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

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Abstract

Non-polybrominated diphenyl ether (non-PBDE) halogenated fire retardants (HFRs) such as new or novel brominated fire retardants (NBFRs) and dechlorance plus (DPs) have been widely spreading in the environment and are recognized as emerging persistent organic pollutants (POPs) in the recent years, mainly due to the continuous increase of its global demand specially 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, DPs, and PBDD/Fs are ubiquitous in the indoor environment due to the large-volume release on 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 of 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), DPs, 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, toxic effects of NBFRs, DPs, and PBDD/Fs based from *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 to assess their risks. Future works are encouraged to focus on indoor $PM_{2.5}$-bound HFR levels to further evaluate their toxic effects to human health.

Keywords: Fire retardants; Polybrominated dibenzo-*p*-dioxins/furans (PBDD/Fs); Indoor dust; Dechlorance 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; Chao *et al.*, 2014a; Covaci *et al.*, 2011; Sverko *et al.*, 2011; 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 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 pentaBDEs, octaBDEs, and decaBDEs (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 (Brits *et al.*, 2016; Ezechiáš *et al.*, 2014; Hassan and Shoeib, 2015; 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 (Chen *et al.*, 2012; Fernandes *et al.*, 2008; Johnson-Restrepo and Kannan, 2009). 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 (Chao *et al.*, 2014b; Lorber, 2008; Kang *et al.*, 2011; 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, DPS, AND PBDD/FS

Epidemiological Effects of NBFRs, DPs, and PBDD/Fs

NBFRs, DPs, and PBDD/Fs are ubiquitously contaminating and existing in the environment and continuously bioaccumulating in biota and human bodies. Although levels of NBFRs and DPs 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 DPs, most of the studies providing data for their toxicity focused on *in vivo* testing and are commonly compared to their brominated 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 24h, 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-

188 regulating *CY21A2*, which is the enzyme responsible for directing substrates away from sex
189 hormone synthesis and towards aldosterone and cortisol synthesis in primary porcine testicular
190 cells (Mankidy *et al.*, 2014). Another study using rat hepatoma cell line H4IIE and human
191 adrenocarcinoma cell line H295R demonstrated EH-TBB's antagonism with both estrogen
192 receptors (ER) and androgen receptors (AR) and elevated steroidogenesis of estrogen (Saunders
193 *et al.*, 2013). In this *in vitro* study, the anti-androgenic response of EH-TBB was weak, which
194 might have been due to limitations in the dosing concentration. The maximum anti-estrogenic
195 effect (62%) was produced at 0.5 mg L^{-1} EH-TBB. BEH-TEBP was shown to produce a maximal
196 anti-androgenic effect of 74% at 300 mg L^{-1} (Saunders *et al.*, 2013). Also, maximum exposure of
197 30 mg L^{-1} BEH-TEBP resulted in a moderate 1.96-fold increase in testosterone concentration
198 compared to controls. BEH-TEBP exposure also resulted in the greatest increase of 17-β-estradiol
199 concentrations, eliciting a maximal response of a 5.29-fold change as compared to the controls
200 (Saunders *et al.,* 2013).

201 ***Genotoxicity***

202 *In vivo* exposure to EH-TBB might be associated with DNA or chromosomal damage or
203 differential gene expression. A study by Bearr *et al.* (2010) showed EH-TBB to induce repairable
204 DNA damage in the liver tissues of *Pimephales promelas* (fathead minnows) via dietary exposure.
205 During the exposure period, significant increases in DNA strand breaks from the liver cells were

206 observed. However, such increases were not found after the recovery period (Bearr *et al.*, 2010).
207 Scanlan *et al.* (2015) reported that daphnids (*Daphnia magna*) that were exposed to five different
208 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
209 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
210 L^{-1} were used) caused differential mRNA levels at all concentrations. Exposure at 0.0486 µg L^{-1},
211 however, resulted in the largest number of differentially expressed genes. In all five
212 concentrations, three genes (a trichohyalin-like protein, peroxidase, and an unknown protein)
213 were differentially expressed, which may be useful biomarkers of exposure to FM-550 (Scanlan
214 *et al.,* 2015).
215 Dietary exposure to BEH-TEBP caused a significant increase in percent tail DNA in liver
216 tissues of fathead minnows on days 28 and 56, which was 3.4 and 6.3 times greater than in the
217 controls, respectively (Bearr *et al.*, 2010). Several i*n vivo* studies in Wistar rats exposed to BEH-
218 TEBP through dermal and intraperitoneal injection failed to identify genotoxic effects in the form
219 of micronucleated erythrocytes in the bone marrow (USEPA 2015). Consistent results were also
220 found in various *in vitro* studies using isolated human lymphocytes, where no elicited
221 chromosomal aberrations were found (USEPA 2015). Egloff *et al.* (2011) indicated that chicken
222 embryonic hepatocytes (CEH) administered with BEH-TEBP did not affect the mRNA
223 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 day^{-1} ^{14}C-labeled BTBPE for a duration of 10

242 days. In the majority of the tissues, less than 0.01% of the dose was found (Nomeir *et al.,* 1993).
243 In another study by Hakk *et al.* (2004), male Sprague-Dawley (SD) rats were given a single dose
244 of 2 mg kg^{-1} bw^{-1} ^{14}C-labeled BTBPE by gavage. 100% of the dose was recovered in the feces.
245 The same research group also demonstrated that elimination of radioactivity by bile is less than
246 1%, which suggests that fecal elimination was primarily from unabsorbed BTBPE. Due to this
247 low level of absorption, the tissue levels of BTBPE were low. 72h after being given a single dose,
248 more than 0.1% of the dose was found only in the gastrointestinal tract and carcass. No
249 compound-related effects were observed in rats after being fed up to 10% BTBPE in the diet, at
250 an estimated concentration of 35 mg kg^{-1} bw^{-1} day^{-1}, for 14 days (Hakk *et al.,* 2004). Nomeir *et al.*
251 (1993) also reported that exposure through inhalation of 5 or 20 mg L^{-1} BTBPE in the atmosphere
252 for 21 days showed no gross pathological changes in Fischer 344 rats; however, unspecified
253 histopathological lesions were observed in the lungs.

254 ***Reproductive and developmental toxicity***

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

258 ***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, 1250, 2500, and 5000 mg kg^{-1} dry sediment concentrations of DBDPE. It was observed in midges that 313, 625, and 2500 mg kg^{-1} of exposure caused lethargy and loss of equilibrium. Two dead midges were also observed from 2500 and 5000 mg kg^{-1} exposure. Larval midges were also found dead at all concentrations except at the 1250 mg kg^{-1} exposure. However, these

277 responses were not concentration-dependent and were therefore considered insignificant. In
278 oligochaetes, no mortalities or sublethal effects were observed at any of the concentrations. No
279 mortality and overt signs of toxicity were observed in trout at all concentrations after 96 hours. It
280 was assumed that one of the replicates might have been contaminated. No toxic effects have been
281 observed in either daphnids or algae (Hardy *et al.*, 2012). In repeated dose studies by Hardy *et al.*
282 (2002); Hardy *et al.* (2010); Hardy *et al.* (2011), the lowest NOAELs were the highest doses
283 tested: 1000 mg kg^{-1} day^{-1} (SD rats, 90-day) and 1250 mg kg^{-1} day^{-1} (Female Crl:CD® BR
284 VAF/Plus® rats and New Zealand White rabbits exposed prenatally).

285 ***Genotoxicity***

286 In an *in vitro* study by Egloff *et al*. (2011), DBDPE was administered to CEH, and it was
287 found that DBDPE significantly upregulated the expression of *CYP1A4/5* at 0.1 and 0.2 μM to a
288 maximum of 29- and 53-fold, respectively. Also, iodothyronine deiodinase 1 (DIO1) mRNA
289 levels significantly increased in CEH treated with 0.1 μM DBDPE (Egloff *et al.,* 2011). In
290 another study, no clinical signs of toxicity were observed in male SD rats exposed to DBDPE
291 (Wang *et al.*, 2010). It was observed that exposure to 100 mg kg^{-1} day^{-1} DBDPE did not cause any
292 significant changes in body, liver, or kidney weight. However, a decrease in creatinine (Cr) levels
293 and aspartate aminotransferase (AST) and alkaline phosphatase (ALP) activities, and elevated
294 total bile acid (TBA) levels indicated that DBDPE exposure induces hepatotoxicity in rats,

295 indicating possible oxidative stress due to the accumulation of DBDPE or its metabolites. An
296 increase in T3 levels was also observed, and it was noted that DBDPE may alter thyroid hormone
297 homeostasis. DBDPE was also shown to significantly increase the expression of *CYP3A2* by
298 1.24-fold in the liver tissue of rats (Wang *et al.*, 2010).

299 ***Toxic effects of DP in cellular and animal studies***

300 ***Acute toxicity***

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

307 ***Neurotoxicity***

308 An *in vivo* study by Chen *et al.* (2017) investigated the developmental neurobehavioral
309 toxicity of DP using embryo-larval stages of zebrafish. The embryos were waterborne-exposed to
310 DP at 15, 30, and 60 mg L^{-1} beginning from 6 hpf. Larval teratology, motor activity, motoneuron
311 axonal growth, and muscle morphology were examined at different developmental stages.
312 Reactive oxygen species (ROS) levels and 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

331 weight^{-1} (ww) (Liang *et al.,* 2014). Liver proteasomes were collected after 14 days and were
332 analyzed using two-dimensional (2D) electrophoresis. 39 protein spots out of the 740 spots that
333 were detected were found to be altered in abundance in more than one DP exposure concentration
334 compared to the controls. The 39 proteins were analyzed using matrix-assisted laser
335 desorption/ionization tandem time-of-flight (MALDI-TOF-TOF), and 27 were identified using
336 mass spectrometry (MS). Exposure to DP down-regulated signal transduction-related proteins
337 (Ras-related protein Rab-6B and BAI1-associated protein 2-like 1b), Annexin A4 (ANXA4), and
338 T-complex protein 1 subunit epsilon (CCT5). In contrast, increased abundance of CDHR2 and
339 up-regulation of heat shock cognate protein 70 (HSC70) were observed following DP exposure.
340 These differentially expressed proteins may induce cell proliferation, apoptosis, and oxidative
341 stress in juvenile Chinese sturgeons (Liang *et al*., 2014). Oxidative stress in other test organisms
342 such as quail, mice, and earthworms caused by DP exposure was also investigated (Wu *et al.*,
343 2012; Li *et al.*, 2013; Zhang *et al.*, 2014). A recent study by Gagné *et al.* (2017) reported that DP
344 induces oxidative stress in *Mytilus edulis* (blue mussels.) The study investigated the *in vivo* and *in*
345 *vitro* effects of DP exposure on histopathology, lipid peroxidation (LPO) levels, cyclooxygenase
346 (COX) activity, phagocytosis capacity and efficiency, and DNA strand breakage in the blue
347 mussel following a 29-day exposure (0.001, 0.01, 0.1, and 1.0 μg L^{-1} DP). No significant change
348 in hemocyte phagocytosis rate or viability was found for either *in vivo* or *in vitro* exposure.

Effects of i*n 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 *Vicia faba* and *Tetrahymena 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, 1500 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 1500 μg L^{-1} DP. DP concentrations ranging from 300 to 1500 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 cellular and animal studies

Immunotoxicity and developmental toxicity

Olsman *et al.* (2007); Ao *et al.* (2009); Haijima *et al.* (2010); 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 or 2,3,7,8-TeBDD showed nearly identical potencies for endpoints that detect immunotoxicity, such as thymus weight and thymocyte numbers and spleen

385 weight and splenocyte numbers (Ao *et al.*, 2009). Additionally, PeBDD caused dose-independent
386 inhibition of IL-5 production by splenocytes (Ao *et al.*, 2009). Another recent study presented
387 relative potencies for immune suppression of several PBDD/Fs and their chlorinated analogs in
388 female B6C3F1/N mice. 1PeBDF, 4PeBDF, and some chlorinated analogs suppressed the
389 immunoglobulin M (IgM) antibody response (Frawley *et al*., 2014).

390 ***Genotoxicity and neurotoxicity***

391 Frawley *et al.* 2014 reported that thyroxine transport protein (*Ttr)* and xenobiotic metabolizing
392 enzyme (XME) gene expression, which are used to assess aryl hydrocarbon (AhR)-mediated
393 responses, were suppressed and upregulated, respectively, by PBDD/Fs. TriBDD, however, had
394 no effect on antibody response. It was concluded in the study that the brominated analogs were
395 more potent for immunotoxicity compared to their chlorinated analogs (Frawley *et al*., 2014).
396 AhR-mediated responses to PBDD/Fs were studied using three mammalian and one fish dioxin-
397 specific bioassays (Olsman *et al*., 2007). All of the tested PBDD/Fs induced AhR-mediated
398 activity. Further, the relative potencies of individual PBDD/Fs were similar to those of their
399 chlorinated analogs using the three mammalian cell lines under investigation. On the other hand,
400 the relative potencies obtained using a fish cell line were comparatively lower than those in the
401 mammalian cell lines, which could be attributed to the differences in the cell line and reporter
402 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 additive fire retardant 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 isomers of 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 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

440 contamination levels of anti-DP compared with syn-DP were found in house dusts from Hong
441 Kong, China, and Canada (Li *et al.*, 2015a; Zheng *et al.*, 2015; Deng *et al.*, 2016; Fan *et al.*,
442 2016). In contrast, syn-DP exhibited higher levels than anti-DP in Egyptian house dusts (Hassan
443 and Shoeib, 2015). However, in Pakistan, differences in DP contamination were observed in
444 house dusts sampled from different areas (Khan *et al.*, 2016). Additionally, house dust samples
445 from e-waste recycling areas have also beem shown to exhibit higher DP contamination
446 compared to samples from non-e-waste recycling areas (Zheng *et al.*, 2015). Furthermore,
447 workplaces and cars in Egypt were found to exhibit higher DP levels compared to houses (Hassan
448 and Shoeib, 2015) while kindergarten schools exhibited lower DP contamination compared to
449 houses in Hong Kong (Deng *et al.*, 2016).

450 NBFRs are also known to widely exist, and several researchers worldwide have shown interest
451 in the detection of contamination levels in the indoor environment. Chinese studies have reported
452 levels of NBFR in indoor dusts collected from houses, offices, e-waste recycling sites, cars, and
453 other public areas (Cao *et al.*, 2014; Qi *et al.*, 2014; Zheng *et al.*, 2015; Peng *et al.*, 2017). Human
454 activities and geographical distribution influences indoor NBFR pollution levels (Qi *et al*., 2014).
455 Indoor dust from urban areas and public buildings showed significantly higher levels of NBFRs
456 than rural areas and family homes indicating the different applications of NBFRs (Qi *et al*., 214).
457 A temporal trend study on NBFRs revealed that NBFR concentrations are relatively stable during

458 any season and that human activities do not affect seasonal variations in NBFR contamination
459 (Cao *et al.*, 2014). In e-waste recycling areas, different pollutant patterns have been observed at
460 different sites, which could be attributed to the different kinds of e-waste dismantled during
461 recycling activities at each site (Zheng *et al.*, 2015). As to human exposure, Zheng *et al.* (2015)
462 and Peng *et al.* (2017) both reported that human exposure to NBFRs via dust ingestion is higher
463 in toddlers compared with adults. In these studies (Cao *et al.*, 2014; Qi *et al.*, 2014; Zheng *et al.*,
464 2015; Peng *et al.*, 2017), DBDPE was the dominant compound, exhibiting the highest
465 contamination level in all sampling areas, suggesting that DBDPE had been used or released in
466 large amounts in China. Furthermore, indoor dust samples collected from e-waste recycling areas
467 showed relatively higher NBFR contamination compared to other areas. The levels of NBFR in
468 the indoor environment in other Asian countries have also been investigated (Ali *et al.*, 2014;
469 Hassan and Shoeib, 2015; Mizouchi *et al.*, 2015; Khan *et al.*, 2016; Kurt-Karakus *et al.*, 2017). In
470 Pakistan, DBDPE levels in house dust (Khan *et al.*, 2016) were found to be higher compared to
471 those found in universities, clothing stores, and electronics stores (Ali *et al.*, 2014). However,
472 these levels were relatively lower compared to DBDPE levels in house dust collected from Japan
473 (Mizouchi *et al.*, 2015), except for one Pakistani rural home and one home from a colder area in
474 Pakistan, in which the values were higher. Ali *et al.* (2014) reported lower BTBPE levels than
475 DBDPE in universities, clothing stores, and electronics stores. EH-TBB, BTBPE, and BEH-

476 TEBP concentrations in Egyptian and Turkish indoor environments were studied (Hassan and
477 Shoeib, 2015; Kurt-Karakus *et al.*, 2017). Low NBFR contaminations were found in homes,
478 workplaces, and cars in Egypt. The use of flame retardants is not regulated in Egypt, therefore,
479 imported goods incorporated with NBFRs maybe one source of NBFR contamination.
480 Consequently, the levels found in Egyptian dusts were among the lowest NBFR contamination
481 reported compared to other countries (Hassan and Shoeib, 2015). Higher EH-TBB, BTBPE, and
482 BEH-TEBP concentrations were found in Turkish indoor dusts (Kurt-Karakus *et al*., 2017). EH-
483 TBB were among the highest concentrations, followed by BTBPE, while most BEH-TEBP levels
484 were less than the method detection limit (Kurt-Karakus *et al*., 2017). In indoor air samples
485 collected from Turkish homes and offices, EH-TBB was also found to be the most dominant
486 compound (Kurt-Karakus *et al*., 2017).

487 Contamination levels of NBFRs in the United States and other parts of Europe have also been
488 reported. In the United States, levels of NBFRs were measured in the indoor dust from houses
489 and fire stations (Brown *et al.*, 2014; Schreder and La Guardia, 2014). Dust samples from
490 California homes and in living quarters from California fire stations were investigated for EH-
491 TBB, BTBPE, DBDPE, and BEH-TEBP contamination. Dust samples from the fire stations
492 showed higher concentrations compared to those from houses, with EH-TBB being the most
493 dominant compound in both sampling areas. NBFRs released during fire events might have

494 transferred to the living quarters of fire stations through the firefighters (Brown *et al*., 2014).
495 Lower levels of EH-TBB and BEH-TEBP and higher levels of BTBPE and DBDPE were found
496 in house dust collected from Washington compared to house dust from California, with EH-TBB
497 also found to be the most dominant NBFR (Schreder and La Guardia, 2014). In Canadian house
498 dusts, lower levels of EH-TBB and BTBPE were obtained compared to American house dusts,
499 with EH-TBB present in higher concentrations than BTBPE (Fan *et al.*, 2016). In European
500 countries, dust samples from various indoor environments were investigated for NBFR
501 contamination (Cequier *et al.*, 2014; Fromme *et al.*, 2014; Al-Omran and Harrad, 2016; Cristale
502 *et al.*, 2016; Kuang *et al.*, 2016). Living rooms from the United Kingdom were shown to exhibit
503 higher levels of NBFRs compared to kitchens, with DBDPE having the highest concentrations in
504 both areas (Kuang *et al.*, 2016). However, in another UK study, BEH-TEBP exhibited the highest
505 concentrations in house dusts (Al-Omran and Harrad, 2016). Similar results were obtained in a
506 German study, where BEH-TEBP was the dominant NBFR in house dusts (Fromme *et al.*, 2014).
507 In Norway, NBFR levels in school classrooms were higher compared to those of residential
508 living rooms, with DBDPE showing the highest concentrations in both environments (Cequier *et*
509 *al.*, 2014). In Spain, NBFRs in indoor dust from schools were not detectable except for BEH-
510 TEBP. The highest level of NBFR contamination was found in dusts collected from theatres,
511 followed by homes, and universities/research institutions (Cristale *et al.*,2014).

512

513 **PBDD/FS IN THE INDOOR ENVIRONMENT**

514 The global concentrations of PBDD/Fs in the indoor environment are listed in Table 2. In
515 indoor environments, PBDD/Fs have mainly been studied in dust. Most of the recent studies are
516 from Asian countries including Japan, Vietnam, and Taiwan but there are also some from western
517 countries such as Sweden and the USA. House dusts collected from a residential house in an e-
518 waste recycling site in Vietnam showed higher average PBDD/F concentrations compared to
519 general urban Vietnamese environment house dusts (Tue *et al.*, 2010). Workshop floor dust
520 collected from an e-waste recycling site in Taizhou, China, however, showed higher average
521 PBDD/F levels compared to that of Vietnam (Ma *et al.*, 2009). However, the maximum PBDD/F
522 concentration found by Ma *et al*. (2009) were still below the maximum PBDD/F levels found in
523 an American residential house dust (Tue *et al*., 2013). In Japan, PBDD/F is among one of the
524 major dioxin-like compounds in indoor dust. Suzuki *et al*. (2010) reported that levels of PBDD/Fs
525 in Japanese office dusts were similar to those of house dusts. Moreover, Japanese PBDD/Fs
526 house dust levels were in a range similar to those found in Vietnam. In Taiwan, indoor dust levels
527 of PBDD/Fs in school classrooms from rural areas were higher compared to urban school
528 classrooms (Gou *et al.,* 2016b). In addition, Taiwanese school classrooms' PBDD/F levels were
529 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 a waste electrical 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*., 215). 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; Chao *et al.*, 2016; Deng *et al.*, 2016; Li *et al.*, 2015a; Xu *et al.*, 2015). To our knowledge, there are no known reports that have

569 investigated the levels of $PM_{2.5}$-bound DP, NBFRs, or PBDD/Fs in the indoor environment.
570 Respirable fine particulates are reported to have correlations to various cardiopulmonary health
571 effects such as cardiovascular and respiratory diseases (de Oliveira *et al.*, 2012; Dominici *et al.*,
572 2006; Zhang *et al.*, 2013; Xing *et al.*, 2016). Numerous studies have turned their focus on $PM_{2.5}$
573 levels due to the possibility of these small particles being deposited deep into the lungs, thus
574 causing respiratory ailments and diseases, as well as other negative health problems (Zhang *et al.*,
575 2013; Gautam *et al.*, 2016; Hwang *et al.*, 2016; Xing *et al.*, 2016; Lee *et al.*, 2016; Lu *et al.*,
576 2016; Ma *et al.*, 2017). People with a known history of cardiopulmonary problems face higher
577 risk of mortality due to the increasing $PM_{2.5}$ concentrations in the atmosphere while normal
578 people also face a higher risk of developing respiratory problems (Dominici *et al.*, 2006; de
579 Oliveira *et al.*, 2012; Xing *et al.*, 2016; Li *et al.*, 2017). $PM_{2.5}$ is the essential issue for human
580 health in both the indoor and outdoor environment. **Although most environmental scientists**
581 **recognize that high levels of $PM_{2.5}$-bound HFRs including PBDEs are well known in the**
582 **indoor environment, few reports have considered their toxic effects for human health via**
583 **inhalation. Moreover, with $PM_{2.5}$-bound PBDEs being a very important concern, then**
584 **$PM_{2.5}$-bound NBFRs, DP, and PBDD/Fs should be of important concern also. Future works**
585 **will be continuously encouraged to investigate indoor levels of $PM_{2.5}$-bound NBFRs, DPs,**
586 **and PBDD/Fs to further evaluate their body burden percentage via inhalation pathway and**
587 **to assess the health risks or the health effects of direct inhalation.**
588

589 ## CONCLUSIONS

590 There is currently a significant increase in global demand for DP and NBFRs as substitutes
591 to the banned conventional brominated flame retardants. Global data on the indoor environment,

592 particularly, indoor dust, have reported the presence of NBFRs, DP, and PBDD/Fs. **Currently,**
593 **there is a limited global toxicological data for these chemicals. The toxicological data for**
594 **NBFRs, DP, and PBDD/Fs, which includes acute toxicity, developmental toxicity,**
595 **immunotoxicity, neurotoxicity, reproductive toxicity, genotoxicity, or disruption of**
596 **hormones, are reported in various *in vitro* and *in vivo* studies.** Most previous studies focused
597 only on non-dietary intake of HFRs such as PBDEs, DP, and NBFRs, and there is a lack of study
598 on simultaneous levels in indoor dust and fine particulate samples. Therefore, in order to assess
599 their risks and potential for adverse health effects through main exposure routes, including dust
600 ingestion and inhalation of respirable fine particles, additional studies are required to further
601 observe their levels in the indoor environment, particularly in dust and fine particulate samples.
602

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608

609 ## DISCLAIMER

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

611

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