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TOX/2019/10

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Committee view on phosphate-based flame retardants and the potential for developmental toxicity – first draft

This paper presents a first draft COT view on the potential for developmental toxicity of phosphate-based flame retardants, following the COT discussion of TOX/2018/39 in October 2018 and TOX/2019/09 at the present meeting.

Members are invited to comment on the structure and contents of the draft opinion.

NCET at WRc/IEH-C under contract supporting the PHE Secretariat
March 2019

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Committee view on phosphate-based flame retardants and the potential for developmental toxicity

First draft Committee view.

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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Committee view on phosphate-based flame retardants and the potential for developmental toxicity v0-1

Background

1. Due to the stringent requirements of the Furniture and Furnishings (Fire) (Safety) Regulations introduced in 1988 in the UK, the use of flame retardants is greater in the UK than the rest of Europe.

2. Until recently, brominated flame retardants (BFRs) such as polybrominated diphenyl ethers (PBDEs) were the most common chemical flame retardant used for furnishing and textiles (Hendriks and Westerink, 2015). In 2004, penta-BDE and octa-BDE were banned in the European Union (EU) based on their neurotoxic properties, bioaccumulation and persistence (Noyes and Stapleton, 2014); mixtures of deca-BDE have been restricted in the EU since 2008; and in 2009, PBDEs were included in the Persistent Organic Pollutants (POPs) list (Noyes and Stapleton, 2014).

3. The restrictions on PBDEs have led to an increase in alternative chemical flame retardants (Dodson et al., 2012; Stapleton et al., 2011), some of which include phosphate-based flame retardants (PFRs), or commercial mixtures of PFRs and non-PBDE BFRs, e.g. Firemaster 550®[1] (Dodson et al., 2012; Rock et al., 2018).

4. PFRs show some structural similarity to other classes of organophosphates, such as organophosphate (OP) pesticides, which have been shown to interfere with neurodevelopment by cholinergic and noncholinergic pathways (Pope, 1999). The United States Consumer Product Safety Commission (CPSC) and the Agency for Toxic Substances and Disease Registry (ATSDR) identified children as a potentially susceptible population to PFR exposure (ATSDR, 2012; CPSC, 2006).

5. Therefore, the Committee was asked for an opinion on the potential for PFRs to cause developmental toxicity.

Introduction to PFRs

6. PFRs have a structural similarity with OP pesticides as they share the same generic OP chemical structure (Dishaw et al., 2014) (Figure 1). The generic structure

[1] Firemaster 550® is a mixture of two brominated compounds (bis (2-ethylhexyl)-2,3,4,5-tetrabromophthalate (TBPH) and 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (TBB)) and two phosphate-based compounds (triphenyl phosphate (TPHP) and a mixture of isopropylated triarylphosphate isomers (ITPs)) (Rock et al., 2018).

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is comprised of a central phosphorous atom (P) with a phosphoric (=O) bond, a leaving group (X) and two other side groups (R1 and R2) (Elersek and Filipic, 2011).

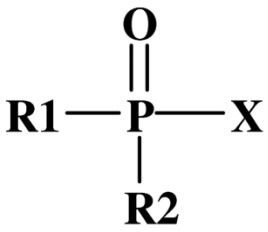

Figure 1. Generic structure of organophosphates

7. PFRs may be grouped into non-halogenated (e.g. triphenylphosphate (TPHP) and tricresylphosphate (TCP)), and halogenated PFRs (e.g. tris (2-chloroisopropyl) phosphate (TCPP) and tris (1,3-dichloro-2-propyl) phosphate (TDCPP) (IPCS, 1997). More information on the chemical structures and physico-chemical properties of these compounds is presented in TOX/2018/39.

Cholinergic and non-cholinergic mechanisms of neurotoxicity

8. OP compounds such as OP pesticides and PFRs have been associated with both cholinergic and non-cholinergic mechanisms of neurotoxicity as described in TOX/2018/39 and TOX/2019/09.

9. The cholinergic mechanism functions via inhibition of AChE and is generally well researched and described (Elersek and Filipic, 2011). OP neurotoxicity occurs via the phosphorylation and subsequent inhibition of AChE due to a nucleophilic reaction of the leaving group to a critical serine residue within the AChE active site. The reverse hydrolysis reaction to reactivate the AChE is slow resulting in AChE inhibition. This inhibition causes an accumulation of the neurotransmitter acetylcholine and an overstimulation of cholinergic receptors (Pope, 1999).

10. The inhibition of AChE is dependent on three main factors; 1) the affinity of the OP for the AChE binding site; 2) strength of the bond between the phosphor moiety and the leaving group; and 3) the rate of the hydrolysis reaction between the active site serine and the phosphor moiety that leads to regeneration of the activity of the enzyme. Potent neurotoxins, such a nerve agents, have a high affinity for the AChE inhibition binding site, as they have an easily cleaved bond between the phosphor moiety and the leaving group and slow hydrolysis of the serine-phosphor bond once formed (Elersek and Filipic, 2011; Moshiri *et al.*, 2012). In contrast, the leaving groups of less toxic OP compounds, such as pesticides, have a low affinity for the AChE active site, usually due the presence of alkyl or aryl functional groups or side groups, resulting in less potent neurotoxicity (Elersek and Filipic, 2011). As PFRs generally have larger alkyl chains in the leaving/side groups they may also exhibit reduced affinity for AChE and therefore limited neurotoxicity of PFRs via inhibition of AChE may be anticipated. Dishaw (2015) suggested that PFRs do not

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have a strong binding affinity for AChE and exhibit low acute toxicity compared with OP pesticides.

11. An early study tested the inhibitory activity of various halogenated and non-halogenated PFRs on AChE, isolated from organs of the electric ray *Torpedo ocellata (*at concentrations that were considered to be realistic in terms of likely human exposure). Authors reported that PFRs are not potent AChE inhibitors, when compared to the OP pesticide diisopropyl phosphorofluoridate used as the control (Eldefrawi et al., 1977).

12. Other authors noted that human exposure to PFRs is usually chronic, low level exposure, rather than acute exposure to high doses that are associated with OP pesticide cholinergic toxicity (Abou-Donia et al., 2016). Other factors that influence the interaction of OPs with AChE are discussed in TOX/2019/09. The Committee considered that, in general, PFRs appear to be, at most, only weak inhibitors of AChE.

13. The non-cholinergic mechanisms of OP neurotoxicity are less understood. Some non-cholinergic mechanisms are thought to include the inhibition of neuropathy target esterase (NTE), which leads to Organophosphate Induced Delayed Neurotoxicity (OPIDN), a neurodegenerative disorder characterised by a latent period of several weeks between exposure and the manifestation of neurological effects (e.g. ataxia or paralysis) (Abou-Donia et al., 2016). Sufficient NTE must be irreversibly inhibited before OPIDN develops (Ehrich et al., 1997). Therefore the delay in initiation of neurological effects is thought to be due to this progressive inhibition of NTE by reaction with OP compounds (Jokanovic et al., 2011).

14. A number of structural features appear to be essential for the neurotoxicity observed in OPIDN including the presence of an ortho-methyl group in an aromatic series (as seen in ortho-TCP). This is readily metabolised to a cyclic phosphate which is similar in structure to the potent neurotoxin, saligenin, that inhibits NTE. Such metabolism must occur for the chemical to be neurotoxic. Esters with no ortho-substituents, such as TPHP, are not neurotoxic as metabolism does not occur. In addition, neurotoxicity is decreased by further substitution on the phenyl ring with additional methyl groups in the meta or para positions by providing alternative hydroxylation pathways without the formation of a cyclic ester due to steric hindrance (i.e. meta-TCP). The size of the substituent on the ortho position also affects the neurotoxicity potency. Larger and more branched substituents e.g. a butyl group, interfere with metabolic activation to neurotoxic metabolites, due to steric hindrance (ATSDR, 2012; Weiner and Jortner, 1999).

15. Other non-cholinergic mechanisms may include the neurotransmitter gamma-aminobutyric acid (GABA), as various studies have demonstrated PFRs exert antagonistic effects on GABA in mice (Umezu et al., 1998). Gant et al. (1987) have shown that PFRs including TPHP and ortho-TCP can bind to the GABA regulated chloride channel with IC_{50}s 18 and less than 10µM, respectively. This property is

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unrelated to AChE inhibition and is not shared by the OP neurotoxic agents with the exception of soman that had an IC_{50} of 24 µM.

16. Dishaw et al. (2011) compared the neurotoxicity of a number of PFRs to chlorpyrifos using PC12 cells, an *in vitro* model for neurodevelopmental toxicity. Further details are described in TOX/2019/09. Authors reported that the potency of PFRs for neurodevelopment toxicity was similar or greater than that of an OP pesticide (chlorpyrifos). Overall, authors concluded that PFRs may also elicit similar toxicity to OP pesticides based on non-cholinergic mechanisms (Dishaw *et al.*, 2014; Dishaw *et al.*, 2011). The Committee noted, however, that the high concentrations (50 µM) of PFRs were used in this study which are not considered to be realistic compared to human exposure to PFRs.

17. In a later paper studying effects in early life stage zebrafish, PFRs were demonstrated to elicit overt and neurodevelopmental toxicity at concentrations similar to, or below that of chlorpyrifos (PFRs 3.3-10 µM; chlorpyrifos 10 µM (Dishaw *et al.*, 2014).

Exposure to PFRs

Potential routes of exposure

18. PFR exposure occurs through inhalation and ingestion of dust released from furnishings and consumer products, and through dermal contact with the products in which PFRs are found (Ali et al., 2012; Dishaw, 2015; Schreder et al., 2016; Zheng et al., 2017). Infants and young children have a greater potential for oral exposure due to hand-to-mouth and thumb-sucking behaviour (Butt et al., 2016), as well as a greater potential for both inhalation exposure, due to increased breathing rates, and dermal exposure, due to increased contact with treated textiles (Abdallah et al., 2015) and crawling activity on carpets (Dishaw, 2015). TCEP and TPHP have been detected in human breast milk also indicating the potential for oral PFR exposure for infants during lactation (Kim et al., 2014).

19. Exposure estimates and biomonitoring results are described in TOX/2018/39.

20. Exposure to flame retardants, not specifically PFRs, from dust has been estimated based on the US Environmental Protection Agency (EPA) ingestion rates of 100 mg dust/day and 20 mg dust/day for children and adults respectively. The average cumulative exposure to flame retardants from dust ingestion was estimated to be 16 µg/day for children (1.6 µg/kg bw/day for a 10 kg child) and 0.3 µg/day for adults (0.004 µg/kg bw/day for a 70 kg adult) (Stapleton *et al.*, 2009). Authors reported that PBDEs and TPHP and TDCPP accounted for the majority of exposure.

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Toxicity of PFRs

Sensitive groups for this assessment

21. Based on the greater potential for exposure, infants and young children are being considered for this assessment, as well as potential effects on the developing fetus.

Human data

22. The effect of PFRs in humans was discussed in TOX/2018/39 and TOX/2019/09, including the endpoints of neurotoxicity, developmental toxicity, teratogenicity, and endocrine effects.

23. Limited human data indicate a potential correlation between PFR exposure and reduced cognitive performance and poorer social behaviours, although the Committee noted some inconsistency in the findings between studies.

24. Lipscomb et al. (2017) assessed personal exposure to flame retardants of 69 3-5 year old children for 7 days. Total PFRs (sum of TCEP, TCPP, TDCPP and TPHP) were associated with less responsibility ($p<0.001$) and greater externalising problems ($p<0.05$). Similar results of reduced cognitive performance and exposure to TCEP were reported in 6-8 year old children (Hutter et al., 2013). In the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study, higher total PFR metabolites[2] measured in maternal urine during pregnancy and DPHP alone were associated with decreased working memory and reduced intelligence quotient (IQ) scores of the children at 7 years old. Exposures to other neurotoxicants that had been found to be related to child IQ or attention-deficit/hyperactivity disorder in the cohort were controlled for in the study (Castorina et al., 2017).

25. While different outcomes in the human studies were identified as significant, they all related to cognitive function or performance of children. The Committee commented that in some cases it was not clear whether these studies had sufficiently adjusted for potential exposure to other chemicals or factors that may affect cognitive performance.

In vivo/in vitro data

26. A number of PFRs are reported to induce signs of neurotoxicity in acute and repeat dose studies (ATSDR, 2012). However, no juvenile neurotoxicity studies in experimental animals were located. ATSDR (2012) considered the results of oral embryo-fetal studies conducted in experimental animals with TCEP, TDCPP, TPHP, TCPP,TCP, tri-n-butyl phosphate (TnBP) and TBEP and concluded that PFRs are not fetotoxic or teratogenic even at doses that cause maternal toxicity (reduced body weight). The highest dose tested in all studies was 1,500 mg/kg bw/day TBEP.

[2] sum of bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), diphenyl phosphate (DPHP), isopropyl phenyl phenyl phosphate (ip-PPP) and tertbuylphenyl phenyl phosphate (tb-PPP))

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27. There is some evidence of limited PFR accumulation in the placenta in the rat. Rats treated with up to 3.3 mg/kg bw/day Firemaster (comprising brominated flame retardant and TPHP) accumulated TPHP in the placenta, although to a lesser degree compared with the brominated components. The mean placental TPHP levels were 6.5 ± 2.02 ng/g w/w in male placenta. However, there is no evidence of placental transfer of PFRs to the fetus as placental levels were higher than fetal levels. The authors concluded that the placenta may be a critical target organ for some PFRs and may impact fetal development (Baldwin et al., 2017; Phillips et al., 2016).

Discussion

28. PFRs are found ubiquitously in household dust and biomonitoring data suggests that exposure is widespread and increasing overtime. Young children and infants have been identified as a particularly susceptible subpopulation for greater exposure via the oral, inhalation and dermal routes. There is little information available on the levels of exposure to PFRs, but there was concern for potential exposures e.g. to infants sleeping on new mattresses.

29. PFRs share a structural similarity with OP pesticides and other OP compounds. However, the presence of alkyl or aryl functional groups as leaving groups, as seen in PFRs, is thought to result in the leaving group having a lower affinity for the AChE active site, thereby causing less inhibition and subsequent neurotoxicity compared with OP pesticides. Some *in vitro* and *in vivo* studies have demonstrated AChE inhibition by PFRs but only at high concentrations. The Committee considered the concentrations used were not relevant to human exposure. Although no IC_{50} data were available, the Members considered that PFRs appear to be only weak inhibitors of ACHE, at most, based on the paper by (Eldefrawi et al., 1977).

30. It has additionally been hypothesised that PFRs may also elicit similar toxicity as OP pesticides based on non-cholinergic mechanisms although high concentrations, not representative of human exposure, were required for PFRs to elicit OPIDN. Some PFRs and OP pesticides cause OPIDN and OPICN, via the inhibition of NTE. A number of structural features are essential for this neurotoxicity to occur, including the presence of an ortho-methyl group on the aromatic ring, as seen in ortho-TCP. This allows metabolism to a neurotoxic metabolite. PFRs with no ortho-substituents, such as TPHP are not neurotoxic via inhibition of NTE. Moreover, those with substituents in the meta or para positions, and larger more branched PFRs, such as those with longer chain substituents, exhibit less neurotoxicity than those with ortho-substituents.

31. TPHP and commercial TCP (isomeric mixture) are both commonly used flame retardants. The commercial TCP mixture contains ortho-TCP only as a contaminant at very low concentrations (<0.1 %). Studies have demonstrated that commercial TCP had reduced neurotoxic potential compared to ortho-TCP alone. In addition, due to its structure (lack of ortho-methyl groups) TPHP is not neurotoxic via inhibition of NTE.

32. There is a small potential for toxicity to occur though inhibition of the GABA regulated chloride channel. Inhibition of this channel appears to be a property of PFR type molecules and not shared with nerve agents. There is however only one published study, making it difficult to assess the relevance of this finding to developmental toxicity.

33. A number of epidemiology studies in children were presented, suggesting some potential effects on cognitive function in children. There were, however, inconsistencies between studies. The Committee considered the CHAMACOS study to be a well-designed cohort study. Different outcomes were identified as being significant across the epidemiological evidence, although all were generally related to cognitive function or performance of children.

34. Although the CHAMACOS study appeared to adjust for other neurotoxicants that are related to child IQ or attention-deficit/hyperactivity disorder in the cohort, it was unclear whether other studies had adjusted sufficiently for potential exposure to other chemicals or factors affecting cognitive performance.

35. Overall, the Committee noted that the mode of action for any potential neurotoxic effect is unlikely to be the same as for OP pesticides.

COT conclusion

36. Overall, the Committee determined that the experimental evidence suggested that PFRs were not similar to OPs in terms of activity and therefore there was a lack of biological plausibility of the potential for PFRs to exhibit similar effects to OPs. There was no evidence of a direct developmental effect of PFRs. However the epidemiological evidence has suggested a potential neurodevelopmental effect, although there were limitations to this evidence.

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References

Abdallah, M.A.E., Pawar, G. and Harrad, S. (2015) Evaluation of in vitro vs. in vivo methods for assessment of dermal absorption of organic flame retardants: A review. *Environment International,* 74, 13-22.

Abou-Donia, M.B., Salama, M., Elgama, M., Elkholi, I. and Wang, Q. (2016) Organophosphorus Flame Retardants (OPFR): Neurotoxicity. *Journal of Environment and Health Sciences,* 2, 1-30.

Ali, N., Van den Eede, N., Dirtu, A.C., Neels, H. and Covaci, A. (2012) Assessment of human exposure to indoor organic contaminants via dust ingestion in Pakistan. *Indoor air,* 22, 200-211.

ATSDR (2012) Toxicological profile for phosphate ester flame retardants. US Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, Georgia.

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 Developmental Firemaster 550 Exposure in Wistar Rats. *Scientific Reports,* 7.

Butt, C.M., Hoffman, K., Chen, A., Lorenzo, A., Congleton, J. and Stapleton, H.M. (2016) Regional comparison of organophosphate flame retardant (PFR) urinary metabolites and tetrabromobenzoic acid (TBBA) in mother-toddler pairs from California and New Jersey. *Environment international,* 94, 627-634.

Castorina, R., Bradman, A., Stapleton, H.M., Butt, C., Avery, D., Harley, K.G., Gunier, R.B., Holland, N. and Eskenazi, B. (2017) Current-use flame retardants: Maternal exposure and neurodevelopment in children of the CHAMACOS cohort. *Chemosphere,* 189, 574-580.

CPSC (2006) CPSC Staff Preliminary Risk Assessment of Flame Retardant (FR) Chemicals in Upholstered Furniture Foam. United States Consumer Product Safety Commission. Bethesda, MD 20814.

Dishaw, L.V. (2015) Halogenated Organophosphate Flame Retardants: Developmental Toxicity and Endocrine Disruptive Effects. Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Environment in the Graduate School of Duke University.

Dishaw, L.V., Hunter, D.L., Padnos, B., Padilla, S. and Stapleton, H.M. (2014) Developmental exposure to organophosphate flame retardants elicits overt toxicity and alters behavior in early life stage zebrafish (danio rerio). *Toxicological Sciences,* 142, 445-454.

Dishaw, L.V., Powers, C.M., Ryde, I.T., Roberts, S.C., Seidler, F.J., Slotkin, T.A. and Stapleton, H.M. (2011) Is the PentaBDE replacement, tris (1,3-dichloro-2-propyl) phosphate (TDCPP), a developmental neurotoxicant? Studies in PC12 cells. *Toxicol Appl Pharmacol,* 256, 281-9.

Dodson, R.E., Perovich, L.J., Covaci, A., Van Den Eede, N., Ionas, A.C., Dirtu, A.C., Brody, J.G. and Rudel, R.A. (2012) After the PBDE phase-out: A broad suite of flame retardants in repeat house dust samples from California. *Environmental Science and Technology,* 46, 13056-13066.

Egloff, C., Crump, D., Porter, E., Williams, K.L., Letcher, R.J., Gauthier, L.T. and Kennedy, S.W. (2014) Tris(2-butoxyethyl)phosphate and triethyl phosphate alter embryonic development, hepatic mRNA expression, thyroid hormone levels, and circulating bile acid concentrations in chicken embryos. *Toxicology and applied pharmacology,* 279, 303-310.

Ehrich, M., Correll, L. and Veronesi, B. (1997) Acetylcholinesterase and neuropathy target esterase inhibitions in neuroblastoma cells to distinguish organophosphorus compounds causing acute and delayed neurotoxicity. *Fundam Appl Toxicol,* 38, 55-63.

Eldefrawi, A.T., Mansour, N.A., Brattsten, L.B., Ahrens, V.D. and Lisk, D.J. (1977) Further toxicologic studies with commercial and candidate flame retardant chemicals. Part II. *Bull Environ Contam Toxicol,* 17, 720-6.

Elersek, T. and Filipic, M. (2011) Organophosphorous Pesticides - Mechanisms of Their Toxicity,Pesticides - The Impacts of Pesticides Exposure. Prof. Margarita Stoytcheva (Ed.), ISBN: 978-953-307-531-0.

Gant, D.B., Eldefrawi, M.E. and Eldefrawi, A.T. (1987) Action of organophosphates on GABAA receptor and voltage-dependent chloride channels. *Fundam Appl Toxicol,* 9, 698-704.

Hendriks, H.S. and Westerink, R.H. (2015) Neurotoxicity and risk assessment of brominated and alternative flame retardants. *Neurotoxicol Teratol,* 52, 248-69.

Hoffman, K., Stapleton, H.M., Lorenzo, A., Butt, C.M., Adair, L., Herring, A.H. and Daniels, J.L. (2018) Prenatal exposure to organophosphates and associations with birthweight and gestational length. *Environment international,* 116, 248-254.

Hutter, H.P., Haluza, D., Piegler, K., Hohenblum, P., Fröhlich, M., Scharf, S., Uhl, M., Damberger, B., Tappler, P., Kundi, M., Wallner, P. and Moshammer, H. (2013) Semivolatile compounds in schools and their influence on cognitive performance of children. *International journal of occupational medicine and environmental health,* 26, 628-635.

IPCS (1997) Flame Retardants: A General Introduction. Environmental Health Criteria 192. International Programme on Chemical Safety. World Health Organization, Geneva. ISBN: 92 4 157192 6.

Jokanovic, M., Kosanovic, M., Brkic, D. and Vukomanovic, P. (2011) Organophosphate induced delayed polyneuropathy in man: an overview. *Clin Neurol Neurosurg,* 113, 7-10.

Kim, J.W., Isobe, T., Muto, M., Tue, N.M., Katsura, K., Malarvannan, G., Sudaryanto, A., Chang, K.H., Prudente, M., Viet, P.H., Takahashi, S. and Tanabe, S. (2014)

Organophosphorus flame retardants (PFRs) in human breast milk from several Asian countries. *Chemosphere,* 116, 91-97.

Kim, S., Jung, J., Lee, I., Jung, D., Youn, H. and Choi, K. (2015) Thyroid disruption by triphenyl phosphate, an organophosphate flame retardant, in zebrafish (Danio rerio) embryos/larvae, and in GH3 and FRTL-5 cell lines. *Aquatic Toxicology,* 160, 188-196.

Lipscomb, S.T., McClelland, M.M., MacDonald, M., Cardenas, A., Anderson, K.A. and Kile, M.L. (2017) Cross-sectional study of social behaviors in preschool children and exposure to flame retardants. *Environmental Health: A Global Access Science Source,* 16.

Moshiri, M., Darchini-Maragheh, E. and Balali-Mood, M. (2012) Advances in toxicology and medical treatment of chemical warfare nerve agents. *Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences,* 20, 81-81.

Noyes, P.D. and Stapleton, H.M. (2014) PBDE flame retardants. *Endocrine Disruptors,* 2, e29430.

Phillips, A.L., Chen, A., Rock, K.D., Horman, B., Patisaul, H.B. and Stapleton, H.M. (2016) Editor's Highlight: Transplacental and Lactational Transfer of Firemaster(R) 550 Components in Dosed Wistar Rats. *Toxicological sciences : an official journal of the Society of Toxicology,* 153, 246-257.

Pope, C.N. (1999) Organophosphorus pesticides: do they all have the same mechanism of toxicity? *J Toxicol Environ Health B Crit Rev,* 2, 161-81.

Preston, E.V., McClean, M.D., Claus Henn, B., Stapleton, H.M., Braverman, L.E., Pearce, E.N., Makey, C.M. and Webster, T.F. (2017) Associations between urinary diphenyl phosphate and thyroid function. *Environment international,* 101, 158-164.

Rock, K.D., Horman, B., Phillips, A.L., McRitchie, S.L., Watson, S., Deese-Spruill, J., Jima, D., Sumner, S., Stapleton, H.M. and Patisaul, H.B. (2018) EDC IMPACT: Molecular effects of developmental FM 550 exposure in Wistar rat placenta and fetal forebrain. *Endocrine Connections,* 7, 305-324.

Schreder, E.D., Uding, N. and La Guardia, M.J. (2016) Inhalation a significant exposure route for chlorinated organophosphate flame retardants. *Chemosphere,* 150, 499-504.

Stapleton, H.M., Klosterhaus, S., Eagle, S., Fuh, J., Meeker, J.D., Blum, A. and Webster, T.F. (2009) Detection of organophosphate flame retardants in furniture foam and U.S. house dust. *Environmental Science and Technology,* 43, 7490-7495.

Stapleton, H.M., Klosterhaus, S., Keller, A., Ferguson, P.L., Van Bergen, S., Cooper, E., Webster, T.F. and Blum, A. (2011) Identification of flame retardants in polyurethane foam collected from baby products. *Environmental Science and Technology,* 45, 5323-5331.

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Umezu, T., Yonemoto, J., Soma, Y. and Suzuki, T. (1998) Tris(2-chloroethyl)phosphate increases ambulatory activity in mice: pharmacological analyses of its neurochemical mechanism. *Toxicol Appl Pharmacol,* 148, 109-16.

Wang, Q., Lam, J.C.W., Han, J., Wang, X., Guo, Y., Lam, P.K.S. and Zhou, B. (2015) Developmental exposure to the organophosphorus flame retardant tris(1,3-dichloro-2-propyl) phosphate: Estrogenic activity, endocrine disruption and reproductive effects on zebrafish. *Aquatic Toxicology,* 160, 163-171.

Weiner, M.L. and Jortner, B.S. (1999) Organophosphate-induced delayed neurotoxicity of triarylphosphates. *Neurotoxicology,* 20, 653-73.

Zheng, X., Qiao, L., Covaci, A., Sun, R., Guo, H., Zheng, J., Luo, X., Xie, Q. and Mai, B. (2017) Brominated and phosphate flame retardants (FRs) in indoor dust from different microenvironments: Implications for human exposure via dust ingestion and dermal contact. *Chemosphere,* 184, 185-191.

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