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Investigation of Urinary Metabolites of Organophosphate Esters in Hanoi, Vietnam: Assessment Exposure and Estimated Daily Intake

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Abstract

In recent years, organophosphate esters (OPEs) have become one of the most common additives in various consumer products worldwide, therefore the exposure and impact of OPEs on human health are drawing a lot of attention. In this study, three metabolites of OPEs including bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), diphenyl phosphate (DPhP) and diethyl phosphate (DEP) were investigated in first-morning void urine samples taken from a population (age range: 3–76 years old) in Hanoi, Vietnam. The most dominant urinary OPE metabolite was DEP with the geometric mean of specific gravity adjust (SG-adjusted) concentration were 1960 ng mL^{-1} and detected frequency (DF) of 98%. Followed by DPhP (8.01 ng mL^{-1}, DF: 100%) and BDCIPP (2.18 ng mL^{-1}, DF: 51%). The results indicated that gender and age might have associations with the OPE metabolites variation in urine samples. The levels of OPE metabolites in urine samples from females were slightly higher than in males. An increase in age seems to have an association with a decrease in DPhP levels in urine. Exposure doses of parent OPEs were evaluated from the unadjusted urinary concentration of corresponding OPE metabolite. The estimated exposure doses of triethyl phosphate (TEP) (mean: 534,000 ng kg^{-1} d^{-1}) were significantly higher than its corresponding reference dose, suggesting the high potential risk from the current exposure doses of TEP to human health. The results of this work provided the initial information on the occurrence of three OPE metabolites in urine from Hanoi, Vietnam and estimated exposure dose of corresponding parent OPEs.

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From the mid-2000s, the consumption of organophosphate esters (OPEs) had been increased dramatically in many regions due to their application as the main replacement chemicals for polybrominated diphenyl ethers (PBDEs), which had been restricted in many countries (Butt et al. 2014) due to the toxic impacts on human health (Berghuis et al. 2015; Linares et al. 2015). In 2015, 680 thousand tons of OPEs were manufactured worldwide, and its estimated yearly increase was about 15% (Gustavsson et al. 2018). Worldwide, OPEs were applied as additives in various household and industrial items (plastic, textiles, mattresses, furniture, electronics, foam, resins, hydraulic fluids, lacquers and nail polish) (Mendelsohn et al. 2016; Salamova et al. 2014; Van der Veen and de Boer 2012). In addition, many OPEs are used as agricultural and household organophosphorus pesticides (Pundir et al. 2019), which are used widely to control insect crops and houses in many countries (Jayatilaka et al. 2019; Yang et al. 2019).

OPEs are additives without chemically bound to the main materials, therefore they can easily diffuse out of main

products and go into surrounding environments during the life cycle of products (Wang et al. 2014). Combination with the common use of OPEs, these chemicals had been ubiquitously spread into living environments such as indoor air (Hoang et al. 2023), indoor and outdoor dust (Al-Omran et al. 2021; Hoang et al. 2023), atmospheres (Zhang et al. 2019), and natural environments (water, sediment, soil and biota) (Chen et al. 2022; Wang et al. 2019b; Ye et al. 2022; Zhang et al. 2022a). Furthermore, OPEs and some metabolites of OPE were also frequently presented in agro-foods (vegetables, fruit, meat, fish, egg, and milk) (He et al. 2018b; Yang et al. 2019; Zhang et al. 2022b) and drinking water (Choo and Oh 2020). There are concerns about OPEs exposure and the influence of these compounds on human health. OPEs exposure to humans mostly through ingestion of foods, drinking water and dust contaminated by OPEs, inhalation of OPEs in air and fine dust, and dermal contact with OPEs in goods and indoor environments (Cequier et al. 2015; He et al. 2018b; Lee et al. 2016). Previous reports have pointed out the negative influences on human health (including carcinogenic and neurotoxic impacts) of OPEs (Niu et al. 2019). Tri(1,3-dichloro-2-propyl) phosphate (TDCIPP) was recognized as a carcinogenic chemical with high biological and neurotoxicity (Lu et al. 2017; Niu et al. 2019). Triethyl phosphate (TEP) was recorded which may have some neurotoxic properties and/or potential mutagenic effects in humans at high exposure doses (Lai et al. 2022). Triphenyl phosphate (TPhP) has been pointed out to have associations with male reproductive system effects (Meeker and Stapleton 2010).

In human body, OPEs are hydrolyzed to their diester metabolites, and these OPE metabolites are excreted through urine (Liu et al. 2016). For instant, the main conversion products of TDCIPP, TPhP and TEP in human and/or animal bodies were BDCIPP, DPhP and DEP, respectively (Wang et al. 2016; Yao et al. 2021). Therefore, these OPE diester metabolites (BDCIPP, DPhP and DEP) in urine were commonly used as the biomarker of their parent chemicals (TDCIPP, TPhP and TEP, respectively) (Hoffman et al. 2014; Krystek et al. 2019). However, it is noticeable that DPhP and DEP are non-specific metabolites, DPhP is degraded from some other aryl-OPEs (Wang et al. 2019a; Zheng et al. 2021) and DEP is a metabolite of some organophosphorus pesticides (Yang et al. 2019). Some previous reports have shown the ubiquitous presence of OPE metabolites (such as BDCIPP, DPhP, DEP, bis(1-chloro-2-propyl) phosphat, bis-2(butoxyethyl) phosphate, bis(2-chloroethyl) hydrogen phosphate, di-cresyl phosphate, bis(butoxyethyl) phosphate, dipropyl phosphate, dibutyl phosphate) in human (children and/or adults) urine in many areas in the United States (U.S) (Dodson et al. 2014; Jayatilaka et al. 2019; Preston et al. 2017; Thomas et al. 2017; Wang et al. 2019a), Canada (Kosarac et al. 2016), Australia (Van den Eede et al. 2015), Norway (Cequier et al. 2015), and China (He et al. 2018b; Lu et al. 2017; Sun et al. 2018; Tao et al. 2018). Among those reports, the frequently detected metabolites of OPEs in urine were BDCIPP, DPhP and DEP (He et al. 2018a; Sun et al. 2018; Wang et al. 2019a).

In developing countries, such as Vietnam, the appearance of OPEs was reported in various environments (air, dust and water) (Hoang et al. 2023; Truong et al. 2023). Especially, in our recent studies in Hanoi city in Vietnam, the wide spread of OPEs were observed in indoor environment (air and dust) with high levels (median of total OPEs concentration were 101 and 7580 ng g^{-1}, respectively) (Hoang et al. 2023), and in surface water in urban Hanoi with the total concentration was also at elevated levels (range: 46–3644 ng L^{-1}, average: 1409 ng L^{-1}) (Truong et al. 2023). However, the study on the organic pollutants in urine from Vietnam was limited. Previous studies had only focused on metals and some organic chemicals (polycyclic aromatic hydrocarbons, PBDEs, polychlorinated biphenyls, persistent pesticides and phthalate metabolites) in urine from a group of electronic waste recyclers or a small group of people in Vietnam (Schecter et al. 2018; Thai et al. 2015), which leads to the information shortage on the OPE metabolites levels in urine from Vietnam.

For a general view of the occurrence of urinary OPE metabolite levels and exposure to OPEs in the population of Hanoi citizens in Vietnam, the three most frequently detected urinary OPE metabolites (BDCIPP, DPhP, and DEP) were selected for analysis in urine samples taken randomly from Hanoi, Vietnam. This work aimed to (1) Determine the levels of urinary metabolites of OPE (BDCIPP, DPhP and DEP) from a population in Hanoi, Vietnam; (2) to determine the associations between gender/age and urinary OPE metabolites concentration of the study group; (3) estimate the exposure doses to parent OPEs (TDCIPP, TPhP and TEP) of citizen in Hanoi, Vietnam.

Materials and Methods

Chemicals and Materials

Three organophosphate metabolites standards BDCIPP, DPhP and DEP (Table S1) and internal standards BDCIPP-d10, DPhP-d10 and DEP-d10 were supplied by Toronto Research Chemicals Inc. (Canada). In this study, solvents (acetonitrile, methanol and acetone) were used at analytical grade and supplied by Merck Co. (Germany). The polymeric solid phase extraction Strata-X-AW (60 mg 3 mL^{-1}) sorbents were purchased from Phenomenex Inc. (Italy), and the nylon filter (Millex® hydrophilic PTFE syringe filter, 13 mm, 0.2 µm) were provided by Merck Co. (Germany). All the glassware was washed and rinsed with solvents prior to usage. A mixed-stock solution containing all analytes was

prepared in acetonitrile at a concentration of 10 mg L^{-1} and was kept at − 20 °C. Calibration solutions (0.02–100 µg L^{-1}) used in routine applications were prepared in acetonitrile.

Sample Collection, Extraction and Analysis

Sixty-one urine samples were sampled in January 2023 from 61 volunteers, who have been living in Hanoi, Vietnam. The volunteers were chosen randomly, and the information about the participant's gender (male, n = 26; female, n = 35) and ages (3–76 years old) was collected before sampling (Table S2). Female volunteers were not in their menstrual period during the sampling time. Each individual gave a single first-morning void urine sample into a 100 mL glass container, which was precleaned with heat at 450° C before use. The obtained samples were taken to the laboratory within 1 h and then preserved at − 20° C until analysis. The protocol of this study was reviewed and approved by the Hanoi University of Public Health Institutional Review Board, No: 337/2023/YTCC-HD3.

The method of extraction of OPEs metabolites in urine samples was carried out according to Sun's method (Sun et al. 2018) with small modifications. A 2 mL urine sample was spiked with an internal standards mixture (BDCIPP-d10, DPhP-d10 and DEP-d10: 20 µg mL^{-1}), added 1 mL of ammonium acetate buffer (10 mM, pH = 5), and mixed with a vortex shaker in 1 min. Then the mixture was extracted by solid phase extraction with a cartridge Strata-X-AW (60 mg 3 mL^{-1}) that had been conditioned with 2 mL of methanol, and 2 mL of ultrapure water, sequentially at a flow rate of 1 mL min^{-1}, after that washed by 2 mL of ultrapure water, and vacuum-dried for 30 min before being eluted with 2 mL methanol containing 5% ammonium hydroxide. The eluent was then concentrated down to approximately dry under a stream of N_2. Finally, re-dissolve the residue and diluted to a final volume of 500 µL with acetonitrile, and filtered through a nylon filter (13 mm, 0.2 µm) prior to LC–MS/MS analysis.

The compounds BDCIPP, DPhP and DEP were analyzed with high-performance liquid chromatography (HPLC, Waters, model: Xevo TQ-XS) coupled with electrospray triple quadrupole mass spectrometer (Waters, USA), operated in the electrospray negative ionization (ESI-) for DPhP and DEP, and electrospray positive ionization (ESI +) for BDCIPP, with atmospheric-pressure chemical ionization (APCI) mode. Using an ACQUITY UPLC C18 column (leghth 150 mm, i.d. 2.1 mm and film thickness 1.7 µm, Phenomenex, Torrance, USA). 5 µL of extracted sample was injected into the chromatographic separation column at maintained temperature of 60 °C. The mobile phase consisted of 0.05% (v/v) trifluoroacetic acid in MilliQ water (A) and 0.01% (v/v) formic acid in acetonitrile (B), at a flow rate of 0.2 mL min^{-1}. The gradient flow started at 80:20 A/B followed by an increase of phase B to 100% in 2 min, and held for 3 min. Then an increase of phase A to 80% and phase B decrease to 20% over 3 min and held for and equilibrated for 6 min. Details on the MS/MS parameters used are presented in Table S3.

The chemical parameters of urine samples such as pH, specific gravity (SG), total creatinine (Cr), and total protein were measured by using a digital ACON Mission U120 Smart urine refractometer (Acon Biotech, Hangzhou, Co., Ltd, China).

Quality Assurance and Quality Control

In each batch of samples, three procedural blanks, three spiked blanks (analytes added into solvents), and three spiked samples (analytes added into real urine samples) were extracted and analyzed according to the procedure of real urine samples. The blank samples were not found trace levels of BDCIPP, DPhP and DEP. The recoveries of BDCIPP, DPhP and DEP spiked in the urine matrix were 96.2, 85.1 and 102%, respectively. The limits of quantification (LOQs) and method detection limit (MDLs) of BDCIPP, DPhP and DEP from the spiked blanks and spiked matrix are shown in Table S4.

Data Analysis

Reported urinary BDCIPP, DPhP and DEP values were subtracted from the concentrations detected in blanks (average value). To justify for variances in dilution of urine caused by age, urine flow, disease, body mass index and sex (Braun et al. 2011), the raw (unadjusted) concentrations were converted to the specific gravity (SG)-adjusted concentrations using the following equation (Sun et al. 2018; Thomas et al. 2017):

$$C_{SG} = C \times (1.024 - 1)/(SG - 1) \quad (1)$$

where C_{SG} is the SG-adjusted concentration of OPE metabolite (ng mL^{-1}), C is the raw concentration of OPE metabolite (ng mL^{-1}), and the specific gravity value is SG (Sun et al. 2018; Thomas et al. 2017). Descriptive statistics, statistical tests and discussion of the urinary OPE metabolites concentrations in this study used the SG-adjusted values. In addition, we also corrected the raw concentration for creatinine (Cr)-adjusted values (ng g^{-1} creatine) to serve as a reference for future studies.

A value of half of MDL was used for the concentration below method detection limit (MDL), and the non-detected (ND) was set as zero. Mann–Whitney U tests were performed to investigate the variances in urinary OPE metabolite concentrations of individuals with gender and age. Connections between each urinary OPE metabolites were examined by operating Spearman's correlation rank analysis.

$p < 0.05$ was set as the statistical significance value. We used IBM SPSS Statistics software (Version 26.0, SPSS Inc., NY, U.S.) to conduct all the statistical analyses.

The unadjusted values of OPE metabolite in urine samples were used to estimate the exposure doses of corresponding OPEs, using Eq. (2) (Wang et al. 2019a) as follows:

$$\mathrm{ED} = \left[\left(C_m/\mathrm{MW}_m\right) \times \mathrm{MW}_p \times V_{ur}\right]/\mathrm{MF} \quad (2)$$

where ED is the estimated exposure dose of parent OPE (ng kg^{-1} d^{-1}), C_m is the unadjusted concentrations of OPE metabolite detected urine samples (ng mL^{-1}). MW_m is the OPE metabolite's molecular weight and MW_p is the molecular weight of corresponding OPEs. V_{ur} is the daily urine excretion volume (22.2 and 20 mL kg^{-1} d^{-1} for children and adults, respectively) (Chen et al. 2018). Urine metabolite excreted molar fraction (MF) was 0.18 for DEP and 0.63 for DPhP and BDCIPP (Lynn et al. 1981; Suzuki et al. 1984).

Results and Discussion

Levels of OPE Metabolites in Urine

The chemical parameters of urine samples collected from 61 volunteers aged 3–76 years, including 33 females and 25 males were shown that pH values ranged from 5 to 8, with no glucose detected in urine samples, creatine content is between 0.1 and 1 g L^{-1}, specific gravity between 1.005 and 1.030 and a few samples proteins are present (Table S5). The results showed that the volunteers were in normal health.

The occurrence of BDCIPP, DPhP and DEP detected in 61 urine samples from Hanoi, Vietnam ranged from not detected (ND) to 8080 ng mL^{-1} (uncorrected concentration) (Table S6). Due to extremely high of detected urinary OPE metabolite concentrations (especially DEP, uncorrected concentration of 503–8080 ng mL^{-1}), a resurvey on the occupation of participants was undertaken to collect more information on OPEs exposure in working environments. Two urine samples with urinary DEP concentration at relatively high levels (sample: U55 and U58, uncorrected DEP concentration of 3700 and 8080 ng mL^{-1}, respectively) were collected from two female workers (age 31–34 years old), who were frequently exposure to OPEs in their workplace (thermal cuts/reshape PU foam in a small workshop). Therefore, those two samples were not used for further discussion in this study. Table 1 shows the concentrations (unadjusted, SG-adjusted and Cr-adjusted) and the detected frequencies (DF) of three urinary OPE metabolites (BDCIPP, DPhP and DEP) in urine samples, with details are shown in Table S6. Comparison between the urinary OPE metabolites (unadjusted and SG-adjusted) values of this study with other studies is shown in Table 2. The detected urinary SG-adjusted concentration of BDCIPP, DPhP and DEP in Hanoi, Vietnam were from 0.02 to 120,000 ng mL^{-1}. DEP was the most predominant urinary OPE metabolite observed in this study with the geometric mean (GM) SG-adjusted value of 1960 ng mL^{-1} (range: 402–120,000 ng mL^{-1}, DF: 98%), which was

Table 1 Concentrations (Unadjusted, specific gravity (SG)-adjusted and creatinine (Cr)-adjusted concentration) of DEP, DPhP and BDCIPP in urine samples (n = 59) collected from Hanoi, Vietnam

OPE metabolite	MDL[a]	DF[b]	GM[c]	AM[d]	Range	SD[e]	Percentile				
							5th	25th	50th	75th	95th
Unadjusted (ng mL^{-1})											
DEP	0.1	98	1890	2060	503–5990	945	723	1620	2070	2570	3320
DPhP	0.18	100	7.74	7.95	5.9–20.2	2.24	6.06	6.77	7.39	8.25	11.5
BDCIPP	0.02	51	2.20	5.42	0.03–49.6	14.5	0.05	0.43	4.49	13.3	40.6
SG-adjusted (ng mL^{-1})											
DEP			1960	2490	402–12000	2250	728	1390	1970	2560	7240
DPhP			8.01	10.0	4.72–60.7	10.0	4.85	5.73	6.52	8.91	25.1
BDCIPP			2.18	9.30	0.02–238	45.4	0.04	0.36	3.73	16.0	67.8
Cr-adjusted (ng g^{-1})											
DEP			13,200	21,200	333–58,100	15,000	934	9900	20,700	31,400	48,600
DPhP			52.6	71.0	4.72–163	40.5	6.19	54.2	70.2	100	133
BDCIPP			20.0	55.7	0.46–717	172	0.62	3.54	31.1	116	438

[a]*MDL* method detected limit (ng mL^{-1})

[b]*DF* detection frequency (%)

[c]*GM* geometric mean

[d]*AM* arithmetic mean (99% confidence intervals)

[e]*SD* standard deviation

Table 2 Comparison of urinary DEP, DPhP and BDCIPP levels (geometric mean or median concentrations) and detected frequencies reported from other regions

Locations	Year of sampling	Population	n[a]	OPE metabolite SG-adjusted (unadjusted) concentration (ng mL^{-1})						OPE metabolite detection frequency (DF) (%)			References
				DEP		DPhP		BDCIPP		DEP	DPhP	BDCIPP	
Hanoi, Vietnam	2023	Children and adults	59	1960	(1890)	8.01	(7.74)	2.18	(2.20)	98	100	51	This study
		Children	17	1730	(1570)	9.47	(8.83)	1.39	(1.47)	100	100	53	
		Adults	42	2070	(2040)	7.41	(7.34)	2.65	(2.62)	98	100	50	
United States (U.S)													
Atlanta	2010–2011	Firefighter	145	–	(4.2)	–	(4)	–	(3.3)	88	100	97	Jayatilaka et al. (2019)
Atlanta	2015	Adults	158	–	(0.73)	–	(0.26)	–	(0.3)	92	70	78	Jayatilaka et al. (2019)
New York	2018	Adults	19	0.348	–	1.06	–	0.414	–	100	100	100	Wang et al. (2019a)
New Jersey	2013–2014	Mothers	22	–	–	1.9	–	2.4	–	–	100	95	Butt et al. (2014)
		Children	26	–	–	3	–	5.6	–	–	92	100	
Boston	2010–2011	Adults	42–47	–	–	1.8 – 2.99	–	–	–	–	95	100	Preston et al. (2017)
North America	2011	Adults	9	–	–	2.97	–	0.41	–	–	100	100	Cooper et al. (2011)
Seattle	2013–2014	Children	20–21	–	–	3.4–8.2	–	2.7–6.8	–	–	100	85–95	Thomas et al. (2017)
California	2015	Mothers	28	–	–	1.2	–	3.3	–	–	100	100	Butt et al. (2016)
		Children	33	–	–	2.9	–	10.9	–	–	100	100	
California	–	Adults	13	–	–	–	(1.5)	–	(2.5)	–	100	100	Petropoulou et al. (2016)
California	2011	Adults	16	–	–	–	(0.44)	–	(0.09)	–	62	94	Dodson et al. (2014)
North Carolina	2011–2012	Pregnant woman	39	–	–	–	(1.9)	–	(1.3)	–	97.4	97.4	Hoffman et al., (2014)
Canada	2010–2012	Pregnant woman	24	–	–	–	(2.88)	–	(0.27)	–	92	29	Kosarac et al. (2016)
Australia	2010–2013	Children and adults	72	–	–	–	(24.4)	–	(1)	–	97	92	Van den Eede et al. (2015)
			23	–	–	–	(63.4)	–	(0.66)	–	100	96	
Norway													
Oslo	2012	Mothers	244	–	–	0.63	–	0.08	–	–	97	52	Cequier et al. (2015)
		Children	112	–	–	1	–	0.23	–	–	97	61	
China													
Shanghai	2016–2017	Children and adults	180	0.376	–	0.032	–	0.005	–	91	68	21	Sun et al. (2018)
South China	2015	Children	411	–	–	0.28	–	0.05	–	–	99	29	Chen et al. (2018)
Central China	2016–2017	–	26	–	–	0.21	–	0.24	–	–	87	79	Tao et al. (2018)
Qingyuan City	2014	Adults	221	–		–	(0.85)	–	(0.25)	–	100	76	Lu et al. (2017)

[a]The number of samples

"–"data unavailable

remarkably greater than the levels of DPhP (SG-GM: 8.01 ng mL^{-1}, range: 4.72–60.7 ng mL^{-1}, DF: 100%) and BDCIPP (SG-GM: 2.18 ng mL^{-1}, range: 0.02–238 ng mL^{-1}, DF: 51%). The presence of all three targeted metabolites of OPE in urine samples, implies the widespread exposure of OPEs to the Hanoi citizen in Vietnam.

The high DF (98%) of DEP in urine samples in Vietnam were in agreement with some previous reports, such as in New York, U.S (DF: 100%) (Wang et al. 2019a), Atlanta, U.S (DF of DEP: 88–92%) (Jayatilaka et al. 2019) and Shanghai, China (91%) (Sun et al. 2018). However, the GM concentration of DEP in urine observed in Vietnam (SG-adjusted value: 1960 ng mL^{-1}, unadjusted value: 1890 ng mL^{-1}) was approximately 3–4 orders of magnitude higher than those appeared in the U.S (Jayatilaka et al. 2019; Wang et al. 2019a) and China (Sun et al. 2018). The extremely high levels and DF of DEP in urine samples indicated the frequency of exposure with high doses to its parent chemicals of citizens in Hanoi, Vietnam. DEP is the metabolite of TEP, which is a common flame retardant and plasticizer (Jayatilaka et al. 2019). TEP was found in indoor and outdoor dust samples in Hanoi, Vietnam (Hoang et al. 2023) and China (Wang et al. 2020). Furthermore, DEP can be metabolized from organophosphorus pesticides (Yang et al. 2019), such as diazinon and chlorpyrifos (Maravgakis et al. 2012). Diazinon and chlorpyrifos were commonly applied in agriculture in Vietnam (Phung et al. 2012; Van Cong et al. 2022). The residues of diazinon and/or chlorpyrifos were found on agricultural products such as vegetables, fruit, meat, beef, chicken and milk (Am 2019; Dallegrave et al. 2018; Gazzotti et al. 2009; Marete et al. 2020; Nematollahi et al. 2022; Słowik-Borowiec et al. 2012). In this research, urine samples were collected mostly from urban citizens, who have less contact with agricultural activities, therefore, the exposure sources of organophosphorus pesticides to the participants were probably from agro-foods and/or household insecticides (Jaga and Dharmani 2003). Therefore, the exposure sources of TEP and organophosphorus pesticides to citizens in Hanoi, Vietnam might come from industrial, domestic, and agricultural, and food origins.

The ubiquitous present of DPhP (DF: 100%) in urine samples same to this study was also observed in many areas of the U.S (DF: 92–100%) (Butt et al. 2014, 2016; Hoffman et al. 2014; Petropoulou et al. 2016; Preston et al. 2017; Thomas et al. 2017; Wang et al. 2019a), Canada (92%) (Kosarac et al. 2016), Australia (97–100%) (Van den Eede et al. 2015), Norway (97%) (Cequier et al. 2015) and China (99–100%) (Chen et al. 2018; Lu et al. 2017). In term of concentration, the urinary concentrations of DPhP in Hanoi, Vietnam (SG-adjusted value: 8.01 ng mL^{-1}, unadjusted value: 7.74 ng mL^{-1}) was approximately 1–2 order of magnitude greater than those observed in China (Chen et al. 2018; Lu et al. 2017; Sun et al. 2018; Tao et al. 2018) and it was at a higher level (3–18 times higher) than those recorded in many areas in the U.S (Butt et al. 2014, 2016; Cooper et al. 2011; Dodson et al. 2014; Hoffman et al. 2014; Jayatilaka et al. 2019; Petropoulou et al. 2016; Preston et al. 2017; Thomas et al. 2017; Wang et al. 2019a), Canada (Kosarac et al. 2016) and Norway (Cequier et al. 2015). However, when compared to the DPhP concentration in urine from Australia (24.4–63.4 ng mL^{-1} unadjusted concentration) (Van den Eede et al. 2015), the urinary DPhP values detected in this study were much lower (3–8 times lower). Since DPhP is a non-specific metabolite, its parent chemical is not only TPhP but several other aryl-OPEs (Funk et al. 2019; Wang et al. 2019a; Zheng et al. 2021). Therefore, the frequent appearances of DPhP in urine samples suggested the high frequent exposure to its parent chemicals of participants, and implied the common application of aryl-OPEs in daily items (such as plastic, polyurethane foams, hydraulic fluids, nail polish, varnishes and lacquers) in Hanoi, Vietnam.

The DF (51%) of BDCIPP in urine in Hanoi, Vietnam was higher than those observed in Canada (DF: 29%) (Kosarac et al. 2016), Shanghai (21%) (Sun et al. 2018) and South China (29%), China (Chen et al. 2018), but similar to urine collected in Norway (52–61%) in 2012 (Cequier et al. 2015). However, many studies in the U.S (DF > 90%) (Butt et al. 2014, 2016; Cooper et al. 2011; Hoffman et al. 2014; Petropoulou et al. 2016; Preston et al. 2017; Thomas et al. 2017; Wang et al. 2019a) and Australia (> 92%) (Van den Eede et al. 2015) showed much higher DF of BDCIPP in urine than those reported in this study. The GM value of BDCIPP (SG-adjusted value: 2.18 ng mL^{-1}, unadjusted value: 2.20 ng mL^{-1}) in this study was higher (about 1–3 orders of magnitudes) than those reported in some cities in the U.S (Cooper et al. 2011; Dodson et al. 2014; Hoffman et al. 2014; Jayatilaka et al. 2019; Wang et al. 2019a), Canada (Kosarac et al. 2016), Australia (Van den Eede et al. 2015), Norway (Cequier et al. 2015) and China (Chen et al. 2018; Lu et al. 2017; Sun et al. 2018; Tao et al. 2018), comparable to those recorded for Atlanta firefighter (unadjusted value: 3.3 ng mL^{-1}) (Jayatilaka et al. 2019), mothers (SG-adjusted value: 3.3 ng mL^{-1}) (Butt et al. 2016) and adults (unadjusted value: 2.5 ng mL^{-1}) from California, U.S (Petropoulou et al. 2016), and mothers from New Jersey (SG-adjusted value: 2.4 ng mL^{-1}) (Butt et al. 2014). In comparison with the urinary BDCIPP levels from children in the U.S (SG-adjusted GM value: 5.6–10.9 ng mL^{-1}) (Butt et al. 2014, 2016; Thomas et al. 2017) the values detected in Hanoi, Vietnam were 2–5 times lower. This difference in the DF and concentration of BDCIPP in urine between countries is probably due to the variation of OPE usage habits of between these regions. While in the U.S, alternative flame retardants (mostly OPEs) had been replaced PBDEs in consumer products since the 2000s (Butt et al. 2016; Cristale et al. 2013;

Gustavsson et al. 2018; Thomas et al. 2017; Xu et al. 2021), it seems that PBDEs were still the additives to in many items (Hoang et al. 2021), and OPEs may have been not yet completely substituted PBDEs in Vietnam. In general, the urinary BDCIPP, DPhP and DEP values detected in Hanoi, Vietnam were at greater levels than most of those reported in some other regions, these results might reflect the high exposure to TDCIPP, TPhP and TEP in Hanoi, Vietnam.

Relationship of Gender and Age with Urinary OPE Metabolite Levels

In order to determine the variation in urinary values of BDCIPP, DPhP and DEP by sex and age, GM of urinary BDCIPP, DPhP and DEP SG-adjusted values of each sex/age groups were compared (Table 3). Results of nonparametric statistical tests indicated no significant differences in the urinary BDCIPP, DPhP and DEP concentrations and DFs between gender ($p = 0.299–0.757$) (Table S7) or age ($p = 0.079–0.943$) (Table S8). However, when comparing the GM of BDCIPP, DPhP and DEP levels between gender and age groups, there were some slight differences. The GM urinary levels of BDCIPP, DPhP and DEP from females (4.64; 8.56 and 2050 ng mL^{-1}, respectively) were slightly higher than males (0.92; 7.37 and 1860 ng mL^{-1}, respectively). The higher urinary levels of BDCIPP and DPhP in female than males were also observed from a popular in New York, U.S. (Wang et al. 2019a). These results demonstrate the difference in exposure to OPEs between genders, which may be affected by their daily habits and behavior. For instance, females generally consume more cosmetic products than males, and some OPEs are applied in cosmetics (Mendelsohn et al. 2016; Ye et al. 2022) or a part of cosmetic products (such as plastic parking items) (Marklund et al. 2003; Shi et al. 2015), consequently, leading to the higher exposure to OPEs of female.

To examine the variation of BDCIPP, DPhP and DEP levels in urine with age, participants were divided into two major age groups: Children and teenagers (under 18 years old), and adults (from above 18 years old). Between the two age groups, children and teenagers had a higher urinary DPhP level (GM: 9.74 ng mL^{-1}) than did the adults (GM: 7.41 ng mL^{-1}), which suggested the higher exposure to TPhP and some other aryl-OPEs in younger ages. In addition, the results of Spearman's correlation rank analysis suggested a decrease in urinary DPhP levels associated with an increase in age ($r = -0.255$, $p = 0.051$) (Table S9). This seems to be an international trend since many previous reports showed the same result (Butt et al. 2014; Butt et al. 2016; Sun et al. 2018; Van den Eede et al. 2015). Elevated exposure to aryl-OPEs in younger ages may associate with the hand-to-mouth behaviors, metabolism and demographic characteristic difference between children and adults (Butt et al. 2014; Butt et al. 2016; Sun et al. 2018; Van den Eede et al. 2015). Exposure to TPhP may impact the reproductive system (Fang et al. 2003; Meeker and Stapleton 2010), and it could be more susceptible when the exposure dose is elevated during childhood, because there may be potential adverse consequences appear later in life (WHO 2006). However, the knowledge on toxicities of TPhP and other aryl-OPEs is still limited, more information on the long-time influence of OPEs on human health need to be filled in future.

In terms of BDCIPP and DEP, the urinary GM concentrations of these chemicals appeared to be slightly higher in the elder age group (working ages) than those in younger age group. These age groups comprised university students and workers, who probably have longer contact time with many electronic items daily (Sun et al. 2018). Furthermore, exposure to OPEs in working environments could probably be one of the important sources attributed to the higher urinary BDCIPP and DEP levels among these working age groups.

Daily Exposure Assessment

In this work, uncorrected urinary values of BDCIPP, DPhP and DEP were used to estimate the exposure doses to their parent compounds (TDCIPP, TPhP and TEP, respectively), and each OPE metabolite was assumed to be degraded from single parent chemical (parent/metabolite chemical: TDCIPP/BDCIPP, TPhP/DPhP and TEP/DEP) (Table 4, detailed in Table S10). The mean and

Table 3 Urinary DEP, DPhP and BDCIPP concentrations (ng mL^{-1}, SG-adjusted) differences between genders and ages groups

		n[a]	DEP				DPhP				BDCIPP			
			DF%	GM	AM	p*	DF%	GM	AM	p	DF%	GM	AM	p
Gender	Male	26	96	1860	2320	0.175	100	7.37	8.42	0.194	54	0.92	2.92	0.698
	Female	33	100	2050	2630		100	8.56	11.2		48	4.64	14.3	
Age	< 18 yrs.[b]	17	100	1730	2120	0.262	100	9.74	12.8	0.079	53	1.39	2.78	0.943
	≥ 18 yrs	42	98	2070	2640		100	7.41	8.85		50	2.65	11.9	

[a]The number of samples

[b]*yrs* years old

*p values were obtained from Mann–Whitney U test

Table 4 Exposure doses (ng kg^{-1} d^{-1}) to OPEs (TEP, TPhP, TDCIPP) estimated from urinary OPE metabolite concentrations (DEP, DPhP and BDCIPP) in Hanoi, Vietnam

OPE metabolite		DEP	DPhP	BDCIPP
Estimated exposure doses of parent OPE (ng kg^{-1} d^{-1})		TEP	TPhP	TDCIPP
Percentile	5th	203,000	251	2.35
	25th	432,000	286	18.5
	50th	530,000	312	192
	75th	652,000	353	618
	95th	897,000	508	1740
Mean		534,000	342	236
Median		530,000	312	192
Gender	Male	508,000	332	151
	Female	555,000	349	303
Age	< 18 yrs.[b]	474,000	426	161
	≥ 18 yrs	559,000	307	267
RfD[a]		125,000	7000	20,000

[a]*RfD* reference dose

[b]*yrs* years old

Presented exposure doses for gender and age are mean values

95th percentile of exposure doses of TEP (534,000 and 897,000 ng kg^{-1} d^{-1}, respectively) were the highest, followed by TPhP (342 and 508 ng kg^{-1} d^{-1}, respectively) and TDCIPP (236 and 1740 ng kg^{-1} d^{-1}, respectively). Higher exposure doses to OPEs were observed for females (mean: 303–555000 ng kg^{-1} d^{-1}) than males (mean: 151–508,000 ng kg^{-1} d^{-1}).

The 95th percentile of calculated exposure doses of TEP, TPhP and TDCIPP in this study were at greater levels than those calculated in the U.S (79.8; 118 and 61.9 ng kg^{-1} d^{-1}, respectively) (Wang et al. 2019a). The mean calculated doses of TPhP and TDCIPP were also noticeably higher than those observed for children from South China (65 and 15 ng $kg^{-1}d^{-1}$, respectively) (Chen et al. 2018). However, the exposure doses of TDCIPP in Hanoi, Vietnam were lesser than those calculated for infants in the U.S. (330 ng $kg^{-1}d^{-1}$) (Hoffman et al. 2017).

According to previous studies, the reference dose (RfD) for TEP were 125,000 ng kg^{-1} d^{-1} (Ding et al. 2015), TPhP was 7000 ng kg^{-1} d^{-1} (Van den Eede et al. 2011), and TDCIPP was 20,000 ng kg^{-1} d^{-1} (Gbadamosi et al. 2022). In the present study, the calculated exposure doses of TPhP and TDCIPP were 1–2 orders of magnitude below their corresponding RfDs, indicating the insignificant risks to citizen health from the current exposure doses of these OPEs. However, the estimated exposure doses of TEP in Hanoi, Vietnam exceeded its RfD, demonstrated the high exposure level to TEP of Hanoi citizens. Although the information on the toxicity of TEP is limited, high exposure dose to TEP may cause certain neurotoxic properties and/or potential mutagenic effects in humans (Lai et al. 2022). Therefore, more attention should be put on the sources, fate and exposure of DEP parent compounds to Hanoi residents in Vietnam.

The information and inferences presented in this study pertain to BDCIPP, DPhP and DEP in human urine and estimated OPEs exposure in a population and at a particular time. Though this study yielded interesting findings, it has some limitations. Small sample size was one of the main limitations of this study, urine sampling was conducted on only a few individuals from a popular in Hanoi, Vietnam. In addition, there was only one single first-morning void urine sample taken from each participant. Thus, the results could just reflect relatively recent exposure (within 24 h) (Hyland et al. 2021; Van den Eede et al. 2015) and the information on the variation of urine OPE metabolite intra-day was lacking. Furthermore, the lack of some individual information (such as health conditions, living environments, and eating habits) was also a limitation. Therefore, interpreting results from this study needs to be cautious. More comprehensive research with bigger sample size in larger areas and more target chemicals are needed to produce comprehensive information on the occurrence, behavior and effects of OPEs in the human body in Vietnam.

Conclusion

Data on the occurrence of three OPE metabolites (BDCIPP, DPhP and DEP) in urine samples collected in Hanoi, Vietnam were presented in this study. In general, the urinary BDCIPP, DPhP and DEP concentrations measured in Hanoi, Vietnam were at a relatively high level when compared to those reported in developed countries. Among the urine samples, high detected frequencies were observed for DPhP and DEP (100 and 98%, respectively). DEP was the dominant urinary OPE metabolite with an extremely high concentration in urine samples. Gender and sex are possible factors that may influence OPEs exposure and/or the variation of urinary OPE metabolites in humans. The calculated exposure doses of TEP were higher than its corresponding RfD, indicated that the current exposure doses of TEP may pose significant impacts to human health. Although the study has limitations, these are initial preliminary results on OPE metabolites in the urine of people in Hanoi (Vietnam's major metropolis) and indicate the extent of exposure of people to OPEs present in the environment. Thereby, there is a need for further research on the behavior and exposure pathways of OPEs in humans to evaluate their effects on Vietnamese people's health. More attention must be paid to the origin and dispersion of OPEs in the environment and the use of OPEs in goods and foods to ensure people's health.

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Declarations

Conflict of interest The authors declare that they have no competing interests.

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