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Novel and Traditional Organophosphate Esters in House Dust from South China: Association with Hand Wipes and Exposure Estimation

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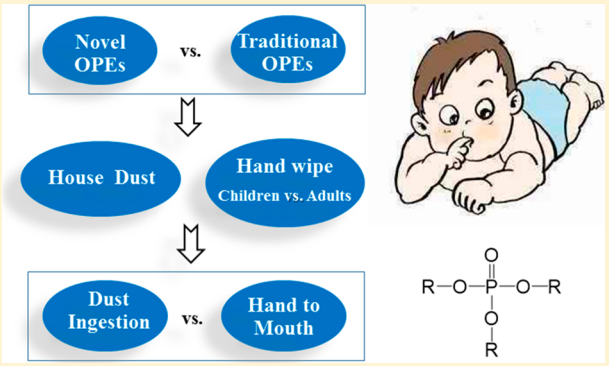
Supporting Information

ABSTRACT: The present study investigated the occurrence of 20 organophosphate esters (OPEs) in house dust from 51 South China homes and the risks of human exposure to OPEs via two pathways: dust ingestion and hand-to-mouth contact. In addition to several traditional OPEs, five out of six novel OPEs, including bisphenol A bis(deiphenyl phosphate) (BPA-BDPP), *t*-butylphenyl diphenyl phosphate (BPDPP), cresyl diphenyl phosphate (CDP), isodecyl diphenyl phosphate (IDDPP), and resorcinol-bis(diphenyl)phosphate (RDP), were frequently detected in house dust (median concentration: 59.7−531 ng/g). Eight of the 20 target OPEs were frequently detected in hand wipes collected from adults and children (n = 51 and 31, respectively), which in combination (referred to as Σ_8OPEs) had a median mass of 76.9 and 58.9 ng, respectively. Increasing dust concentrations of Σ_8OPEs or three individual substances among these eight OPEs, including tris(1-chloro-2-propyl) phosphate (TCIPP), tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), and triphenyl phosphate (TPHP), were strongly associated with their levels in children's hand wipes ($p < 0.05$ in all cases). By contrast, in adults' hand wipes only TPHP exhibited a marginally significant association with dust concentrations (p = 0.04). Levels of Σ_8OPEs in hand wipes from children, but not adults, were inversely influenced by hand washing frequency (p = 0.002), while indoor temperature was inversely associated with hand wipe levels of Σ_8OPEs from both children and adults (p = 0.01 and 0.002, respectively). Exposure estimation suggests that hand-to-mouth contact represents another important pathway in addition to dust ingestion and that children are subjected to higher OPE exposure than adults.



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INTRODUCTION

Organophosphate esters (OPEs) represent a group of halogenated and nonhalogenated compounds sharing a triester structure. They are broadly used as flame retardants in a variety of commercial products, including foams, plastics, textile, furniture, and many others.[1,2] Some OPEs are also used as plasticizers, stabilizers, antifoaming and wetting agents, and as additives in hydraulic fluids and lubricants.[3] Typical halogenated OPEs include tris(2-chloroethyl) phosphate (TCEP), tris(1-chloro-2-propyl) phosphate (TCIPP), tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), and tris(2,3-dibromopropyl) phosphate (TDBPP). Additional nonhalogenated OPEs include tris(2-butoxyethyl) phosphate (TBOEP), tributyl phosphate (TNBP), tris(2-ethylhexyl) phosphate (TEHP), triphenyl phosphate (TPHP), tris(3,5-dimethylphenyl) phosphate (T35DMPP), tris(2-isopropylphenyl) phosphate (T2IPPP), and 2-ethylhexyl-diphenyl phosphate (EHDPHP). A few OPEs (e.g., TDCIPP and TPHP) were listed as High Production Volume (HPV) chemicals, although in many regions their contemporary production volumes are not well documented.[2] Their market demands are expected to have increased in the past decade, following the discontinuation of polybrominated diphenyl ether (PBDE) and hexabromocyclododecane (HBCDD) flame retardants in Europe and the United States (US).

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In addition to the well-known OPEs listed above, several "novel" OPEs were recently identified with commercial applications. These include 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), which are all structurally based on that of TPHP, as well as tetrakis(2-chloroethyl)dichloroisopentyl diphosphate (V6). Some new OPEs may be subject to increasing production to replace the relevant traditional chemicals that have already attracted mounting environmental and health concerns. However, investigations on their environmental occurrences, fate, and human exposure risks remain overall limited.[4−9]

Various studies have reported the occurrences of traditional OPEs in indoor environments.[10−24] Mean or median concentrations of total OPEs were reported to range from 0.2 to 1610 μg/g in in indoor dust from different countries, revealing large variations among regions and country-specific contamination profiles.[10−24] Dust-associated OPEs represent a considerable risk to humans, as they can enter the body via absorption through the skin, inadvertent ingestion from hand-to-mouth contact, or inhalation of resuspended dust particles.[25] Reported associations of dust concentrations of TDCIPP and TPHP with their metabolites in urine or serum implicate the contribution of dust intake to human exposure to these two OPEs.[26−29] Meeker et al. also reported associations of TDCIPP and TPHP concentrations in house dust with altered hormone levels or decreased sperm concentrations in men.[30,31] However, the associations have not been shown for many other OPEs, suggesting that additional measures other than dust concentrations may be stronger indicators for internal exposure.

The occurrence of novel OPEs in indoor environment and associated human exposure risks are not sufficiently investigated. Data are also limited in the simultaneous estimation of OPE exposure risks for children and adults from both dust ingestion and hand-to-mouth contact. Children may be subjected to higher indoor exposure than adults as they spend more time in home environments and have a higher frequency of hand-to-mouth contact indoors than outdoors.[32] Therefore, in the present study we investigated the occurrence of 20 OPEs in South China house dust and their presence on child and adult hands. Specific objectives were to (1) evaluate the concentrations of six novel OPEs (i.e., BPA-BDPP, BPDPP, CDP, IDDPP, RDP, and V6) in house dust and their abundances relative to those of other OPEs; (2) investigate the types and levels of OPEs on adults' and children's hands via hand wipe sampling and the predictors of continuous OPE levels in hand wipes; and (3) estimate and compare exposure risks via dust ingestion and hand-to-mouth contact for adults and children. Hand wipes have been demonstrated as an exposure assessment more comprehensive than just the indoor environment.[8,28,33] Our work contributes to a more in-depth evaluation of indoor OPE contamination and related human exposure risks.

MATERIALS AND METHODS

Participant Recruitment. A total of 51 families from the city of Guangzhou (South China) voluntarily participated in this study from September 2015 to July 2016. These families were recruited through verbal spread and social media. The main recruitment criteria included (1) living in the present home for more than one year; (2) only one family recruited from each building if the building contained multiple homes; (3) adults' occupations not directly involved in the manufacturing of flame retardants or flame retardant-related products; and (4) adults from any two families not working in the same workplaces. To understand hand-to-mouth exposure, one adult from each participating family was recruited for hand wipe sampling. Thirty one out of the 51 families had at least one child aged 1−5 years old. One child from each of these 31 families was also recruited for hand wipe sampling. Participants were requested not to wash their hands during at least 2 h prior to hand wipe sampling. Study participants gave informed consent before providing samples or personal information and were requested to complete a short questionnaire. The questionnaires for children were completed by or with the help from their parents. The questionnaire was designed to collect data on age, sex, height, weight, occupation (for adults only), dwelling size, the number of electronic equipment in homes, hand washing frequency, and hours per day spent in homes. Hand washing frequency was recorded as 0, 1−2, 3−4, 5−6, 7−8, 9−10, and >10 times/day. Indoor temperature and humidity were also recorded by investigators during home visit. Our study was approved by the Institutional Review Board of Jinan University. Table S1 in the Supporting Information summarizes the characteristics of study populations and home environments.

Sample Collection. 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.[21] After the floors of each dwelling's living room and bedrooms were vacuumed, the nylon bag was detached and wrapped with clean aluminum foil. Hand wipes were collected during the home visit for dust sampling. Each participant had both hands wiped with precleaned sterile gauze pads on the palm and back of the hand from wrist to fingertips.[33] The gauze pads were precleaned by sonication with high-performance liquid chromatography (HPLC) grade isopropyl alcohol (repeated three times) and then soaked in isopropyl alcohol prior to use. The collected hand wipes were wrapped with precleaned aluminum foil and kept in clean glass jars. Precleaned gauze pads and sodium sulfate were used as field blanks for hand wipe and dust collection, respectively. Field blank wipes were prepared by wrapping the soaked hand wipe with aluminum foil and then placing into a glass jar. 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 of each kind was prepared for every five homes. Dust was removed from the nylon bag and sieved through a 125-μm stainless cloth sieve (Hogentogler & Co., Inc., Columbia, MD). Sieved dust, hand wipes, and field blanks were stored at −20 °C prior to chemical analysis.

Chemical Analysis. A total of 20 OPEs were determined in the present study, including six novel OPEs (i.e., BPA-BDPP, BPDPP, CDP, IDDPP, RDP, and V6) and 14 traditional OPEs, including EHDPHP, TBOEP, TNBP, TCEP, TCIPP, TDCIPP, TPHP, tricresyl phosphate (TMPP), TDBPP, triethyl phosphate (TEP), TEHP, tripropyl phosphate (TPP), T2IPPP, and T35DMPP (Table S2). Detailed procedures of sample pretreatment and instrumental analysis are provided in the Supporting Information. In brief, approximately 20−50 mg of sieved dust or the entire hand

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Table 1. Concentrations (ng/g) or Masses (ng) of Organophosphate Esters in South China House Dust and Hand Wipes from Child and Adult Participants

	dust (n = 51)			children's hand wipe (n = 31)			adults' hand wipe (n = 51)		
	% detect	median	range	% detect	median	range	% detect	median	range
TCEP	100	0.38	12.3−3130	77	3.0	nd[a]−47.2	69	2.6	nd−76.0
TCIPP	100	0.60	113−20780	90	4.6	<LOQ[b]−115	96	6.7	<LOQ−86.4
TDCIPP	100	2.8	360−20960	90	14.8	<LOQ−41.2	96	7.2	<LOQ−122
TPHP	98	0.53	<LOQ−5030	84	3.3	<LOQ−33.2	90	4.4	<LOQ−16.9
TBOEP	95	0.29	<LOQ−89370	87	3.0	<LOQ−122	96	2.4	<LOQ−36.1
TNBP	92	0.07	<LOQ−1170	18	nd	nd−79.5	22	nd	nd−83.5
TMPP	100	0.19	26.3−1400	13	nd	nd−12.0	25	nd	nd−8.0
TDBPP	0	nd	nd	0	nd	nd	0	nd	nd
T35DMPP	23	<LOQ	nd−132	0	nd	nd	0	nd	nd
TEHP	100	0.74	137−3850	87	16.6	<LOQ−73.3	88	15.6	<LOQ−131
TEP	84	0.02	<LOQ−255	0	nd	nd	0	nd	nd
T2IPPP	41	<LOQ	nd−224	0	nd	nd	0	nd	nd
TPP	0	nd	nd	0	nd	nd	0	nd	nd
EHDPHP	100	0.83	234−6530	87	6.7	<LOQ−23.1	92	8.7	<LOQ−55.0
BPA-BDPP	100	0.53	60−15280	87	3.7	<LOQ−135	88	7.6	<LOQ−140
BPDPP	89	0.08	<LOQ−584	0	nd	nd	4	nd	nd−3.4
CDP	77	0.08	<LOQ−6390	13	nd	nd−13.5	14	nd	nd−104
IDDPP	86	0.26	<LOQ−1400	13	nd	nd−16.7	12	nd	nd−67.5
RDP	94	0.06	<LOQ−1560	13	nd	nd−16.7	15	nd	nd−22.8
V6	8	nd	nd−363	0	nd	nd	0	nd	nd
Σ_8OPEs[c]		9240	2010−94170		58.9	12.0−278		76.9	10.4−327
all OPEs		10580	2180−95230		65.1	6.5−304		88.8	16.1−346

[a]nd = nondetectable. [b]LOQ = limit of quantification. [c]Including BPA-BDPP, EHDPHP, TBOEP, TEHP, TCEP, TCIPP, TDCIPP, and TPHP, which were frequently detected in hand wipes.

wipe sample was transferred to a glass tube, spiked with surrogate standards (i.e., d_{27}-TNBP, d_{12}-TCEP, d_{15}-TDCIPP, d_{15}-TEP, d_{15}-TPHP, and tris(2-butoxy-[13C2]-ethyl) phosphate), and extracted with 5 mL of a mixture of hexane and dichloromethane (1:1, v/v) under sonication. Extraction was repeated three times (5 min each) and the combined extract was cleaned through a Florisil solid-phase extraction (SPE) cartridge. For hand wipes only half of the extract was cleaned through SPE. The final extract was spiked with $^{13}C_{18}$-TPHP and determined on an Agilent 1260 HPLC coupled to a 3200 Q Trap triple quadrupole mass spectrometer (AB Sciex; Toronto, Canada).

An analyte with a response below the instrumental detection limit (IDL; a response three times the standard deviation of the noise) was considered nondetectable (nd). The limit of quantification (LOQ), defined as an analyte response 10 times the standard deviation of the noise, ranged from 2 to 14 ng/g dry weight (dw) for dust analysis and 0.1 to 1.2 ng for hand wipe analysis. To confirm the presence of BPA-BDPP, CDP, and RDP, dust composite extract was analyzed on ultra HPLC-high resolution MS and the results are provided in Supporting Information Tables S3−S4 and Figure S1.

To ensure data quality, a number of quality assurance and control (QA/QC) procedures were undertaken, which included the evaluation of background contamination in field blanks and laboratory procedural blanks, the recoveries of target analytes in spiking experiments, and the recoveries of surrogate standards in authentic samples. QA/QC practice details and the resulting data are summarized in the Supporting Information.

Exposure Assessment. Our study investigated human exposure risks from two approaches: dust ingestion (E_{DI}) and hand-to-mouth contact (E_{HTM}). The estimated daily exposure to OPEs via indoor dust ingestion was determined using the equation[10,34]

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

where E_{DI} is the estimated daily exposure via dust ingestion (ng/kg body weight/day), C is the concentration of a FR chemical 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).

Exposure via hand-to-mouth contact was estimated using the equation[35]

$$E_{HTM} = \frac{M_{surf} \times TE \times SAC \times EF}{BW} \quad (2)$$

where E_{HTM} represents estimated exposure via hand-to-mouth contact (ng/kg bw/day), M_{surf} is the mass of a chemical on the hands (ng), TE is transfer efficiency (%; i.e., fraction of the mass of a chemical transferred at each contact), SAC is the proportion of the hand area contacted each time (%), and EF is the frequency of contact during a day (day^{-1}).

Data Analysis. Reported levels of OPEs were corrected based on the recoveries of relevant surrogate standards and expressed as ng/g dw in dust or ng in hand wipes. A half LOQ was assigned for statistical analyses if a measurement was below LOQ. The Kolmogorov−Smirnov test was used to determine whether dust or hand wipe levels followed a normal distribution. Non-normally distributed data were subjected to logarithmical transformation (base-10) to approximate a normal distribution prior to statistical analyses. Given that the number of hand wipe samples differed between adults and children, we used both Independent-Samples t Test to determine the difference in hand wipe OPE levels between

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adults (n = 51) and children (n = 31) and Paired-Samples t Test for matched adult and children hand wipes from the same homes (n = 31 each). Spearman's correlation analyses were used to determine the correlations of OPE levels between house dust and hand wipes. Linear regression models were employed to determine predictors of continuous OPE levels in hand wipes for adults and children separately.[28] The beta coefficients were exponentiated to produce the multiplicative change in hand wipe levels relative to the reference group for categorical variables or the per-unit change for continuous variables (age only in the present study).[28] Dust concentrations were categorized into tertiles as predictors of OPE levels in hand wipes, while other categorical variables (i.e., sex, hand washing frequency, hours per day spent in homes, dwelling size, indoor temperature, indoor humidity, and the number of electronic equipment in homes) were dichotomized. Statistical analyses were conducted using PASW Statistics 18.0 (IBM Inc.). The level of significance was set at α = 0.05.

RESULTS AND DISCUSSION

Concentrations and Compositions of OPEs in Indoor Dust. In addition to the 10 traditional OPEs (i.e., EHDPHP, TNBP, TBOEP, TMPP, TCEP, TCIPP, TDCIPP, TEP, TEHP, and TPHP), five novel OPEs of interest (i.e., BPA-BDPP, BPDPP, CDP, IDDPP, and RDP) were also frequently detected (detection frequency = 77−100%) in South China house dust (Table 1). V6 was only detected in 8% of the samples. The total concentrations of these six novel OPEs ranged from 142−16 550 ng/g (median: 1230 ng/g) in house dust (Table 1), constituting an average of 19% of the total concentrations of all detected OPEs and even comparable with PBDEs concentrations previously reported in South China house dust (median: 820 ng/g; range: 215−27 950 ng/g).[21] Our data indicate broad applications of these novel OPEs in Chinese household products and subsequent releases to home environments in considerable amounts.

Dust data remain limited for the six novel OPEs (i.e., BPA-BDPP, BPDPP, CDP, IDDPP, RDP, and V6). The concentrations and relative abundances of individual novel OPEs varied greatly among studies (Table S5).[5,6,36,37] BPA-BDPP dominated over other novel OPEs in South China house dust, where its concentrations were generally 1 order of magnitude higher than those reported elsewhere (Table S5). By contrast, IDDPP was more abundant than other novel OPEs in Norwegian and United Kingdom (UK) house dust. The median concentrations of BPA-BDPP, RDP, IDDPP, and V6 were determined to be 35.4, <1.8, 51.3, and 4.1 ng/g in Norwegian dust and 66.8, 1.9, 401, and 16.6 ng/g in UK dust, respectively.[6] BPA-BDPP, RDP, IDDPP, and V6 were also detected in Greek car dust, with median concentrations of 16, 4, 117, and 13 ng/g, respectively.[5] V6 was reported with a median concentration of 12.5 ng/g in U.S. house dust and 103 ng/g in car dust.[7] These findings suggest country-specific demand and applications of these novel OPEs, indicating different human exposure risks.

Bisphenol A bis(diphenyl phosphate) (BPA-BDPP) is often used as a substitute for TPHP, although the latter chemical is still used extensively and found at high levels in indoor environments.[2] BPA-BDPP has a lower volatility and hypothetically migrates from host products to a lesser extent than TPHP.[2] For the same rationale, RDP is used as a substitute for TCEP and TCIPP and also coapplied with TPHP in some cases.[2,38] BPA-BDPP and RDP were also suggested as safe substitutes for DecaBDE,[39] while V6 was suggested as an alternative for PentaBDE, TCIPP, and TDCIPP.[40] It is expected that some of these substitutive OPEs are subject to increasing applications to replace chlorinated OPEs and some other halogenated flame retardants,[40] even without sufficient environmental and toxicity evaluations. It is noted that the TPHP-based substitutive OPEs containing no less than three phenyl groups (i.e., BPA-BDPP, BPDDP, CDP, IDDPP, and RDP) have log K_{ow} (octanol−water partition coefficient) ranging from 4.5 to 7.4, greater than that of most other OPEs. Compared with other OPEs, these TPHP analogues may possess greater bioaccumulation potency and are more resistant to metabolism.[41] Indeed, the bioconcentration factors (BCFs) of RDP, IDDPP, and CDP are estimated to be 20 500, 417 000, and 1711, respectively.[2] Cresyl diphenyl phosphate (CDP) has been reported with reproductive and developmental toxicity and moderate aquatic toxicity.[2] Available data did not suggest carcinogenic or developmental toxicity for BPA-BDPP and RDP, but to date only few environmental exposure and toxicity studies are available for novel OPEs. Therefore, the detection of these novel OPEs in dust from South China and some other regions raises the need for the inclusion of them in future human exposure assessments.

Dust and Hand Wipes. Chemicals in dust may attach to hands via direct contact with surfaces and then enter the body via incidental ingestion through hand-to-mouth contact or dermal absorption.[42] Hand wipe sampling provides an estimation of the amounts of chemicals on hands and subsequent exposure via hand-to-mouth contact. Eight OPEs, including BPA-BDPP, EHDPHP, TBOEP, TEHP, TCEP, TCIPP, TDCIPP, and TPHP, had a detection frequency of 69−100% in sampled hand wipes. They collectively contributed to an average of 92.4% and 95.8% of the total OPE mass in adults' and children's hand wipes, respectively, whereas the other OPEs had a detection frequency generally below 25% (Table 1). Therefore, only these eight OPEs were included for statistical analyses and subsequent discussion.

The total mass of these eight OPEs detected in hand wipes (referred to Σ_8OPEs) did not differ significantly between adults and children (median: 76.9 ng versus 58.9 ng; p = 0.44 for Independent-Samples t Test or 0.92 for Paired-Samples t Test). Composition profiles of selected OPEs differed between hand wipes and dust (Figure 1). In contrast with the dominance of TDCIPP in dust, the proportion of TEHP was comparable with that of TDCIPP in hand wipes (Figure 1). The relatively greater log K_{ow} (9.49) of TEHP may contribute to a better association with skin lipids compared with TDCIPP (log K_{ow} = 3.65), likely resulting in a significant increase from dust to hand wipes in the proportion of TEHP and a decrease of TDCIPP proportion. However, the underlying mechanisms for chemical-specific sorption to human hands and influencing factors require better elucidation in the future.

Concentrations of Σ_8OPEs did not exhibit a significant correlation between adults' hand wipes and house dust (p = 0.09), but the association was statistically significant (p = 0.002) between children's hand wipes and dust (Figure 2). Adults are active at different microenvironments (e.g., workplace, home, and automobiles); thus, adults' hand wipes may not reflect exposure solely at home but integrate exposure from multiple microenvironments.[42] Children spend more time in home than adults (i.e., 20 versus 16 h/day in average) and have a higher frequency of contact with dust or items with dust attached on the surfaces (e.g., toys).[43] Children's hand-to-

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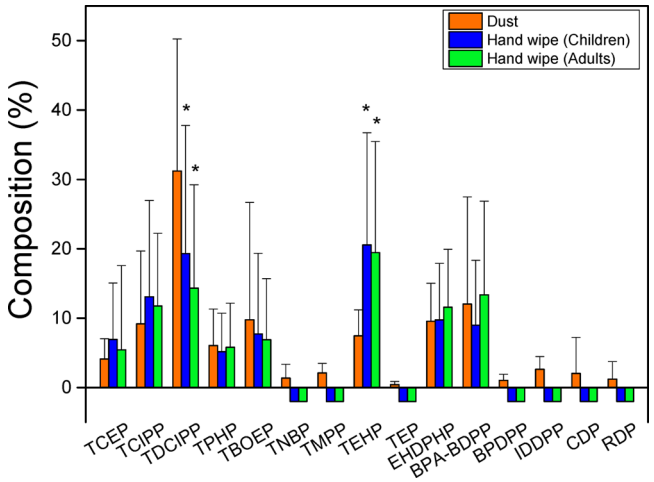

Figure 1. Compositions of organophosphate esters (OPEs) in dust and hand wipes from children and adults. Error bars represent standard deviations. Downside bars represent OPEs with a detection frequency less than 25%. Asterisks indicate that the compositions of an OPE in hand wipes are significantly different from that in dust ($p < 0.01$).

mouth contact frequencies are also significantly greater indoors than outdoors.[32] These factors likely contribute to a significant association of indoor dust with hand wipes from children but not from adults.

We further used linear regression models to determine predictors of continuous levels of OPEs in hand wipes by including demographic and behavioral data. Increasing concentrations of Σ_8OPEs in house dust were strongly associated with their levels in children's hand wipes. Child participants with the highest dust concentrations (3rd tertile) of Σ_8OPEs in their homes averaged 2.88 times (95% CI: 1.40, 5.90) the levels in hand wipes compared with those with the lowest dust concentrations (Table 2). No significant association was observed between dust and adults' hand wipes. When individual OPEs were examined, we found that increasing dust concentrations of TCIPP, TDCIPP, or TPHP, but not any other OPE, were strongly associated with their levels in children's hand wipes. For example, children with the highest dust levels (3rd tertile) of TCIPP, TDCIPP, and TPHP in their homes averaged 5.43 (95% CI: 1.45, 20.32), 4.59 times (95% CI: 1.55, 13.65), and 4.39 times (95% CI: 1.50, 12.88) the levels of these three OPEs in their hand wipes compared with those with the lowest dust levels, respectively (Table 2). Phillips et al. also reported positive and significant correlations between paired dust and children's hand wipes for TCIPP, TPHP, TBOEP, 4-tert-BPDPP, and 2-isopropylphenyl diphenyl phosphate.[8] Significant correlations in TBOEP or TPHP levels were also observed between preschool dust and children's hand wipes in a Swedish study.[29] By contrast, in our adults' hand wipes only TPHP, but not any other individual OPEs or Σ_8OPEs, exhibited a marginally significant association between hand wipe and dust concentrations ($p = 0.04$). The lack of an association for other OPEs may suggest additional sources other than dust contributed to the sorption of OPEs on hands. Weschler and Nazaroff suggested that indoor air may have a considerable contribution of selected OPEs to human hands.[44] Chemical-specific physicochemical properties, such as the octanol–air partition coefficient (K_{oa}), may affect environmental behavior and fate of different OPEs in indoor environments. Stubbings et al. revealed a bell shape relationship between log K_{oa} and the dust/air partition of OPEs and the dust/air concentration ratio peaks at a log K_{oa} of 13–15.[45] Such chemical-specific fate in indoor environments confounds the prediction of OPEs in hand wipes from dust concentrations alone. This merits further investigations.

Other factors may also affect OPE levels on human hands. Our results indicate that hand washing frequency inversely influenced children's hand wipe concentrations of Σ_8OPEs, TPHP, or TBOEP (Tables S6 and S7). Hand washing frequency did not influence Σ_8OPEs or any individual OPEs in adults' hand wipes, with the only exception for TEHP (Tables S6 and S7). Our data indicated a greater influence of hand washing on hand-associated OPEs for children than adults. However, an inverse association of hand washing frequency with hand wipe levels of TDCIPP was reported in a US adult population.[28] Hand washing also appeared to be a significant predictor of pentaBDE concentrations in hand wipes and serum from a US adult population, contributing to 16% of the variation of pentaBDE levels in hand wipes and 20% of the variation in serum.[42] Liu et al. demonstrated that washing with soap and water could remove 76%, 72%, and 67% of TCEP, TCIPP, and TPHP from hands, respectively.[46] Thus, in addition to the prevalence of OPEs in indoor environment,

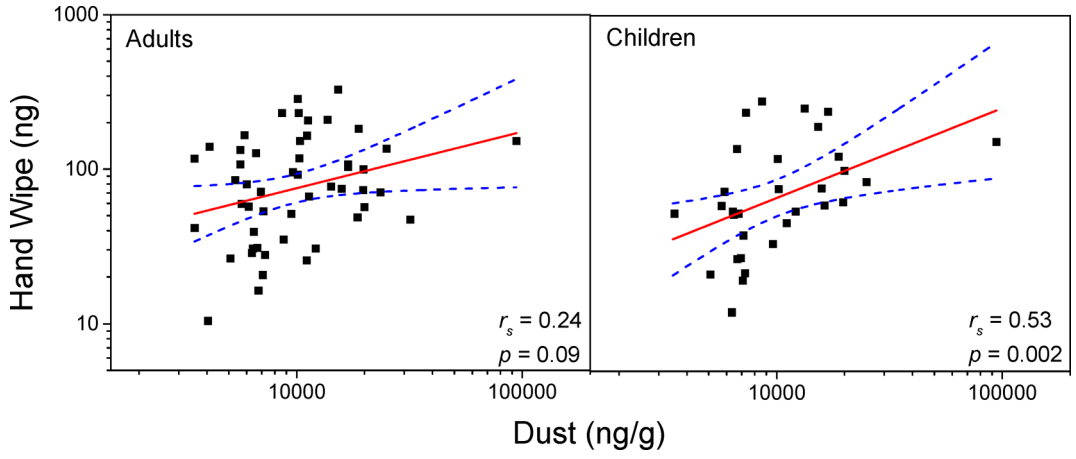

Figure 2. Correlations between dust and hand wipes in the levels of Σ_8OPEs (including BPA-BDPP, EHDPHP, TBOEP, TEHP, TCEP, TCIPP, TDCIPP, and TPHP). Dashed lines represent ±95% confidence bands.

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Table 2. Regression Analyses for Organophosphate Ester Concentrations in Dust As Predictors of Hand Wipe Levels

		children's hand wipes				adults' hand wipes			
		mid dust levels		high dust levels		mid dust levels		high dust levels	
OPE	low dust levels	coefficient[a] (95% CI)	*p*-value	coefficient (95% CI)	*p*-value	coefficient (95% CI)	*p*-value	coefficient (95% CI)	*p*-value
TCEP	reference	1.71 (0.43−6.87)	0.43	1.73 (0.42−7.10)	0.43	0.74 (0.25−2.71)	0.78	2.15 (0.63−7.33)	0.21
TCIPP	reference	1.67 (0.47−5.93)	0.41	5.43 (1.45−20.32)	0.02	0.85 (0.35−2.00)	0.69	2.38 (0.91−6.24)	0.08
TDCIPP	reference	5.28 (1.51−18.49)	0.05	4.59 (1.55−13.65)	0.03	1.49 (0.40−5.51)	0.55	3.66 (0.92−14.52)	0.06
TPHP	reference	3.85 (1.52−9.75)	0.01	4.39 (1.50−12.88)	0.01	1.77 (0.78−4.00)	0.17	2.21 (1.02−4.79)	0.04
TBOEP	reference	0.65 (0.10−4.23)	0.64	1.95 (0.40−9.55)	0.39	1.86 (0.75−4.62)	0.19	1.43 (0.57−3.60)	0.43
TEHP	reference	1.54 (0.43−5.51)	0.49	1.27 (0.36−4.52)	0.70	1.40 (0.54−3.63)	0.48	1.80 (0.71−4.58)	0.21
EHDPHP	reference	0.49 (0.16−1.46)	0.19	0.64 (0.25−1.67)	0.35	0.91 (0.39−2.14)	0.83	0.90 (0.43−1.90)	0.78
BPA-BDPP	reference	1.27 (0.33−4.93)	0.71	1.37 (0.31−6.07)	0.67	0.70 (0.23−2.16)	0.52	2.38 (0.68−8.63)	0.18
Σ_8OPEs	reference	2.01 (1.04−3.87)	0.04	2.88 (1.40−5.90)	0.01	1.55 (0.92−2.60)	0.09	1.63 (0.98−2.72)	0.06

[a]Coefficient = Exponentiated beta coefficient, representing the multiplicative change in hand wipe levels relative to the reference group of dust concentrations.

hand washing also appears to affect the levels on hands, but the influence may be chemical-specific and vary among study populations.

Interestingly, our data also suggested that indoor temperature (>25 °C vs ≤25 °C) was inversely associated with Σ_8OPEs in both children's and adults' hand wipes (10^{β} = 0.49; 95% CI: 0.29, 0.83 and 10^{β} = 0.43; 95% CI: 0.26, 0.70, respectively), whereas indoor humidity had no affect (Table S6). The influence of indoor temperature on hand wipe Σ_8OPEs levels was even more significant for adults than children (p = 0.002 vs p = 0.01). Indoor temperature was also inversely associated with the levels of TNBP, TEHP, and EHDPHP in adults' hand wipes and TCIPP and TEHP levels in children's hand wipes. These associations may be due to overall greater dust concentrations of OPEs in lower versus higher temperature environment, consequently leading to greater levels on hands under lower temperatures. Although our data did not reveal an association of lower temperatures with higher dust concentrations (p = 0.20), Cao et al. reported seasonal variations of OPEs in indoor dust (i.e., greater concentrations in late winter and early spring versus summer).[47] Therefore, our results imply that exposure from hand-to-mouth contact may be more significant under cooler indoor environments. It is noteworthy that two recent studies have shown increased urinary metabolite concentrations of selected OPEs (e.g., TDCIPP and TPHP) in the summer compared to winter months, likely suggesting increased exposure with temperature.[48,49] The underlying factors resulting in these different findings remain unknown, but it may suggest that increased exposure via pathways other than hand-to-mouth contact or dust ingestion likely occur during warmer periods. For example, seasonal fluctuations in outdoor urban air concentrations have been reported for TCEP, TCIPP, TDCIPP, TPHP, and TNBP, with increased concentrations during the warmer periods.[50] Inhalation in outdoor or other microenvironments may constitute an important contribution to internal exposure during warm periods.[50] Therefore, the prevalent exposure pathways driving OPE exposure may be season- or temperature-dependent, which merits future investigations.

None of the other considered demographic or environmental factors, including age, sex, hours/day spent in homes, dwelling size, and the number of electronic equipment, were associated with hand wipe Σ_8OPEs levels (Tables S6 and S7). The age influence on children's hand-to-mouth behavior is not well studied. A meta-analysis of children's hand-to-mouth behavioral data suggested that both indoor and outdoor hand-to-mouth frequencies decrease as age increases from 3 months to <11 years.[32] The same conclusion was reached by Tulve et al., who reported the highest frequency of mouthing behavior for children less than 24 months and the frequency decreased with age.[51] However, other data indicated no differences in the hand-to-mouth frequency during the age range of 1−4 years.[52] It should be noted that our results may be complicated by other factors, such as the variations in the time of hand wipe sampling and hand areas between individual participants. For example, Stapleton et al. measured repeated wipe sampling and suggested that PBDE levels on the hand may not be consistent over time for all individuals.[35] Liu et al. also found that hand wipe levels of TCEP and TCIPP remained stable in three repeated measurements over a 3-month period, whereas TPHP did not.[46] Chemical-specific physicochemical properties in indoor environment and variations between individual participants in personal behavior could substantially confound data interpretation.

Exposure Assessment. The risks of human exposure to OPEs were estimated by evaluating two exposure routes: dust ingestion and hand-to-mouth contact (Table 3). It is noted

Table 3. Estimation of Exposure from Dust Ingestion and Hand-to-Mouth Contact

	median	mean	5th	95th
Children				
hand to mouth[a]	37.2	58.5	11.0	167.4
dust ingestion (average exposure)[a]	22.6	32.2	8.3	64.3
dust ingestion (average exposure)[b]	2.6	3.0	0.9	5.2
dust ingestion (high exposure)[a]	90.6	128.8	33.2	257.3
dust ingestion (high exposure)[b]	10.4	11.8	3.4	21.0
Adults				
hand to mouth[a]	1.5	2.0	0.4	5.4
dust ingestion (average exposure)[a]	1.9	2.7	0.7	5.4
dust ingestion (average exposure)[b]	0.2	0.2	0.1	0.4
dust ingestion (high exposure)[a]	4.9	6.9	1.8	13.7
dust ingestion (high exposure)[b]	0.5	0.6	0.2	1.2

[a]For eight OPEs frequently detected in hand wipes, including BPA-BDPP, EHDPHP, TBOEP, TEHP, TCEP, TCIPP, TDCIPP, and TPHP. [b]For additional OPEs, including TNBP, TMPP, TEP, BPDPP, CDP, IDDPP, and RDP.

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that these two pathways are not completely independent. Dust ingestion represents the holistic exposure via the ingestion of dust particles from various sources (e.g., floor dust, dust particles on the surfaces of furniture or toys, and dust particles present on hands). Hand-to-mouth contact leads to one form of incidental ingestion of contaminants which are either associated with dust particles (or other small particles) present on hands or absorbed to skin lipids following contact with consumer products. It is also noted that two other pathways (i.e., inhalation and dermal absorption) are also important to human exposure,[53,54] but they were not investigated in the present study. Inhalation was not investigated here due to the lack of air concentration data. Estimation of dermal absorption was limited by the lack of hand surface area data (not measured in our study) and experimental data of the absorption fraction or the transdermal permeability coefficient for most OPEs[46,53] Abdallah et al. also points out that accurate estimation of dermal absorption is influenced by other factors, such as transdermal metabolism and removal of dermal contaminants through eccrine sweat and hair follicles.[55] However, knowledge on these factors remains very limited for OPEs.

We assumed an average and high dust ingestion rate (DIR) to be 20 and 50 mg/day for adults and 50 and 200 mg/day for children, respectively.[10,56] On the basis of the collected questionnaires, we determined that the children and adults of the study population had an average body weight of 17 and 64 kg and spent an average of 83.3% and 66.7% of their time in homes, respectively (Table S8). For the eight OPEs frequently detectable in hand wipes, we estimated the adults' median daily exposure rate via dust ingestion to be 1.9 ng/kg bw/day under the average exposure scenarios and 4.9 ng/kg bw/day under the high exposure scenarios. Elevated exposure was estimated for children who have a median daily ingestion rate of 22.6 or 90.6 ng/kg bw/day under the average or high exposure scenarios, respectively. Table 3 also lists the daily ingestion rates of the additional OPEs (i.e., TNBP, TMPP, TEP, BPDPP, CDP, IDDPP, and RDP) which are estimated to be 2.6 and 10.4 ng/kg bw/day for children and 0.2 and 0.5 ng/kg bw/day for adults under the average and high exposure scenarios, respectively. The more time staying in home environment, higher frequency of dust ingestion, and less body weights in combination result in an elevated exposure risk for children compared with adults.

Hand-to-mouth contact appears to represent an important exposure pathway in addition to dust ingestion. On the basis of the parameters summarized in Table S8,[32,35,51,57] the daily exposure to eight OPEs via hand-to-mouth contact was estimated to be 37.2 and 1.5 ng/g kg bw/day for children and adults, respectively (Table 3). For children the median exposure via hand-to-mouth contact is estimated to be approximately 50% greater than that through dust ingestion under the average exposure scenarios, although it is lower than the exposure estimation under the high exposure scenarios. For adults the estimated exposure via hand-to-mouth contact is also comparable to that via dust ingestion under the average exposure scenarios. These estimations suggest that hand-to-mouth contact plays an important role in OPE exposure, particularly for children. This may also be true for many other indoor chemicals that are present on hands.[43]

Previous studies have demonstrated that hand wipes can effectively predict internal exposure to certain flame retardants and are a better predictor than house dust.[43] For example, PentaBDEs measured on toddlers' hands could explain 32% of the serum variability, better than the prediction from indoor dust alone.[43] Hand wipe samples also provided a good prediction of serum PentaBDEs levels in office workers.[42] Another study reported a significant correlation between hand wipe levels of TDCIPP or TPHP and the urinary levels of their metabolites, whereas no association was observed between dust and urinary levels.[28] Hand wipes not only reflect exposure via hand-to-mouth contact, but also integrate information from multiple microenvironments and the influences of behavioral aspects (i.e., hand wash frequencies) and even reflect potential dermal absorption.[8,28,33,35] However, it should be noted that for the OPEs not detectable or detected at very low levels in hand wipes, dust ingestion could play a more important role than hand-to-mouth contact in human exposure.

Limitations of the present study exist in a number of aspects. First, relatively small sample sizes limit the power of statistical analyses. Self-reported behavioral data may be inaccurate for some participants. Second, exposure pathways other than dust ingestion and hand-to-mouth contact, such as dermal exposure and inhalation, could contribute to the overall human exposure,[43] but were not investigated in our study. The relative importance of different exposure pathways may be chemical-specific and season-dependent. For example, Wensing et al. suggested that humans are exposed to chemicals with boiling points above 400 °C mainly via oral and dermal exposure, whereas oral and inhalative exposure are more important for chemicals with boiling points below 400 °C.[58] Considering the wide range of boiling points (i.e., 181−680 °C) for different OPEs, chemical-specific exposure pathways should be assessed in future studies. Third, although we estimated exposure based on dust and hand wipes, the lack of urine or blood samples prevented us from better characterization of internal exposure and its association with different exposure pathways. Available human biomonitoring studies mainly focused on traditional OPEs and the associations of dust or hand wipes with urine/serum were only demonstrated for limited OPEs (e.g., TDCIPP, TPHP, TCIPP, and monosubstituted isopropylated triaryl phosphate).[8,28,59] Future studies are needed to better characterize internal exposure to novel OPEs and the validity of using hand wipes to predict internal exposure.

It merits attention that in addition to the OPEs included in the present study more new analogues have been produced or exist as impurities in flame retardant mixtures. For example, Phillips et al. identified several isopropylated and *tert*-butylated triarylphosphate isomers in commercial flame retardant mixtures, as well as in house dust Standard Reference Material SRM 2585, demonstrating their environmental relevance.[60] Impurities of RDP, including meta-hydroxylated RDP, RDP with the loss of a phenyl group, and RDP oligomers, were reported in plastics and dust collected on electric/electronic material.[38] The growing body of the suite of OPE chemicals increases the overall exposure risk, but most novel OPEs have rarely been included in human exposure assessments. Metabolic transformation of novel OPEs, particularly TPHP-based analogues, should also be explored for the kinetics, products, and associated biological effects. Overall, given the broad occurrence of OPEs in indoor and outdoor environments and potential toxic effects, more in-depth and large-scale human exposure studies are warranted to better characterize exposure pathways and risks, particularly for novel OPEs.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.8b02933.

Tables S1−S8, Figure S1, detailed description of mass spectrometric confirmation of selected novel OPEs (PDF)

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The authors declare no competing financial interest.

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