TOX/2018/39

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

Phosphate-Based Flame Retardants and the Potential for Developmental Toxicity: A Scoping Paper

Issue

1. The Committee is asked to consider the potential for developmental toxicity of phosphate-based flame retardants, which are being introduced in UK products to replace brominated flame retardants as these are banned or restricted for use.

Background

2. Due to the stringent requirements of the Furniture and Furnishings (Fire) (Safety) Regulations 1988 in the UK, the use of flame retardants is greater in the UK than the rest of Europe. The legislation has set levels of fire resistance for domestic furniture, furnishings and upholstery products that are largely achieved by the use of chemical flame retardants.

3. Flame retardants are commonly used on furnishings and upholstery (e.g. sofas, carpets, curtains and fabric blinds) (NIH, 2016), as well as polyurethane foam used in child car seats and mattresses (Cooper *et al.*, 2016). They are also added or applied to electronics and electrical devices such as computers and televisions as well as many materials used in building and construction, such as electrical wires and cables and insulation material (NIH, 2016).

4. 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, two commercial mixtures of PBDEs, namely penta-BDE and octa-BDE, were banned in the European Union (EU) and phased out in the United States based on their neurotoxicity as well as the potential for bioaccumulation and persistence (Noyes and Stapleton, 2014). In addition, mixtures of deca-BDE have been restricted in the EU since 2008. In 2009, PBDEs were also listed on the Persistent Organic Pollutants (POPs) list (Noyes and Stapleton, 2014).

5. The bans and restrictions in the use of PBDEs have led to an increase in the use of alternative chemical flame retardants (Dodson *et al.*, 2012; Stapleton *et al.*, 2011). In 2010, the Department for Environment, Food and Rural Affairs (Defra) conducted a review of alternative flame retardant technologies and concluded that while many of the alternatives have been well researched and considered fit for

purpose, there are many other flame retardants that have not been adequately assessed for either their long term performance as a flame retardant or for their potential impact on exposure to humans (Defra, 2010).

6. Alternative chemical flame retardants include (organo)phosphate-based flame retardants (PFRs), or commercial mixtures of PFRs and non-PBDE BFRs, e.g. Firemaster 550®[1] (FM550) (Dodson et al., 2012; Rock et al., 2018). Defra have collated a draft list of current use flame retardants, which has been gathered from the available literature and the REACH registration to build some understanding of the (potentially) most used flame retardants on the market. The list, provided in Annex 2, is not exhaustive and represents a preliminary piece of work on the subject.

7. Reviews of available toxicity data for some PFRs have been conducted and where adequate data are 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). Of these reviews, the United States Consumer Product Safety Commission (CPSC) and the Agency for Toxic Substances and Disease Registry (ATSDR) identify children as a potentially susceptible population to PFR exposure (ATSDR, 2012; CPSC, 2006).

8. Other classes of organophosphates, such as organophosphate (OP) pesticides have been shown to interfere with neurodevelopment by cholinergic and nonchlorinergic pathways (Pope, 1999). Therefore this scoping paper aims to investigate the potential for developmental toxicity following exposure to PFRs, with a focus on children and the developing fetus.

9. The COT has previously considered a number of topics that are relevant to this report. In 2015, the COT published a statement on potential risks of PBDEs in the infant diet [2]. In 1999 and 2014, the Committee also published reports considering the long-term health effects following repeated exposure to low doses of OPs, such as neuropsychological outcomes and peripheral neuropathy[3]. These reports concluded that neuropsychological abnormalities can occur as a long-term complication of acute OP poisoning, however data relating to positive neurological and neuropsychological findings following chronic low-level exposure to OP pesticides was less convincing. It is noted that developmental toxicity was not considered as part of either the 1999 or 2014 reports.

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[1] Firemaster 550® (FM550) 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).

[2] COT statement on polybrominated diphenyl ethers (PBDEs) (2015) https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cot-statement-2015/cot-statement-on-polybrominated-diphenyl-ethers-pbdes

[3] COT report on organophosphates (1999) https://cot.food.gov.uk/cotreports/cotwgreports/organophosphates and COT statement on organophosphate (2014) https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2014/cotstatorg

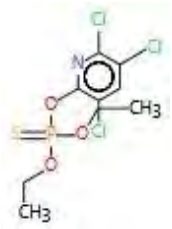
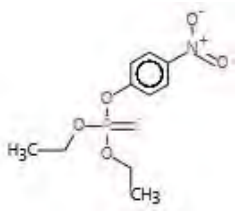
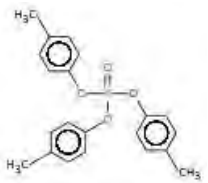
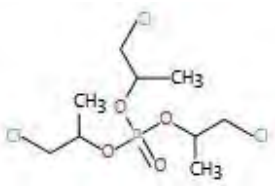
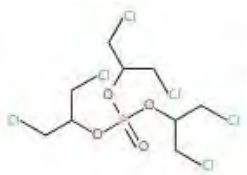
Introduction to PFRs

10. PFRs are effective flame retardants for textiles as the phosphate esters impart durable flame resistance to hydroxyl-containing fibre-forming polymers such as cellulose (Defra, 2010; IPCS, 1997). 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). The addition of the halogen to the PFR structure reduces the water solubility and vapour pressure of the flame retardant, increasing the retention of the flame retardant in the polymer (IPCS, 1997). More recently, a third group of PFRs has emerged, namely metal-based PFRs such as aluminium diethylphosphinate (ALPI), which may also have the potential to dissociate into their respective metal ion constituents (e.g. aluminium (Al^{3+})) (Hendriks and Westerink, 2015). Limited data were located regarding the potential adverse effects of ALPI, however Hendriks and Westerink (2015) reported low toxicity observed *in vitro* and *in vivo,* indicating that ALPI has a low neurotoxic potential. It is considered that phosphate esters used in PFRs share a structural similarity with OP pesticides (Dishaw *et al.*, 2014), see Table 1.

11. Both PBDEs and PFRs tend to be incorporated in the textile polymers during or after polymerisation (IPCS, 1997). Therefore, they are considered to be additives as they are not chemically bound to the treated textiles and hence can migrate into the surrounding environment or volatilize into the air during breakdown of the textile or polymer (Noyes *et al.*, 2015). Dishaw (2015) reported that PFRs have been detected at concentrations similar to or exceeding those reported for PBDEs in numerous environmental and biological matrices.

12. The chemical structures and physico-chemical properties of non-halogenated (TPHP and TCP) and halogenated PFRs (TCPP and TDCPP) and two organophosphate (OP) pesticides (chlorpyrifos and parathion) are presented in Table 1 (ATSDR, 2012; ChemID, 2018; PubChem, 2018).

Table 1. Physicochemical properties of non-halogenated and halogenated PFRs and OP pesticides

Physical Property	**Organophosphate Pesticides**		**Non-halogenated PFRs**		**Halogenated PFRs**	
Chemical Name (CAS RN)	Chlorpyrifos (2921-88-2)	Parathion (56-38-2)	Triphenylphosphate (TPHP) (115-86-6)	Tricresylphosphate (TCP) (1330-78-5)	Tris (2-chloroisopropyl) phosphate (TCPP) (13674-84-5)	Tris (1,3-dichloro-2-propyl) phosphate (TDCPP) (13674-87-8)
Chemical Structure						
Chemical Formulae	$C_9H_{11}Cl_3NO_3PS$	$C_{10}H_{14}NO_5PS$	$C_{18}H_{15}O_4P$	$C_{21}H_{21}O_4P$	$C_9H_{18}Cl_3O_4P$	$C_9H_{15}Cl_6O_4P$
Melting point (ºC)	42	6	50.5	-33	-40	27
Boiling point (ºC)	Decomposes at 160°C	375	370	265	>270; gradually decomposes when heated over 200 °C	237
Density (g/cm^3)	1.4	1.26	1.21	1.162	1.29	1.48
Water Solubility	1.12 mg/L at 24 ºC	11 mg/L at 20 ºC	1.9 mg/L at 25 ºC	0.36 mg/L at 25 °C	1200 mg/L at 25 °C	7 mg/L at 24 ºC
Log Kow	4.96	3.83	4.59	5.11	2.59	3.65
Vapour Pressure	0.00002 mmHg (temperature not reported)	$6.68x10^{-6}$ mm Hg at 20 ºC	$6.28x10^{-6}$ mm Hg at 25 °C	$6.00x10^{-7}$ mm Hg at 25 °C	$2.02x10^{-5}$ mm Hg at 25 °C	$5.2 x10^{-2}$ mm Hg at 25 °C

Mode of action

13. OP pesticides and PFRs share the same generic OP chemical structure, see Figure 1. The generic structure 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). The mode of action (MoA) of OP neurotoxicity occurs via the phosphorylation and subsequent inhibition of acetylcholinesterase (AChE). This is executed by a nucleophilic substitution of the leaving group by the oxygen molecule in the serine residue in the AChE active site. This inhibition causes an accumulation of the neurotransmitter acetylcholine and an overstimulation of cholinergic receptors (Pope, 1999). This ultimately leads to cholinergic intoxication syndrome (Dishaw, 2015). It is noted that the rate of AChE inhibition depends on the affinity of the leaving group to AChE (Elersek and Filipic, 2011).

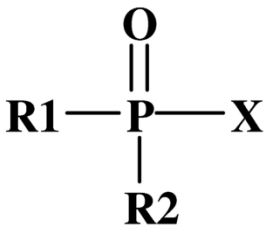


Figure 1. Generic structure of organophosphates

14. OPs are also associated with Organophosphate Induced Delayed Neurotoxicity (OPIDN); a neurodegenerative disorder characterised by a latent period between exposure and the manifestation of neurological effects (e.g ataxia or paralysis) (Abou-Donia *et al.*, 2016). The molecular target for OPIDN (also referred to as Organophosphate-Induced Delayed Polyneuropathy) is neuropathy target esterase (NTE), an integral membrane protein in vertebrate neurons (Jokanovic *et al.*, 2011). The delay in initiation of effects is thought to be due to the progressive inhibition of NTE by reaction with OP pesticides (Jokanovic *et al.*, 2011).

15. Studies have shown that high doses of some PFRs (dose levels not reported), namely tris(2-chloroethyl) phosphate (TCEP) and TCP, can inhibit AChE via the same phosphorylation mechanism and cause symptoms of cholinergic intoxication (ATSDR, 2012). In contrast, an earlier study testing the inhibitory activity of various halogenated and non-halogenated PFRs on AChE, isolated from organs of the electric ray, *Torpedo ocellata,* showed that phosphate esters are not potent AChE inhibitors, when compared to the OP pesticide (control) diisopropyl phosphorofluoridate (DFP) (Eldefrawi et al., 1977), see Table 2.

Table 2. The effect of PFRs on membrane-bound AChE and acetylcholine receptors (AChR) of *Torpedo* electroplax (adapted from Eldefrawi et al., 1977).

Commercial Flame Retardant	Candidate PFR Chemical(s); as reported by Eldefrawi et al., 1977	Inhibition (% of control)	
		AChE	AChR
Antiblaze 19	Mixture of cyclic phosphonates	103.4	98.8
Antiblaze 78	Mixture of monomeric chloroethyl phosphonates and high boiling phosphonates	114.5	101.4
Fyrol CEF	Tris (beta chloroethyl phosphate)	73.7	107.2
Fyrol FR-2	Tris (dichloropropyl) phosphate	79.1	93.9
Fyrol 76	An oligomeric vinyl phosphonate	114.8	103.2
Phosflex 179-C	Tri (orthocresol) phosphate	82..2	109.8
Phosflex 300	Mixed triaryl phosphate esters containing halogen	75.1	110.1
Phosflex 400	Mixed triaryl phosphate esters containing halogen	92.9	107.0
Pyrovatex CP	N-methylol dimethyl phosphopropionamide	80.8	94.2
TDBPP	Tris(2,3-dibromopropyl) phosphate	81.1	99.9
THPOH*	Tetrakis(hydroxymethyl) phosphonium hydroxide	79.5	76.7

*THPOH was reported to cause visible protein aggregation when added to the membrane preparation.

16. Pre- and peri-natal exposure to low levels of some OP pesticides such as chlorpyrifos and parathion have also been shown to produce deficits in learning and memory (Dishaw *et al.*, 2014). For chlorpyrifos, the behavioural changes have been shown to be gender-selective in rats (Levin *et al.*, 2002). Mechanistic data suggest that these effects may be caused by a noncholinergic MoA, rather than AChE inhibition (Pope, 1999; Slotkin and Seidler, 2007). For example, studies with chlorpyrifos and parathion indicate modulation of presynaptic muscarinic receptor-mediated functions (Pope, 1999) and chlorpyrifos has been shown to affect the macromolecular synthesis in the cerebellum of the developing brain as well as the disruption of adenylyl cyclase activity and G-protein function in noncholinergic systems (Pope, 1999).

17. Similar effects have also been reported for PFRs. For example, TCEP has been shown to have antagonistic effects on the neurotransmitter gamma-aminobutyric acid (GABA) in mice (Umezu *et al.*, 1998). It is therefore considered that PFRs may also elicit similar toxicity to OP pesticides based on noncholinergic mechanisms (Dishaw *et al.*, 2014).

18. Dishaw et al. (2011) compared the neurotoxicity of four PFRs (TCEP, TCPP, TDCPP and tris (1,3- dibromopropyl) phosphate (TDBPP)) to chlorpyrifos using PC12 cells, a model for neurodevelopmental toxicity. TCEP and TCPP promoted cell differentiation into the cholinergic phenotype, whereas TDCPP and TDBPP promoted differentiation into both cholinergic and noncholinergic (dopaminerigic) phenotypes (Dishaw *et al.*, 2011). Furthermore, TDCPP caused neurotoxicity at concentrations less than or equivalent to those needed to cause the same effects with chlorpyrifos (Dishaw *et al.*, 2011). The authors concluded that these data indicate that PFRs have the potential to be developmental neurotoxins via disruption of the critical stages of brain development, such as causing deficiencies in the number of neurones and altered neurodifferentiation. This may lead to irrevocable changes in brain function. Overall, it was considered by the authors that the potency of PFRs for neurodevelopment toxicity was similar or greater than that of an OP pesticide (chlorpyrifos) (Dishaw *et al.*, 2011).

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).

20. 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). It is also considered that adults may wash their hands more frequently, reducing the potential for exposure in adults (Butt *et al.*, 2016).

21. 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).

Exposure estimates

22. Data from the United States Environmental Protection Agency (EPA) estimates children (between 1 and 5 years old) and adults ingest 100 and 20 mg dust/day, respectively. Using such data and a geometric mean of concentrations of flame retardants detected in dust samples, Stapleton et al. (2009) calculated that the average cumulative exposure to flame retardants from dust ingestion is 16000 ng/day for children and 325 ng/day for adults. The authors reported that the majority of flame retardant exposure is accounted for by PBDEs and the PFRs, TPHP and TDCPP (Stapleton *et al.*, 2009).

23. California EPA (2015) reported an Acceptable Daily Intake (ADI) for TDCPP of 0.005 mg/kg/day based on non-cancer health effects (derivation not reported). The authors estimated that exposures of TDCPP from furniture foam alone are the two-fold higher than the ADI for adults and may be up to five-fold higher in children (California EPA, 2015). The authors also noted that as children have a smaller body mass relative to adults, the dosage received by the children in mg/kg bw is substantially greater (California EPA, 2015). No exposure estimates for inhalation or dermal exposure were available.

Biomonitoring

24. Limited data for PFRs measured in human samples prior to the restriction of PDBEs, were located (Hudec *et al.*, 1981; LeBel and Williams, 1983; LeBel and Williams, 1986). However, since the restriction of PBDEs several studies have been published which report levels of urinary biomarkers of PFR metabolites are up to five times greater in children when compared to their mothers (Butt *et al.*, 2014; Butt *et al.*, 2016; Cequier *et al.*, 2015).

25. Studies have also shown significant correlations between the levels of PFRs in indoor dust and air with levels of PFR biomarkers or metabolites in urine (Cequier *et al.*, 2015; Fromme *et al.*, 2014). One study investigated the suitability of human hair as an indicator of exposure, and compared levels of PFRs in hair and urine from 48 mothers and 54 children to dust collected from their respective households (Kucharska *et al.*, 2015). Higher correlations between hair and dust were reported than between hair and urine, and it was noted that the hair samples were indicative of all microenvironments of personal exposure including school and work places, rather than just the household. The authors concluded that hair may be used as an indicator of exposure to PFRs in biomonitoring studies (Kucharska *et al.*, 2015).

26. It is noted that there may be additional exposure to phosphate esters used in PFRs based on their widespread use as flame retardants in transport (e.g. aeroplanes and cars) (Allen *et al.*, 2013; Brommer and Harrad, 2015), plasticisers in food contact materials and children's toys (Ionas *et al.*, 2014; Poma *et al.*, 2018) and in commercial preparations (e.g. paints, lubricants, plastic, and hydraulic fluids) (Wang *et al.*, 1995). In 2007 and 2013 the COT published a statement and a position paper on effects of cabin air, which included considering exposure to TCP as a degradation product of engine jet oil[4].

Environmental exposure

27. A number of studies investigating the occurrence and exposure to PFRs have been published. The majority of occurrence and exposure data located were related

[4] COT statement on the review of the cabin air environment, ill-health in aircraft crews and the possible relationship to smoke/fume events in aircraft (2007) https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2007/cotstatementbalpa0706
COT position paper on cabin air (2013) https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2013/cotpospacabair

to dust samples taken from hand wipes used by children and mothers or collected from surfaces and furnishings in homes and day care centres (Langer *et al.*, 2016; Larsson *et al.*, 2018; Stapleton *et al.*, 2014; Sugeng *et al.*, 2017). A method for detecting exposure to flame retardants using commercially available silicone wristbands has also been developed (Kile *et al.*, 2016). The authors report that this is a particularly useful and simple technique for measuring passive exposure for children, as compliance of the children was considered reasonable and the stability of the PFRs in the wristbands was considered to be robust (Kile *et al.*, 2016).

28. Dodson *et al.* (2012) measured the concentrations of flame retardants, including PFRs, in the dust from 16 houses in 2006 and again in 2011 in California, USA. Whilst PBDEs were still detected, halogenated PFRs were reported to be the most abundant flame retardants measured in the study, with up to 14-fold increases in PFR concentrations in houses during the study period. The households with the biggest increases reported either substantial remodelling or purchasing of new furniture between sampling times and as a result the authors suggested that PFRs are being used as PDBE replacements (Dodson *et al.*, 2012). The authors also reported that the concentrations of PFRs detected in the study were amongst some of the highest concentrations detected in the world (Dodson *et al.*, 2012). Only Japan had concentrations of halogenated PFRs comparable or higher than those reported in California; the authors considered this was due to a much earlier voluntary phase out of PBDE flame retardants in Japan in the 1990's (Dodson *et al.*, 2012; McDonald, 2005).

29. Whilst it is noted that exposure to some PFRs may be higher than others (Stapleton *et al.*, 2009), no quantitative data regarding the temporal release of PFRs from furnishings or textiles were located. Preston *et al.* (2017) reports that due to the widespread use of PFRs, exposure to PFRs may be relatively constant over time, resulting in a "pseudo persistence" in the human body, irrespective of half-life (Preston *et al.*, 2017).

Toxicity of PFRs

Sensitive groups for this assessment

30. Children have been identified in literature as being particularly susceptible to exposure to flame retardants based on a number of variables, including greater hand-to-mouth activity, increased contact with treated textiles and potential dietary exposure via breast milk (Dishaw, 2015). Furthermore, PFRs are considered to have a similar MoA to OP pesticides and *in vitro* studies indicate that PFRs have potential for neurodevelopmental toxicity (Dishaw *et al.*, 2011). Therefore data relating to the developing fetus and *in utero* exposure have also been considered.

Acute and chronic data

31. Acute toxicity data relating to PFRs in humans were limited to poisoning incidents resulting in neurotoxicity. Furthermore, ATSDR (2012) reports that the available literature from animal studies is limited to acute high dose experiments aimed primarily at determining lethal concentrations, rather than signs of toxicity.

32. Some recent chronic human data are available; however studies focussing on children and infants are limited. Oral repeat-dose, reproductive and developmental toxicity studies in rats and mice for a number of individual PFRs have been conducted, however these studies tend to have been published between the 1970's and 1990's (ATSDR, 2012). Since the restrictions on PBDEs, however, it has been recognised that data relating to the potential toxicity associated with PFR exposure are lacking, particularly when compared to available data on PBDEs and other BFRs (Behl *et al.*, 2016; Dodson *et al.*, 2012). Consequently, a number of *in vitro* and *in vivo* toxicity studies aiming to assess the neurological and developmental toxicity of PFRs have recently been conducted (Behl *et al.*, 2015; Moser *et al.*, 2015).

Human data

33. Chronic exposure to low levels of OP pesticides is associated with an increased risk of asthma, thought to be due to a chronic dysregulation of the parasympathetic airway (Eskenazi *et al.*, 1999). PFRs have also been associated with asthma in adults in Japan (Araki et al., 2014 as cited in Canbaz *et al.* (2016). In contrast, a study investigating the PFRs in dust collected from mothers' mattresses at a median infant age of 2 months (n=220), showed no association between the development of childhood asthma at 4 and 8 years old (Canbaz *et al.*, 2016).

34. PFRs have also been associated with allergic disorders such as chronic rhinitis and atopic dermatitis in adults in Japan (Araki et al., 2014 as cited in Canbaz *et al.* (2016). No data on rhinitis or dermatitis were located in infants.

Neurotoxicity

35. An incident of TCP poisoning of 58 cases was reported in Bombay, India in 1960 (Abou-Donia *et al.*, 2016). The authors reported that the observed effects seen following the incident were consistent with cholinergic toxicity that is elicited by OP pesticides. No child or infant-specific data were located regarding the cholinergic toxicity of PFRs, however, the authors considered that, in general, PFRs have low cholinergic potency and do not pose significant health hazards to adults or children via cholinergic neurotoxicity. Furthermore, they noted that low level chronic exposure to PFRs usually occurs in humans, rather than acute high doses that are associated with OP pesticide cholinergic toxicity.

36. PFRs have also been associated with OPIDN (see paragraph 14). A 5-year old girl exposed to TCEP in household timber (600 mg/kg wood) was reported to develop characteristics of OPIDN such as weakness in the arms and abdominal

muscles. Nine months later she was admitted to hospital with dystelectatic pneumonia and spinal muscle atrophy (Abou-Donia *et al.*, 2016).

37. Abou-Donia *et al.* (2016) also reports that PFRs and OP pesticides may also cause Organophosphate-Induced Chronic Neurotoxicity (OPICN). OPICN is a disorder involving neuronal degeneration and subsequent structural, functional, physiological, and neurological and neurobehavioral abnormalities and is largely characterised by chronic neurobehavioral alterations[5]. This action can occur following a single acute OP exposure or small sub-acute exposures at sub-lethal dose levels, and results in long-term cognitive deficits and sensorimotor dysfunctions, in the absence of acute cholinergic toxicity. Abou-Donia *et al.* (2016) does not report an example of PFRs causing OPICN in humans, however an example of tris(2-butoxyethyl) phosphate (TBEP) causing OPICN in Sprague Dawley rats is reported. Furthermore, the following examples (Castorina *et al.*, 2017; Lipscomb *et al.*, 2017) provide examples of PFRs affecting neurobehaviour in children and infants.

Developmental toxicity

38. Few human toxicity data are available, particularly in respect to children and infants. However, the limited data indicate a correlation between PFR exposure and reduced cognitive performance and poorer social behaviours. Lipscomb *et al.* (2017) assessed personal exposure to flame retardants of 69 children aged between 3-5 years for 7 days. The children were recruited from 28 preschool classrooms in two regions of Oregon, USA and flame retardant exposure was measured via a silicone passive wristband that was worn continuously around the child's wrist or ankle. Social behaviour of the children was measured by the children's teacher using the Social Skills Improvement System Rating Scale (SSI-RS), a standardised assessment form that uses rating scales to determine frequency of children's behaviour. Total PFRs (representative of TCEP, TCPP, TDCPP and TPHP) were associated with less responsibility (p<0.001) and greater externalising problems (p<0.05) (Lipscomb *et al.*, 2017). The authors defined externalising behaviours as hyperactivity, inattention, aggressive and oppositional behaviours and noted that children with externalising behaviours were more likely to develop mental illness later in life (Lipscomb *et al.*, 2017).

39. Similar results of reduced cognitive performance and exposure to TCEP were reported in children aged between 6-8 years (Hutter et al., 2013). Furthermore, a measurement of maternal PFR exposure (measured via a urine sample at <20 weeks of gestation) as part of the Center for the Health Assessment of Mothers and

[5] OPCIN may also be referred to as Chronic Organophosphate Induced Neuropsychiatric Disorder (COPIND). In the 1999 COT report and the 2014 COT statement on organophosphates, data on COPIND was reviewed. In 2014 the COT concluded that whilst there is an excess of multiple neuropsychiatric symptoms in people who have been exposed to organophosphates at levels insufficient to cause overt acute poisoning, it is difficult to determine whether the symptoms are a consequence of chemical toxicity or via psychological mechanisms that do not involve organophosphates.

Children of Salinas (CHAMACOS) cohort was also conducted to assess the effects of prenatal exposure on the developing infant (Castorina et al., 2017). Increased prenatal total PFR metabolites (representative of bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), diphenyl phosphate (DPHP), isopropyl phenyl phenyl phosphate (ip-PPP) and tertbuylphenyl phenyl phosphate (tb-PPP)) and DPHP alone were associated with decreased working memory and reduced intelligence quotient (IQ) scores of the children at 7 years old (Castorina *et al.*, 2017).

Teratogenicity

40. No data regarding the teratogenic potential of PFRs in humans were located.

In utero data

41. No data regarding the placental transfer in humans were located.

Endocrine effects

42. PFRs have been associated with potential endocrine perturbations by sex in regards to human pregnancy and gestational length. A cohort of the Pregnancy Infection and Nutrition (PIN) study were recruited *(n*=349) and urine was sampled from women at a single time point between weeks 24-30 of gestation (Hoffman *et al.*, 2018). Mothers with high urinary concentrations of ip-PPP gave birth to female babies 1 week earlier than mothers with lower urinary ip-PPP (95 % confidence interval (CI): -1.85, -0.15 weeks, *p*=0.02). Furthermore, male babies with maternal urinary exposure to DPHP were born approximately 5 days later (95% CI: 0.01, 1.50 weeks; *p*=0.05) (Hoffman *et al.*, 2018).

43. Preston *et al.* (2017) reported an association of increased urinary DPHP levels with increased mean total thyroxine (TT4) levels in adult females; however no data on the potential thyroid toxicity to children were located.

In vivo/in vitro data

Neurotoxicity

44. 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.

Developmental toxicity

45. ATSDR (2012) reports that developmental endpoints in general are not particularly sensitive to PFRs.

Teratogenicity

46. 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.

In utero data

47. The flame retardant, FM550 was administered to Wistar rats (*n*=48 dams) at approximate doses of 0, 1 or 3.3 mg/kg bw/day via a food pellet treat on days 9 to 18 of gestation (Baldwin *et al.*, 2017). Dams were killed on day 18 of gestation and one placenta per sex per litter was collected for analysis. A statistically significant dose dependent increase in TPHP and the brominated component, (bis (2-ethylhexyl)-2,3,4,5 tetrabromophthalate (TBPH)) were detected in placentas associated with male fetuses only (Baldwin *et al.*, 2017). In a similar study investigating placental transfer, FM550 was administered to Wistar rats (*n*=18 dams) at approximate doses of 0, 1 or 3.3 mg/kg bw/day via a food pellet treat on days 9 to 18 of gestation (Phillips *et al.*, 2016). Dams were killed between days 18 to 21 of gestation and whole fetuses were examined for FM550 components. Average TPHP and isopropylated triarylphosphate isomers (ITPs) levels were below the limit of detection at all dose levels, suggesting that limited placental transfer of PFRs to the fetus occurs (Phillips *et al.*, 2016). The authors concluded that this may be due to the rapid metabolism of TPHP by the liver of the dams, as metabolites of TPHP and ITPs were detected in the urine of the dams collected during gestation, or may be due to the sensitivity of the assay (Phillips *et al.*, 2016). Therefore, whilst there is evidence of PFR accumulation in the placenta in the rat, there is no evidence thus far of placental transfer.

48. Baldwin *et al.* (2017) investigated pup behaviour following maternal exposure to FM550. Wistar rats (*n*=34 dams) were administered FM550 at approximate doses of 0.3, 1 or 3.3 mg/kg bw/day via a food pellet treat from day 9 of gestation to postnatal day 21. Sex specific effects were reported including increased anxiety in males (latency to enter the light side of a light/dark box) and increased hyperactivity in females (Baldwin *et al.*, 2017). The authors concluded that the placenta may be a critical target organ for FM550 and may impact fetal development. Baldwin *et al.* (2017) also reported that the rats in the study were exposed both during gestation and lactation and considered that the lactational transfer, particularly for the brominated components of FM550, are more effective than gestational transfer (Baldwin *et al.*, 2017). Therefore, it is not clear as to whether the effects observed are a result of the individual components of FM550 or exposure to the mixture of BFRs and PFRs.

Endocrine effects

49. Preliminary studies using *in vitro* cell lines (GH3 and FRTL-5), chick embryos and zebrafish (*Danio rerio*) embryos and larvae suggest that PFRs may disrupt normal thyroid function (Abou-Donia *et al.*, 2016; Egloff *et al.*, 2014; Kim *et al.*, 2015). Long term exposure to concentrations of TDCPP to zebrafish embryos are also reported to significantly increase plasma estradiol and testosterone levels in females, but had no effect in males (Wang *et al.*, 2015).

Summary

50. 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.

51. PFRs are considered to have a similar mechanism of action and toxicity to OP pesticides. Data suggest that PFRs may have an effect on neurobehaviour and social development, as well as on the developing fetus via an effect on the placenta. There is evidence to suggest that these effects may affect males and females differently. Differences in cognitive performance between males and females have also been reported for the OP pesticide, chlorpyrifos. There is also *in vitro* data implying that PFRs may have endocrine disrupting potential.

52. Based on their persistence and use in older furniture, PBDEs are still being reported in house dust samples. Furthermore, individuals may also be exposed to BFRs. Therefore; individuals are likely to be exposed to a mixture of flame retardants including from PFRs.

53. It is noted that there are gaps in the available data for PFRs, particularly relating to endocrine disruption potential and juvenile toxicity effects. FM550 and 'Flame Retardants' are listed as part of the nominated substances for research for the National Toxicology Program (NTP) (NTP, 2018). As such, research for a number of PFRs, including TPHP, TCP, TCPP and 2-ethylhexyl diphenyl phosphate (EHDP) is currently ongoing (NIH, 2016; NTP, 2018).

Questions for the Committee

54. Members are asked to provide general comments on the paper and in particular:

i. Based on this scoping paper is the Committee able to make any comment on the potential for developmental toxicity of PFRs?

ii. Are there aspects of covered on which the Committee requires more information?

iii. Do members consider that this should be taken forward to a full paper?

NCET at WRc/IEH-C under contract supporting the PHE Secretariat
October 2018

Abbreviations

AChE	Acetylcholinesterase
AchR	Acetylcholine receptor
ADI	Acceptable Daily Intake
ALPI	Aluminium diethylphosphinate
ATSDR	Agency for Toxic Substances and Disease Registry
BDCIPP	Bis(1,3-dichloro-2-propyl) phosphate
BFRs	Brominated flame retardants
CHAMACOS	Center for the Health Assessment of Mothers and Children of Salinas
CI	Confidence Interval
COPIND	Chronic Organophosphate Induced Neuropsychiatric Disorder
COT	Committee on Toxicity of chemicals in food, consumer products and the environment
CPSC	Consumer Product Safety Commission
Defra	Department for Environment, Food and Rural Affairs
DFP	Diisopropyl phosphorofluoridate
DPHP	Diphenyl phosphate
EHDP	2-Ethylhexyl diphenyl phosphate
EPA	Environmental Protection Agency
FM550	Firemaster 550®
GABA	Gamma-aminobutyric acid
ip-PPP	Isopropyl phenyl phenyl phosphate
IQ	Intelligence Quotient
ITPs	Isopropylated triarylphosphate isomers
MoA	Mode of Action
NTP	National Toxicology Programe
OP	Organophosphate
OPICN	Organophosphate-Induced Chronic Neurotoxicity

OPIDN	Organophosphate-Induced Delayed Neurotoxicity
PBDEs	Polybrominated Diphenyl Ethers
PFRs	Phosphate-Based Flame Retardants
PIN	Pregnancy Infection and Nutrition
POPs	Persistent Organic Pollutants
SSI-RS	Social Skills Improvement System Rating Scale
tb-PPP	Tertbuylphenyl phenyl phosphate
TBB	2-Ethylhexyl-2,3,4,5-tetrabromobenzoate
TBEP	Tris(2-butoxyethyl) phosphate
TBPH	Bis (2-ethylhexyl)-2,3,4,5tetrabromophthalate
TnBP	Tri-n-butyl phosphate
TCEP	Tris(2-chloroethyl) phosphate
TCP	Tricresyl phosphate
TCPP	Tris (2-chloroisopropyl) phosphate
TDBPP	Tris (1,3- dibromopropyl) phosphate
TDCPP	Tris (1,3-dichloro-2-propyl) phosphate
TPHP	Triphenylphosphate
TT4	Total Thyroxine

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

Phosphate-Based Flame Retardants and the Potential for Developmental Toxicity: A Scoping Paper

Details of Literature search carried out by NCET at WRc/IEH-C

A provisional literature search was conducted by NCET at WRc/IEH-C under contract to PHE on 22/8/18 (unlimited date range) using the following search terms in PubMed and Scopus. Search terms used were:

Scopus

((TITLE-ABS-KEY (*phosphate* OR *phosphorus OR "organophosphate ester" OR "OPE" OR "PBFR")) AND (TITLE-ABS-KEY ("flame retardant*"))) AND ((CAS Reg Number) OR (Chemical Name) OR OR TITLE-ABS-KEY (Chemical Name)" OR TITLE-ABS-KEY (Abbreviations) AND ((TITLE-ABS-KEY (child* OR juvenile OR baby OR babies OR infant* OR toddler* OR mother* OR embryo* OR foetus*)) AND (TITLE-ABS-KEY (*toxic* OR *neuro OR *behaviour OR *behavior OR "growth rate" OR "breast milk*" OR lactation OR "endocrine disruptor*" OR estrogen* OR oestrogen* OR thyroids* OR hormone* OR *function OR exposure*))): 155 refs

PubMed

(((((((organophosphates[MeSH Terms]) OR (*phosphate*[Title/Abstract] OR *phosphorus[Title/Abstract] OR "organophosphate ester"[Title/Abstract] OR "OPE"[Title/Abstract] OR "PBFR"[Title/Abstract]))) AND (((((retardants, flame OR flame retardants[MeSH Terms])) OR "flame retardant*"[Title/Abstract])) AND (((CAS Registry Number])) OR (Chemical Name [Title/Abstract] OR “Abbreviation”[Title/Abstract]) AND (((children OR infants OR mothers OR embryos OR fetuses[MeSH Terms])) OR (child*[Title/Abstract] OR juvenile[Title/Abstract] OR baby[Title/Abstract] OR babies[Title/Abstract] OR infant*[Title/Abstract] OR toddler*[Title/Abstract] OR mother*[Title/Abstract] OR embryo*[Title/Abstract] OR foetus*[Title/Abstract]))) AND (((breast milk OR breast milks OR lactation OR endocrine disruptors OR estrogens OR thyroid[MeSH Terms])) OR (*toxic*[Title/Abstract] OR *neuro[Title/Abstract] OR *behaviour[Title/Abstract] OR *behavior[Title/Abstract] OR "growth rate"[Title/Abstract] OR "breast milk*"[Title/Abstract] OR lactation[Title/Abstract] OR "endocrine disruptor*"[Title/Abstract] OR estrogen*[Title/Abstract] OR oestrogen*[Title/Abstract] OR thyroid*[Title/Abstract] OR hormone*[Title/Abstract] OR *function[Title/Abstract] OR exposure*[Title/Abstract]))): 182 refs

A total of 216 references were identified from these searches.

The list of PFRs was identified by an initial literature search and correlated with PFRs listed in Danish EPA (2016).

A sensitivity analysis was performed to determine the most appropriate search strategy for locating exposure data. A trial was conducted using one PFR and the search term “exposure”; and a separate search was performed using the search terms “exposure”, “oral”, “dermal”, “inhal*” and “ingest*”. No additional literature was located using the more detailed search terms and so therefore, subsequent searches for the remaining chemicals were conducted using “exposure” only.

Exclusion criteria included but were not limited to*;* papers available in languages other than English*, in vitro*, invertebrate, avian or aquatic models, methodology for analysis or detection of PBFR compounds, other sources of PFR compounds (e.g. car dust, commercial airplanes) and other receptor (e.g. non-pregnant adults).

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

Phosphate-Based Flame Retardants and the Potential for Developmental Toxicity: A Scoping Paper

Draft list of current use flame retardants.

This has been gathered by Defra from the available literature and the REACH registration to build some understanding of the (potentially) most used flame retardants on the market. The list is not exhaustive and represents a preliminary piece of work on the subject.

NCET at WRc/IEH-C under contract supporting the PHE Secretariat
October 2018

Substance	Other names	CAS RN	Type FR	End use application					REACH Registration y/n	CoRAP	Precautionary measures	PBT assessment	Tonnes per year (REACH reg)		Reference	Substitute for
				Electronics	Buildings and construction	Transport	Storage and distribution	Textiles								
Bis(hexachlorocyclopentadieno) Cyclooctane	Dechlorane Plus	13560-89-9	Halogenated	x	x				y			vPvB	100-1000		Amec	DecaBDE
Brominated poly(phenylether)		Confidential	Halogenated	x	x	x	x	x	?	?		?	?		Amec	DecaBDE
Decabromodiphenyl ethane	DBDPE, EBP	84852-53-9	Halogenated	x	x	x	x	x	y	PBT			10,000-100,000		Amec	DecaBDE
Ethylene Bis-tetrabromophthalimide		32588-76-4	Halogenated	x	x	x	x		y	PBT			100-1000		Amec	DecaBDE
Tetrabromobiphenol A Bis (2,3-dibromopropyl ether)		21850-44-2	Halogenated	x	x	x			y	PBT			100-1000		Amec	DecaBDE
Tris(tribromoneopentyl) Phosphate		19186-97-1	Halogenated	x	x			x	n						Amec	DecaBDE
Tris(tribromophenoxy) triazine			Halogenated						n						Amec	DecaBDE
Brominated epoxy polymers		68928-70-1	Halogenated	x	x	x			n						Amec	DecaBDE
Mixture of brominated epoxy polymer(s) and bromobenzyl acrylate		Confidential	Halogenated	x			x		?						Amec	DecaBDE
Brominated epoxy resin end-capped with tribromophenol		135229-48-0	Halogenated	x	x	x			n						Amec	DecaBDE
Brominated polyacrylate		59447-57-3	Halogenated	x		x	x		n						Amec	DecaBDE
Brominated polystyrene		88497-56-7	Halogenated	x					n						Amec	DecaBDE
Substituted amine phosphate mixture		Confidential	Phosphorous	x	x	x	x		?						Amec	DecaBDE
Triphenyl phosphate	TPHP, TPP	115-86-6	Phosphorous	x					y	EDC			100-1000		Amec	DecaBDE
Bisphenol A bis-(diphenyl phosphate)	BAPP	181028-79-5	Phosphorous	x					y		long term harm to aquatic life		1000+	13 active registrations	Amec	DecaBDE
Polyphosphonate		68664-06-2	Phosphorous	x	x	x		x	n						Amec	DecaBDE
Phosphoric acid, mixed esters with [1,1'-bisphenyl-4-4'-diol] and phenol;	BPBP	1003300-73-9	Phosphorous	x		x			n						Amec	DecaBDE
Poly[phosphonate-co-carbonate]		77226-90-5	Phosphorous	x	x	x			n						Amec	DecaBDE
Resorcinol Bis-Diphenylphosphate	RDP	125997-21-9	Phosphorous	x					n						Amec	DecaBDE
Aluminium diethylphosphinate		225789-38-8	Inorganic	x		x		x	n						Amec	DecaBDE
Aluminium hydroxide		21645-51-2	Inorganic	x	x	x	x	x	y				1000,000-10,000,000		Amec	DecaBDE
Ammonium polyphosphate		68333-79-9	Inorganic	x	x	x	x	x	y		irritation and harmful		10,000-100,000		Amec	DecaBDE
Antimony trioxide		1309-64-4	Inorganic	x	x	x	x	x	y	carcinogenic	carcinogenic		10,000+		Amec	DecaBDE
Magnesium hydroxide		1309-42-8	Inorganic	x	x	x	x		y				100,000-1000,000		Amec	DecaBDE
red phosphorus		7723-14-0	Inorganic	x		x			y	fatal if swallowed			1000-10,000		Amec	DecaBDE
Zinc borate		1332-07-6	Inorganic	x	x	x	x		n						Amec	DecaBDE
Benzene, ethenyl-, polymer with 1,3-butadiene brominated	Emerald 3000, FR-122P, GreenCrest, Brominated co-polymer of styrene and butadiene	1195978-93-8	polymeric / halogenated	N/A	N/A	N/A	N/A	N/A	n						Amec	HBCDD
Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2,3-dibromo-2-methylpropxy)]	TBBPA-bis brominated ether derivative, Pyroguard SR-130	97416-84-7	Halogenated	N/A	N/A	N/A	N/A	N/A	y	EDC, PBT/vPvB, exp to env			1000-10,000		Amec	HBCDD as a FR in EPS
Tetrabromobisphenol-A bis (allylether)	BE 51	25327-89-3	Halogenated	N/A	N/A	N/A	N/A	N/A	n						Amec	HBCDD as a FR in EPS
1,2,5,6-tetrabromocyclooctane	TBCO, Saytex BC-48	3194-57-8	Halogenated	N/A	N/A	N/A	N/A	N/A	n						Amec	HBCDD as a FR in EPS
2,4,6-tribromophenyl allyl ether	Pyroguard FR 100	3278-89-5	Halogenated	N/A	N/A	N/A	N/A	N/A	n						Amec	HBCDD as a FR in EPS
Tetrabromobisphenol A bis(2,3-dibromopropylether)	TBBPADBPE, GC SAM 55, FR 720	21850-44-2	Halogenated	N/A	N/A	N/A	N/A	N/A	y	EDC, PBT/vPvB, High (aggregated)			100-1000		Amec	HBCDD as a FR in EPS
Tetrabromobisphenol A bis(2,3-dibromopropylether) &dicumyl peroxide (bis(α,α-dimethylbenzyl) peroxide)	TBBPADBPE and dicumyl peroxide, SAN 55 E (EPS)	21850-44-2/80-43-3	Halogenated	N/A	N/A	N/A	N/A	N/A	y	PBT/vPvB, consumer use, exp to env, exp of workers, high (aggregated) tonnage, high RCR, wide dispersive use			10,000-100,000		Amec	HBCDD as a FR in EPS
1,2-dibromo-4-(1,2-dibromoethyl)cyclohexane	SAYTEX BCL 462	3322-93-8	Halogenated	N/A	N/A	N/A	N/A	N/A	n						Amec	HBCDD as a FR in EPS
Clays: sepiolite (complex magnesium silicate), playgorskite/attapulgite, (magnesium aluminium phyllosilicate) or combinations thereof	Understood to be not yet marketed (a US patent is published)	N/A	?	N/A	N/A	N/A	N/A	N/A	n						Amec	HBCDD as a FR in EPS