# Role of flame-retardants as EDCs in metabolic disorders

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**Abstract**

The destructive potential of fire is well known and thus it makes sense to prevent it from happening at all, or slow its rate of spread and to be able to stop it as soon as it happens in undesirable situations. Flame retardants (FRs), as the name indicates, are chemical substances with the capability of slowing down or preventing the growth of fire, have been used in many households and industrial products for a while now. Many kinds of FRs are currently in use, such as halogenated, organophosphosphate, nitrogenous, inorganic and intumescent coatings. These products are also well known to have many side effects, including carcinogenicity, reproductive toxicity, endocrine disruption, and immune system disorders. Not all fire retardants are made or function the same way thus vary in extent of fire-retardant capacity as well as toxic side effects. Herein we succinctly describe various classes of chemical FRs, and associated biological hazards to humans. We have also described underlying mechanisms or pathways that may possibly be involved in inducing endocrine disruption leading to obesity, diabetes, oxidative stress and inflammatory responses.

**Keywords:** Biological hazard; brominated fire retardants; obesity; oxidative stress; type 2 diabetes

## Introduction

The objective of this chapter is to provide a succinct overview of a specific group of chemicals, namely flame retardants (FRs) that are known to have endocrinal disruptive properties. A number of industries producing various daily-life commodities utilize FRs for the protection of goods from being burnt out by the fire. In spite of enforcement of strict safety protocols, there is a possibility of such chemicals to escape into the environment as pollutants. Pollutants, by virtue of their nature, are chemicals that are exogenous to the environment; thus, pose a threat not only to humans but also to flora and fauna of the ecosystem (Speight, 2017). Bioremediation in the ecosystem is responsible for degrading indigenous pollutants to clear up the environment; however, chemicals such as FRs are often resistant to biodegradation, hence are hazardous (Speight and Arjoon, 2012). Some chemicals for industrial applications were designed with long half-lives for their cost-effectiveness; however ended up as environmental hazards owing to an extremely slow biodegradation (Calafat and Needham, 2007). Endocrinal system in humans and animals plays a vital role in ensuring the homeostasis. The endocrine system includes various organs consisting of endocrinal glands such as thyroid, parathyroid, adrenal, pituitary and pineal. Endocrine system also consists of single cells and small clusters of neuroendocrine cells in various organs such as the lung and gastrointestinal tract, and the paraganglia (La Perle and Dintzis, 2018). On a pharmacological viewpoint, endocrine disruption caused by the chemicals can have serious health issues including obesity, diabetes and may lead to development of severe malignancies, such as breast, prostate and testicular cancers (Diamanti-Kandarakis et al., 2009). Recent epidemiological data have shown a link between EDCs and metabolic diseases. Whilst experimental data based on *in vitro* studies and those executed on various animal models have suggested multiple possible pathways by which EDCs alter normal hormonal functions and promote metabolic disease, the exact mechanisms remain elusive (Papalou et al., 2019). To this end, our focus in this chapter will be on various types of FRs that have majorly polluted our environment and the associated human health risks pertaining to endocrinal disorders as a result of exposure to this particular pollutant group.

## Flammability and the flame retardants

Flammability is a process that involves various steps before a substance is completely destroyed by the fire. These steps include; a) preheating of the material, b) decomposition, c) ignition, and d) combustion and propagation. When an external source heats the materials, it results in an increase in the temperature of the material at a rate dependent upon the intensity of the ignition source, thermal conductivity of the material, specific heat of the material, and latent heat of fusion and vaporization of the material. An extreme rise in a material's temperature can cause decomposition of the materials and the weak bonds of materials start to break down the material into gaseous compounds. An increasing concentration of the decomposed gaseous compounds allows for sustained oxidation in the presence of an ignition source and the available oxygen rich environment makes the material ignite without the need of the ignition source, leading to the self-propagating combustion of the material (Pearce and Liepins, 1975). However, decreasing the rate of heating, ignition and combustion by the addition of specific chemicals that can physically or chemically hinder the flammability process can significantly retards the flammability and such chemicals are dubbed as FRs.

FRs have the ability to constrain, minimize or delay the spread of fire by quashing the chemical reaction in the fire. They may also work by creating an external protective layer on a material (Rahman et al., 2001), thereby serving as an insulation coating to reduce the chances of catching fire by decreasing the rate of heating. FRs have found their use in various daily-life products, for example plastics, textiles, electronics, construction materials and furnishing foams to reduce fire hazards (Patisaul et al., 2013), thus the market share of FRs is worth billions of dollars. In 2016, an estimated worldwide consumption was 2.3 million metric tons with an annual increase in production by 3 % globally (De Boer and Stapleton, 2019).

Based on their method of incorporation in polymers, FRs are either additive or reactive (Renner, 2000). Additive FRs are usually mixed or dissolved within the polymeric materials, whilst reactive type retardants are chemically attached with the polymeric materials through covalent bonds (Speight, 2017; Renner, 2000). Most of the additive FRs are volatile and may leach out in the environment easily, whereas reactive mixtures tend to leach out far less than the additive counterpart does. Due to their increasing use, widespread exposure within the environment with FRs is inevitable and many documented evidences show the presence of FRs in various environmental media, including indoor and outdoor air (Abdallah and Covaci, 2014), water (surface or groundwater) (Regnery and Püttmann, 2010), oceans (Bollmann et al., 2012) and even in human milk (Sundkvist et al., 2010). Thus, FRs present serious health risks to humans and wildlife (Legler and Brouwer, 2003).

Based on their activity, FRs work either in their vapour phase or the condensed phase, as depicted in Figure 1. Furthermore, they differ from each other by their mechanism of action and FRs may act through chemical or physical mechanisms to impede the combustion process during pre-heating, decomposition, ignition and flame propagation (Lu and Hamerton, 2002; Chen and Wang, 2010). Overall, more than 175 different types of FRs are known, which are generally classified under five major categories that include halogenated, organophosphate, nitrogenous, inorganic and intumescent coatings (Segev et al., 2009). Here, we have briefly discussed various FRs.

**[Insert Figure 1]**

***Halogenated FRs***

Halogenated FRs interrupt combustion of materials mostly in their vapor phase. Most notable halogenated FRs are those which are based on chlorine or bromine, however, brominated chemicals remained the most used FRs. Chlorinated FRs include 1,4-di(2-hydroxyethoxy)-2,3,5,6-tetrachlorobenzene (TCHQD) and 1,4-di(ethoxycarbonylmethoxy)-2,3,5,6-tetrachlorobenzene (TCHQA). Among various brominated FRs (BFRs), the most notable are polybromodiphenyl ethers (PBDPE), polybrominated biphenyls (PBBP), decabromodiphenyl ethane (DBDPEh), tetrabromobisphenol A (TBBPA), brominated epoxy resin (BEP), and hexabromocyclododecane (HBCD) (Chen and Wang, 2010).

***Organophosphate FRs***

Due to restriction in the use of PBDPE as a FR, focus has been shifted towards the use of alternative FRs commercially (Stapleton et al., 2009). Phosphorous is an abundant element, thus widely employed in various chemicals that have shown potential as FRs. For example phosphines, phosphine oxides, phosphonium compounds, phosphonates, phosphites and phosphate are widely utilized as polymeric composites for fire retardancy (Levchik and Weil, 2004).

***Nitrogenous FRs***

Some nitrogen containing compounds have also shown potential as halogen-free FRs owing to their relatively nontoxicity and high smoke suppression during combustion, and they are recyclable (Chen et al., 2006). However, very few nitrogenous RFs have made it to the market. For example, melamine in polyurethane foams and melamine cyanurate in polyamides (TROITZSCH, 1998).

More recently, nitrogen-phosphorous synergies have also been utilized as materials for flame retardancy (Liu et al., 2017; Ai et al., 2019; Li et al., 2019; Rahimi-Aghdam et al., 2020).

***Inorganic FRs***

Among various inorganic FRs, metal oxides and hydroxides are the most common. Magnesium hydroxide and aluminum hydroxide are widely used metal hydroxide FRs because of their low cost, reduced toxicity, anti-corrosive properties and smoke suppression capability (Ramazani et al., 2008; Qu et al., 2009; Kim, 2003). Other metal hydroxides that have been extensively utilized are layered double hydroxides (LDH) (Edenharter et al., 2016). More recently, organic-inorganic nano-composites based on silicon materials, such as clay (Chen and Schiraldi, 2019), kaolin (Jose et al., 2019), silsesquioxanes (Zhang et al., 2017), and silicon dioxide ($SiO_2$) (Liu et al., 2018), have been widely accepted as a new concept for flame retardation.

***Intumescent coatings***

Paints containing flame retardants are applied as thin coats thus have a limited amount of flame retardance which is insufficient to suppress fire or save the material from excessive heat. On the other hand, intumescent coatings applied as foams that swell and take a thick bubbly shape protect the material from fire or excessive heat (Rhys, 1980). Intumescent coatings are usually made of halogenated, organophosphate, nitrogenous or inorganic FRs, individually or admixture of different FRs, and are applied as surface coatings. For example, an admixture of ammonium polyphosphate (nitrogen-phosphorous synergy) and diglycidyl ether of bisphenol A (DGEBA) epoxy resin, cured by low molecular weight polyamide is as an attractive intumescent coating with effective flame retardant properties (Wang et al., 2008).

**Flame retardants as environmental pollutants**

The extensive utilization of FRs in various commodities has given them access to the environment. FRs become pollutants by contamination of wastewaters or discharges from industry, such as producers of FRs for use and/or consumers of FRs which incorporate them into other products, via leaking from products during preparation, upon breakdown of foam products or by discarding products, via percolation from landfills, incineration and reprocessing of waste products or attachment onto the surface and interstices of dust particles (Hartmann et al., 2004). Moreover, additive FRs are more prone to contaminate the environment than their reactive counterpart (Alaee and Wenning, 2002). Once a FR makes its appearance in the environment, it can spread via transportation in water or deposition into sediment or become airborne by settling upon pollens and dust particles to reach far sites from the manufacture unit. Accordingly, FRs play a profound role in contamination of soil, water, air and other ecosystems vastly (Law et al., 2008; Quintana et al., 2008; Law et al., 2006). The brominated flame retardants are employed extensively owing to their excellent performance, efficiency and cost effectiveness (Prasada Rao et al., 2011). Hence, we will further focus on the impact of FRs, with special focus on BFRs such as polybromodiphenyl ethers (PBDPEs) and polybrominated biphenyls (PBBPs) on endocrine disruption and associated health issues pertaining to diabetes, obesity, oxidative stress and inflammatory responses.

**Endocrine disruption by FRs**

According to the U.S. Environmental Protection Agency (EPA), "*an endocrine disruptor is an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process*" (Diamanti-Kandarakis et al., 2009). Several types of endocrine disruptors, also known as exogenous substances, ranging from natural to synthetic origin have been identified namely, tributyltin (TBT), diethylstilbestrol (DES), persistent organic pollutants (POPs), bisphenol A, polybrominated diphenyl ethers (PBDPEs), polybrominated biphenyls (PBBPs), parabens and phytoestrogens (Darbre, 2017). Previous studies demonstrated that the exogenous substances discharged into the environment result in injurious effects on human and animal health. Such harmful implications in humans have been observed in the form of physiological disruption of the endocrine system, which basically regulates metabolism through hormonal control to provide desired level of energy and store it in the body as a fuel (Darbre, 2017; Langford et al., 2007). Physiologically, EDCs act by various mechanisms that may alter the hormonal and homeostasis systems. This results in interference with nuclear/non-nuclear steroid hormone receptors, non-steroid neurotransmitter receptors (for example serotonin receptor, dopamine receptor, and norepinephrine receptor) and orphan receptors. Enzymatic pathways related to steroid synthesis and metabolism may also be disturbed by EDC's exposure. Various other mechanisms that are important for endocrine and reproductive systems have also witnessed disturbances by EDCs (Diamanti-Kandarakis et al., 2009).

Since our environment, indoors and outdoors, is heavily polluted by industrial/household waste and sewage, burning of litter in open places, automobile exhausts and many other sources, the exposure of humans and animals to environmental pollutants is inevitable. Increasing understanding of endocrinology and perturbation in normal hormonal functions by exposure to

EDCs is an area of great interest and debate. A plethora of pollutants found in the environment may act similarly or differently, and consequently may disturb endocrine functions, thus it is very difficult to decouple the harmful effect of a certain pollutant from others. Consequently, many issues have arisen which are crucial to understanding the mechanism of actions and concerns of exposure to EDCs. For example, exposure to EDCs at an adult level may have different consequences compared with exposure at a fetal or infancy stage. Similarly, developmental complications may not be immediately apparent, instead may appear in adulthood or during aging. Individuals, or more generally a population are rarely exposed to a single EDC, rather a mixture of EDCs are present in the environment. In many instances, a synergy of chemicals may be involved, thus making it very difficult to pin point the exact pollutant producing negative effects on health. Dose-response is another factor that requires our attention. EDCs may evolve endocrine dysfunction at a low-dose level in certain individuals or population, and similar level of manifestations may require a high-dose level in other individuals or population. Lastly, transgenerational effects may arise, where the endocrine dysfunction appears in the subsequent generations (Diamanti-Kandarakis et al., 2009). Thus, all these factors play their role in understanding endocrine disruption by EDCs.

To this end, FRs are among the EDCs that are known to be hazardous to normal functioning hormones. Hence, we have presented a general picture of various metabolic mechanisms that are affected by the EDCs including most commonly used FRs. To remain in the scope of this chapter, a succinct overview of various metabolic pathways that are believed to be involved in the prognosis of obesity, diabetes, oxidative stress and various inflammatory responses as a result of endocrine dysfunction by EDCs (particularly BFRs) is presented in the following section.

***FRs induced obesity and diabetes***

Exposure to FRs may induce endocrinal disruption leading to specific abnormalities such as obesity, diabetes mellitus or the improper functioning of thyroid hormones. Hence detailed studies are required to identify the classes of pollutant involved, sources, route of exposure and mechanistic pathway of such inappropriate modulation of the endocrine system (Tabb and Blumberg, 2006). Several authors in recent years suggest that these exogenous substances potentially affect body hormonal control, causing imbalances in the regulatory system, resulting in severe complications such as an abnormal increase in body weight or abnormal functioning of the pancreas which leads to obesity and diabetes mellitus, respectively (Darbre, 2017).

Obesity has become a critical health issue and WHO declared obesity as one of the major health issues in the world (Newbold et al., 2007). Obesity or excessive weight gain is associated with various metabolic disorders including insulin resistance, hyperinsulinemia, hypertension and hyperlipidemia. All these problems collectively contribute towards the development of type-2 diabetes mellitus (T2D) and coronary heart disease. Genetics, poor diet and insufficient exercise are considered as a prime contributor of obesity. However, recent research has indicated another unheeded factor i.e., environmental chemicals or EDCs which are a key source of air, water and food contamination (Hoppe and Carey, 2007; Baillie-Hamilton, 2002). Many EDCs have been identified to significantly alter the adipose tissue functioning in various animal models after developmental exposures, as depicted in Figure 2. Although animal models have shown compelling evidence of obesogenicity yet endocrine disruption by EDCs in humans remains elusive (Gore et al., 2015).

**[Insert Figure 2]**

We now know that BFRs have found a widespread use in daily life and a few of them have high production demands, such as PBDPEs, tetrabromobisphenol A (TBBPA), and hexabromocyclododecane (HBCD) (Vos et al., 2003). Thus, their appearance in the environment is significant and inevitable. PBDPEs are the most commonly used flame retardant over the years. Being highly lipophilic dicyclic aromatic ethers, they are easily taken up by human adipose tissue where they can reside in high concentrations (Darnerud and Risberg, 2006; Johnson-Restrepo et al., 2005; Naert et al., 2006) and may appear in the breast milk (Fängström et al., 2005; Kalantzi et al., 2004). They are also found accumulated in mammals (Ikonomou et al., 2002), fish (Allchin et al., 1999), and birds (Lindberg et al., 2004; Hoppe and Carey, 2007). PBDPEs are formulated as a mixture of penta-, octa- and deca- bromodiphenyl ethers, based on an average bromine content (Bocio et al., 2003; McDonald, 2002; Rahman et al., 2001). Depending on the position of attachment and number of bromine atoms, there are 209 PBDPE compounds, each termed congeners with a specific number (Lorber, 2008). PBDPEs are chemically and toxicologically analogous to polychlorinated biphenyls (PCBs), which are linked to hyperglycemia and dyslipidemia (Lorber, 2008). The alteration in hormonal sensitivity of adipose tissue by PBDPEs has been examined in male rat (Jones et al., 2008). The findings of this study showed marked increase in lipolysis and decrease in glucose oxidation, both of which are associated with obesity, insulin resistance, and type 2 diabetes (Lee et al., 2007) (Boden, 2003; Boden et al., 1994; Hoppe and Carey, 2007). Thus, the abnormal health issues such as disturbance of lipid and glucose metabolism may be associated with PBDPEs (Lim et al., 2008).

The diabetogenesis may be correlated to environmental pollutants. Lee and co-workers (Lee et al., 2006; Lee et al., 2007) draw attention regarding an influential factor, i.e., existence of obesity and diabetes in relation to environmental pollutants depending upon their high concentrations in blood. Figure 3 provides a mechanistic insight into various possible pathways where EDCs may act to deregulate the normal functioning of pancreas. In toxicology, theory of disruption of glucose and lipid metabolism in mammals by pollutants has been well established (Griffin et al., 2007), yet EDC's effects on human require thorough toxicological and epidemiological studies. Most of the studies using animal models are acute exposures (i.e., less than two weeks) while few are chronic ones (i.e., more than 3 months) (Azmi et al., 2005). Although these results suggest that diabetes could be exacerbated on xenobiotics exposures but still biologically plausible explanation needs to prove this correlation. In recent past, Hugo and coworkers demonstrated that BPA (a common compound used in various plastic manufacturing and as a mixture in FR epoxy resin mixtures) at environmentally relevant doses (0.1 and 1 nM) inhibited the release an adipocyte-specific hormone, namely adiponectin, which is believed to increases insulin sensitivity in humans. Consequently, an increased susceptibility to insulin resistance and obesogenicity may appear, however the exact mechanism by which BPA acts remained poorly understood (Hugo et al., 2008)

Hence detailed further investigations are required to provide substantial evidences which relates association of such health implications on exposure to environmental pollutants such as FRs (Remillard and Bunce, 2002; Allchin et al., 1999).

**[Insert Figure 3]**

***FRs induced oxidative stress and inflammatory responses***

In particular, polybrominated diphenyl ether and polybrominated biphenyls play a role in endocrine dysfunction, thus result in oxidative stress and inflammatory events (Safe and

Hutzinger, 1984; Birnbaum and Staskal, 2004). BFRs are produced and used extensively; accordingly, they are very prone to contaminate the environment, and affect human and animal health and homeostasis (De Wit, 2002). The human population is exposed primarily through food products, mostly from contaminated animal fats (Lauby-Secretan et al., 2013). They are efficiently absorbed, distributed in the body and deposited in adipose cells. They are bio-transformed or metabolized in the human body by the cytochrome P450 enzyme system, in particular, by cytochrome P450-dependent monooxygenase (Lauby-Secretan et al., 2013). They can readily cross the placental barrier and are teratogenic; thus, might have serious effects on a fetus (Legler and Brouwer, 2003). They also appear in the breast milk of exposed humans; therefore, they can further affect a breast-feeding child (Darnerud, 2003; Jacobson et al., 1984). BFRs are a group of structurally similar chemical substances, consisting of two bromine-decorated aromatic rings. This structural similarity influences the toxic capability, and numerous congener's attachment to dioxin-receptor (aryl hydrocarbon receptor – AhR). In essence, most of the highly toxic congeners play insignificant part, as they are in very minute titer. However, some exceptions might be there which avidly bind with dioxin-receptor and result in dioxin-receptor mediated carcinogenic property. Some other similar consequences pertaining to structural similarity might include neuro-behavioral effects, the imbalance in thyroid hormone homeostasis and the effects on the hepatic metabolic pathways (Darnerud, 2003).

Arene oxides and quinones, also known as highly reactive metabolic species, are produced owing to biotransformation of BFRs, are genotoxic and mutagenic. The production of reactive oxygen species (ROS), lipid peroxidation, oxidative and alkylating gene adducts can ultimately cause genotoxicity; thereby leading to the formation of oncogene which eventually initiates cancer. Thus, BFRs activate AhR which is a key to open the events associated with carcinogenesis mediated by dioxin-receptor. Due to persistent stimulation of the receptors, normal cell-cycle control and cell proliferation is lost, apoptosis is inhibited, cell-to-cell adhesion and signaling is impaired, and cell plasticity and invasiveness is increased (Lauby-Secretan et al., 2013). From this angle, BFRs may induce tumors in rodents and cholangiocarcinomas in mice and rats (Program, 1993).

TBBPA is a relatively new FR that made its entry in the market recently. Owing to its high efficiency, lipophilicity and superior stability, it has been utilized as an FR in many products (Guan et al., 2018), thus there is a great possibility TBBPA may contaminate the environment. TBBPA induces oxidative stress, as reported recently, which may leads to apoptosis in zebrafish embryos and larvae (Wu et al., 2016), while some other studies reported hepatotoxicity by the creation of reactive oxygen species (ROS) (Wang, 2014). A recent study by Guan and coworkers revealed that TBBPA induces higher levels of ROS that leads to an increased oxidative stress level, which produces detrimental effects on mitochondria thereby promoting apoptosis, as depicted in Figure 4 (Zhang et al., 2019).

**[Insert Figure 4]**

Furthermore, these compounds are also immune-toxicants and can compromise the normal functioning of the immune system. They can excite the production of inflammatory mediators. Vasiliu and co-workers in their study proved that no association exists between a brominated flame retardants serum titer and incidence of diabetes mellitus (Vasiliu et al., 2006). Although an earlier study found they may result in hypothyroidism and its associated disorders in individuals having prolonged exposure to their use (Bahn et al., 1980). A number of investigations have shown that BFRs exposure have reduced the serum levels of thyroxine (T4) hormone in rodents (Fowles et al., 1994; Zhou et al., 2001; Zhou et al., 2002; Hallgren et al., 2001). This is achieved by interfering with function and regulation of the thyroid gland, metabolism of thyroid hormone and/or transportation mechanism of thyroid hormone (Brouwer and Van den Berg, 1986). BFRs are often linked with neoplasms in the thyroid gland in rodents (Dunnick et al., 1997). Several animal studies have revealed that hypothyroidism due to BFRs is the consequence of interference with either thyroid hormone metabolism (Visser, 1996; Schuur et al., 1998; Lans et al., 1993) or thyroid hormone transport (Brouwer et al., 1998; Morse et al., 1996; Meerts, 2001).

Some BFRs can act as hormones, estrogen agonists or antagonists, and can lead to serious consequences such as reproductive disorders and carcinogenesis. To investigate antagonistic activity of BFRs to estrogen, an *in vitro* receptor-mediated reporter gene assay employing human breast cancer cells was exploited. In this assay, an estrogen receptor-mediated luciferase reporter genome complex, which was decorated with three estrogen response characters, was presented and incorporated in the genetic material of the T47Dcells (Legler et al., 1999). Introduction of xenobiotic estrogens leads to diffusion of chemical entities across the plasma membrane, attachment to the endogenous estrogen receptors, stimulation of the receptor, and ultimately, annexing to the ligand-receptor structure to estrogen response elements located in the promoter site of the luciferase gene. Thus, luciferase protein is tempted and conveniently measured by rupturing or lysing the cells, adding luciferin substrate, and quantifying light photon generation. In research studies with BFR exposure, brominated diphenyl ether-47 exhibited weak estrogenic activity compared with that of estradiol. Some polybrominated bisphenol resembling structures, such as monobromobisphenol A and dibromobisphenol A, demonstrated greater estrogenic activity than those of brominated diphenyl ethers. In other investigations, polybrominated biphenol tetrabromo bisphenol A also demonstrated attachment to estrogen receptors, and encouraged proliferation of estrogen-dependent MCF-7 cells (Körner et al., 1998; Samuelsen et al., 2001) and MtT/E2 cells (Kitamura et al., 2002). PBDPEs also exhibit antagonistic activity to estrogen when investigated *in vitro* at micromolar titers in conjunction with estradiol, including brominated diphenyl ether-153, brominated diphenyl ether-166 and brominated diphenyl ether-190 (Meerts, 2001). However, Villeneuve and co-workers could not find any compelling evidence of estrogenic potency of brominated diphenyl ether-47, brominated diphenyl ether-100 and brominated diphenyl ether-75 (Villeneuve et al., 2002). This incongruity might be attributed to estrogens that originate in human breast cancer cells (ER-CALUX) compared with the MVLN reporter gene assay (Legler et al., 1999). Only a few research investigations on exclusive estrogenic properties of brominated flame retardants *in vivo* are available. Irrespective of its *in vitro* estrogenic effects, investigations involving *in ovo* introduction of tetrabromobisphenol A have demonstrated no estrogenic activity in birds, such as quail and chicken embryos (Berg et al., 2001). This apparent deficiency in estrogenic characteristics might be owing to the prompt biotransformation of tetrabromobiphenol A *in vivo*, as revealed in both rats (Meerts, 1999) and quail (Halldin et al., 2001).

**Conclusions**

Fire has played a major role in shaping human society and is an essential component of many religions and ancient mythologies. Stopping or retarding unwanted fire has always been desired, this coupled with advances of chemical know-how, we have a variety of chemical substances for this specific task, known as fire retardants. With over 175 distinctive types, they are mostly classified as halogenated, organophosphate, nitrogenous, inorganic and intumescent coatings. Of them, the brominated flame retardants have had the most success and are also cost effective and efficient. Due to the widespread use of FRs, they have polluted our ecosystem and many of these compounds have shown significant biological activity such as disruption of the endocrine system, causing obesity and diabetes, elucidating oxidative stress and inflammatory responses. With heighten awareness of the toxicities associate with the use of FRs and given their importance, the need for more efficient, safe and cost-effective flame retardants is deepened and forthcoming new classes of improved fire retardants in the near future is imminent.

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## Figure Legends

**Figure 1:** A depiction of flame retardant mechanisms illustrating different zones. Modified with permission from (Wang et al., 2017).

**Figure 2:** Adipocyte formation pathways and various sites of action of EDCs. Reproduced with permission from (Heindel et al., 2017).

**Figure 3:** Blood glucose level regulation by pancreatic beta cells and exposed site to metabolism disruptors. Reproduced with permission from (Heindel et al., 2017).

**Figure 4:** TBBPA induces oxidative stress and mitochondrial damage leading to intracellular apoptosis. Reproduced with permission (Zhang et al., 2019).