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**A Critical Review of Human Exposure to Organophosphate Esters with a
Focus on Dietary Intake**

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Highlights

- Food ingestion and dermal uptake from dust are main human exposure pathways
- Chlorinated OPEs are main OPEs in drinking water
- The sum of average EDI values for all exposure pathways are below reference doses
- Exposure assessments should examine all pathways simultaneously
- Research into dermal uptake from OPE-treated materials is a priority

Graphical Abstract

Abstract

Organophosphate esters (OPEs) are common additives in a wide range of commercial and industrial products. Elevated and prolonged exposure to OPEs may induce several adverse effects. This is concerning as they are ubiquitous in air, indoor dust, drinking water, and other environmental matrices. However, information on the presence of OPEs in foodstuffs and consequent health risks remains scant. This review critically evaluates available information on levels and sources of OPEs in food, discusses the relative significance of diet as a pathway of human exposure, identifies knowledge gaps, and suggests directions for future research. For toddlers, dermal uptake from dust ingestion appears the predominant pathway of exposure to chlorinated OPEs, as well as ethylhexyl diphenyl phosphate (EHDPP) and triphenyl phosphate (TPHP). In contrast, diet appears the main pathway of exposure to all eight OPEs considered for adults, and for tri n-butyl phosphate (TnBP), tris 2-ethylhexyl phosphate (TEHP), and tris (2-butoxyethyl) phosphate (TBOEP) for toddlers. While summed exposures via all pathways are within reference dose (RfD) values, they do not include high-end exposure estimates, and for highly-exposed individuals, the margin between exposure and RfD values is smaller. Moreover, our exposure estimates are based on a meta-analysis of multiple exposure assessments conducted over a range of points in space and time. There is an urgent need for assessments of human exposure to OPEs that examine all relevant pathways in a spatially and temporally-consistent fashion. Given food is an important exposure pathway to OPEs, regular monitoring of their presence as well as their metabolites (that may have toxicological significance) in foodstuffs is recommended. While dermal uptake from indoor dust appears an important human exposure pathway, no evaluations exist of exposure via dermal uptake from OPE-containing products such as foam-filled furniture. This review also highlights very few data exist on OPEs in drinking water.

39 **Keywords:** Organophosphate esters, Foodstuffs, Indoor dust; Indoor air; Drinking
40 water; Dermal uptake
41

1. Introduction

Organophosphate esters (OPEs) are a class of anthropogenic organic compounds found ubiquitously in many environmental media due to their release from commercial and industrial products (ATSDR, 2012). Widely used as flame retardants in furniture, textiles, building materials, electronics and other processing chemicals, they are also often used as plasticisers in floor polish and wax, coatings, engineering thermoplastics, and epoxy resins (Greaves and Letcher, 2014). In common with other chemical contaminants, human exposure to OPEs can potentially occur via inhalation, ingestion of food, water and/or dust, as well as through dermal contact with dust, soil and/or consumer products (ATSDR, 2012).

Chemically, OPEs comprise a heterogeneous class of phosphoric acid esters in which the hydrogen in the phosphate group is replaced by an alkyl, aryl, or chlorinated alkyl group (Guo et al., 2016). OPEs are usually employed as additive flame retardants (FRs) in various consumer products, i.e. they are physically added to materials rather than chemically bonded to the matrix. Applications of OPEs include use as FRs in textiles, rubber, cellulose, polyurethane foam, electronic equipment, cotton, cutting oils, etc. (Veen and de Boer, 2012). Additionally, OPEs such as TPHP and TBOEP are used in unsaturated polyester resins, floor wax and stabilizers for anti-foaming and as additives to floor polishes, lubricants, lacquers and hydraulic fluids. For instance, the common chlorinated OPEs (i.e., tris(2-chloroethyl) phosphate (TCEP), tris(chloropropyl) phosphate (TCIPP) and tris(1,3-dichloro-2-propyl) phosphate (TDCIPP)) are applied in flexible and rigid PUFs (Wei et al., 2015).

Consequently, they are susceptible to release into the environment via leaching, volatilisation, as well as abrasion (Guo et al., 2016; Pang et al., 2017). Following release into the environment, they may accumulate in indoor environments and following release from such environments ultimately be transported over long distances by air and water (Hou et al., 2016). As a result,

there has been widespread detection of OPEs in air, water, soil, indoor environments, and biota, including humans (Gao et al., 2014).

Owing to their persistent, bioaccumulative, and toxic properties, several brominated flame retardants (BFRs) have been listed under the Stockholm Convention on Persistent Organic Pollutants (POPs) (Stockholm Convention on POPs, 2013). In 2018, the global consumption of FRs reached 2.6 million tonnes and is predicted to approach 3.1 million tonnes by 2023 (BCC Research, 2018). The global production and use of OPEs has increased rapidly in recent years. It is likely therefore that the use of OPEs has increased as replacements for restricted BFRs, with worldwide consumption of OPEs projected to reach 860,000 t in 2023 from 680,000 t in 2015 to 816,000 t in 2018 (BBC Research, 2018; Wang et al., 2015). OPEs have been estimated to account for 20 % of the total consumption of FRs in Western Europe (Wei et al., 2015).

Unfortunately, some OPEs, especially those that are chlorinated, are thought to be persistent in the environment (Lai et al., 2015), with human exposure demonstrated by their detection in human milk (Kim et al., 2014). Concerns about such exposure are compounded by toxicological studies revealing that high concentrations and prolonged exposure to OPEs can induce adverse effects including carcinogenicity, neurotoxicity, kidney toxicity, reproductive toxicity, liver toxicity, and endocrine disruption (Hou et al., 2016; Wei et al., 2015). The presence and concentrations of OPEs in various biotic and abiotic environmental matrices has been reviewed (Wei et al., 2015; Sugeng et al., 2017; Hou et al., 2016; Greaves and Letcher, 2017). However, information on the worldwide presence of OPEs in foodstuffs remains scant and the sources of contamination, i.e. whether the presence of OPEs in food is due to migration from food packaging, bioaccumulation, uptake from the agricultural environment, contamination during industrial processing, or some other sources, remain unclear. Currently, data on concentrations of OPEs in food is restricted to samples from China, USA, Belgium,

Sweden, and Australia (Zhao et al., 2019; Zhang et al., 2016; Wang and Kannan, 2018; Poma et al., 2017; 2018; He et al., 2018a), while there exists no data from other European countries, North America, South America, and Africa. It is on this premise that this critical review will: (a) discuss the pathways of human exposure to OPEs; (b) assess the current state-of-knowledge on OPEs in diet; and (c) evaluate the relative significance of dietary exposure compared to other human exposure pathways.

2. Methodology

The search for research articles, reviews, book, conference proceedings and other online resources was carried out between November 20, 2018 to October 20, 2020 using the following electronic databases: Scopus, ScienceDirect and Web of Science core collection. The search terms used were: ‘‘organophosphate esters (OPEs)’’, ‘‘organophosphorus flame retardants’’ ‘‘foodstuffs’’ and ‘‘human exposure’’ and only articles published between 2014 and 2020 were selected. ScienceDirect and Scopus returned a total of 2506 and 1105 publications respectively, with a further 554 articles located on Web of Sciences core collection. Further screening based on suitability of the titles and abstracts of articles, identified 121 full-text articles from ScienceDirect, 95 full text articles from Scopus and 103 full-text articles from Web of Science core collection respectively. After duplicate studies ($n = 130$) were removed, 189 publications were left for further screening. After full text screening, 114 articles were excluded based on factors such as article not written in English, full text not available, as well the nature of the samples analysed, the sampling methodology, statistical data presented, articles with no human exposure data and those not related to risk assessment of OPEs. This left 75 articles consisting of 66 research papers, 5 review papers and four official reports. In addition, screening of references cited in these 75 articles, identified a further 15 publications (comprising 14 research articles and one official report published before 2014). In total therefore, 90 articles were included in this review.

3. Physicochemical properties and pathways of human exposure to OPEs

Several key physicochemical properties essentially define the environmental behaviour and fate of OPEs; in particular, their availability for uptake by biota and routes of human exposure (Table S1). As well as the ambient temperature experienced by OPE-treated materials, emissions of OPEs via volatilisation will depend on their vapour pressure and concentrations in the treated products (Carlsson et al., 1997; Ni et al., 2007). Meanwhile, the extent of OPE bioaccumulation is dependent on their octanol: water partition coefficient (K_{ow}) and the rate at which they metabolise in biota (Regnery and Püttmann, 2010). For example, halogenated OPEs were reported to be more persistent in the environment and more resistant to degradation than alkyl and aryl OPEs (Marklund et al., 2005; Bester, 2006).

The three main pathways via which humans are exposed to chemicals, are ingestion, inhalation, and dermal absorption. These broad categories may further be broken down into sub-categories such as ingestion of dust, food, and drink, as well as dermal uptake resulting from contact with dust and with products containing chemicals. The relative contribution that each pathway makes to overall exposure depends *inter alia* on the physicochemical properties and commercial applications of the chemicals, as well as lifestyle and demographic factors related to the exposed individual. Evidence to date has demonstrated that human exposure to OPEs can occur via dermal contact (Abdallah et al., 2016), ingestion of contaminated dust (Abdallah and Covaci, 2014), inhalation of air (Schreder et al., 2016), and more recently diet (Poma et al. 2018; Zhao et al., 2019) (Fig.1).

Fig. 1: Schematic representation of the pathways of transmission of OPEs from treated products to humans

3.1 Human Exposure to OPEs via Inhalation

A summary of studies reporting concentrations of OPEs in indoor air are provided as supplementary information (Table S2), with a summary of estimated daily intakes (EDIs) of OPEs through air inhalation reported in various studies presented in Table S3. Schreder et al. (2016) observed that estimated exposure to OPEs via inhalation exceeded estimated exposure from dust ingestion. Adult inhalation intake of TCIPP was estimated at 4540 ng/day, which was 31 times that from dust ingestion for TCIPP in the studied population (Schreder et al., 2016). Moreover, in a study carried out examining exposure via indoor air inhalation, dust ingestion, and dermal uptake in Albany, New York, USA; Kim et al. (2019) reported TCIPP (27–43 %) and triethyl phosphate (TEP) (11–33 %) were the two major contributors of total human exposure via inhalation. In a similar study carried out by Cao et al. (2019), inhalation was shown to be one of the main human exposure routes for volatile OPEs such as tri iso-butyl phosphate (TiBP), TnBP, TCIPP, and TEP. Moreover, in a study of exposure occurring via air inhalation, indoor dust ingestion and dermal uptake, Zhou et al. (2017) reported that under a

154 median exposure scenario, air inhalation contributed 5.7 ng Σ OPEs.kg bw⁻¹.day⁻¹ representing
155 73 % of total exposure for German adults. A similarly high contribution of inhalation was
156 reported for adults in a study of living rooms of private homes in Norway by Xu et al. (2016).
157 According to Xu et al. (2016), the estimated inhalation exposure to Σ OPEs has the highest
158 median value among all pathways considered (median = 34 ng.kg bw⁻¹.day⁻¹), followed by dust
159 ingestion (median = 13 ng.kg bw⁻¹.day⁻¹). Xu et al. (2016) showed that inhalation is the major
160 exposure pathway for low molecular weight, relatively more volatile OPEs, like TCEP and
161 TCIPP, while dust ingestion is the main route for less volatile OPEs such as TBOEP, TPHP,
162 and tris(methylphenyl)phosphate (TMPP). Fig. 2 shows the range of mean estimates of human
163 exposure via inhalation found in the literature for four individual OPEs clearly indicating that
164 human exposure via inhalation for children and adults follows the order TCIPP >> TCEP >
165 TDCIPP > TPHP.

Fig. 2: Box-plot showing the range of mean estimates of human exposure to TCEP, TCIPP, TDCIPP, and TPHP via air inhalation.

3.2 Human Exposure to OPEs via Dust Ingestion.

A summary of concentrations of OPEs reported in indoor dust is provided in supplementary material (Table S4), while EDIs from ingestion of indoor dust are collated in Table S5. Several studies have showed that ingestion of dust (indoor and outdoor) is an important human exposure pathway to OPEs (Brommer et al., 2012; 2015; Abdallah and Covaci et al., 2014; Stubbings et al., 2018; Cao et al., 2019; Kim et al., 2019). According to Cao et al. (2019) assuming that toddlers stay at home all the time, while adults spend only 62.5 % of their time at home; the mean estimated daily intakes (EDIs) for toddlers and adults for Σ_{14} OPEs were 35

178 and 6.7 ng. kg bw⁻¹. day⁻¹, respectively. The 95th percentile EDIs for toddlers and adults were
 179 91 and 33 ng. kg bw⁻¹. day⁻¹, respectively (Cao et al., 2019). The estimated EDIs for this study
 180 are comparable with those of 160 and 32 ng. kg bw⁻¹. day⁻¹ calculated for toddlers and adults
 181 respectively in Germany (Brommer et al., 2012). Similar values were reported for toddlers and
 182 adults from New Zealand (median: 17.5 ng. kg bw⁻¹. day⁻¹ and 1.2 ng. kg bw⁻¹. day⁻¹) (Ali et
 183 al., 2012), and Sweden (median: 18 ng. kg bw⁻¹. day⁻¹ and 0.85 ng. kg bw⁻¹. day⁻¹) (Luongo
 184 and Ostman, 2015). These EDIs are lower than those reported in the U.S. for adults (median:
 185 13 ng. kg bw⁻¹. day⁻¹) (Xu et al., 2016), in Japan for toddlers (median: 112 ng. kg bw⁻¹. day⁻¹
 186 and 115 ng. kg bw⁻¹. day⁻¹) based on ingestion of floor and elevated surface dust respectively
 187 (Tajima et al., 2014), and Egypt (median: 52 ng. kg bw⁻¹. day⁻¹ and 13 ng. kg bw⁻¹. day⁻¹) for
 188 toddlers and adults respectively (Abdallah and Covaci, 2014). In a study carried out by He et
 189 al. (2015), the median EDIs of Σ_{12} OPEs for adults and toddlers via dust ingestion in an e-waste
 190 recycling area were 7.02 ng. kg bw⁻¹. day⁻¹ and 80.2 ng. kg bw⁻¹. day⁻¹. These values were
 191 substantially higher than the EDIs for adults and toddlers in urban locations (2.06 ng. kg bw⁻¹.
 192 day⁻¹ and 23.5 ng. kg bw⁻¹. day⁻¹), rural areas (2.0 ng. kg bw⁻¹. day⁻¹ and 22.6 ng. kg bw⁻¹.
 193 day⁻¹) and college dormitories (3.2 ng. kg bw⁻¹. day⁻¹ and 2.06 ng. kg bw⁻¹. day⁻¹) in China
 194 (He et al., 2015) (Table S5). Zhou et al. (2017) also reported that under a median dust exposure
 195 scenario, dust ingestion was the most significant exposure pathway to Σ_{10} OPEs for toddlers
 196 contributing 69 % (41 ng. kg bw⁻¹. day⁻¹) of their total exposure followed by dermal uptake
 197 which contributes 27 % (16 ng. kg bw⁻¹. day⁻¹), and air inhalation 4 % (2.4 ng. kg bw⁻¹. day⁻¹)
 198 (Table S5). Figure 3 summarises visually the range of reported mean estimates of human
 199 exposure via dust ingestion for four major OPEs for adults and toddlers. These results show
 200 that – normalised to body weight - toddlers are more highly exposed to these four OPEs than
 201 adults.

Fig. 3: Box plot showing the range of mean reported estimates of human exposure via dust ingestion to TCEP, TCIPP, TDCIPP, and TPHP

3.3 Human dermal uptake of OPEs

Recently, a few studies have raised concerns about dermal absorption as a potentially significant pathway of exposure to OPEs (Abdallah et al., 2016; Mendelsohn et al., 2016; Liu et al., 2017a, b; Bello et al., 2018; Frederiksen et al., 2018). Table S6 summarises estimates of dermal exposure to OPEs published to date. Hoffman et al. (2015) found a significant positive association between levels of TDCIPP and TPHP on hand wipes and the concentrations of their metabolites in urine, suggesting that hand-to-mouth contact and/or dermal absorption may be important exposure pathways to OPEs. More recently, a study examining the exposure to TPHP through nail polish application, suggested the primary exposure route of TPHP is dermal

216 absorption (Mendelsohn et al., 2016). Similarly, in a study carried out by Bello et al. (2018),
 217 high levels of urinary biomarkers of TCIPP were detected post-shift in applicators of spray
 218 polyurethane foam (SPF) used as thermal insulating material in construction, indicating dermal
 219 absorption as an important exposure pathway to TCIPP to such individuals.

220 In addition, *in vitro* skin absorption studies (Abdallah et al., 2016; Hughes et al., 2001) reveal
 221 that a relatively high percentage of TCEP, TCIPP, and TDCIPP can be absorbed by human or
 222 mouse skin. Assessments of dermal exposure to OPEs are however, limited. Two studies
 223 reported OPE intakes via dermal absorption from contact with indoor dust (Cequier et al., 2014;
 224 Abdallah et al., 2016). Abdallah et al. (2016) investigated human dermal uptake of Σ_3 OPEs
 225 using human *ex vivo* and cultured EPISKINTM 3-D human skin equivalent (3D-HSE) models.
 226 They reported that the median EDIs via dermal absorption of Σ_3 OPEs (TCEP, TCIPP, and
 227 TDCIPP) for toddlers and adults via indoor dust ingestion were 36 ng.kg bw⁻¹. day⁻¹ and 4.1
 228 ng. kg bw⁻¹. day⁻¹ which were lower than the reported values of 108 ng.kg bw⁻¹. day⁻¹ and 23
 229 ng. kg bw⁻¹. day⁻¹ (Σ_8 OPEs) for school children and women by Cequier et al. (2014). Abdallah
 230 et al. (2016) also investigated the impact of hand-washing on reducing dermal exposure to
 231 OPEs. They found that depending on the physicochemical properties of the OPEs, hand-
 232 washing reduces the overall human dermal uptake of the OPEs (Abdallah et al., 2016). The
 233 same authors noted that as well as from adhered indoor dust, OPEs on the skin surface might
 234 also arise from dermal contact with flame-retarded consumer products (i.e. fabrics, mobile
 235 phones), which may constitute a more significant exposure route due to high concentrations of
 236 OPEs in these products (Abdallah et al, 2016, 2018). In summary, the evidence to date suggests
 237 that human exposure to selected individual OPEs via dermal absorption occurs in this order:
 238 TPHP >> TCIPP > TDCIPP > TCEP (Fig. 4). This contrasts with the situation for air inhalation

for which such exposure was greater for the chlorinated OPEs. Figure 4 also shows that toddlers are much more exposed than adults.

Fig. 4: Box plot showing the range of reported mean estimates of human exposure to TCEP, TCIPP, TDCIPP, and TPHP via dermal absorption from indoor dust.

3.4 Human Exposure to OPEs via drinking water

To date, several studies have reported concentrations of OPEs in source and finished water from municipal water plant (MWP), terminal tap water from water utilities, surface water from

river (Liu et al., 2019; Benotti et al., 2009; Rodil et al., 2012), bottled, household tap and filtered water produced from tap water by public purifying machine/household filtering apparatus (Li et al., 2014; Ding et al., 2015; Lee et al., 2016; Kim and Kannan, 2018; Park et al., 2018). Reported concentrations of individual OPEs are shown in Table S7. Concentrations of Σ_{14} OPEs range in the USA between 3.02 and 366 ng/L for tap water (Kim and Kannan, 2018), and 8-720 ng/L for source and finished water (Benotti et al., 2009). In China, concentrations in municipal water from Nanjing ranged between 3.6-180 ng/L (Liu et al., 2019), while in Hangzhou they fall in the range 123-338 ng/L in tap water, 0.9-11.2 ng/L in bottled water, and 17.2-126 ng/L in filtered drinking water produced from tap water by household filtering system (Ding et al., 2015). Elsewhere, concentrations in surface and tap water from Spain range between 40-140 ng/L (Rodil et al., 2012). (Table S7).

The level of human exposure to OPEs received via drinking water has been evaluated in only a small number of studies (Kim and Kannan, 2018; He et al., 2019; Lee et al., 2016; Liu et al., 2019; Ding et al., 2015). According to He et al. (2019), who assumed water ingestion rates of (0.322 L/day, 0.502 L/day and 1.0445 L/day) for toddlers, older children, and adults in Chongqing, China; the mean EDIs for the same age groups for Σ_{11} OPEs were 1.02, 0.684 and 0.939 ng. kg bw⁻¹.day⁻¹, respectively. The value obtained for toddlers exceeded the 0.22 ng. kg bw⁻¹.day⁻¹ obtained for Σ_{14} OPEs under a typical drinking water exposure scenario in the USA (Kim and Kannan, 2018). For Σ_{14} OPEs under a high exposure scenario, Kim and Kannan (2018) obtained an EDI value that ranged between 1.17 ng.kg bw⁻¹.day⁻¹ and 9.65 ng. kg bw⁻¹.day⁻¹ depending on the age group considered. In Korea, Lee et al. (2016) found that the median EDI values via drinking water for Σ_{10} OPEs for toddlers, children, teenagers and adults were: 2.55 ng. kg bw⁻¹.day⁻¹, 2.10 ng. kg bw⁻¹.day⁻¹, 1.27 ng. kg bw⁻¹.day⁻¹, and 1.81 ng. kg bw⁻¹.day⁻¹ respectively. These values were about 12 times higher than those obtained in the USA by Kim and Kannan (2018).

274 Kim and Kannan (2018) observed that TCIPP and TBOEP combined contributed > 50% of the
 275 total EDI via water ingestion among the Σ_{14} OPEs evaluated. They also reported that indirect
 276 water ingestion during swimming can contribute to a total OPE exposure of up to 15.8
 277 ng/swimming event for children and 9.28 ng/swimming event for adults. In Hangzhou and
 278 Quzhou, Eastern China, Ding et al. (2015) found that at 7.07 ng.kg bw⁻¹.day⁻¹ and 6.95 ng. kg
 279 bw⁻¹.day⁻¹ for adults and children, the mean EDIs for Σ_9 OPEs via tap water, exceeded those
 280 via filtered water produced from tap water via household filtering systems (2.22 ng. kg bw⁻¹
 281 .day⁻¹ and 2.19 ng. kg bw⁻¹.day⁻¹), well water (0.17 ng. kg bw⁻¹.day⁻¹ and 0.16 ng. kg bw⁻¹
 282 .day⁻¹) and barreled water purchased in packaged polycarbonate plastic barrels (1.06 ng. kg
 283 bw⁻¹.day⁻¹ and 1.05 ng. kg bw⁻¹.day⁻¹) respectively. In Nanjing, China, Liu et al. (2019) found
 284 median EDIs for Σ_5 OPEs for male and female adults were in the range 4.2-7.1 ng. kg bw⁻¹.day⁻¹
 285 and 3.6-6.1 ng. kg bw⁻¹.day⁻¹ respectively. Liu et al. (2019) also observed that for individual
 286 OPEs, TEP, TCEP, and TCPP made the biggest contributions to human exposure via water
 287 ingestion. Under a high exposure scenario, assuming ingestion of water contaminated at the
 288 95th percentile concentration, Liu et al. (2019) found the EDI value for Σ OPEs to vary between
 289 45.2-64.8 ng.kg bw⁻¹.day⁻¹ and 38.9-55.7 ng.kg bw⁻¹.day⁻¹ for male and female adults. These
 290 values exceed substantially estimates of high Σ OPE exposure scenarios (95th percentile) via
 291 ingestion of tap water in Korea (8.23-16.5 ng.kg bw⁻¹.day⁻¹) (Lee et al. 2016) and in Eastern
 292 China at high exposure scenario (median) (6.8-11.56 ng.kg bw⁻¹.day⁻¹) (Ding et al. 2015).
 293 Table S8 summarises human exposure data via water ingestion, while Figure 5 illustrates the
 294 range of mean estimates of the exposure of adults and children to TCEP, TCIPP, and TBOEP
 295 via water ingestion. This clearly shows that children are more exposed to these OPEs via water
 296 ingestion than adults.

Fig. 5: Box-plot showing the range of mean estimates of human exposure to TCEP, TCIPP, and TBOEP via water ingestion

3.5 Infant Exposure to OPEs via breast milk

There is growing concern over the presence of OPEs in human milk, which serves as the main source of nutrition for breast-fed infants (Beser et al, 2019). A small number of studies have reported concentrations of several OPEs in human breast milk. In a study carried out by He et al. (2018b) in South East Queensland, Australia; TCEP, TnBP, and TEHP were measured in human milk at concentration ranges of <0.13–0.47, 0.26–2.1, and 1.2–6.2 ng/mL, respectively. These concentrations are about 186 - 60 times lower than those reported for TCEP and TnBP in tap water in Korea (Park et al., 2018). Similarly, Ma et al. (2019) reported concentrations of Σ_{12} OPEs ranging from 0.67 to 7.8 ng/mL with a mean value of 3.6 ± 1.4 ng/mL (Table S9). This was consistent with the average concentration of Σ_{11} OPEs (3.4 ng/g) reported by Sundkvist et al. (2010) in pooled human milk samples from Sweden.

Concentrations of OPEs in human milk vary with several factors including mother's age and diet (Kim et al., 2014). Assuming a daily intake of 450 mL breast milk for infants 0–1 year old, He et al. (2018b) found that breastfeeding would result in average estimated daily intakes (EDIs) of 4.6, 26 and 76 ng.kg bw⁻¹.day⁻¹ for TCEP, TnBP, and TEHP respectively. According to Ma et al. (2019), the respective mean and the high-end EDIs of Σ OPEs via human milk were 542 and 911 ng.kg bw⁻¹.day⁻¹ for infants less than 1 month of age; 505 and 850 ng.kg bw⁻¹.day⁻¹ for infants from 1 to 3 months of age; 397 and 668 ng.kg bw⁻¹.day⁻¹ for infants from >3 to 6 months of age; and 300 and 504 ng.kg bw⁻¹.day⁻¹ for infants from >6 to 12 months of age (Table S10). The decreasing EDI with increasing infant age was attributed to increasing body weight and decreasing milk ingestion level with age. Table S10 shows the reported data on infant exposure to individual OPEs via human milk. Analysis of these data show nursing infant exposures to individual OPEs fall in the order: TDCIPP > TCEP >> TPHP > TCIPP (Fig. 6).

Fig. 6: Box-plot showing the range of mean estimates of breast-fed infant exposure to TCEP, TCIPP, TDCIPP, and TPHP via ingestion of human milk

3.6 Human Dietary Intake of OPEs

OPEs enter the human diet primarily via two routes. First, via bioaccumulation into plants and animals from contaminated air, soil, water, animal diet etc. Second, foodstuffs can be contaminated by OPEs during production, industrial processing (e.g., packing, canning, and drying) and storage, due to their presence in several materials used in food processing as well as in food contact and packaging materials (Campone et al., 2010; Ding et al., 2018; Poma et al., 2018; Wang and Kannan, 2018). Moreover, cooking processes may reduce the levels of OPE contamination in food (Ding et al., 2018; Zhao et al., 2019). Table S11 summarises the concentrations of OPEs detected in foodstuffs to date.

In surveys of fish worldwide, concentrations of Σ OPEs have been reported to be as high as 15,000 ng g⁻¹ (lipid weight - lw) (Sundkvist et al., 2010) (Table S11). Rice was reported as a significant source of exposure to OPEs in China (Zhang et al., 2016). In the study of Poma et al. (2018), fish-oil food supplements were the most contaminated food samples with a total mean Σ OPE concentration of 225 ng.g⁻¹ (wet weight – ww), followed by grain, cheese, and other food (meat and chicken stocks) with concentrations of 36.9, 20.1, and 18.8 ng.g⁻¹ ww respectively (Table S11). These observed values exceeded those detected in duplicate diet samples by Xu et al. (2017) who found the sum of the average concentrations of four OPEs (EHDPP, TCEP, TPHP, and TCIPP) to be 7.7 ng.g⁻¹ ww (Xu et al., 2017). In the Philippines, Kim et al., (2011) reported concentrations of the sum of nine OPEs (including TCEP, TCIPP, and TDCIPP) in fish from Manila Bay to range between 110 to 1900 ng.g⁻¹ lw.

Table S12 summarises reported human dietary intakes of OPEs from several studies from different countries. According to Malarvannan et al. (2015), mean dietary intakes of TCIPP, TPHP, EHDPP, TBOEP, TDCIPP, and TCEP through eel consumption were: 0.10, 0.034, 0.028, 0.017, 0.012, and 0.10 ng.kg bw⁻¹.day⁻¹ respectively; while high-end intake estimates were: 2.5, 0.84, 0.74, 0.43, 0.29, and 0.25 ng.kg bw⁻¹.day⁻¹, respectively (Table S12).

Looking beyond exposure via consumption of specific foodstuffs and considering overall dietary exposure, estimated dietary exposures to Σ OPEs at different locations vary, including between the United States (adults: 25.1 ng.kg bw⁻¹.day⁻¹, children: 56.6 ng.kg bw⁻¹.day⁻¹) (Wang and Kannan, 2018), China (adults: 55 ng.kg bw⁻¹.day⁻¹, children: 98 ng.kg bw⁻¹.day⁻¹) (Ding et al., 2018), (male adults: 539 ng.kg bw⁻¹.day⁻¹, female adults: 600 ng.kg bw⁻¹.day⁻¹) (Zhang et al., 2016), (Chinese adults: 44.3 ng.kg bw⁻¹.day⁻¹) (Zhao et al., 2019), Sweden (adults: 85 ng.kg bw⁻¹.day⁻¹) (Poma et al., 2017), and Belgium (adults: 103 ng.kg bw⁻¹.day⁻¹) (Poma et al., 2018) (Table S12). EDI values for toddlers, children, and teenagers exceed those for adults.

Fig. 7 depicts the range of estimates of dietary exposure of adults and children to four selected individual OPEs, showing clearly that children's exposure via diet occurs in the order: TCIPP >> TPHP > TCEP > TDCIPP (Fig. 7). In contrast, adult dietary exposure is of a broadly similar level for TCIPP, TDCIPP, and TPHP, but slightly lower for TCEP. Importantly, while this figure suggests that the average dietary exposure data obtained from ten studies for adults exceeded those for children; only two studies evaluated the EDI for children and in both these studies (Wang and Kannan, 2018; Ding et al., 2018), the EDIs for children were higher than those for adults measured in the same study.

Fig. 7: Box-plot showing the range of mean estimates of dietary exposure to TCEP, TCIPP, TDCIPP, and TPHP

4. Relative Significance of Different Exposure Pathways to OPEs

As highlighted above, measurable exposure to OPEs occurs through ingestion of contaminated house dust and food, inhalation of contaminated air, and dermal absorption. While Ji et al. (2014) argued that exposure via contact with dust, air and water should not be underestimated or ignored and that indoor air and water may be more important than diet as pathways of human exposure to OPEs; some recent studies have highlighted the importance of diet as a pathway

of human exposure to OPEs (Zhang et al., 2016; Poma et al., 2017; Ding et al., 2018; Wang and Kannan, 2018).

This section examines the significance of food ingestion in the context of its contribution to total human exposure to the following OPEs based on available literature data: TCEP, TCIPP, TDCIPP, TPHP, TnBP, TBOEP, TEHP, and EHDPP. The average of the reported mean human exposure estimates for each of these eight OPEs via dust, water, human milk and food ingestion, air inhalation, and dermal absorption, were used to evaluate the relative significance of each exposure pathway for both toddlers and adults. These average EDI values for each exposure pathway considered for adults and toddlers are listed in Table 1 and their relative contributions to overall exposure to each individual OPE illustrated in Figure 8 for toddlers and Figure 9 for adults.

Table 1: Obtained mean estimated daily intake (EDI) values for adults and toddlers for all exposure pathways

		Mean EDI values (ng.kg bw ⁻¹ .day ⁻¹)							
Exposure pathway	Age group	TCEP	TCIPP	TDCIPP	TPHP	TnBP	TBOEP	TEHP	EHDPP
Air inhalation	Adults	3.63	16.9	4.20	0.124	1.57	9.66	0.354	0.0996
	Toddlers	0.37	1.80	0.06	0.090	1.17	0.0164	0.040	0.214
Dust ingestion	Adults	2.36	9.37	2.83	0.980	0.090	2.36	0.521	0.315
	Toddlers	4.04	4.49	1.77	3.11	0.694	21.0	1.52	2.17
Dermal uptake	Adults	4.53	10.2	9.63	17.8	0.110	3.20	0.319	7.84
	Toddlers	103	208	221	401	0.420	2.03	0.280	227
Food ingestion	Adults	32.2	21.3	11.9	27.0	4.31	12.7	47.2	12.8
	Toddlers	3.61	12.4	2.91	3.65	12.0	46.8	7.23	0.940
	Adults	1.52	1.49	0.151	-	0.850	0.202	-	-

Water ingestion	Toddlers	0.239	0.618	0.0164	-	0.293	0.220	-	-
Human milk ingestion	Infants	4.40	65.3	4.00	14.5	57.2	152	38.9	5.13
Total EDI (Σ exposure pathways)	Adults	44.2	59.3	28.7	45.9	6.93	28.1	48.4	21.1
	Toddlers	111	227	226	408	14.6	70.1	9.07	230
Total Carcinogenic risk (TCR)	Adults	9.72×10^{-7}	-	-	-	6.24×10^{-8}	-	1.55×10^{-7}	-
	Toddlers	2.44×10^{-6}	-	-	-	1.31×10^{-7}	-	2.90×10^{-8}	-
RfD values (ng.kg bw ⁻¹ .day ⁻¹)	-	7000 ^a	10000 ^a	20000 ^a	-	10000 ^a	-	100000 ^a	-
SFO ((ng/kg bw/day) ⁻¹)	-	2×10^{-8} ^b	-	-	-	9×10^{-9} ^b	-	3.2×10^{-9} ^b	-

394 ^a Reference dose (RfD) values of USEPA (2017).

395 ^b Oral cancer slope factor (SFO) values (USEPA, 2017; Li et al., 2018)

396

397 This data analysis shows that for toddlers, dermal uptake of OPEs from indoor dust was the
398 major exposure pathway for all the chlorinated OPEs i.e. TCEP (103 ng.kg bw⁻¹.day⁻¹, 93 %),
399 TCIPP (208 ng.kg bw⁻¹.day⁻¹, 92 % Σ exposure), and TDCIPP (221 ng.kg bw⁻¹.day⁻¹, 98 %);
400 as well as for aryl OPEs such as TPHP (401 ng.kg bw⁻¹.day⁻¹, 98%) and EHDPP (227 ng.kg
401 bw⁻¹.day⁻¹, 98 %). It should be noted here that this high contribution of dermal uptake from
402 indoor dust for these OPEs is driven very substantially by the mean exposure estimates via this
403 pathway reported in a single study of childcare centres in the USA (Stubbings et al, 2018). This
404 illustrates that the estimates provided here are averages across a number of different studies
405 conducted at different points in time and space.

406 Consequently, the contributions made by different exposure pathways will vary considerably
407 between individuals depending on lifestyle factors. In contrast, the diet (excluding human milk

408 ingestion) was found to be the principal pathway of exposure for toddlers to alkyl OPEs such
409 as TnBP ($12 \text{ ng.kg bw}^{-1}.\text{day}^{-1}$, 84 %), TBOEP ($47 \text{ ng.kg bw}^{-1}.\text{day}^{-1}$, 67 %), and TEHP (7.2
410 $\text{ng.kg bw}^{-1}.\text{day}^{-1}$, 80 %) followed by dust ingestion and air inhalation, with dermal uptake least
411 important (Fig. 8).

412

Fig. 8: Relative significance of exposure of toddlers via air inhalation, dermal uptake, diet, and dust ingestion for individual OPEs

For adults, food ingestion appears the main human exposure pathway for all eight OPEs evaluated, contributing 32.2 ng.kg bw⁻¹.day⁻¹ and 75% Σexposure for TCEP, 21.3 ng.kg bw⁻¹.

day⁻¹, 37% for TCIPP, 11.9 ng.kg bw⁻¹. day⁻¹, 42 % for TDCIPP, 4.31 ng.kg bw⁻¹. day⁻¹, 71%
 for TnBP, 27.0 ng.kg bw⁻¹. day⁻¹, 59 % for TPHP, 47.2 ng.kg bw⁻¹. day⁻¹, 97% for TEHP, 12.8
 ng.kg bw⁻¹. day⁻¹, 61% for EHDPP, and 12.7 ng.kg bw⁻¹.day⁻¹, 46 % for TBOEP (Fig. 9).

Fig. 9: Relative significance of exposure of adults via air inhalation, dermal uptake, diet, and dust ingestion for individual OPEs

For water ingestion, only five OPEs (TCEP, TCIPP, TDCIPP, TnBP, and TBOEP) have been evaluated in any depth. For adults and toddlers, the mean EDIs of these five OPEs are in the

order: TCEP > TCIPP > TnBP > TBOEP > TDCIPP and TCIPP > TnBP > TCEP > TBOEP > TDCIPP respectively (Fig S1). This shows that the chlorinated OPEs are the main OPEs both adults and toddlers are exposed to via water ingestion. In addition, data on infant exposure to OPEs via human milk ingestion as shown in Fig. S1, reveals that TBOEP, TCIPP, TnBP and TEHP are the main OPEs infants are exposed to through breast feeding.

EDI ($\text{ng.kg bw}^{-1}.\text{day}^{-1}$) values for OPEs were compared with the oral reference dose (RfD $\text{ng.kg bw}^{-1}.\text{day}^{-1}$) which is an indicator of risk assessment of human exposure to non-carcinogenic toxic substances proposed by the U.S. EPA (2014). Based on the availability of laboratory animal exposure data from several organ/system specific RfDs, the USEPA (2017) derived a revised RfD value for each OPE by dividing the human equivalent dose (HED) by an uncertainty factor (UF). The HED is obtained by multiplying the no observed adverse effect level (NOAEL) by a dosimetric adjustment factor (DAF) (Li et al., 2018, USEPA, 2017) (Table 1).

The sum of the average EDIs via all exposure pathways for toddlers and adults for the eight OPEs evaluated were used to evaluate the risk of such overall exposure via comparison with the corresponding reference dose (RfD) values (Fig. 10 and Fig. 11). This comparison indicated that EDI values of the sum of all exposure pathways for toddlers and adults were lower than the established reference dose values for all OPEs considered in this review (USEPA, 2017; Li et al., 2018).

We also considered carcinogenic effects arising from chronic daily exposure to OPEs for both adults and toddlers using published oral cancer slope factors (SFOs) (USEPA, 2017; Li et al., 2018). Carcinogenic risk estimates were obtained by multiplying the estimated daily intake (EDI) value for a given OPE by its SFO value, which are currently only available for TCEP, TnBP and TEHP (USEPA, 2017; Li et al., 2018). Our estimate of the total carcinogenic risk (TCR) via the sum of all exposure pathways for adults for all three of these OPEs (TCEP, TnBP

and TEHP) were below the acceptable risk value of 1×10^{-6} (Ding et al., 2015). However, while toddler exposures to TnBP and TEHP also fell below a TCR of 1×10^{-6} ; for TCEP, the TCR 2.44×10^{-6} for toddlers exceeded the acceptable risk value (Table 1). This suggests concern over the carcinogenic risk from TCEP for toddlers when considering the sum of the exposure pathways considered in this review.

Fig 10: Comparison of average estimated daily intake (EDI) values via all exposure pathways for selected OPEs for toddlers with the corresponding reference doses (RfDs ng.kg bw⁻¹.day⁻¹) adopted from USEPA (2017)

Fig 11: Comparison of average estimated daily intake (EDI) values via all exposure pathways for selected OPEs for adults with the corresponding reference doses (RfDs ng.kg bw⁻¹.day⁻¹) adopted from (USEPA, 2017; Li et al., 2018)

5 Conclusions, research priorities, gaps and future directions

This study summed the average of the mean estimates of exposure to OPEs via a range of pathways and used these to derive estimates of the relative contributions of each pathway to overall exposure to individual OPEs for both adults and toddlers. For toddlers, dermal uptake from dust ingestion was highlighted as the predominant pathway of exposure to chlorinated OPEs, as well as EHDPP and TPHP. In contrast, diet was identified as the main pathway of exposure to all eight OPEs considered for adults, and for TnBP, TEHP, and TBOEP for toddlers. Reassuringly, these summed exposures were below the reference dose (RfD) values reported by the USEPA (2017). However, it is important to stress that our summed exposures do not include high-end exposure estimates and that for highly-exposed individuals, the margin

between exposure and the RfD values will be smaller. Moreover, assessment of total cancer risk raises concerns about exposure of toddlers to TCEP when exposure via all pathways is considered. A further caveat is that this review relied on a meta-analysis of mean exposure estimates from multiple exposure assessments conducted over a range of points in space and time, with concomitant uncertainty in both the magnitude and the relative contribution of different exposure pathways. Therefore, there is an urgent need for comprehensive assessments of human exposure to OPEs that examine all relevant pathways in a spatially and temporally-consistent fashion.

This review reveals that relatively few studies have determined the magnitude of human dietary exposure to OPEs. Given our finding that food is an important exposure pathway to these chemicals, regular monitoring of the presence of OPEs in foodstuffs is recommended. Moreover, the currently available literature reveals that human dietary exposure to OPEs occurs principally via industrially processed food groups, such as grains, oils, and dairy products (Li et al., 2019; Poma et al., 2018). For this reason, surveillance of OPEs in processed foodstuff samples should likely have higher priority compared to raw foodstuffs in future studies. This is especially important for EHDPP, which is capable of migrating from packaging materials to the foodstuffs (Wang and Kannan, 2018; Poma et al., 2018; Li et al., 2019). Moreover, several studies have highlighted that OPE derivatives can be generated by enzyme-catalysed metabolism of OPEs in biota as well as through other degradation routes, such as microbial metabolism/biotransformation, base-catalysed hydrolysis, and photodegradation (Li et al., 2019; Cequier et al., 2015; Greaves et al., 2016). This suggests that OPE derivatives could potentially co-exist with parent OPEs in environmental samples or foodstuffs (Fu et al., 2017). More importantly, some studies have stated that compared to their parent OPE triesters, such metabolites/degradation products are more biologically active with respect to several toxicological endpoints (Li et al., 2019; Su et al., 2014). However, to date, there is to our

knowledge only two published report on OPE derivatives/by-products in foodstuffs that reported the presence of OPEs metabolites in diet samples (Poma et al., 2019; He et al., 2018a). Thus, inclusion of possible OPE metabolites in future dietary exposure studies is recommended.

While dermal uptake from indoor dust is revealed as an important human exposure pathway, there appear to date to be no evaluations of exposure via dermal uptake from OPE-containing products such as foam-filled furniture. Given the widespread use of chlorinated OPEs at percent concentrations in furniture foam (Stubbings et al, 2018), investigation of this exposure pathway seems prudent. This review also highlights that there are very few data on OPEs in drinking water and more research is needed to ascertain the level and human exposure to these compounds through water ingestion.

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References

- Abdallah, M. A.-E., Covaci, A., 2014. Organophosphate flame retardants in indoor dust from Egypt: Implications for human exposure. *Environ. Sci. Technol.* 48, 4782-4789.
- Abdallah, M. A.-E., Pawar, G., Harrad, S., 2016. Human dermal absorption of chlorinated organophosphate flame retardants: implications for human exposure. *Toxicol. and Appl. Pharmacol.* 291, 28-37.
- Abdallah, M. A.-E., Harrad, S., 2018. Dermal contact with furniture fabrics is a significant pathway of human exposure to brominated flame retardants. *Environ. Int.* 118, 26–33.

525 Agency for Toxic Substances and Disease Registry (ATSDR), 2012. U.S. Department of
526 Health and Human Services. Public Health Service (2012) Toxicological profile for phosphate
527 ester flame retardants.

528 Ali, N., Dirtu, A.C., Van den Eede, N., Goosey, E., Harrad, S., Neels, H., 't Mannetje, A.,
529 Coakley, J., Douwes, J., Covaci, A., 2012. Occurrence of alternative flame retardants in indoor
530 dust from New Zealand: indoor source and human exposure assessment. *Chemosphere* 88,
531 1276–1282.

532 Ali, N., Ali, L., Mehdi, T., Dirtu, A.C., Al-Shammari, F., Neels, H., Covaci, A., 2013. Levels
533 and profiles of organochlorines and flame retardants in car and house dust from Kuwait and
534 Pakistan: implication for human exposure via dust ingestion. *Environ. Int.* 55, 62-70.

535 Bello A, Carignan, C.C., Xue, Y., Stapleton, H.M., Bello, D., 2018. Exposure to
536 organophosphate flame retardants in spray polyurethane foam applicators: role of dermal
537 exposure. *Environ. Int.* 113, 55–65.

538 Benotti, M.J., Trenholm, R.A., Vanderford, B.J., Holady, J.C., Stanford, B.D., Snyder, S.A.,
539 2009. Pharmaceuticals and endocrine disrupting compounds in U.S. drinking water. *Environ.*
540 *Sci. Technol.* 43, 597-603.

541 Beser, M. I.; Pardo, O.; Beltran, J.; Yusa, V., 2019. Determination of 21 perfluoroalkyl
542 substances and organophosphorus compounds in breast milk by liquid chromatography
543 coupled to orbitrap high resolution mass spectrometry. *Anal. Chim. Acta.* 1049, 123–132.

544 BBC Research, 2018. CHM014P Flame retardant Chemicals: technologies and global markets.
545 [https://www.bccresearch.com/market-research/chemicals/flame-retardant-chemicals-markets-](https://www.bccresearch.com/market-research/chemicals/flame-retardant-chemicals-markets-report.html)
546 [report.html](https://www.bccresearch.com/market-research/chemicals/flame-retardant-chemicals-markets-report.html)

547 Brommer, S., Harrad, S., Van den Eede, N., Covaci, A., 2012. Concentrations of
 548 organophosphate esters and brominated flame retardants in German indoor dust samples. *J.*
 549 *Environ. Monit.* 14, 2482-2487.

550 Brommer, S., Harrad, S., 2015. Sources and human exposure implications of concentrations of
 551 organophosphate flame retardants in dust from UK cars, classrooms, living rooms, and offices.
 552 *Environ. Int.* 83, 202-207.

553 Campone, L.; Piccinelli, A. L.; Östman, C.; Rastrelli, L., 2010. Determination of
 554 organophosphorous flame retardants in fish tissues by matrix solid-phase dispersion and gas
 555 chromatography. *Anal. Bioanal. Chem.* 397 (2), 799–806.

556 Cao, D., Lv, K., Gao, W., Fu, J., Wu, J., Fu, J., Wang, Y., Jiang, G., 2019. Presence and human
 557 exposure assessment of organophosphate flame retardants (OPEs) in indoor dust and air in
 558 Beijing, China. *Ecotoxicol. Environ. Saf.* 169, 383–391

559 Carlsson, H., Nilsson, U., Becker, G., Östman, C., 1997. Organophosphate ester flame
 560 retardants and plasticizers in the indoor environment: analytical methodology and occurrence.
 561 *Environ. Sci. Technol.* 31, 2931-2936.

562 Cequier, E., Ionas, A.C., Covaci, A., Marce, R.M., Becher, G., Thomsen, C., 2014. Occurrence
 563 of a broad range of legacy and emerging flame retardants in indoor environments in Norway.
 564 *Environ. Sci. Technol.* 48, 6827-6835.

565 Cequier, E., Sakhi, A.K., Marce, R.M., Becher, G., Thomsen, C., 2015. Human exposure
 566 pathways to organophosphate triesters and a biomonitoring study of mother-child pairs. *Environ.*
 567 *Int.* 75, 159-165.

568 Ding, J., Shen, X., Liu, W., Covaci, A., Yang, F., 2015. Occurrence and Risk Assessment of
 569 Organophosphate Esters in Drinking Water from Eastern China. *Sci. Total Environ.* 538, 959–
 570 965.

571 Ding, J., Deng, T., Xu, M., Wang, S., Yang, F., 2018. Residuals of organophosphate esters in
 572 foodstuffs and implication for human exposure. *Environ. Pollut.* 233, 986-991.

573 Frederiksen, M., Stapleton, H.M., Vorkamp, K., Webster, T.F., Jensen, N.M., Sorensen, J.A.,
 574 Nielsen, F., Knudsen, L.E., Sorensen, L.S., Clausen, P.A., Nielsen, J.B., 2018. Dermal uptake
 575 and percutaneous penetration of organophosphate esters in a human skin ex vivo model.
 576 *Chemosphere* 197, 185–192.

577 Fu, L.F., Du, B.B., Wang, F., Lam, J.C.W., Zeng, L.X., Zeng, E.Y., 2017. Organophosphate
 578 triesters and diesters degradation products in municipal sludge from wastewater treatment
 579 plants in China: spatial patterns and ecological implications. *Environ. Sci. Technol.* 51, 13614–
 580 13623.

581 Gao, Z., Deng, Y., Yuan, W., He, H., Yang, S., Sun, C., 2014. Determination of
 582 organophosphorus flame retardants in fish by pressurized liquid extraction using aqueous
 583 solutions and solid-phase microextraction coupled with gas chromatography-flame
 584 photometric detector. *J. Chromatogr. A* 1366, 31-37.

585 Greaves, A. K., Letcher, R. J., 2014. Comparative Body Compartment Composition and In
 586 Ovo Transfer of Organophosphate Flame Retardants in North American Great Lakes Herring
 587 Gulls. *Environ. Sci. Technol.* 48(14), 7942–7950.

588 Greaves, A.K., Letcher, R.J., 2017. Organophosphate esters: a review on wildlife distribution,
 589 fate and ecotoxicology. *Bull. Environ. Contam. Toxicol.* 98, 2–7.

590 Greaves, A.K., Letcher, R.J., Chen, D., McGoldrick, D.J., Gauthier, L.T., Backus, S.M., 2016.
 591 Retrospective analysis of organophosphate flame retardants in herring gull eggs and relation to
 592 the aquatic food web in the Great Lakes. *Environ Res.* 150, 255–263

593 Guo, X., Mu, T., Xian, Y., Luo, D., Wang, C., 2016. Ultra-performance liquid chromatography
 594 tandem mass spectrometry for the rapid simultaneous analysis of nine organophosphate esters
 595 in milk powder. *Food Chem.* 196, 673-681.

596 He, C.T., Zheng, J., Qiao, L., Chen, S.J., Yang, J.Z., Yuan, J.G., Yang, Z.Y., Mai, B.X., 2015.
 597 Occurrence of organophosphorus flame retardants in indoor dust in multiple
 598 microenvironments of southern China and implications for human exposure. *Chemosphere*
 599 133, 47–52.

600 He, C., Wang, X.Y., Tang, S.Y., Thai, P., Li, Z.R., Baduel, C., Mueller, J.F., 2018a.
 601 Concentrations of organophosphate esters and their specific metabolites in food in Southeast
 602 Queensland, Australia: is dietary exposure an important pathway of organophosphate esters
 603 and their metabolites? *Environ. Sci. Technol.* 52, 12765–12773.

604 He, C.; Toms, L. M. L.; Thai, P.; Van den Eede, N.; Wang, X. Y.; Li, Y.; Baduel, C.; Harden,
 605 F. A.; Heffernan, A. L.; Hobson, P.; Covaci, A., Mueller, J.F., 2018b. Urinary metabolites of
 606 organophosphate esters: Concentrations and age trends in Australian children. *Environ. Int.*
 607 111, 124– 130.

608 He, M.J., Lu, J.F., Wei, S.Q., 2019. Organophosphate esters in biota, water, and air from an
 609 agricultural area of Chongqing, western China: Concentrations, composition profiles, partition
 610 and human exposure. *Environ. Pollut.* 244, 388-397

611 Hoffman, K., Garantziotis, S., Birnbaum, L.S., Stapleton, H.M., 2015. Monitoring Indoor
 612 Exposure to Organophosphate Flame Retardants: Hand Wipes and House Dust. *Environ.*
 613 *Health Perspect.* 123, 160-165.

614 Hou, R., Xu, Y., Wan, Z., 2016. Review of OPFRs in animals and humans: Absorption,
 615 bioaccumulation, metabolism, and internal exposure research. *Chemosphere* 153, 78-90.

616 Hughes, M.F., Edwards, B.C., Mitchell, C.T., Bhooshan, B., 2001. In vitro dermal absorption
 617 of flame-retardant chemicals. *Food Chem. Toxicol.* 39(12), 1263–1270.

618 Ji, Y., Wang, F., Zhang, L., Shan, C., Bai, Z., Sun, Z., Liu, L., Shen, B., 2014. A comprehensive
619 assessment of human exposure to phthalates from environmental media and food in Tianjin,
620 China. *J. Hazard Mater.* 279, 133-140.

621 Kim J.W., Isobe T, Chang K.H., Amano, A., Manega R.H., Zamora P.B., Siringan F.P., Tanabe
622 S., 2011. Levels and distribution of organophosphorus flame retardants and plasticizers in
623 fishes from Manila Bay, the Philippines. *Environ. Pollut.* 159, 3653–3659.

624 Kim, J.W., Isobe, T., Muto, M., Tue, N.M., Katsura, K., Malarvannan, G., Sudaryanto, A.,
625 Chang, K.H., Prudente, M., Viet, P.H., Takahashi, S., Tanabe, S., 2014. Organophosphorus
626 flame retardants (PFRs) in human breast milk from several Asian countries. *Chemosphere* 116,
627 91–97.

628 Kim, U.J., Kannan, K., 2018. Occurrence and distribution of organophosphate flame retardants/
629 plasticizers in surface waters, tap water, and rainwater: implications for human exposure.
630 *Environ. Sci. Technol.* 52 (10), 5625–5633.

631 Kim, U.J., Wang, Y., Li, W., Kannan, K., 2019. Occurrence of and human exposure to
632 organophosphate flame retardants/ plasticizers in indoor air and dust from various
633 microenvironments in the United States. *Environ. Int.* 125, 342–349.

634 Lai, S.C., Xie, Z.Y., Song, T.L., Tang, J.H., Zhang, Y.Y., Mi, W.Y., Peng, J.H., Zhao, Y., Zou,
635 S.C., Ebinghaus, R., 2015. Occurrence and dry deposition of organophosphate esters in
636 atmospheric particles over the northern South China Sea. *Chemosphere* 127, 195–200.

637 Lee, S., Jeong, W., Kannan, K., Moon, H.B., 2016. Occurrence and exposure assessment of
638 organophosphate flame retardants (OPFRs) through the consumption of drinking water in
639 Korea. *Water Res.* 103, 182–188.

640 Li, J., Yu, N.Y., Zhang, B.B., Jin, L., Li, M.Y., Hu, M.Y., Zhang, X.W., Wei, S., Yu, H.X.,
641 2014. Occurrence of organophosphate flame retardants in drinking water from China. *Water*
642 *Res.* 54, 53-61.

643 Li, J., Zhang, Z., Ma, L., Zhang, Y., Niu, Z. 2018. Implementation of USEPA RfD and SFO
 644 for improved risk assessment of organophosphate esters (organophosphate flame retardants and
 645 plasticizers). *Environ. Int.* 114, 21–26. <https://doi.org/10.1016/j.envint.2018.02.027>

646 Li, J., Zhao, L., Letcher, R.J., Zhang, Y., Jian, K., Zhang, J., Su, G., 2019. A review on
 647 organophosphate ester (OPE) flame retardants and plasticizers in foodstuffs: levels,
 648 distribution, human dietary exposure, and future directions. *Environ. Int.* 127, 35–51.

649 Liu, X., Yu, G., Cao, Z., Wang, B., Huang, J., Deng, S. Peng, X., 2017a. Estimation of human
 650 exposure to halogenated flame retardants through dermal adsorption by skin wipe.
 651 *Chemosphere* 168, 272-278.

652 Liu, X., Yu, G., Cao, Z., Wang, B., Huang, J., Deng, S., 2017b. Occurrence of
 653 organophosphorus flame retardants on skin wipes: insight into human exposure from dermal
 654 absorption. *Environ. Int.* 98, 113-119.

655 Liu, X. P., Xiong, L. L., Li, D. K., Chen, C. J., Cao, Q., 2019. Monitoring and exposure
 656 assessment of organophosphorus flame retardants in source and drinking water, Nanjing,
 657 China. *Environ. Monit. Assess.*, 191(2), 119

658 Luongo, G., Ostman, C., 2015. Organophosphate and phthalate esters in settled dust from
 659 apartment buildings in Stockholm. *Indoor Air* 26, 414 - 425.

660 Ma, J., Zhu, H., Kannan, K., 2019. Organophosphorus Flame Retardants and Plasticizers in
 661 Breast Milk from the United States. *Environ. Sci. Technol. Lett.* 6, 525–531

662 Malarvannan, G., Belpaire, C., Geeraerts, C., Eulaers, I., Neels, H., Covaci, A., 2015.
 663 Organophosphorus flame retardants in the European eel in Flanders, Belgium: Occurrence, fate
 664 and human health risk. *Environ. Res.* 140, 604–610.

665 Marklund, A., Andersson, B., Haglund, P., 2005. Organophosphorus flame retardants and
 666 plasticizers in air from various indoor environments. *J. Environ. Monit.* 7, 814-819.

667 Mendelsohn, E., Hagopian, A., Hoffman, K., Butt, C.M., Lorenzo, A., Congleton, J., Webster,
 668 T.F., Stapleton, H.M., 2016. Nail polish as a source of exposure to triphenylphosphate. *Environ*
 669 *Int.* 86, 45–51
 670 Ni, Y., Kumagai, K., Yanagisawa, Y., 2007. Measuring emissions of organophosphate flame
 671 retardants using a passive flux sampler. *Atm. Environ.* 41, 3235–3240.
 672 Pang, L., Yang, H., Yang, P., Zhang, H., Zhao, J., 2017. Trace determination of
 673 organophosphate esters in white wine, red wine, and beer samples using dispersive liquid-
 674 liquid microextraction combined with ultra-high-performance liquid chromatography–tandem
 675 mass spectrometry. *Food Chem.* 229, 445-451.
 676 Park, H., Choo, G., Kim, H., Oh, J.E., 2018. Evaluation of the current contamination status of
 677 PFASs and OPFRs in South Korean tap water associated with its origin. *Sci. Total Environ.*
 678 634, 1505-1512.
 679 Persson, J., Thanh Wang, T., Hagberg, J., 2018. Organophosphate flame retardants and
 680 plasticizers in indoor dust, air and window wipes in newly built low-energy preschools. *Sci.*
 681 *Total Environ.* 628, 159–168
 682 Poma, G., Glynn, A., Malarvannan, G., Covaci, A., Darnelund, P.O., 2017. Dietary intake of
 683 phosphorus flame retardants (PFRs) using Swedish food market basket estimations. *Food*
 684 *Chem. Toxicol.* 100, 1–7.
 685 Poma, G., Sales, C., Bruyland, B., Christia, C., Goscinnny, S., Van Loco, J., Covaci, A., 2018.
 686 Occurrence of organophosphorus flame retardants and plasticizers (PFRs) in Belgian
 687 foodstuffs and estimation of dietary exposure of the adult population. *Environ. Sci. Technol.*
 688 52, 2331–2338.

689 Poma, G., Yin S.S., Tang, B., Fujii, Y., Cuykx, M., Covaci, A. 2019. Occurrence of selected
690 organic contaminants in edible insects and assessment of their chemical safety. *Environmental*
691 *Health Perspectives* 127 (12), 127009-14. <https://doi.org/10.1289/EHP5782>

692 Regnery, J., Püttmann, W., 2010. Occurrence and fate of organophosphorus flame retardants
693 and plasticizers in urban and remote surface waters in Germany. *Water Res.* 44, 4097-4104.

694 Rodil, R., Benito Quintana, J., Concha-Grana, E., Lopez-Mahía, P., Muniategui-Lorenzo, S.,
695 Prada-Rodríguez, D., 2012. Emerging pollutants in sewage, surface and drinking water in
696 Galicia (NW Spain). *Chemosphere* 86, 1040-1049.

697 Schreder, E., Uding, N., La Guardia, M., 2016. Inhalation a significant exposure route for
698 chlorinated organophosphate flame retardants. *Chemosphere* 150, 499-504.

699 Stockholm Convention on Persistent Organic Pollutants, Proposal to list decabromodiphenyl
700 ether (commercial mixture, c-decaBDE) in Annexes A, B and/or C to the Stockholm
701 Convention on Persistent Organic Pollutants Rome, 2013.
702 <http://chm.pops.int/TheConvention/POPsReviewCommittee/Meetings/POPRC9/POPRC>
703 [9Followup/decaBDESubmission/tabid/3570/Default.aspx](http://chm.pops.int/TheConvention/POPsReviewCommittee/Meetings/POPRC9/POPRC) (accessed October 2016).

704 Stubbings, W.A., Schreder, E.D., Thomas, M.B., Romanak, K., Venier, M., Salamova, A.,
705 2018. Exposure to brominated and organophosphate ester flame retardants in US childcare
706 environments: effect of removal of flame-retarded nap mats on indoor levels. *Environ. Pollut.*
707 238, 1056–1068.

708 Su, G., Crump, D., Letcher, R.J., Kennedy, S.W., 2014. Rapid in vitro metabolism of the flame
709 retardant triphenyl phosphate and effects on cytotoxicity and mRNA expression in chicken
710 embryonic hepatocytes. *Environ. Sci. Technol.* 48, 13511-13519.

711 Sugeng, E. J., Cock, M. De, Schoonmade, L. J., Bor, M. V., 2017. Toddler exposure to flame

712 retardant chemicals: Magnitude, health concern and potential risk- or protective factors of
 713 exposure: Observational studies summarized in a systematic review. *Chemosphere* 184, 820–
 714 831.

715 Sundkvist, A.M., Olofsson, U., Haglund, P., 2010. Organophosphorus flame retardants and
 716 plasticizers in marine and fresh water biota and in human milk. *J. Environ. Monit.* 12, 943-951.

717 Tajima, S., Araki, A., Kawai, T., Tsuboi, T., Bamai, Y., Yoshioka, E., Kanazawa, A., Cong,
 718 S., Kishi, R., 2014. Detection and intake assessment of organophosphate flame retardants in
 719 houses in Japanese dwellings. *Sci. Total Environ.* 478, 190-199.

720 USEPA, 2014. Region 4 Human Health Risk Assessment Supplemental Guidance.
 721 [https://www.epa.gov/sites/production/files/201803/documents/hhra_regional_supplemental_](https://www.epa.gov/sites/production/files/201803/documents/hhra_regional_supplemental_guidance_report-march-2018_update.pdf)
 722 [guidance_report-march-2018_update.pdf](https://www.epa.gov/sites/production/files/201803/documents/hhra_regional_supplemental_guidance_report-march-2018_update.pdf) (Accessed July 2020).

723 U.S. EPA (Environmental Protection Agency). 2017. Risk assessment — regional screening
 724 levels (RSLs). <https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables>

725 Van den Eede, N., Dirtu, A. C., Neels, H., Covaci, A., 2011. Analytical developments and
 726 preliminary assessment of human exposure to organophosphate flame retardants from indoor
 727 dust. *Environ. Int.* 37(2), 454–461.

728 Van Der Veen, I., De Boer, J., 2012. Phosphorus flame retardants: properties, production,
 729 environmental occurrence, toxicity and analysis *Chemosphere*, 88 (10), 1119
 730 1153. doi:10.1016/j.chemosphere.2012.03.067

731 Wang, R., Tang, J., Xie, Z., Mi, W., Chen, Y., Wolschke, H., Tian, C., Pan, X., Luo, Y.,
 732 Ebinghaus, R., 2015. Occurrence and spatial distribution of organophosphate ester flame
 733 retardants and plasticizers in 40 rivers draining into the Bohai Sea, north China. *Environ.*
 734 *Pollut.* 198, 172-178. doi: 10.1016/j.envpol.2014.12.037.

735 Wang, Y., Kannan, K., 2018. Concentrations and Dietary Exposure to Organophosphate Esters
 736 in Foodstuffs from Albany, New York, United States. *J. Agric. Food Chem.* 66, 13525–13532.

737 Wei, G.L., Li, D.Q., Zhuo, M.N., Liao, Y.S., Xie, Z.Y., Guo, T.L., Li, J.J., Zhang, S.Y., Liang,
 738 Z.Q., 2015. Organophosphorus flame retardants and plasticizers: sources, occurrence, toxicity
 739 and human exposure. *Environ. Pollut.* 196, 29-46.

740 Xu, F., Giovanoulis, G., van Waes, S., Padilla-Sanchez, J.A., Papadopoulou, E., Magner, J.,
 741 Haug, L.S., Neels, H., Covaci, A., 2016. Comprehensive study of human external exposure to
 742 organophosphate flame retardants via air, dust, and hand wipes: the importance of sampling
 743 and assessment strategy. *Environ Sci Technol.* 50, 7752–7760.

744 Xu, F., Tay, J.H., Covaci, A., Padilla-Sanchez, J.A., Papadopoulou, E., Smastuen, L., Neels,
 745 H., Sellström, U., de Wit, C.A., 2017. Assessment of dietary exposure to organohalogen
 746 contaminants, legacy and emerging flame retardants in a Norwegian cohort. *Environ Int.* 102,
 747 236–243.

748 Yadav, I.C., Devi, N.L., Zhong, G., Li, J., Zhang, G., Covaci, A., 2017. Occurrence and fate of
 749 organophosphate ester flame retardants and plasticizers in indoor air and dust of Nepal:
 750 implication for human exposure. *Environ. Pollut.* 229, 668–678.

751 Zhang, X., Zou, W., Mu, L., Chen, Y., Ren, C., Hu, X., Zhou, Q., 2016. Rice ingestion is a
 752 major pathway for human exposure to organophosphate flame retardants (OPFRs) in China. *J*
 753 *Hazard Mater.* 318, 686–693.

754 Zhao, L., Jian, K., Su, H., Zhang, Y., Li, J., Letcher, R., Su, G., 2019. Organophosphate esters
 755 (OPEs) in Chinese foodstuffs: Dietary intake estimation via a market basket method, and
 756 suspect screening using high resolution mass spectrometry. *Environ. Int.* 128, 343–352.

757 Zhou, L., Hiltcher, M., Püttmann, W., 2017. Occurrence and human exposure assessment of
 758 organophosphate flame retardants in indoor dust from various microenvironments of the
 759 Rhine/Main region, Germany. *Indoor Air* 27(6), 1113–1127.

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