Breast Cancer UK comments on draft screening report on assessment of whether TCEP, TCPP and TDCP in articles should be restricted

The European Chemicals Agency (ECHA) published a draft screening report to consider whether the use of the organophosphate flame retardant tris(2-chloroethyl) phosphate (TCEP) in articles pose a threat to human health or the environment. TCEP is included in Annex XIV as it is classified as "toxic for reproduction". The screening report also covers carcinogenicity and considers tris(2-chloro-1-methylethyl) phosphate (TCPP) and tris[2-chloro-1-(chloromethyl)ethyl] phosphate (TDCP), which are similar compounds with similar uses. Below is Breast Cancer UK's submitted response to this report.

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Breast Cancer UK is a charity which aims to prevent breast cancer by reducing public exposure to carcinogenic and other hazardous chemicals in the environment. We are concerned about the potential role of exposures to environmental chemicals, especially those that occur *in utero*, in increasing breast cancer risk. We consider organophosphate flame retardants (OPFRs) to be potentially harmful to health and the environment and may increase breast cancer risk.

We welcome consideration of whether tris(2-chloroethyl) phosphate (TCEP), tris(2-chloro-1-methylethyl) phosphate (TCPP) and tris[2-chloro-1-(chloromethyl)ethyl] phosphate (TDCP) should be restricted in articles and are grateful for the opportunity to provide feedback on the draft screening report.

Breast Cancer UK welcomes the inclusion of TCPP and TDCP in the screening report and supports strongly ECHA's recommendation that an Annex XV restriction dossier is prepared for all three OPFRs.

The exposure assessment in the draft screening report was targeted to infant exposure of OPFRs in flexible foam found in childcare products and furniture. We believe the restriction proposal should not only be limited to these articles, as flame retardants can be used in textiles, and are commonly found in other environments (such as offices and commercial buildings). Nor should any future report or restriction proposal focus only on infants, who we agree are highly vulnerable to harmful exposures. We also believe *in utero* exposures can be especially harmful and so would suggest a more general exposure assessment that covers all populations.

The report states (**p4**) "The screening assessment identified a risk for children from exposure to TCEP, TCPP and TDCP in polyurethane foams in childcare articles and furniture" and goes on to say if a report is prepared exposure from other uses and articles and to other populations "may need consideration". We suggest this is changed to "will need consideration".

We are concerned about any possible exemption or opt-out that might apply to the UK and Ireland (**RMO2 in Section 2.1**). This is particularly concerning given the UK already has some the highest recorded levels of OPFRs globally (e.g.[1] for levels in dust). This would set different levels of consumer

[1] Brommer and Harrad (2016). Sources and human exposure implications of concentrations of organophosphate flame retardants in dust from UK cars, classrooms, living rooms, and offices. Environment International 83: 202-207.

protection in different EU countries and may allow the use of restricted flame retardants in countries where there is the highest (environmental) concentrations.

There is strong evidence that these OPFRs act as **endocrine disrupting chemicals** (EDCs). Although the report acknowledges there may be "endocrine effects" (**p27**), no details are included. Breast Cancer UK is especially concerned about the role of EDCs in increasing breast cancer risk. There is evidence that oestrogen mimics and other EDCs increase risk (e.g. see[2]). TCEP is an EDC which affects steroidogenesis and induces oxidative stress[3]. Studies suggest TDCP is oestrogenic, anti-oestrogenic[4] and anti-androgenic[5].

The report states that TCEP is potentially carcinogenic (**p22**) and classed as a category 3 **carcinogen** (**p23**). The carcinogenic mechanism is unclear, although it is not considered to be a mutagen. There is also evidence that TDCP is carcinogenic and it is similarly classified (**p26**). In rodents TDCP induces tumours in liver, kidney and testes. OPFR metabolites may also be carcinogenic. A major TDCP metabolite, 3-MCPD, induces mammary tumours in male rodents; this metabolite was found to be genotoxic *in vitro* but not *in vivo*[6]. As mentioned in the report, no carcinogenicity study is available for TCPP. This is especially concerning given this is the most widely used flame retardant in polyurethane foam (**p31**).

TCEP is classified as a **reproductive toxicant** (category 1B). TCPP is included in CoRAP for evaluation, partly due to being a suspected reproductive toxicant (**p20**). Recently published epidemiological studies indicate elevated concentrations of a urinary metabolite of TCPP in women may affect reproductive health and pregnancy outcomes[7] and in men, may affect fertilisation[8]. The report notes (**p22**) the draft EU risk assessment report for TDCP found there was a data gap for effects on female fertility, but "no concern for effects on male fertility or developmental toxicity", yet recent *in vitro* studies (e.g.[9]) suggest TDCP may affect neurodevelopment. One epidemiological study suggests exposure during pregnancy to OPFR mixtures (which include TDCP) may negatively affect IQ and memory in children[10]. This highlights another problem which is the unknown additive or synergistic

[2] Burks et al. (2017). Endocrine disruptors and the tumor microenvironment: A new paradigm in breast cancer biology. Molecular and Cellular Endocrinology 457: 13-19.

[3] Chen et al. (2015a). Exposure of male mice to two kinds of organophosphate flame retardants (OPFRs) induced oxidative stress and endocrine disruption. Environmental Toxicology and Pharmacology 40(1): 310-318 and Chen et al (2015b) TPP and TCEP induce oxidative stress and alter steroidogenesis in TM3 Leydig cells. Reproductive Toxicology 57: 100-110.

[4] Krivoshiev et al. (2016). Assessing in-vitro estrogenic effects of currently-used flame retardants. Toxicology In Vitro 33: 153-62.

[5] Reers et al. (2016). The flame-retardant Tris(1,3-dichloro-2-propyl) phosphate represses androgen signalling in human prostate cancer lines. Journal of Biochemistry and Molecular Toxicology 30(5) 249-257.

[6] OEHHA, (2011) Evidence on the Carcinogenicity of Tris(1,3-dichloro-2-propyl) phosphate. California Environmental Protection Agency, OEHHA, Reproductive and Cancer Hazard Assessment Branch, July 2011, available at: http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/TDCPP070811.pdf

[7] Carignan et al. (2018). Paternal urinary concentrations of organophosphate flame retardant metabolites, fertility measures, and pregnancy outcomes among couples undergoing in vitro fertilization. Environment International 111: 232-238.

[8] Carignan et al. (2017). Urinary Concentrations of Organophosphate Flame Retardant Metabolites and Pregnancy Outcomes among Women Undergoing in Vitro Fertilization. Environmental Health Perspectives 125(8): 087018

[9] Slotkin et al. (2017). Brominated and organophosphate flame retardants target different neurodevelopmental stages, characterized with embryonic neural stem cells and neuronotypic PC12 cells. Toxicology 390: 32-42

[10] Castorina et al. (2017). Current-use flame retardants: Maternal exposure and neurodevelopment in children of the CHAMACOS cohort. Chemosphere 189: 574-580.

effects of FR mixtures. The report notes that TCEP may be **neurotoxic** (**p27**). Studies suggests TDCP is also, and more neurotoxic than TCEP (see review[11]).

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[11] van der Veen and Boer (2012). Phosphorus flame retardants: Properties, production, environmental occurrence, toxicity and analysis. Chemosphere 88: 1119-1153