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Descriptive analysis of organophosphate ester metabolites in a pan-Canadian pregnancy cohort

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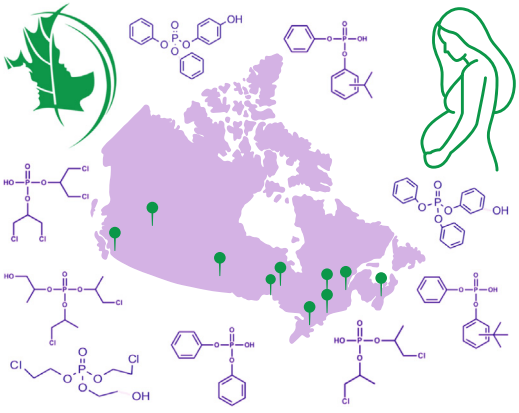
HIGHLIGHTS

- We quantified first trimester urinary concentrations of 16 OPE metabolites.
- Associations with sociodemographic characteristics varied among OPE metabolites.
- OPE metabolite concentrations tended to be higher in the summer than winter.
- This is the largest biomonitoring study of OPE metabolites in pregnancy to date.

GRAPHICAL ABSTRACT



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ABSTRACT

Organophosphate esters (OPEs) are widely used in numerous consumer products for their flame retardant and plasticizing properties. Despite potential widespread exposure, biomonitoring data during critical windows of development are scarce and limited to the most widely studied metabolites. We quantified urinary concentrations of multiple OPE metabolites in a vulnerable Canadian population. Using data and biobanked specimens from the Maternal-Infant Research on Environmental Chemicals (MIREC) study (2008–2011), we measured first trimester urinary concentrations of 15 OPE metabolites as well as one flame retardant metabolite and quantified associations with sociodemographic and sample collection characteristics in 1865 pregnant participants. We applied 2 different analytical methods to quantify OPEs, one using UItra-Performance Liquid Chromatography coupled to tandem mass spectrometry (UPLC-MS/MS) and the other using Atmospheric Pressure Gas Chromatography coupled to mass spectrometry (APGC-MS/MS) with sensitive limits of detection (0.008–0.1 μg/L). We modelled associations between sociodemographic and sample collection characteristics and specific gravity-standardized chemical concentrations. Six OPE metabolites were detected in the majority (68.1–97.4 %) of participants. Bis-(2-chloroethyl) hydrogen phosphate had the highest detection rate (97.4 %). Diphenyl phosphate had the highest geometric mean concentration (0.657 μg/L). Metabolites of

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tricresyl phosphate were detected in few participants. Associations between sociodemographic characteristics varied according to each OPE metabolite. Pre-pregnancy body mass index tended to be positively associated with OPE metabolite concentrations whereas age tended to be inversely associated with OPE concentrations. OPE concentrations were, on average, higher in urine samples collected in the summer than other seasons the winter. We present the largest biomonitoring study of OPE metabolites in pregnant people to date. These findings demonstrate widespread exposure to OPEs and their metabolites and identify subpopulations who may experience heightened exposure.

1. Introduction

Organophosphate esters (OPEs) are a class of chemicals used since the 1970s in numerous consumer products (Andresen et al., 2004; Chupeau et al., 2020; Gold et al., 1978; Patisaul et al., 2021). Following the phaseout of polybrominated diphenyl ethers (PBDEs) in the early 2000s (Blum et al., 2019; US EPA, 2006), OPE use and corresponding presence in environmental and biological media increased over the next two decades (Dodson et al., 2012a, 2012b; Hoffman et al., 2017a; Yang et al., 2019a, 2019b). Despite this increasing potential for exposure, biomonitoring data – particularly during critical developmental windows such as pregnancy – are sparse. OPEs can accumulate in and cross the placenta (Ding et al., 2016; Zhao at el., 2017); thus, exposure to these chemicals during pregnancy has the potential to adversely impact the health of the mother as well as the developing fetus.

Halogenated OPEs such as tris(1,3-dichloroisopropyl) phosphate (TDCIPP), tris-(2-chloroethyl) phosphate (TCEP), and tris-2-(chloroisopropyl) phosphate (TCIPP) are used for their flame retardant and plasticizing properties in electronics, building materials, vehicles, car seats, and upholstered furniture and textiles (Government of Canada, 2020; van der Veen and de Boer, 2012). Nonhalogenated OPEs also have flame retardant properties but are also used as plasticizers in personal care products, such as nail polish, to increase flexibility and durability (Ingle et al., 2019; Mendelsohn et al., 2016; Patisaul et al., 2021; van der Veen and de Boer, 2012). Examples of nonhalogenated OPEs include triphenyl phosphate (TPhP), tri-n-butyl phosphate (TnBP) and tris(2-butoxyethyl) phosphate (TBOEP). Neither halogenated nor nonhalogenated OPEs are chemically bound to products and they may enter environmental media by leaching, volatilization, or abrasion (Chupeau et al., 2020). OPEs have been widely detected in dust (Chupeau et al., 2020; Dodson et al., 2014; Dodson et al., 2012a, 2012b), air (Chupeau et al., 2020; La Guardia et al., 2017; Schreder et al., 2016), polyurethane foam from furniture (Stapleton et al., 2012), gymnastics equipment (Carignan et al., 2016), baby products (Stapleton et al., 2011), food (Poma et al., 2018), and electronic devices such as cell phones (Yang et al., 2019a, 2019b). The primary route of exposure depends on the specific OPE and an individual's life stage; common routes of exposure include inhalation (La Guardia et al., 2017; Schreder et al., 2016), accidental ingestion or dermal absorption of dust (Kim et al., 2019), and ingestion of food, particularly processed food (Gbadamosi et al., 2021; Poma et al., 2018).

Evidence from experimental and epidemiological literature suggests that OPEs are toxic to multiple organ systems (e.g. reproductive, neurological, respiratory, and endocrine) (Chupeau et al., 2020; Patisaul et al., 2021; Vuong et al., 2020). TCEP and TDCIPP have been declared carcinogens in the state of California (California Office of Health Hazard Assessment, 2022; Blum et al., 2019). Based on a draft screening assessment of TCIPP and TDClPP, the Government of Canada is proposing that TCIPP and TDClPP may be harmful to human health (Government of Canada, 2020). Reproductive and developmental effects were the most critical endpoints for TCIPP. Although OPEs have been thought to have minimal neurotoxicity because they do not act on the acetylcholinesterase neurotransmitter (Patisaul et al., 2021), neurotoxic effects may occur via other pathways, neurotransmitters or via toxic metabolites (Naughton and Terry, 2018; Patisaul et al., 2021; Sun et al., 2016).

OPEs are metabolized via Phase-I and Phase-II biotransformation to hydrophilic metabolites that are eliminated via urine (Hou et al., 2016). Due to the relatively rapid metabolism of OPEs, urine - rather than blood or milk - is the preferred matrix for measuring OPE metabolites (Guo et al., 2022). Biomonitoring data of urinary metabolite concentrations in mother-child pairs (Butt et al., 2014, 2016), adults (Dodson et al., 2014), and the general population (Ospina et al., 2018) demonstrate widespread exposure to OPE metabolites. Pregnancy cohort studies in the US (Carignan et al., 2018; Castorina et al., 2017; Hoffman et al., 2017b; Kuiper et al., 2020; Percy et al., 2020; Romano et al., 2017; Varshavsky et al., 2021), Puerto Rico (Ingle et al., 2019), and China (Feng et al., 2016) have similarly reported high detection rates for metabolites of halogenated and nonhalogenated OPEs; however, this body of literature is characterized by small sample sizes, a limited number of measured metabolites, and a focus on specific geographic regions. Specifically, sample size in pregnancy cohort studies ranged from 23 (Feng et al., 2016) to 357 (Percy et al., 2020) and the number of measured metabolites ranged from 2 (Feng et al., 2016) to 9 (Romano et al., 2017) (Table S1). Canadian OPE biomonitoring data are presently limited to small sample sizes (Kosarac et al., 2016; Siddique et al., 2022; Yang et al., 2019a) and there are no Canadian biomonitoring data in pregnancy. We measured 15 OPE metabolites and one flame retardant metabolite (tetra-brominated benzoic acid (TBBA)) in a pan-Canadian pregnancy cohort study of 1865 participants and examined patterns of exposure according to key sociodemographic and sample collection characteristics. Three of these metabolites have not been previously measured in human biomonitoring studies (Fig. S1).

2. Methods

2.1. Study population

The Maternal-Infant Research on Environmental Chemicals (MIREC) study is a national-level pregnancy cohort of 2001 participants from 10 Canadian cities (Vancouver, Edmonton, Winnipeg, Sudbury, Ottawa, Kingston, Toronto, Hamilton, Montreal, and Halifax) (Arbuckle et al., 2013). Briefly, participants were recruited between 2008 and 2011 in their first trimester and followed through delivery. Individuals were eligible for participation in MIREC if they had no serious medical complications, were at least 18 years old, <14 weeks gestation at the time of recruitment and could communicate in either English or French (Arbuckle et al., 2013). The present analysis used stored frozen first trimester urine samples from participants who consented to use of their data and biological specimens in future research. Of the 2001 participants recruited, 43 did not consent to the biobank and 18 withdrew from the study; samples from 1865 of the remaining participants were available for the present analysis.

The MIREC study was approved by the Health Canada and CHU Sainte-Justine (Montreal, QC) Research Ethics Boards as well as by ethics committees at all recruitment sites. Participants provided informed consent prior to participation.

2.2. Data collection

Participants completed detailed questionnaires throughout pregnancy to provide information on their sociodemographic characteristics, health history, and lifestyle including age of residence and occupation. As well, clinic staff collected measurements such as weight and height and extracted information from medical charts. At the first trimester visits (range: 6–13 weeks), participants provided a spot urine sample. Research staff noted the date and time of urine collection as well as the time since last void.

2.3. Laboratory analysis

The Centre de Toxicologie du Québec (CTQ) at the Institut national de santé publique du Québec (INSPQ) analyzed the biobanked samples for OPEs. Two methods were used to measure a total of 15 OPE metabolites including 5 metabolites of halogenated OPEs and 10 metabolites of non halogenated OPEs as well as one metabolite of 2-ethylhexyl tetrabromobenzoate (EH-TBB) (Table 1). EH-TBB is an aromatic brominated compound used in the flame retardant product Firemaster 550 (Butt et al., 2014). In the first method, 250 μL of urine sample was enriched with 20 μL of labeled internal standards (IS) (Table S2). After an enzymatic hydrolysis at 37 °C for 90 min with β-glucuronidase (Roche Diagnostics; Mississauga, Ontario, Canada), the samples were acidified with 350 μL of a 10 % hydrochloric acid solution and the analytes were recovered by automated liquid-liquid extraction. A fraction of 1.8 mL out of the 3 mL of methyl tert-butyl ether (MTBE) was transferred using the Janus robotic station (Perkin Elmer; Waltham, MA, USA). The extracts were then evaporated to dryness before being derivatized with pentafluorobenzyl bromide at 80 °C for 45 min. The analytes were re-extracted using an automated liquid-liquid extraction (LLE) with 3 mL of MTBE. A fraction of 0.9 mL of organic phase was transferred using the Janus robotic station, evaporated and taken up in 200 μL of a mixture of hexane dichloromethane (80:20). This method was performed under very strict extraction procedure conditions to avoid potential contamination coming from laboratory environment (especially for DBP, BClPP and DPhP). Reagent blanks were extracted at each sequence to verify the presence of contamination. The deconjugation efficiency was monitored by the concentration of BPA-d_6 obtained from the BPA-glucuronide-d_6 added in each sample analyzed. The recovery was monitored by comparing the sample IS area with the mean of IS area of the 8 calibrators. The extracts were analyzed by Atmospheric Pressure Gas Chromatography with a tandem quadrupole mass spectrometry system (APGC-MS/MS) (Agilent 7890B gas chromatograph and Agilent 7693 autoinjector (Agilent Technologies; Mississauga, Ontario, Canada), Waters Xevo TQ-XS mass spectrometer, APGC Waters ionization source and MassLynx v4.2 workstation (Waters; Milford, MA, USA)). The column used was a DB-XLB 30 m × 0.25 mm; 0.1 μm film thickness (Agilent Technologies; Mississauga, Ontario, Canada). The temperature program was as follows: initial temperature at 60 °C for 1 min to 320 °C (12 °C/min). This temperature was maintained for 4.1 min for a total run time of 26.77 min. The carrier gas was helium at a constant flow rate of 1.2 mL/min. The injection volume was 1 μL in the pulsed splitless mode. The measurement of the ions generated after positive atmospheric ionization was carried out in Multiple Reaction Monitoring (MRM) mode (Table S3). The following metabolites were measured using this method (Table 1): BCEP, BCIPP, BDClPP, DmCP, DoCP, DpCP, DBP, DiBP, DPHP, ip-PPP, TBBA and tb-PPP. Validation parameters are detailed in Table S4.

In the second method, 250 μL of urine sample was enriched with 10 μL of labeled internal standards (Table S2). After an enzymatic hydrolysis at 37 °C for 90 min with β-glucuronidase, the samples were acidified with 350 μL of a 10 % hydrochloric acid solution and the analytes were recovered by flash-freeze liquid-liquid extraction with 3 mL of a mixture of MTBE:ethyl acetate (80:20). The extracts were evaporated to dryness and taken up in 100 μL of a 40 % acetonitrile solution. The deconjugation efficiency was monitored by the concentration of 4-MLBF obtained from the MLBF-glucuronide. Reagent blanks were extracted at each sequence to verify the presence of contamination. The recovery was monitored by comparing the sample IS area with the mean of IS area of the 8 calibrators. The analytes were then analyzed by Ultra Performance Liquid Chromatography with a tandem quadrupole mass spectrometry system (UPLC-MS/MS) (Waters Acquity Ultra Performance Liquid Chromatograph, Waters Xevo TQ-XS tandem mass spectrometer and MassLynx v4.2 workstation (Waters; Milford, MA, USA)) in MRM mode with an electrospray source (ESI) in positive and negative mode, alternately. The column used was an HSS T3 C18 150 mm × 2.2 mm × 1.8 μm (Waters; Milford, MA, USA). The mobile phases used were constituted of 0.1 % formic acid in water (A) and 0.1 % formic acid in acetonitrile (B). The gradient started at 100 % A held for 1 min; linearly decreased to 70:30 (A:B) from 1.0 to 6.0 min; linearly decreased to 50:50 (A:B) from 6.0 to 9.5 min; linearly decreased to 5:95 (A:B) from 9.5 to 12.5 min and linearly reversed to 100 % A from 12.5 to 14.0 min The flow rate was set at 0.45 mL/min and the column temperature was set at 50 °C. The injection volume was 5 μL. The following metabolites were measured with this method: BCEHEP, BClPHIPP, mOH-TPhP, and

Table 1
OPE metabolites measured in the MIREC study (2008–2011) and corresponding parent compounds.

Parent compound	CAS #	Metabolite name	Metabolite abbreviation
Halogenated			
Tris-(2-chloroethyl) phosphate (TCEP)	115-96-8	Bis(2-chloroethyl) 2-hydroxyethyl phosphate	BCEHEP[a,b]
		Bis-(2-chloroethyl) hydrogen phosphate or Bis-(2-chloroethyl) phosphate	BCEP[c]
Tris(1-chloro-2-isopropyl) phosphate (TCIPP) or tris-2-(chloroisopropyl) phosphate (TCPP) or 2-propanol, 1-chloro-, phosphate (3:1)	13674-84-5	Bis-(2-chloroisopropyl) phosphate	BCIPP[b]
		1-Hydroxyl-2-propyl bis(1-chloro-2-propyl) phosphate	BCIPHIPP[b]
Tris(1,3-dichloroisopropyl) phosphate (TDCIPP)	13674-87-8	Bis(1,3-dichloro-2-propyl) phosphate	BDCIPP[c]
Tricresyl phosphate (TCrP or TCP)	1330-78-5 &	Bis o-cresyl phosphate	DoCP[c]
Tris(methylphenyl) phosphate (TMPP)	78-32-0	Bis p-cresyl phosphate	DpCP[c]
		Bis m-cresyl phosphate	DmCP[c]
Nonhalogenated			
Tri-n-butyl phosphate (TnBP)	126-73-8	Di-n-butyl phosphate	DBP or DnBP[d]
Triisobutyl phosphate (TiBP)	126-71-6	Diisobutyl phosphate	DiBP[c]
Triphenyl phosphate (TPhP)	115-86-6	Diphenyl phosphate	DPhP[b,e]
		Meta isomers of OH-TPhP	mOH-TPhP[a,b]
		Para isomers of OH-TPhP	pOH-TPhP[a,b]
Mono-substituted isopropyl triphenyl phosphate (mono-ITP or ip-TPhP)	64532-94-1	Isopropyl phenyl phenyl phosphate	ip-PPP[b]
tert-butyl triphenyl phosphate (tb-TPhP)	56803-37-3	tert-butyl-phenyl phenyl phosphate	tb-PPP[f]
Other[g]			
2-Ethylhexyl tetrabromobenzoate (EH-TBB)	183658-27-7	Tetra-brominated benzoic acid	TBBA[h]

[a] Molecular structures for these compounds are provided in Fig. S1.
[b] Supplier: Centre de Recherche du CHU, Organic synthesis, Québec, Canada.
[c] Supplier: Toronto Research Chemicals; Toronto, Ontario, Canada.
[d] Supplier: Sigma-Aldrich, Oakville, Ontario, Canada.
[e] DPhP is a metabolite of several other parent compounds not measured in MIREC.
[f] Supplier: SMSF Duke University, Durham, NC, USA.
[g] EH-TBB is commonly used in flame retardant products Firemaster 550.
[h] Supplier: Wellington Laboratories, Guelph, Ontario, Canada.

Table 2
Descriptive statistics of specific gravity standardized OPE metabolites in first trimester urine samples, MIREC study, 2008–2011 (μg/L).

Chemicals	N[a]	LOD	% < LOD	LOQ	25th	50th	75th	95th	Max	Geometric mean (95 % CI)
Halogenated										
BCEHEP	1839	0.012	67.9	0.040	<LOD	<LOD	0.0173	0.0575	0.854	–
BCEP	1839	0.021	2.6	0.070	0.146	0.267	0.563	2.03	36.6	0.301 (0.286, 0.316)
BCIPP	1831	0.016	15.2	0.020	0.0327	0.0648	0.142	0.661	19.5	0.070 (0.065, 0.0746)
BCIPHIPP	1861	0.11	17.7	0.35	0.211	0.418	0.906	4.01	152	0.439 (0.413, 0.466)
BDCIPP	1817	0.053	11.0	0.18	0.161	0.318	0.617	1.85	22.2	0.299 (0.281, 0.319)
Non halogenated										
DBP	1848	0.050	31.9	0.058	<LOD	0.0711	0.128	0.375	22.7	0.0782 (0.0750, 0.0816)
DiBP	1848	0.020	76.3	0.035	<LOD	<LOD	0.0200	0.060	0.774	–
DPhP	1862	0.14	13.4	0.48	0.375	0.658	1.24	4.24	149	0.657 (0.621, 0.696)
mOH-TPhP	1855	0.021	99.4	0.071	<LOD	<LOD	<LOD	<LOD	0.066	–
pOH-TPhP	1859	0.015	72.2	0.050	<LOD	<LOD	<LOD	0.041	0.758	–
ip-PPP	1801	0.015	58.2	0.035	<LOD	<LOD	0.0236	0.0701	0.945	–
tb-PPP	1760	0.008	41.0	0.026	<LOD	0.0133	0.0231	0.0508	0.546	–
DmCP	1842	0.015	85.9	0.049	<LOD	<LOD	<LOD	0.0284	0.525	–
DoCP	1853	0.021	99.4	0.069	<LOD	<LOD	<LOD	<LOD	0.122	–
DpCP	1861	0.026	98.9	0.087	<LOD	<LOD	<LOD	<LOD	0.157	–
Other (non OPE metabolite)										
TBBA	1804	0.0090	76.0	0.014	<LOD	<LOD	0.0112	0.0388	2.58	–

LOD: limit of detection, LOQ limit of quantification.
[a] Sample size differs because laboratory results were not available for all samples.

pOH-TPhP. Validation parameters were detailed in the supplementary data in Table S4.

The limits of detection (LODs) for the OPEs measured were between 0.008 and 0.1 μg/L. The intra-day precision for both methods varied between 4.1 and 12 % and the inter-day precision varied between 4.6 and 13 % depending on the analytes (Table S4). The internal reference materials used to control the quality of the analyses were the 3 in house reference materials (Low, Medium, High QC) prepared by the CTQ, INSPQ. The overall quality and accuracy of the analytical methods was monitored by participation in the following interlaboratory program: the Organic Substances in urine Quality Assessment Scheme (OSEQAS; CTQ/INSPQ, Québec, Canada) for the analytes BDClPP and DPhP. Machine readings values were available for all measurements below the LOD.

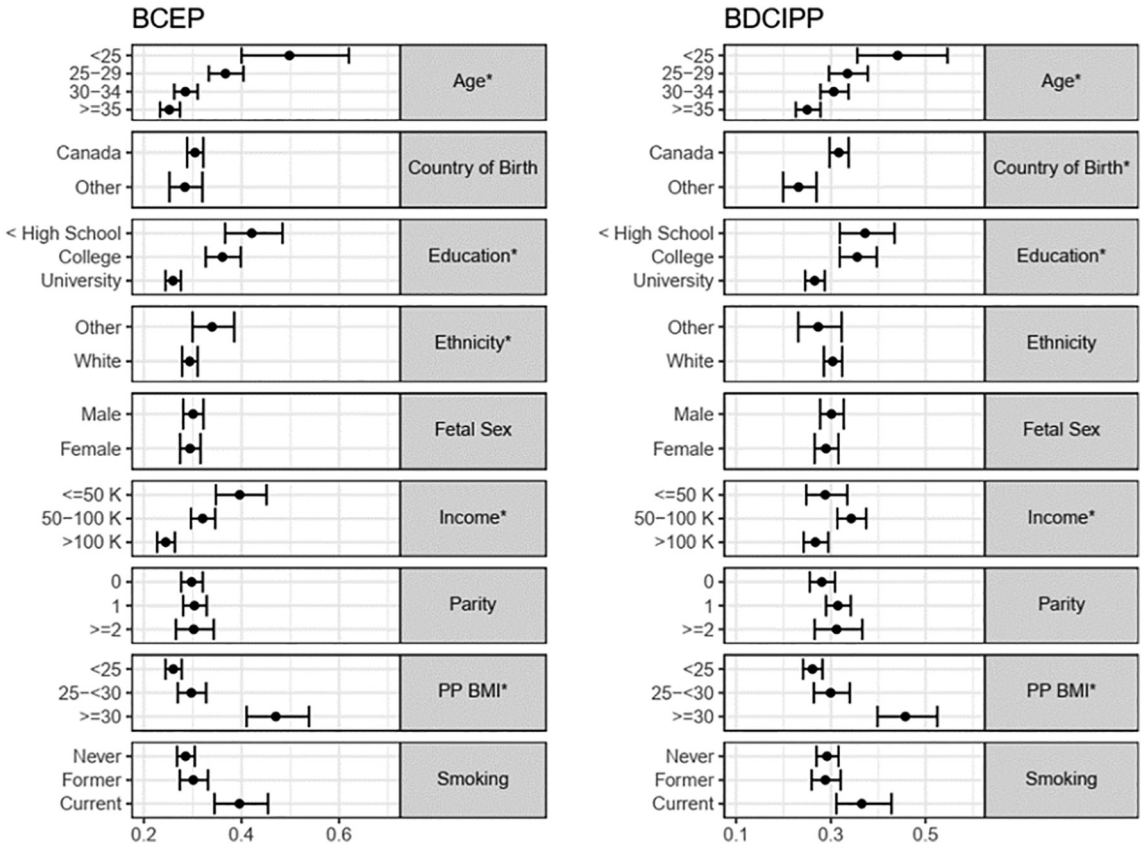

Fig. 1. Geometric mean (95 %) (μg/L) concentrations of halogenated metabolites BCEP and BDCIPP (μg/L) according to sociodemographic determinants. Associations with overall *p*-value <0.05 noted by *.

Urinary specific gravity (SG) measurements were performed to account for urinary dilution using a refractometer.

2.4. Statistical analysis

We calculated the descriptive statistics of all chemicals using machine readings data for values below the LOD. Machine readings values of 0 or <0 were substituted with one-half of the smallest positive value. For chemicals with a detection rate >60 % we reported the geometric mean and calculated Spearman's correlation coefficients. We calculated SG-standardized concentrations using the following formula adapted from Just et al. (Just et al., 2010) and Duty et al. (Duty et al., 2005): $P_c = P_i\,[(SG_m - 1)/(SG_i - 1)]$ where P_c is the *SG*-adjusted metabolite concentration (μg/L), P_i is the observed metabolite concentration, and SG_i is the specific gravity of the urine sample and SG_m is the median SG for the cohort.

To investigate whether chemical concentrations differed according to sociodemographic and sample collection characteristics, we calculated the geometric mean concentrations within the strata of each characteristic and tested for differences between the group specific means. The specific gravity standardized $\log_{10}$-transformed analyte concentrations were the dependent variables and the sociodemographic characteristics were the independent variables. Separate models were developed for each individual characteristic and analyte. We used rank transformation and the non-parametric Kruskal Wallis test, rather than ANOVA, because the normality assumption was violated. When the homoscedasticity assumption was violated, log transformation was performed. We calculated the statistical significance of the overall group effect. When the overall group effect was statistically significant (p-value <0.05), we calculated pairwise comparisons by Wilcoxon's test. The pairwise p-values were corrected for multiple comparisons using the Bonferroni correction.

3. Results

The majority of participants in this analysis were over 30 years of age, born in Canada, non-smokers, were college or university educated and had a pre-pregnancy body mass index (BMI) <25 kg/m^2. Thirty five percent worked in an office setting and 36 % lived in homes built before 1960 (Table S5). Out of the 16 measured analytes, 6 were detected in >60 % of participants. BCEP was most frequently detected (97.4 %) followed by DPhP (86.6 %). DPhP had the highest geometric mean (0.657 μg/L); DCIPHIPP had the highest 95th maximum concentrations (152 μg/L). Metabolites of tricresyl phosphate were rarely detected. <5 % of participants had detectable concentrations of mOH-TPhP, DpCP, or DoCP (Table 2 and Table S6). Spearman correlation coefficients among metabolites with at least 60 % detection rates ranged from 0.06 (DBP and BCIPHIPP) to 0.9 (BCIPP and BCIPHIPP; both metabolites of TCIPP). Correlation coefficients among halogenated compounds (BCEP, BCIPP, BDCIPP, BCIPHIPP) ranged from 0.3 to 0.9 whereas the correlation between the non-halogenated compounds DBP and DPhP was 0.2 (Table S7).

We observed several patterns with sociodemographic characteristics (Figs. 1-3; Tables S8-S16). Age was inversely associated with BCEP, BDCIPP and DPhP (Table S8). The difference in metabolite concentrations between participants 25 or younger and those older than 35 was most pronounced for BCEP. Pre-pregnancy BMI was positively associated with BCEP, BCIPP, BDCIPP, BCIPHIPP, and DPhP (Table S9). Compared to participants of higher income, BCEP concentrations tended be higher in participants with household incomes lower than $50,000 (Table S10). Participants with a high school education or lower tended to have higher geometric mean concentrations of BCEP, BDCIPP, and DPhP than those with a university education (Table S11). Patterns of association with country of birth and ethnicity were mixed (Tables S12 and S13). Participants born outside of Canada tended to have lower geometric mean concentrations of

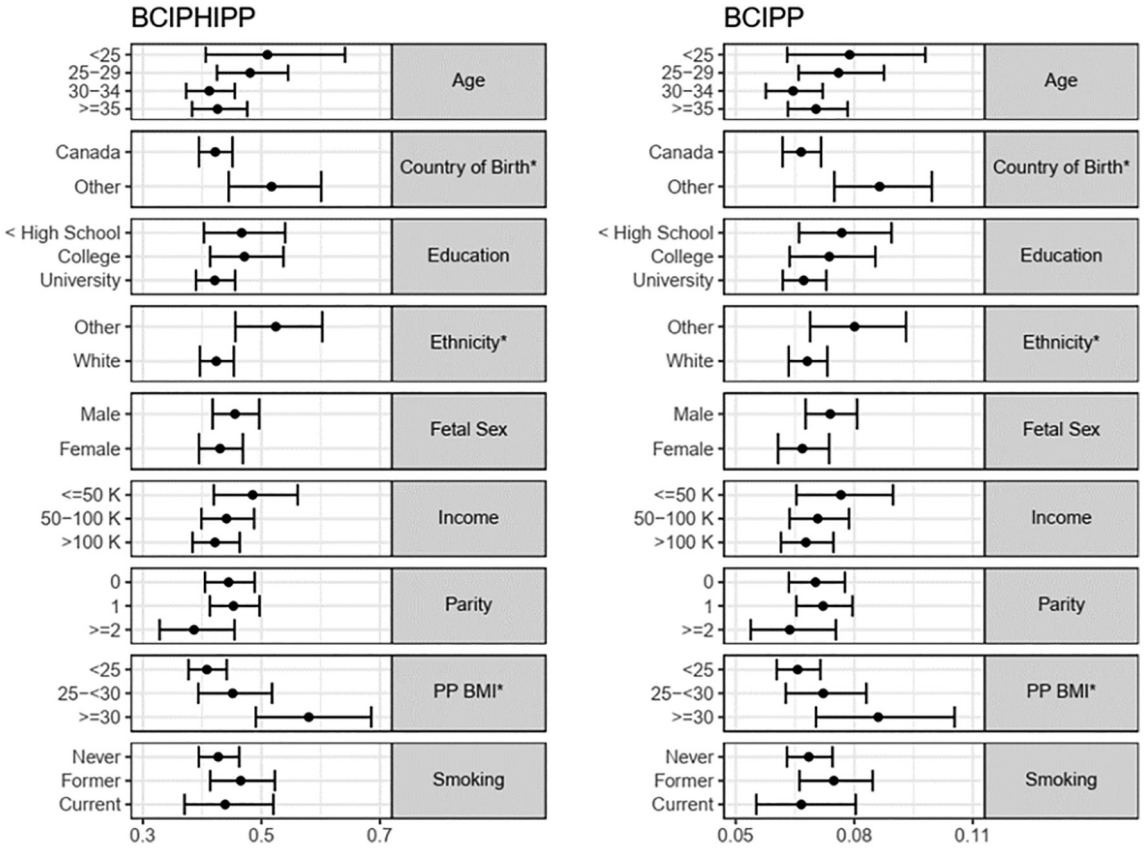

Fig. 2. Geometric mean (95 %) concentrations of halogenated TCPP metabolites (BCIPP, BCIPHIPP) (μg/L) according to sociodemographic determinants. Pre-pregnancy body mass index (PP BMI). Associations with overall p-value <0.05 noted by *.

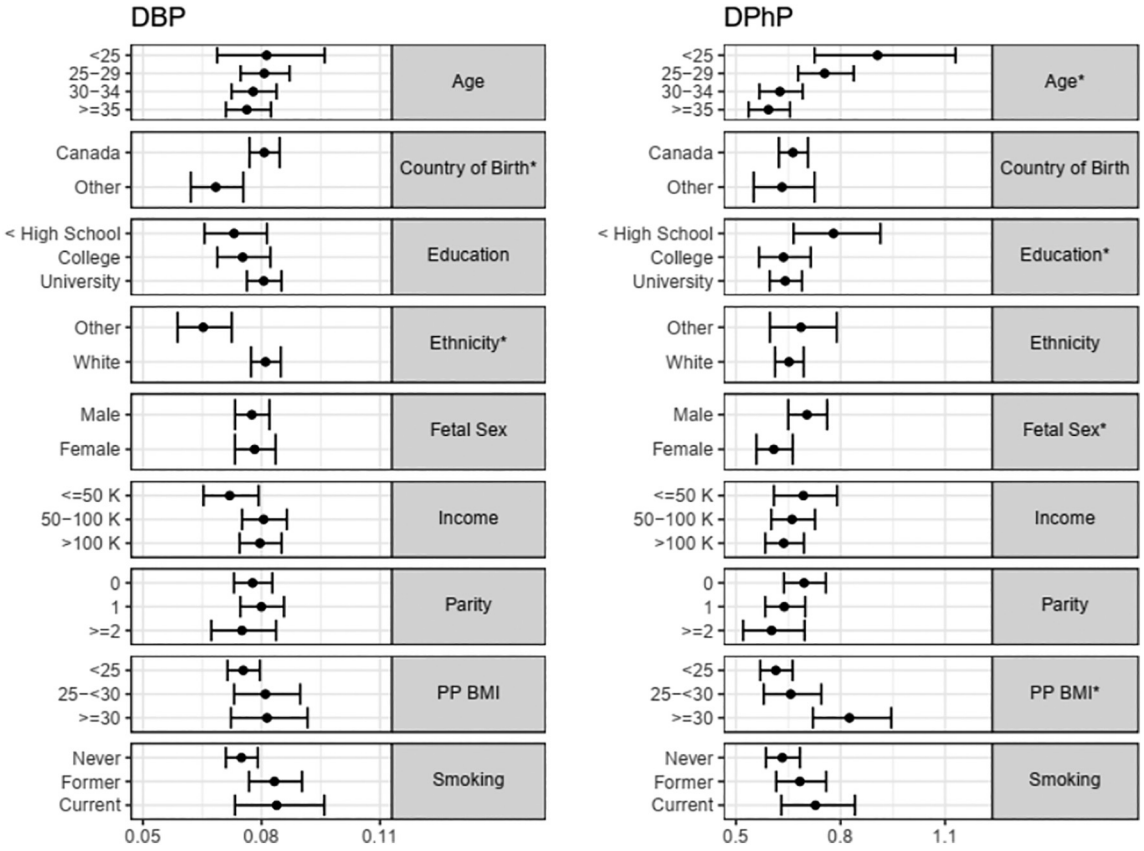

Fig. 3. Geometric mean (95 %) concentrations of nonhalogenated metabolites DBP and DPhP (μg/L) according to sociodemographic determinants. Associations with overall p-value <0.05 noted by *. Pre-pregnancy body mass index (PP BMI).

BDCIPP and DBP but higher concentrations of BCIPHIPP and BCIPP. Participants whose self-reported ethnicity was white had higher concentrations of DBP but lower concentrations of BCIPHIPP, BCEP, and BCIPP than non-white participants. We did not observe any associations with parity or smoking status in the 1st trimester (Figs. 1-3; Tables S12–13). Participants who carried male fetuses had higher concentrations of DPhP (GM = 0.704 μg/L) than those carrying females fetuses (GM = 0.608 μg/L) (overall p-value = 0.02) (Table S16). We also observed no association between age of residence and concentrations of any of the metabolites (Table S17). We observed an overall association between occupation and BCEP concentrations (p = 0.049); however, no pairwise comparisons were statistically significant and the confidence intervals for the occupation specific geometric means were overlapping. No associations were observed between occupation and any of the other OPE metabolites (Table S18).

We observed several associations between sample collection characteristics and OPE concentrations. DPhP concentrations tended to be higher among samples collected later in the day (Tables 3 and S19). Concentrations of DPhP, DBP, BDCIPP, and BCEP were positively related to time since last urination; samples collected 170 min or more since the last urination had, on average, higher concentrations (Tables 3 and S20). Urinary concentrations of BCEP, BCIPP, BDCIPP, and BCIPHIPP were, on average, higher in samples collected during the summer than samples collected during other seasons. The geometric mean concentrations of BCEP and BDCIPP in summer were nearly twice as high as in winter (Tables 3 and S21).

4. Discussion

In this cohort of Canadian pregnant people, six different OPE metabolites (BCEP, BDCIPP, BCIPP, DPhP, BCIPHIPP, DBP) were detected in >60 % of participants. We present the first identified biomonitoring data collected during pregnancy of BCIPHIPP, DoCP, DpCP, DmCP, and tb-PPP. Few participants had detectable concentrations of TCP (DmCP, DoCP, DpCP) and TPhP (mOH-TPhP and pOH-TPhP). BCEP had the highest detection rate (97 %) and DPhP had the highest geometric mean concentration (0.657 μg/L). DPhP is a non-specific metabolite of TPHP; the observed concentrations may, therefore, be related to exposure to other compounds (e.g. 2-ethylhexyl diphenyl phosphate) (Ballesteros-Gomez et al., 2015). These findings suggest pervasive exposure to the halogenated compounds TCEP, TDCIPP, and TCIPP as well as the nonhalogenated compounds TnBP and TPhP at the time of sample collection (2008–2011). We also observed that concentrations of commonly detected OPEs differed according to age, pre-pregnancy BMI, and socioeconomic status.

Detection rates of BCEP, BDCIPP, BCIPP, DPhP and DBP in MIREC were comparable to other pregnancy cohort studies (Fig. S2) considering expected variability due to different laboratories measuring these analytes with different analytical methods and limits of detection, study recruitment regions, and timing of sample collection. Median concentrations of these metabolites in MIREC participants were comparable or lower than those observed in pregnancy cohorts from the US (Carignan et al., 2016; Castorina et al., 2017; Kuiper et al., 2021; Percy et al., 2020; Romano et al., 2017), China (Feng et al., 2016), and Puerto Rico (Ingle et al., 2019) (Fig. 4, Table S1). Varshavsky et al. (Varshavsky et al., 2021), in their analysis of 132 participants who resided in California, reported the highest concentrations of OPE metabolites with BDCIPP and DPhP concentrations 3–4 times higher than any other pregnancy cohort. The historically stringent California flammability standards have been implicated in higher PBDE concentrations among California residents (Zota et al., 2008) but it is not clear how or whether current legislation impacts OPE concentrations. We observed moderate to high detection among two metabolites

Table 3
Geometric means (95 % CI) (μg/L) of OPEs according to sample collection characteristics.

	BCEP	BCIPP	BDCIPP	DBP	DPhP	BCIPHIPP
Time of urine collection						
06:00–09:00	0.360	0.0662	0.384	0.0547	0.556	0.388
	(0.254, 0.509)	(0.0456,0.0964)	(0.242, 0.611)	(0.0379, 0.0789)	(0.375, 0.824)	(0.239, 0.631)
09:00–12:00	0.292	0.0679	0.303	0.0781	0.533	0.417
	(0.268, 0.314)	(0.0613,0.0752)	(0.276, 0.334)	(0.0732, 0.0835)	(0.483, 0.589)	(0.380, 0.458)
12:00–15:00	0.309	0.0707	0.291	0.0781	0.729	0.441
	(0.284, 0.337)	(0.0630,0.0794)	(0.263, 0.322)	(0.0726, 0.0840)	(0.668, 0.796)	(0.400, 0.492)
15:00–18:00	0.295	0.0698	0.286	0.0780	0.855	0.463
	(0.265, 0.328)	(0.0612,0.0794)	(0.253, 0.324)	(0.0716, 0.0863)	(0.770, 0.945)	(0.408, 0.525)
18:00–24:00	0.431	0.115	0.445	0.109	0.966	0.766
	(0.314, 0.590)	(0.0667,0.197)	(0.324, 0.612)	(0.0809, 0.146)	(0.692, 1.345)	(0.424, 1.383)
P-value[a]	0.11	0.70	0.21	0.10	<0.01	0.41
Time since last urination (minutes)						
≤75	0.250	0.0662	0.244	0.0726	0.557	0.440
	(0.228, 0.274)	(0.0576, 0.0760)	(0.212,0.282)	(0.0665,0.0792)	(0.491,0.633)	(0.390,0.496)
76–120	0.286	0.0667	0.307	0.0776	0.653	0.431
	(0.261, 0.313)	(0.0588, 0.0756)	(0.278,0.338)	(0.0715,0.0842)	(0.589,0.724)	(0.386,0.482)
121–170	0.349	0.0747	0.292	0.0772	0.688	0.433
	(0.308, 0.395)	(0.0646, 0.0865)	(0.252,0.338)	(0.0693,0.0861)	(0.606,0.781)	(0.369,0.508)
>170	0.361	0.0756	0.363	0.0865	0.757	0.452
	(0.326, 0.401)	(0.0668, 0.0855)	(0.326,0.404)	(0.0800,0.0935)	(0.679,0.845)	(0.398,0.512)
P-value	<0.01	0.76	<0.01	0.02	<0.01	0.99
Season of urine collection						
Spring	0.264	0.0681	0.249	0.0759	0.614	0.431
	(0.239,0.292)	(0.0591,0.0786)	(0.220,0.281)	(0.0699,0.0824)	(0.546,0.691)	(0.380,0.488)
Summer	0.437	0.0876	0.490	0.0837	0.735	0.542
	(0.394,0.484)	(0.0785,0.0977)	(0.439,0.5471)	(0.0769,0.0910)	(0.655,0.825)	(0.480,0.612)
Fall	0.287	0.0616	0.269	0.0767	0.631	0.402
	(0.263,0.314)	(0.0541,0.0701)	(0.240,0.301)	(0.0703,0.0834)	(0.569,0.701)	(0.361,0.445)
Winter	0.248	0.0666	0.249	0.0773	0.660	0.401
	(0.224,0.275)	(0.0582,0.0762)	(0.222,0.280)	(0.0708,0.0845)	(0.584,0.746)	(0.350,0.460)
P-value	<0.01	<0.01	<0.01	0.29	0.07	<0.01

[a] p-value is the overall group effect from the ANOVA model.

(BCIPHIPP (82 % detection) and tb-PPP (59 % detection)) not previously measured during pregnancy. Given that the majority of participants were exposed to the chemicals, we encourage their inclusion in future biomonitoring research in pregnancy.

Our observed associations with certain sociodemographic characteristics are largely consistent with previous literature. Authors have reported inverse (Buckley et al., 2022; Romano et al., 2017; Van den Eede et al., 2015) and null (Hoffman et al., 2017b; Romano et al., 2017) associations between OPE metabolite concentrations and age depending on the specific metabolite. It is possible that younger individuals may use more personal care products that contain DPhP or have greater exposure to electronic equipment or upholstery products containing OPEs. Our observation of positive associations with pre-pregnancy BMI is consistent with previous research (Hoffman et al., 2017b; Romano et al., 2017; Varshavsky et al., 2021). Considering that OPEs are not lipophilic or stored in adipose tissue, dietary and personal care products use patterns rather than physiology may be the explanation for this pattern. Individuals of higher BMI may also have greater levels of exposure due to differences in consumption of processed food (Poma et al., 2018). Concentrations of OPEs such as DPhP that are added to personal care products may be higher in individuals of overweight or obese BMI due to greater body surface area. We also observed that lower socioeconomic status – whether defined by income or education – was positively associated with BCEP, BDCIPP, and DPhP. Previous studies have reported similar findings for isopropylphenyl phenyl phosphate (ip-PPP)

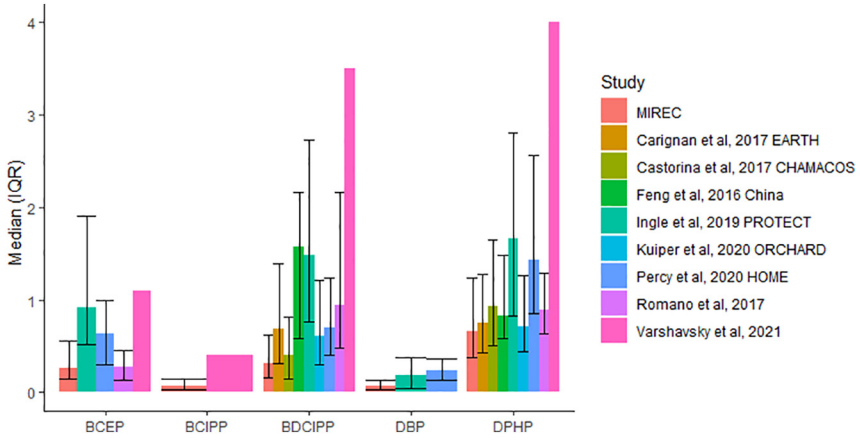

Fig. 4. Median (IQR) specific gravity standardized concentrations of OPE metabolites (μg/L) measured in MIREC and other biomonitoring pregnancy cohort studies. First trimester measurements are reported for studies that measured OPEs more than once. Note that an IQR was not reported by Varshavsky et al., 2021.

(Hoffman et al., 2017b; Romano et al., 2017) but not the metabolites measured in MIREC possibly due to insufficient power to detect differences. Zota et al. (Zota et al., 2010) hypothesized that socioeconomic status related disparities in PBDE concentrations may be explained by the presence of disintegrating foam furniture, poor ventilation, and dietary differences that lead to increased chemical absorption. It is possible that these structural factors are also relevant to socioeconomic disparities in OPE exposure. Although we did not observe an association with age of housing, we did not have the granularity of data to assess housing quality which may be a more relevant determinant of exposure than age of the residence. We also observed several differences by country of birth and ethnicity; individuals born outside of Canada and those who were non-white tended to have higher concentrations of both BCIPHIPP and BCIPP. Due to sample size constraints, we dichotomized these two constructs of immigrant and minority status; future work with larger and more diverse samples are needed to disentangle potential differences in exposure according to ethnicity and country of birth and to explore potential intersectionality with other sociodemographic indicators such as socioeconomic status.

Both times since last urination and season of collection were associated with OPE metabolite concentrations. None of the identified pregnancy cohorts or previous biomonitoring studies has evaluated time since last urination as a potential predictor. In contrast, several studies reported higher OPE concentrations in the summer than winter (Hoffman et al., 2017b; Percy et al., 2020). We observed higher concentrations in the summer for all 6 metabolites with 4 metabolites having statistically significant associations (BCEP, BCIPP, BDCIPP, BCIPHIPP). It is possible that higher temperatures increase volatilization and subsequent inhalation doses. Compared to studies with one recruitment site (Hoffman et al., 2017b; Percy et al., 2020), the MIREC population reflects 10 different Canadian cities with variable mean seasonal temperatures.

This is the largest biomonitoring study of OPEs in pregnancy to date. First trimester measurements are advantageous because they are prior to the development of any pregnancy complications and physiological changes of pregnancy that can impact kidney function and chemical excretion (e.g. increased glomerular filtration rate) (Weaver et al., 2016). The extensive sociodemographic and sample collection characteristics available in the MIREC study strengthened our ability to understand patterns and determinants of OPE exposure. In addition, the multi-site recruitment strategy allows us to depict exposure patterns among participants from 10 different Canadian cities. Due to the analysis of only one first trimester spot urine sample per participant and short OPE half-lives, the observed OPE concentrations in MIREC participants may not reflect exposure throughout pregnancy. The use of one single spot urine sample may also result in random error due to sampling variability; however, the extent of this error in MIREC is likely minimal due to the large and geographically diverse sample size. Most OPEs are rapidly cleared from blood and metabolized to diesters which are eliminated in urine in <24 h (Carignan et al., 2016; Mendelsohn et al., 2016). Previous estimates of the intraclass correlation coefficients (ICCs) throughout pregnancy have reported weak to moderate stability throughout pregnancy with ICCs reported to be 0.16–0.34 (Percy et al., 2020), 0.43–0.60 (Romano et al., 2017), and 0.5 (Hoffman et al., 2014) for different metabolites. Although continual exposure via air or dust and occasional exposure via ingestion of food are likely routes of exposure, we have limited capacity to comment on the specific sources and routes of exposure to the metabolites or the parent OPE compounds. People may be exogenously exposed to metabolites as both parent compounds and metabolites have been measured in dust (Tan et al., 2019; Van den Eede et al., 2015) and food (He et al., 2018). DPhP and DBP, for example, have been detected in food samples at a higher frequency than the parent compounds (He et al., 2018). Our findings may also not reflect patterns of exposure in populations with differing socioeconomic profiles. We explored differences by country of birth and ethnicity but had limited sample size to evaluate specific ethnic groups. Due to the cross-sectional and descriptive nature of this analysis, we cannot draw any conclusions about directionality of associations or causality nor was this the intent of this analysis.

5. Conclusion

The majority of participants in this large pan-Canadian pregnancy cohort study had detectable urinary concentrations of BCEP, BCIPP BDCIPP, BCIPHIPP, DBP, and DPhP. These findings are suggestive of widespread exposure to OPEs, including those that have been proposed to be of concern for human health such as TCIPP and TDCIPP. Future research in the MIREC cohort will investigate associations between OPE concentrations and health outcomes.

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CRediT authorship contribution statement

Jillian Ashley-Martin: Conceptualization, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Susan MacPherson:** Formal analysis, Data curation, Supervision, Writing – review & editing. **Zhao Zhao:** Formal analysis, Writing – review & editing. **Éric Gaudreau:** Methodology, Investigation, Writing – review & editing. **Gilles Provencher:** Methodology, Investigation, Writing – review & editing. **Mandy Fisher:** Project administration, Funding acquisition, Writing – review & editing. **Michael M. Borghese:** Writing – review & editing. **Maryse F. Bouchard:** Writing – review & editing. **Linda Booij:** Writing – review & editing. **Tye E. Arbuckle:** Conceptualization, Project administration, Funding acquisition, Writing – review & editing.

Data availability

The data that has been used is confidential.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.163327.

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