Science of the Total Environment 686 (2019) 1113–1119

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Isopropylated and *tert*-butylated triarylphosphate isomers in house dust from South China and Midwestern United States

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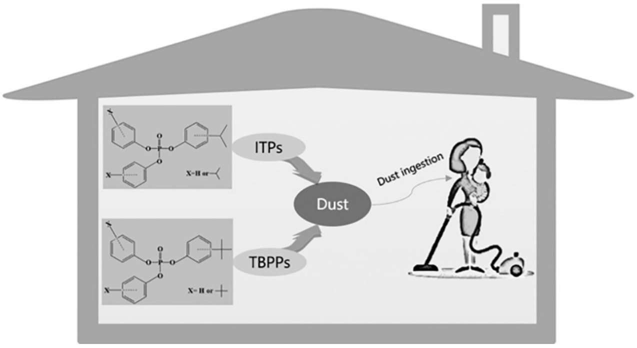
HIGHLIGHTS

- Isopropylated and *tert*-butylated triarylphosphate ester (ITP and TBPP) isomers were detected in house dust.
- High detection frequencies suggest broad applications of ITP and TBPP isomers in household products.
- The profiles of ITP or TBPP isomers were dominated by 2IPPDPP and 4tBPDPP, respectively.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 16 March 2019
Received in revised form 17 May 2019
Accepted 3 June 2019
Available online xxxx

Editor: Adrian Covaci

Keywords:
Isopropylated triarylphosphate esters
tert-butylated triarylphosphate esters
Organophosphate esters
House dust
Daily intake

ABSTRACT

In the present study we determined the concentrations and compositions of a suite of isopropylated and *tert*-butylated triarylphosphate ester (ITP and TBPP) isomers in house dust from the city of Guangzhou located in South China and the city of Carbondale in Midwestern United States. These two groups of organophosphate esters (OPE) are structurally analogous to triphenyl phosphate (TPHP), but have rarely been investigated for environmental occurrences and human exposure risks. The majority of target ITP and TBPP isomers were 100% detected in house dust from the two locations. Median concentrations of ΣITPs (including all ITP isomers) and ΣTBPPs (including all TBPP isomers) were 63.4 ng/g (range: 16.0–500 ng/g) and 35.4 ng/g (8.1–198 ng/g) in South China house dust, respectively, compared with 476 ng/g (140–1610 ng/g) for ΣITPs and 81.3 ng/g (35.2–800 ng/g) for ΣTBPPs in Midwestern U.S. dust. The profiles of ITP or TBPP isomers were similar between the two locations and were dominated by 2-isopropylphenyl diphenyl phosphate (2IPPDPP) and 4-*tert*-butylphenyl diphenyl phosphate (4tBPDPP), respectively. Although the levels of ΣITPs and ΣTBPPs were generally one order of magnitude lower than those of TPHP in the same dust samples, the broad occurrences of most of these isomers in house dust from the two locations likely suggest their wide applications in household consumer products. Estimated intakes of ΣITPs and ΣTBPPs via dust ingestion were generally three orders of magnitude lower than the reference dose proposed for TPHP. However, these emerging OPE chemicals merit continuous environmental surveillance, given their possible applications as specific commercial mixtures or as components/impurities in other flame retardant/plasticizer mixtures.

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https://doi.org/10.1016/j.scitotenv.2019.06.055
0048-9697/© 2019 Published by Elsevier B.V.

1. Introduction

Organophosphate esters (OPEs) represent a group of halogenated or non-halogenated, tri-ester based chemicals. They are widely applied in commercial products as plasticizers, flame retardants, stabilizers, or antifoaming and wetting agents (Reemtsma et al., 2008; van der Veen and de Boer, 2012). To date >20 OPEs have been found in commercial applications or as impurities in commercial OPE mixtures. Some of them, such as triphenyl phosphate (TPHP), tris(2-chloroethyl) phosphate (TCEP), tris(1-chloro-2-propyl) phosphate (TCIPP), and tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), have been ubiquitously found in various environmental compartments (e.g., water, air, dust, and sediment), demonstrating their global occurrence and distributions (van der Veen and de Boer, 2012). In vitro and in vivo studies reported a variety of toxic impacts following exposure to OPEs, including endocrine disruptive, developmental, neurological, and reproductive effects in experimental animals (Isales et al., 2015; Noyes et al., 2015; Preston et al., 2017; Schang et al., 2016; Slotkin et al., 2017).

As one of the representative triaryl OPEs, TPHP has been commercially used as one of the most effective flame retardants in many polymers, the total consumption of TPHP in the United States (U.S.) in 2006 was 4500–22,700 tones and 20,000–30,000 tones in Europe in 2000 (van der Veen and de Boer, 2012). Large amounts of applications have resulted in TPHP distributions in global environment, raising substantial environmental and health concerns. A number of TPHP-related OPEs, such as bisphenol A bis(diphenyl phosphate) (BPA-BDPP) and resorcinol-bis(diphenyl) phosphate (RDP), have been suspected as potential TPHP replacements for commercial use (van der Veen and de Boer, 2012).

Recently a suite of isopropylated and *tert*-butylated triarylphosphate ester isomers (referred to as ITPs and TBPPs), all structurally resembling that of TPHP, were identified in flame retardant mixtures and technical OPE mixtures (Fig. 1). Isomers of ITPs were found in flame retardant mixture Firemaster (FM) 550 (Chemtura Corporation, Vermont, U.S.) and an ITP mixture (Jinan Great Chemical Industry Corporation, Ltd., Shandong, China) (Phillips et al., 2017; Stapleton et al., 2012). These isomers include 2-isopropylphenyl diphenyl phosphate (2IPPDPP), 3-isopropylphenyl diphenyl phosphate (3IPPDPP), 4-isopropylphenyl diphenyl phosphate (4IPPDPP), 2,4-diisopropylphenyl diphenyl phosphate (24DIPPDPP), bis(2-isopropylphenyl) phenyl phosphate (B2IPPPP), bis(3-isopropylphenyl) phenyl phosphate (B3IPPPP), bis(4-isopropylphenyl) phenyl phosphate (B4IPPPP), bis(2,4-diisopropylphenyl) phenyl phosphate (B24DIPPPP), tris(3-isopropylphenyl) phosphate (T3IPPP), and tris(4-isopropylphenyl) phosphate (T4IPPP). TBPP isomers were identified in Firemaster 600 (FM 600)-treated foam (obtained from a North Carolina foam manufacturer) (Phillips et al., 2017), which include 4-*tert*-butylphenyl diphenyl phosphate (4tBPDPP), bis(4-*tert*-butylphenyl) phenyl phosphate (B4tBPPP), and tris(4-*tert*-butylphenyl) phosphate (T4tBPP). Environmental relevance of some of these ITP and TBPP isomers was also demonstrated as they were detected in a National Institute of Standards and Technology house dust standard reference material, SRM 2585, which was collected from homes, cleaning services, hotels, and motels in several states of the U.S. during 1993 and 1994 (Phillips et al., 2017). Metabolites of ITPs and TBPPs have been reported in very limited studies, such as Phillips et al. (2018), Carignan et al. (2017), and Doherty et al. (2019). The latter two studies revealed associations between urinary isopropylphenyl phenyl phosphate (ip-PPP; a metabolite of ITP) and adverse health outcomes in humans, such as cognitive development in young children and pregnancy outcomes (e.g., implantation and live birth) among women undergoing in vitro fertilization (IVF).

House dust has been considered as an important exposure source of indoor chemicals to humans. Human exposure to dust-associated chemicals may occur through inhalation, ingestion, or dermal contact (Whitehead et al., 2011). Numerous studies have reported the presence of OPEs in house dust and estimated the associated human exposure risks (Ali et al., 2016; Brommer and Harrad, 2015; Cao et al., 2014; Cequier et al., 2014; Cristale et al., 2016; Kademoglou et al., 2017). Human studies also revealed significant associations between dust concentrations of selected OPEs and their urinary metabolites (Carignan et al., 2013; Cequier et al., 2015; Hoffman et al., 2015; Larsson et al., 2018; Phillips et al., 2018). However, very few studies have been conducted to investigate environmental occurrences of these various ITP and TBPP isomers, particularly in indoor environments. In the present study, we investigated these emerging OPE chemicals in house dust from South China and Midwestern U.S. The main objectives were to determine and compare their levels and compositions in house dust from the two different regions, and explore their relationships with other legacy and emerging OPEs that have received much more attention. Our data will contribute to a more comprehensive understanding of OPE contamination in indoor environments and potential human exposure risks.

2. Materials and methods

2.1. Chemicals and reagents

Reference standards of 14 ITP and TBPP isomers (Table S1), including 2IPPDPP, 4IPPDPP, 24DIPPDPP, B2IPPPP, B4IPPPP, B24DIPPPP, tris(2-isopropylphenyl) phosphate (T2IPPP), T3IPPP, T4IPPP, 2-*tert*-butylphenyl diphenyl phosphate (2tBPDPP), 4tBPDPP, bis(2-*tert*-butylphenyl) phenyl phosphate (B2tBPPP), B4tBPPP, and T4tBPP, were purchased from Wellington Laboratories (Guelph, ON, Canada). Isotopically labelled TPHP, including d_{15}-TPHP and $^{13}C_{18}$-TPHP, were used as the surrogate and internal standard, respectively, and were purchased from Wellington Laboratories. High performance liquid chromatography (HPLC) solvents (Optima grade) were purchased from Fisher Scientific (Hanover Park, IL).

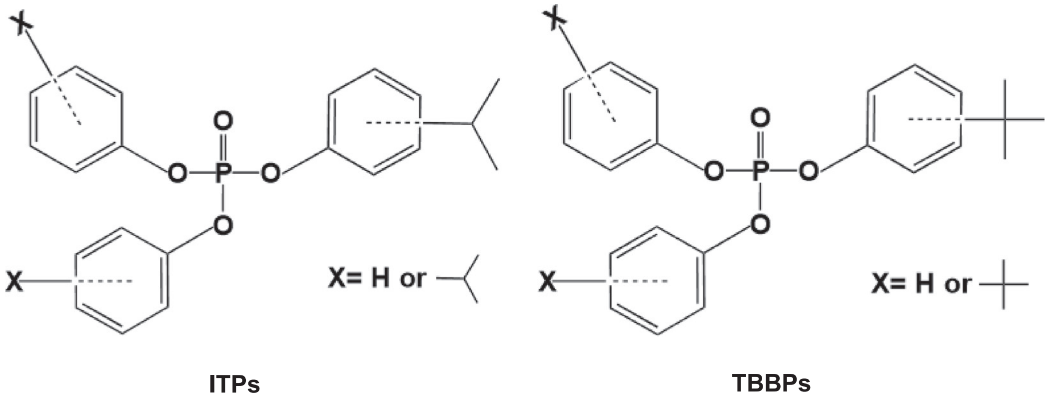

Fig. 1. General structures of isopropylated and *tert*-butylated triarylphosphate ester (ITP and TBPP) isomers.

2.2. Sample collection

House dust was collected during 2015 and 2016 from 30 homes in the city of Guangzhou, South China and 17 homes in the city of Carbondale, Illinois (U.S.) following the procedure described previously (Tan et al., 2018). In brief, a customized, pre-cleaned nylon bag with a pore size of approximately 25 μm was connected to the floor attachment of a commercial vacuum cleaner (Electrolux, ZMO1511, 1400 W) (Peng et al., 2017; Tan et al., 2018). After vacuuming living room and bedroom floors, the nylon bag was detached, wrapped with clean aluminum foil, and kept in a cooler for transportation. Pre-cleaned sodium sulfate was used as field blanks, which was vacuumed and prepared in the same way as for dust collection. A field blank was prepared for every five homes. Dust and sodium sulfate were removed from the nylon bag and sieved through a 125-μm stainless cloth sieve (Hogentogler & Co., Inc., Columbia, MD, U.S.). Sieved dust and field blanks were stored at −20 °C prior to chemical analysis.

2.3. Chemical analysis

Sieved dust (approximately 20 mg–50 mg) was spiked with d_{15}-TPHP and sonicated in 5 mL of a mixture of hexane and dichloromethane (1:1, *v*/v) for 10 min. The extraction was repeated twice. The combined extract was concentrated and cleaned through a Florisil solid-phase extraction cartridge. After the cartridge was pre-rinsed in sequence with 8 mL methanol, 10 mL dichloromethane and 10 mL hexane, it was loaded with the combined extract and washed with 4 mL hexane (discarded). Target analytes were eluted out with 16 mL hexane and then 25 mL ethyl acetate. The final extract was concentrated to approximately 200 μL and spiked with $^{13}C_{18}$-TPHP prior to instrumental analysis.

Determination of ITP and TBPP isomers was conducted using a HPLC (Shimadzu LC-30A) coupled to a triple quadrupole mass spectrometer (AB Sciex 5500 Q Trap, Toronto, Canada), which was equipped with a TurboIonSpray® electrospray ionization (ESI) probe operated in the multiple reaction monitoring (MRM) mode (Table S1). The HPLC was equipped with a C18 column (2.1 mm × 100 mm, 5 μm particle size, 100 Å; Kinetex® EVO, Phenomenex, Torrance, CA, U.S.). The mobile phase consisted of water (A) and methanol (B), each containing 0.1% formic acid (*v*/v). A flow rate of 0.2 mL/min was used. The gradient was programmed as: 5% B ramped to 40% B within 2 min (linear); ramped to 100% B in 15 min (linear, held for 6 min); followed by a linear change to 5% B in 1 min (held for 4 min).

Identification and quantification of TPHP and other OPEs was conducted following the analytical procedures described by Tan et al. (2019) and their concentrations are listed in Supplementary data (Table S2). These concentration data were used for correlative analyses with ITPs and TBPPs.

2.4. Quality assurance/control and data analysis

Target ITP and TBPP isomers (50 ng each) were spiked with six replicates of a dust composite prepared by pooling dust from multiple homes. These replicates, as well as two matrix blanks (i.e., dust composite without spiking target analytes), were processed with the same analytical procedures described above. Recoveries (mean ± standard deviation) of spiked ITP and TBPP isomers, after subtracting the original values in dust composite, ranged from 50 ± 8.8% to 90 ± 7.2% in the six replicates, except for T4IPPP and B4tBPPP which exhibited lower recoveries (i.e., 46.3 ± 18% and 40.3 ± 7.0%, respectively). A procedural blank (pre-cleaned sodium sulfate) was processed along with every five dust samples. Only 2IPPDPP and 4tBPDPP were detected in procedural blanks and field blanks, but with concentrations generally below their limits of quantification (LOQs). The SRM 2585 was also analyzed in three replicates following the same analytical procedures, which exhibited results for most ITP or TBPP isomers comparable to the data reported by Phillips et al. (2017) (Table S3).

An analyte with a response below the instrumental detection limit (IDL; a response three times the standard deviation of the noise) was considered non-detectable (nd). The LOQ of each chemical, defined as an analyte response 10 times the standard deviation of the noise, ranged from 0.2 to 2.3 ng/g dry weight or dw (Table S1). Reported levels of ITP and TBPP isomers (ng/g) were adjusted based on the recovery of d_{15}-TPHP after subtracting blank contamination wherever applicable. A half LOQ was assigned to the measurements below LOQ if an analyte exhibited a detection frequency (DF) >60% and its geometric standard deviation greater than three. Otherwise, a LOQ/√2 was assigned (Liu et al., 2017). Prior to statistical analyses, concentration data were logarithmically transformed to approximate a normal distribution. Relationships between individual chemicals were examined via Spearman's correlation analyses (PASW Statistics 18.0, IBM Inc.). The level of significance was set at $\alpha = 0.05$.

2.5. Exposure assessment

Daily intake of OPEs via indoor dust ingestion was estimated using the equation below (Abdallah and Covaci, 2014; He et al., 2016):

$$E_{DI} = \frac{DIR \times C \times IEF}{BW} \quad (1)$$

where E_{DI} is the estimated daily intake (ng/kg body weight/day), *DIR* is the dust ingestion rate (g/day), *C* is the concentration of ITP or TBPP isomers in house dust (ng/g), *IEF* represents the hours spent in homes daily (i.e., indoor exposure fraction), and *BW* is body weight (kg).

3. Results and discussion

3.1. Concentrations and compositions of ITPs and TBPP isomers in house dust

Most target ITP isomers were 100% detected in house dust from both China and Midwestern U.S. (Table 1). The exceptions were T4IPPP which was detected in 0% and 50% of the dust samples from the two regions, respectively, while B4IPPPP was detected in <50% of South China dust samples and T2IPPP in <80% of samples from Midwestern U.S. These data demonstrate broad occurrence of ITP isomers in indoor environments. Concentrations of ΣITPs (including all ITP isomers) ranged from 16.0 to 500 ng/g (median: 63.4 ng/g) in South China house dust,

Table 1

Concentrations (ng/g) of isopropylated and *tert*-butylated triarylphosphate ester (ITP and TBPP) isomers in South China and Midwestern U.S. house dust.

	South China ($n = 30$)			Midwestern U.S. ($n = 17$)		
	% Detect	Median	Range	% Detect	Median	Range
2IPPDPP	100%	28.6	6.1–327	100%	184	65.7–728
4IPPDPP	100%	9	2.2–80.2	100%	95.9	30.1–475
24DIPPDPP	100%	8.7	2.4–81.7	100%	83.6	23.5–223
B2IPPPP	100%	5.9	1.9–42.2	100%	34	7.2–93.3
B4IPPPP	46%	2.5	nd-6.8	100%	13.7	2.6–42.9
B24DIPPPP	100%	1.6	0.5–6.7	100%	20	4.1–56.6
T2IPPP	100%	7.9	1.7–64.3	78%	33.7	nd-108
T3IPPP	100%	4.3	1.0–23.8	100%	26.8	6.5–108
T4IPPP	0%	nd[a]	nd	50%	0.8	nd-1.6
∑ITPs		63.4	16.0–500		476	140–1610
2tBPDPP	0%	nd	nd	72%	1.1	nd-18.0
4tBPDPP	100%	23.3	6.5–170	100%	59.2	23.3–619
B2tBPPP	0%	nd	nd	61%	0.9	nd-2.6
B4tBPPP	100%	12.5	2.79–45.8	100%	10.6	4.2–127
T4tBPP	100%	1.3	0.3–15.4	100%	3.3	1.2–53.6
∑TBPPs		35.4	8.1–198		81.3	35.2–800

[a] nd = non-detectable.

approximately one order of magnitude lower than those in Midwestern U.S. dust (140–1610 ng/g; median: 476 ng/g) (Table 1). However, the composition profiles of ITP isomers appeared to be similar between the two regions, which were dominated by 2IPPDPP (42% and 38% of the ΣITP concentrations, respectively), followed by 4IPPDPP, 24DIPPDPP, and other isomers (Fig. 2). This pattern is very similar to the composition profiles in house dust SRM 2585 and FM 550 mixture (Phillips et al., 2017), as well as in a technical ITP mixture obtained from a Chinese manufacturer (Jinan Great Chemical Industry Corporation, Ltd.) (Fig. 2). It has been reported that 2IPPDPP is the most abundant ITP isomer in the technical ITP mixture, followed by B2IPPPP, 24DIPPDPP, and 4IPPDPP, while in the FM 550 product, 2IPPDPP and 24DIPPDPP have almost equal proportions by weight and are more abundant than any other ITP isomers (Phillips et al., 2017). Therefore, the dominance of 2IPPDPP over other ITP isomers in house dust is likely due to its relative abundance in technical mixtures and household consumer products where flame retardant or plasticizer mixtures are applied. However, information on their industrial sources and applications remains very limited.

Among the five TBPP isomers, 4tBPDPP, B4tBPPP and T4tBPP were detected in almost all house dust samples collected from South China and Midwestern U.S. The isomers 2tBPDPP and B2tBPPP were not detected in any South China samples, whereas their detection frequencies were 72% and 61% in U.S. samples, respectively (Table 1). The total concentrations of TBPP isomers (referred to as ΣTBPPs) were also significantly greater in Midwestern U.S. dust than in South China dust (median: 81.3 versus 35.4 ng/g; $p < 0.01$). In both regions, 4tBPDPP appeared to be the most abundant TBPP isomer, followed by B4tBPPP and T4tBPP, a pattern also observed in house dust SRM 2585 and a technical TBPP mixture (Fig. 2). By contrast, B4tBPPP and T4tBPP were found to be more abundant than 4tBPDPP in FM 600-treated foam (Phillips et al., 2017; Fig. 2). It is unknown whether TBPP isomers are also present in other flame retardant or plasticizer mixtures. However, it is likely that different technical TBPP or flame retardant/plasticizer mixtures could differ in the compositions of TBPP isomers.

To date very few studies have investigated environmental occurrences of ITP and TBPP isomers. A U.S. dust study investigated a relatively full list of ITP and TBPP isomers and reported geometric mean concentrations of ΣITPs and ΣTBPPs to be 190 and 580 ng/g, respectively (Phillips et al., 2018). Selected individual isomers have been screened in a limited number of indoor studies. For example, T2IPPP and T4tBPP were frequently detected (i.e. DF > 70%) in U.S., Canada, and New Zealand house dust, with a median concentration of 52.4, 20.4, and 11.9 ng/g for T2IPPP and 41.8, 4.9, and 6.5 ng/g for T4tBPP, respectively (Vykoukalova et al., 2017). In South China house dust, T2IPPP was reported with a median concentration of 60 ng/g (Tan et al., 2017). Overall, data on the environmental occurrences of ITP and TBPP isomers remain extremely limited compared with numerous studies on TPHP and other major OPE chemicals.

3.2. Relationships with other OPEs in house dust

As structural analogues to TPHP, ITPs and TBPPs exhibited concentrations generally one order of magnitude lower than those of TPHP (median: 608 ng/g) in the same South China house dust and 1–2 orders of magnitude lower in Midwestern U.S. dust (median TPHP concentration: 1580 ng/g) (Tan et al., 2019). Nevertheless, the combined concentrations of ITP and TBPP isomers (median: 128 ng/g) surpassed those of selected OPEs such as tributyl phosphate (TNBP), cresyl diphenyl phosphate (CDP), and resorcinol bis(diphenyl phosphate) (RDP) (median

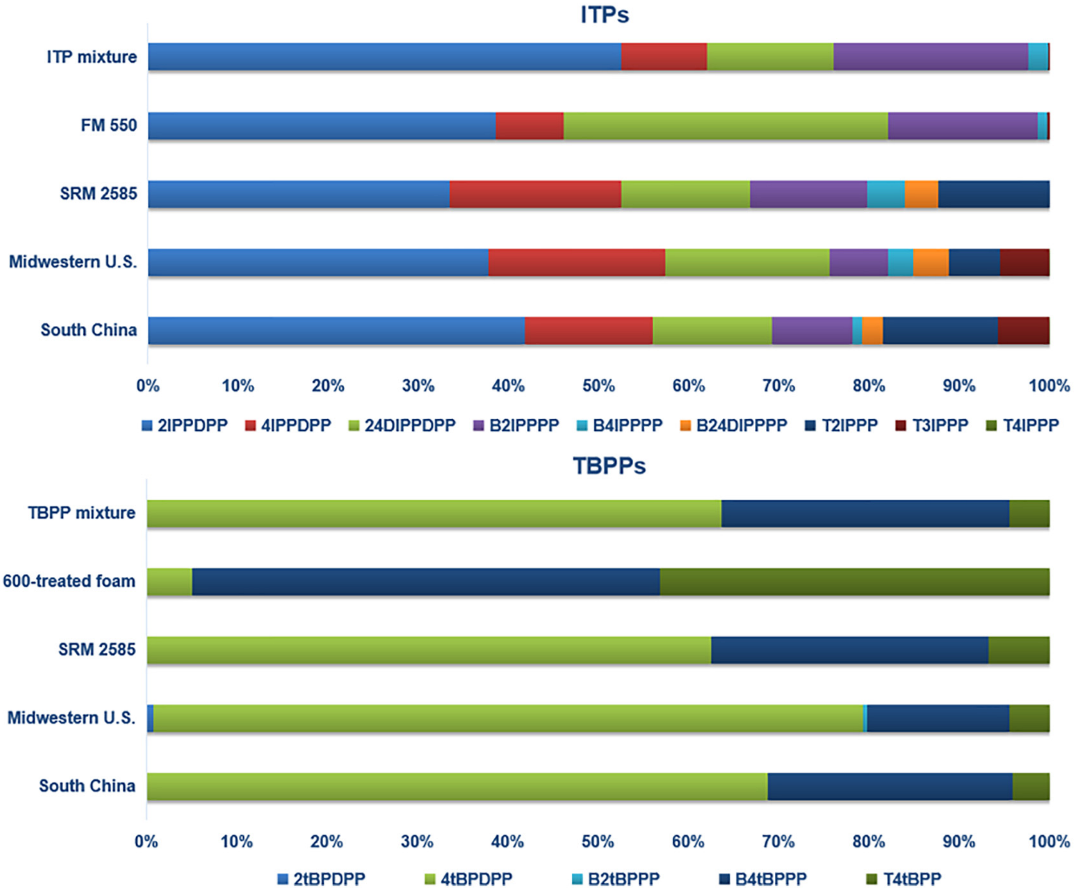

Fig. 2. Mean compositions of ITP and TBPP isomers in house dust from South China and Midwestern Unites States. Compositions of these isomers in Firemaster 550, Firemaster 600, and house dust standard reference material, SRM 2585, which are cited from Phillips et al. (2017), are also presented for comparison.

concentrations ranging from 40 to 164 ng/g) in South China house dust (Table S2). In Midwestern U.S. dust, the total concentrations of ITP and TBPP isomers (median: 770 ng/g) even surpassed eight traditional and emerging OPEs, including TCEP, tris(2-ethylhexyl) phosphate (TEHP), tricreseyl phosphate (TMPP), TNBP, bisphenol A bis(diphenyl phosphate) (BPA-BDPP), CDP, isodecyl diphenyl phosphate (IDDPP), and RDP (median range: 90–673 ng/g; Table S2).

Correlative analyses reveal region-specific relationships between ΣITPs or ΣTBPPs and other OPEs detected in the same dust (Table 2, Fig. S1). In South China dust, concentrations of ΣITPs exhibited significant correlations with those of TPHP ($p < 0.05$), EHDPHP ($p < 0.01$), and TEHP ($p < 0.01$), while significant correlations were also observed between ΣTBPPs with TMPP ($p < 0.001$) or BPA-BDPP ($p < 0.001$). By contrast, in Midwestern U.S. dust, significant correlations were only observed between ΣITPs and TNBP ($p < 0.05$) and between ΣTBPPs and TMPP ($p < 0.05$) and BPA-BDPP ($p < 0.01$).

The different inter-chemical relationship patterns between South China and Midwestern U.S. dust may be attributed to region-specific applications of different mixtures. These mixtures may differ in formulations and application purposes. It is likely that ITP or TBPP isomers could have been produced as independent formulations or exist as impurities or minor components in other commercial mixtures. For example, in the flame retardant mixture FM 550 produced by Chemtura (U.S.), ITP isomers in total contributed to an average of 31.9% (by weight) of the mixture, while TPHP, 2-ethylhexyltetrabromobenzoate (EH-TBB), and bis(2-ethylhexyl)-3,4,5,6-tetrabromo-phthalate (BEH-TEBP) constituted approximately 29.7%, 13.9%, and 19.8%, respectively (Phillips et al., 2017). By contrast, ITP isomers constituted approximately 98% by weight of an ITP mixture produced by Jinan Great Chemical Industry Corporation (China) (Phillips et al., 2017). Similarly, while TBPP isomers constituted approximately 80% of a TBPP mixture produced by a European manufacture (Ubichem, Worcestershire, United Kingdom), their compositions in total constituted approximately 51% in the flame retardant mixture FM 600-treated foam obtained from a North Carolina (U.S.) manufacturer, where the percentages of EH-TBB, BEH-TEBP, and TPHP were 25.0%, 16.3%, and 1.7% by weight, respectively (Phillips et al., 2017). These data suggest that the commercial mixtures of ITPs and TBPPs produced by various manufacturers may differ in formulations. Available information indicates that ITP or TBPP isomers are present as components in a few commercial mixtures, such as Reofos 35, 60, 65, and 95 (Great Lakes Solutions, Vermont, U.S.), Durad 110, 150, 220, and 300 (Lanxess Energizing Chemistry, Connecticut, U.S.), and Phosflex 71B (ICL Industrial Products, Beer Sheva, Israel), as summarized in Phillips et al. (2017). However, information on their contemporary applications in general and region-specific applications in particular remains overall limited. Therefore, continuous environmental surveillance is warranted for a better characterization of their sources and contamination patterns.

3.3. Environmental and health implications

Daily intakes of ITPs and TBPPs via dust ingestion were estimated for adults and toddlers from the two studied regions (Table 3). The estimations were based on Eq. (1), by assuming an average and high dust

Table 2

Correlation coefficients among OPEs, ITPs and TBPPs in house dust from South China and Midwestern U.S.

	TBOEP	TCEP	TCIPP	TDCIPP	TEHP	TMPP	TNBP	TPHP	EHDPHP	BPA-BDPP	CDP	IDDPP	RDP	ITPs	TBPPs
South China															
TBOEP	1.00														
TCEP	−0.06	1.00													
TCIPP	0.10	0.16	1.00												
TDCIPP	−0.08	0.38^{*}	0.09	1.00											
TEHP	0.37^{*}	0.05	0.14	−0.23	1.00										
TMPP	−0.04	0.03	0.01	0.12	$0.53^{\dagger}$	1.00									
TNBP	0.22	−0.14	0.19	0.11	0.02	−0.25	1.00								
TPHP	0.06	0.18	0.04	0.09	$0.41^{\#}$	0.36^{*}	0.13	1.00							
EHDPHP	0.13	0.14	0.38^{*}	0.08	$0.57^{\dagger}$	0.19	$0.45^{\#}$	$0.48^{\dagger}$	1.00						
BPA-BDPP	0.32^{*}	0.09	−0.01	0.29	0.35^{*}	$0.45^{\#}$	−0.11	0.15	0.12	1.00					
BPDPP	−0.02	0.17	0.08	0.22	0.17	$0.61^{\dagger}$	-0.32^{*}	0.05	0.04	0.33^{*}					
CDP	0.09	−0.08	0.05	−0.08	$0.40^{\#}$	0.24	−0.01	$0.43^{\#}$	0.35^{*}	−0.14	1.00				
IDDPP	−0.06	0.17	−0.30	0.09	0.17	0.35^{*}	−0.21	0.26	0.09	0.38^{*}	0.07	1.00			
RDP	0.23	−0.10	−0.14	0.10	0.08	0.12	0.35^{*}	0.35^{*}	0.09	0.23	0.06	0.02	1.00		
ITPs	0.21	−0.02	0.17	−0.05	$0.43^{\#}$	0.26	0.06	0.40^{*}	$0.42^{\#}$	0.06	0.27	0.08	0.26	1.00	
TBPPs	0.06	0.02	0.21	0.20	0.16	$0.54^{\dagger}$	−0.19	−0.04	0.13	0.35^{*}	0.01	0.20	0.00	0.03	1.00
Midwestern U.S.															
TBOEP	1.00														
TCEP	$0.75^{\dagger}$	1.00													
TCIPP	−0.06	0.04	1.00												
TDCIPP	0.13	0.01	0.08	1.00											
TEHP	0.25	0.11	-0.49^{*}	−0.40	1.00										
TMPP	−0.24	−0.37	0.10	0.36	−0.02	1.00									
TNBP	0.08	0.40	−0.15	−0.30	0.32	−0.07	1.00								
TPHP	−0.10	0.34	0.26	−0.35	−0.16	−0.19	0.49^{*}	1.00							
EHDPHP	−0.06	0.07	−0.23	−0.26	0.36	0.33	0.45	0.20	1.00						
BPA-BDPP	0.16	0.02	−0.41	0.03	0.56^{*}	0.36	−0.20	−0.34	0.29	1.00					
BPDPP	0.10	0.27	−0.11	0.10	0.41	0.31	0.24	0.10	0.37	0.44					
CDP	0.07	−0.15	0.36	−0.15	−0.15	0.28	−0.29	0.07	0.10	0.24	1.00				
IDDPP	0.02	−0.08	−0.13	−0.34	0.45	0.04	0.18	−0.20	0.15	0.37	0.37	1.00			
RDP	0.11	0.02	0.11	0.14	0.07	−0.18	−0.14	−0.15	−0.43	0.15	0.30	0.28	1.00		
ITPs	0.30	0.26	0.16	0.35	−0.30	0.03	-0.58^{*}	−0.17	−0.36	0.11	0.15	−0.24	0.10	1.00	
TBPPs	0.24	0.20	0.12	0.38	0.10	0.49^{*}	0.27	0.13	0.11	0.10	−0.12	−0.35	−0.16	0.09	1.00

TBOEP = tris (2-butoxyethyl) phosphate; TCEP = tris(2-chloroethyl) phosphate; TCIPP = tris (2-chloroisopropyl) phosphate; TDCIPP = tris(1,3-dichloro-2-propyl) phosphate; TEHP = tris(2-ethylhexyl) phosphate; TMPP = tricresyl phosphate; TNBP = tributyl phosphate; TPHP = triphenyl phosphate; EHDPP = 2-ethylhexyl-diphenyl phosphate; BPA-BDPP = bisphenol A bis(diphenyl phosphate); CDP = cresyl diphenyl phosphate; IDDPP = isodecyl diphenyl phosphate; RDP = resorcinol bis(diphenyl phosphate).

[*] $p < 0.05$.

[#] $p < 0.01$.

[†] $p < 0.001$.

ingestion rate (DIR) to be 50 and 200 mg/day for toddlers and 20 and 50 mg/day for adults, respectively (Abdallah and Covaci, 2014; Ali et al., 2013). Information on the body weights and indoor exposure fractions was cited from Tan et al. (2019) and described in Table S4. We estimated the median daily intake of ITPs and TBPPs by South China toddlers to be 0.3 and 0.2 ng/kg bw/day under the average exposure scenarios and 1.1 and 0.6 ng/kg bw/day under the high exposure scenarios, respectively (Table 3). The median intake by Midwestern U.S. toddlers was approximately 1.6 ng/kg bw/day for ITPs and 0.3 ng/kg bw/day for TBPPs under the average exposure scenarios and 6.5 for ITPs and 1.1 for TBPPs under the high exposure scenarios, respectively. Compared with toddlers, the estimated intakes by adults are generally one order of magnitude lower (Table 3). Elevated exposure for toddlers versus adults is mainly attributed to higher dust ingestion rate and lower body weight for toddlers, as well as more time spent indoors for toddlers than adults.

The total intakes of ITPs and TBPPs are three orders of magnitude lower than the reference dose of TPHP (i.e. 7000 ng/kg bw/day) estimated from the lowest reported chronic non-observed-adverse-effect-level (NOAEL) divided by a safety factor of 10,000 (Bjornsdotter et al., 2018; Hartmann et al., 2004; Saito et al., 2007; van den Eede et al., 2011). However, it is premature to come to any conclusion on the potential health risks of ITPs and TBPPs due to limited knowledge on their sources, human exposure pathways, and toxic effects. Continuous monitoring of these TPHP analogues are warranted, considering the below environmental and health implications.

Although most of these ITP and TBPP isomers were not reported for their environmental occurrences until very recently, reports on their industrial applications can be traced back to the 1970s. Early reports indicate that in the 1970s ITPs have been developed as TMPP replacements and TBPP isomers have been used in hydraulic applications (Weil et al., 2006). Thus, these isomers could have already been employed in various industrial applications. Current data reveal their presence in flame retardant mixtures (e.g., FM 550 and FM 600) with considerable percentages (Phillips et al., 2017). It is possible that they are also present in other commercial flame retardant or plasticizer mixtures. The lack of environmental and toxicological data on these isomers may result in continuous usage in certain applications. Therefore, it merits future surveillance on their environmental occurrences and distributions.

Knowledge is extremely limited on the exposure pathways and toxicokinetic of ITP and TBPP isomers. Although our data indicate relatively low abundances of ITP and TBPP isomers in dust when compared with other major OPEs, other exposure pathways (e.g., dermal contact, inhalation, and dietary intake) in addition to dust ingestion may exist (Abdallah, 2016; Frederiksen et al., 2018). A better elucidation of exposure risks depends on more investigations of their possible sources, dietary and non-dietary pathways, and population-dependent exposure routes and rates. Metabolism of ITP and TBPP isomers was reported by (Phillips et al., 2018) which indicated that ITP isomers could be metabolized into diphenyl phosphate (DPHP, a main metabolite of TPHP) and ip-PPP, while TBPP isomers could be metabolized into DPHP and *tert*-butylphenyl phenyl phosphate (tb-PPP). Specific gravity (SG)-corrected concentrations of ip-PPP were determined to be 6.85 ng/mL (geometric mean) in urine from a U.S. children population, even surpassing the concentrations of any other OPE metabolites detected (Phillips et al., 2018). Urinary tb-PPP was determined to be 0.26 ng/mL in the same population. Urinary ip-PPP was also frequently detected in a North Carolina (U.S.) adult population, as well in paired New Jersey (U.S.) mother and children samples with a significant correlation (Butt et al., 2014; Hammel et al., 2016). Therefore, exposure to ITP and TBPP isomers not only contributes to DPHP levels in human bodies, but also substantially elevates the overall internal exposure to OPE metabolites.

Table 3
Estimated daily intake (EDI; ng/kg bw/day) of isopropylated and *tert*-butylated triarylphosphate ester (ITP and TBPP) isomers by toddlers and adults under different exposure scenarios.

	Toddler				Adult			
	Mean	Median	5th	95th	Mean	Median	5th	95th
South China (average dust ingestion[a])								
ITPs	0.5	0.3	0.1	1.3	0.02	0.01	0.01	0.06
TBPPs	0.3	0.2	0.05	0.8	0.01	0.01	0.01	0.04
South China (high dust ingestion[b])								
ITPs	1.8	1.1	0.6	5.1	0.06	0.03	0.02	0.2
TBPPs	1	0.6	0.2	3	0.03	0.02	0.01	0.1
Midwestern U.S. (average dust ingestion[a])								
ITPs	2.1	1.6	0.9	4.3	0.1	0.09	0.05	0.2
TBPPs	0.6	0.3	0.1	2.1	0.04	0.02	0.01	0.1
Midwestern U.S. (high dust ingestion[b])								
ITPs	8.5	6.5	3.7	17.1	0.3	0.2	0.1	0.6
TBPPs	2.5	1.1	0.5	8.2	0.1	0.04	0.02	0.3

[a] Assuming 50 mg/day for toddlers and 20 mg/day for adults (Abdallah and Covaci, 2014; Ali et al., 2013);

[b] Assuming 200 mg/day for toddlers and 50 mg/day for adults (Abdallah and Covaci, 2014; Ali et al., 2013).

Zebrafish (*Danio rerio*) exposure studies indicated that among a variety of OPEs (including TPHP) and brominated flame retardants, ITPs and tetrabromo-bisphenol A (TBBPA) exhibited the greatest number and variety of developmental malformations, such as yolk sac edema, pericardial edema, impaired touch-responses, and deformities of the trunk, snout, body axis, caudal fin, jaw, and pectoral fins (Noyes et al., 2015). In another study of evaluating a variety of OPEs and flame retardants, T4IPPP was also prioritized as the "highest priority" chemical, along with TPHP and 2-ethylhexyl diphenyl phosphate, in the induction of potential developmental neurotoxicity (Behl et al., 2015). Human studies suggest that ITP isomers may adversely affect cognitive development in young children, including fine motor skills and early language abilities, whereas this association was not observed for TPHP and several other OPEs (Doherty et al., 2019). Both urinary DPHP and ip-PPP concentrations were also reported to be negatively associated with the success for several IVF outcomes (Carignan et al., 2017). Therefore, ITP isomers could be more potent than TPHP or have different mechanisms of toxicity. Toxicokinetic of ITPs and TBPPs following uptake and the effects of metabolic modification on their toxicities require further investigations.

4. Conclusions

In the present study we determined the concentrations and compositions of ITP and TBPP isomers in house dust from South China and Midwestern U.S. To date, these two groups of OPE chemicals structurally analogous to TPHP have rarely been investigated for industrial applications, environmental occurrences, potential toxicities and toxicokinetic, and human exposure risks. Our results demonstrated broad occurrences of most of these isomers in house dust from the two regions, suggesting their wide applications in household consumer products. Although their levels were generally one to two orders of magnitude lower than TPHP in dust from both regions, the total concentrations of ITP and TBPP isomers surpassed many other traditional or emerging OPEs detected in the same dust. Estimated intakes of ΣITPs and ΣTBPPs via dust ingestion were both far below the reference dose for TPHP. However, these emerging OPE chemicals merit continuous environmental surveillance, given their possible applications as specific commercial mixtures or as components/impurities in other flame retardant/plasticizer mixtures, as well as considerable contributions to the total levels of OPE metabolites in human bodies.

Acknowledgement

The present study was financially supported by the Guangdong Innovative and Entrepreneurial Research Team Program (No. 2016ZT06N258) and the National Natural Science Foundation of China

(No. 21777059) and China Postdoctoral Science Foundation (No. 2018M633281). The authors thank the families voluntarily participating in our study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2019.06.055.

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