

Organophosphate Esters in Children and Adolescents in Liuzhou City, China: Concentrations, Exposure Assessment and Predictors

Meng Yu

Tongji Medical College of Huazhong University of Science and Technology: Huazhong University of Science and Technology
Tongji Medical College

Xiang Li

Tongji Medical College of Huazhong University of Science and Technology: Huazhong University of Science and Technology
Tongji Medical College

Bingqing Liu

Women's Hospital School of Medicine Zhejiang University

Yaping Li

Tongji Medical College of Huazhong University of Science and Technology: Huazhong University of Science and Technology
Tongji Medical College

Ling Liu

Tongji Medical College of Huazhong University of Science and Technology: Huazhong University of Science and Technology
Tongji Medical College

Limei Wang

Tongji Medical College of Huazhong University of Science and Technology: Huazhong University of Science and Technology
Tongji Medical College

Lulu Song

Tongji Medical College of Huazhong University of Science and Technology: Huazhong University of Science and Technology
Tongji Medical College

Youjie Wang

Tongji Medical College of Huazhong University of Science and Technology: Huazhong University of Science and Technology
Tongji Medical College

Liqin Hu

Wuhan Childrens Hospital: Wuhan Women and Children Medical Care Center

Surong Mei (✉ surongmei@hust.edu.cn)

Huazhong University of Science and Technology Tongji Medical College

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Abstract

Dermal contact with dust is commonly considered an important pathway of exposure to organophosphate esters (OPEs), but the importance of OPE uptake from diet is unclear. Herein, we used hand wipes to estimate OPE exposure from indoor dust and examined whether urinary OPE metabolite concentrations were influenced by sociodemographic characteristics, OPE amount in hand wipes, and dietary factors. OPEs were measured in urine and hand wipes from 6–18-year old children and adolescents (n=929) in Liuzhou, China. Sociodemographic and dietary factors were obtained from questionnaire. Six OPE metabolites were detected in >70% of the urine samples, and seven OPEs were detected in >50% of the hand wipes. Estimated daily intakes (EDIs) were calculated using urinary OPE metabolites to investigate the total daily intake of OPEs, in which 0.36–10.1% of the total intake was attributed to the exposure from dermal absorption. In multivariate linear regression models, sex, age, and maternal education were significant predictors of urinary OPE metabolite concentrations. Urinary diphenyl phosphate (DPHP) is positively associated with its parent compounds 2-ethylhexyl-diphenyl phosphate (EHDPP) and triphenyl phosphate (TPHP) in hand wipes. High versus low vegetable intake was associated with a 23.7% higher DPHP (95% confidence interval (CI): 0.51%, 52.1%). Barreled water drinking was associated with a 30.4% (95% CI: 11.8%, 52.0%) increase in bis(1-chloro-2-propyl) 1-hydroxy-2-propyl phosphate (BCIPHIPP) compared to tap water drinking. Our results suggested the widespread exposure to OPEs in children and adolescents. In addition to dermal absorption, dietary intake may be an important exposure source of certain OPEs.

1. Introduction

Organophosphate esters (OPEs) are increasingly used as flame retardants and plasticizers in consumer and industrial products due to the phase-out of some polybrominated diphenyl ethers (PBDEs). It was reported that phosphorous and brominated flame retardants accounted for 11% and 23% of the total global consumption of flame retardants in 2008, respectively. However, the percentage contribution of phosphorous flame retardants increased to 30%, and brominated flame retardants attenuated to 20% in 2017 (Wang et al., 2020). Because OPEs are frequently physically mixed with polymers, they can easily be released from treated products into the external environment, leading to a frequent detection of OPEs in air (Hou et al., 2021), sediments and waters (Ye et al., 2021), foodstuffs (Li et al., 2019a), and biota (Pantelaki and Voutsas, 2020). Concerns regarding these replacement OPEs have mounted, because toxicological studies suggested that some OPEs are considered endocrine disruptors (Liu et al., 2012), and carcinogenic- (Böckers et al., 2020), neurodevelopment- (Rock et al., 2020), and reproductive toxicants (Xu et al., 2017b).

Humans can be exposed to OPEs through different pathways, including dust ingestion and inhalation, dermal absorption, and dietary intake (Cequier et al., 2015; Liu et al., 2017). After being absorbed, OPEs could be rapidly metabolized (several hours to days) and excreted into the urine (Hou et al., 2016). Urinary OPE metabolite concentrations reflect integrated exposure from different pathways and have been extensively recognized as biomarkers of exposure to OPEs. A growing body of studies have estimated the total daily intake of OPEs through the monitoring of urinary OPE metabolite concentrations in the general population (Zhang et al., 2018b), children (Bastiaansen et al., 2021; Chen et al., 2018; Zhang et al., 2018a), and pregnant women (Bai et al., 2019; Chen et al., 2019). Additionally, the contamination levels of OPEs in indoor dust have been used to estimate nondietary exposure, which was considered one of the most important exposure pathways. To identify individual's exposure from indoor microenvironments, hand wipes could be an effective metric because it reflects the exposure from dermal contact with dust and other media (e.g., indoor consumer products) (Larsson et al., 2018). Similar dermal exposure estimates were obtained for several halogenated flame retardants (HFRs) when the exposure assessment was based on direct measurements from hand wipes or the indirect measurement from indoor dust (Tay et al., 2018). Human dermal absorption of OPEs could be estimated using the mass of OPEs in hand wipes, which has been reported in biomonitoring studies (Liu et al., 2017; Xu et al., 2016).

Although several studies have previously suggested that dermal contact with dust and inhalation are two more important pathways (He et al., 2018c; Wei et al., 2015; Xu et al., 2016), there is increasing concern regarding the occurrence of OPEs in foods, and the importance of diet as an exposure source of OPEs has been studied (Li et al., 2019a). Zhang et al. (2016) monitored the residue levels of OPEs in 75 commonly consumed foods in China and detected OPEs in 100% of the food samples. He and Wang (2018) collected 87 food samples from Southeast Queensland, Australia, and found that OPEs and their metabolites were both frequently detected in various foodstuffs. However, the associations between dietary factors and the body

burden of OPEs in humans are unclear. In a Norwegian adult cohort, Xu et al. (2017a) detected OPEs in duplicate diet samples (n=61) and found that meat intake was the primary dietary exposure source of OPEs. A study conducted in eastern China showed that postpartum women (n=50) who consumed more vegetables before pregnancy had a higher tris(2-chloroisopropyl) phosphate (TCIPP) level in placentas than those who consumed few vegetables (Ding et al., 2016). A study of toddlers aged 15–18 months in the USA (n=41), using dietary survey data, reported that meat and fish consumption may be linked with increased bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) and diphenyl phosphate (DPHP) concentrations in urine (Thomas et al., 2017). Nevertheless, research using a larger sample size is warranted to verify the previous results.

Children and adolescents have more rapid nutrient absorption, metabolic and ventilation rates, and larger ratio of surface area to body weight as compared to adults (Van den Eede et al., 2015), thus, the body burden of OPEs in children and adolescents may be higher. The monitoring surveys in China suggested that children and adolescents are ubiquitously exposed to OPEs, especially chlorinated alkyl phosphates (Chen et al., 2018; Ding et al., 2019). Childhood and adolescence are in the critical periods of development, and developing organ systems are more susceptible to chemical exposure, including OPEs (Scheuplein et al., 2002). Considering increasing exposure to OPEs and their potential health risks, determining the factors that may impact OPE exposure in children and adolescents has been of growing concern. However, the related studies are very limited, especially in China (Bastiaensen et al., 2020; Bastiaensen et al., 2019; Bastiaensen et al., 2021; Phillips et al., 2018).

Therefore, we measured OPEs in urine and hand wipe samples from children and adolescents aged 6–18 years in Liuzhou, China. The purpose of this study was to determine 1) the exposure levels of OPEs in children and adolescents; 2) the contribution of dermal exposure dose to the total daily intake of OPEs; and 3) the associations between urinary OPE metabolites and OPE mass in hand wipes, as well as sociodemographic characteristics and dietary factors.

2. Methods

2.1 Study design

From February 2018 to May 2018, a total of 1388 children and adolescents (6–18 years old) were recruited from a cross-sectional study in Liuzhou, China. The participants were selected from eight schools, including three primary schools, three middle schools, and two high schools. Of participants, 1194 persons provided urine samples and 1228 persons provided hand wipe samples, in which 1034 persons had paired urine-hand wipes. After exclusion of participants with missing data on dietary assessment, our final analysis consisted of 929 children and adolescents who provided urine and hand wipe samples, and had complete data on dietary assessment. The detailed information on the selection of the study participants was provided in Fig. S1.

Informed consent was provided by the participant's parents. Ethical approvals were obtained from Tongji Medical College, Huazhong University of Science and Technology.

2.2 Dietary assessment

Information on dietary factors was obtained using food frequency questionnaires, which is frequently used in large sampling campaigns. The questionnaire was provided to obtain the dietary patterns for the study participants, and they completed the questionnaire with their parents and were guided by trained researchers. In the questionnaire, seven frequently consumed food groups were administrated in the food items, including four foods of animal origin (meat, fish, eggs, and dairy products) and three foods of plant origin (vegetables, fruits, and beans). The consumption rate (per week) of the seven food groups is detailed in Table S1 and was categorized into tertiles for further analysis (Table 1). Additionally, the daily source of drinking water was recorded, and a four-category option was set in this item, including tap water, barrelled water, purified water, and others (e.g., well water).

Table 1
Sociodemographic and dietary characteristics of children and adolescents.

Variable	Mean \pm SD or n (%)
Age (year)	12.5 \pm 3.2
Sex	
Male	431 (46.4)
Female	498 (53.6)
Maternal education	
Less than high school	482 (51.9)
High school	229 (24.7)
College or above	218 (23.4)
Meat (times/week)	
≤ 2	287 (30.9)
3–5	360 (38.8)
≥ 6	282 (30.4)
Fish (times/week)	
0	328 (39.5)
1	331 (35.6)
≥ 2	270 (29.1)
Eggs (times/week)	
≤ 2	270 (29.1)
3	374 (40.2)
≥ 4	285 (30.7)
Dairy products (times/week)	
≤ 2	333 (35.8)
3–5	301 (32.4)
≥ 6	295 (31.8)
Fruits (times/week)	
≤ 3	378 (40.7)
4–5	259 (27.9)
≥ 6	292 (31.4)
Vegetables (times/week)	
≤ 4	289 (31.1)
5–6	176 (19.0)
≥ 7	464 (49.9)
Beans (times/week)	

Variable	Mean ± SD or n (%)
≤1	367 (39.5)
2	233 (25.1)
≥3	329 (35.4)
Drinking water	
Tap water	586 (63.1)
Barreled water	205 (22.1)
Purified water	131 (14.0)
Others	7 (0.8)

2.3 Sample collection

During the school visit, a 5 mL polypropylene container marked with a unique identification number was given to each participant for spot urine collection. The collected urine samples were placed in carton and transferred to the laboratory.

The collection of hand wipes was performed as described in our previous study (Tao et al., 2018). Briefly, a sterile gauze pad (6×8 cm) soaked in 5 mL of isopropanol was used to wipe the palm and back of each subject's hands. Subsequently, the collected hand wipe samples were enclosed in 50 mL polystyrene centrifuge tubes. Meanwhile, field blank samples were collected from all the schools.

2.4 Sample analyses

Prior to urine analysis, specific gravity (SG) was detected using refractometer (Atago PAL-10S, Tokyo, Japan), and urinary OPE metabolites were adjusted for dilution before statistical analyses. Eight urinary OPE metabolites, including tris(2-chloroethyl) phosphate (TCEP), 1-hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate (BCIPHIPP), BDCIPP, dibutyl phosphate (DBP), DPHP, 4-hydroxyphenyl-diphenyl phosphate (4-OH-DPHP), bis(2-butoxyethyl) phosphate (BBOEP), and di-ocresyl phosphate & di-p-cresyl phosphate (DoCP & DpCP) were measured according to our previous method (Hu et al., 2019). 0.2 ng and 2 ng standard solutions spiked in the pooled urine samples were used as quality control (QC) samples. The mean spiked recovery from QC samples was acceptable and ranged from 79%–119%.

The hand wipes samples were analyzed for TCEP, TCIPP, tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), triphenyl phosphate (TPHP), 2-ethylhexyl diphenyl phosphate (EHDPP), tris(2-butoxyethyl) phosphate (TBOEP), tricresyl phosphate (TCrP), and tris(2-ethylhexyl) phosphate (TEHP). The OPE measurement in hand wipes was modified based on a previous study (Tao et al., 2018). 2 ng and 20 ng standard solutions spiked in sample matrices were used as QC samples. The average spiked recovery of OPEs in the QC samples exhibited acceptable accuracy, with a range from 82–108%.

2.5 Exposure assessment

Estimated daily intakes (EDIs) were assessed using urinary OPE metabolite concentrations to determine the total daily intake of OPEs in children and adolescents. The calculation for EDIs (ng/kg bw/day) was described as:

$$EDI = \frac{C_{mOPEs} \times V_{urine}}{F_{ue} \times bw} \times \frac{MW_p}{MW_m} \quad (1)$$

where C_{mOPEs} (ng/mL) is the SG-corrected concentrations of individual OPE metabolites in case of this study; V_{urine} (mL/day) is the reference value of daily urinary volume (Zhang et al., 2018b); F_{ue} (unitless) is the urinary excreted molar fraction of metabolite to its corresponding parent compound (Van den Eede et al., 2013); bw (kg) is the body weight; MW_p and MW_m (g/mol)

are the molecular weights of the parent compound and its metabolite respectively. The parameters for estimating EDI were showed in Table S2–S3.

Dermal exposure dose (DED, ng/kg bw/day) of OPEs was estimated based on the amount of OPEs in hand wipes and was calculated as:

$$DED = \frac{C_S \times SA \times AF \times ED}{bw} \quad (2)$$

where C_S (ng/m²) is individual OPE concentration on hand surface; SA (m²) is the exposed surface area (USEPA, 2011); AF (unitless) is absorption factor adopted from human ex vivo skin experiments (Abou-Elwafa Abdallah et al., 2016); ED (h day⁻¹) is the exposure time, which was assumed as 24 h; and bw (kg) is the body weight. The parameters of SA among different age group and AF of individual OPEs were showed in Table S4–S5.

2.7 Statistical analyses

Extracted samples with OPE concentrations below the LOD were substituted with LOD/ $\sqrt{2}$. Compounds with a detection frequency >50% were included in all statistical analyses, whereas we did not analyze TEHP in hand wipes due to the greatly varied concentrations of TEHP in the QC samples. The concentrations of urinary OPE metabolites were natural log-transformed due to the lack of normally distributed. Spearman correlation coefficients (r_s) were used to determine the associations between OPE metabolites in urine and OPEs in hand wipes.

Multivariate linear regression model was applied to investigate the potential predictors of urinary OPE metabolite concentrations. The following variables were included in the models: subject's sex and age (categorical variable), maternal education, the source of drinking water, the consumption frequency (per week) of seven food groups (meat, fish, eggs, dairy products, fruits, vegetables, and beans), and the concentrations of OPEs in hand wipes. OPE metabolites in urine and their corresponding parent compound in hand wipes were simultaneously entered into multivariable models, as described in Fig S2. Age was categorized as 6–11 years, 12–15 years, or 16–18 years. Maternal education was categorized as less than high school, high school, or college or above. The hand wipe levels were categorized into quartiles, except for TCEP and TBOEP. TCEP and TBOEP were categorized into tertiles and dichotomy, respectively, due to their low detection frequencies. Additionally, we tested multicollinearity using the variance inflation factor (VIF), with all VIFs <5. To interpret the regression models containing ln-transformed outcome variables, the regression coefficient (β) and 95% confidence interval (CI) was converted to percent change (%change) and 95% CI in urinary OPE metabolite concentrations.

All analyses were carried out using STATA 12.0 (StataCorp, College Station, TX, USA). A two-sided $P < 0.05$ was considered significant.

3. Results And Discussion

3.1 Study population

Of participants, 46.4% of children and adolescents were male and 53.6% were female, with a mean age of 12.5 ± 3.2 years old (Table 1). A total of 51.9% of mothers attained less than a high school degree, 24.7% attained equal to a high school degree, and 23.4% participated in college. The majority of food groups was generally categorized into tertiles, except for vegetable intake. A total of 49.9% of the participants were divided into the third tertile due to their high proportion of seven meals per week for vegetable consumption. The source of drinking water was mainly tap water (63.1%), followed by barreled water (22.1%), purified water (14.0%), and others (0.8%).

3.2 Concentrations of urinary OPE metabolites

Table 2 displayed the concentration distributions of urinary OPE metabolites in children and adolescents. Six OPE metabolites (TCEP, BCIPHIPP, BDCIPP, DPHP, BBOEP, and DoCP & DpCP) were detected in >70% of the urine samples, suggesting widespread

exposure to OPEs for the study participants. BCIPHIPP, TCEP, DPHP, and BDCIPP were the primary four metabolites in the urine samples, with SG-corrected median concentrations of 0.37 ng/mL, 0.27 ng/mL, 0.22 ng/mL, and 0.19 ng/mL, respectively.

Table 2
Descriptive statistics for OPEs and their urinary metabolites.

Analytes	Parent compound	>LOD (%)	LOD	GM	Percentile				Max
					25th	50th	75th	95th	
SG-corrected urine (ng/mL)									
TCEP	TCEP	79.3	0.092	0.28	0.13	0.27	0.55	1.60	11.0
BCIPHIPP	TCIPP	85.7	0.097	0.35	0.20	0.37	0.63	1.79	28.8
BDCIPP	TDCIPP	78.1	0.064	0.18	0.07	0.19	0.41	1.04	6.06
DBP	TBP	25.2	0.058	0.07	<LOD	<LOD	0.08	1.08	7.70
4-OH-DPHP	TPHP	42.0	0.043	0.08	<LOD	<LOD	0.24	1.95	11.2
DPHP	TPHP/EHDPP	91.7	0.036	0.24	0.10	0.22	0.49	2.03	25.5
BBOEP	TBOEP	89.6	0.012	0.12	0.03	0.16	0.37	1.07	7.43
DoCP & DpCP	TCrP	70.7	0.032	0.06	0.03	0.05	0.10	0.29	1.89
Handwipes (ng/wipe)									
TCEP		65.0	0.66	1.04	0.47	0.90	1.72	4.99	27.4
TCIPP		87.1	2.50	9.58	4.63	9.49	18.1	59.4	847
TDCIPP		81.1	0.80	2.09	1.01	2.02	3.85	13.2	64.3
TPHP		89.9	1.00	4.08	2.09	3.76	6.86	30.5	378
EHDPP		98.6	0.67	10.1	5.57	10.9	20.2	56.5	222
TBOEP		53.0	0.31	0.39	<LOD	0.32	0.55	1.59	448
TCrP		93.0	0.30	0.80	0.48	0.78	1.26	3.20	80.2
Note: SG, specific gravity; LOD, limit of detection; GM, geometric mean; Max, maximum.									

Median concentrations of urinary OPE metabolites in several studies were compared in Table S6. BCIPHIPP, BDCIPP, and DPHP are commonly analyzed urinary biomarkers of exposure to OPEs and are frequently detected in urine samples around the world. Compared to the concentrations in children or adolescents from the USA (Hoffman et al., 2018; Ospina et al., 2018), Belgium (Bastiaensen et al., 2021), Norway (Cequier et al., 2015), and Australia (He et al., 2018a; He et al., 2018b), these urinary metabolite concentrations in our study were relatively lower, but comparable to the results from other studies in China (Chen et al., 2018; Zhang et al., 2018a; Zhang et al., 2018b). BBOEP was detected in 90% of the urine samples. The concentration of BBOEP in our participants was higher than that in children from central and southern China (Chen et al., 2018; Zhang et al., 2018a), comparable to that in adolescents from eastern China (Ding et al., 2019), but lower than the levels in children from Australia (He et al., 2018b). A larger amount of flame retardant usage or widespread exposure of OPEs may partly explain a higher urinary OPE metabolite concentrations in children from the developed countries. It was reported that the total OPE consumption in Europe and the USA was much higher than that in China for the same duration (Tao et al., 2021). The contamination levels of OPEs in indoor dust and air (Hou et al., 2021) and foods (Li et al., 2019a) are more pronounced in the developed countries. TCEP, as the parent compound of OPEs, could be detected in 80.5% of our participants. The concentration of urinary TCEP was comparable to that in adolescents from eastern China (Ding et al., 2019), but higher than that in children from Japan (Bastiaensen et al., 2019), Australia (He et al., 2018b), and Hong Kong, China (Li et al., 2019b). TCEP was found to be the most abundant OPEs in suspended particulate matters and gaseous phases (Ding et al., 2019; Mäkinen et al., 2009), and

inhalation of TCEP was considered the greatest contributor of daily intake for TCEP (Xu et al., 2017a). Due to limited data available from multiple environmental compartments, whether a higher body burden of TCEP in children and adolescents of Liuzhou city is attributed to a higher contamination of TCEP in indoor air remains to be confirmed.

3.3 Concentrations of OPEs in hand wipes

The concentration distributions of OPEs in hand wipes from children and adolescents were shown in Table 2. Seven OPEs were detected in >50% of the hand wipe samples. EHDPP and TCIPP were detected at the highest median concentrations of 10.9 ng/wipe and 9.49 ng/wipe, respectively.

Concentrations of OPEs in hand wipes from various studies were summarized in Table S7. Two aryl phosphate compounds (TPHP and EHDPP) were ubiquitously detected in the general population. The median concentrations of TPHP and EHDPP in the present study were similar to those in a study of adults and children aged 1–5 years from South China (Tan et al., 2018), but slightly lower than the results reported from children aged 3–6 years in the USA (Hammel et al., 2020; Phillips et al., 2018). The detection frequency of TCrP in hand wipes is heterogeneous among different studies, but the median concentration of TCrP in our participants was comparable to that in toddlers or adults (Sugeng et al., 2017; Tao et al., 2018). Chlorinated alkyl phosphates (TCEP, TCIPP, and TDCIPP) were also frequently detected, with TCIPP having the highest median concentration of 9.49 ng/wipe among this subclass of compounds. This finding was different from other studies reporting TDCIPP as the most abundant in chlorinated alkyl phosphates, suggesting differential exposure in different subpopulations (Phillips et al., 2018), or a possible regional difference between domestic and foreign exposure (Stapleton et al., 2014; Tan et al., 2018). OPEs were detected in almost 100% of the hand wipe samples in our study, while the concentrations of OPEs, particularly TBOEP, were significantly lower than those in studies of children from other countries. TBOEP was 3–4 orders of magnitude lower than that reported from the USA (Phillips et al., 2018), Sweden (Larsson et al., 2018), and Norway (Xu et al., 2016), probably because ceramic flooring, not flooring treated with polish or wax is commonly used in schools in China (Zhao et al., 2020).

3.4 Exposure assessment

To investigate the total daily intake of OPEs, EDIs of individual OPEs were calculated and displayed in Table 3. Due to the lack of data on toxicokinetics of OPEs, only EDI_{TCIPP} , EDI_{TDCIPP} , EDI_{TPHP} , and EDI_{TBOEP} could be estimated in the present study. We only discussed the EDI values estimated based on F_{ue}-S₉-fraction, because F_{ue} values from S₉ fraction experiment contains both phase I and phase II metabolism (Van den Eede et al., 2013). The median EDIs of TCIPP and TPHP in our study were much lower than those reported in 0–5-year old children from central China (TCIPP: 94.9 ng/kg bw/day; TPHP: 267 ng/kg bw/day) (Zhang et al., 2018a) and 14–15-year old adolescents from Belgium (TCIPP: 57.4 ng/kg bw/day; TPHP: 197.7 ng/kg bw/day) (Bastiaensen et al., 2021), but comparable to the levels in 6–14-year old children from South China (TCIPP: 22.6 ng/kg bw/day; TPHP: 33.1 ng/kg bw/day) (Chen et al., 2018). For TDCIPP, the median EDI was similar to that in several studies of general population (Bastiaensen et al., 2021; Chen et al., 2018; Zhang et al., 2018a; Zhang et al., 2018b). The EDI of TBOEP were heterogeneous in different studies, but generally within the same range. Compared to the reference dose (RfD) made for human exposure to TCIPP (10000 ng/kg bw/day), TDCIPP (20000 ng/kg bw/day), TPHP (20000 ng/kg bw/day), and TBOEP (15000 ng/kg bw/day) (Poma et al., 2019), the high exposure levels (95th percentile EDIs) of the study participants were 2–3 orders of magnitude lower. Considering that RfD values were obtained based on toxicological data, the EDIs of individual OPEs in the present study could be over- or underestimated.

Table 3
Estimated daily intakes (ng/kg bw/day) of OPEs.

Compound	RfD ^a (ng/kg bw/day)	Dermal exposure			Total daily exposure						Proportion (%)		
		Median	5th	95th	S9			HLM			S9	HLM	
					Median	5th	95th	Median	5th	95th	Median	Median	
TCEP		0.31	0.10	1.83									
TCIPP	10000	2.63	0.40	22.9	27.6	5.34	140	23.4	4.53	119	10.1	11.9	
TDCIPP	20000	0.32	0.06	2.36	7.70	1.20	45.8	11.4	1.78	67.7	4.69	3.17	
TPHP	20000	0.98	0.16	10.3	31.7	4.50	340	14.7	2.09	158	3.25	7.02	
TBOEP	15000	0.09	0.27	17.2	28.4	1.57	191	5.61	0.31	37.8	0.36	1.84	
EHDPP		3.10	0.04	0.45									
TCrP		0.24	0.06	1.22									
Σ ₇ OPEs		10.7	2.32	49.7									

Note: RfD, reference dose; HLM, human liver microsomes; S9, S9 fraction.

^a Adopted from Poma et al. (2019).

To investigate the contribution of dermal exposure to OPEs, the OPE intake via skin wipes and its proportion to total daily intake were estimated (Table 3). The median DED of Σ₇OPEs was 10.7 (5.56–19.3) ng/kg bw/day, in which TCIPP and EHDPP exposure via skin wipes were predominant contributors. The average proportion of OPE exposure via skin wipes ranged from 0.36% (TBOEP) to 10.1% (TCIPP) as total daily intake was estimated based on FUE-S9-fraction, suggesting a significant contribution of dermal absorption. In the present study, daily dermal exposure to OPEs of the study participants were higher than those estimated via hand wipes or house dust for adults (Cao et al., 2019; Huang et al., 2020; Liu et al., 2017; Xu et al., 2016), but lower than those estimated via house dust or air for toddlers (Huang et al., 2020; Liu et al., 2017). Different from other studies, we only considered the exposed surface area of hands and head as recommended by Pan et al. (2020). OPE uptake from dermal absorption could be higher if more skin area or whole body is included. Additionally, we adopted the absorption factors of TCEP (28%), TCIPP (25%), and TDCIPP (13%) from human ex vivo skin experiments to investigate the daily dermal exposure to OPEs, and utilized the average absorption rate (22%) of TCEP, TCIPP, and TDCIPP to estimate other OPEs (including TPHP, EHDPP, TBOEP, and TCrP).

3.5 Correlation between urine and hand wipes

We found that the TPHP and EHDPP levels in hand wipes were significantly correlated with their metabolite DPHP in urine ($r_s = 0.068–0.142$, $P < 0.05$), whereas no significant correlations were observed between other OPEs in hand wipes and the corresponding urinary metabolites (Table 4). Hand wipes are theoretically a good integrated indicator of internal exposure, as they measured hand-to-mouth contact with dust and other exposure media (e.g., indoor consumer products), and may provide information on an individual's activity pattern. Several studies have reported strong correlations between the TCIPP and TDCIPP amount in hand wipes and their urinary metabolites of BCIPHIPP and BDCIPP, respectively (Phillips et al., 2018; Tao et al., 2018), whereas our study did not confirm these previous findings, possibly because the levels of OPEs on hands could be affected by individual's hand washing frequency and engaged activity before sampling (Larsson et al., 2018; Liu et al., 2017). However, hand washing frequency in our study was not related to the OPE concentrations in hand wipes (data not shown). Given that children and adolescents have a frequent contact with cell phone, the activity of cell phone touching was studied, as cell phones may act as a potential source of OPEs (Yang et al., 2019). There was no significant association between cell phone touching and the quantities of OPEs in hand wipes (data not shown).

Table 4
Spearman correlation coefficients for OPE and OPE metabolites levels measured in paired hand wipes and SG-corrected urine with >50% detection ^a.

Compound	TCEP	BCIPHIPP	BDCPP	DPHP	BBOEP	DoCP & DpCP
TCEP	0.034	0.016	0.073*	0.058	-0.072*	0.011
TCIPP	-0.069 *	-0.048	0.022	0.042	-0.003	0.013
TDCIPP	-0.007	-0.059	0.016	0.018	-0.144*	0.002
TPHP	0.033	0.047	0.097*	0.068*	-0.010	0.043
EHDPP	-0.045	-0.029	0.105*	0.142*	0.024	0.024
TBOEP	-0.030	-0.039	-0.010	-0.004	-0.016	-0.054*
TCrP	-0.048	0.035	0.035	0.062*	0.087*	0.001

Note: ^a Significant level are marked with bold text and asterisks (* $P < 0.05$).

In the present study, OPE intake via dermal absorption could partially explain the body burden of OPEs. To determine the potential predictors for urinary OPE metabolite concentrations, factors (sociodemographic variables, dietary patterns, and OPE levels in hand wipes) that may impact OPE exposure were all included in multivariable linear regression models (Table 5). After adjusting for sex, age, maternal education, and dietary patterns, a strong correlation continued to be found for EHDPP in the highest quartile in hand wipes and urinary DPHP ($P < 0.001$). Although the association between TPHP and DPHP was no longer significant, there was a suggestive dose response relationship between TPHP and DPHP (Fig. 1). Similarly, the levels of other OPEs in hand wipes were not related to their corresponding urinary metabolites in the multivariable models. These results implied that hand wipes could be an effective exposure metric for TPHP and EHDPP, whereas the exposure of other OPEs may be linked to additional predictors. Furthermore, we discussed the associations of sociodemographic and dietary variables with urinary OPE levels after adjusted for other variables in Table 5.

Table 5

Results of regression analyses for predicting urinary OPE metabolites ^a.

OPE metabolites	Variables	%change (95% CI)
TCEP	Age	
	6–11 years (Ref)	
	12–15 years	97.6 (68.5, 132) *
	16–18 years	34.4 (13.5, 59.2) *
	Sex	
	Male (Ref)	
	Female	-14.3 (-24.9, -2.31) *
	Drinking water	
	Tap water (Ref)	
	Barreled water	2.39 (-13.2, 20.7)
	Purified water	-8.67 (-24.8, 10.8)
	Others	-58.2 (-80.3, -10.9) *
BCIPHIPP	Age	
	6–11 years (Ref)	
	12–15 years	41.7 (22.1, 64.4) *
	16–18 years	18.0 (0.86, 38.0) *
	Drinking water	
	Tap water (Ref)	30.4 (11.8, 52.0) *
	Barreled water	16.7 (-2.51, 39.8)
	Purified water	-22.5 (-61.7, 57.0)
Others		
BDCIPP	Age	
	6–11 years (Ref)	
	12–15 years	-4.24 (-19.0, 13.2)
	16–18 years	-48.4 (-56.6, -38.5) *
	Beans (times/week)	
	≤1 (Reference)	
	2	2.11 (-15.0, 22.6)
≥3	-19.7 (-32.4, -4.61) *	
DPHP	Age	
	6–11 years (Ref)	
	12–15 years	5.96 (-12.4, 28.2)

Note: ^a Significant level are marked with bold text and asterisks (* $P < 0.05$).

OPE metabolites	Variables	%change (95% CI)
	16–18 years	-42.1 (-52.5, -29.4) *
	Meat (times/week)	
	≤2 (Ref)	
	3–5	-18.9 (-33.3, -1.43) *
	≤6	-9.52 (-26.9, 12.0)
	Vegetables (times/week)	
	≤4 (Ref)	
	2	13.3 (-10.3, 43.2)
	≥3	23.7 (0.51, 52.1) *
BBOEP	Age	
	6–11 years (Ref)	
	12–15 years	-21.6 (-38.9, 0.65)
	16–18 years	-6.74 (-28.1, 21.0)
	Sex	
	Male (Ref)	
	Female	22.3 (0.75, 48.5) *
	Maternal education	
	Less than high school (Ref)	
	High school	22.2 (-4.40, 56.1)
	College or above	50.9 (17.5, 93.6) *
	Drinking water	
	Tap water (Ref)	
	Barreled water	5.11 (-17.6, 34.1)
	Purified water	-27.3 (-45.3, -3.46) *
	Others	33.1 (-56.4, 306)
Note: ^a Significant level are marked with bold text and asterisks (* $P < 0.05$).		

3.6 Urinary OPE metabolites and sociodemographic characteristics

It was not surprising that the urinary BDCIPP, DPHP, and BBOEP concentrations were inversely associated with age (categorical variable), because children have rapid metabolic and ventilation rates and large ratio of surface area to body weight, in addition to frequent hand-to-mouth activity (Miller et al., 2002; Tulve et al., 2002). Nevertheless, the levels of urinary TCEP and BCIPHIPP in the study participants aged 12–15 years were highest, followed by adolescents aged 16–18 years, and children aged 6–11 years were lowest. Contradictory to previous studies (Bastiaensen et al., 2019; He et al., 2018b; Van den Eede et al., 2015), we observed positive associations of urinary TCEP and BCIPHIPP concentrations with age. To our knowledge, we did not observe a determinant activity pattern in which senior students had an increased potential for exposure to OPEs compared to schoolchildren, while a recent study found that urinary TCEP and BCIPHIPP levels were high in adolescents aged 12–15 years in eastern China (Ding et al., 2019). The concentration of urinary TCEP were high in males, while urinary BBOEP was high in

females, indicating differences in metabolism and exposure patterns between genders (Hoffman et al., 2015). Maternal education level was a proxy for socioeconomic status that was positively associated with the urinary BBOEP in our participants. A potential explanation of this result is that newer furniture and electronics entered into these highly educated mothers' households, which led to the transition of indoor exposure patterns from PBDEs to OPEs (Percy et al., 2020).

3.7 Urinary OPE metabolites and dietary patterns

High vegetable intake in the past week (≥ 7 times) was associated with a 23.7% higher DPHP concentration in urine compared to the lowest vegetable intake (≤ 4 times) [%change = 23.7; 95% confidence interval (CI): 0.51, 52.1]. Medium meat intake (3–5 times) was associated with a 18.9% lower DPHP concentration, although there was lack of statistical significance for the highest meat intake category (≥ 6 times). In comparison with frequently consumed tap water, barreled water was associated with a 30.4% increased BCIPHIPP concentration in urine, purified water drinking was related to a 27.3% lower BBOEP concentration, and other drinking water was associated with a 58.2% lower TCEP concentration.

High vegetable intake was suspected to be an important factor that influence the concentrations of urinary OPE metabolites, which was first reported in children and adolescents. Zhang et al. (2016) detected 75 commonly consumed foods sampled from 4 representative areas in China and found that vegetables were severely contaminated by TCEP and TEHP. TPHP and EHDPP were not abundant OPEs in vegetables, thus, we could not conclude that the higher DPHP concentration in urine was attributed to the high contamination of its parent compounds in vegetables. However, a study in Australia reported the ubiquitous occurrence of DPHP in vegetables. The contamination level of DPHP (median: 0.99 ng/g wet weight) in vegetables was obviously higher than its parent compound TPHP (He and Wang, 2018). Considering the ubiquitously co-existence of organophosphate di-esters (di-OPEs) and tri-esters (tri-OPEs) in various environmental compartments (Björnsdotter et al., 2018; Hou et al., 2017; Tan et al., 2019), the direct intake of di-OPEs from foodstuffs cannot be ignored.

Negative associations between food consumption and urinary metabolite concentrations are challenging to interpret and are rarely reported. Eggs, fish, and meat which are categorized as animal-based foods, had the lowest contamination concentrations of OPEs compared to other food groups (Li et al., 2019a). The very low OPE concentrations in the animal-based foods might be due to the rapid metabolism and/or excretion of OPEs (Greaves et al., 2016; Poma et al., 2018). It seems reasonable that increased meat and egg consumption were associated with lower urinary metabolite concentrations. Although a small study of toddlers in the USA (n=41) suggested that meat and fish consumption were related to higher DPHP and BDCIPP concentrations in urine, these associations were not statistically significant (Thomas et al., 2017). Moreover, a previous study showed that the OPE levels in bean products were negligible (Ding et al., 2018), thus, an inverse association between high consumption of beans and the urinary BDCIPP concentration is also possible.

Tap water is the most common and cheapest drinking water in China and contains abundant OPEs, particularly halogeno-OPEs, compared to other water sources (e.g., barreled water, bottled water, purified water, and well water) (Ding et al., 2015). A possible hypothesis is that purified water, barreled water, and other drinking water may be associated with lower concentrations of urinary OPE metabolites. Due to the limited number of participants in the other drinking water group, the result that other drinking water was associated with a lower TCEP concentration in urine should be interpreted with caution. However, it is unexpected that barreled water drinking was associated with an increase in urinary BCIPHIPP. Li et al. (2019c) analyzed the concentrations of OPEs in tap water samples from 79 cities in China, in which the contamination of OPEs in tap water from Liuzhou (the sample site of our study) was not severe. In addition, most barreled water-producing manufacturers are regional, and different manufacturing techniques are used according to the enterprise scale and cost. In the sample site of our study, regional barreled water could be a potential source of exposure to OPEs for residents. Considering the limited data on drinking water around the world, more research on different types of drinking water is needed.

3.8 Limitation and strength

The main strengths of our study include the large sample size for an exposure study of OPEs and the focus on the vulnerable population of children and adolescents. This is a relatively comprehensive study that examines the relationship between urinary OPE metabolites and dietary factors. The dietary factors include the consumption rate of seven common food groups and the

sources of daily drinking water. Additionally, the OPE levels in hand wipes were included in the multivariable linear regression models given that dermal contact with dust is commonly considered an important exposure pathway for humans.

Several limitations exist. First, organophosphate diesters could be generated from bio-transformation of OPEs, as well as environmental degradation of parent OPEs and industrial production (Liu et al., 2021). Meanwhile, some of organophosphate diesters are metabolized by various OPEs. For example, DPHP could be generated from TPHP (Su et al., 2014), EHDPP (Shen et al., 2019), and resorcinol bis(diphenylphosphate) (RDP) metabolism (Ballesteros-Gómez et al., 2015). Therefore, the suitability of usage of organophosphate diesters as metabolites of OPEs are needed further assessment. Second, given that other newly discovered OPEs exhibit great detection frequencies and are abundant in multiple environmental matrices (e.g., bis-(2-ethylhexyl)-phenyl phosphate (BEHPP), tris(2,4-di-tertbutylphenyl) phosphate (TDTBPP)), these novel OPEs should be monitored in the forthcoming studies. Third, we could not examine long-term exposure to OPEs using a cross-sectional study, and many of OPEs are rapidly metabolized in the human body; thus, a spot urine sample could not be representative of the average body burden of our participants. Fourth, single hand wipe sample could be a potential weakness for OPE measurements, as it is unknown how OPE levels vary in a single person over time. Herein, we measured OPEs in urine and hand wipe samples, whereas the inclusion of other exposure metrics (e.g., passive air samples and indoor dust) may provide additional information on exposure to OPEs. Last, in the present study, food items combined with food frequency questionnaires were used to estimate human dietary intake of OPEs, but this method only provides an approximately estimate of dietary habits during a designed period of sample time (Xu et al., 2017a).

4. Conclusion

Our study indicated the widespread exposure to OPEs in children and adolescents. OPE intake via skin wipes could be an important contributor to the total daily of OPEs. Additionally, dietary intake is also a significant exposure source of certain OPEs, particularly vegetable consumption and barreled water drinking. More research is warranted to verify our preliminary findings and evaluate the potential health risks from chronic dietary exposure to OPEs.

Declarations

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Availability of data and materials

All data generated or analyzed during this study are included in this published article (and its supplementary information).

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Author contributions

Project development: Youjie Wang and Surong Mei. Data collection and management: Bingqing Liu, Liqin Hu, and Lulu Song. Sample testing: Meng Yu, Xiang Li, Yaping Li, Ling Liu, and Limei Wang. Data analysis: Meng Yu, Lulu Song, and Liqin Hu. Manuscript writing/editing: Meng Yu and Liqin Hu. Supervision: Surong Mei. All authors read and approved the final manuscript.

Ethics approval and consent to participants

Ethical approvals were obtained from Tongji Medical College, Huazhong University of Science and Technology. Informed consent was provided by the participant's parents prior to enrollment.

Consent for publication

Not applicable.

Competing financial interests

The authors declare no competing financial interests.

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Figures

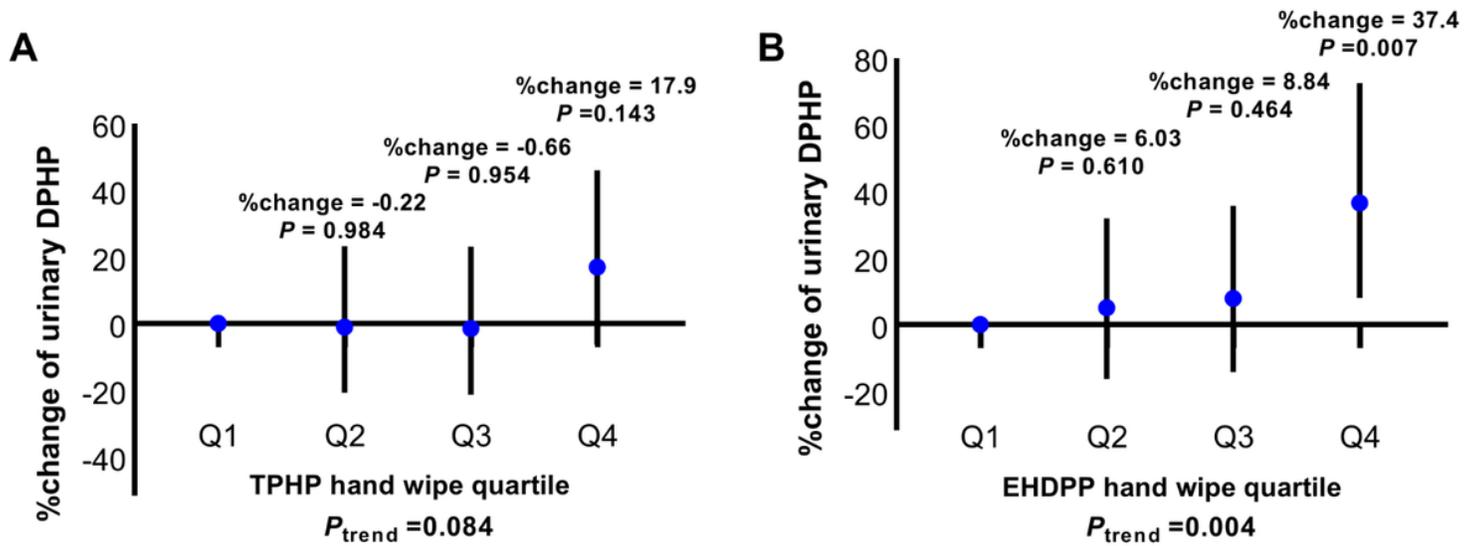


Figure 1

Adjusted linear regression associations between TPHP (A) and EHDPP (B) levels on hand wipes and their urinary metabolite DPHP. Models are adjusted for sex and age, maternal education, and all food groups.

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