

# A critical review of human exposure to organophosphate esters with a focus on dietary intake

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

3

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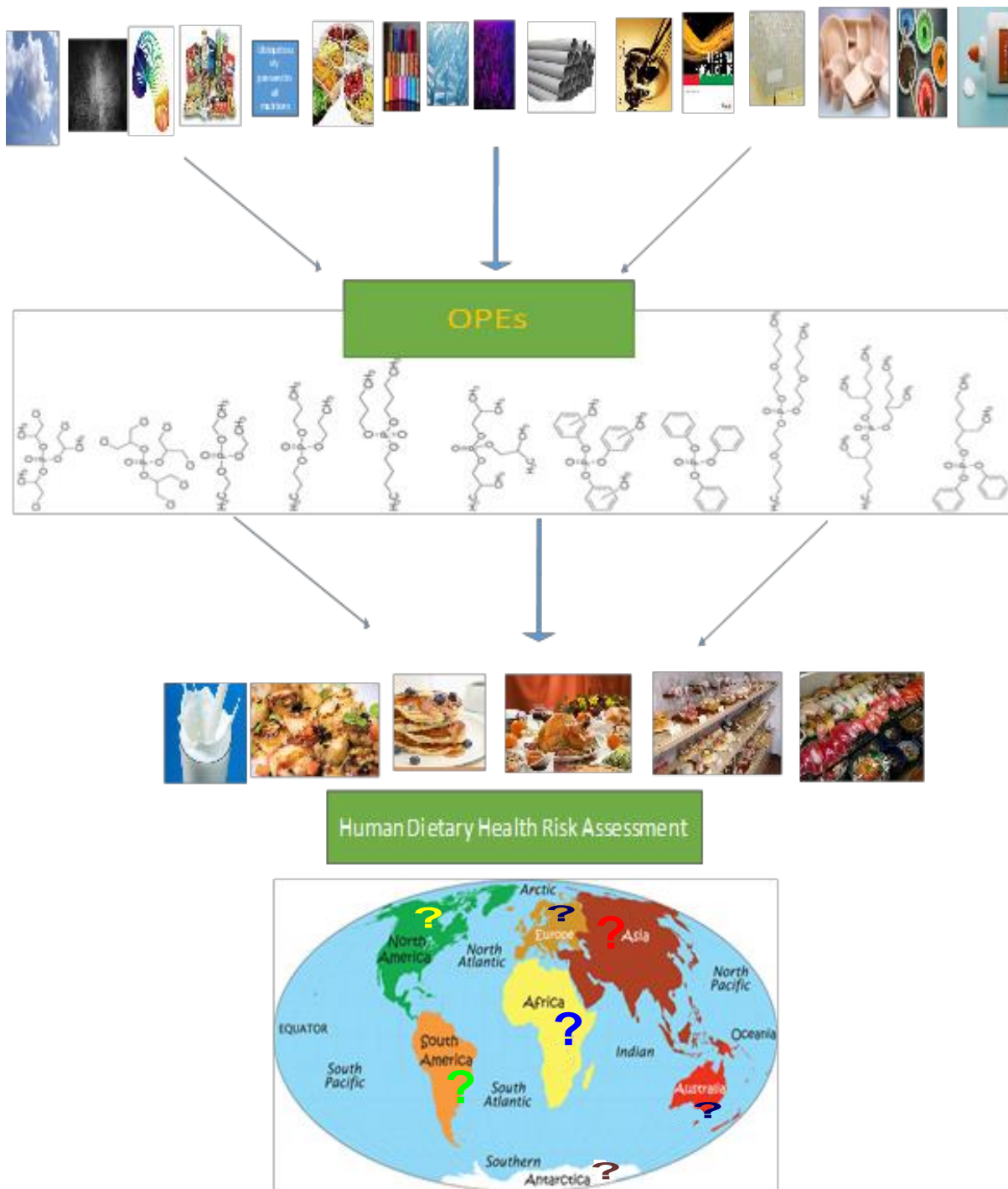
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## **Highlights**

- 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

13 Graphical Abstract



14

15 **Abstract**

16 Organophosphate esters (OPEs) are common additives in a wide range of commercial and  
17 industrial products. Elevated and prolonged exposure to OPEs may induce several adverse  
18 effects. This is concerning as they are ubiquitous in air, indoor dust, drinking water, and other  
19 environmental matrices. However, information on the presence of OPEs in foodstuffs and  
20 consequent health risks remains scant. This review critically evaluates available information  
21 on levels and sources of OPEs in food, discusses the relative significance of diet as a pathway  
22 of human exposure, identifies knowledge gaps, and suggests directions for future research. For  
23 toddlers, dermal uptake from dust ingestion appears the predominant pathway of exposure to  
24 chlorinated OPEs, as well as ethylhexyl diphenyl phosphate (EHDPP) and triphenyl phosphate  
25 (TPHP). In contrast, diet appears the main pathway of exposure to all eight OPEs considered  
26 for adults, and for tri n-butyl phosphate (TnBP), tris 2-ethylhexyl phosphate (TEHP), and tris  
27 (2-butoxyethyl) phosphate (TBOEP) for toddlers. While summed exposures via all pathways  
28 are within reference dose (RfD) values, they do not include high-end exposure estimates, and  
29 for highly-exposed individuals, the margin between exposure and RfD values is smaller.  
30 Moreover, our exposure estimates are based on a meta-analysis of multiple exposure  
31 assessments conducted over a range of points in space and time. There is an urgent need for  
32 assessments of human exposure to OPEs that examine all relevant pathways in a spatially and  
33 temporally-consistent fashion. Given food is an important exposure pathway to OPEs, regular  
34 monitoring of their presence as well as their metabolites (that may have toxicological  
35 significance) in foodstuffs is recommended. While dermal uptake from indoor dust appears an  
36 important human exposure pathway, no evaluations exist of exposure via dermal uptake from  
37 OPE-containing products such as foam-filled furniture. This review also highlights very few  
38 data exist on OPEs in drinking water.

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

## 42 **1. Introduction**

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

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

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

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

68 Owing to their persistent, bioaccumulative, and toxic properties, several brominated flame  
69 retardants (BFRs) have been listed under the Stockholm Convention on Persistent Organic  
70 Pollutants (POPs) (Stockholm Convention on POPs, 2013). In 2018, the global consumption  
71 of FRs reached 2.6 million tonnes and is predicted to approach 3.1 million tonnes by 2023  
72 (BCC Research, 2018). The global production and use of OPEs has increased rapidly in recent  
73 years. It is likely therefore that the use of OPEs has increased as replacements for restricted  
74 BFRs, with worldwide consumption of OPEs projected to reach 860,000 t in 2023 from  
75 680,000 t in 2015 to 816,000 t in 2018 (BBC Research, 2018; Wang et al., 2015). OPEs have  
76 been estimated to account for 20 % of the total consumption of FRs in Western Europe (Wei  
77 et al., 2015).

78 Unfortunately, some OPEs, especially those that are chlorinated, are thought to be persistent in  
79 the environment (Lai et al., 2015), with human exposure demonstrated by their detection in  
80 human milk (Kim et al., 2014). Concerns about such exposure are compounded by  
81 toxicological studies revealing that high concentrations and prolonged exposure to OPEs can  
82 induce adverse effects including carcinogenicity, neurotoxicity, kidney toxicity, reproductive  
83 toxicity, liver toxicity, and endocrine disruption (Hou et al., 2016; Wei et al., 2015). The  
84 presence and concentrations of OPEs in various biotic and abiotic environmental matrices has  
85 been reviewed (Wei et al., 2015; Sugeng et al., 2017; Hou et al., 2016; Greaves and Letcher,  
86 2017). However, information on the worldwide presence of OPEs in foodstuffs remains scant  
87 and the sources of contamination, i.e. whether the presence of OPEs in food is due to migration  
88 from food packaging, bioaccumulation, uptake from the agricultural environment,  
89 contamination during industrial processing, or some other sources, remain unclear. Currently,  
90 data on concentrations of OPEs in food is restricted to samples from China, USA, Belgium,



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

## 97 **2. Methodology**

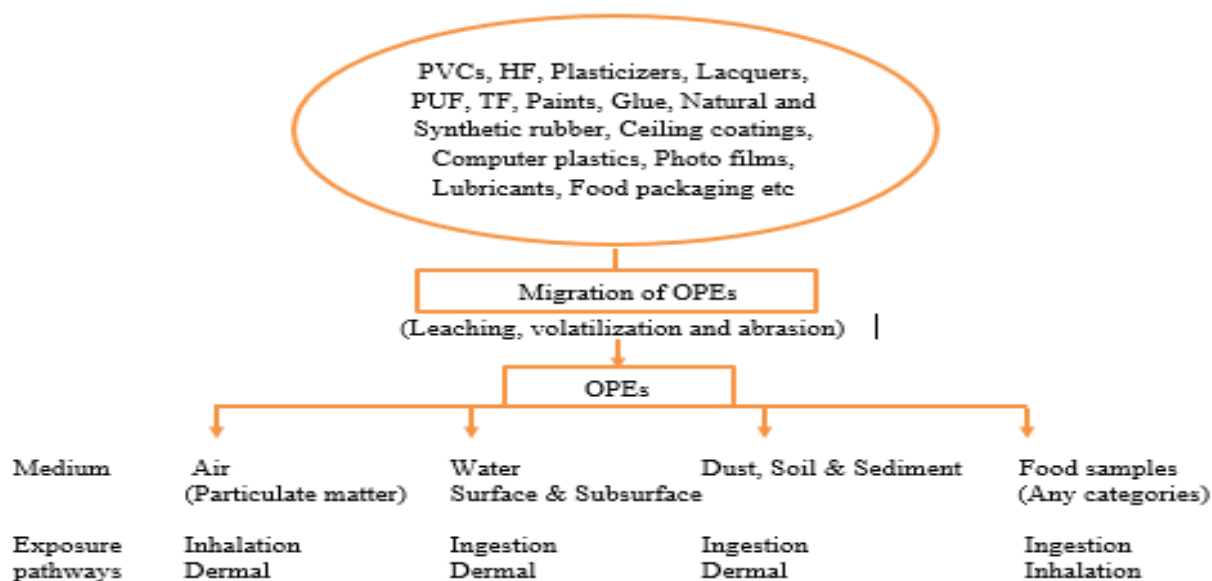
98 The search for research articles, reviews, book, conference proceedings and other online  
99 resources was carried out between November 20, 2018 to October 20, 2020 using the following  
100 electronic databases: Scopus, ScienceDirect and Web of Science core collection. The search  
101 terms used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

116

### 117 **3. Physicochemical properties and pathways of human exposure to OPEs**

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

127 The three main pathways via which humans are exposed to chemicals, are ingestion, inhalation,  
128 and dermal absorption. These broad categories may further be broken down into sub-categories  
129 such as ingestion of dust, food, and drink, as well as dermal uptake resulting from contact with  
130 dust and with products containing chemicals. The relative contribution that each pathway  
131 makes to overall exposure depends *inter alia* on the physicochemical properties and  
132 commercial applications of the chemicals, as well as lifestyle and demographic factors related  
133 to the exposed individual. Evidence to date has demonstrated that human exposure to OPEs  
134 can occur via dermal contact (Abdallah et al., 2016), ingestion of contaminated dust (Abdallah  
135 and Covaci, 2014), inhalation of air (Schreder et al., 2016), and more recently diet (Poma et al.  
136 2018; Zhao et al., 2019) (Fig.1).



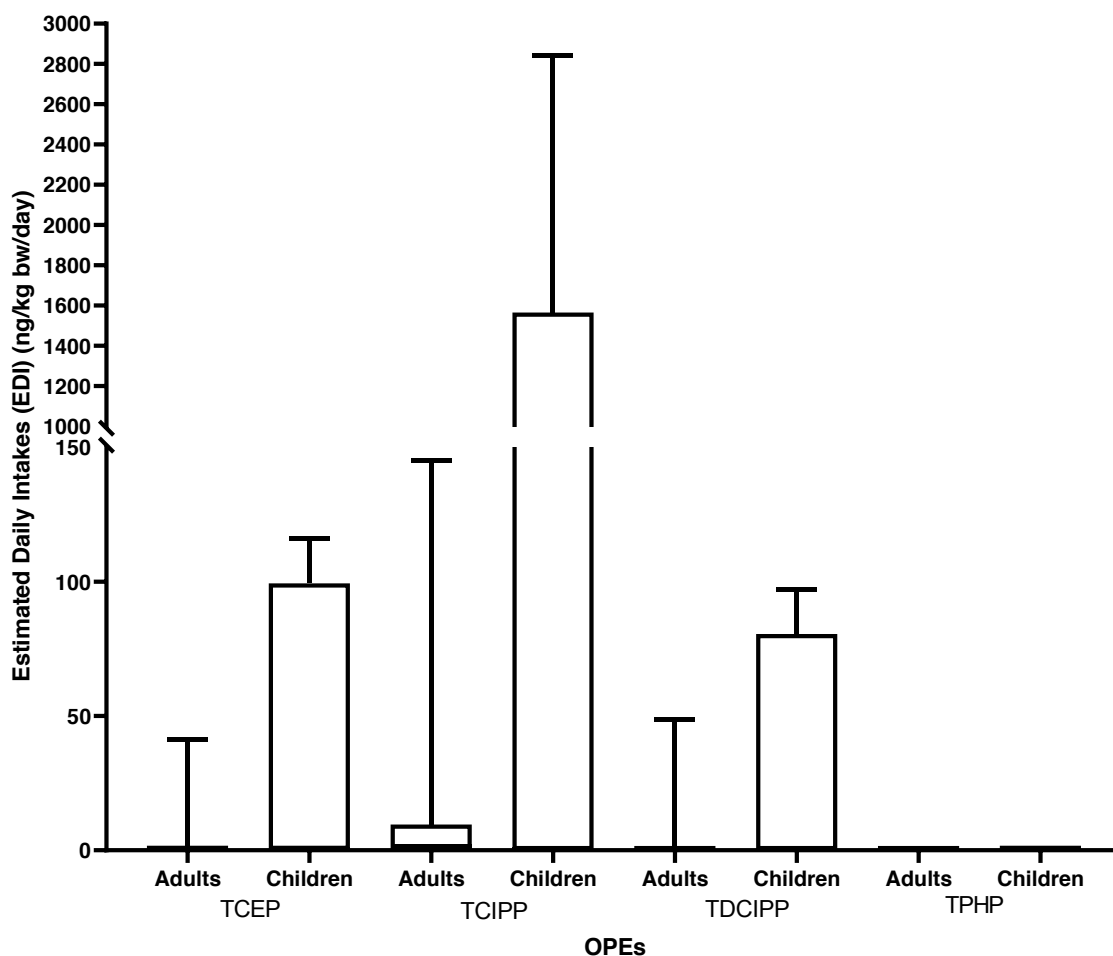
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138 **Fig. 1: Schematic representation of the pathways of transmission of OPEs from treated**  
 139 **products to humans**

140 **3.1 Human Exposure to OPEs via Inhalation**

141 A summary of studies reporting concentrations of OPEs in indoor air are provided as  
 142 supplementary information (Table S2), with a summary of estimated daily intakes (EDIs) of  
 143 OPEs through air inhalation reported in various studies presented in Table S3. Schreder et al.  
 144 (2016) observed that estimated exposure to OPEs via inhalation exceeded estimated exposure  
 145 from dust ingestion. Adult inhalation intake of TCIPP was estimated at 4540 ng/day, which  
 146 was 31 times that from dust ingestion for TCIPP in the studied population (Schreder et al.,  
 147 2016). Moreover, in a study carried out examining exposure via indoor air inhalation, dust  
 148 ingestion, and dermal uptake in Albany, New York, USA; Kim et al. (2019) reported TCIPP  
 149 (27–43 %) and triethyl phosphate (TEP) (11–33 %) were the two major contributors of total  
 150 human exposure via inhalation. In a similar study carried out by Cao et al. (2019), inhalation  
 151 was shown to be one of the main human exposure routes for volatile OPEs such as tri iso-butyl  
 152 phosphate (TiBP), TnBP, TCIPP, and TEP. Moreover, in a study of exposure occurring via air  
 153 inhalation, indoor dust ingestion and dermal uptake, Zhou et al. (2017) reported that under a

154 median exposure scenario, air inhalation contributed  $5.7 \text{ ng } \Sigma\text{OPEs.kg bw}^{-1}.\text{day}^{-1}$  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  $\Sigma\text{OPEs}$  has the highest  
158 median value among all pathways considered (median =  $34 \text{ ng.kg bw}^{-1}.\text{day}^{-1}$ ), followed by dust  
159 ingestion (median =  $13 \text{ ng.kg bw}^{-1}.\text{day}^{-1}$ ). 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  $\text{TCIPP} \gg \text{TCEP} >$   
165  $\text{TDCIPP} > \text{TPHP}$ .



166

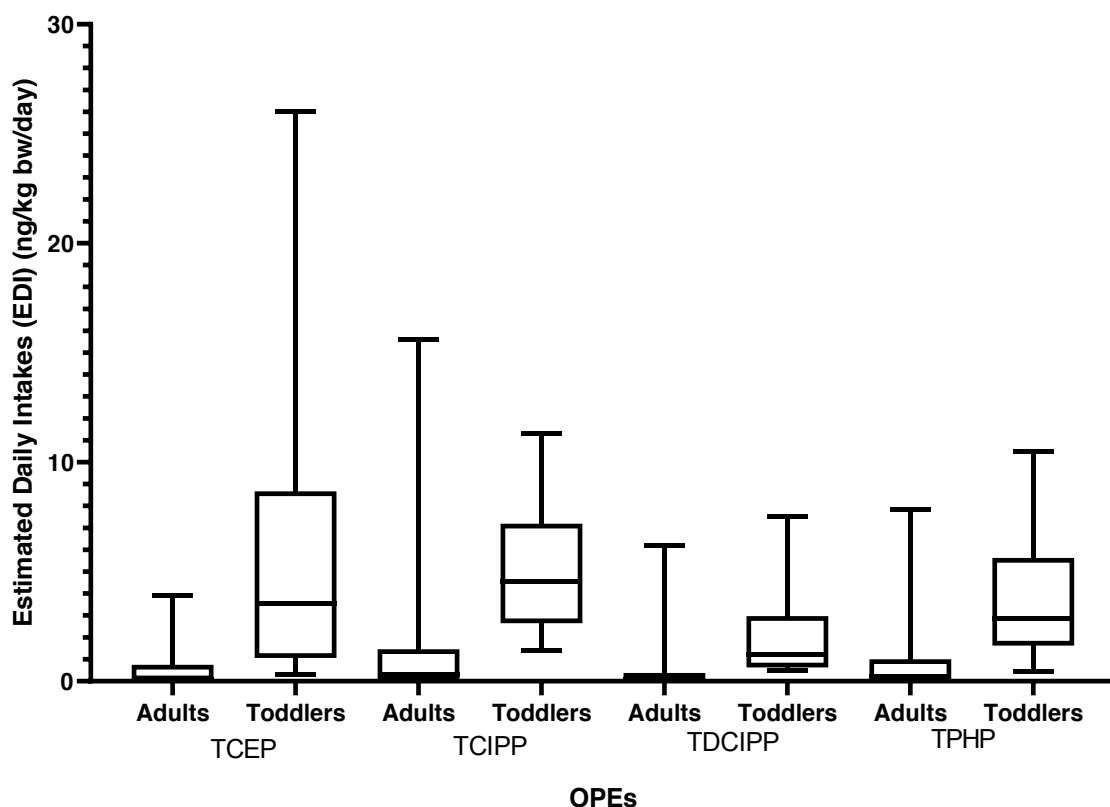
167 **Fig. 2: Box-plot showing the range of mean estimates of human exposure to TCEP,**  
 168 **TCIPP, TDCIPP, and TPHP via air inhalation.**

169

170 **3.2 Human Exposure to OPEs via Dust Ingestion.**

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

178 and 6.7 ng. kg bw<sup>-1</sup>. day<sup>-1</sup>, respectively. The 95<sup>th</sup> percentile EDIs for toddlers and adults were  
179 91 and 33 ng. kg bw<sup>-1</sup>. day<sup>-1</sup>, respectively (Cao et al., 2019). The estimated EDIs for this study  
180 are comparable with those of 160 and 32 ng. kg bw<sup>-1</sup>. day<sup>-1</sup> 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<sup>-1</sup>. day<sup>-1</sup> and 1.2 ng. kg bw<sup>-1</sup>. day<sup>-1</sup>) (Ali et  
183 al., 2012), and Sweden (median: 18 ng. kg bw<sup>-1</sup>. day<sup>-1</sup> and 0.85 ng. kg bw<sup>-1</sup>. day<sup>-1</sup>) (Luongo  
184 and Ostman, 2015). These EDIs are lower than those reported in the U.S. for adults (median:  
185 13 ng. kg bw<sup>-1</sup>. day<sup>-1</sup>) (Xu et al., 2016), in Japan for toddlers (median: 112 ng. kg bw<sup>-1</sup>. day<sup>-1</sup>  
186 and 115 ng. kg bw<sup>-1</sup>. day<sup>-1</sup>) based on ingestion of floor and elevated surface dust respectively  
187 (Tajima et al., 2014), and Egypt (median: 52 ng. kg bw<sup>-1</sup>. day<sup>-1</sup> and 13 ng. kg bw<sup>-1</sup>. day<sup>-1</sup>) 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  $\Sigma_{12}$ OPEs for adults and toddlers via dust ingestion in an e-waste  
190 recycling area were 7.02 ng. kg bw<sup>-1</sup>. day<sup>-1</sup> and 80.2 ng. kg bw<sup>-1</sup>. day<sup>-1</sup>. These values were  
191 substantially higher than the EDIs for adults and toddlers in urban locations (2.06 ng. kg bw<sup>-1</sup>.  
192 day<sup>-1</sup> and 23.5 ng. kg bw<sup>-1</sup>. day<sup>-1</sup>), rural areas (2.0 ng. kg bw<sup>-1</sup>. day<sup>-1</sup> and 22.6 ng. kg bw<sup>-1</sup>.  
193 day<sup>-1</sup>) and college dormitories (3.2 ng. kg bw<sup>-1</sup>. day<sup>-1</sup> and 2.06 ng. kg bw<sup>-1</sup>. day<sup>-1</sup>) 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  $\Sigma_{10}$ OPEs for toddlers  
196 contributing 69 % (41 ng. kg bw<sup>-1</sup>. day<sup>-1</sup>) of their total exposure followed by dermal uptake  
197 which contributes 27 % (16 ng. kg bw<sup>-1</sup>. day<sup>-1</sup>), and air inhalation 4 % (2.4 ng. kg bw<sup>-1</sup>. day<sup>-1</sup>)  
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.



202

203

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

206

### 207 3.3 Human dermal uptake of OPEs

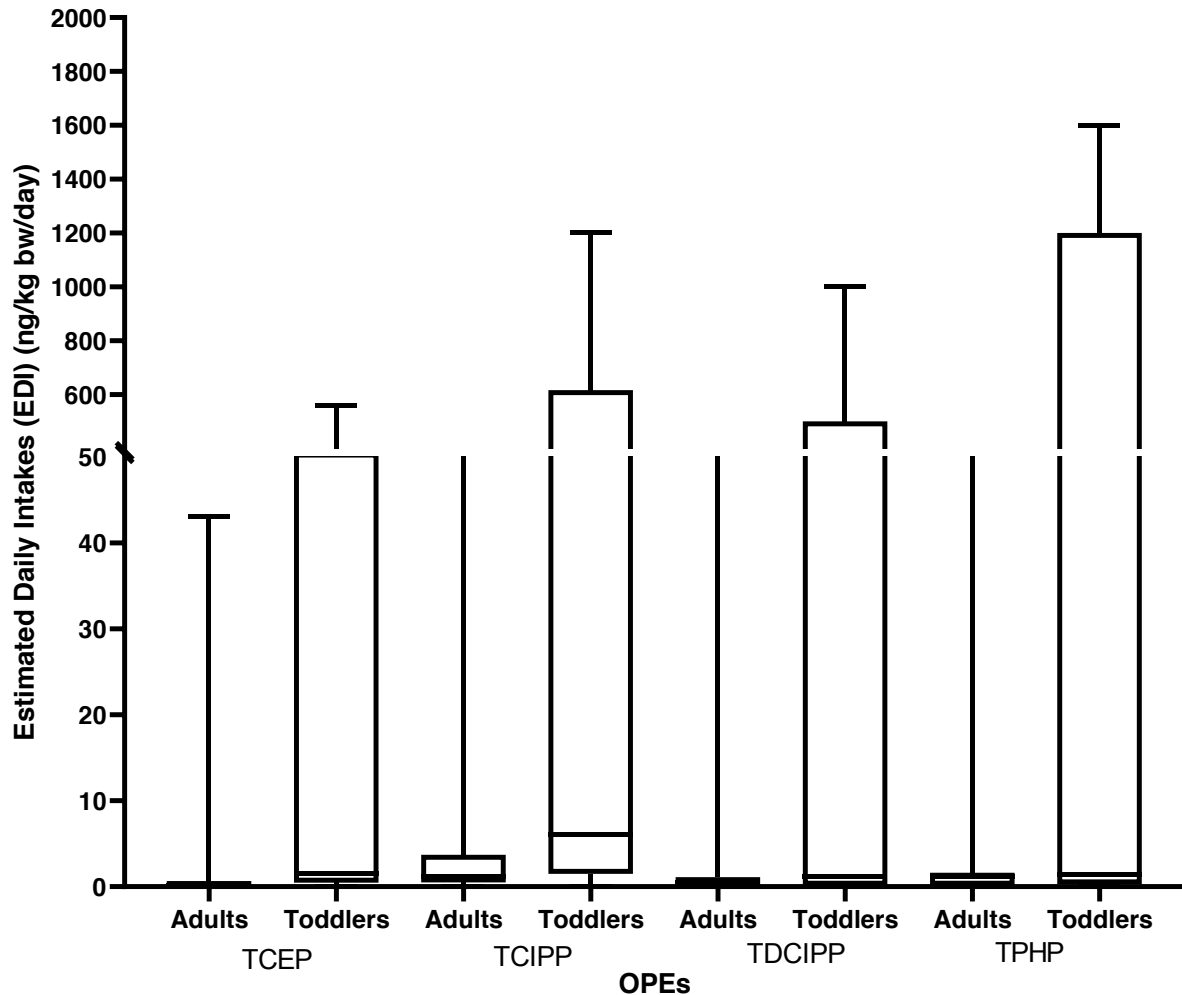
208 Recently, a few studies have raised concerns about dermal absorption as a potentially  
 209 significant pathway of exposure to OPEs (Abdallah et al., 2016; Mendelsohn et al., 2016; Liu  
 210 et al., 2017a, b; Bello et al., 2018; Frederiksen et al., 2018). Table S6 summarises estimates of  
 211 dermal exposure to OPEs published to date. Hoffman et al. (2015) found a significant positive  
 212 association between levels of TDCIPP and TPHP on hand wipes and the concentrations of their  
 213 metabolites in urine, suggesting that hand-to-mouth contact and/or dermal absorption may be  
 214 important exposure pathways to OPEs. More recently, a study examining the exposure to TPHP  
 215 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  $\Sigma_3$ OPEs  
225 using human *ex vivo* and cultured EPISKIN<sup>TM</sup> 3-D human skin equivalent (3D-HSE) models.  
226 They reported that the median EDIs via dermal absorption of  $\Sigma_3$ OPEs (TCEP, TCIPP, and  
227 TDCIPP) for toddlers and adults via indoor dust ingestion were 36 ng.kg bw<sup>-1</sup>. day<sup>-1</sup> and 4.1  
228 ng. kg bw<sup>-1</sup>. day<sup>-1</sup> which were lower than the reported values of 108 ng.kg bw<sup>-1</sup>. day<sup>-1</sup> and 23  
229 ng. kg bw<sup>-1</sup>. day<sup>-1</sup> ( $\Sigma_8$ 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



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



241

242

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

245

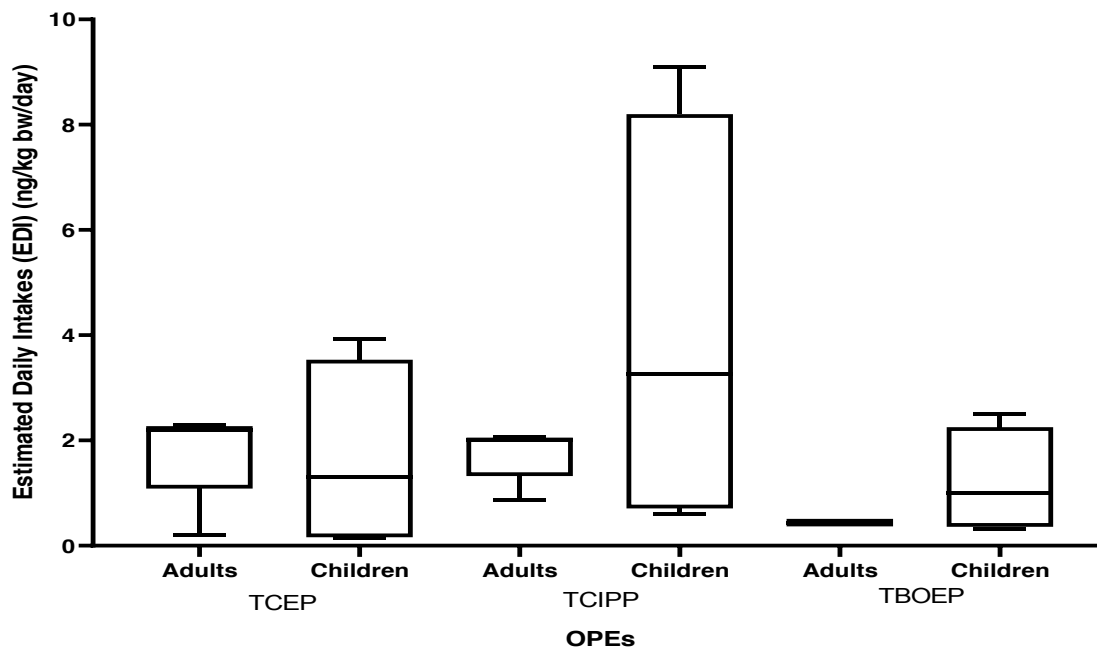
### 246 3.4 Human Exposure to OPEs via drinking water

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

249 river (Liu et al., 2019; Benotti et al., 2009; Rodil et al., 2012), bottled, household tap and  
250 filtered water produced from tap water by public purifying machine/household filtering  
251 apparatus (Li et al., 2014; Ding et al., 2015; Lee et al., 2016; Kim and Kannan, 2018; Park et  
252 al., 2018). Reported concentrations of individual OPEs are shown in Table S7. Concentrations  
253 of  $\Sigma_{14}$ OPEs range in the USA between 3.02 and 366 ng/L for tap water (Kim and Kannan,  
254 2018), and 8-720 ng/L for source and finished water (Benotti et al., 2009). In China,  
255 concentrations in municipal water from Nanjing ranged between 3.6-180 ng/L (Liu et al.,  
256 2019), while in Hangzhou they fall in the range 123-338 ng/L in tap water, 0.9-11.2 ng/L in  
257 bottled water, and 17.2-126 ng/L in filtered drinking water produced from tap water by  
258 household filtering system (Ding et al., 2015). Elsewhere, concentrations in surface and tap  
259 water from Spain range between 40-140 ng/L (Rodil et al., 2012). (Table S7).

260 The level of human exposure to OPEs received via drinking water has been evaluated in only  
261 a small number of studies (Kim and Kannan, 2018; He et al., 2019; Lee et al., 2016; Liu et al.,  
262 2019; Ding et al., 2015). According to He et al. (2019), who assumed water ingestion rates of  
263 (0.322 L/day, 0.502 L/day and 1.0445 L/day) for toddlers, older children, and adults in  
264 Chongqing, China; the mean EDIs for the same age groups for  $\Sigma_{11}$ OPEs were 1.02, 0.684 and  
265 0.939 ng. kg bw<sup>-1</sup>.day<sup>-1</sup>, respectively. The value obtained for toddlers exceeded the 0.22 ng.  
266 kg bw<sup>-1</sup>.day<sup>-1</sup> obtained for  $\Sigma_{14}$ OPEs under a typical drinking water exposure scenario in the  
267 USA (Kim and Kannan, 2018). For  $\Sigma_{14}$ OPEs under a high exposure scenario, Kim and Kannan  
268 (2018) obtained an EDI value that ranged between 1.17 ng.kg bw<sup>-1</sup>.day<sup>-1</sup> and 9.65 ng. kg bw<sup>-1</sup>.  
269 day<sup>-1</sup> depending on the age group considered. In Korea, Lee et al. (2016) found that the  
270 median EDI values via drinking water for  $\Sigma_{10}$ OPEs for toddlers, children, teenagers and adults  
271 were: 2.55 ng. kg bw<sup>-1</sup>.day<sup>-1</sup>, 2.10 ng. kg bw<sup>-1</sup>.day<sup>-1</sup>, 1.27 ng. kg bw<sup>-1</sup>.day<sup>-1</sup>, and 1.81 ng. kg  
272 bw<sup>-1</sup>.day<sup>-1</sup> respectively. These values were about 12 times higher than those obtained in the  
273 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  $\Sigma_{14}$ 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<sup>-1</sup>.day<sup>-1</sup> and 6.95 ng. kg  
279 bw<sup>-1</sup>.day<sup>-1</sup> for adults and children, the mean EDIs for  $\Sigma_9$ OPEs via tap water, exceeded those  
280 via filtered water produced from tap water via household filtering systems (2.22 ng. kg bw<sup>-1</sup>  
281 .day<sup>-1</sup> and 2.19 ng. kg bw<sup>-1</sup>.day<sup>-1</sup>), well water (0.17 ng. kg bw<sup>-1</sup>.day<sup>-1</sup> and 0.16 ng. kg bw<sup>-1</sup>  
282 .day<sup>-1</sup>) and barreled water purchased in packaged polycarbonate plastic barrels (1.06 ng. kg  
283 bw<sup>-1</sup>.day<sup>-1</sup> and 1.05 ng. kg bw<sup>-1</sup>.day<sup>-1</sup>) respectively. In Nanjing, China, Liu et al. (2019) found  
284 median EDIs for  $\Sigma_5$ OPEs for male and female adults were in the range 4.2-7.1 ng. kg bw<sup>-1</sup>.day<sup>-1</sup>  
285 <sup>1</sup> and 3.6-6.1 ng. kg bw<sup>-1</sup>.day<sup>-1</sup> 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 95<sup>th</sup> percentile concentration, Liu et al. (2019) found the EDI value for  $\Sigma$ OPEs to vary between  
289 45.2-64.8 ng.kg bw<sup>-1</sup>.day<sup>-1</sup> and 38.9-55.7 ng.kg bw<sup>-1</sup>.day<sup>-1</sup> for male and female adults. These  
290 values exceed substantially estimates of high  $\Sigma$ OPE exposure scenarios (95<sup>th</sup> percentile) via  
291 ingestion of tap water in Korea (8.23-16.5 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>) (Lee et al. 2016) and in Eastern  
292 China at high exposure scenario (median) (6.8-11.56 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>) (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.



297

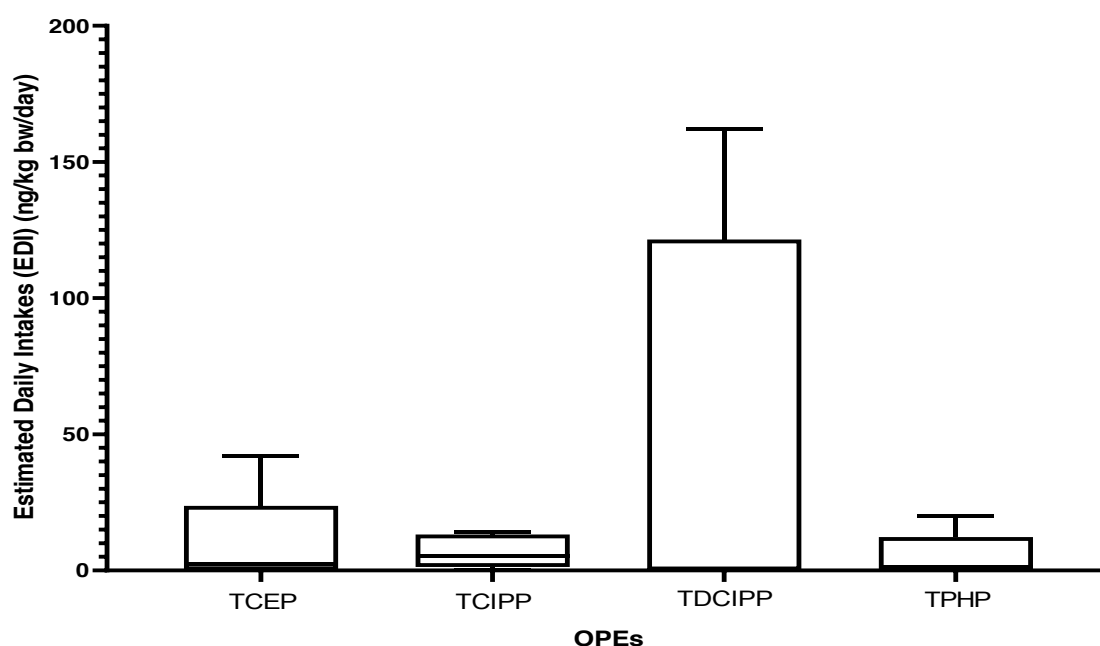
298 **Fig. 5: Box-plot showing the range of mean estimates of human exposure to TCEP,**  
 299 **TCIPP, and TBOEP via water ingestion**

300

301 **3.5 Infant Exposure to OPEs via breast milk**

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

312 Concentrations of OPEs in human milk vary with several factors including mother's age and  
313 diet (Kim et al., 2014). Assuming a daily intake of 450 mL breast milk for infants 0–1 year old,  
314 He et al. (2018b) found that breastfeeding would result in average estimated daily intakes  
315 (EDIs) of 4.6, 26 and 76 ng.kg bw<sup>-1</sup>.day<sup>-1</sup> for TCEP, TnBP, and TEHP respectively. According  
316 to Ma et al. (2019), the respective mean and the high-end EDIs of ΣOPEs via human milk were  
317 542 and 911 ng.kg bw<sup>-1</sup>.day<sup>-1</sup> for infants less than 1 month of age; 505 and 850 ng.kg bw<sup>-1</sup>  
318 <sup>1</sup>.day<sup>-1</sup> for infants from 1 to 3 months of age; 397 and 668 ng.kg bw<sup>-1</sup>.day<sup>-1</sup> for infants from >3  
319 to 6 months of age; and 300 and 504 ng.kg bw<sup>-1</sup>.day<sup>-1</sup> for infants from >6 to 12 months of age  
320 (Table S10). The decreasing EDI with increasing infant age was attributed to increasing body  
321 weight and decreasing milk ingestion level with age. Table S10 shows the reported data on  
322 infant exposure to individual OPEs via human milk. Analysis of these data show nursing infant  
323 exposures to individual OPEs fall in the order: TDCIPP > TCEP >> TPHP > TCIPP (Fig. 6).



324  
325 **Fig. 6: Box-plot showing the range of mean estimates of breast-fed infant exposure to**  
326 **TCEP, TCIPP, TDCIPP, and TPHP via ingestion of human milk**

327

### 328 3.6 Human Dietary Intake of OPEs

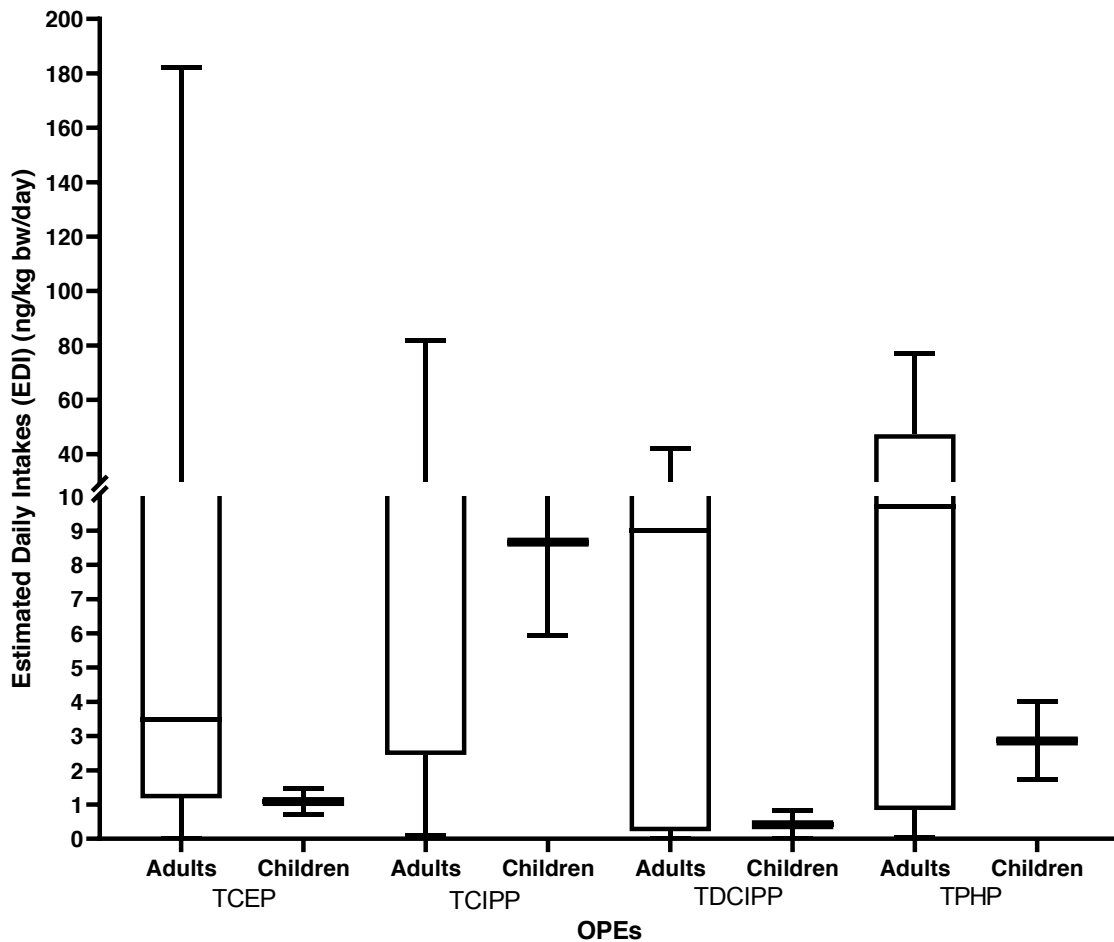
329 OPEs enter the human diet primarily via two routes. First, via bioaccumulation into plants and  
330 animals from contaminated air, soil, water, animal diet etc. Second, foodstuffs can be  
331 contaminated by OPEs during production, industrial processing (e.g., packing, canning, and  
332 drying)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

337 In surveys of fish worldwide, concentrations of  $\Sigma$ OPEs have been reported to be as high as  
338 15,000 ng g<sup>-1</sup> (lipid weight - lw) (Sundkvist et al., 2010) (Table S11). Rice was reported as a  
339 significant source of exposure to OPEs in China (Zhang et al., 2016). In the study of Poma et  
340 al. (2018), fish-oil food supplements were the most contaminated food samples with a total  
341 mean  $\Sigma$ OPE concentration of 225 ng.g<sup>-1</sup> (wet weight – ww), followed by grain, cheese, and  
342 other food (meat and chicken stocks) with concentrations of 36.9, 20.1, and 18.8 ng.g<sup>-1</sup> ww  
343 respectively (Table S11). These observed values exceeded those detected in duplicate diet  
344 samples by Xu et al. (2017) who found the sum of the average concentrations of four OPEs  
345 (EHDPP, TCEP, TPHP, and TCIPP) to be 7.7 ng.g<sup>-1</sup> ww (Xu et al., 2017). In the Philippines,  
346 Kim et al., (2011) reported concentrations of the sum of nine OPEs (including TCEP, TCIPP,  
347 and TDCIPP) in fish from Manila Bay to range between 110 to 1900 ng.g<sup>-1</sup> lw.

348 Table S12 summarises reported human dietary intakes of OPEs from several studies from  
349 different countries. According to Malarvannan et al. (2015), mean dietary intakes of TCIPP,  
350 TPHP, EHDPP, TBOEP, TDCIPP, and TCEP through eel consumption were: 0.10, 0.034,  
351 0.028, 0.017, 0.012, and 0.10 ng.kg bw<sup>-1</sup>.day<sup>-1</sup> respectively; while high-end intake estimates  
352 were: 2.5, 0.84, 0.74, 0.43, 0.29, and 0.25 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>, respectively (Table S12).

353 Looking beyond exposure via consumption of specific foodstuffs and considering overall  
354 dietary exposure, estimated dietary exposures to  $\Sigma$ OPEs at different locations vary, including  
355 between the United States (adults: 25.1 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>, children: 56.6 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>)  
356 (Wang and Kannan, 2018), China (adults: 55 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>, children: 98 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>)  
357 (Ding et al., 2018), (male adults: 539 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>, female adults: 600 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>)  
358 (Zhang et al., 2016), (Chinese adults: 44.3 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>) (Zhao et al., 2019), Sweden  
359 (adults: 85 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>) (Poma et al., 2017), and Belgium (adults: 103 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>)  
360 (Poma et al., 2018) (Table S12). EDI values for toddlers, children, and teenagers exceed those  
361 for adults.

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



370

371

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

374

375 **4. Relative Significance of Different Exposure Pathways to OPEs**

376 As highlighted above, measurable exposure to OPEs occurs through ingestion of contaminated  
 377 house dust and food, inhalation of contaminated air, and dermal absorption. While Ji et al.  
 378 (2014) argued that exposure via contact with dust, air and water should not be underestimated  
 379 or ignored and that indoor air and water may be more important than diet as pathways of human  
 380 exposure to OPEs; some recent studies have highlighted the importance of diet as a pathway



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

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

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

		Mean EDI values (ng.kg bw <sup>-1</sup> .day <sup>-1</sup> )							
Exposure pathway	Age group	TCEP	TCIPP	TDCIP P	TPH P	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 ( $\Sigma$ 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	$9.72 \times 10^{-7}$	-	-	-	$6.24 \times 10^{-8}$	-	$1.55 \times 10^{-7}$	-
	Toddlers	$2.44 \times 10^{-6}$	-	-	-	$1.31 \times 10^{-7}$	-	$2.90 \times 10^{-8}$	-
RfD values (ng.kg bw <sup>-1</sup> .day <sup>-1</sup> )	-	7000 <sup>a</sup>	10000 <sup>a</sup>	20000 <sup>a</sup>	-	10000 <sup>a</sup>	-	100000 <sup>a</sup>	-
SFO ((ng/kg bw/day) <sup>-1</sup> )	-	$2 \times 10^{-8}$ <sup>b</sup>	-	-	-	$9 \times 10^{-9}$ <sup>b</sup>	-	$3.2 \times 10^{-9}$ <sup>b</sup>	-

394 <sup>a</sup> Reference dose (RfD) values of USEPA (2017).

395 <sup>b</sup> Oral cancer slope factor (SFO) values (USEPA, 2017; Li et al., 2018)

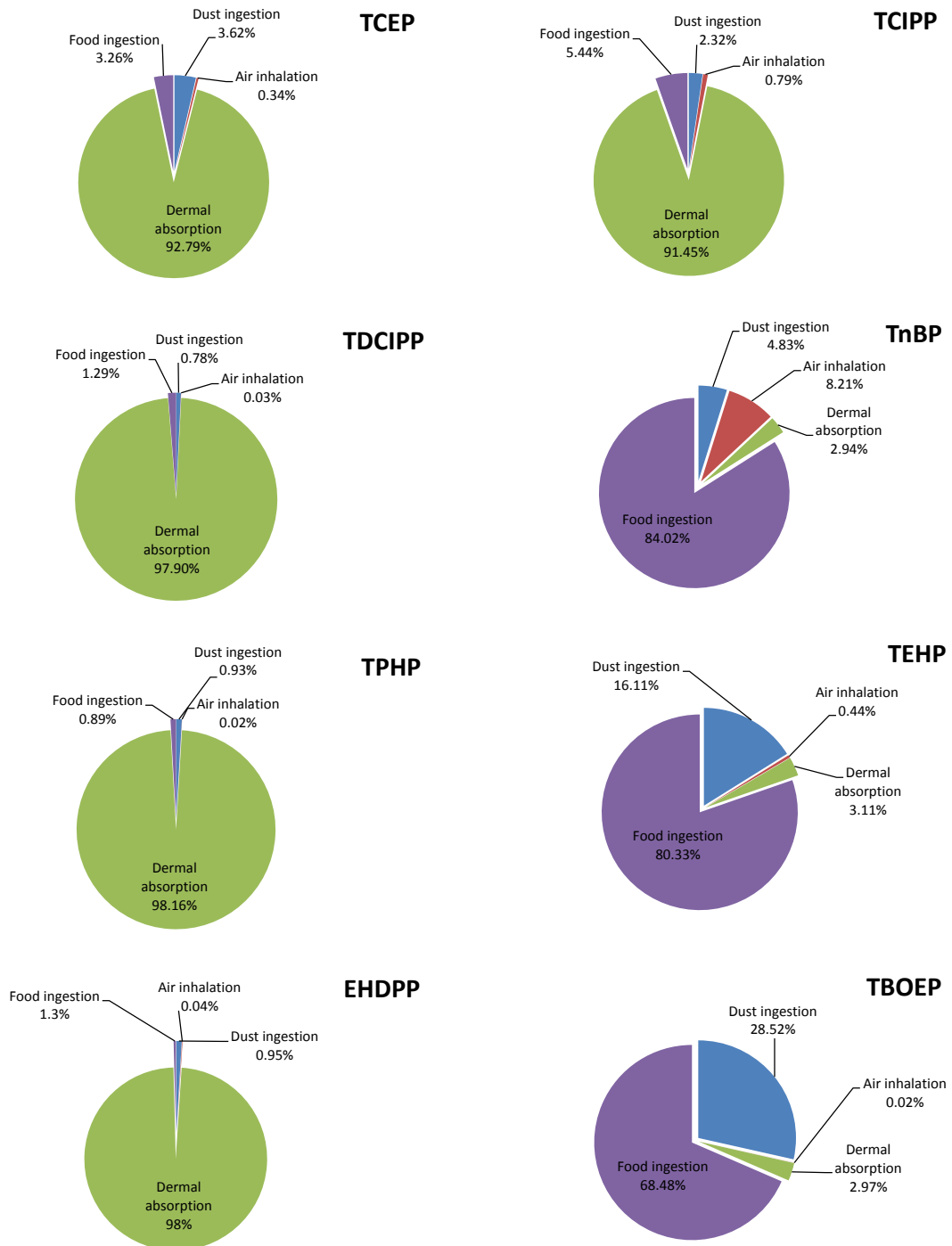
396

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 ( $103 \text{ ng.kg bw}^{-1}.\text{day}^{-1}$ , 93 %),  
399 TCIPP ( $208 \text{ ng.kg bw}^{-1}.\text{day}^{-1}$ , 92 %  $\Sigma$ exposure), and TDCIPP ( $221 \text{ ng.kg bw}^{-1}.\text{day}^{-1}$ , 98 %);  
400 as well as for aryl OPEs such as TPHP ( $401 \text{ ng.kg bw}^{-1}.\text{day}^{-1}$ , 98%) and EHDPP ( $227 \text{ ng.kg}$   
401  $\text{bw}^{-1}.\text{day}^{-1}$ , 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 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>, 84 %), TBOEP (47 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>, 67 %), and TEHP (7.2  
410 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>, 80 %) followed by dust ingestion and air inhalation, with dermal uptake least  
411 important (Fig. 8).

412



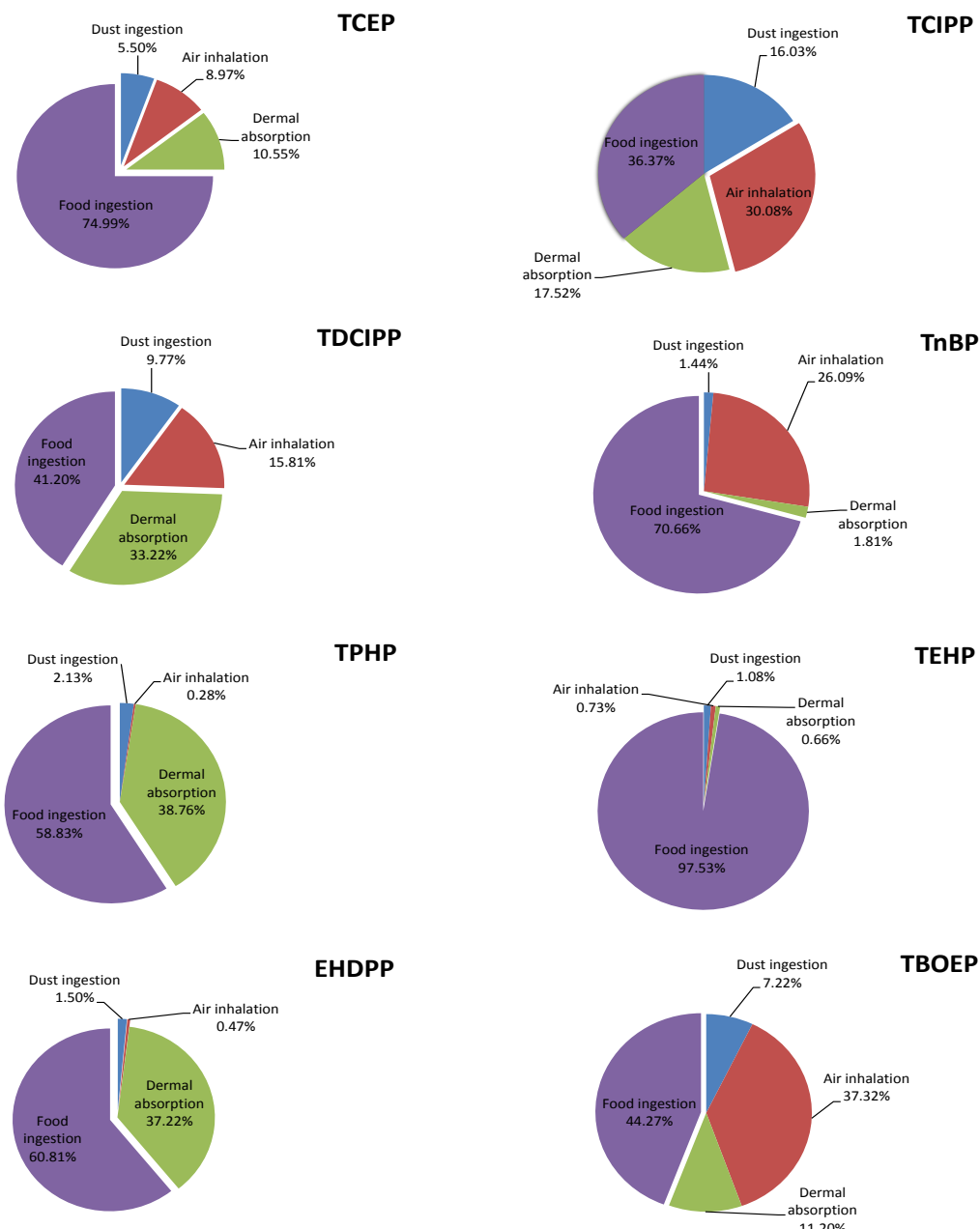
413

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

416

417 For adults, food ingestion appears the main human exposure pathway for all eight OPEs  
 418 evaluated, contributing 32.2 ng.kg bw<sup>-1</sup>. day<sup>-1</sup> and 75% Σexposure for TCEP, 21.3 ng.kg bw<sup>-1</sup>.

419 day<sup>-1</sup>, 37% for TCIPP, 11.9 ng.kg bw<sup>-1</sup>. day<sup>-1</sup>, 42 % for TDCIPP, 4.31 ng.kg bw<sup>-1</sup>. day<sup>-1</sup>, 71%  
 420 for TnBP, 27.0 ng.kg bw<sup>-1</sup>. day<sup>-1</sup>, 59 % for TPHP, 47.2 ng.kg bw<sup>-1</sup>. day<sup>-1</sup>, 97% for TEHP, 12.8  
 421 ng.kg bw<sup>-1</sup>. day<sup>-1</sup>, 61% for EHDPP, and 12.7 ng.kg bw<sup>-1</sup>.day<sup>-1</sup>, 46 % for TBOEP (Fig. 9).



422  
 423 **Fig. 9: Relative significance of exposure of adults via air inhalation, dermal uptake, diet,**  
 424 **and dust ingestion for individual OPEs**

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

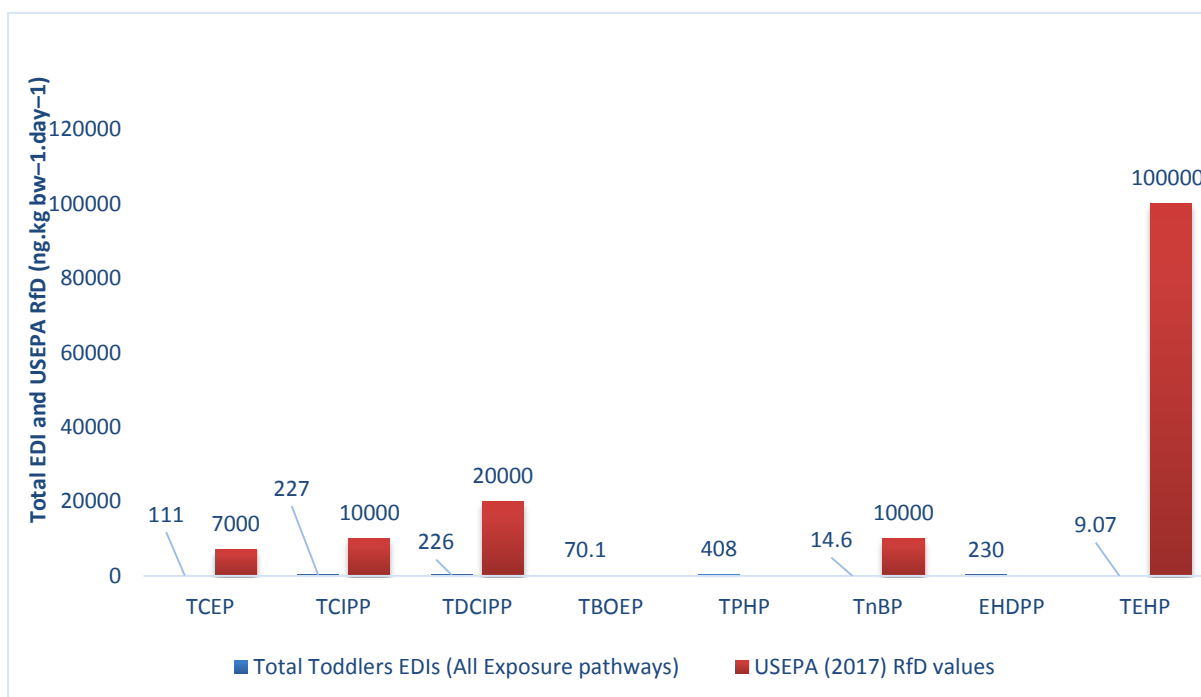
427 order: TCEP > TCIPP > TnBP > TBOEP > TDCIPP and TCIPP > TnBP > TCEP > TBOEP >  
428 TDCIPP respectively (Fig S1). This shows that the chlorinated OPEs are the main OPEs both  
429 adults and toddlers are exposed to via water ingestion. In addition, data on infant exposure to  
430 OPEs via human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

432 EDI ( $\text{ng.kg bw}^{-1}.\text{day}^{-1}$ ) values for OPEs were compared with the oral reference dose (RfD  
433  $\text{ng.kg bw}^{-1}.\text{day}^{-1}$ ) which is an indicator of risk assessment of human exposure to non-  
434 carcinogenic toxic substances proposed by the U.S. EPA (2014). Based on the availability of  
435 laboratory animal exposure data from several organ/system specific RfDs, the USEPA (2017)  
436 derived a revised RfD value for each OPE by dividing the human equivalent dose (HED) by  
437 an uncertainty factor (UF). The HED is obtained by multiplying the no observed adverse effect  
438 level (NOAEL) by a dosimetric adjustment factor (DAF) (Li et al., 2018, USEPA, 2017) (Table  
439 1).

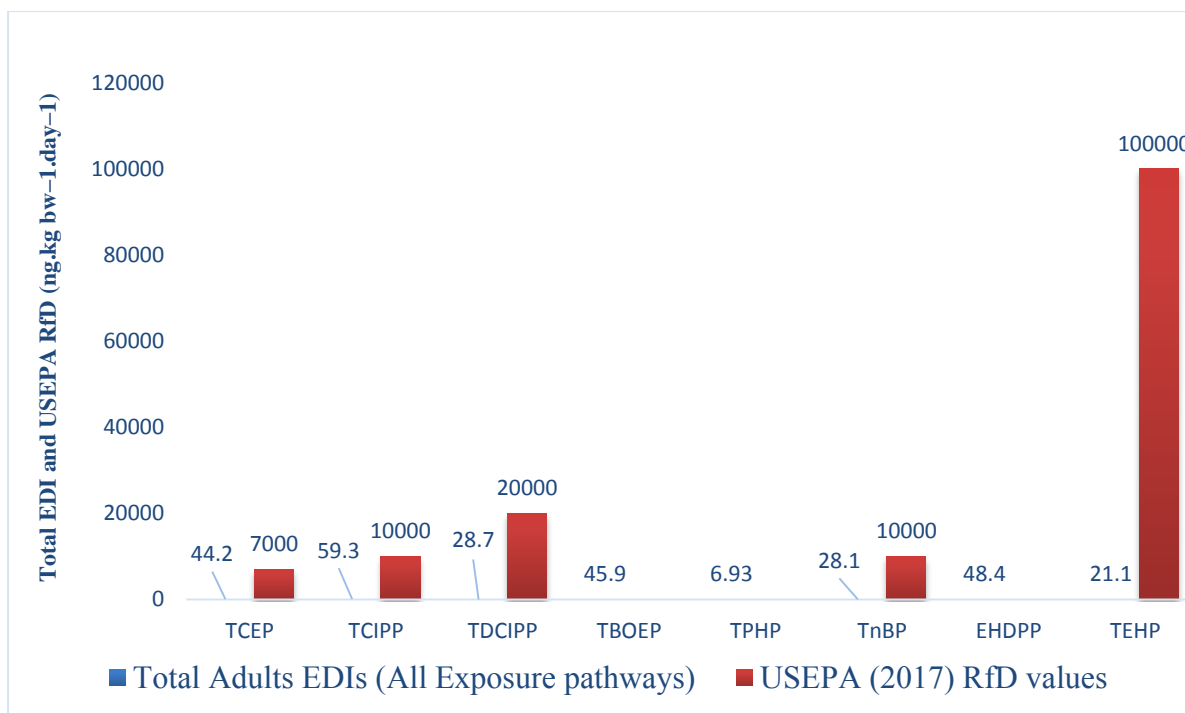
440 The sum of the average EDIs via all exposure pathways for toddlers and adults for the eight  
441 OPEs evaluated were used to evaluate the risk of such overall exposure via comparison with  
442 the corresponding reference dose (RfD) values (Fig. 10 and Fig. 11). This comparison indicated  
443 that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

446 We also considered carcinogenic effects arising from chronic daily exposure to OPEs for both  
447 adults and toddlers using published oral cancer slope factors (SFOs) (USEPA, 2017; Li et al.,  
448 2018). Carcinogenic risk estimates were obtained by multiplying the estimated daily intake  
449 (EDI) value for a given OPE by its SFO value, which are currently only available for TCEP,  
450 TnBP and TEHP (USEPA, 2017; Li et al., 2018). Our estimate of the total carcinogenic risk  
451 (TCR) via the sum of all exposure pathways for adults for all three of these OPEs (TCEP, TnBP

452 and TEHP) were below the acceptable risk value of  $1 \times 10^{-6}$  (Ding et al., 2015). However, while  
 453 toddler exposures to TnBP and TEHP also fell below a TCR of  $1 \times 10^{-6}$ ; for TCEP, the TCR  
 454  $2.44 \times 10^{-6}$  for toddlers exceeded the acceptable risk value (Table 1). This suggests concern over  
 455 the carcinogenic risk from TCEP for toddlers when considering the sum of the exposure  
 456 pathways considered in this review.



457  
 458 **Fig 10: Comparison of average estimated daily intake (EDI) values via all exposure**  
 459 **pathways for selected OPEs for toddlers with the corresponding reference doses (RfDs**  
 460 **ng.kg bw<sup>-1</sup>.day<sup>-1</sup>) adopted from USEPA (2017)**



461

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

465

466 **5 Conclusions, research priorities, gaps and future directions**

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



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

484 This review reveals that relatively few studies have determined the magnitude of human dietary  
485 exposure to OPEs. Given our finding that food is an important exposure pathway to these  
486 chemicals, regular monitoring of the presence of OPEs in foodstuffs is recommended.  
487 Moreover, the currently available literature reveals that human dietary exposure to OPEs occurs  
488 principally via industrially processed food groups, such as grains, oils, and dairy products (Li  
489 et al., 2019; Poma et al., 2018). For this reason, surveillance of OPEs in processed foodstuff  
490 samples should likely have higher priority compared to raw foodstuffs in future studies. This  
491 is especially important for EHDPP, which is capable of migrating from packaging materials to  
492 the foodstuffs (Wang and Kannan, 2018; Poma et al., 2018; Li et al., 2019). Moreover, several  
493 studies have highlighted that OPE derivatives can be generated by enzyme-catalysed  
494 metabolism of OPEs in biota as well as through other degradation routes, such as microbial  
495 metabolism/biotransformation, base-catalysed hydrolysis, and photodegradation (Li et al.,  
496 2019; Cequier et al., 2015; Greaves et al., 2016). This suggests that OPE derivatives could  
497 potentially co-exist with parent OPEs in environmental samples or foodstuffs (Fu et al., 2017).  
498 More importantly, some studies have stated that compared to their parent OPE triesters, such  
499 metabolites/degradation products are more biologically active with respect to several  
500 toxicological endpoints (Li et al., 2019; Su et al., 2014). However, to date, there is to our

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

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

512

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516

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