TOX/2019/23

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

Committee statement on phosphate-based flame retardants and the potential for neurodevelopmental toxicity – second draft

1. This paper presents a second draft COT statement on the potential for developmental toxicity, in particular neurodevelopmental toxicity, of phosphate-based flame retardants, following the discussion at the October 2018 and March 2019 meetings. This draft incorporates as tracked changes the amendments requested at the March 2019 meeting.

2. We are aware of a recent longitudinal birth cohort study by Doherty et al (2019) that investigated PFR metabolites in maternal urine during pregnancy and behavioural development in their offspring at 36 months. 199 mother-child pairs were recruited in the study from pre-natal clinics before 20 weeks of gestation. Women were recruited if they were English-speaking, older than 16 years of age, carrying a singleton pregnancy and intending to deliver at a North Carolina hospital. PFRs and metabolites were measured in urine samples collected at 26-29 weeks' gestation. The children's behaviour was assessed using the Behavioural Assessment System for Children (BASC-2) parent-rating scale for pre-school children (PRS-P). The PRS-P is a parent-completed questionnaire that reflects the parent's perceptions of their child's behaviour, including both positive and negative behavioural qualities. It is unclear whether data were adjusted to control for exposure to other neurotoxicants. Authors reported that bis(1,3-dichloro-2-propyl phosphate) (BDCIPP) and diphenyl phosphate (DPHP) concentrations were associated with adverse effects, isopropyl-phenyl phenyl phosphate (ip-PPP) concentrations with protective effects, and 1-hydroxyl-2-propyl bis(1-chloro-2-propyl) phosphate (BCIPHIPP) with no behavioural effects. Overall, authors concluded that greater maternal exposure to some PFRs during pregnancy may be associated with adverse behavioural development in children such as withdrawal, attention problems and other behavioural issues.

3. This finding correlates with other epidemiological data described in previous papers TOX/2018/39 and TOX/2019/09. A short sentence has been added in paragraph 25 of the statement alongside the summary of the other epidemiological data.

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

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

TOX/2019/23 Annex A

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

Committee statement on phosphate-based flame retardants and the potential for neurodevelopmental toxicity

Second draft Committee statement.

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

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

Committee statement on phosphate-based flame retardants and the potential for neurodevelopmental toxicity v0-2

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). Reviews of available toxicity data for some PFRs have been conducted and where adequate data were available, health based guidance values have been derived (ATSDR, 2012; CPSC, 2006; IPCS, 1997). Furthermore, a hazard screening of 88 PFR components has also been conducted (Danish EPA, 2016). 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).

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[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).

5. Therefore, the Committee was asked for an opinion on the potential for PFRs to cause developmental toxicity, and in particular neurodevelopmental 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 is comprised of a central phosphorus atom (P) with a phosphoric (=O) bond, a leaving group (X) and two other side groups (R1 and R2) (Elersek and Filipic, 2011).

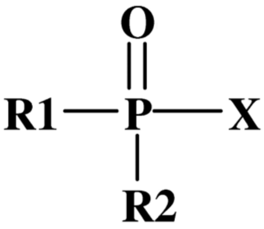

Figure 1. Generic structure of organophosphates

7. PFRs may be grouped into non-halogenated (e.g. triphenylphosphate (TPHP) and tricresylphosphate (TCP)), and halogenated PFRs (e.g. tris(2-chloroethyl) phosphate (TCEP), 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 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). In addition, some have functional groups, not present in PFRs, that require metabolic activation before exerting effects at AChE (Elersek and Filipic, 2011). As PFRs generally have larger alkyl chains in the leaving/side groups, they have reduced affinity for AChE and therefore limited neurotoxicity of PFRs via inhibition of AChE may be anticipated. Dishaw (2015) suggested that PFRs do not 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. The PFRs tested showed 70-115 % of AChE activity and 75-110 % AChR binding compared to OP pesticide control diisopropyl phosphorofluoridate with 0.3 % AChE activity and 99.8 % AChR binding. Authors therefore reported that PFRs are not potent AChE inhibitors (Eldefrawi et al., 1977)(see also TOX/2018/39).

12. Other factors that influence the interaction of OPs with AChE are discussed in TOX/2019/09. The Committee considered that, in general, PFRs were only weak inhibitors of AChE and therefore this mechanism was not of importance for PFRs.

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. This is readily metabolised to a cyclic phosphate which is similar in structure to saligenin that inhibits NTE. Such metabolism must occur for the chemical to induce OPIDN. Ortho-TCP does have such a structure, but it is not used as a flame retardant due to the potential for neurotoxicity, though it may be present as a minor contaminant of the mixed-isomer TCP PFR. Esters with no ortho-substituents, such as TPHP, are not neurotoxic by this mechanism as the necessary metabolism does not occur. In addition, this type of neurotoxicity is decreased by further substitution on the phenyl ring with additional methyl groups in the meta or para positions, e.g. meta- or para-TCP, by providing alternative hydroxylation pathways without the formation of a cyclic ester due to steric hindrance. Finally, 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). The Committee noted that the chicken is a model for assessing the development of OPIDN and the available study of some PFRs showed that they generally do not induce OPIDN in chickens (Weiner and Jortner, 1999).

15. Other non-cholinergic mechanisms may include the neurotransmitter gamma-aminobutyric acid (GABA), as various studies have demonstrated some PFRs such as TCEP and TPHP exert antagonistic effects on GABA. Umezu et al. (1998) reported that TCEP was a GABA antagonist and not a cholinergic agonist in mice. Gant et al. (1987) investigated the effect of PFRs including TPHP, Antiblaze (a mixture of cyclic phosphates) and Fyrol-CEF on GABA receptors or voltage-dependent chloride channel, as well as testing ortho-TCP. Authors reported that TPHP and ortho-TCP can bind to the GABA regulated chloride channel with IC_{50}s 18 and < 10 µM, respectively. This property is 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. The authors concluded that although some PFRs inhibit GABA receptor function and binding to chloride channels, there is a poor correlation with delayed neurotoxicity. Nevertheless, such inhibition may contribute to their toxicity.

16. Dishaw et al. (2011) compared the effects of a number of PFRs to chlorpyrifos using PC12 cells by investigating differentiation into cholinergic or dopaminergic phenotypes, changes in DNA synthesis, oxidative stress and cell growth. Further details are described in TOX/2019/09. The authors reported that the potency of PFRs for neurotoxicity was similar or greater than that of the OP pesticide comparator. Overall, the authors concluded that PFRs may also elicit similar toxicity to OP pesticides based on non-cholinergic mechanisms. The Committee noted, however, that the high concentrations (50 µM) of PFRs were used in this study are not considered to be realistic compared to human exposure to PFRs. Moreover, as PC12 cells do not express cytochrome P450 enzymes and no metabolic activation system was used in the cell culture, it is difficult to extrapolate these results to the in vivo situation.

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).

18. Overall, the Committee concluded that, based on structural considerations, a non-cholinergic mode of action was unlikely for PFRs. Based on their low potency, PFRs are unlikely to cause neurotoxicity at human exposure levels via effects on GABA receptors.

Exposure to PFRs

Potential routes of exposure

19. 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).

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

21. 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.

Toxicity of PFRs

Sensitive groups for this assessment

22. 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

23. 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.

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

25. Lipscomb et al. (2017), in a small cross sectional study, 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 ($p<0.05$). In another cross sectional study, 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) longitudinal birth cohort study, higher total PFR metabolites 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 (p,p'-dichlorodiphenyltrichloroethylene (DDT) and p,p'-dichloro-

diphenyldichloroethylene (DDE) that had been found to be related to child IQ or attention-deficit/hyperactivity disorder in the cohort were controlled for in the study. Authors concluded that due to the widespread exposure to PFRs among pregnant women and children further studies are needed with a wider range of biochemical measurements to investigate the potential neurodevelopmental effects of PFRs (Castorina et al., 2017). In another longitudinal birth cohort study, Doherty et al. (2019) investigated PFR metabolites in maternal urine during pregnancy and behavioural development in their offspring at 36 months. They found bis(1,3-dichloro-2-propyl phosphate) (BDCIPP) and diphenyl phosphate (DPHP) concentrations were associated with adverse effects, isopropyl-phenyl phenyl phosphate (ip-PPP) concentrations with protective effects, and 1-hydroxyl-2-propyl bis(1-chloro-2-propyl) phosphate (BCIPHIPP) with no behavioural effects.

26. Whilst all the epidemiological studies to date found some positive associations relating to cognitive function or performance of children, the specific outcomes identified were often different. The Committee commented on the limited number of epidemiological studies available, with half of them being cross sectional and thus limited by their design, the potential for multiple testing given the large number of cognitive/behavioural domains investigated against the various PFRs, and finally, that only in one study was it clear there had been sufficient adjustment for potential exposure to other chemicals or factors that may affect cognitive performance.

In vivo/in vitro data

27. 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. TCEP did induce brain lesions in the hippocampus and thalamus in a 16 week study in rats (175 mg/kg bw/day TCEP), and in the brain stem and cerebral cortex in a 2 year study in rats (88 mg/kg bw/day TCEP). Females appeared to be more sensitive than males. No lesions were reported with any of the other PFRs. ATSDR derived an intermediate Minimal Risk Level (oral) of 0.6 mg/kg bw/day based on necrosis of the hippocampal neurones in female rats (ATSDR, 2012).

28. 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 than the brominated components. The mean placental TPHP levels were 6.5 ± 2.02 ng/g w/w in placentas of male foetuses. However, there is no evidence of placental transfer of PFRs to the fetus as placental levels were higher than fetal levels (Baldwin et al., 2017; Phillips et al., 2016).

Discussion

29. PFRs are found ubiquitously in household dust and biomonitoring data suggests that exposure is widespread and increasing over time. Young children and infants have been identified as a potentially susceptible subpopulation due to 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.

30. PFRs share a structural similarity with OP pesticides and other OP compounds. However, the presence of alkyl or aryl functional groups in PFRs results in these leaving groups 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 were only weak inhibitors of AChE, based on the papers by Abou-Donia et al. (2016) and Eldefrawi et al. (1977).

31. It has additionally been hypothesised that PFRs may also elicit similar toxicity as OP pesticides by non-cholinergic mechanisms. OP pesticides cause OPIDN 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, a minor contaminant of the mixed-isomer TCP PFR. 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 small ortho-substituents.

32. TPHP and commercial TCP (isomeric mixture) are both commonly used flame retardants. Due to its structure (lack of ortho-methyl groups) TPHP is not neurotoxic via inhibition of NTE. 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. Because of the activity of ortho-TCP, the Committee recommends continued efforts to keep concentrations of this isomer in commercial mixtures low.

33. There is some evidence for neurotoxicity of some PFRs to occur though inhibition of the GABA regulated chloride channel. Inhibition of this channel appears to be a property of a small number of PFR-type molecules tested at high concentrations, and is not shared with nerve agents.

34. Overall, the Committee agreed that the data presented did not support a plausible mechanism for any neurotoxic effect of PFRs at human exposure levels through inhibition of AChE, NTE or GABA receptors. Adequately conducted studies would be needed to exclude potential effects via other mechanisms.

35. 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.

36. 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.

37. 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

38. 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 limited epidemiological evidence available has suggested potential neurodevelopmental effects, although there were limitations to this evidence and a lack of specificity in the relationships identified.

COT
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