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Co-Existence of Organophosphate Di- and Tri-Esters in House Dust from South China and Midwestern United States: Implications for Human Exposure

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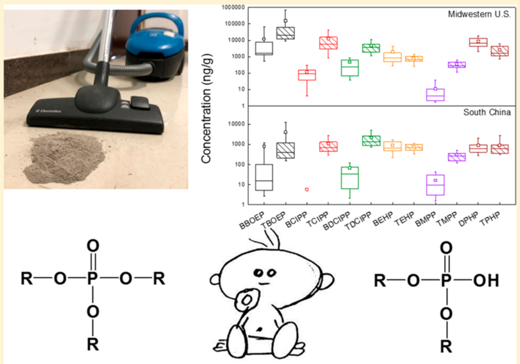
Supporting Information



ABSTRACT: Despite numerous studies on the contamination of organophosphate triesters (tri-OPEs) in indoor environments, organophosphate diesters (di-OPEs) have rarely been investigated. The present study aimed to investigate whether di-OPEs coexist with tri-OPEs in house dust collected from Guangzhou ($n = 30$), South China and the city of Carbondale ($n = 17$) located in the Midwestern United States (U.S.). Median concentrations of bis(2-butoxyethyl) phosphate (BBOEP), bis(1-chloro-2-propyl) phosphate (BCIPP), bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), bis(2-ethylhexyl) phosphate (BEHP), bis(2-methylphenyl phosphate) (BMPP), and diphenyl phosphate (DPHP) were determined to be 15.9, < LOQ, 33.6, 654, 9.5, and 605 ng/g in South China house dust, and 1580, 90.6, 234, 867, 4.0, and 6500 ng/g in Midwestern U.S. dust, respectively. The total concentrations of di-OPEs (referred to Σ_{di}OPEs) constituted an average of 22.9% and 21.3% of the total concentrations of tri-OPEs in dust from these two locations, respectively. Median concentration ratios of DPHP and BEHP to their respective tri-OPEs (i.e., TPHP and TEHP) were determined to be 1.1 and 1.0 in South China dust and 3.7 and 1.4 in Midwestern U.S. dust, respectively, indicating possible commercial applications for these two di-OPEs. Correlative analyses reveal chemical- and region-specific relationships between di-OPEs and their respective tri-OPEs, suggesting that the relative importance of different sources (e.g., direct commercial use, impurity in tri-OPE formulas, and tri-OPE degradation) could vary for different di-OPEs. Our findings demonstrate wide occurrences of di-OPEs in an indoor environment from the studied locations and raise concerns on human exposure to dust associated di-OPEs. Future studies are needed to explore more possible di-OPEs in indoor environments and elucidate their sources, human exposure pathways, and toxicokinetics.

INTRODUCTION

Organophosphate triesters (tri-OPEs) represent a group of halogenated and nonhalogenated chemicals possessing a triester structure which are broadly used as flame retardants, plasticizers, stabilizers, antifoaming and wetting agents, and as additives in hydraulic fluids and lubricants in numerous commercial products.[1−3] Typical halogenated tri-OPEs include tris(2-chloroethyl) phosphate (TCEP), tris(1-chloro-2-propyl) phosphate (TCIPP), and tris(1,3-dichloro-2-propyl) phosphate (TDCIPP). More OPEs are nonhalogenated and typical ones include triphenyl phosphate (TPHP), tris(2-butoxyethyl) phosphate (TBOEP), tributyl phosphate (TNBP), tris(2-ethylhexyl) phosphate (TEHP), and 2-ethylhexyl-diphenyl phosphate (EHDPHP). As a consequence of substantial, long-term use, tri-OPEs have been demonstrated to be universally present in global environments.[1,2]

In vitro and in vivo studies have demonstrated rapid transformation of selected tri-OPEs to their diester metabolites (referred to as di-OPEs).[4−9] For example, a herring gull (*Larus argentatus*) hepatic microsomal assay revealed the biotransformation of TBOEP, TCIPP, TDCIPP, triethyl phosphate (TEP), TNBP, and TPHP, to their corresponding di-OPEs, i.e., bis(2-butoxyethyl) phosphate (BBOEP), bis(1-chloro-2-propyl) phosphate (BCIPP), bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), diethyl phosphate (DEP), dibutyl phosphate (DNBP), and diphenyl phosphate (DPHP).[4] Human studies reported frequent detection of selected di-OPEs (e.g., BBOEP, BCIPP, BDCIPP, and DPHP) in urine.[10−15] Urinary di-OPEs

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Table 1. Concentrations (ng/g) of Organophosphate Di-Esters (di-OPEs) in South China and Midwestern U.S. House Dust

		South China (n = 30)			Midwestern U.S. (n = 17)		
	LOQ[a] (ng/g dw)	detect (%)	median	range	detect (%)	median	range
BBOEP	2	90	15.9	<LOQ-12880	100	1580	96.0−85950
BCEP	16	0	<LOQ		0	<LOQ	
BCIPP	10	13	<LOQ	<LOQ-124	76	90.6	<LOQ-530
BDCIPP	12	77	33.6	<LOQ-699	94	234	<LOQ-2550
BEHP	2	100	654	38.7−4490	100	867	237−14070
BMPP	2	90	9.5	<LOQ-66.5	82	4.0	<LOQ-62.8
DPHP	4	100	605	31.24−4070	100	6500	903−27460
Σ_{di}OPEs			2000	81.1−15110		16 060	3060−100 000

[a] LOQ = limit of quantification.

were often utilized as a noninvasive approach to evaluate human exposure to tri-OPEs.[10−12] In addition to the occurrence in human urine, some di-OPEs were also detected in sewage sludge.[16,17]

Indoor environments (e.g., homes, schools, and vehicles) have been suggested to constitute important microenvironments where humans are exposed to tri-OPEs.[12,13,18] A portion of tri-OPEs may migrate from household consumer products, as they are not chemically bound, and partition between indoor air and suspended particles or associated with settled dust.[18] A number of tri-OPEs have been ubiquitously found in indoor dust around the world and their total concentrations (referred to as Σ_{tri}OPEs) were reported to range up to 1610 μg/g in house dust.[19−25] Ubiquitous and abundant presence of tri-OPEs in indoor dust has raised concerns on potential human exposure, mainly via dust ingestion, inhalation, and dermal contact.[26] House dust concentrations of selected tri-OPEs (e.g., TDCIPP and TCIPP) have been reported to be significantly associated with the levels of their respective metabolites in human urine,[12,27−29] demonstrating significant contributions of indoor exposure to the overall human exposure scenarios.

While the vast majority of indoor studies have focused on tri-OPEs, we hypothesized that di-OPEs could also be present in indoor dust. This hypothesis is based on the speculation that di-OPE chemicals are present as impurities in commercial tri-OPE mixtures and household consumer products where tri-OPEs are applied, or directly used for commercial applications. Very little information is available on the occurrence of di-OPEs in indoor environments, possibly because they are usually recognized as metabolites in organisms, instead of the chemicals already present in the environment prior to exposure. Therefore, this study was undertaken to investigate the coexistence of di-OPEs and their parent tri-OPEs in indoor dust. Specific objectives were to (1) identify the types of di-OPEs in house dust and characterize their relative abundances to respective tri-OPEs; (2) compare the compositional patterns of di- and tri-OPEs in dust from two different locations (i.e., South China and Midwestern United States or U.S.) to understand region-specific contamination patterns; and (3) estimate human exposure risks via dust ingestion. Our work will contribute to better characterizations of indoor OPE contamination and human exposure risks.

■ MATERIALS AND METHODS

Chemicals and Reagents. Reference standards of seven di-OPEs (Table 1), including BBOEP, bis(2-chloroethyl) phosphate (BCEP), BCIPP, BDCIPP, bis(2-ethylhexyl) phosphate (BEHP), bis(2-methylphenyl) phosphate (BMPP), and DPHP, were purchased from Toronto Research Chemicals (Toronto, Canada). Deuterated di-OPEs, including BCIPP-d_{12}, BCEP-d_8, BDCIPP-d_{10}, BBOEP-d_{18}, BEHP-d_{34}, BMPP-d_{14}, and DPHP-d_{10}, were employed as surrogate standards and purchased from Toronto Research Chemicals. A total of 14 tri-OPEs were also measured (Table S1 of the Supporting Information, SI), including EHDPHP, TBOEP, TCEP, TCIPP, TDCIPP, TEHP, tricresyl phosphate (TMPP), TNBP, TPHP, bisphenol A bis(diphenyl phosphate) (BPA-BDPP), *t*-butylphenyl diphenyl phosphate (BPDPP), cresyl diphenyl phosphate (CDP), isodecyl diphenyl phosphate (IDDPP), and resorcinol-bis(diphenyl) phosphate (RDP). Reference standards of native and isotopically labeled tri-OPEs were purchased from AccuStandard (New Haven, CT) and Wellington Laboratories (Guelph, ON, Canada). High performance liquid chromatography (HPLC) solvents (Optima grade) were purchased from Fisher Scientific (Hanover Park, IL).

Sample Collection. House dust was collected from 30 homes (all condominiums) in the city of Guangzhou, South China and 17 homes (14 single-family houses and three condominiums) in the city of Carbondale (Illinois) located in the Midwestern U.S. Guangzhou is a capitol city of Guangdong Province and representative of South China's culture and economic status. Carbondale is a midsized University town in Illinois. However, it should be noted that this city may not be best representative of the entire Midwestern U.S. region given that its median household income is below that of Illinois or the Midwestern region (www.census.gov/programs-surveys/acs/). The selection of Carbondale is partly due to the feasibility of and access to sampling. Basic home characteristics are summarized in Table S2.

A customized nylon bag with a pore size of approximately 25 μm was precleaned with acetone. It was attached to the floor attachment of a commercial vacuum cleaner (Electrolux, ZMO1511, 1400 W) prior to dust collection.[30] After the floors of each dwelling's living room and bedrooms were vacuumed, the nylon bag was detached and wrapped with clean aluminum foil. Field blanks for dust collection were prepared by vacuuming precleaned sodium sulfate and then storing the nylon bag in the same way as used for dust collection. A field blank was prepared for every five homes. Dust or sodium sulfate was removed from the nylon bag at the analytical laboratory and sieved through a 125-μm stainless cloth sieve (Hogentogler & Co., Inc., Columbia, MD). Sieved dust and field blanks were stored at −20 °C prior to chemical analysis.

Chemical Analysis. Approximately 20−50 mg of sieved dust was transferred to a glass tube, spiked with surrogate standards and extracted with 5 mL of a mixture of hexane and

Table 2. Concentration Ratios of Each Organophosphate Di-Ester (di-OPE) to Its Respective Tri-Ester(s) (tri-OPE) in South China and Midwestern U.S. Dust[a]

di/tri-OPE pairs	dust South China	dust Midwestern U.S.	degradation during sample analysis
BBOEP/TBOEP	0.04 (0−0.50)	0.11 (0.02−0.20)	0.01 ± 0.002
BCEP/TCEP	0	0	0
BCIPP/TCIPP	0 (0−0.07)	0.01 (0−0.04)	0
BDCIPP/TDCIPP	0.02 (0−0.58)	0.05 (0−0.31)	0
BEHP/TEHP	1.0 (0.08−5.0)	1.4 (0.20−29.1)	0.006 ± 0.001
BMPP/TMPP	0.03 (0−0.18)	0.03 (0.002−0.23)	0.001 ± 0.0001
DPHP/TPHP	1.1 (0.09−4.4)	3.7 (0.70−28.1)	0.02 ± 0.002
DPHP/EHDPHP	1.5 (0.06−11.7)	5.7 (0.80−43.3)	0.007 ± 0.001
DPHP/BPDPP	8.2 (1.8−57.8)	3.6 (0.24−41.2)	0.23 ± 0.01
DPHP/BPA-BDPP	1.5 (0.04−29.2)	30.4 (4.9−91.4)	0.01 ± 0.002
DPHP/RDP	12.4 (0.23−564)	22.4 (1.0−74.0)	0.05 ± 0.02
DPHP/CDP	11.4 (0.03−111)	14.5 (0.93−150)	0.02 ± 0.003
DPHP/IDDPP	4.2 (0.24−22.2)	81.2 (11.7−253)	0.01 ± 0.002

[a] Ratios of each di-/tri-OPE pair are calculated for individual samples and the data below represent the median ratios and the ranges (in parentheses). For comparison, the degradation rates (mean ± standard deviation; unitless) from a tri-OPE to its respective di-OPE during sample analysis is also presented.

dichloromethane (HEX:DCM, 1:1, v/v) under sonication. The extraction was repeated three cycles (25 min each). Following centrifugation, the supernatants were combined, dried under gentle nitrogen flow, and then reconstituted with 0.5 mL of water containing 5% methanol (v/v) and 0.2% formic acid (v/v). The extract was cleaned through an Oasis WAX cartridge (3 cc, 60 mg sorbent, 30 μm particle size; Waters Corporation) which was preconditioned in sequence with 6 mL of methanol (containing 1% ammonia, v/v), 6 mL of acetonitrile, and 6 mL of water (containing 0.2% formic acid, *v*/*v*). After the sample was loaded, the cartridge was washed with 3 mL of water containing 5% methanol and 0.2% formic acid (*v*/*v*). Subsequently, di-OPEs were eluted out with 2 mL of methanol, followed by 3 mL of methanol containing 1% ammonia (*v*/*v*). The final extract was concentrated to approximately 200 μL, filtered through a 0.22 μm nylon filter (VWR International), and stored in −20 °C prior to instrumental analysis.

The analysis of 14 tri-OPEs in collected dust followed the same procedures as described in Tan et al.[30] Approximately 20−50 mg of sieved dust was transferred to a glass tube, spiked with surrogate standards, and extracted with 5 mL of a mixture of HEX/DCM (1:1, *v*/*v*) under sonication. Extraction was repeated three times (5 min each). The combined extract was concentrated and cleaned through a cartridge packed with 2 g of Florisil (Biotage, Charlotte, NC). After the cartridge was prerinsed in sequence with 8 mL methanol, 10 mL DCM, and 10 mL HEX, the sample was loaded, and the first fraction eluted with 4 mL HEX was discarded. The second fraction contained target tri-OPEs and was eluted out with 13 mL HEX, followed by 25 mL ethyl acetate. The second fraction was concentrated and spiked with $^{13}C_{18}$-TPHP prior to instrumental analysis.

Determination of di-OPEs and tri-OPEs was conducted on a Shimadzu HPLC coupled to an AB Sciex 5500 Q Trap triple quadrupole mass spectrometry (MS/MS, Toronto, Canada). The MS was equipped with a TurboIonSpray electrospray ionization (ESI) probe (positive for tri-OPEs and negative for di-OPEs) and operated in the multiple reaction monitoring (MRM) mode (Table S1). Detailed information on instrumental analysis, including the mobile phases, HPLC programs, and mass spectral parameters, are introduced in the SI. The limit of quantification (LOQ), defined as an analyte response 10 times the standard deviation of the noise when injecting a standard mixture solution ($n = 8$) in methanol, ranged from 2 to 16 ng/g dry weight (dw) for di-OPEs and 2−10 ng/g dw for tri-OPEs.

Quality Assurance and Control. Thorough QA/QC procedures for di-OPE analysis were conducted to ensure data quality. Procedural contamination from the analytical steps aforementioned was evaluated by running a procedural blank (precleaned sodium sulfate) with every batch of five dust samples. BBOEP, BDCIPP, BEHP, BMPP, and DPHP exhibited an average of < LOQ − 0.9 ng in the final extracts of procedural blanks, whereas BCEP and BCIPP were not detected. To evaluate the recovery efficiencies of analytical procedures, sodium sulfate was spiked with 50 ng each of the target di-OPEs and their surrogate standards and processed in five replicates. Di-OPEs and deuterated di-OPEs were also spiked into five replicates of a dust composite collected from an empty room without any furniture or office supplies. Two procedural blanks (sodium sulfate only) and two matrix blanks (dust composite) were also processed after spiking with deuterated di-OPEs (no target di-OPEs were spiked). After adjustment with surrogate standard responses, recoveries of the spiked di-OPEs ranged from 59.5 ± 6.6% (BCEP) to 114 ± 8.5% (BBOEP) in sodium sulfate after subtracting the mean contamination levels in procedural blanks. The di-OPEs spiked into dust composite also exhibited recoveries ranging from 57.2 ± 5.5% (BCEP) to 123 ± 9.8% (BMPP), after subtracting the original concentrations measured in dust composite (i.e., < LOQ for BBOEP, BCIEP, and BDCIPP, 11.6 ng/g for BMPP, 31.4 ng/g for BCIPP, 84.0 ng/g for DPHP, and 230 ng/g for BEHP). To examine if the di-OPEs detected in dust was originated from potential degradation during sample treatment, we spiked 50 ng each of TBOEP, TCEP, TCIPP, TDCIPP, TEHP, TMPP, and TPHP, as well as deuterated di-OPEs into sodium sulfate ($n = 5$). In addition to TPHP, other tri-OPEs that could be transformed to DPHP include BPA-BDPP, BPDPP, CDP, EHDPHP, IDDPP, and RDP (collectively referred to as DPHP-related tri-OPEs).[15,31,32] Thus, each of these substances was also separately spiked into three sodium

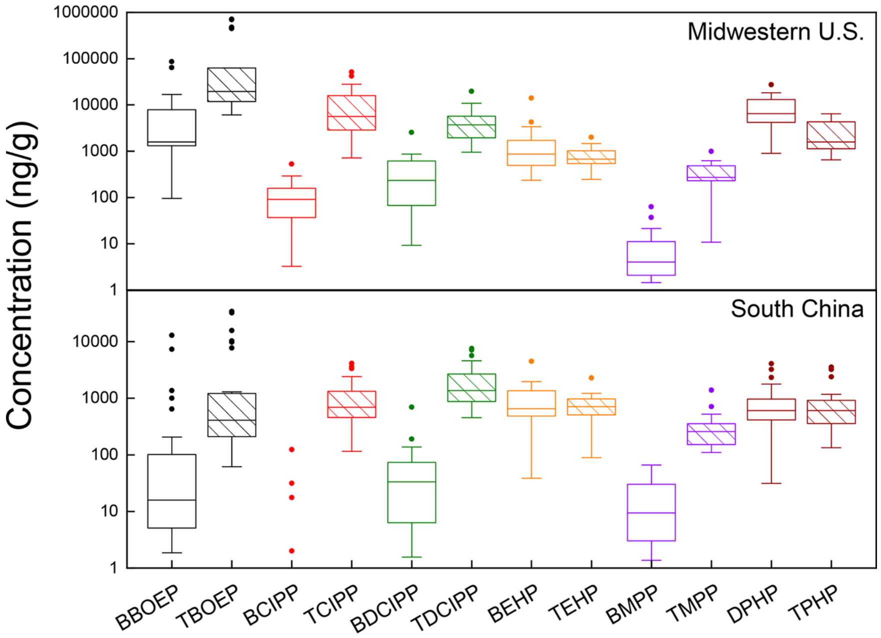

Figure 1. Comparisons of the concentrations (ng/g) of organophosphate diesters (di-OPEs) and triesters (tri-OPEs) in South China and Midwestern United States house dust. Hatched boxes represent tri-OPE data. Box: 1−3 quartiles; bottom bar: 1st quartile −1.5 × interquartile range (IQR); top bar: 3rd quartile + 1.5* IQR. Dots represent outliers. The box plot for BCIPP concentrations in South China dust is not available due to a low detection frequency (13%).

sulfate samples for degradation evaluations. The rates of degradation (i.e., the mass ratio of a di-OPE to its corresponding tri-OPE) from BPDPP to DPHP were determined to be 22.7 ± 1.3%, whereas other tri-OPEs exhibited degradation rates generally below 4.8 ± 1.8% (Table 2).

Exposure Assessment. By assuming 100% absorption of contaminants from ingested dust in line with other studies,[33] the estimated daily intake of OPEs via indoor dust ingestion was determined using the following equation:[34,35]

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

where E_{DI} represents the estimated daily intake (ng/kg body weight/day), C is a chemical's concentration in house dust (ng/g), IEF is the indoor exposure fraction (hours spent over a day in homes), DIR is the dust ingestion rate (g/day), and BW is body weight (kg).

Data Analysis. Reported levels of di-OPEs or tri-OPEs were adjusted based on their respective surrogate standard responses and reported as ng/g dw in dust. Given that our preliminary study indicated that bis(2-methylphenyl) phosphate and bis(4-methylphenyl) phosphate coelute during LC−MS/MS analysis, we considered the quantification results for bis(2-methylphenyl) phosphate represent the total concentration of all isomers of BMPP. For an analyte with detection frequency greater than 60%, the regression probability plotting method was applied to assign values to any measurements below LOQ for statistical analysis (Statistical Analysis System, SAS 9.1).[36] Non-normally distributed data were logarithmically transformed to approximate a normal distribution prior to statistical analyses. Outliers of each data set were identified via box plot after log-transforming original data, but were still included for statistical analyses. Nonparametric statistical methods were therefore employed to minimize potential effects of outliers on analysis outcomes.[37] Spearman's correlation analyses were used to determine the relationships between individual di-OPE or tri-OPE concentrations in dust (PASW Statistics 18.0, IBM Inc.). Mann−Whitney tests were employed to determine compositional differences of individual di- or tri-OPE chemicals between two locations (PASW Statistics 18.0). The level of significance was set at $\alpha = 0.05$.

RESULTS AND DISCUSSION

Concentrations of Di-OPEs in House Dust. Detection frequencies (DFs) of BBOEP, BDCIPP, BEHP, BMPP, and DPHP ranged from 77% to 100% in South China house dust and 82%−100% in Midwestern U.S. house dust (Table 1). BCIPP was detected with a DF of 13% in South China house dust and 76% in U.S. dust, whereas BCEP was not found in any of the samples. Median concentrations of BBOEP, BCIPP, BDCIPP, BEHP, BMPP, and DPHP were determined to be 15.9, < LOQ, 33.6, 654, 9.5, and 605 ng/g in South China house dust, and 1580, 90.6, 234, 867, 4.0, and 6500 ng/g in Midwestern U.S. house dust, respectively (Table 1 and Figure 1). It merits attention that the concentrations of DPHP in Midwestern U.S. house dust even surpassed those of most tri-OPEs (median: 90.0−5600 ng/g) in the same dust samples except TBOEP (median: 19 500 ng/g) (Table S3). Combined together, the total concentrations of di-OPEs (referred to Σ_{di}OPEs) constituted an average of 22.9% and 21.3% of the total concentrations of tri-OPEs (Σ_{tri}OPEs) in house dust from these two locations, respectively.

In contrast with numerous indoor tri-OPE studies, di-OPEs have rarely been investigated in indoor environment. The only data available were from a recent European study which reported the occurrence of DPHP (106−79 660 ng/g) in dust from different microenvironments (i.e., living room, bedroom, office, car, and public microenvironments) in Spain and The Netherlands.[38] Most available di-OPE reports were from epidemiological and laboratory exposure studies. DPHP and BDCIPP were commonly detected in human urine, with median or mean concentrations reported in various studies ranging up to 720 and 10.9 ng/mL, respectively.[12−15,31,39−44] The metabolism of selected tri-OPEs into their di-OPE derivatives has been well demonstrated in vivo and in vitro.[4−9] However, a common recognition of di-OPEs as tri-OPE metabolites may constitute one of the reasons for very limited studies on their environmental occurrences.

To determine if the di-OPEs found in dust were completely or partially originated from OPE degradation during sample analysis, we calculated the concentration ratios of each di-OPE to its respective tri-OPE chemical(s) (referred to as $R_{di/tri}$, unitless) in house dust (Table 2). The median R values for the DPHP − TPHP pair were determined to be 1.1 and 3.7 in South China and Midwestern U.S. dust, respectively. As DPHP can also be formed from the degradation of EHDPHP, BPA-BDPP, BPADP, CDP, IDDPP, or RDP,$_{di/tri}$[15,31,32] the concentration ratios of DPHP to the combination of these tri-OPEs (including TPHP) were determined to be 0.27 and 0.82 in dust from the two locations, respectively. As shown in QA/QC experiments, the rates of degradation from TPHP and other structurally related tri-OPEs to DPHP during sample treatments were only 0.007−0.05, except for BPDPP which exhibited a higher degradation rate (0.23). On the basis of these degradation rates and measured dust concentrations, we estimated tri-OPE degradation during sample treatments contributed approximately 7.4% and 7.3% of DPHP concentrations detected in South China and Midwestern U.S. house dust, respectively. High $R_{di/tri}$ values were also determined for BEHP (i.e., 1.0 and 1.4), whereas its degradation rate during sample treatments is only 0.006. The $R_{di/tri}$ values for other di-OPEs (e.g., BBOEP, BDCIPP, and BMPP) were also at least 1 order of magnitude greater than their respective degradation rates (Table 2). These results indicate that the measured concentrations of di-OPEs mostly reflect their original abundances in house dust.

Relationships Between Di- and Tri-OPEs in House Dust. In addition to the significant differences in Σ_{di}OPEs or Σ_{tri}OPEs concentrations ($p < 0.001$ in both cases), compositions of di-OPEs or tri-OPEs also differed largely between the two locations (Figure 2). In contrast with the dominance by DPHP (mean: 54.0%) in U.S. dust, BEHP (42.6%) and DPHP (41.6%) exhibited similar compositions and dominated over other di-OPEs in South China dust. Dust compositions of BBOEP, BEHP, and DMPP differed significantly between the two locations. For tri-OPEs, TBOEP concentrations constituted an average of 53.2% of Σ_{tri}OPEs in U.S. dust, whereas in South China dust TDCIPP (19.6%) and TBOEP (18.1%) appeared to be comparably more abundant than other tri-OPEs. Some emerging tri-OPEs (i.e., TCEP, TDCIPP, TBOEP, TEHP, TMPP, EHDPHP, BPDPP, BPA-BDPP, and IDDPP) exhibited dramatic differences between the two locations. For example, BPA-BDPP constituted 11.7% of Σ_{tri}OPEs in South China dust, whereas it was a very minor component (0.5%) in Midwestern U.S. dust.

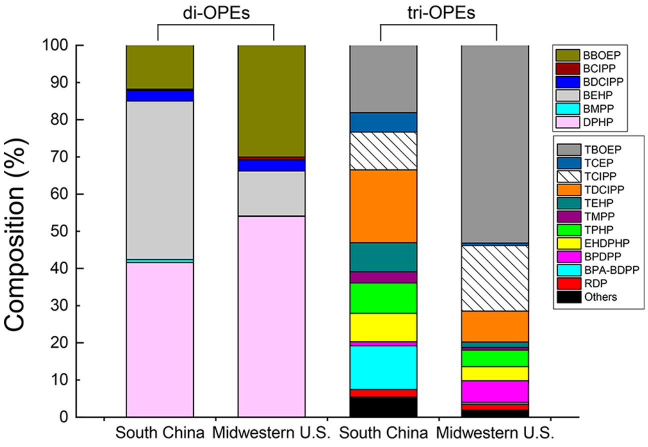

Figure 2. Mean compositions of organophosphate diesters (left two columns) and triesters (right two columns) in house dust from South China and Midwestern Unites States.

Correlations between di-OPEs and their respective tri-OPEs also exhibited chemical-specific and region-specific patterns. In Midwestern U.S. dust, significant concentration correlations were observed for the BBOEP−TBOEP, BCIPP−TCIPP, and BDCIPP−TDCIPP pairs (Table 3 and Figure S1 of the Supporting Information, SI). However, both DPHP and BEHP exhibited no correlation with their respective tri-OPEs. Significant correlations were also observed between BBOEP and TBOEP and between DPHP and TPHP in South China dust, but not observed for any other di/tri-OPE pairs (Table 3).

The strong correlations between BBOEP and TBOEP ($p \leq 0.001$ in both locations) and between BCIPP and TCIPP ($p < 0.001$ in U.S. only) suggest that the occurrence of these two di-OPEs have a tight connection with their parent chemicals. Both BBOEP and BCIPP exhibited low $R_{di/tri}$ ratios determined in indoor dust from the two locations, i.e., the median ratios were 0.04 and 0.11 for the BBOEP−TBOEP pair, and 0 and 0.01 for the BCIPP−TCIPP pair. It is speculated that BBOEP or BCIPP exists as an impurity in commercial TBOEP or TCIPP formulas applied to certain household consumer products, leading to strong correlations between each other in house dust. Alternatively, they may be degraded from tri-OPEs during the manufacturing of consumer products where tri-OPEs are added or transformed from tri-OPEs under environmental conditions. As we stated earlier, potential degradation of tri-OPEs in dust cannot be completely excluded. Photo-, thermal, and microbial degradation, as well as hydrolysis, has been reported for selected tri-OPEs, although in most of these studies the degradation products were not elucidated.[45−49]

DPHP was significantly correlated with TPHP alone or the combination of DPHP-related tri-OPEs (including TPHP, EHDPHP, BPA-BDPP, BPDPP, CDP, IDDPP, and RDP) in South China house dust ($r_s = 0.53$, $p < 0.01$ and $r_s = 0.38$, $p < 0.05$, respectively). By contrast, no correlation was found in U.S. dust. Nevertheless, the high $R_{di/tri}$ values for DPHP determined in dust from both locations (i.e., median 1.1 and 3.7) suggest that tri-OPE degradation or the presence as an impurity in commercial tri-OPE formulas unlikely constituted the main sources of DPHP associated with house dust. Instead, a large proportion, if not all, of the DPHP present in house dust could be directly originated from the application of DPHP in household consumer products as a commercial flame retardant, plasticizer, or an agent for other purposes. Indeed, DPHP has been reported as a catalyst in polymerization processes and as an additive in paints and coatings.[38] It is also suspected that DPHP could have been used as one of the TPHP alternatives, following substantial research and public concerns on the environmental and health impacts of TPHP.[1] However, relevant information is not found from the literature to the best of our knowledge.

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Table 3. Correlation Matrix for the Concentrations of Organophosphate Di- And Tri-esters in House Dust from South China and Midwestern U.S.[a]

	BBOEP	BCIPP	BDCIPP	BEHP	BMPP	DPHP	TBOEP	TCIPP	TDCIPP	TEHP	TMPP	TPHP	EHDPHP	BPA-BDPP	BPDPP	CDP	IDDPP	RDP
South China																		
BBOEP	1.00																	
BCIPP	N/A[b]	1.00																
BDCIPP	0.14	N/A	1.00															
BEHP	0.40*	N/A	0.31	1.00														
BMPP	0.44*	N/A	−0.12	0.60$^{\&}$	1.00													
DPHP	0.09	N/A	0.16	0.36	0.30	1.00												
TBOEP	0.81$^{\&}$	N/A	0.34	0.32	0.20	0.04	1.00											
TCIPP	0.11	N/A	0.52$^{\#}$	0.26	−0.07	0.20	0.32	1.00										
TDCIPP	−0.04	N/A	0.20	0.06	−0.03	−0.03	0.19	−0.03	1.00									
TEHP	−0.29	N/A	0.14	0.19	0.14	0.09	−0.08	0.27	0.17	1.00								
TMPP	0.19	N/A	0.30	0.47$^{\#}$	0.34	0.23	0.20	0.21	−0.11	0.21	1.00							
TPHP	−0.05	N/A	0.10	0.19	−0.003	0.53$^{\#}$	0.21	0.26	0.14	0.44*	0.33	1.00						
EHDPHP	−0.34	N/A	−0.11	0.04	0.11	0.19	−0.09	0.14	0.30	0.68$^{\&}$	0.02	0.45*	1.00					
BPA-BDPP	−0.15	N/A	−0.03	0.18	−0.10	0.38*	−0.05	0.29	−0.23	0.45*	0.33	0.57$^{\#}$	0.38*	1.00				
BPDPP	−0.001	N/A	0.19	0.49$^{\#}$	0.28	0.44*	0.16	0.31	0.12	0.35	0.58$^{\#}$	0.69$^{\&}$	0.26	0.56$^{\#}$	1.00			
CDP	−0.04	N/A	−0.13	0.02	−0.21	−0.19	−0.19	−0.07	−0.15	−0.10	0.01	−0.21	−0.02	0.21	−0.14	1.00		
IDDPP	−0.16	N/A	0.17	0.18	0.09	0.45*	0.11	0.18	0.31	0.36	0.07	0.57$^{\#}$	0.53$^{\#}$	0.36	0.46*	−0.43*	1.00	
RDP	−0.08	N/A	−0.03	0.21	−0.06	0.10	−0.01	0.06	−0.16	0.31	0.40*	0.26	0.17	0.69$^{\&}$	0.32	0.44*	0.18	1.00
Midwestern U.S.																		
BBOEP	1.00																	
BCIPP	0.11	1.00																
BDCIPP	−0.15	0.66$^{\#}$	1.00															
BEHP	0.08	0.53*	0.28	1.00														
BMPP	−0.20	−0.22	−0.30	0.20	1.00													
DPHP	0.23	0.74$^{\#}$	0.82$^{\&}$	0.46	−0.10	1.00												
TBOEP	0.71$^{\#}$	0.10	−0.19	−0.08	−0.23	0.11	1.00											
TCIPP	0.04	0.88$^{\&}$	0.57*	0.42	0.07	0.63$^{\#}$	−0.04	1.00										
TDCIPP	0.02	0.20	0.57*	0.04	−0.31	0.45	0.10	0.11	1.00									
TEHP	0.21	−0.35	−0.44	−0.31	−0.06	−0.29	0.16	−0.51*	−0.47	1.00								
TMPP	−0.30	0.15	0.22	0.28	−0.04	0.07	−0.44	0.13	0.33	−0.12	1.00							
TPHP	−0.12	0.03	−0.14	0.24	0.54*	−0.002	−0.15	0.26	−0.36	−0.19	−0.23	1.00						
EHDPHP	−0.32	−0.15	−0.39	0.39	0.33	−0.38	−0.21	−0.21	−0.34	0.30	0.24	0.19	1.00					
BPA-BDPP	0.27	0.24	−0.15	0.38	0.34	0.16	−0.07	0.39	−0.21	−0.25	0.19	0.06	0.01	1.00				
BPDPP	0.05	−0.07	−0.23	0.06	0.17	−0.10	−0.12	−0.10	−0.44	0.40	−0.13	−0.21	0.06	0.29	1.00			
CDP	0.26	−0.17	−0.36	−0.04	−0.18	−0.25	0.03	−0.41	−0.05	0.51*	0.25	−0.37	0.18	0.16	0.29	1.00		
IDDPP	0.27	0.11	0.19	−0.37	−0.26	0.26	−0.03	0.16	0.06	−0.03	−0.40	−0.20	−0.63$^{\#}$	0.21	0.16	0.03	1.00	
RDP	−0.16	0.03	−0.15	−0.26	−0.22	−0.18	0.04	−0.11	0.09	0.34	0.24	0.06	0.29	−0.30	−0.36	0.37	−0.21	1.00

[a] ($^{*}p < 0.05$; $^{\#}p < 0.01$; $^{\&}p < 0.001$). Shaded data represent the correlation outcomes between each di-OPE and its respective tri-OPE(s). [b] Not available due to very low detection frequency (13%) of BCIPP in South China dust.

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Table 4. Estimated Daily Intake (EDI; ng/kg bw/day) of Organophosphate Di-Esters (Di-OPEs) and Tri-Esters (Tri-OPEs) by Toddlers and Adults under Different Exposure Scenarios

	toddler				adult			
	mean	median	5th	95th	mean	median	5th	95th
South China (average dust ingestion[a])								
Σ_{di}OPEs	11.5	8.4	1.9	32.2	0.6	0.4	0.1	1.6
Σ_{tri}OPEs	54.6	43.3	17.6	126	2.8	2.2	0.9	6.4
South China (high dust ingestion[b])								
Σ_{di}OPEs	45.8	33.6	7.6	129	1.5	1.1	0.2	4.1
Σ_{tri}OPEs	219	173	70.2	502	7.0	5.5	2.2	16.1
Midwestern U.S. (average dust ingestion[a])								
Σ_{di}OPEs	79.9	54.4	15.6	322	4.5	3.1	0.9	18.1
Σ_{tri}OPEs	617	183	98.7	2480	34.8	10.3	5.6	140
Midwestern U.S. (high dust ingestion[b])								
Σ_{di}OPEs	319	218	62.3	1290	11.2	7.7	2.2	45.3
Σ_{tri}OPEs	2470	731	395	9920	86.9	25.7	13.9	349

[a] Assuming 50 mg/day for toddlers and 20 mg/day for adults. [b] Assuming 200 mg/day for toddlers and 50 mg/day for adults.

Similar to DPHP, BEHP also exhibited high $R_{di/tri}$ values in dust from both locations (median 1.0 and 1.4, respectively). The lack of significant correlations between BEHP and TEHP in dust from both locations further suggests that BEHP may be directly used as a commercial chemical for certain applications. This may constitute a main source to the levels of BEHP found in house dust, although it cannot be excluded that BEHP may be present as an impurity in commercial TEHP formula or formed via TEHP degradation. However, we could not find any report indicating the use of BEHP as a commercial chemical. Information on the environmental transformation of TEHP is also limited.

Examination of the relationships among individual di-OPEs or between di-OPEs and tri-OPEs other than their parent tri-OPEs also revealed chemical-specific and region-specific patterns (Table 3 and Figure S1). For example, in South China house dust BDCIPP did not exhibit a significant correlation with any other di-OPEs or tri-OPEs with the exception of TCIPP ($p = 0.004$). By contrast, it was found to be significantly correlated with TDCIPP ($p = 0.02$), TCIPP ($p = 0.02$), DPHP ($p < 0.001$), and BCIPP ($p = 0.004$), and marginally correlated with TEHP ($p = 0.07$) in Midwestern U.S. dust. For BEHP, it exhibited no significant correlation with any di- or tri-OPEs except for BCIPP ($p = 0.03$) in U.S. dust, but had significant correlations with TMPP ($p = 0.01$), BPDPP ($p = 0.006$), BMPP ($p < 0.001$), and BBOEP ($p = 0.03$) in South China dust.

Overall, the occurrences of di-OPEs in house dust exhibit chemical-specific relationships with their respective parent tri-OPEs and other tri- or di-OPEs, likely indicating that the relative importance of different sources (e.g., direct commercial use, impurity in tri-OPE formulas, and tri-OPE degradation) varied for different di-OPEs. The relationship patterns also differ between regions for some chemicals (e.g., DPHP and BEHP), possibly due to region-specific commercial application histories. It should be noted that different furnishing conditions and other home characteristics may contribute to differences in dust contamination levels and profiles between South China and Midwestern U.S. For example, 13 out of 30 studied Guangzhou homes had wooden floors, while the rest 17 homes had tile floors. By contrast, most (15/17) Carbondale homes under study were equipped with carpet floors (Table S2). The year of house/condominium built also varied between the two locations (Table S2). However, as we are not sure about the exact sources of di-OPEs in indoor environments, linking regional differences in dust OPE concentrations/profiles with home characteristics may be premature based on our present data. Future exploration of di-OPEs' possible commercial applications and tri-OPEs' environmental behavior and fate will facilitate the elucidation of potential sources of di-OPEs in home environments.

Exposure Assessment and Health Implications. The risks of human exposure to di- and tri-OPEs via dust ingestion were estimated for adults and toddlers from the two studied locations (Table 4). We assume an average and high dust ingestion rate (DIR) to be 20 and 50 mg/day for adults and 50 and 200 mg/day for toddlers, respectively.[34,50] Adults and toddlers are assumed to spend an average of 66.7% and 83.3% of their time in homes, respectively (Table S4).[30] We also assume the average body weights for toddlers and adults to be 9.9 and 62 kg in China and 12.3 and 70 kg in U.S., respectively (Table S4).[51−53] On the basis of eq 1, we estimated the median daily intake of di-OPEs by South China adults via dust ingestion to be 0.4 and 1.1 ng/kg bw/day under the average and high exposure scenarios, respectively, whereas the median intake by U.S. adults was approximately 3.1 and 7.7 ng/kg bw/day under the average and high exposure scenarios, respectively. Elevated exposure was estimated for toddlers who have a median daily intake of 8.4 and 33.6 ng/kg bw/day under the average and high exposure scenarios in South China, and 54.4 and 218 ng/kg bw/day under the average and high exposure scenarios in Midwestern U.S., respectively. Elevated exposure for toddlers versus adults results from a combination of factors, including lower body weight, higher dust ingestion rate, and more time spent indoors for toddlers. The estimated daily intakes of di-OPEs via dust ingestion constitute more than 20% (in average) of the intake of all tri-OPEs for both toddlers and adults (Table 4). However, the estimated intakes of both di-OPEs and tri-OPEs under the high exposure scenarios are respectively 2−3 and 1−2 orders of magnitude lower than the reference doses (RfD) estimated for individual tri-OPEs, i.e., ranging from 13 000 ng/kg bw/day (for TMPP) to 80 000 ng/kg bw/day (for TCIPP) (Table S5).[33] This indicates no or relatively low risks.

It is unknown how environmental occurrences of di-OPEs contribute to internal OPE exposure. In the case of DPHP, it has been frequently detected in human urine with concentrations greater than other tri-OPE metabolites in most studies.

However, a few studies did not observe a significant correlation between dust-associated TPHP and urinary DPHP.[11,12] These findings have been interpreted as that sources other than dust ingestion, such as inhalation, dermal contact, and diet,[28,54] could also contribute to internal TPHP exposure. However, the contribution of DPHP present in house dust to internal exposure has rarely been examined. Additionally, dietary sources of DPHP also exist. For example, He et al. has reported the presence of several di-OPEs (e.g., DPHP, DNBP, and BEHP) in food from southeast Queensland, Australia.[54] In one of the very few studies evaluating di-OPE toxicity, DPHP was reported to induce dose- and sex-specific perturbation of metabolic profiles in adult mice following neonatal exposure.[55] Therefore, the contribution of dust or diet associated di-OPEs to human exposure should not be overlooked. It also merits attention that in addition to the seven di-OPEs of interest, other di-OPEs may exist in indoor environments, which could further increase the exposure risks.

Knowledge Gaps. With respect to di-OPE exposure, knowledge remains lacking or limited in a number of aspects, including their environmental occurrences, exposure pathways and toxicokinetics. The current investigation of di-OPEs in dust or other environmental compartments is mainly based on the availability of relevant reference standards. The structures of tri-OPEs are complex in the substitution of esters with aryl or phenyl groups or a diverse combination of them. Isomers sharing the same base structure, but with different substitution patterns, could exist for a tri-OPE. For example, recent studies reported a number of isomers of isopropylated and *tert*-butylated triarylphosphate esters (ITPs and TBPPs) in flame retardant mixtures (e.g., Firemaster 550 and Firemaster 600) and house dust Standard Reference Material SRM 2585.[56] These isomers share a common base structure with TPHP and their total concentrations surpassed that of TPHP in Firemaster mixtures and house dust.[56] Additional di-OPEs derived from these TPHP-related isomers are potentially present, which, along with other emerging tri-OPEs and possible derivatives, add to the complexity of the group of organophosphate esters and enhance the overall human exposure risks.

Studies are needed to better understand environmental behavior and fate of di- and tri-OPEs. Although our QA/QC practices demonstrate minimal tri-OPE degradation during sample treatments, potential degradation of tri-OPEs to respective di-OPEs in dust or other environmental compartments, or even during sample storage stages, cannot be completely excluded. In addition to the fate of tri-OPEs which may influence environmental occurrence of di-OPEs, the environmental stability of di-OPEs also merits future studies. Other than settled dust, air, and suspended particles should also be investigated to understand the distribution patterns of di-OPEs in indoor environment and the factors (e.g., temperature) influencing their distributions.

The routes of exposure to di-OPEs need better elucidation. It is assumed that humans are exposed to di-OPEs following the pathways similar to those for tri-OPEs. However, the relative importance of different pathways (e.g., dust ingestion, inhalation, dermal contact, hand-to-mouth contact, and diet) to di-OPE exposure may be chemical-dependent and also differ from the scenarios for tri-OPE exposure. This is likely due to the changes of physicochemical properties from tri-OPEs to di-OPEs, which generally decrease their lipophilicity and bioaccumulation factor, while increasing the volatility, although exceptions occur (Table S6).

Knowledge also remains lacking in the toxicokinetics of di-OPEs following uptake. Although a number of studies have addressed metabolic transformation of tri-OPEs to di-OPEs in vivo or in vitro and reported associated toxic effects, very little has been done to elucidate the toxicokinetics of di-OPEs themselves, including their potential toxicity, possible transformation to mono-OPEs or other derivatives, and the effects of metabolic modification on di-OPEs' toxicities. Studies are also needed to investigate reference doses for di-OPEs and estimate the contribution of di-OPE intake to the overall health risks following exposure to organophosphate ester-based chemicals.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.9b00229.

Tables S1−S6, Figure S1, and a detailed description of analytical procedures for di- and tri-OPEs (DOCX)

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