing, and recent data suggest that both TDCPP and FM 550 are likely endocrine disruptors. Based on the studies described here, it appears that several FRs have the ability to interfere with the HPT and HPG axes. Future studies should examine health effects of these non-PBDE flame retardant chemicals during key developmental stages regulated by HPT and HPG. In addition, more research is needed on effects of exposure to environmentally relevant mixtures of these FRs, particularly during perinatal periods, to better understand the risks for human health.

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## Abbreviations

| | |
|---|---|
| **FR** | Flame Retardant |
| **PBDE** | Polybrominated Diphenyl Ether |
| **OPFR** | Organophosphate Flame Retardant |
| **TDCPP** | Tris (1,3 dichloro-2-propyl) phosphate |
| **OH-BDE** | Hydroxylated Polybrominated Diphenyl Ether |
| **EH-TBB** | 2-ethylhexyl-2,3,4,5 tetrabromobenzoate |
| **BEH-TEBP** | bis (2-ethylhexyl) tetrabromophthalate |
| **TH** | Thyroid Hormone |
| **DI** | deiodinase enzyme |
| **T4** | Thyroxine |
| **T3** | Triiodothyronine |
| **TR** | Thyroid receptor |
| **PUF** | Polyurethane foam |
| **TPP** | Triphenyl phosphate |
| **ITP** | isopropylated triphenyl phosphate |
| **FM 550** | Firemaster® 550 |
| **LH** | Leutenizing hormone |
| **FSH** | Follicle stimulating hormone |
| **TBBA** | Tetrabromobenzoic acid |

| | |
|---|---|
| **DEHP** | Di-2-ethylhexylphthalate |
| **SHBG** | Sex hormone binding globulin |
| **UGT** | Uridine diphosphate-glucuronosyltransferases |
| **SULT** | Sulfotransferase |
| **BDCPP** | Bis (1,3-dichloropropyl) phosphate |
| **HPT** | Hypothalamic-pituitary-thyroid |
| **HPG** | Hypothalamic-pituitary-gonad |
| **E2** | Estradiol |
| **T** | Testosterone |
| **VTG** | Vitellogenin |
| **AR** | Androgen receptor |
| **MEHP** | Mono-2-ethylhexyl phthalate |
| **TBMEHP** | Mono (2-ethylhexyl)-2,3,4,5-tetrabromophthalate |
| **DPP** | Diphenyl phosphate |
| **AHR2** | Arylhydrocarbon receptor 2 |

## Highlights

- Widespread exposure to flame retardants occurs in indoor environments
- Indoor exposure is associated with body burdens
- Highest human exposures occur in early development, a sensitive window
- PBDEs elicit neurodevelopmental and thyroid hormone disrupting effects
- OPFRs also appear to be endocrine active

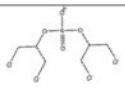
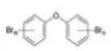
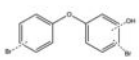
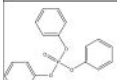
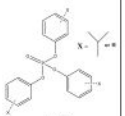
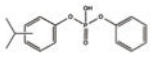
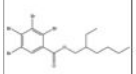
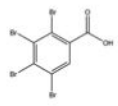
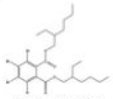
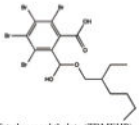
| Practical Abbreviation (structural abbreviation) (CAS #) | Chemical Name | Log $K_{ow}$ | Molecular Weight (g/mol) | Major Metabolite | [Max] in House Dust (median) *geometric mean | Estimated Production Volume | Matrix for Measuring Human Exposure | Reference |
|---|---|---|---|---|---|---|---|---|
|  TDCIPP/TDCPP [tDiCiPrP] (13674-87-8) | 2-Propanol, 1,3,-dichloro-,phosphate (3:1) | 3.27 | 430.9 |  Bis (1,3-dichloro-2-propyl) phosphate (BDCPP) | 56 μg/g (1.58 μg/g*) | 10,000,000-50,000,000 lb/yr [CDAT] | BDCPP in urine 88-3,469 pg/mL min/max GM=410 pg/mL | [19,63] |
|  PBDE (varies by congener) | Polybrominated Diphenyl Ethers | 5.83-12.67 | 328.00-136 6.85 |  Hydroxylated Polybrominated Diphenyl Ether (OH-BDE) | 0.78-30.1 μg/g (4.2 μg/g*) | Phased out | PBDE Serum 7.4-26.2 ng/g lipid (IQR) 14.9 ng/g lipid=GM | [61,86,87] |
|  TPP/TPHP [tPhP] (115-86-6) | Phosphoric Acid/ triphenyl ester/ triphenyl phosphate | 4.59 | 326.28 |  Diphenyl Phosphate (DPP) | 1,798 μg/g (6.8 μg/g*) | 10,796,422 lb/yr [CDAT] | DPP in urine 569-63,796 pg/mL min/max GM=2,974 pg/mL | [19,63] |
|  iTPP (varies by congener, 68937-41-7 for PV) (structure varies based on *ortho/meta/para* isomers of mono/di/tri ITPs) | Isopropylated triaryl phosphates | 6.16-10.52 | 368.37-452.54 |  isopropylphenyl, phenyl phosphate (IPP)* **hypothesized metabolite* | n/a | 14,904,236 lb/yr [CDAT] | n/a | n/a |
|  EH-TBB / TBB [EtH-TeBBzo] (183658-27-7) | Benzoid acid, 2,3,4,5 tetrabromo-2-ethylhexyl ester; 2-ethylhexyl 2,3,4,5 tetrabromobenzoate | 5.82 | 530.67 |  2,3,4,5 tetrabromobenzoic acid (TBBA) | 15 μg/g (133 ng/g) | Withheld [CDAT] | TBBA in urine GM= 5.6 pg/mL Max=340.6 pg/mL | [4,84] |
|  BEH-TEBP / TBPH [bEtH-TeBHt] | 1,2 Benzenedicarboxylic acid, 3,4,5,6, tetrabromo-1, 2, bis(2-ethylhexyl) ester | 9.34 | 706.14 |  Tetrabromophthalate (TBMEHP) | 10.6 μg/g (142 ng/g) | 1,000,000-10,000,000 lb/yr [CDAT] | n/a | [4,84] |

**Figure 1.**

Structures, Physical Properties and Dust Concentrations of Selected Flame Retardants. Log $K_{ow}$ values were taken from EPA's modeling software EPISuite and from a recent review [85] The Production Volume estimates were taken from EPA's Chemical Data Access Tool (CDAT), which contains the 2012 Chemical Data Reporting (CDR) information. All dust, serum, and urine measurements are reported from US cohorts.

## Table 1

Reproductive, Thyroid, and Neurodevelopmental Effects of Selected Flame Retardants.

| Chemical | Effects | References |
|---|---|---|
| PBDEs<br>OH-BDEs | Reproduction<br>• PBDEs ↑ time to pregnancy in humans<br>• PBDEs ↓ head circumference, weight, and length at birth in humans<br>• PBDEs ↑ risk for cryptorchidism in humans | [22,23,61,85] |
| | Thyroid<br>• PBDEs ↓ serum $T_4$ and $T_3$ levels in rats and ↑ serum $T_4$ levels in humans<br>• PBDEs alter expression of rat thyroid metabolizing enzymes<br>• OH-BDEs competitively bind to thyroid hormone transport proteins, metabolizing enzymes, and thyroid receptor (human and rodent cells)<br>• PBDEs cause follicular hypertrophy | [39*,42,48,53,86-88] |
| | Neurodevelopment<br>• PBDEs ↓ synaptic plasticity in rats<br>• PBDEs delay motor skills in rats and humans<br>• PBDEs ↓ IQ and developmental scores in humans<br>• OH-BDEs alter calcium signaling/neurotransmitter release (*rat cells*) | [22,24*,26,31,32,89,90] |
| TDCPP | Reproduction/Embryogenesis<br>• Altered HPG axis hormone levels (E2, T, VTG, prolactin) in fish and humans<br>• Androgen/estrogen receptor antagonist in human cells<br>• Altered expression of HPG axis related genes in fish and human cells<br>• ↓ Sperm quality in humans<br>• ↓ Fecundity in fish<br>• Altered methylation pattern of developmental genes in fish | [64**-66,91] |
| | Thyroid<br>• Altered hormone levels (↓T4, ↑T3) in fish chickens, and humans<br>• ↑ Deiodinase and thyroid stimulating hormone expression in fish<br>• ↑ mRNA expression of TRα and downstream targets | [66-69] |
| | Neurodevelopment<br>• ↓ Neuronal viability, growth, and replication and ↑ oxidative stress in rat cells<br>• Altered patterns of neurodifferentiation in rat cells<br>• Altered expression of genes that regulate apoptosis, synaptogenesis, and neurite outgrowth in rat cells | [70,71*] |
| TPP<br>iTPPs | Reproduction/Embryogenesis<br>• Altered HPG axis hormone levels (E2, T, VTG) in fish<br>• Sex-dependent changes in HPG axis related genes in fish<br>• Androgen/Estrogen receptor antagonist in rodent and human cells<br>• Sperm count ↓ in humans | [65-67,69,72,73] |

| Chemical | Effects | References |
|---|---|---|
| | • ↓fecundity in fish<br>• Cardiotoxic in developing fish | |
| | Thyroid<br>• mRNA expression genes downstream from TRα in zebrafish | [69] |
| TBB<br>TBPH | Development<br>• FM 550 ↑ body weight in rats<br>• FM 550 ↓ performance in behavioral tests in rats<br>• FM550 ↑ liver DNA strand breaks in fathead minnows<br>• FM 550 ↑ PPAR γ | [75,76**,77*,78*] |
| | Thyroid<br>• FM 550 ↑ serum T4 in rats<br>• TBMEHP ↓ serum T3 in rats | [76**,93] |
| | Reproduction<br>• TBB and TBPH cause antiandrogenic effects in the YES/YAS reporter assays<br>• TBPH ↑ production of testosterone and estrogen in primary porcine testicular cells | [79,80] |