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Letter

Organophosphate Esters and Their Metabolites in Breast Milk from the United States: Breastfeeding Is an Important Exposure Pathway for Infants

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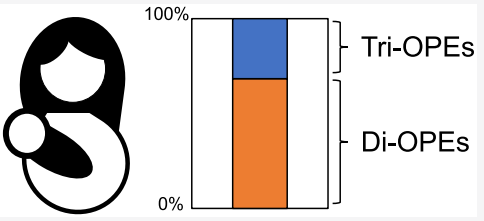
ABSTRACT: Organophosphate esters (OPEs) are among the synthetic chemicals found in the highest concentrations in the indoor environment due to their use as flame retardants and plasticizers. In fish and wildlife, metabolites of OPEs have been found to build up in tissues. In this study, 28 triester OPEs (tri-OPEs) and their seven corresponding diester (di-OPE) and three hydroxyl metabolites were measured in breast milk collected from 50 U.S. mothers. Tris(1-chloro-2-propyl) phosphate, used in foam for insulation and furniture and the target compound with the largest U.S. production volume, was the most abundant tri-OPE (median level of 1.47 ng/mL). Di-*n*-butyl phosphate (DNBP), the metabolite of tri-*n*-butyl phosphate (TNBP), which has broad uses in adhesives, plastics, and hydraulic fluids, was the most abundant OPE metabolite (median level of 7.44 ng/mL) detected in these samples. Overall, the Σdi-OPE concentrations (median level of 8.32 ng/mL) were twice as high as the Σtri-OPE concentrations (median of 3.85 ng/mL). The estimated daily intakes of tri- and di-OPEs through lactation were up to 50 times higher than those through diet and dust ingestion. This is the first study to simultaneously determine OPEs and their metabolites in breast milk, and our findings indicate that breastfeeding is a significant source of OPE exposure for infants.



INTRODUCTION

Organophosphate esters (OPEs) are man-made industrial chemicals that have been widely used as flame retardants, plasticizers, and antifoaming agents in a range of industrial processes and consumer products for the past several decades.[1,2] With the phase-out of polybrominated diphenyl ether (PBDE) flame retardants, the level of global consumption of some OPEs [e.g., tris(2-chloroisopropyl) phosphate (TCIPP) and tris(1,3-dichloropropyl) phosphate (TDCIPP)] as common PBDE replacements has increased significantly over the past several years.[3] Because OPEs are not chemically bound to products in which they are used, they can evaporate or weather off to the surrounding environment.[4] As a result, OPEs have become ubiquitous in the environment, including in air,[5−7] indoor dust,[8−10] sediment,[11,12] soil,[13] water,[8,14] and wildlife,[15] and humans are exposed through inhalation,[16,17] dermal exposure,[18] food[19] and water intake,[20,21] and accidental ingestion of soil or dust.[22] OPE exposure has been linked specifically to the presence of flame retardant products in the indoor environment. For example, children living in homes with higher numbers of baby products containing flame retardants have been found to have higher levels of exposure to certain OPEs,[23] and the presence of OPE flame retardants in couches has been associated with levels in house dust.[24] In daycares, levels of flame retardants in dust declined after flame retardant nap mats were removed and replaced with a flame retardant-free product.[25]

A growing body of evidence suggests that exposure to OPE flame retardants is associated with a range of adverse health effects, including cancers and cytotoxicity as well as neurodevelopmental and endocrine disorders.[2,26−32] Some information about the toxicity of OPE plasticizers is also available. For example, increases in the frequency of liver tumors were found in two-year cancer studies in which mice were exposed to tris(2-ethylhexyl) phosphate (TEHP); the same type of study found increased incidence and severity of urinary bladder tumors upon exposure to tri-*n*-butyl phosphate (TNBP).[33,34] Laboratory animals exposed to tris(2-butoxyethyl) phosphate (TBOEP) showed effects on the heart and liver as well as on the nervous system, including nerve degeneration and decreased nerve conduction velocity.[35]

Many OPEs can rapidly metabolize in the human liver with half-lives ranging from several hours to days.[36] Some oxidative dealkylation and hydroxylation products of triester OPEs (tri-OPEs), including di- and hydroxyl-OPEs (di-OPEs and OH-OPEs, respectively), have been detected in human urine.[37−39]

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Table 1. Detection Frequencies (DF, percent), the Mean [with their standard errors (SE)], Median, Minimum, and Maximum Concentrations of Tri- and Di-OPEs in Breast Milk (nanograms per milliliter; n = 50), and Contributions (percent) of Each Individual Compound to the Σtri-OPE and Σdi-OPE Concentrations

	DF	mean ± SE	median	minimum	maximum	contribution
			Tri-OPEs			
TEP	29	0.133 ± 0.0210	<0.180	<0.180	1.11	2.9
TNBP	82	0.784 ± 0.161	0.439	<0.140	5.15	17
TBOEP	73	0.325 ± 0.0862	0.177	<0.131	3.66	7.1
TEHP	96	0.960 ± 0.121	0.784	<0.006	3.35	21
TCIPP	82	2.28 ± 0.385	1.47	<0.455	14.8	50
TCEP	2	0.00585	<0.010	<0.010	0.00585	0.13
TPHP	61	0.0820 ± 0.0094	0.0494	<0.062	0.241	1.8
EHDP	39	0.0244 ± 0.00801	<0.001	<0.001	0.341	0.53
Σtri-OPEs	100	4.59 ± 0.496	3.85	0.482	16.4	100
			Di-OPEs			
DNBP	68	11.7 ± 1.67	7.44	<3.80	40.5	97
BBOEP	36	0.0816 ± 0.0300	<0.010	<0.010	1.31	0.68
BDCIPP	28	0.0164 ± 0.00536	<0.001	<0.001	0.219	0.14
BCIPP	4	0.00139 ± 0.000629	<0.001	<0.001	0.0256	0.01
DPHP	88	0.211 ± 0.0368	0.126	<0.103	1.39	1.7
Σdi-OPEs	98	12.1 ± 1.68	8.32	0.47	41.1	100

Moreover, several di-OPEs such as bis(1,3-dichloroisopropyl) phosphate (BDCIPP) and diphenyl phosphate (DPHP) have been recently found in dust and food,[40,41] suggesting coexisting exposures to both tri- and di-OPEs. Although relatively little is known about the toxicity of OPE metabolites, some may have stronger toxic effects than their respective parent compounds due to longer half-lives in the body.[42] Exposure to BDCIPP and DPHP, the metabolites of TDCIPP and triphenyl phosphate (TPHP), respectively, has been associated with poorer semen quality in men.[43] *p*-OH-TPHP (*p*-hydroxyl triphenyl phosphate) and DPHP can affect the thyroid by competitively displacing thyroxine from the human transthyretin transport protein.[44] DPHP is more able to alter transcripts in lipid metabolism in chicken embryonic hepatocytes than its parent compound, TPHP.[45] In addition, DPHP induced dose- and sex-specific perturbation of metabolic profiles in adult mice following neonatal exposure.[46]

Children are generally more susceptible to adverse effects of environmental exposures, including OPEs, due to their rapid development and growth.[47,48] For infants, breastfeeding is a major exposure pathway to environmental contaminants.[49−51] Previous studies have reported that early life OPE exposure through lactation is higher than that for PBDEs exposure.[52−55] In addition, the levels of BDCIPP and DPHP in infants' urine were significantly higher than in adults[23,56] and breastfed infants had higher levels of the two TCIPP metabolites in urine than older children,[57] suggesting higher postnatal exposures to OPE metabolites through breastfeeding. However, coexisting exposures to both OPEs and their metabolites in breast milk have not been investigated. In this study, 28 tri-OPEs and their corresponding metabolites, including seven di-OPEs and three OH-OPEs, were simultaneously analyzed in breast milk samples collected from U.S. mothers and daily intakes through breastfeeding were estimated for both compound groups. This is the first study to assess the lactational exposure to OPE metabolites.

MATERIALS AND METHODS

Sample Collection. Breast milk samples (n = 50) were collected from breastfeeding primiparous women residing in or near Seattle, WA, between March and October 2019. Participants were instructed to manually express breastmilk into a provided precleaned glass jar. The samples were picked up from participants within 24 h after collection and stored at −4 °C until they were shipped to Indiana University, where they were stored at −20 °C until they were analyzed. All recruitment and sample collection protocols were approved by the Indiana University Institutional Review Board.

Laboratory Analysis. Samples were thawed, spiked with surrogate standards, extracted using ultrasonication, and cleaned on Oasis HLB (for tri-OPEs) and Oasis WAX (for di- and OH-OPEs) cartridges. The samples were analyzed for 28 tri-OPEs, seven di-OPEs, and three OH-OPEs, and all of the analytes are listed in Table S1. The analysis was performed on an ultraperformance liquid chromatograph coupled to a triple-quadruple mass spectrometer (Agilent 1290 Infinity II UPLC−6470 QQQ-MS). The details of the analytical methods, quality control measures, and data analysis are included in the Supporting Information and in a previous publication.[58]

RESULTS AND DISCUSSION

Population Characteristics. A summary of demographic and behavioral characteristics of the sampled population is provided in Tables S2 and S3. Participants were 24−42 years of age (mean ± standard deviation: 34 ± 4 years), with average residency in Seattle, WA, of 13 ± 11 years. Ninety-six percent of participants received higher education, and more than half lived in middle or upper-middle class neighborhoods. Fifty-eight percent of women had a body mass index within the normal range of 18.5−24.9, while 36% were overweight or obese.

Concentrations of Tri-OPEs. Eight of the 28 targeted tri-OPEs were detected in breast milk (Table 1 and Figure S1), including four alkyl OPEs [triethyl phosphate (TEP), TNBP, TBOEP, and TEHP], two chlorinated OPEs [TCIPP and tris(2-chloroethyl) phosphate (TCEP)], and two aryl OPEs [TPHP and 2-ethylhexyl diphenyl phosphate (EHDP)]. The total tri-OPE concentrations (Σtri-OPE, the sum of eight tri-OPE concentrations) ranged from 0.482 to 16.4 ng/mL with a

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median concentration of 3.85 ng/mL, which was comparable to that reported in breast milk from Sweden (3.37 ng/g)[53] and the United States (3.46 ng/g).[55] In comparison with other environmental contaminants, the levels of OPEs were higher than those of PBDEs (2.05 ng/g)[59,60] and other emerging contaminants such as per- and polyfluoroalkyl substances (PFAS) and melamine derivatives detected at a median range of 0.16−2.2 ng/mL in breast milk from the United States.[61,62]

The flame retardant TCIPP was detected in 82% of the samples at a median concentration of 1.47 ng/mL and was the most abundant tri-OPE, contributing 50% to the Σtri-OPE concentrations. While TCIPP was also reported as a dominant OPE in breast milk collected between 1997 and 2006 in Sweden (median level of 1.53 ng/mL) and in a small Australian sample from 2015 (5.3−14 ng/mL), it was detected much less frequently in samples from U.S. mothers taken between 2009 and 2012.[55] In a study measuring TCIPP levels in whole blood and serum as well as metabolites in urine, significant levels of the parent compound were found in serum.[63] Taken together, the results suggest that measurement of TCIPP metabolites in urine may not adequately characterize exposure. Interestingly, the other two chlorinated OPEs, TCEP and TDCIPP, were rarely or not detected in any of the samples, with only a single detection of TCEP. Recent studies in the United States,[55] Spain,[54] and Vietnam[52] failed to detect TCEP and TDCIPP, possibly due to a shift in use away from these two designated carcinogens.[64] Two alkyl-OPE plasticizers, TEHP and TNBP, were detected in most of the samples (96% and 82%, respectively) at median concentrations of 0.784 and 0.439 ng/mL, accounting for 21% and 17% of the ∑tri-OPE concentrations, respectively. These TEHP concentrations were lower than those in breast milk from Australian women (1.2−6.2 ng/mL).[65] TNBP concentrations in this study were lower than those found in breast milk from Vietnam,[52] Sweden,[53] and Spain[54] (median levels of 2.00−10.9 ng/mL) but comparable to those from the United States (0.525 ng/mL).[55] TBOEP, TEP, TPHP, and EHDP were detected at lower concentrations (median levels of <0.001−0.0494 ng/mL), similar to previous reports from Asia, Europe, and the United States.[52−55]

TNBP, TPHP, TEHP, and TCIPP concentrations were significantly and positively associated with each other, suggesting similar sources for these compounds [r = 0.37−0.63; p < 0.05 (Figure S2)]. However, these associations need to be interpreted with caution because of the fast biotransformation rates for some of these OPEs.

Concentrations of OPE Metabolites. Five di-OPEs were detected in these samples, including di-*n*-butyl phosphate (DNBP), bis(2-butoxyethyl) phosphate (BBOEP), BDCIPP, bis(1-chloro-2-propyl) phosphate (BCIPP), and DPHP. None of the targeted OH-OPEs were detected in any of the samples. The five di-OPEs were detected in 4−88% of the samples with the total di-OPE concentrations (Σdi-OPE, the sum of five di-OPE concentrations) ranging from 0.47 to 41.1 ng/mL. The median Σdi-OPE concentration was 8.32 ng/mL, more than twice as high as the median Σtri-OPE concentration in these samples. DNBP was the most abundant OPE metabolite (median of 7.44 ng/mL) and contributed 97% to the Σdi-OPE concentrations. The rest of the di-OPEs were detected at much lower concentrations. A rapid biotransformation of TNBP to DNBP in liver microsomes in crucian carp,[66] herring gulls,[67] and rats[68] has been previously reported and may explain the relatively high levels of DNBP found in breast milk. For example, among several targeted tri-OPEs, TNBP was metabolized most quickly in herring gulls' liver microsomes [depletion rate of 73 ± 4 pmol min^{-1} (mg of protein)$^{-1}$], followed by TBOEP (53 ± 8 pmol min^{-1} mg^{-1}), TCIPP (27 ± 1 pmol min^{-1} mg^{-1}), TPHP (22 ± 2 pmol min^{-1} mg^{-1}), and TDCIPP (8 ± 1 pmol min^{-1} mg^{-1}).[67] While previous reports of the fast biotransformation of TNBP in wildlife may offer an explanation for the high levels of the metabolite rather than the parent compound detected in breast milk in this study, it should be noted that there is no evidence of the TNBP metabolism pathway in humans and the differences that may exist among species should be considered.[42,69] Finding high concentrations of DNBP is concerning given the toxicity of the parent compound. TNBP has been listed as a suspected carcinogen by the European Union, and there is evidence of hormone disruption potential.[70,71] The compound has varied uses that may result in exposure, including as a plasticizer in vinyl, as a solvent in inks, dyes, and adhesives, such as for plywood, in floor waxes and finishes, in paints, in aircraft hydraulic fluid, and in pesticides.[72,73]

Although no associations were found among the concentrations of di-OPEs, DNBP and DPHP concentrations were significantly and positively correlated with the concentrations of their respective tri-OPE parent compounds, TNBP (r = 0.45; p < 0.05) and TPHP [r = 0.37; p < 0.05 (Figure S2)], suggesting similar sources for the parent compounds and their respective metabolites and/or substantial metabolism to the di-OPE. Significant associations have also been previously observed for tri- and di-OPE concentrations in fish.[58]

Parent:Metabolite Concentration Ratios. A relative abundance of each di-OPE was calculated as a ratio of the molar concentration of this di-OPE and the sum of the molar concentrations of that di-OPE and its parent tri-OPE [di-OPE/(di-OPE + tri-OPE)] (Figure 1). The relative abundance

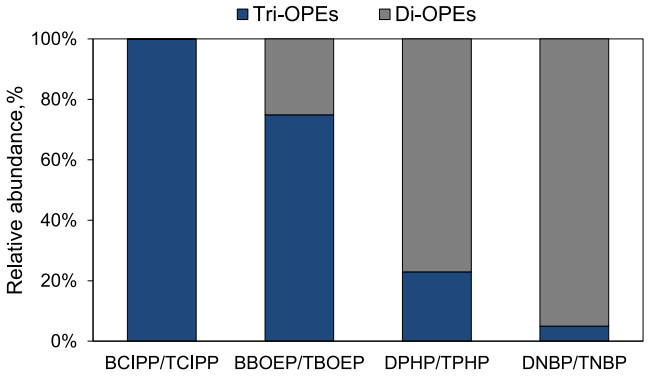

Figure 1. Relative percent abundances of tri-OPEs and their respective di-OPE metabolites in breast milk (based on molar concentrations).

ratios can provide critical information about the metabolic rate of a parent compound and the stability of a metabolite.[25,58] Four pairs of the parent tri-OPEs and their respective di-OPE metabolites are discussed here, including BCIPP and TCIPP, BBOEP and TBOEP, DPHP and TPHP, and DNBP and TNBP. BCIPP, a metabolite of TCIPP, and BBOEP, a metabolite of TBOEP, had relative abundances of 0.10% and 25%, respectively, indicating that the tri-OPE parent compound is more abundant than its di-OPE metabolite. The predominance of TCIPP can be attributed to its slow biotransformation in humans[74] and its increased usage in the

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U.S. market.[57] In contrast, TBOEP metabolizes rapidly in humans (half-life of <4 h),[75] suggesting that an alternative metabolism pathway resulting in a metabolite other than BBEOP may dominate. In an *in vitro* study using human liver and serum enzymes, TBOEP metabolized to several hydroxylated metabolites, such as bis(2-butoxyethyl) hydroxyethyl phosphate (BBOEHEP), which was more abundant than BBOEP.[76] Urinary BBOEHEP concentrations were at least 2 orders of magnitude higher than those of BBOEP when TBOEP was administered orally.[75] Compared to BCIPP and BBOEP, DPHP and DNBP (the metabolites of TPHP and TNBP, respectively) had higher relative abundances of 77% and 95%, respectively. These findings suggest that TPHP and TNBP can be metabolized quickly to DPHP and DNBP, respectively, which are then likely to be transferred from maternal blood to breast milk. However, it should be noted that other OPEs such as resorcinol bis(diphenyl phosphate) and EHDP can also metabolize to DPHP, and TPHP may not be the only source of this di-OPE. The higher abundance of OPE metabolites in breast milk can increase their lactational intake for infants and may offer an explanation for the previously found high DPHP and BDCIPP concentrations in infants' urine.[23,56]

Relationships with Behavioral and Demographic Characteristics. Significant negative correlations were observed among TNBP, TEHP, DNBP, Σdi-OPE, and Σtri-OPE concentrations in breast milk and maternal age [r = −0.463 to −0.298; $p < 0.05$ (Table S4)]. Somewhat higher ∑tri-OPE concentrations were observed among women with lower handwashing frequency, although the difference was not significant (Figure S3). No significant associations were found between tri- and di-OPEs levels and other demographic factors.

Exposure Assessment. Lactational estimated daily intake (EDI) rates of tri- and di-OPEs were calculated for infants between the ages of 0 and 12 months using established lactation rates for each age group[77] (Table S5). The highest ∑tri-OPE EDI was observed for infants who were <1 month of age {689 ng [kg of body weight (bw)]$^{-1}$ day^{-1}}, followed by 1−3 months of age [643 ng (kg of bw)$^{-1}$ day^{-1}], 3−6 months of age [505 ng (kg of bw)$^{-1}$ day^{-1}], and 6−12 months of age [381 ng (kg of bw)$^{-1}$ day^{-1}], similar to previous studies.[55] The lactational ∑tri-OPE EDI was higher than that via accidental dust ingestion,[22] dermal absorption,[78] and inhalation,[78] indicating that breastfeeding is a significant source of OPE exposure for infants. The highest intake was estimated for TCIPP [189−342 ng (kg of bw)$^{-1}$ day^{-1}], which was up to 50 times higher than that for other tri-OPEs.

The ∑di-OPE EDI was 1820 ng (kg of bw)$^{-1}$ day^{-1} for infants who were <1 month of age, which was up to 3 times higher than that for ∑tri-OPEs. The ∑di-OPE EDIs via dietary intake for adults[40] and accidental dust ingestion for toddlers[41] were up to 50 times lower [130 and 54.4 ng (kg of bw)$^{-1}$ day^{-1}, respectively] than the lactational EDIs. Lactational intake of DNBP reached 1760 ng (kg of bw)$^{-1}$ day^{-1}. These findings are concerning as DNBP exposure has been associated with chronic kidney disease.[79] Dust ingestion EDIs of di-OPEs for infants were also estimated on the basis of a previous study that measured di-OPEs in indoor dust (details for these calculations are included in the Supporting Information).[41] The EDIs of BBOEP and BDCIPP via dust ingestion ranged from 3.43 to 6.58 ng (kg of bw)$^{-1}$ day^{-1} and from 0.51 to 0.98 ng (kg of bw)$^{-1}$ day^{-1} for infants who were 0−12 months of age, respectively (Table S6),[41] which were 2−7 times higher than those through lactation. The DPHP EDI through dust ingestion ranged from 14.1 to 27.1 ng (kg of bw)$^{-1}$ day^{-1} (Table S6), which was comparable to the lactational intake.

This is the first study to simultaneously determine OPEs and their metabolites in breast milk. The results highlight considerable coexisting exposures to OPE flame retardants and plasticizers and their metabolites with significant toxicity concerns ranging from cancer to nervous system effects, disruption of thyroid, and lipid metabolism and suggest that breastfeeding is a significant exposure pathway to these compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.estlett.0c00916.

List of target analytes; details of sampling, data and instrumental analyses, and quality control measures; demographic and behavioral characteristics of participants; results of the Spearman correlations between chemical concentrations in breast milk and various demographic and behavioral characteristics; distribution of tri- and di-OPE concentrations in breast milk; estimated lactational daily intake rates; estimated daily intake rates for di-OPE via dust ingestion; and Pearson correlation matrix for tri- and di-OPE concentrations (PDF)

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Notes

The authors declare no competing financial interest.

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