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

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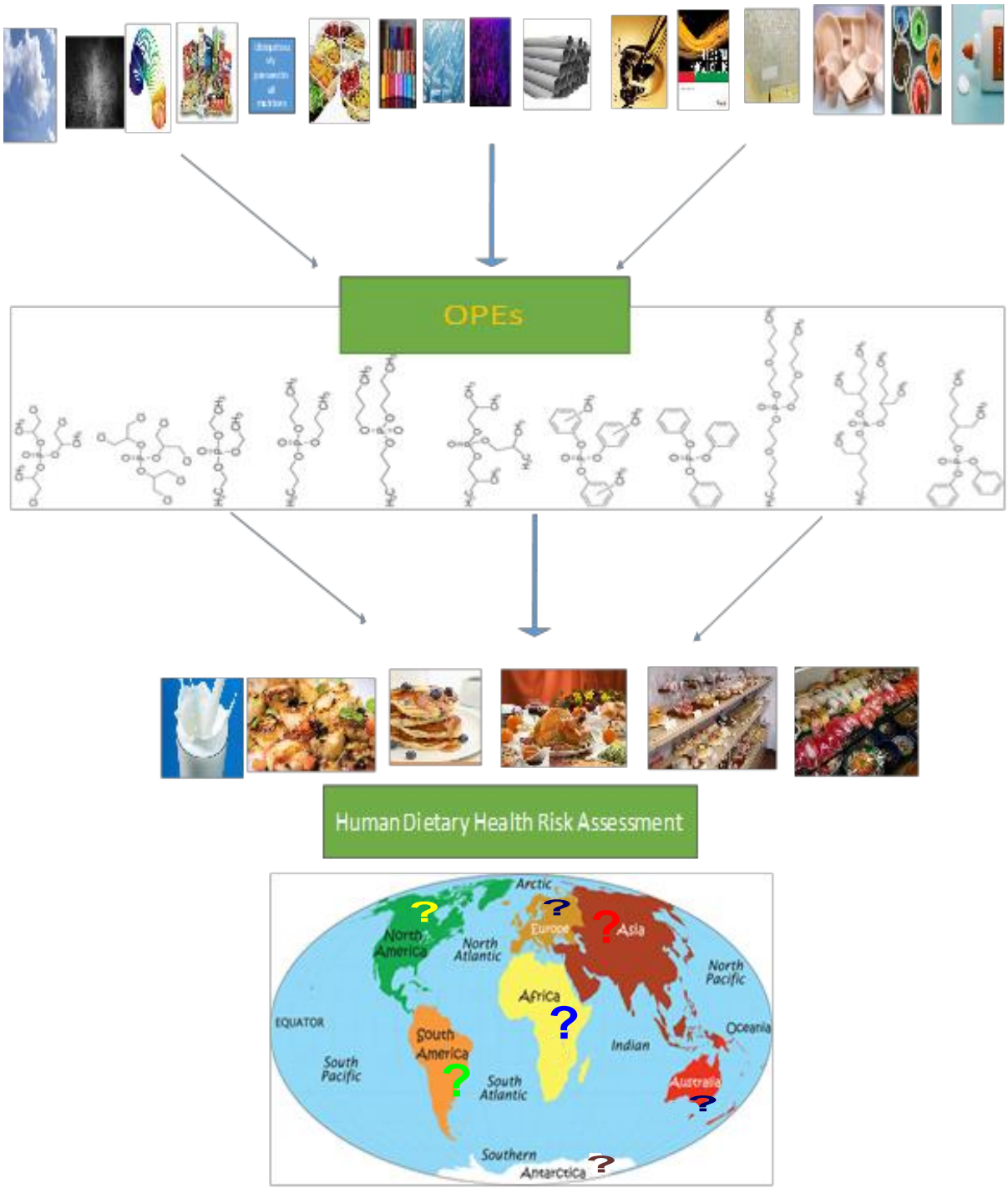
Highlights

- 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

13 **Graphical Abstract**



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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.

Keywords: Organophosphate esters, Foodstuffs, Indoor dust; Indoor air; Drinking water; Dermal uptake

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).

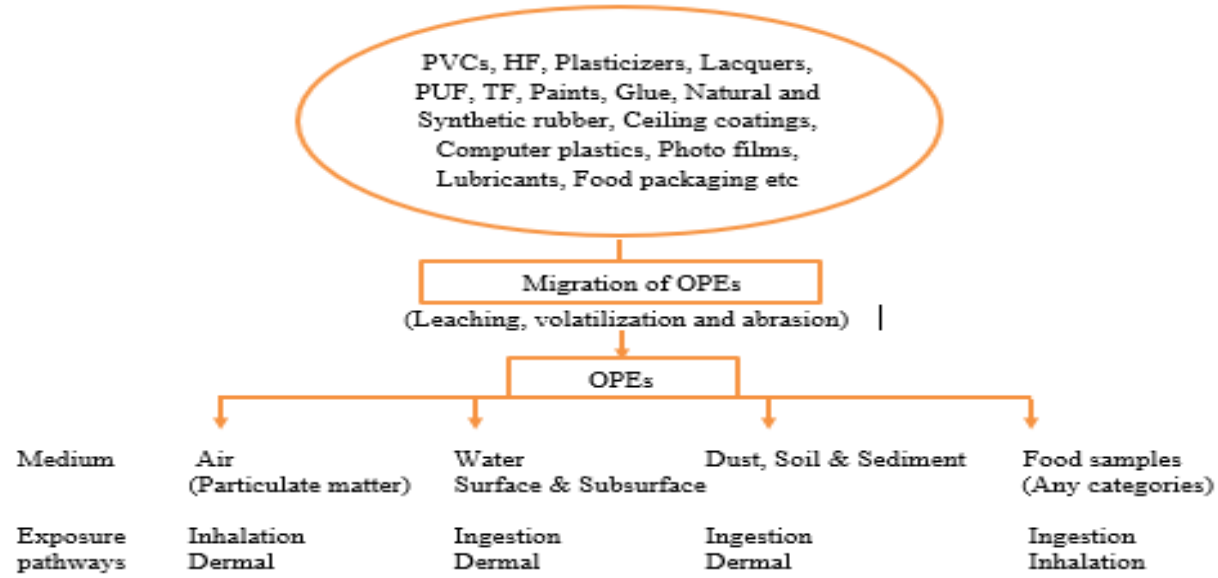


Fig. 1: Schematic representation of the pathways of transmission of OPEs from treated products to humans

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

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

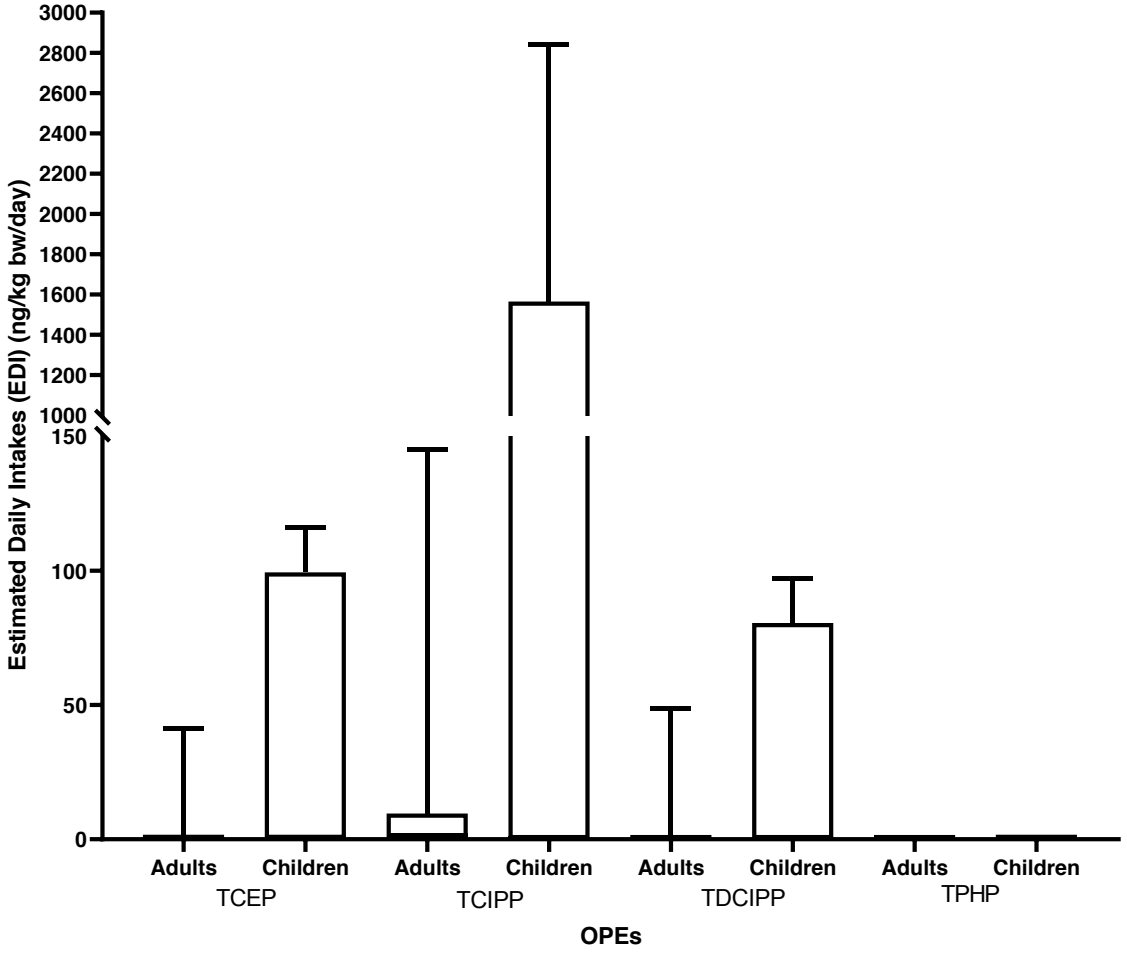


Fig. 2: Box-plot showing the range of mean estimates of human exposure to TCEP, TCIPP, TDCIPP, and TPHP via air inhalation.

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

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

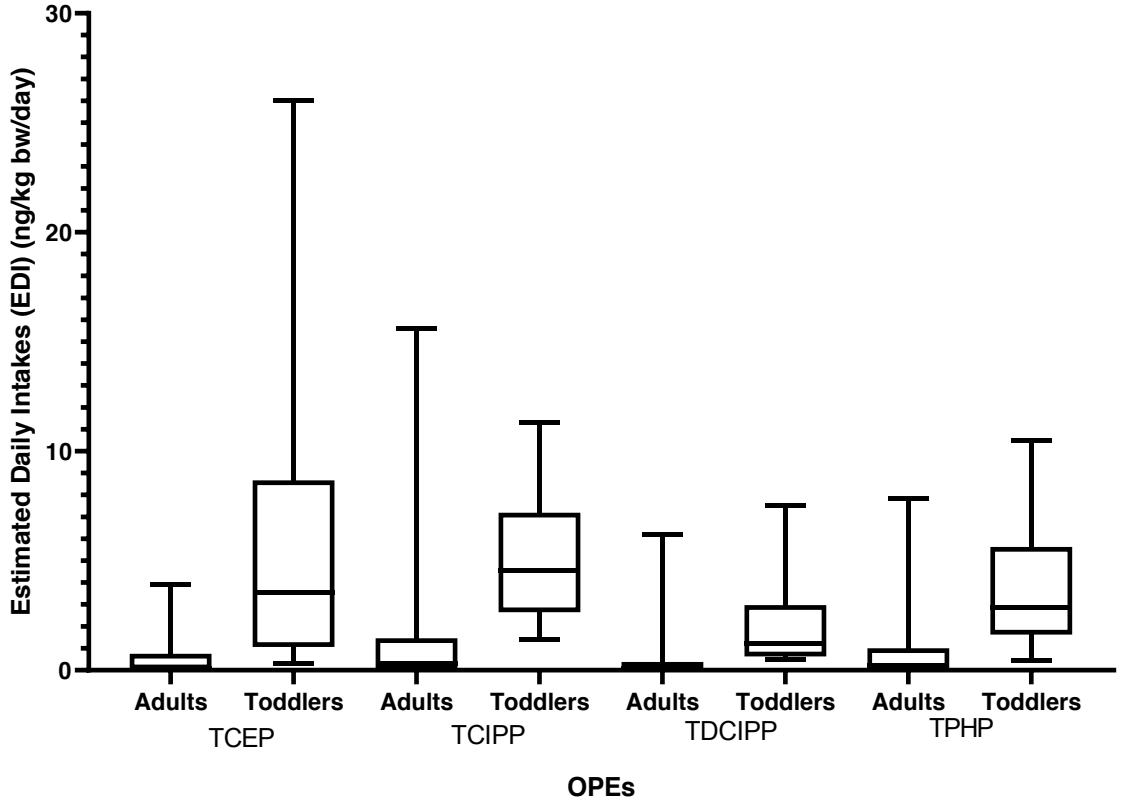


Fig. 3: Box plot showing the range of mean reported estimates of human exposure via dust ingestion to TCEP, TCIPP, TDCIPP, and TPHP

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

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

In addition, *in vitro* skin absorption studies (Abdallah et al., 2016; Hughes et al., 2001) reveal that a relatively high percentage of TCEP, TCIPP, and TDCIPP can be absorbed by human or mouse skin. Assessments of dermal exposure to OPEs are however, limited. Two studies reported OPE intakes via dermal absorption from contact with indoor dust (Cequier et al., 2014; Abdallah et al., 2016). Abdallah et al. (2016) investigated human dermal uptake of Σ_3OPEs using human *ex vivo* and cultured EPISKIN^{TM} 3-D human skin equivalent (3D-HSE) models. They reported that the median EDIs via dermal absorption of Σ_3OPEs (TCEP, TCIPP, and TDCIPP) for toddlers and adults via indoor dust ingestion were 36 ng.kg bw^{-1}. day^{-1} and 4.1 ng. kg bw^{-1}. day^{-1} which were lower than the reported values of 108 ng.kg bw^{-1}. day^{-1} and 23 ng. kg bw^{-1}. day^{-1} (Σ_8OPEs) for school children and women by Cequier et al. (2014). Abdallah et al. (2016) also investigated the impact of hand-washing on reducing dermal exposure to OPEs. They found that depending on the physicochemical properties of the OPEs, hand-washing reduces the overall human dermal uptake of the OPEs (Abdallah et al., 2016). The same authors noted that as well as from adhered indoor dust, OPEs on the skin surface might also arise from dermal contact with flame-retarded consumer products (i.e. fabrics, mobile phones), which may constitute a more significant exposure route due to high concentrations of OPEs in these products (Abdallah et al, 2016, 2018). In summary, the evidence to date suggests that human exposure to selected individual OPEs via dermal absorption occurs in this order: 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.

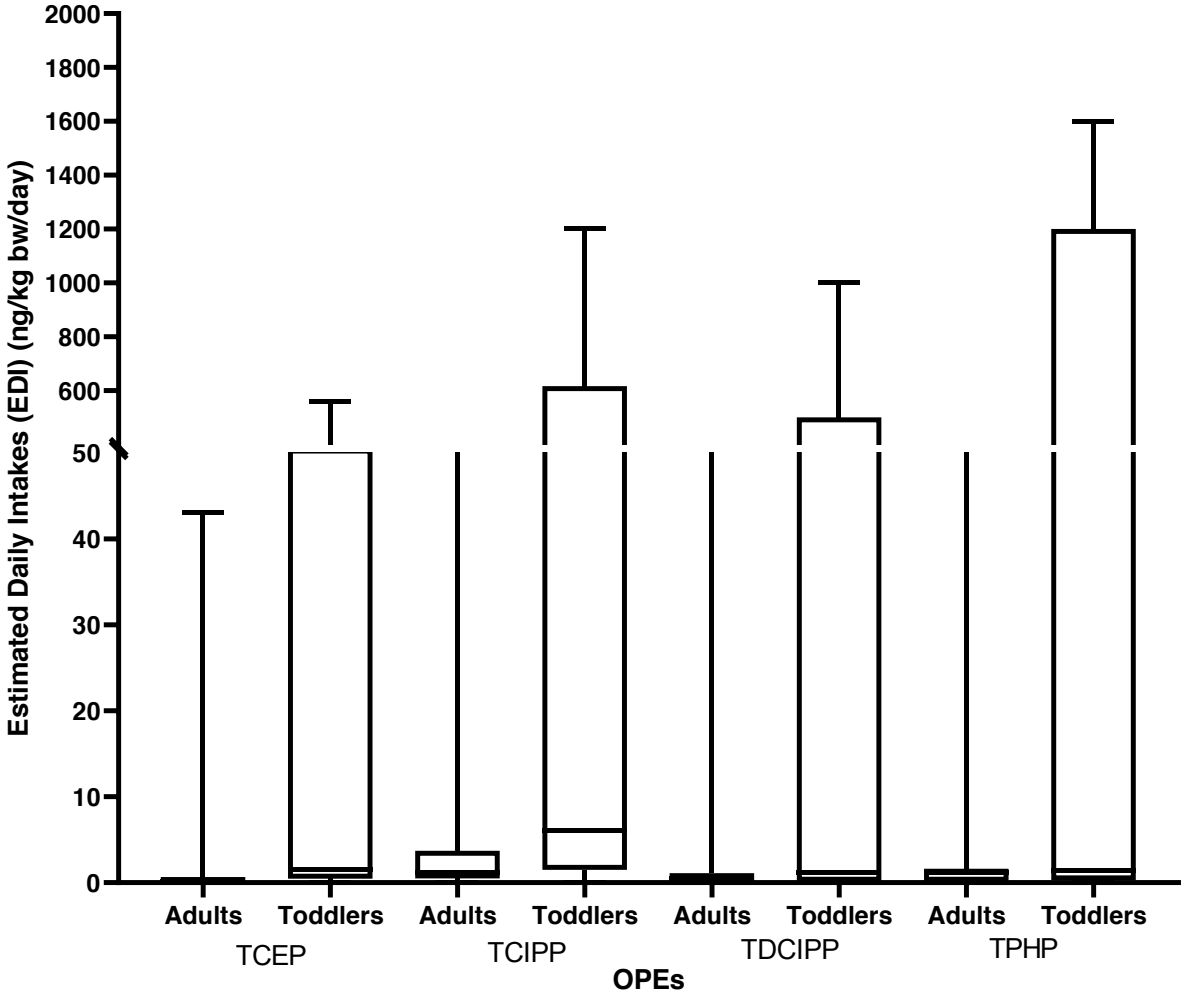


Fig. 4: Box plot showing the range of reported mean estimates of human exposure to TCEP, TCIPP, TDCIPP, and TPHP via dermal absorption from indoor dust.

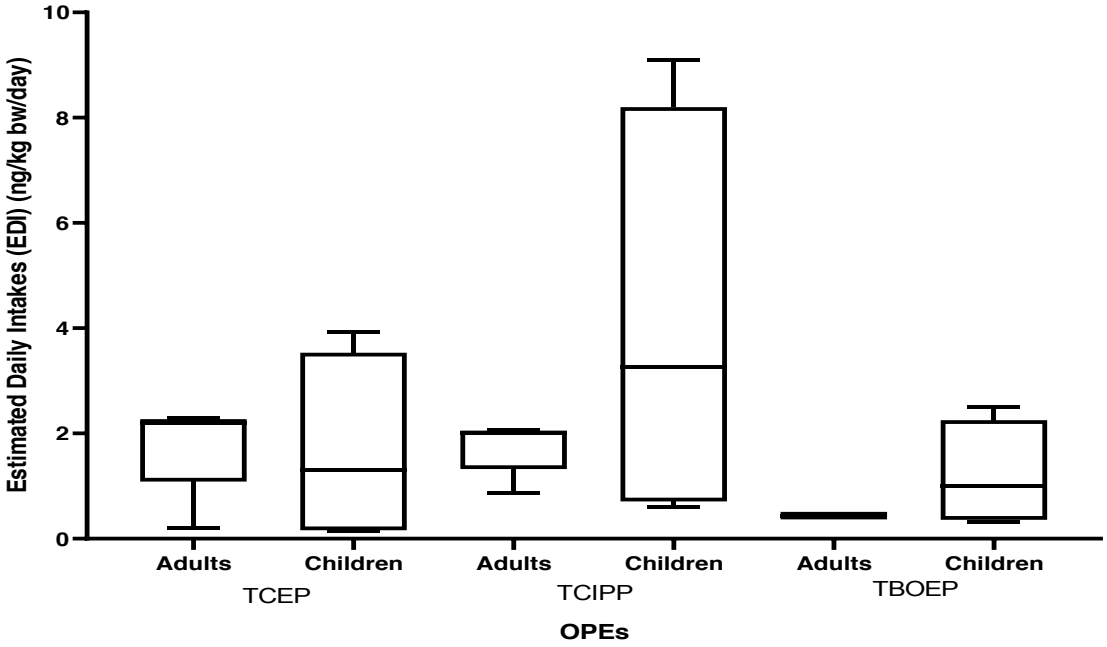
3.4 Human Exposure to OPEs via drinking water

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).

Kim and Kannan (2018) observed that TCIPP and TBOEP combined contributed > 50% of the total EDI via water ingestion among the Σ_{14}OPEs evaluated. They also reported that indirect water ingestion during swimming can contribute to a total OPE exposure of up to 15.8 ng/swimming event for children and 9.28 ng/swimming event for adults. In Hangzhou and Quzhou, Eastern China, Ding et al. (2015) found that at 7.07 ng.kg $bw^{-1}.day^{-1}$ and 6.95 ng. kg $bw^{-1}.day^{-1}$ for adults and children, the mean EDIs for Σ_9OPEs via tap water, exceeded those via filtered water produced from tap water via household filtering systems (2.22 ng. kg $bw^{-1}.day^{-1}$ and 2.19 ng. kg $bw^{-1}.day^{-1}$), well water (0.17 ng. kg $bw^{-1}.day^{-1}$ and 0.16 ng. kg $bw^{-1}.day^{-1}$) and barreled water purchased in packaged polycarbonate plastic barrels (1.06 ng. kg $bw^{-1}.day^{-1}$ and 1.05 ng. kg $bw^{-1}.day^{-1}$) respectively. In Nanjing, China, Liu et al. (2019) found median EDIs for Σ_5OPEs for male and female adults were in the range 4.2-7.1 ng. kg $bw^{-1}.day^{-1}$ and 3.6-6.1 ng. kg $bw^{-1}.day^{-1}$ respectively. Liu et al. (2019) also observed that for individual OPEs, TEP, TCEP, and TCPP made the biggest contributions to human exposure via water ingestion. Under a high exposure scenario, assuming ingestion of water contaminated at the 95th percentile concentration, Liu et al. (2019) found the EDI value for ΣOPEs to vary between 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 values exceed substantially estimates of high ΣOPE exposure scenarios (95th percentile) via ingestion of tap water in Korea (8.23-16.5 ng.kg $bw^{-1}.day^{-1}$) (Lee et al. 2016) and in Eastern China at high exposure scenario (median) (6.8-11.56 ng.kg $bw^{-1}.day^{-1}$) (Ding et al. 2015). Table S8 summarises human exposure data via water ingestion, while Figure 5 illustrates the range of mean estimates of the exposure of adults and children to TCEP, TCIPP, and TBOEP via water ingestion. This clearly shows that children are more exposed to these OPEs via water ingestion than adults.



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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 $\sum_{12}$OPEs ranging from 0.67 to 7.8 ng/mL with a mean value of 3.6±1.4 ng/mL (Table S9). This
310 was consistent with the average concentration of Σ_{11}OPEs (3.4 ng/g) reported by Sundkvist et
311 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 ΣOPEs 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).

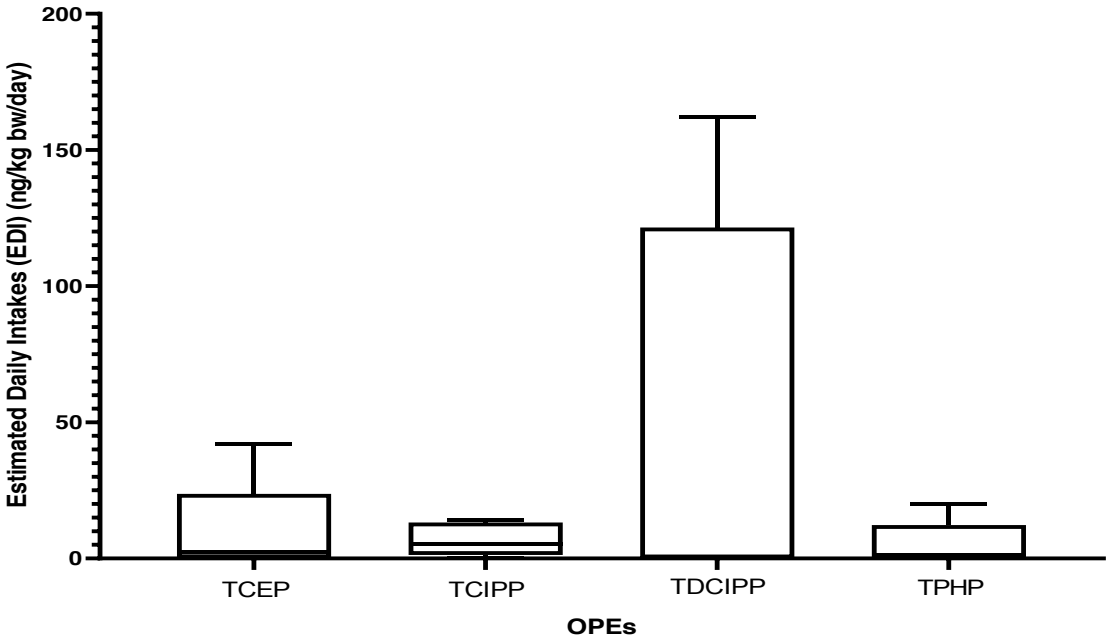


Fig. 6: Box-plot showing the range of mean estimates of breast-fed infant exposure to TCEP, TCIPP, TDCIPP, and TPHP via ingestion of human milk

3.6 Human Dietary Intake of OPEs

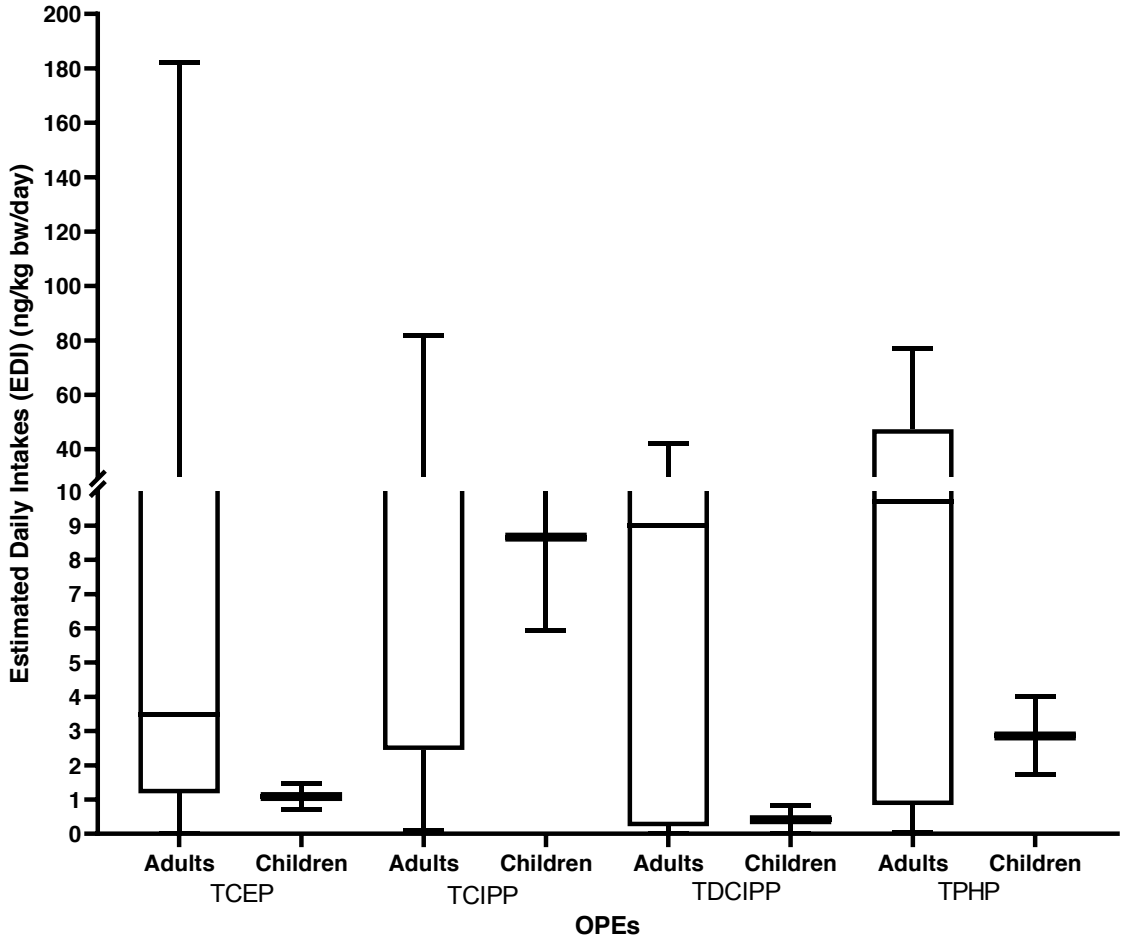
OPEs enter the human diet primarily via two routes. First, via bioaccumulation into plants and animals from contaminated air, soil, water, animal diet etc. Second, foodstuffs can be contaminated by OPEs during production, industrial processing (e.g., packing, canning, and drying) and storage, due to 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 ΣOPEs 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 ΣOPE 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 ΣOPEs 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.



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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

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 (∑exposure pathways)	Adults Toddlers	44.2 111	59.3 227	28.7 226	45.9 408	6.93 14.6	28.1 70.1	48.4 9.07	21.1 230
Total Carcinogenic risk (TCR)	Adults Toddlers	$9.72x10^{-7}$ $2.44x10^{-6}$	- -	- -	- -	$6.24x10^{-8}$ $1.31x10^{-7}$	- -	$1.55x10^{-7}$ $2.90x10^{-8}$	- -
RfD values (ng.kg bw^{-1}. day^{-1})	-	7000 [a]	10000 [a]	20000 [a]	-	10000 [a]	-	100000 [a]	-
SFO ((ng/kg bw/day)$^{-1}$)	-	$2x10^{-8}$ [b]	-	-	-	$9x10^{-9}$ [b]	-	$3.2x10^{-9}$ [b]	-

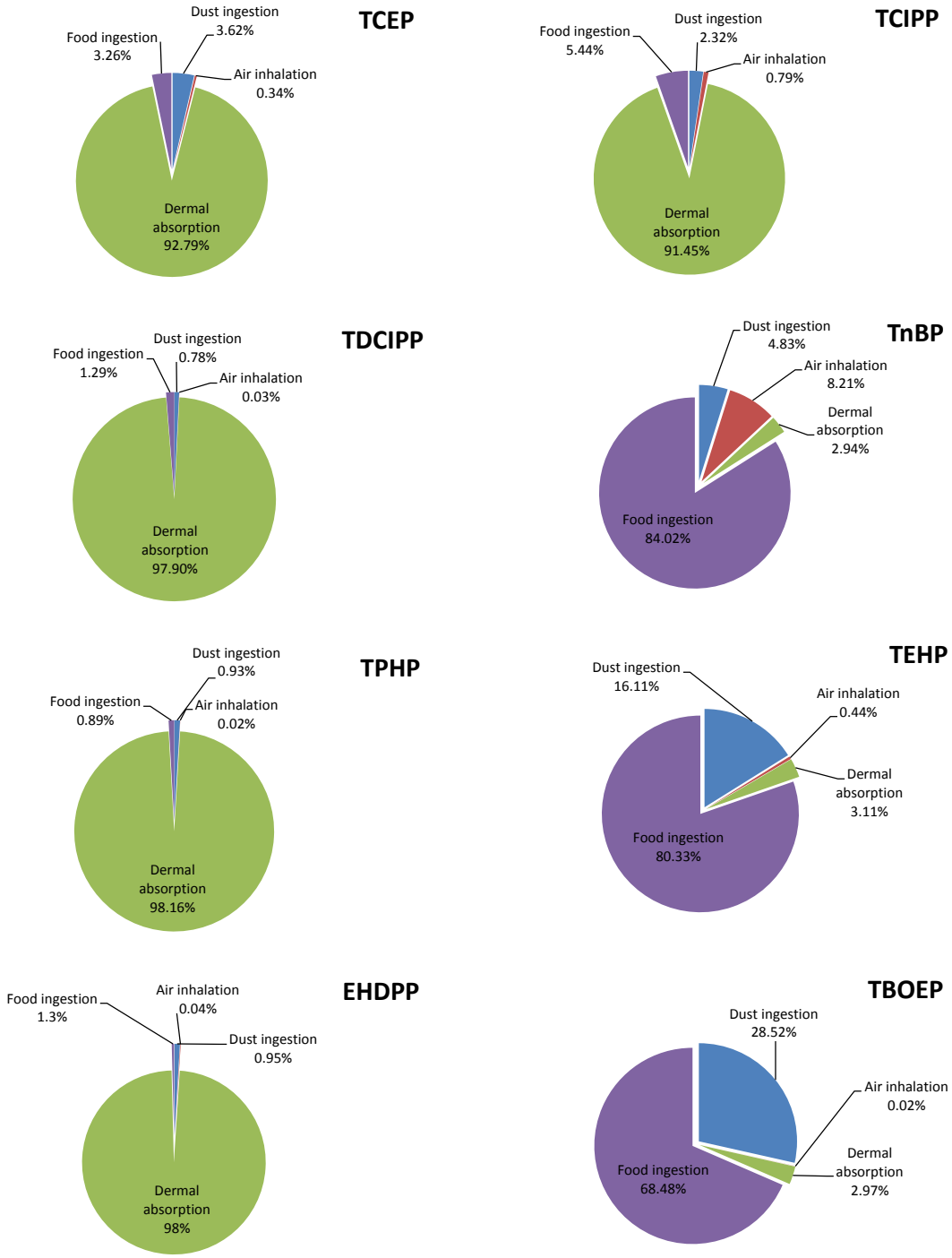
[a] Reference dose (RfD) values of USEPA (2017).
[b] Oral cancer slope factor (SFO) values (USEPA, 2017; Li et al., 2018)

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

Consequently, the contributions made by different exposure pathways will vary considerably 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 $bw^{-1}.day^{-1}$, 84 %), TBOEP (47 ng.kg $bw^{-1}.day^{-1}$, 67 %), and TEHP (7.2
410 ng.kg $bw^{-1}.day^{-1}$, 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

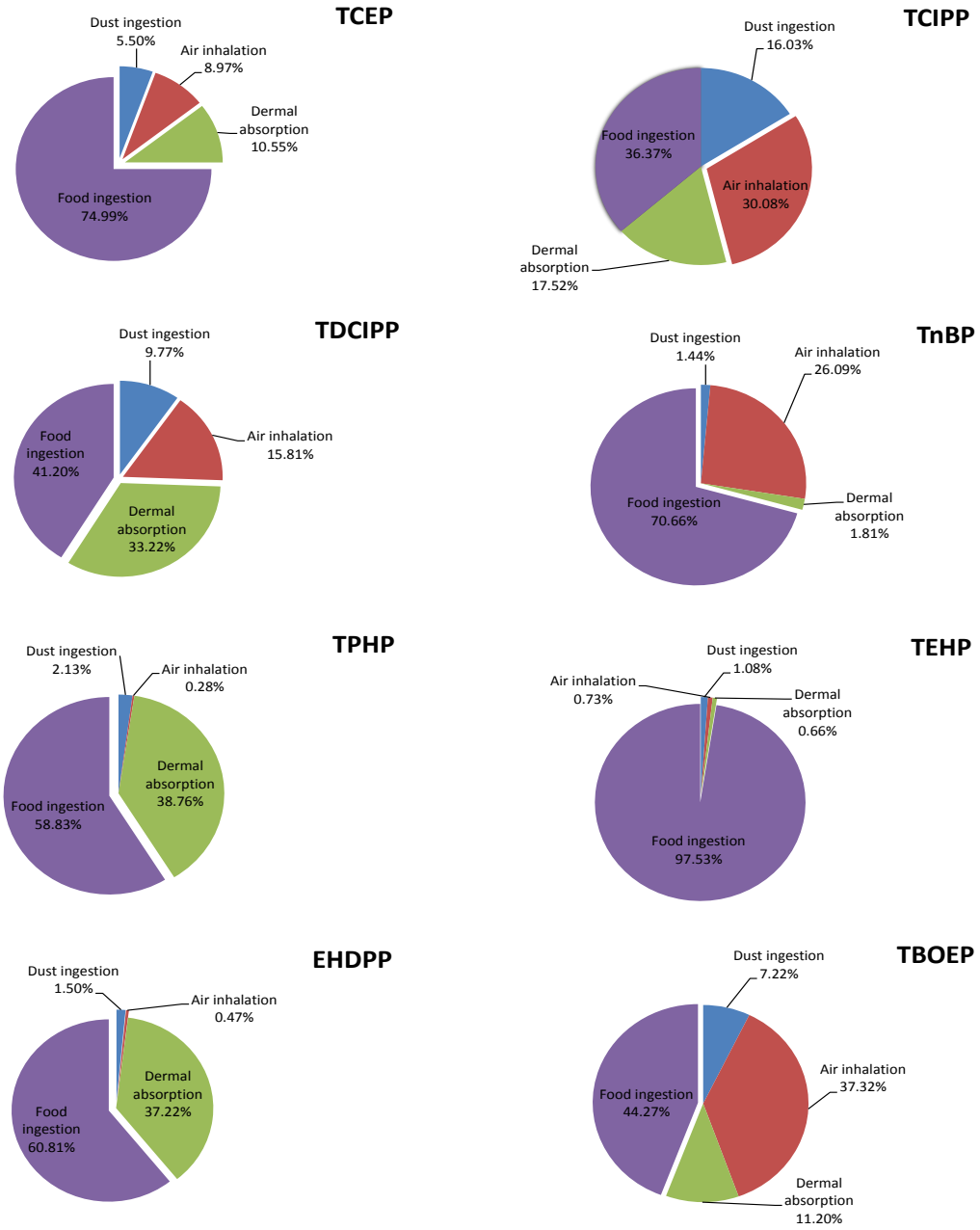
417 For adults, food ingestion appears the main human exposure pathway for all eight OPEs

418 evaluated, contributing 32.2 ng.kg bw^{-1}. day^{-1} and 75% Σexposure for TCEP, 21.3 ng.kg bw^{-1}.

419 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%

420 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

421 ng.kg bw^{-1}. day^{-1}, 61% for EHDPP, and 12.7 ng.kg bw^{-1}.day^{-1}, 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

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 (ng.kg $bw^{-1}.day^{-1}$) values for OPEs were compared with the oral reference dose (RfD ng.kg $bw^{-1}.day^{-1}$) 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 $1x10^{-6}$ (Ding et al., 2015). However, while toddler exposures to TnBP and TEHP also fell below a TCR of $1x10^{-6}$; for TCEP, the TCR $2.44x10^{-6}$ 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.

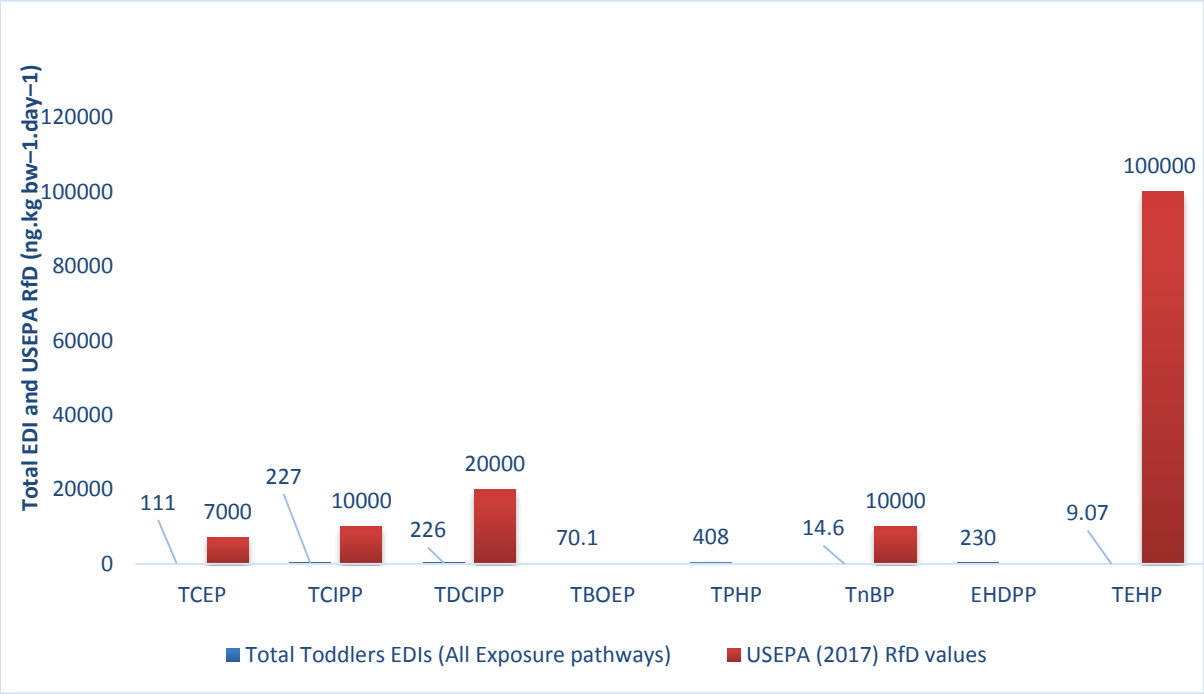


Fig 10: Comparison of average estimated daily intake (EDI) values via all exposure pathways for selected OPEs for toddlers with the corresponding reference doses (RfDs ng.kg $bw^{-1}.day^{-1}$) adopted from USEPA (2017)

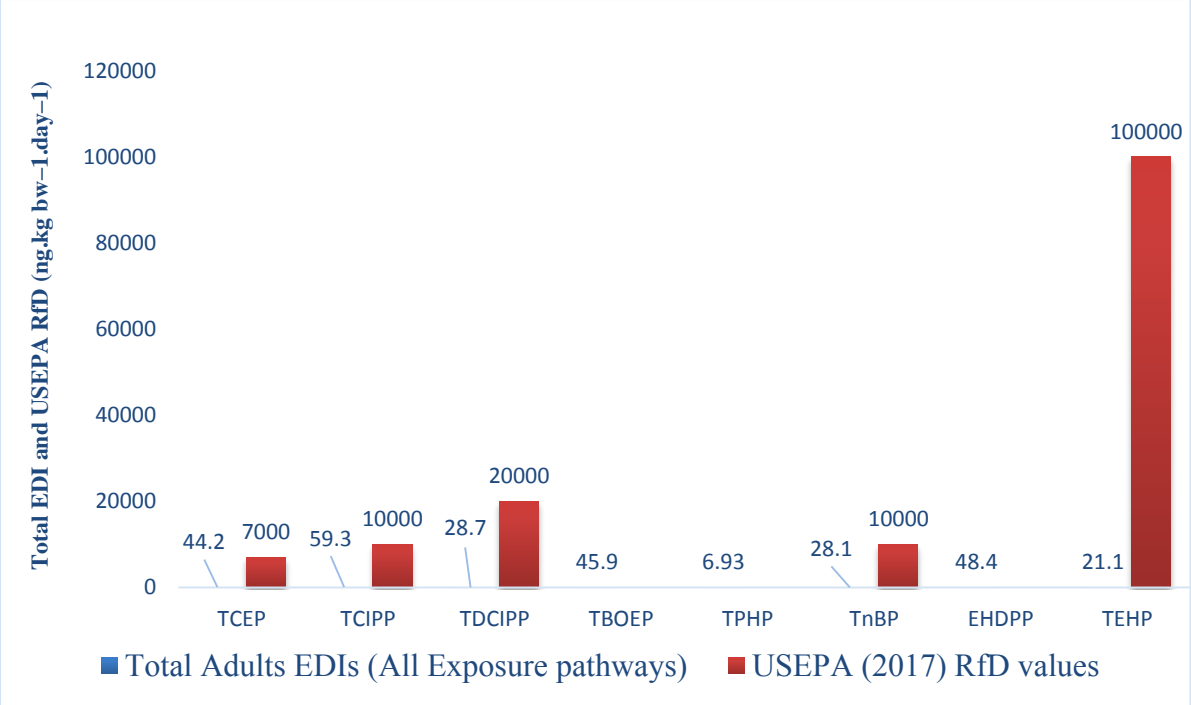


Fig 11: Comparison of average estimated daily intake (EDI) values via all exposure pathways for selected OPEs for adults with the corresponding reference doses (RfDs ng.kg bw^{-1}.day^{-1}) adopted from (USEPA, 2017; Li et al., 2018)

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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