Aerosol and Air Quality Research, 18: 2047–2063, 2018

ISSN: 1680-8584 print / 2071-1409 online
doi: 10.4209/aaqr.2018.03.0095

Levels of Non-PBDE Halogenated Fire Retardants and Brominated Dioxins and their Toxicological Effects in Indoor Environments - A Review

Yi-Chyun Hsu[1], Rachelle Anne D. Arcega[2], Yan-You Gou[3], Lemmuel L. Tayo[2], Yi-Hsien Lin[4], Sheng-Lun Lin[5,6,7], How-Ran Chao[3,8*]

[1] *Department of Environmental Engineering, Kun Shan University, Tainan 71003, Taiwan*
[2] *School of Chemical, Biological, Materials Engineering and Sciences, Mapúa University, Manila 1002, Philippines*
[3] *Emerging Compounds Research Center, Department of Environmental Science and Engineering, College of Engineering, National Pingtung University of Science and Technology, Pingtung 91201, Taiwan*
[4] *Department of Plant Medicine, College of Agriculture, National Pingtung University of Science and Technology, Pingtung 91201, Taiwan*
[5] *Department of Civil Engineering and Geomatics, Cheng Shiu University, Kaohsiung 83347, Taiwan*
[6] *Center for Environmental Toxin and Emerging-Contaminant Research, Cheng Shiu University, Kaohsiung 83347, Taiwan*
[7] *Super Micro Mass Research and Technology Center, Cheng Shiu University, Kaohsiung 83347, Taiwan*
[8] *Institute of Food Safety Management, College of Agriculture, National Pingtung University of Science and Technology, Pingtung 91201, Taiwan*

ABSTRACT

Non-polybrominated diphenyl ether (non-PBDE) halogenated fire retardants (HFRs) such as new or novel brominated fire retardants (NBFRs) and dechlorane plus (DP) have been widely spread in the environment and recognized as emerging persistent organic pollutants (POPs) in the recent years, mainly due to the continuous increase in their global demand, especially after the worldwide restrictions on PBDE use. Polybrominated dibenzo-*p*-dioxins/furans (PBDD/Fs) are the unintentional byproducts of PBDE commercial formulations in the indoor environment. Although HFRs, including NBFRs, DP, and PBDD/Fs, are ubiquitous in the indoor environment due to the large-volume release from the surfaces of consumer products, only a few *in vitro* and *in vivo* studies have addressed their toxic effects. In this review article, global data on NBFRs, including decabromodiphenyl ethane (DBDPE), 1,2-bis(2,4,6-tribromophenoxy) ethane (BTBPE), bis(2-ethylhexyl)-3,4,5,6-tetrabromophthalate (BEH-TEBP), and 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB), DP, including syn-DP and anti-DP, and PBDD/Fs in indoor aerosol and dust are summarized from recent literature. Based on the gathered data, indoor dust is a major sink for indoor contamination and is of great concern due to the fact that dust ingestion is one of the primary routes for human exposure to these chemicals. Lastly, the toxic effects of NBFRs, DP, and PBDD/Fs identified in *in vitro* and *in vivo* studies are summarized and discussed based on the current published reports. However, there is still a lack of sufficient toxicity data for assessing their risks. Future works are encouraged to focus on indoor $PM_{2.5}$-bound HFR levels to further evaluate their toxic effects on human health.

Keywords: Fire retardants; Polybrominated dibenzo-*p*-dioxins/furans (PBDD/Fs); Indoor dust; Dechlorane plus (DP); Novel brominated fire retardants (NBFRs); Toxicity.

INTRODUCTION

Halogenated fire retardants (HFRs), including polybrominated diphenyl ethers (PBDEs), dechlorane plus (DP), and new or novel brominated fire retardants (NBFRs), as well as polybrominated dibenzo-*p*-dioxins/furans (PBDD/Fs) are globally emerging persistent organic pollutants (POPs) in the indoor environment especially in the case of indoor fine particulates ($PM_{2.5}$) and indoor dust. PBDEs, DP, and NBFRs are emitted from various electronic products, building materials, furniture, mattresses, carpet pads, and textiles (Alaee *et al.*, 2003; Covaci *et al.*, 2011; Sverko *et al.*, 2011; Chao *et al.*, 2014a; Redfern *et al.*, 2017). The commercial formulation of octa-BDEs and penta-BDEs have been listed in the United Nations Stockholm Convention on Persistent Organic Pollutants Annex A in

* Corresponding author.
Tel.: +886-87703202 ext. 7517; Fax: +886-87740256
E-mail address: hrchao@mail.npust.edu.tw

2009 (Stockholm Convention, 2016) and were banned in the European Union (EU) and has been phased out in the US market on a voluntary basis since 2004 (Costa and Giordano, 2007). Decabromodiphenyl ether (BDE-209) and DP may possibly be persistent and bio-accumulative in the biota and environment through global long-range transport of air pollutants (LRTAP). These two chemicals may be candidates for Annex A and D, respectively, and are under either review or evaluation by the Stockholm Convention (Stockholm Convention, 2016). The EU and some states in the US are recommending restriction or phase out of deca-BDE use, but deca-BDE is still manufactured and widely used in most countries (Chao *et al.*, 2014a). Owing to current legislative restrictions on PBDEs, the demand for flame retardant alternatives to PBDEs has recently increased. PBDD/Fs are unintentionally released from various textiles, plastics, and building materials combustion processes, and consumer products containing BFRs, and are also present as impurities in technical mixtures of BFRs, particularly in technical mixtures of penta-BDEs, octa-BDEs, and deca-BDEs (Hanari *et al.*, 2006). Certain brominated POPs, including unintentional PBDE-by-products such as PBDD/Fs and flame-retardant alternatives to PBDEs, including NBFRs, are emerging. Thus, monitoring their levels and fate in the indoor environment is of great importance. PBDD/Fs have structural similarity with PBDEs. The process of pyrolysis of certain commercial PBDEs results in the formation and release of PBDD/Fs (Hanari *et al.*, 2006; Ren *et al.*, 2011). Despite the prohibition of the use of PBDEs, alternative BFRs, such as NBFRs, are continuously produced and applied to decrease flammability, delay ignition, and to meet the fire safety requirements for combustible materials. Global demands of NBFRs have increased due to their being replacements for banned PBDE commercial formulations such as decabromodiphenyl ethane (DBDPE) as a replacement for deca-BDE, 1,2-bis(2,4,6-tribromophenoxy) ethane (BTBPE) as a replacement for octa-BDE, and bis(2-ethylhexyl)-3,4,5,6-tetrabromophthalate (BEH-TEBP) and 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB) as a replacement for penta-BDE (Ezechiáš *et al.*, 2014; Hassan and Shoeib, 2015; Brits *et al.*, 2016; Yu *et al.*, 2016). In current global studies on HFRs related to environmental contamination, most scientists are interested in PBDE contamination, and very little attention is being paid to DP and NBFRs. There have been a significant number of PBDE studies considering PBDE contamination of foodstuff, in human specimens, soil, indoor dust, and indoor and outdoor air, including gas and total suspended particulate matter (TSP) (Wu *et al.*, 2015; Chou *et al.*, 2016; Gou *et al.*, 2016a). However, only a few studies have focused on PBDEs as respirable fine particulates ($PM_{2.5}$) (Li *et al.*, 2015b; Chao *et al.*, 2016). Unlike PBDEs, the levels and fate of DP, NBFRs, and PBDD/Fs in indoor air and dust are scarce. Contamination of PBDD/Fs and NBFRs in the indoor environment is emerging based on possibly higher levels of these chemicals indoors than outdoors and the fact that people tend to stay indoors more than 90% of the time.

Exposure to HFRs and their unintentionally released chemicals, PBDD/Fs, occurs in the indoor environment and enters the human body through several routes, including ingestion, inhalation, and dermal contact. Dietary intake and dust ingestion are probably the two main pathways for human exposure to PBDEs (Fernandes *et al.*, 2008; Johnson-Restrepo and Kannan, 2009; Chen *et al.*, 2012). Much attention has been paid to indoor dust, which is a major sink for accumulation of PBDEs and an important non-dietary pathway for human exposure to PBDEs in the indoor environment (Lorber, 2008; Kang *et al.*, 2011; Chao *et al.*, 2014b; Newton *et al.*, 2015). Until now, no reports have shown a non-dietary exposure route of non-PBDE HFRs for humans in the indoor environment. PBDEs and PBDD/Fs possibly have the same environmental fate as DP and NBFRs in the indoor environment based on their similar chemical and physical properties. Currently, most environmental scientists recognize that DP and NBFRs have the same exposure routes and bioaccumulation in the human body as PBDEs.

THE TOXICOLOGICAL EFFECTS OF NBFRS, DP, AND PBDD/FS

Epidemiological Effects of NBFRs, DP, and PBDD/Fs

NBFRs, DP, and PBDD/Fs are ubiquitously contaminating and existing in the environment and continuously bioaccumulating in biota and human bodies. Although levels of NBFRs and DP in the environmental and biological samples can be found in large amount of reports, very few studies have been made regarding their toxicity to human health particularly in the case of epidemiological studies (Ezechiáš *et al.*, 2014). For PBDD/Fs, similar with NBFRs and DP, most of the studies providing data for their toxicity focused on *in vivo* testing and are commonly compared to their chlorinated counterparts.

Toxicity Information in Cellular and Animal Studies for EH-TBB and BEH-TEBP

The USEPA (2015) evaluated EH-TBB and BEH-TEBP and found them to have low acute toxicity, low genotoxicity, moderate carcinogenicity, moderate reproductive toxicity, moderate developmental toxicity, moderate neurotoxicity, and moderate repeated dose toxicity. Most studies evaluating the toxic effects of EH-TBB or BEH-TEBP were performed using the commercial FR mixture Firemaster® 550 (FM-550) and Firemaster® BZ-54 (FM BZ-54). FM-550 consists of ~30% EH-TBB and ~8% BEH-TEBP (bromine content: 27–28%), and FM BZ-54 consists of BEH-TEBP and EH-TBB with bromine content of 54.1% (Chemtura, 2006).

Acute Toxicity

Scanlan *et al.* (2015) designed a study of acute toxicity and determined the lethal concentration 50 (LC_{50}) values of several BFRs, including FM-550, in *Daphnia magna* (daphnia) exposed to BFRs. FM-550's nominal LC_{50} value was determined to be 0.0486 mg L^{-1}, which makes it the second most toxic chemical among the tested BFRs (Scanlan *et al.*, 2015). Studies of acute toxicity in Wistar rats showed that a single dose of 5,000 mg kg^{-1} FM-550 did not produce lethality, outwardly observable effects, or

gross changes at necropsy after 15 days (USEPA, 2015). Experimental data also showed that it was possible for BEH-TEBP to be absorbed after oral exposure with a commercial mixture FM-550 (Patisaul *et al.*, 2013). BEH-TEBP was found in the tissues of pregnant Wistar rats after exposure to the commercial mixture; however, BEH-TEBP was not found in the offspring even though exposure had occurred from gestation to lactation (Patisaul *et al.*, 2013).

Developmental Toxicity

In utero or childhood exposure to FM-550 might cause developmental toxicity. In a study by Bailey and Levin (2015), adolescent *Danio rerio* (zebrafish) were exposed to 0, 1.0, or 3.0 mg L^{-1} of FM-550 for 24 h, and larvae at 4 hours post fertilization (hpf) – 5 days post fertilization (dpf) were exposed to 0.01, 0.1, or 1.0 mg L^{-1} of FM-550. The results indicate that the 1.0 mg L^{-1} dose of FM-550 caused significant malformations in larval zebrafish compared to adolescent zebrafish (Bailey and Levin, 2015). In an *in vivo* study by Patisaul *et al.* (2013), elevated body weight at a high-dose exposure (1,000 μg day^{-1}) was the most significant developmental effect of FM-550 in Wistar rats. This effect became evident prior to adolescence and continued into adulthood for both sexes. An increase in body weight, especially in the males, was interpreted as a symptom of morbid obesity (Patisaul *et al.*, 2013).

Neurotoxicity

EH-TBB might serve as an endocrine disruptor that disrupts thyroid hormone secretions or causes neurobehavioral and neurological toxicity in the prenatal, postnatal, or childhood periods. Pregnant Wistar rats were given 0 (control), 0.1 (low-dose), or 1 (high-dose) mg kg^{-1} bw^{-1} day^{-1} FM-550 in their diet through gestation day 8 until postnatal day 21 (Patisaul *et al.*, 2013). It was observed that thyroxine (T4) was significantly elevated in the exposed pregnant rats (65% higher than controls both in the high-dose and low-dose exposure); however, it was unclear why it increased with exposure, indicating that EH-TBB might be responsible for inhibiting thyroid hormone conjugating system activities responsible for clearing T4 from the body. On the other hand, T4 levels in offspring were significantly decreased (Patisaul *et al.*, 2013). A study by Bailey and Levin (2015) revealed that the most sensitive indicator of FM-550's neurobehavioral toxicity in zebrafish is shoaling behavior, which was greatly affected by all doses of FM-550 following developmental exposure. Another study also showed that perinatal exposure to FM-550 at levels below no-observed-adverse-effect level (NOAEL) of 50 mg kg^{-1} day^{-1} has effects on the neurodevelopment of Wistar rats in a sex-specific manner (Baldwin *et al.*, 2017). Behavioral outcomes of Baldwin's study showed heightened anxiety in male rats while hyperactivity was observed in female rats (Baldwin *et al.*, 2017). The contradictory result was found in Patisaul's report, which revealed heightened anxiety in female rats and not in males (Patisaul *et al.*, 2013). Pregnant Fischer rats that were gavaged with doses of 200 mg kg^{-1} (low dose) and 500 mg kg^{-1} (high dose) mono(2-ethyhexyl) tetrabromophthalate (TBMEHP), which is a metabolite of BEH-TEBP, showed that serum T3 was significantly reduced in a dose-dependent manner, but no effects were observed on serum T4 (Springer *et al.*, 2012). This decrease was attributed to TBMEHP acting as deiodinase inhibitor, preventing conversion of T4 to T3 (Springer *et al.*, 2012). This result is in accordance with a study by Patisaul *et al.* (2013), which showed BEH-TEBP to have inhibitory activities towards T4 being converted to T3 (Patisaul *et al.*, 2013).

Reproductive Toxicity

We found several *in vitro* studies showing that EH-TBB affects reproduction (Saunders *et al.*, 2013; Mankidy *et al.*, 2014). The findings of Mankidy's study showed that EH-TBB did not affect sex-steroid production; however, it affected the synthesis of aldosterone and cortisol by up-regulating *CY21A2*, which is the enzyme responsible for directing substrates away from sex hormone synthesis and towards aldosterone and cortisol synthesis in primary porcine testicular cells (Mankidy *et al.*, 2014). Another study using rat hepatoma cell line H4IIE and human adrenocarcinoma cell line H295R demonstrated EH-TBB's antagonism with both estrogen receptors (ER) and androgen receptors (AR) and elevated steroidogenesis of estrogen (Saunders *et al.*, 2013). In this *in vitro* study, the anti-androgenic response of EH-TBB was weak, which might have been due to limitations in the dosing concentration. The maximum anti-estrogenic effect (62%) was observed at 0.5 mg L^{-1} EH-TBB. BEH-TEBP was shown to produce a maximal anti-androgenic effect of 74% at 300 mg L^{-1} (Saunders *et al.*, 2013). Also, maximum exposure of 30 mg L^{-1} BEH-TEBP resulted in a moderate 1.96-fold increase in testosterone concentration compared to controls. BEH-TEBP exposure also resulted in the greatest increase of 17-β-estradiol concentrations, eliciting a maximal response of a 5.29-fold change as compared to the controls (Saunders *et al.*, 2013).

Genotoxicity

In vivo exposure to EH-TBB might be associated with DNA or chromosomal damage or differential gene expression. A study by Bearr *et al.* (2010) showed EH-TBB to induce repairable DNA damage in the liver tissues of *Pimephales promelas* (fathead minnows) via dietary exposure. During the exposure period, significant increases in DNA strand breaks from the liver cells were observed. However, such increases were not found after the recovery period (Bearr *et al.*, 2010). Scanlan *et al.* (2015) reported that daphnids (*Daphnia magna*) that were exposed to five different concentrations of FM-550 (1/2 LC_{50} (0.243 mg L^{-1}), 1/10 LC_{50} (0.0486 mg L^{-1}), where LC_{50} was equal to 0.0486 mg L^{-1}, and three additional dilutions: 0.243 μg L^{-1}, 0.0486 μg L^{-1}, and 0.0486 ng L^{-1} were used) caused differential mRNA levels at all concentrations. Exposure at 0.0486 μg L^{-1}, however, resulted in the largest number of differentially expressed genes. In all five concentrations, three genes (a trichohyalin-like protein, peroxidase, and an unknown protein) were differentially expressed, which may be useful biomarkers of exposure to FM-550 (Scanlan *et al.*, 2015).

Dietary exposure to BEH-TEBP caused a significant increase in percent tail DNA in liver tissues of fathead minnows on days 28 and 56, which was 3.4 and 6.3 times greater than in the controls, respectively (Bearr *et al.*, 2010). Several *in vivo* studies in Wistar rats exposed to BEH-TEBP through dermal and intraperitoneal injection failed to identify genotoxic effects in the form of micronucleated erythrocytes in the bone marrow (USEPA, 2015). Consistent results were also found in various *in vitro* studies using isolated human lymphocytes, where no elicited chromosomal aberrations were found (USEPA, 2015). Egloff *et al.* (2011) indicated that chicken embryonic hepatocytes (CEH) administered with BEH-TEBP did not affect the mRNA expression of any of the genes of interest in CEH and did not induce any toxic effects.

BEH-TEBP and its metabolite, TBMEHP, was shown to cause other toxic effects in *in vitro* studies. *In vitro* experiments using murine fatty acid oxidation (FAO) and NIH 3T3 L1 cells showed that TBMEHP activates both PPARα- and PPARγ-mediated gene transcription and is capable of stimulating PPARγ-mediated adipocyte differentiation (Springer *et al.*, 2012). Mankidy *et al.* (2014) showed that expression of *CYP11A1* was 3.5 and 6.6 times greater in primary porcine testicular cells exposed to 0.15 and 15.0 mg L^{-1} BEH-TEBP, respectively, relative to the controls. Cells exposed to 0.15 mg L^{-1} BEH-TEBP showed no change in the expression of *CYP19A1*, but expression of mRNA for *CYP19A1* was 3.3 times greater when the cells were exposed to 15 mg L^{-1} BEH-TEBP (Mankidy *et al.*, 2014).

Toxicity Information in the in vitro and in vivo Studies for BTBPE

Acute Toxicity

In a study by Nomeir *et al.* (1993) of Fischer 344 rats given a diet of 0.05–5% ^{14}C-labeled BTBPE for one day, a very limited amount of radioactivity of less than 1% of the ingested dose was eliminated in the urine, but of 80–100% of the dose ingested, a high percentage of fecal excretion was observed. In most of the tissues, there were undetectable levels of radiolabeled compounds. It was concluded that BTBPE gastrointestinal absorption is poor in rats. However, it was found that the adipose tissue, kidney, skin, and the thymus contained the highest concentration in rats given a diet of 500 mg kg^{-1} bw^{-1} day^{-1} ^{14}C-labeled BTBPE for a duration of 10 days. In the majority of the tissues, less than 0.01% of the dose was found (Nomeir *et al.*, 1993). In another study by Hakk *et al.* (2004), male Sprague-Dawley (SD) rats were given a single dose of 2 mg kg^{-1} bw^{-1} ^{14}C-labeled BTBPE by gavage. 100% of the dose was recovered in the feces. The same research group also demonstrated that elimination of radioactivity by bile is less than 1%, which suggests that fecal elimination was primarily from unabsorbed BTBPE. Due to this low level of absorption, the tissue levels of BTBPE were low. 72 h after being given a single dose, more than 0.1% of the dose was found only in the gastrointestinal tract and carcass. No compound-related effects were observed in rats after being fed up to 10% BTBPE in the diet, at an estimated concentration of 35 mg kg^{-1} bw^{-1} day^{-1}, for 14 days (Hakk *et al.*, 2004). Nomeir *et al.* (1993) also reported that exposure through inhalation of 5 or 20 mg L^{-1} BTBPE in the atmosphere for 21 days showed no gross pathological changes in Fischer 344 rats; however, unspecified histopathological lesions were observed in the lungs.

Reproductive and Developmental Toxicity

Egloff *et al.* (2011) studied the reproductive and developmental toxicity of BTBPE in chickens. It was found that BTBPE had no hatching effects and did not cause a delay in embryonic development.

Genotoxicity

Egloff *et al.* (2011) have also observed differences in β-actin amplification. BTBPE was also found to induce *CYP1A4/5* mRNA levels to a maximum of 115- and 18-fold at doses greater than or equal to 0.03 μM and 0.1 μM, respectively. Moreover, iodothyronine deiodinase 3 (DIO3) expression was down-regulated in a concentration-dependent manner to a maximum of 2.5-fold following exposure to BTBPE (Egloff *et al.*, 2011). In bacteria from an Ames test and in the yeast, *S. cerevisiae*, BTBPE was found to be not mutagenic according to the World Health Organization/International Programme on Chemical Safety (WHO/IPCS) evaluation (2005) for genotoxicity and carcinogenicity. No information was available for BTBPE on human health endpoints.

Toxic Effects in the in vitro and in vivo Studies for DBDPE

Acute Toxicity

In a study by Hardy *et al.* (2012), DBDPE toxicity was tested on five different aquatic species, including *Chironmus riparius* (sediment midge), *Lumbriculus variegates* (sediment oligochaete), *Oncorhynchus mykiss* (rainbow trout), daphnia, and *Pseudokirchneriella subcapitata* (algae) at 313, 625, 1,250, 2,500, and 5,000 mg kg^{-1} dry sediment concentrations of DBDPE. It was observed in midges that 313, 625, and 2,500 mg kg^{-1} of exposure caused lethargy and loss of equilibrium. Two dead midges were also observed from 2,500 and 5,000 mg kg^{-1} exposure. Larval midges were also found dead at all concentrations except at the 1,250 mg kg^{-1} exposure. However, these responses were not concentration-dependent and were therefore considered insignificant. In oligochaetes, no mortalities or sublethal effects were observed at any of the concentrations. No mortality and overt signs of toxicity were observed in trout at all concentrations after 96 hours. It was assumed that one of the replicates might have been contaminated. No toxic effects have been observed in either daphnids or algae (Hardy *et al.*, 2012). In repeated dose studies by Hardy *et al.* (2002), Hardy *et al.* (2010), and Hardy *et al.* (2011), the lowest NOAELs were the highest doses tested: 1,000 mg kg^{-1} day^{-1} (SD rats, 90-day) and 1,250 mg kg^{-1} day^{-1} (Female Crl:CD® BR VAF/Plus® rats and New Zealand White rabbits exposed prenatally).

Genotoxicity

In an *in vitro* study by Egloff *et al.* (2011), DBDPE

was administered to CEH, and it was found that DBDPE significantly up-regulated the expression of *CYP1A4/5* at 0.1 and 0.2 μM to a maximum of 29- and 53-fold, respectively. Also, iodothyronine deiodinase 1 (DIO1) mRNA levels significantly increased in CEH treated with 0.1 μM DBDPE (Egloff *et al.*, 2011). In another study, no clinical signs of toxicity were observed in male SD rats exposed to DBDPE (Wang *et al.*, 2010). It was observed that exposure to 100 mg kg^{-1} day^{-1} DBDPE did not cause any significant changes in body, liver, or kidney weight. However, a decrease in creatinine (Cr) levels and aspartate aminotransferase (AST) and alkaline phosphatase (ALP) activities, and elevated total bile acid (TBA) levels indicated that DBDPE exposure induces hepatotoxicity in rats, indicating possible oxidative stress due to the accumulation of DBDPE or its metabolites. An increase in T3 levels was also observed, and it was noted that DBDPE may alter thyroid hormone homeostasis. DBDPE was also shown to significantly increase the expression of *CYP3A2* by 1.24-fold in the liver tissue of rats (Wang *et al.*, 2010).

Toxic Effects of DP in the in vitro and vivo Studies

Acute Toxicity

A study by Dou *et al.* (2015) investigated the acute toxicity and mutagenicity of DP using luminous bacteria, *Vicia faba* and *Tetrahymena thermophile,* as test organisms. The DP concentrations used in the study were 0.591, 2.95, 14.8, 73.8, and 369 μg L^{-1} for a bioassay measuring light emission, which is representative of the bacteria's cellular metabolism. The luminosities fluctuated at around 100% after exposure to different DP concentrations, which suggests that there is no acute toxicity to luminous bacteria under these concentrations.

Neurotoxicity

An *in vivo* study by Chen *et al.* (2017) investigated the developmental neurobehavioral toxicity of DP using embryo-larval stages of zebrafish. The embryos were waterborne-exposed to DP at 15, 30, and 60 mg L^{-1} beginning from 6 hpf. Larval teratology, motor activity, motoneuron axonal growth, and muscle morphology were examined at different developmental stages. Reactive oxygen species (ROS) levels and lipid peroxidation levels (LPO) product malonaldehyde (MDA), as well as mRNA transcript expression levels of axonal growth-related and apoptosis-related genes were also analyzed to elucidate the potential mechanisms of DP-induced developmental neurobehavioral toxicity. The results showed that DP exposure significantly altered embryonic spontaneous movement, reduced touch-induced movement and free-swimming speed, and decreased the swimming speed of larvae in response to dark stimulation. These changes occurred at DP doses that resulted in no significant teratogenesis in zebrafish. Exposure to DP also significantly inhibited axonal growth of primary motoneurons and induced apoptotic cell death and lesions in the muscle fibers of zebrafish. ROS and MDA formation as well as the mRNA transcript levels of apoptosis-related genes *bax* and *caspase-3* were significantly increased at 30 and 60 mg of L^{-1} DP exposure.

Genotoxicity

DP did not show any signs of overt cytotoxicity in CEH injected with 0.01 and 3 μM DP and did not affect the mRNA expression levels of 11 transcripts, which cover mechanisms such as xenobiotic metabolism, thyroid hormone homeostasis, lipid regulation, and growth (Crump *et al.*, 2011). Available toxicity data from the USEPA HPV (2008) and the data presented by Crump *et al.* (2011) indicate that DP has minimal to no overt toxic effects on test organisms even with dose exposures exceeding its environmental prevalence. In another study, *Acipenser sinensis* (juvenile Chinese sturgeons) were injected intraperitoneally with DP at doses of 1, 10, and 100 mg kg^{-1} wet $weight^{-1}$ (ww) (Liang *et al.*, 2014). Liver proteasomes were collected after 14 days and were analyzed using two-dimensional (2D) electrophoresis. 39 protein spots out of the 740 spots that were detected were found to be altered in abundance in more than one DP exposure concentration compared to the controls. The 39 proteins were analyzed using matrix-assisted laser desorption/ionization tandem time-of-flight (MALDI-TOF-TOF), and 27 were identified using mass spectrometry (MS). Exposure to DP down-regulated signal transduction-related proteins (Ras-related protein Rab-6B and BAI1-associated protein 2-like 1b), Annexin A4 (ANXA4), and T-complex protein 1 subunit epsilon (CCT5). In contrast, increased abundance of CDHR2 and up-regulation of heat shock cognate protein 70 (HSC70) were observed following DP exposure. These differentially expressed proteins may induce cell proliferation, apoptosis, and oxidative stress in juvenile Chinese sturgeons (Liang *et al.*, 2014). Oxidative stress in other test organisms such as quail, mice, and earthworms caused by DP exposure was also investigated (Wu *et al.*, 2012; Li *et al.*, 2013; Zhang *et al.*, 2014). A recent study by Gagné *et al.* (2017) reported that DP induces oxidative stress in *Mytilus edulis* (blue mussels.) The study investigated the *in vivo* and *in vitro* effects of DP exposure on histopathology, LPO levels, cyclooxygenase (COX) activity, phagocytosis capacity and efficiency, and DNA strand breakage in the blue mussel following a 29-day exposure (0.001, 0.01, 0.1, and 1.0 μg L^{-1} DP). No significant change in hemocyte phagocytosis rate or viability was found for either *in vivo* or *in vitro* exposure. Effects of *in vivo* DP exposure included a lack of histopathological lesions found in the gonads of blue mussels at any of the doses. *In vitro* DP exposure effects included an 82% and 67% increase in LPO levels observed at 0.01 and 1.0 μg L^{-1} DP doses, respectively, a decrease in COX activity, and no significant difference in DNA strand breakage frequency measured in hemolymph cells. However, a previous study was the first to report that DP induced DNA damage in the hemocytes of blue mussels at all of the concentrations tested, which were 5.6, 56, and 100 μg L^{-1} DP (Barón *et al.*, 2016).

Dou *et al.* (2015) investigated the genotoxicity of DP using *V. faba* and *T. thermophile.* Micronucleus tests were performed on the root tips of *V. faba*, which can predict the genotoxic potential of DP with exposures at 2.4, 12, 60, 300, 1,500 μg L^{-1} DP. The test showed no significant difference between the treatment and control groups,

indicating no genotoxicity of DP. A comet assay was performed on *T. thermophile* to measure DNA damage at 2.4, 12, 60, 300, and 1,500 μg L^{-1} DP. DP concentrations ranging from 300 to 1,500 μg L^{-1} showed that high levels elicited DNA damage while lower concentrations did not. This suggests that DP may pose a potential risk at concentrations greater than or equal to 300 μg L^{-1}.

Disrupting Hormones

A study by Kang *et al.* (2016) was the first to identify DP as disruptor of thyroid hormone balance in zebrafish. There was a previous study that reported an association between thyroid hormone levels and DP concentrations in serum in mother-infant pairs near an e-waste recycling area in China (Ben *et al.*, 2014), but its endocrine disruption potential was not investigated. A study by Kang *et al.* (2016) examined oral and water-borne exposure pathways of DP to zebrafish, and toxicological responses, including oxidative stress and endocrine disruption, were evaluated. DP was delivered to adult male zebrafish via gavage feeding and was carried out twice on days 0 and 2, at up to 3 μg g^{-1} bw^{-1} ww^{-1}. Blood, liver, testis, and brain were collected on day 6 and were evaluated for oxidative damage and endocrine disruption. Hepatic catalase activity significantly increased following DP exposure, implying its oxidative damage potential. Moreover, plasma T4 concentrations increased along with up-regulation of corticotropin releasing hormone and thyroid stimulating hormone β genes in the brain. Transcriptional responses of sex hormone-related genes in the brain were also observed following DP exposure, suggesting possible sex hormone disrupting potentials of DP.

Toxic Effects of PBDD/Fs in the in vitro and in vivo Studies

Immunotoxicity and Developmental Toxicity

Olsman *et al.* (2007), Ao *et al.* (2009), Haijima *et al.* (2010), and Frawley *et al.* (2014) studied the possible toxic effects of PBDD/Fs on developmental brain and immune functions.

In female C57BL/6J mice, 2,3,7,8-TeCDD and 2,3,7,8-TeBDD showed nearly identical potencies for endpoints that detect immunotoxicity, such as thymus weight and thymocyte numbers and spleen weight and splenocyte numbers (Ao *et al.*, 2009). Additionally, PeBDD caused dose-independent inhibition of IL-5 production by splenocytes (Ao *et al.*, 2009). Another recent study presented relative potencies for immune suppression of several PBDD/Fs and their chlorinated analogs in female B6C3F1/N mice. 1PeBDF, 4PeBDF, and some chlorinated analogs suppressed the immunoglobulin M (IgM) antibody response (Frawley *et al.*, 2014). It was also reported that thyroxine transport protein (*Ttr)* and xenobiotic metabolizing enzyme (XME) gene expression, which are used to assess aryl hydrocarbon (AhR)-mediated responses, were suppressed and up-regulated, respectively, by PBDD/Fs. TriBDD, however, had no effect on antibody response. It was concluded in the study that the brominated analogs were more potent for immunotoxicity compared to their chlorinated analogs (Frawley *et al.*, 2014). AhR-mediated responses to PBDD/Fs were studied using three mammalian and one fish dioxin-specific bioassays (Olsman *et al.*, 2007). All of the tested PBDD/Fs induced AhR-mediated activity. Further, the relative potencies of individual PBDD/Fs were similar to those of their chlorinated analogs using the three mammalian cell lines under investigation. On the other hand, the relative potencies obtained using a fish cell line were comparatively lower than those in the mammalian cell lines, which could be attributed to the differences in the cell line and reporter system characteristics (Olsman *et al.*, 2007). Furthermore, pregnant C57BL/6J mice exposed to TeCDD or TeBDD *in utero* and via lactation showed nearly identical responses to fear conditioning tests and had deficits in contextual and auditory retention tests, indicating that both TeCDD and TeBDD disrupt emotional and memory functions and have similar developmental toxicities (Haijima *et al.*, 2010).

DP AND NBFRs IN THE INDOOR ENVIRONMENT

DP and NBFRs are non-PBDE HFRs that exist widely in indoor environments (Table 1) and have different physical and chemical properties showing variations in persistence and fate in such environments. The commercial formulation of DP is a highly-chlorinated fire retardant additive that has been popularly used in cable coating, computer monitors, furniture, and plastic roofing materials for over 40 years (Sverko *et al.*, 2011; Khan *et al.*, 2016; Li *et al.*, 2016). Although there is limited data on toxicity and no regulations for its use and production, DP is continuously of great concern to the USEPA due to the consideration that it is produced as a high volume chemical. DP was first identified in environmental samples from the Great Lakes in 2006 (Hoh *et al.*, 2006). Since then, DP has become an emerging POP due to its ubiquitous existence in the environment, continuous use as an alternative fire retardant in the place of PBDEs, and growing demand for global use (Sverko *et al.*, 2011). DP has similar physicochemical properties to those of PBDEs, especially in terms of its high molecular weight and log K_{ow} (Zheng *et al.*, 2010). DP has also been detected in human serum and hair samples (Cequier *et al.*, 2015; Zheng *et al.*, 2015), as well as in the indoor environment, such as in indoor dust (Cequier *et al.*, 2015; Khan *et al.*, 2016; Li *et al.*, 2016). The DP isomers (syn-DP and anti-DP) in indoor dust have been positively and significantly associated with Norwegian female adult serum, indicating that their similarities originate from the same sources and have a similar environmental fate in the indoor environment (Cequier *et al.*, 2015). Indoor dust DP has also been found to have significant positive associations with the hair of Chinese residents living in an e-waste recycling area (Zheng *et al.*, 2010). This study also showed similarity in f_{anti} ratios between hair and dust suggesting that dust ingestion might be one of the major pathways for human exposure to DP (Zheng *et al.*, 2010). According to a Pakistani study by Khan *et al.* (2016), DP levels were heavily present indoors but not outdoors, and high correlations were observed

Table 1. Global data for DP and NBFR contamination in indoor environments.

Country	Sample Type (number)	Concentration							References
		anti-DP	syn-DP	∑DP[a]	EH-TBB	BTBPE	BEH-TEBP	DBDPE	
Indoor Dust (ng g^{-1} dw)									
China (Shanghai)	Living room (n = 15)	–[b]	–	20	50	20	100	1600	Peng *et al*., 2017
	Bedroom (n = 15)	–	–	20	40	10	90	900	Peng *et al*., 2017
	Balcony (n = 7)	–	–	10	10	20	30	600	Peng *et al*., 2017
	Car (n = 4)	–	–	40	20	10	100	300	Peng *et al*., 2017
	Computer lab (n = 7)	–	–	20	40	20	300	3900	Peng *et al*., 2017
Turkey (Besiktas urban)	Home (n = 3)	–	–	–	390	82	< MDL	–	Kurt-Karakus *et al*., 2017
	Office (n = 6)	–	–	–	< MDL	770	86	–	Kurt-Karakus *et al*., 2017
Turkey (Bahcesehir, sub-urban)	Home (n = 4)	–	–	–	330	110	< MDL	–	Kurt-Karakus *et al*., 2017
	Office (n = 3)	–	–	–	950	130	< MDL	–	Kurt-Karakus *et al*., 2017
Turkey (Gokturk, rural)	Home (n = 3)	–	–	–	< MDL	160	< MDL	–	Kurt-Karakus *et al*., 2017
United Kingdom	House (n = 5)	–	–	–	5.8	15	320	157	Al-Omran *et al*., 2016
Pakistan (Kashmir)	House (n = 5)	0.34	5.92	–	–	–	–	5.51	Khan *et al*., 2016
Pakistan (Chitral)	House (n = 5)	4.67	4.19	–	–	–	–	580.2	Khan *et al*., 2016
Pakistan (Swat)	House (n = 5)	0.49	0.75	–	–	–	–	17.67	Khan *et al*., 2016
Pakistan (Gujranwala)	House (n = 5)	2.62	5.01	–	–	–	–	72.25	Khan *et al*., 2016
Pakistan (Gujranwala rural)	House (n = 5)	0.1	0.26	–	–	–	–	24.26	Khan *et al*., 2016
Pakistan (Gujrat industrial)	House (n = 5)	11.15	5.56	–	–	–	–	1319.97	Khan *et al*., 2016
Pakistan (Gujrat rural)	House (n = 5)	0.06	0.09	–	–	–	–	82.05	Khan *et al*., 2016
Pakistan (Faisalabad industrial)	House (n = 7)	0.5	0.87	–	–	–	–	125.29	Khan *et al*., 2016
Pakistan (Faisalabad rural)	House (n = 7)	30	0.73	–	–	–	–	41.66	Khan *et al*., 2016
Canada	House (n = 40)	5.6	2.6	–	96	7.4	–	–	Fan *et al*., 2016
	House (n = 40)	5.9	2.5	–	75	8	–	–	Fan *et al*., 2016

[a] Sum of all DPs, including syn- and anti-DP.
[b] Not analyzed.

Table 1. Global data for DP and NBFR contamination in indoor environments. (cont'd).

Country	Sample Type (number)	Concentration							References
		anti-DP	syn-DP	∑DP[a]	EH-TBB	BTBPE	BEH-TEBP	DBDPE	
Spain (Barcelona)	House (n =5)	–[b]	–	–	< MDL	21.4	21.4	307	Cristale *et al*., 2016
	Schools (n = 4)	–	–	–	< MDL	< MDL	150	< MDL	Cristale *et al*., 2016
	Theatres (n = 3)	–	–	–	< MDL	19.9	344	647	Cristale *et al*., 2016
	Res. Institution (n = 2)	–	–	–	8.1	24.6	189	596	Cristale *et al*., 2016
United Kingdom	Kitchen (n = 30)	–	–	–	4.1	1.2	36	74	Kuang *et al*., 2016
	Living room (n = 30)	–	–	–	12	4.5	75	120	Kuang *et al*., 2016
Hong Kong	Kindergartens	0.94–6.6	0.32–2.2	–	–	–	–	–	Deng *et al*., 2016
	House	2.9–5.4	0.70–1.7	–	–	–	–	–	Deng *et al*., 2016
Canada	House (n = 40)	5.6	2.6	–	–	–	–	–	Fan *et al*., 2016
	House (n = 40)	5.9	2.5	–	–	–	–	–	Fan *et al*., 2016
Egypt	House (n = 17)	0.01	0.3	–	0.8	0.2	0.1	–	Hassan and Shoeib, 2015
	Workplaces (n = 5)	1.3	0.3	–	7.1	1.3	0.09	–	Hassan and Shoeib, 2015
	Cars (n = 9)	2.4	1	–	5.8	2.4	–	–	Hassan and Shoeib, 2015
China	House (n=81)	2.8	1	–	–	–	–	–	Li *et al*., 2015
Japan	House (n = 10)	–	–	–	–	–	–	220	Mizouchi *et al*., 2015
	Elementary school (n =18)	–	–	–	–	–	–	50	Mizouchi *et al*., 2015
China (Longtang)	E-waste recycling (n = 9)	80	23	–	7.5	28	88	1160	Zheng *et al*., 2015
	E-waste recycling (n = 7)	1150	401	–	29	148	160	10900	Zheng *et al*., 2015
	E-waste recycling (n = 13)	2100	1000	–	–	101	7120	26300	Zheng *et al*., 2015
China (Dali)	E-waste recycling (n = 13)	250	146	–	36	40	193	6400	Zheng *et al*., 2015
China (Guiyu)	E-waste recycling (n = 14)	2378	1050	–	60	3870	49	45400	Zheng *et al*., 2015

[a] Sum of all DPs, including syn- and anti-DP.
[b] Not analyzed.

Table 1. Global data for DP and NBFR contamination in indoor environments. (cont'd).

Country	Sample Type (number)	Concentration							References
		anti-DP	syn-DP	∑DP[a]	EH-TBI	BTBPE	BEH-TEBP	DBDPE	
Egypt (Cairo)	House (n = 17)	–[b]	–	–	0.8	0.2	0.1	–	Hassan and Shoeib, 2015
	Workplaces (n =5)	–	–	–	7.1	1.3	0.09	–	Hassan and Shoeib, 2015
	Cars (n = 9)	–	–	–	5.8	2.4	–	–	Hassan and Shoeib, 2015
China	Office (n = 23)	–	–	–	22.5	8420	321	2320	Cao *et al*., 2014
	Office (n = 17)	–	–	–	14.3	47.5	315	4620	Cao *et al*., 2014
	Office (n = 16)	–	–	–	15	13.6	508	3010	Cao *et al*., 2014
Pakistan	Universities (n = 16)	–	–	–	–	9.5	–	60	Ali *et al*., 2014
	Clothing stores (n = 15)	–	–	–	–	6.5	–	31	Ali *et al*., 2014
	Electronics stores (n = 30)	–	–	–	–	17	–	140	Ali *et al*., 2014
United States (California)	Houses (n = 59)	–	–	–	377	22.3	186	82.8	Brown *et al*., 2014
	Fire stations (n = 27)	–	–	–	2687	28.4	2076	161	Brown *et al*., 2014
China	Houses (n = 81)	–	–	–	130	11	120	1100	Qi *et al*., 2014
Norway (Oslo)	Residential living rooms (n = 47)	–	–	–	2.54	3.76	78.5	147	Cequier *et al*., 2014.
	School classrooms (n = 6)	–	–	–	3.32	6.55	103	156	Cequier *et al*., 2014.
Germany (Munich)	Houses (n = 20)	–	–	–	4.2	10	436	323	Fromme *et al*., 2014
United States (Washington)	Houses (n = 20)	–	–	–	190	70	115	173	Schreder *et al*., 2014
Indoor Air (pg m^{-3})									
Turkey (Besiktas urban)	Home (n = 3)								
	Office (n = 6)	–	–	–	150	< MDL	2.80	–	Kurt-Karakus *et al*., 2017
		–	–	–	480	< MDL	140	–	Kurt-Karakus *et al*., 2017
Turkey (Bahcesehir, sub-urban)	Home (n = 4)								
	Office (n = 3)	–	–	–	840	1.50[b]	3	–	Kurt-Karakus *et al*., 2017
		–	–	–	26	< MDL	2.5	–	Kurt-Karakus *et al*., 2017

[a] Sum of all DPs, including syn- and anti-DP.
[b] Not analyzed.

between PBDEs and DP in both indoor and outdoor dust as well as in indoor and outdoor dust in different altitudinal zones. Wang *et al.* (2011) indicated that DP is positively related to BFRs including PBDEs in house dust collected from e-waste recycling areas, but no correlations were found in urban areas in south China. In constrast, there were no correlations between levels of DP and PBDEs in the same indoor dust samples from Canada (Zhu *et al.*, 2007). Li *et al.* (2015a) revealed indoor dust DP in urban areas to be almost 2-fold higher than in rural areas, and f_{syn} was siginificantly correlated with f_{syn} latitude and longitude calculated as the ratio of syn-DP to ΣDP in an indoor dust DP survey in China. As to the individual distribution of the isomers to total DP concentrations, higher contamination levels of anti-DP compared with syn-DP were found in house dusts from Hong Kong, China, and Canada (Li *et al.*, 2015a; Zheng *et al.*, 2015; Deng *et al.*, 2016; Fan *et al.*, 2016). In contrast, syn-DP exhibited higher levels than anti-DP in Egyptian house dusts (Hassan and Shoeib, 2015). However, in Pakistan, differences in DP contamination were observed in house dusts sampled from different areas (Khan *et al.*, 2016). Additionally, house dust samples from e-waste recycling areas have also been shown to exhibit higher DP contamination compared to samples from non-e-waste recycling areas (Zheng *et al.*, 2015). Furthermore, workplaces and cars in Egypt were found to exhibit higher DP levels compared to houses (Hassan and Shoeib, 2015) while kindergarten schools exhibited lower DP contamination compared to houses in Hong Kong (Deng *et al.*, 2016).

NBFRs are also known to widely exist, and several researchers worldwide have shown interest in the detection of contamination levels in the indoor environment. Chinese studies have reported levels of NBFR in indoor dusts collected from houses, offices, e-waste recycling sites, cars, and other public areas (Cao *et al.*, 2014; Qi *et al.*, 2014; Zheng *et al.*, 2015; Peng *et al.*, 2017). Human activities and geographical distribution influences indoor NBFR pollution levels (Qi *et al.*, 2014). Indoor dust from urban areas and public buildings showed significantly higher levels of NBFRs than rural areas and family homes indicating the different applications of NBFRs (Qi *et al.*, 2014). A temporal trend study on NBFRs revealed that NBFR concentrations are relatively stable during any season and that human activities do not affect seasonal variations in NBFR contamination (Cao *et al.*, 2014). In e-waste recycling areas, different pollutant patterns have been observed at different sites, which could be attributed to the different kinds of e-waste dismantled during recycling activities at each site (Zheng *et al.*, 2015). As to human exposure, Zheng *et al.* (2015) and Peng *et al.* (2017) both reported that human exposure to NBFRs via dust ingestion is higher in toddlers compared with adults. In these studies (Cao *et al.*, 2014; Qi *et al.*, 2014; Zheng *et al.*, 2015; Peng *et al.*, 2017), DBDPE was the dominant compound, exhibiting the highest contamination level in all sampling areas, suggesting that DBDPE had been used or released in large amounts in China. Furthermore, indoor dust samples collected from e-waste recycling areas showed relatively higher NBFR contamination compared to other areas. The levels of NBFR in the indoor environment in other Asian countries have also been investigated (Ali *et al.*, 2014; Hassan and Shoeib, 2015; Mizouchi *et al.*, 2015; Khan *et al.*, 2016; Kurt-Karakus *et al.*, 2017). In Pakistan, DBDPE levels in house dust (Khan *et al.*, 2016) were found to be higher compared to those found in universities, clothing stores, and electronics stores (Ali *et al.*, 2014). However, these levels were relatively lower compared to DBDPE levels in house dust collected from Japan (Mizouchi *et al.*, 2015), except for one Pakistani rural home and one home from a colder area in Pakistan, in which the values were higher. Ali *et al.* (2014) reported lower BTBPE levels than DBDPE in universities, clothing stores, and electronics stores. EH-TBB, BTBPE, and BEH-TEBP concentrations in Egyptian and Turkish indoor environments were studied (Hassan and Shoeib, 2015; Kurt-Karakus *et al.*, 2017). Low NBFR contaminations were found in homes, workplaces, and cars in Egypt. The use of flame retardants is not regulated in Egypt; therefore, imported goods incorporated with NBFRs may be one source of NBFR contamination. Consequently, the levels found in Egyptian dusts were among the lowest NBFR contamination reported compared to other countries (Hassan and Shoeib, 2015). Higher EH-TBB, BTBPE, and BEH-TEBP concentrations were found in Turkish indoor dusts (Kurt-Karakus *et al.*, 2017). EH-TBB were among the highest concentrations, followed by BTBPE, while most BEH-TEBP levels were less than the method detection limit (Kurt-Karakus *et al.*, 2017). In indoor air samples collected from Turkish homes and offices, EH-TBB was also found to be the most dominant compound (Kurt-Karakus *et al.*, 2017).

Contamination levels of NBFRs in the United States and other parts of Europe have also been reported. In the United States, levels of NBFRs were measured in the indoor dust from houses and fire stations (Brown *et al.*, 2014; Schreder and La Guardia, 2014). Dust samples from California homes and in living quarters from California fire stations were investigated for EH-TBB, BTBPE, DBDPE, and BEH-TEBP contamination. Dust samples from the fire stations showed higher concentrations compared to those from houses, with EH-TBB being the most dominant compound in both sampling areas. NBFRs released during fire events might have transferred to the living quarters of fire stations through the firefighters (Brown *et al.*, 2014). Lower levels of EH-TBB and BEH-TEBP and higher levels of BTBPE and DBDPE were found in house dust collected from Washington compared to house dust from California, with EH-TBB also found to be the most dominant NBFR (Schreder and La Guardia, 2014). In Canadian house dusts, lower levels of EH-TBB and BTBPE were obtained compared to American house dusts, with EH-TBB present in higher concentrations than BTBPE (Fan *et al.*, 2016). In European countries, dust samples from various indoor environments were investigated for NBFR contamination (Cequier *et al.*, 2014; Fromme *et al.*, 2014; Al-Omran and Harrad, 2016; Cristale *et al.*, 2016; Kuang *et al.*, 2016). Living rooms from the United Kingdom were shown to exhibit higher levels of NBFRs compared to kitchens, with DBDPE having the highest concentrations in both areas

(Kuang *et al.*, 2016). However, in another UK study, BEH-TEBP exhibited the highest concentrations in house dusts (Al-Omran and Harrad, 2016). Similar results were obtained in a German study, where BEH-TEBP was the dominant NBFR in house dusts (Fromme *et al.*, 2014). In Norway, NBFR levels in school classrooms were higher compared to those of residential living rooms, with DBDPE showing the highest concentrations in both environments (Cequier *et al.*, 2014). In Spain, NBFRs in indoor dust from schools were not detectable except for BEH-TEBP. The highest level of NBFR contamination was found in dusts collected from theatres, followed by homes, and universities/research institutions (Cristale *et al.*, 2014).

PBDD/Fs IN THE INDOOR ENVIRONMENT

The global concentrations of PBDD/Fs in the indoor environment are listed in Table 2. In indoor environments, PBDD/Fs have mainly been studied in dust. Most of the recent studies are from Asian countries including Japan, Vietnam, and Taiwan but there are also some from western countries such as Sweden and the USA. House dusts collected from a residential house in an e-waste recycling site in Vietnam showed higher average PBDD/F concentrations compared to general urban Vietnamese environment house dusts (Tue *et al.*, 2010). Workshop floor dust collected from an e-waste recycling site in Taizhou, China, however, showed higher average PBDD/F levels compared to that of Vietnam (Ma *et al.*, 2009). However, the maximum PBDD/F concentration found by Ma *et al.* (2009) were still below the maximum PBDD/F levels found in an American residential house dust (Tue *et al.*, 2013). In Japan, PBDD/F is among one of the major dioxin-like compounds in indoor dust. Suzuki *et al.* (2010) reported that levels of PBDD/Fs in Japanese office dusts were similar to those of house dusts. Moreover, Japanese PBDD/F house dust levels were in a range similar to those found in Vietnam. In Taiwan, indoor dust levels of PBDD/Fs in school classrooms from rural areas were higher compared to urban school classrooms (Gou *et al.*, 2016b). In addition, Taiwanese school classrooms' PBDD/F levels were in the same order of magnitude as those found in Japanese and Vietnamese house dusts, but lower compared to Swedish and American house dusts (Gou *et al.*, 2016b). These differences in the indoor dust levels of PBDD/Fs emphasize large variations in the overall global data.

These variations in PBDD/F levels are mainly attributed to the presence of potential emission sources indoors. Electrical and electronic equipment, textiles, furniture, and construction materials incorporated with flame retardants are materials that could be potential sources of PBDD/Fs. Among these materials, electrical and electronic equipment is regarded to be an important source of PBDD/Fs, which is supported by the very high concentrations of PBDD/Fs recorded in dust from an electrical waste and electronic equipment recycling plant in Sweden (Remberger *et al.*, 2014). Extremely high PBDD/F concentration of 3,800 ng g^{-1} dw^{-1} was also found in dust from a new car in Sweden compared to house dusts, which may indicate that new cars could be reservoirs for PBDD/Fs (Remberger *et al.*, 2014). Not only are PBDD/Fs possibly correlated with different indoor emission sources, but several studies have reported significant correlations between PBDD/Fs and PBDEs (Ma *et al.*, 2009; Gou *et al.*, 2016b). ΣPBDD/Fs were found to be significantly correlated with ΣPBDEs in workshop floor dust from a Chinese e-waste recycling facility ($r = 0.769$, $p < 0.01$) (Ma *et al.*, 2009) and in indoor dust from Taiwanese school classrooms ($r = 0.862$, $p < 0.001$) (Gou *et al.*, 2016b). NBFRs and DP may also be connected with PBDD/Fs in the indoor dust, but no studies have looked into this possible correlation yet.

Although there is an ample amount of scientific evidence confirming the presence of NBFRs, DPs, and PBDD/Fs in indoor environments, there is still a lack of evidence linking their indoor levels with their toxicity. However, results from studies using animal models suggest that there is a strong emerging evidence showing that exposure to high levels of these chemicals may possibly cause adverse health-related outcomes.

FUTURE WORKS FOR HFRS AND PBDD/Fs IN THE INDOOR ENVIRONMENT

After over two decades of use, most studies have focused only on PBDE levels in the indoor environment as compared to DP, NBFRs, and PBDD/Fs, which are now considered to be the modern day substitutes for PBDE-containing flame retardants. Spatial and longitudinal investigations of these emerging HFRs should be conducted to further assess the risks of these compounds to human health. Although current studies show that PBDEs levels in indoor dust are not related to indoor air PBDE concentrations (possibly because of small sample size; Fromme *et al.*, 2009; Toms *et al.*, 2009), it has been hypothesized that a pattern of non-dietary PBDE exposure probably exists and that the possible route of PBDE exposure is release from the surface of electronics and transfer to human bodies through accumulation of airborne PBDEs on indoor dust, as revealed in our previous study (Ni *et al.*, 2011; Shy *et al.*, 2015). Ni *et al.* (2011) indicated that human exposure to $PM_{2.5}$-bound PBDEs might have a minor contribution to total non-dietary PBDE exposure. In terms of global scientific reports, few studies have considered $PM_{2.5}$-bound PBDE levels in the indoor environment (Beser *et al.*, 2014; Li *et al.*, 2015a; Xu *et al.*, 2015; Chao *et al.*, 2016; Deng *et al.*, 2016). To our knowledge, there are no known reports that have investigated the levels of $PM_{2.5}$-bound DP, NBFRs, or PBDD/Fs in the indoor environment. Respirable fine particulates are reported to have correlations to various cardiopulmonary health effects such as cardiovascular and respiratory diseases (Dominici *et al.*, 2006; de Oliveira *et al.*, 2012; Zhang *et al.*, 2013; Xing *et al.*, 2016). Numerous studies have turned their focus on $PM_{2.5}$ levels due to the possibility of these small particles being deposited deep into the lungs, thus causing respiratory ailments and diseases, as well as other negative health problems (Zhang *et al.*, 2013; Gautam *et al.*, 2016; Hwang *et al.*, 2016; Lee *et al.*, 2016; Lu *et al.*, 2016; Xing *et al.*, 2016; Ma *et al.*, 2017). People with a known history of cardiopulmonary problems face

Table 2. Global concentrations of PBDD/Fs in indoor environments.

Country	Dust type (number)	ΣPBDD/Fs (ng g^{-1} dw^{-1})	ΣPBDD/Fs (pg TEQ g^{-1} dw^{-1})	References
China	Workshop floor dust, e-waste recycling area (n = 5)	90–143	945–2020	Ma *et al*., 2009
Japan	House dust (n = 19)	1.1–12	1.8–87[a]	Suzuki *et al*., 2010
	Office dust (n = 14)	1.6–29	1.8–87[a]	Suzuki *et al*., 2010
Vietnam	House dust, urban (n = 2)	1.5–2.3	–	Tue *et al*., 2010
	House dust, e-waste recycling area (n = 10)	7.7–63	–	Tue *et al*., 2010
USA	House dust (n=21)	0.33–150	< MDL–270	Tue *et al*., 2013
Sweden	House dust (n = 5)	2.7–53	21–160	Remberger *et al*., 2014
	New car dust (n = 1)	3800	14000	Remberger *et al*., 2014
	Recycling plant dust (n = 3)	280–1300	–	Remberger *et al*., 2014
Taiwan	Normal classroom dust, urban (n = 6)	2.34–6.55	0.0179–0.0837[b]	Gou *et al*., 2016
	Normal classroom dust, rural (n = 4)	0.742–10.7	0.00639–0.0824[b]	Gou *et al*., 2016
	Computer classroom dust, urban (n = 6)	3.84–12.5	0.0307–0.132[b]	Gou *et al*., 2016
	Computer classroom dust, rural (n = 4)	2.37–15.4	0.0191–0.0987[b]	Gou *et al*., 2016

[a] CALUX assay with the unit of pg = CALUX-TEQ g^{-1} dw^{-1}.
[b] According to PCDD/Fs WHO_{2005}TEF, unit: ng-WHO_{2005}TEQ g^{-1} dw^{-1}.

higher risk of mortality due to the increasing $PM_{2.5}$ concentrations in the atmosphere while normal people also face a higher risk of developing respiratory problems (Dominici *et al.*, 2006; de Oliveira *et al.*, 2012; Xing *et al.*, 2016; Li *et al.*, 2017). $PM_{2.5}$ is the essential issue for human health in both the indoor and outdoor environment. Although most environmental scientists recognize that high levels of $PM_{2.5}$-bound HFRs including PBDEs are well known in the indoor environment, few reports have considered their toxic effects for human health via inhalation. Moreover, with $PM_{2.5}$-bound PBDEs being a very important concern, then $PM_{2.5}$-bound NBFRs, DP, and PBDD/Fs should be of important concern also. Future works will be continuously encouraged to investigate indoor levels of $PM_{2.5}$-bound NBFRs, DP, and PBDD/Fs to further evaluate their body burden percentage via inhalation pathway and to assess the health risks or the health effects of direct inhalation.

CONCLUSIONS

There is currently a significant increase in global demand for DP and NBFRs as substitutes for the banned conventional brominated flame retardants. Global data on the indoor environment, particularly on indoor dust, have reported the presence of NBFRs, DP, and PBDD/Fs. Currently, there is limited global toxicological data for these chemicals. The toxicological data for NBFRs, DP, and PBDD/Fs, which includes acute toxicity, developmental toxicity, immunotoxicity, neurotoxicity, reproductive toxicity, genotoxicity, or disruption of hormones, are reported in various *in vitro* and *in vivo* studies. Most previous studies focused only on the non-dietary intake of HFRs, such as PBDEs, DP, and NBFRs, and there is a lack of study on simultaneous levels of indoor dust and fine particulate matter. Therefore, in order to assess their risks and the potential for adverse health effects through the main exposure routes, including dust ingestion and inhalation of respirable fine particles, additional studies are required to further observe their levels in the indoor environment, particularly in dust and fine particulate samples.

ACKNOWLEDGMENTS

This study was financially supported by the Ministry of Science and Technology in Taiwan under the grant (MOST 106-2221-E-020-001-MY3). We thank Ms. Danielle E. Que from the Department of Environmental Engineering, National Cheng Kung University, Taiwan for assistance with collection of several studies and improvements in the quality of this manuscript.

DISCLAIMER

The authors declare no conflicts of interest with regard to this study.

REFERENCES

Alaee, M., Arias, P., Sjödin, A. and Bergman, Å. (2003). An overview of commercially used brominated flame retardants, their applications, their use patterns in different countries/regions and possible modes of release. *Environ. Int.* 29: 683–689.

Ali, N., Mehdi, T., Malik, R.N., Eqani, S.A.M.A.S., Kamal, A., Dirtu, A.C., Neels, H. and Covaci, A. (2014). Levels and profile of several classes of organic contaminants in matched indoor dust and serum samples from occupational settings of Pakistan. *Environ. Pollut.* 193: 269–276.

Al-Omran, L.S. and Harrad, S. (2016). Distribution pattern of legacy and "novel" brominated flame retardants in different particle size fractions of indoor dust in Birmingham, United Kingdom. *Chemosphere* 157: 124–131.

Ao, K., Suzuki, T., Murai, H., Matsumoto, M., Nagai, H., Miyamoto, Y., Tohyama, C. and Nohara, K. (2009). Comparison of immunotoxicity among tetrachloro-, pentachloro-, tetrabromo- and pentabromo-dibenzo-*p*-dioxins in mice. *Toxicology* 256: 25–31.

Bailey, J.M. and Levin, E.D. (2015). Neurotoxicity of Firemaster 550® in zebrafish (*Danio rerio*): Chronic developmental and acute adolescent exposures. *Neurotoxicol. Teratol.* 52: 210–219.

Baldwin, K.R., Phillips, A.L., Horman, B., Arambula, S.E., Rebuli, M.E., Stapleton, H.M. and Patisaul, H.B. (2017). Sex specific placental accumulation and behavioral effects of dvelopmental Firemaster 550 exposure in Wistar rats. *Sci. Rep.* 7: 7118.

Barón, E., Dissanayake, A., Vilà-Cano, J., Crowther, C., Readman, J.W., Jha, A.N., Eljarrat, E. and Barceló, D. (2016). Evaluation of the genotoxic and physiological effects of decabromodiphenyl Ether (BDE-209) and dechlorane plus (DP) flame retardants in marine mussels (*Mytilus galloprovincialis*). *Environ. Sci. Technol.* 50: 2700–2708.

Bearr, J.S., Stapleton, H.M. and Mitchelmore, C.L. (2010). Accumulation and DNA damage in fathead minnows (*Pimephales promelas*) exposed to 2 brominated flame-retardant mixtures, Firemaster® 550 and Firemaster® BZ-54. *Environ. Toxicol. Chem.* 29: 722–729.

Ben, Y.J., Li, X.H., Yang, Y.L., Li, L., Zheng, M.Y., Wang, W.Y. and Xu, X.B. (2014). Placental transfer of dechlorane plus in mother–infant pairs in an e-waste recycling area (Wenling, China). *Environ. Sci. Technol.* 48: 5187–5193.

Beser, M.I., Beltran, J. and Yusa, V. (2014). Design of experiment approach for the optimization of polybrominated diphenyl ethers determination in fine airborne particulate matter by microwave-assisted extraction and gas chromatography coupled to tandem mass spectrometry. *J. Chromatogr. A* 1323: 1–10.

Brits, M., de Vos, J., Weiss, J.M., Rohwer, E.R. and de Boer, J. (2016). Critical review of the analysis of brominated flame retardants and their environmental levels in Africa. *Chemosphere* 164: 174–189.

Brown, F.R., Whitehead, T.P., Park, J.S., Metayer, C. and Petreas, M.X. (2014). Levels of non-polybrominated diphenyl ether brominated flame retardants in residential

house dust samples and fire station dust samples in California. *Environ. Res.* 135: 9–14.

Cao, Z., Xu, F., Covaci, A., Wu, M., Yu, G., Wang, B., Deng, S. and Huang, J. (2014). Differences in the seasonal variation of brominated and phosphorus flame retardants in office dust. *Environ. Int.* 65: 100–106.

Cequier, E., Ionas, A.C., Covaci, A., Marcé, R.M., Becher, G. and Thomsen, C. (2014). Occurrence of a broad range of legacy and emerging flame retardants in indoor environments in Norway. *Environ. Sci. Technol.* 48: 6827–6835.

Cequier, E., Marcé, R.M., Becher, G. and Thomsen, C. (2015). Comparing human exposure to emerging and legacy flame retardants from the indoor environment and diet with concentrations measured in serum. *Environ. Int.* 74: 54–59.

Chao, H.R., Huang, H.L., Hsu, Y.C., Lin, C.W., Lin, D.Y., Gou, Y.Y. and Chen, K.C. (2014a). Impact of brominated POPs on the neurodevelopment and thyroid hormones of young children in an indoor environment - Review. *Aerosol Air Qual. Res.* 14: 1320–1332.

Chao, H.R., Que, D.E., Gou, Y.Y., Chuang, C.Y., Chang, T.Y. and Hsu, Y.C. (2016). Indoor and outdoor concentrations of polybrominated diphenyl ethers on respirable particulate in central and southern Taiwan. *Aerosol Air Qual. Res.* 16: 3187–3197.

Chao, H.R., Shy, C.G., Huang, H.L., Koh, T.W., Tok, T.S., Chen, S.C.C., Chiang, B.A., Kuo, Y.M., Chen, K.C. and Chang-Chien, G.P. (2014b). Particle-size dust concentrations of polybrominated diphenyl ethers (PBDEs) in Southern Taiwanese houses and assessment of the PBDE daily intakes in toddlers and adults. *Aerosol Air Qual. Res.* 14: 1299–1309.

Chemtura (2006). Flame retardants product guide. https://www.biesterfeld-spezialchemie.com/fileadmin/bsc_fr/docs/Chemtura_Flame_Retardants.pdf, Last Access: 05 March 2018.

Chen, X., Dong, Q., Chen, Y., Zhang, Z., Huang, C., Zhu, Y. and Zhang, Y. (2017). Effects of dechlorane plus exposure on axonal growth, musculature and motor behavior in embryo-larval zebrafish. *Environ. Pollut.* 224: 7–15.

Chou, H.M., Kao, C.C., Chuang, K.P., Lin, C., Shy, C.G., Chen, R.F., Tsai, C.C., Chuang, C.Y., Cheng, Y.C., Chen, C.C. and Chao, H.R. (2016). levels of polybrominated diphenyl ethers in air-conditioner filter dust used to assess health risks in clinic and electronic plant employees. *Aerosol Air Qual. Res.* 16: 184–194.

Costa, L.G. and Giordano, G. (2007). Developmental neurotoxicity of polybrominated diphenyl ether (PBDE) flame retardants. *Neurotoxicology* 28: 1047–1067.

Covaci, A., Harrad, S., Abdallah, M.A., Ali, N., Law, R.J., Herzke, D. and de Wit, C.A. (2011). Novel brominated flame retardants: A review of their analysis, environmental fate and behaviour. *Environ. Int.* 37: 532–556.

Cristale, J., Hurtado, A., Gómez-Canela, C. and Lacorte, S. (2016). Occurrence and sources of brominated and organophosphorus flame retardants in dust from different indoor environments in Barcelona, Spain. *Environ. Res.* 149: 66–76.

Crump, D., Chiu, S., Egloff, C. and Kennedy, S.W. (2008). Effects of hexabromocyclododecane and polybrominated diphenyl ethers on mRNA expression in chicken (Gallus domesticus) hepatocytes. *Toxicol. Sci.* 106: 479–487.

Crump, D., Chiu, S., Gauthier, L.T., Hickey, N.J., Letcher, R.J. and Kennedy, S.W. (2011). The effects of Dechlorane Plus on toxicity and mRNA expression in chicken embryos: A comparison of *in vitro* and *in ovo* approaches. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* 154: 129–134.

de Oliveira, B.F.A., Ignotti, E., Artaxo, P., do Nascimento Saldiva, P.H., Junger, W.L. and Hacon, S. (2012). Risk assessment of $PM_{2.5}$ to child residents in Brazilian Amazon region with biofuel production. *Environ. Health* 11: 64.

Deng, W.J., Zheng, H.L., Tsui, A.K.Y. and Chen, X.W. (2016). Measurement and health risk assessment of $PM_{2.5}$, flame retardants, carbonyls and black carbon in indoor and outdoor air in kindergartens in Hong Kong. *Environ. Int.* 96: 65–74.

Dominici, F., Peng, R.D., Bell, M.L., Pham, L., McDermott, A., Zeger, S.L. and Samet, J.M. (2006). Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA.* 295: 1127–1134.

Dou, J., Jin, Y., Li, Y., Wu, B. and Li, M. (2015). Potential genotoxicity and risk assessment of a chlorinated flame retardant, dechlorane plus. *Chemosphere* 135: 462–466.

Egloff, C., Crump, D., Chiu, S., Manning, G., McLaren, K.K., Cassone, C.G., Letcher, R.J., Gauthier, L.T. and Kennedy, S.W. (2011). *In vitro* and *in ovo* effects of four brominated flame retardants on toxicity and hepatic mRNA expression in chicken embryos. *Toxicol. Lett.* 207: 25–33.

Ezechiáš, M., Covino, S. and Cajthaml, T. (2014). Ecotoxicity and biodegradability of new brominated flame retardants: A review. *Ecotoxicol. Environ. Saf.* 110: 153–167.

Fan, X., Kubwabo, C., Rasmussen, P.E. and Wu, F. (2016). Non-PBDE halogenated flame retardants in Canadian indoor house dust: Sampling, analysis, and occurrence. *Environ. Sci. Pollut. Res.* 23: 7998–8007.

Fernandes, A., Dicks, P., Mortimer, D., Gem, M., Smith, F., Driffield, M., White, S. and Rose, M. (2008). Brominated and chlorinated dioxins, PCBs and brominated flame retardants in Scottish shellfish: Methodology, occurrence and human dietary exposure. *Mol. Nutr. Food Res.* 52: 238–249.

Frawley, R., DeVito, M., Walker, N.J., Birnbaum, L., White, K., Jr., Smith, M., Maynor, T., Recio, L. and Germolec, D. (2014). Relative potency for altered humoral immunity induced by polybrominated and polychlorinated dioxins/furans in female B6C3F1/N mice. *Toxicol. Sci.* 139: 488–500.

Fromme, H., Korner, W., Shahin, N., Wanner, A., Albrecht, M., Boehmer, S., Parlar, H., Mayer, R., Liebl, B. and Bolte, G. (2009). Human exposure to polybrominated diphenyl ethers (PBDE), as evidenced by data from a duplicate diet study, indoor air, house dust, and

biomonitoring in Germany. *Environ. Int.* 35: 1125–1135.

Fromme, H., Hilger, B., Kopp, E., Miserok, M. and Völkel, W. (2014). Polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD) and "novel" brominated flame retardants in house dust in Germany. *Environ. Int.* 64: 61–68.

Gagné, P.L., Fortier, M., Fraser, M., Parent, L., Vaillancourt, C. and Verreault, J. (2017). Dechlorane plus induces oxidative stress and decreases cyclooxygenase activity in the blue mussel. *Aquat. Toxicol.* 188: 26–32.

Gautam, S., Yadav, A., Tsai, C.J. and Kumar, P. (2016). A review on recent progress in observations, sources, classification and regulations of $PM_{2.5}$ in Asian environments. *Environ. Sci. Pollut. Res.* 23: 21165–21175.

Gou, Y.Y., Hsu, Y.C., Chao, H.R., Que, D.E., Tayo, L.L., Lin, C.H., Huang, S.M., Tsai, C.H. and Shih, S.I. (2016a). Pollution characteristics and diurnal variations in polybrominated diphenyl ethers in indoor and outdoor air from vehicle dismantler factories in southern Taiwan. *Aerosol Air Qual. Res.* 16: 1931–1941.

Gou, Y.Y., Que, D.E., Chuang, C.Y., Chao, H.R., Shy, C.G., Hsu, Y.C., Lin, C.W., Chuang, K.P., Tsai, C.C. and Tayo, L.L. (2016b). Dust levels of polybrominated diphenyl ethers (PBDEs) and polybrominated dibenzo-*p*-dioxins/furans (PBDD/Fs) in the Taiwanese elementary school classrooms: Assessment of the risk to school-age children. *Sci. Total Environ.* 572: 734–741.

Haijima, A., Endo, T., Zhang, Y., Miyazaki, W., Kakeyama, M. and Tohyama, C. (2010). In utero and lactational exposure to low doses of chlorinated and brominated dioxins induces deficits in the fear memory of male mice. *Neurotoxicology* 31: 385–390.

Hakk, H., Larsen, G. and Bowers, J. (2004). Metabolism, tissue disposition, and excretion of 1,2-bis(2,4,6-tribromophenoxy)ethane (BTBPE) in male Sprague-Dawley rats. *Chemosphere* 54: 1367–1374.

Hanari, N., Kannan, K., Okazawa, T., Kodavanti, P.R.S., Aldous, K.M. and Yamashita, N. (2006). Occurrence of polybrominated biphenyls, polybrominated dibenzo-*p*-dioxins, and polybrominated dibenzofurans as impurities in commercial polybrominated diphenyl ether mixtures. *Environ. Sci. Technol.* 40: 4400–4405.

Hardy, M.L., Margitich, D., Ackerman, L. and Smith, R.L. (2002). The subchronic oral toxicity of ethane, 1,2-bis(pentabromophenyl) (SAYTEX 8010) in rats. *Int. J. Toxicol.* 21: 165–170.

Hardy, M.L., Mercieca, M.D., Rodwell, D.E. and Stedeford, T. (2010). Prenatal developmental toxicity of decabromodiphenyl ethane in the rat and rabbit. *Birth Defects Res. B Dev. Reprod. Toxic.* 89: 139–146.

Hardy, M.L., Aufderheide, J., Krueger, H.O., Mathews, M.E., Porch, J.R., Schaefer, E.C., Stenzel, J.I. and Stedeford, T. (2011). Terrestrial toxicity evaluation of decabromodiphenyl ethane on organisms from three trophic levels. *Ecotoxicol. Environ. Saf.* 74: 703–710.

Hardy, M.L., Krueger, H.O., Blankinship, A.S., Thomas, S., Kendall, T.Z. and Desjardins, D. (2012). Studies and evaluation of the potential toxicity of decabromodiphenyl ethane to five aquatic and sediment organisms. *Ecotoxicol. Environ. Saf.* 75: 73–79.

Hassan, Y. and Shoeib, T. (2015). Levels of polybrominated diphenyl ethers and novel flame retardants in microenvironment dust from Egypt: An assessment of human exposure. *Sci. Total Environ.* 505: 47–55.

Hoh, E., Zhu, L. and Hites, R.A. (2006). Dechlorane plus, a chlorinated flame retardant, in the Great Lakes. *Environ. Sci. Technol.* 40: 1184–1189.

Hwang, S.L., Guo, S.E., Chi, M.C., Chou, C.T., Lin, Y.C., Lin, C.M. and Chou, Y.L. (2016). Association between atmospheric fine particulate matter and hospital admissions for chronic obstructive pulmonary disease in southwestern Taiwan: A population-based study. *Int. J. Environ. Res. Public Health* 13: 366.

Johnson-Restrepo, B. and Kannan, K. (2009). An assessment of sources and pathways of human exposure to polybrominated diphenyl ethers in the United States. *Chemosphere* 76: 542–548.

Kang, H., Moon, H.B. and Choi, K. (2016). Toxicological responses following short-term exposure through gavage feeding or water-borne exposure to dechlorane plus in zebrafish (*Danio rerio*). *Chemosphere* 146: 226–232.

Kang, Y., Wang, H.S., Cheung, K.C. and Wong, M.H. (2011). Polybrominated diphenyl ethers (PBDEs) in indoor dust and human hair. *Atmos. Environ.* 45: 2386–2393.

Khan, M.U., Li, J., Zhang, G. and Malik, R.N. (2016). New insight into the levels, distribution and health risk diagnosis of indoor and outdoor dust-bound frs in colder, rural and industrial zones of Pakistan. *Environ. Pollut.* 216: 662–674.

Kuang, J., Ma, Y. and Harrad, S. (2016). Concentrations of "legacy" and novel brominated flame retardants in matched samples of UK kitchen and living room/bedroom dust. *Chemosphere* 149: 224–230.

Kurt-Karakus, P.B., Alegria, H., Jantunen, L., Birgul, A., Topcu, A., Jones, K.C. and Turgut, C. (2017). Polybrominated diphenyl ethers (PBDEs) and alternative flame retardants (NFRs) in indoor and outdoor air and indoor dust from Istanbul-Turkey: Levels and an assessment of human exposure. *Atmos. Pollut. Res.* 8: 801–815.

Lee, K.L., Lee, W.J., Mwangi, J.K., Wang, L.C., Gao, X. and Chang-Chien, G.P. (2016). Atmospheric $PM_{2.5}$ and depositions of polychlorinated dibenzo-*p*-dioxins and dibenzofurans in Kaohsiung area, southern Taiwan. *Aerosol Air Qual. Res.* 16: 1775–1791.

Li, H., Liu, H., Mo, L., Sheng, G., Fu, J. and Peng, P. (2016). Airborne polybrominated diphenyl ethers (PBDEs), polybrominated dibenzo-*p*-dioxins/furans (PBDD/Fs), and dechlorane plus (DP) in concentrated vehicle parking areas. *Environ. Sci. Pollut. Res. Int.* 23: 10702–10713.

Li, W.L., Qi, H., Ma, W.L., Liu, L.Y., Zhang, Z., Zhu, N.Z., Mohammed, M.O.A. and Li, Y.F. (2015a). Occurrence, behavior and human health risk assessment of dechlorane plus and related compounds in indoor dust of China. *Chemosphere* 134: 166–171.

Li, Y., Chen, L., Ngoc, D.M., Duan, Y.P., Lu, Z.B., Wen, Z.H. and Meng, X.Z. (2015b). Polybrominated diphenyl

ethers (PBDEs) in $PM_{2.5}$, PM_{10}, TSP and gas phase in office environment in Shanghai, China: occurrence and human exposure. *PLoS One* 10: e0119144.

Li, Y., Yu, L., Zhu, Z., Dai, J., Mai, B., Wu, J. and Wang, J. (2013). Accumulation and effects of 90-day oral exposure to dechlorane plus in quail (Coturnix coturnix). *Environ. Toxicol. Chem.* 32: 1649–1654.

Li, Y., Yang, L., Chen, X., Gao, Y., Jiang, P., Zhang, J., Yu, H. and Wang, W. (2017). $PM_{2.5}$-bound pahs in indoor and outdoor of hotels in urban and suburban of Jinan, China: concentrations, sources, and health risk impacts. *Aerosol Air Qual. Res.* 17: 2463–2473.

Liang, X., Li, W., Martyniuk, C.J., Zha, J., Wang, Z., Cheng, G. and Giesy, J.P. (2014). Effects of dechlorane plus on the hepatic proteome of juvenile chinese sturgeon (Acipenser sinensis). *Aquat. Toxicol.* 148: 83–91.

Lorber, M. (2008). Exposure of americans to polybrominated diphenyl ethers. *J. Exposure Sci. Environ. Epidemiol.* 18: 2–19.

Lu, H.Y., Mwangi, J.K., Wang, L.C., Wu, Y.L., Tseng, C.Y. and Chang, K.H. (2016). Atmospheric $PM_{2.5}$ characteristics and long-term trends in Tainan city, southern Taiwan. *Aerosol Air Qual. Res.* 16: 2488–2511.

Ma, J., Addink, R., Yun, S., Cheng, J., Wang, W. and Kannan, K. (2009). Polybrominated dibenzo-*p*-dioxins/dibenzofurans and polybrominated diphenyl ethers in soil, vegetation, workshop-floor dust, and electronic shredder residue from an electronic waste recycling facility and in soils from a chemical industrial complex in eastern China. *Environ. Sci. Techno.l* 43: 7350–7356.

Ma, Q., Wu, Y., Tao, J., Xia, Y., Liu, X., Zhang, D., Han, Z., Zhang, X. and Zhang, R. (2017). Variations of chemical composition and source apportionment of $PM_{2.5}$ during winter haze episodes in Beijing. *Aerosol Air Qual. Res*. 17: 2791–2803.

Mankidy, R., Ranjan, B., Honaramooz, A. and Giesy, J.P. (2014). Effects of novel brominated flame retardants on steroidogenesis in primary porcine testicular cells. *Toxicol. Lett.* 224: 141–146.

Mizouchi, S., Ichiba, M., Takigami, H., Kajiwara, N., Takamuku, T., Miyajima, T., Kodama, H., Someya, T. and Ueno, D. (2015). Exposure assessment of organophosphorus and organobromine flame retardants via indoor dust from elementary schools and domestic houses. *Chemosphere* 123: 17–25.

Newton, S., Sellstrom, U. and de Wit, C.A. (2015). Emerging flame retardants, pbdes, and hbcdds in indoor and outdoor media in Stockholm, Sweden. *Environ. Sci. Technol.* 49: 2912–2920.

Ni, H.G., Cao, S.P., Chang, W.J. and Zeng, H. (2011). Incidence of polybrominated diphenyl ethers in central air conditioner filter dust from a new office building. *Environ. Pollut.* 159: 1957–1962.

Nomeir, A.A., Markham, P.M., Ghanayem, B.I. and Chadwick, M. (1993). Disposition of the flame retardant 1,2-bis(2,4,6-tribromophenoxy)ethane in rats following administration in the diet. *Drug Metab. Dispos.* 21: 209.

Olsman, H., Engwall, M., Kammann, U., Klempt, M., Otte, J., van Bavel, B. and Hollert, H. (2007). Relative differences in aryl hydrocarbon receptor-mediated response for 18 polybrominated and mixed halogenated dibenzo-*p*-dioxins and -furans in cell lines from four different species. *Environ. Toxicol. Chem.* 26: 2448–2454.

Patisaul, H.B., Roberts, S.C., Mabrey, N., McCaffrey, K.A., Gear, R.B., Braun, J., Belcher, S.M. and Stapleton, H.M. (2013). Accumulation and endocrine disrupting effects of the flame retardant mixture Firemaster® 550 in rats: An exploratory assessment. *J. Biochem. Mol. Toxicol.* 27: 124–136.

Peng, C., Tan, H., Guo, Y., Wu, Y. and Chen, D. (2017). Emerging and legacy flame retardants in indoor dust from east China. *Chemosphere* 186: 635–643.

Qi, H., Li, W.L., Liu, L.Y., Zhang, Z.F., Zhu, N.Z., Song, W.W., Ma, W.L. and Li, Y.F. (2014). Levels, distribution and human exposure of new non-bde brominated flame retardants in the indoor dust of China. *Environ. Pollut.* 195: 1–8.

Redfern, F.M., Lee, W.J., Yan, P., Mwangi, J.K., Wang, L.C. and Shih, C.H. (2017). Overview and perspectives on emissions of polybrominated diphenyl ethers on a global basis: Evaporative and fugitive releases from commercial pbde mixtures and emissions from combustion sources. *Aerosol Air Qual. Res.*17: 1117–1131.

Remberger, M., Kaj, L., Hansson, K., Momina, B., Brorström-Lundén, E., Haglund, P., Liljelind, P., Bergek, S., Andersson, R. and Kitti-Sjöström, A. (2014). Screening of emerging brominated flame retardants (BFRs) and polybrominated dibenzofurans (PBDFs), In *IVL Rapport B*, p. 63.

Ren, M., Peng, P., Cai, Y., Chen, D., Zhou, L., Chen, P. and Hu, J. (2011). PBDD/F impurities in some commercial deca-bde. *Environ. Pollut.* 159: 1375–1380.

Saunders, D.M.V., Higley, E.B., Hecker, M., Mankidy, R. and Giesy, J.P. (2013). *In vitro* endocrine disruption and tcdd-like effects of three novel brominated flame retardants: TBPH, TBB, & TBCO. *Toxicol. Lett.* 223: 252–259.

Scanlan, L.D., Loguinov, A.V., Teng, Q., Antczak, P., Dailey, K.P., Nowinski, D.T., Kornbluh, J., Lin, X.X., Lachenauer, E., Arai, A., Douglas, N.K., Falciani, F., Stapleton, H.M. and Vulpe, C.D. (2015). Gene transcription, metabolite and lipid profiling in eco-indicator daphnia magna indicate diverse mechanisms of toxicity by legacy and emerging flame-retardants. *Environ. Sci. Technol.* 49: 7400–7410.

Schreder, E.D. and La Guardia, M.J. (2014). Flame retardant transfers from U.S. households (dust and laundry wastewater) to the aquatic environment. *Environ. Sci. Technol.* 48: 11575–11583.

Shy, C.G., Hsu, Y.C., Shih, S.I., Chuang, K.P., Lin, C.W., Wu, C.W., Chuang, C.Y. and Chao, H.R. (2015). Indoor level of polybrominated diphenyl ethers in the home environment and assessment of human health risks. *Aerosol Air Qual. Res.* 15: 1494–1505.

Springer, C., Dere, E., Hall, S.J., McDonnell, E.V., Roberts, S.C., Butt, C.M., Stapleton, H.M., Watkins, D.J., McClean, M.D., Webster, T.F., Schlezinger, J.J.

and Boekelheide, K. (2012). Rodent thyroid, liver, and fetal testis toxicity of the monoester metabolite of bis-(2-ethylhexyl) tetrabromophthalate (TBPH), a novel brominated flame retardant present in indoor dust. *Environ. Health Perspect.* 120: 1711–1719.

Suzuki, G., Someya, M., Takahashi, S., Tanabe, S., Sakai, S.I. and Takigami, H. (2010). Dioxin-like activity in Japanese indoor dusts evaluated by means of *in vitro* bioassay and instrumental analysis: Brominated dibenzofurans are an important contributor. *Environ. Sci. Technol.* 44: 8330–8336.

Sverko, E., Tomy, G.T., Reiner, E.J., Li, Y.F., McCarry, B.E., Arnot, J.A., Law, R.J. and Hites, R.A. (2011). Dechlorane plus and related compounds in the environment: A review. *Environ. Sci. Technol.* 45: 5088–5098.

Toms, L.M., Hearn, L., Kennedy, K., Harden, F., Bartkow, M., Temme, C. and Mueller, J.F. (2009). Concentrations of polybrominated diphenyl ethers (PBDEs) in matched samples of human milk, dust and indoor air. *Environ. Int.* 35: 864–869.

Tue, N.M., Suzuki, G., Takahashi, S., Isobe, T., Trang, P.T.K., Viet, P.H. and Tanabe, S. (2010). Evaluation of dioxin-like activities in settled house dust from Vietnamese e-waste recycling sites: Relevance of polychlorinated/brominated dibenzo-*p*-dioxin/furans and dioxin-like PCBs. *Environ. Sci. Technol.* 44: 9195–9200.

Tue, N.M., Takahashi, S., Subramanian, A., Sakai, S. and Tanabe, S. (2013). Environmental contamination and human exposure to dioxin-related compounds in e-waste recycling sites of developing countries. *Environ. Sci. Process. Impact.* 15: 1326-1331.

United States Environmental Protection Agency (USEPA). 2015. Flame Retardants Used in Flexible Polyurethane Foam: An Alternatives Assessment Update. EPA Publication 744-R15-002. https://www.epa.gov/saferchoice/flame-retardants-used-flexiblepolyurethane-foam. Last Accesse: 1 March 2018.

Wang, F., Wang, J., Dai, J., Hu, G., Wang, J., Luo, X. and Mai, B. (2010). Comparative tissue distribution, biotransformation and associated biological effects by decabromodiphenyl ethane and decabrominated diphenyl ether in male rats after a 90-day oral exposure study. *Environ. Sci. Technol.* 44: 5655–5660.

Wang, J., Tian, M., Chen, S.J., Zheng, J., Luo, X.J., An, T.C. and Mai, B.X. (2011). Dechlorane plus in house dust from e-waste recycling and urban areas in south China: Sources, degradation, and human exposure. *Environ. Toxicol. Chem.* 30: 1965–1972.

WHO/IPCS (World Health Organization), 2005. Concise International Chemical Assessment Document 66. 2.4.6-Tribromophenol and other simple brominated phenols. Geneva, Switzerland. http://www.who.int/ipcs/publications/cicad/cicad_66_web_version.pdf. Last Access: 1 March 2018.

Wu, B., Liu, S., Guo, X., Zhang, Y., Zhang, X., Li, M. and Cheng, S. (2012). Responses of mouse liver to dechlorane plus exposure by integrative transcriptomic and metabonomic studies. *Environ. Sci. Technol.* 46: 10758–10764.

Wu, M.H., Pei, J.C., Zheng, M., Tang, L., Bao, Y.Y., Xu, B.T., Sun, R., Sun, Y.F., Xu, G. and Lei, J.Q. (2015). Polybrominated diphenyl ethers (PBDEs) in soil and outdoor dust from a multi-functional area of Shanghai: Levels, compositional profiles and interrelationships. *Chemosphere* 118: 87–95.

Xing, J., Cui, K., Tang, H., Lee, W.J., Wang, L.C., Zhu, J. and Huang, Q. (2017). Part II: $PM_{2.5}$ and polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) in the ambient air of northern China. *Aerosol Air Qual. Res*. 17: 2010–2026.

Xing, Y.F., Xu, Y.H., Shi, M.H. and Lian, Y.X. (2016). The impact of $PM_{2.5}$ on the human respiratory system. *J. Thorac. Dis.* 8: E69–E74.

Xu, F., Liu, Y., Wang, J., Zhang, G., Zhang, W., Liu, L., Wang, J., Pan, B. and Lin, K. (2015). Characterization of heavy metals and brominated flame retardants in the indoor and outdoor dust of e-waste workshops: Implication for on-site human exposure. *Environ. Sci. Pollut. Res. Int.* 22: 5469–5480.

Yu, G., Bu, Q., Cao, Z., Du, X., Xia, J., Wu, M. and Huang, J. (2016). Brominated flame retardants (BFRs): A review on environmental contamination in China. *Chemosphere* 150: 479–490.

Zhang, A., Qi, Q., Jiang, L., Zhou, F. and Wang, J. (2013). Population exposure to $PM_{2.5}$ in the urban area of Beijing. *PLoS One* 8: e63486.

Zhang, L., Ji, F., Li, M., Cui, Y. and Wu, B. (2014). Short-term effects of dechlorane plus on the earthworm Eisenia fetida determined by a systems biology approach. *J. Hazard. Mater*. 273: 239–246.

Zheng, J., Wang, J., Luo, X.J., Tian, M., He, L.Y., Yuan, J.G., Mai, B.X. and Yang, Z.Y. (2010). Dechlorane plus in human hair from an e-waste recycling area in south China: Comparison with dust. *Environ. Sci. Technol.* 44: 9298–9303.

Zheng, X., Xu, F., Chen, K., Zeng, Y., Luo, X., Chen, S., Mai, B. and Covaci, A. (2015). Flame retardants and organochlorines in indoor dust from several e-waste recycling sites in south China: Composition variations and implications for human exposure. *Environ. Int.* 78: 1–7.

Zhu, J., Feng, Y.L. and Shoeib, M. (2007). Detection of dechlorane plus in residential indoor dust in the city of Ottawa, Canada. *Environ. Sci. Technol.* 41: 7694–7698.

Received for review, March 14, 2018
Revised, May 31, 2018
Accepted, June 25, 2018