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Beyond Phthalate Diesters: Existence of Phthalate Monoesters in South China House Dust and Implications for Human Exposure

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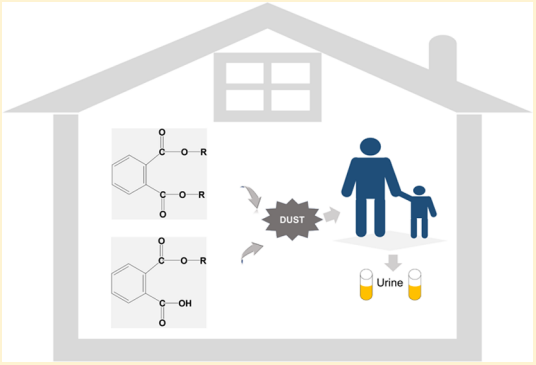
Supporting Information

ABSTRACT: Despite phthalate monoesters (mono-PAEs) being commonly recognized as metabolic products of phthalate diesters (di-PAEs), investigations on their environmental occurrences, particularly in indoor environments, remain limited. The present study demonstrated the presence mono-PAEs, along with a variety of di-PAEs, in house dust collected from 83 South China families. Among 15 target mono-PAEs, monobutyl phthalate (median concentration, 21.54 μg/g) dominated over other mono-PAEs in indoor dust, followed by monoethylhexyl phthalate (9.44 μg/g), monoisobutyl phthalate (5.14 μg/g), monomethyl phthalate (MMP; 2.05 μg/g), and several others. The total concentrations of detectable mono-PAEs (median, 45.40 μg/g) constituted an average of 6.7 ± 3.7% of the total concentrations of their parent diesters in the same dust. Molar concentration ratios of mono-PAEs to their respective di-PAEs varied greatly among chemicals (median, 0.001−3.1), with the highest ratios determined for the MMP/dimethyl phthalate and mono-/diisopropyl phthalate pairs (i.e., 3.1 and 1.5, respectively). In addition, no significant associations were observed between dust-associated mono- or di-PAEs and urinary mono-PAEs detected in both children (n = 48) and adult participants (n = 41). We hypothesized that mono-PAEs in dust could originate from different sources (e.g., impurities in di-PAE formulas, degradation from di-PAEs, and direct application as commercial additives), while the relative importance of various origins could differ between chemicals. Our findings demonstrate broad occurrences of mono-PAEs in indoor environments, but future studies are needed to better elucidate their sources, fate in indoor and outdoor environments, and potential human health risks.



INTRODUCTION

Diesters of 1,2-benzenedicarboxylic acid, commonly known as phthalates or referred to as di-PAEs, have been widely used as plastic additives to increase the flexibility, transparency, durability, and longevity of commercial plastic goods.[1] The global production of di-PAEs was estimated to reach 11 billion pounds in 2011 and has been growing rapidly during the past decade.[2] Releases from host products during manufacturing, usage, and disposal have resulted in global di-PAE distributions.[3−5] Numerous studies have also demonstrated a variety of toxic effects of di-PAEs, mainly including reproductive toxicity, endocrine disruption, hepatotoxicity, and nephrotoxicity.[6−8] Consequently, the use of selected di-PAEs has been restricted in many countries and regions. For example, butyl benzyl phthalate (BBzP), dibutyl phthalate (DBP), di-2-ethylhexyl phthalate (DEHP), dioctyl phthalate (DOP), diisononyl phthalate (DiNP), and diisodecyl phthalate (DiDP) were restricted from use in toys and childcare articles (i.e., ≤0.1% in concentrations by mass) marketed in the United States (US) and European Union[9] and also restricted in the coatings for toys manufactured in China.[10]

In vitro and in vivo studies reveal relatively fast metabolism of di-PAEs, normally following hydrolysis to form primary metabolite monoester phthalates (referred to as mono-PAEs) and then conjugations.[11,12] Low-molecular-weight di-PAEs are mainly ended into their monoester products (free and conjugated forms) that are excreted via urine, while the high-molecular weight diesters can undergo further biotransformation through hydroxylation and oxidation of the formed monoesters.[13,14] For example, metabolism of DEHP in vivo could produce mono-2-ethylhexyl phthalate (MEHP) and its secondary metabolites, including mono-2-ethyl-5-carboxypentyl phthalate (MECPP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), and mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP).[14] Although other metabolites could be formed, urinary mono-PAEs are commonly used to evaluate human exposure to phthalates.[13,15,16]

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Table 1. Concentrations and Detection Frequencies (DF, %) of Phthalate Monoesters (Mono-PAEs) and Diesters (Di-PAEs) in House Dust (μg/g) from South China

mono-PAEs		DF	median	range	Di-PAEs		DF	median	range
MMP	monomethyl phthalate	100	2.05	0.27−11.93	DMP	dimethyl phthalate	95	0.56	<LOQ-6.35
MEP	monoethyl phthalate	100	1.11	0.17−11.92	DEP	diethyl Phthalate	100	6.67	0.42−56.67
MiPrP	monoisopropyl phthalate	98	0.05	<LOQ-0.73	DiPrP	diisopropyl phthalate	93	0.03	<LOQ-0.46
MiBP	monoisobutyl phthalate	100	5.14	11.02−124.0	DiBP	diisobutyl phthalate	100	23.92	6.03−148.7
MBP[a]	monobutyl phthalate	100	21.54	3.21−104.1	DBP	dibutyl phthalate	100	64.91	13.23−258.4
MPeP	monopentyl phthalate	0	<LOQ	<LOQ	DPeP	dipentyl phthalate	0	<LOQ	<LOQ-0.27
MHxP	monohexyl phthalate	33	<LOQ	<LOQ-0.54	DHxP	dihexyl phthalate	0	<LOQ	<LOQ
MCHP	monocyclohexyl phthalate	0	<LOQ	<LOQ	DCHP	dicyclohexyl phthalate	98	0.02	<LOQ-0.32
MiHeP	mono-2-heptyl phthalate	0	<LOQ	<LOQ	DiHeP	diisoheptyl phthalate	100	0.63	0.03−30.13
MiNP	monoisononyl phthalate	0	<LOQ	<LOQ	DiNP	diisononyl phthalate	100	25.12	9.55−96.51
MBzP[b]	monobenzyl phthalate	55	0.02	<LOQ-0.22	BBzP	butyl benzyl phthalate	100	0.41	<LOQ-19.91
					DBzP	dibenzyl phthalate	72	0.007	<LOQ-0.23
MEHP	monoethylhexyl Phthalate	100	9.44	2.33−45.22	DEHP	di-2-ethylhexyl phthalate	100	609.7	134.9−2500
MECPP	mono (2-ethyl-5-carboxypentyl) phthalate	100	0.35	0.03−5.15					
MEOHP	mono (2-ethyl-5-oxohexyl) phthalate	96	0.17	<LOQ-1.90					
MEHHP	mono (2-ethyl-5-hydroxyhexyl) phthalate	100	0.97	0.15−209.2					
$\sum_{15}$mono-PAEs			45.40	11.22−223.1	$\sum_{13}$di-PAEs			735.6	202.8−2757

[a]Both DBP and BBzP can be metabolized into MBP. [b]Both BBzP and DBzP can be metabolized into MBzP.

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While mono-PAEs have been treated by most studies as di-PAEs' metabolic/degradation products, very few studies also reported their existence in consumer products or as environmental contaminants. Limited investigations revealed the presence of selected mono-PAEs in consumer products where di-PAEs were applied.[17,18] For example, monobutyl phthalate (MBP) and MEHP were found within ranges of 6.4−11.8 and 30.5−41.8 μg/g in three poly(vinylchloride) (PVC) toy products, respectively.[17] MEHP was also detected in 31 household PVC products (e.g., sofa, chair, floor mat, and other goods) manufactured in a few different Asian countries or regions.[18] Selected mono-PAEs were also found in drinking water, lake/river/sea water, and sediments.[19−21] These limited data may suggest the likelihood of mono-PAEs present in consumer products and consequent releases to the environment. Degradation of di-PAEs through various mechanisms, such as hydrolysis and microbial and photolytical breakdown, could also produce mono-PAEs in the environment. However, relevant environmental studies on mono-PAEs are overall limited.

Indoor environments have been suggested as one of the important circumstances where humans are exposed to di-PAEs. Given that indoor dust and air have been reported with universal occurrences with di-PAEs,[3,22] humans could be exposed to indoor di-PAEs via dust ingestion, inhalation, and dermal contact.[23,24] Indoor dust has also been used as a convenient and efficient matrix for investigating indoor contamination of di-PAEs, many other anthropogenic pollutants, and related human exposure risks.

We hypothesized in this study that mono-PAEs could exist along with di-PAEs in indoor dust. This hypothesis was based on the assumption that some mono-PAEs are purposely added to or present as impurities in household consumer products. To test this hypothesis, we determined 15 mono-PAEs, as well as a variety of di-PAEs, in indoor dust collected from South China families. Urine samples were also collected from adult and children volunteers from some families and determined for human internal exposure. Specific objectives of this work were to (1) identify and characterize mono-PAEs in house dust and their relationships with di-PAEs and (2) explore the relationships between dust-associated di/mono-PAEs and urinary mono-PAEs. Our work will contribute to a better elucidation of indoor PAE contamination and human exposure risks.

MATERIALS AND METHODS

Chemicals and Reagents. Reference standards of 15 mono-PAEs (Table 1) were purchased from AccuStandard (New Haven, CT), including monomethyl phthalate (MMP), monoethyl phthalate (MEP), monoisopropyl phthalate (MiPrP), MBP, monoisobutyl phthalate (MiBP), monopentyl phthalate (MPeP), monohexyl phthalate (MHxP), monocyclohexyl phthalate (MCHP), mono-2-heptyl phthalate (MiHeP), MEHP, MECPP, MEOHP, MEHHP, monoisononyl phthalate (MiNP), and monobenzyl phthalate (MBzP). Isotopically labeled mono-PAEs, including MBP-d4 and MBzP-d4 (AccuStandard), were used as surrogate standards, while *tert*-butyl paraben-d_9 (Toronto Research Chemicals, Toronto, Canada) was used as an internal standard. Reference standards of 23 di-PAEs as well as 12 isotopically labeled di-PAEs were purchased from AccuStandard (New Haven, CT) (Tables S1 and S2). Thirteen of the 23 di-PAEs are theoretically considered as parent chemicals of the 15 target mono-PAEs. Coumaphos-d_{10} (Toronto Research Chemicals) was used as an internal standard for di-PAE analysis. High-performance liquid chromatography grade solvents and Optima-grade water were purchased from Fisher Scientific (Hanover Park, IL).

Sample Collection. A total of 83 homes (all condominiums) located in the city of Guangzhou (South China) were recruited for this study during the period of 2018−2019. Floor dust was collected from each dwelling's living room and bedrooms via a commercial vacuum cleaner (Electrolux, ZMO1511, 1400 W) attached with a customized and precleaned nylon bag (pore size = approximately 25 μm).[25] After collection, the nylon bags were wrapped with precleaned aluminum foil. Precleaned sodium sulfate was used as field blanks (one field blank prepared for every 10 homes). Dust or sodium sulfate was removed from the nylon bags at the analytical laboratory and sieved through a 125 μm stainless cloth sieve. Sieved dust and field blanks were stored at −20 °C prior to chemical analysis. At the same day of dust collection, morning urine was also collected from an adult and/or a child from each of 48 recruited families. A total of 41 adults and 48 children donated their urine. Urine was collected in precleaned glass jars and transported to the analytical lab on ice. Empty glass jars were used as filed blanks for urine collection and a field blank was prepared for every 20 samples. Urine samples were stored at −80 °C prior to chemical analysis. Informed consent was obtained from adult participants on behalf of their children prior to sample collection. Participants were also required to fill out a short questionnaire to collect demographic data and information on home environments (see details in Table S3). The questionnaires for children were completed by their parents. The study protocol was approved by the Jinan University's Ethical Review Board.

Chemical Analysis. Approximately 20−70 mg of sieved dust was transferred to a 15 mL glass tube. After spiking with surrogate standards (Table S2), the sample was sequentially extracted under a shaking water bath with 3 mL of a mixture of methanol and water (6:4, v/v), 3 mL of a mixture of acetonitrile (ACN; containing 0.2% formic acid) and water (8:2, v/v), 3 mL of a mixture of ACN and isopropanol (1:1, v/v), and 3 mL of a mixture of hexane and isopropanol (1:1, v/v). The tube was centrifuged after each extraction, and the supernatant extract was collected. The combined extract was concentrated to 2 mL and reconstituted to 6 mL with water, followed by solid-phase extraction with an HLB cartridge (3 cc, 60 mg sorbent, Waters Corporation) that was preconditioned with 6 mL of ACN and then 6 mL of methanol. After sample loading, the cartridge was washed in sequence with 1 mL of water containing 5% ACN and 0.2% formic acid, 1 mL of water containing 0.2% formic acid, and 1 mL of water. After the cartridge was dried under vacuum for 5 min, target analytes were eluted out with 5 mL of ACN and then 5 mL of methanol. The final extract was concentrated to about 100 μL, filtered through a 0.22 μm centrifugal filter (VWR International), and spiked with internal standards (*tert*-butyl paraben-d_9 and coumaphos-d_{10}) prior to instrumental analysis.

Urine samples were treated with enzymatic deconjugation followed by liquid−liquid extraction. After the urine specific gravity (SG) was measured by a handheld refractometer (Atago, Japan), an aliquot of 1 mL of urine was spiked with 10 μL of surrogate standards and then buffered with 200 μL of ammonium acetate (pH = 5.0; 7.7 g of ammonium acetate dissolved in 100 mL of water) and 10 μL of β-glucuronidase (≥100 000 units/mL, from *Helix pomatia*, Sigma-Aldrich). The

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sample was then incubated at 37 °C overnight. After spiking with 3 mL of a mixture of methyl *tert*-butyl ether and ethyl acetate (5:1, v/v), the sample was extracted under an ultrasound bath for 30 min and then centrifuged for 10 min to collect the supernatant extract. The extraction step was repeated twice. The combined extract was concentrated to nearly dryness, reconstituted with 100 μL of a mixture of ACN and water (6:4, v/v), and spiked with internal standard prior to instrumental analysis.

The determination of most di-PAEs and mono-PAEs was conducted on a ultraperformance liquid chromatograph coupled with an AB Sciex 3200 or 5500 Q Trap triple quadrupole mass spectrometer (MS/MS, Toronto, Canada), whereas DEHP was determined on an Agilent gas chromatograph coupled with an Agilent 5977 A single quadrupole mass analyzer in electron impact ionization modes (Agilent Technologies, Palo Alto, CA). Detailed information on instrumental analysis is summarized in the Supporting Information. The limit of quantification (LOQ) of a target chemical was defined as an analyte response 10 times of the standard deviation of the noise when injecting a standard mixture solution (n = 8) or 10 times of the standard deviation of the background if the procedural blanks contain this chemical. The LOQs are summarized in the Supporting Information (Table S2).

Quality Assurance and Control. A procedural blank was processed along with every batch of 10 samples for evaluating procedural contamination. Only MiBP, MBP, and MEHP were detected in the final extracts of procedural blanks (n = 9) for urine analysis, with average masses of 0.3, 0.3, and 0.1 ng, respectively. None of the mono-PAEs was detectable in procedural blanks (n = 8) for dust analysis. However, ten di-PAEs, including dimethyl phthalate (DMP), diethyl phthalate (DEP), DBP, diisobutyl phthalate (DiBP), DEHP, dicyclohexyl phthalate (DCHP), diheptyl phthalate (DHeP), DiDP, diphenyl phthalate (DPP), and BBzP, were detectable with a concentration of 0.1−11 ng in the final extracts of procedural blanks, accounting for 0.02−3.9% of the median levels detected in dust samples. Blank contamination was subtracted from the final concentration data. To evaluate recovery efficiencies of analytical procedures, 20 ng of each of the target mono- and di-PAEs, along with their surrogate standards, was spiked into six replicates of precleaned sodium sulfate. Five nanogram of each of the target mono-PAEs and corresponding surrogate standards was spiked into six replicates of a urine composite pooled from five volunteers. Additional two replicates of sodium sulfate or urine composite were processed as matrix blanks after spiking with surrogate standards only (no target PAEs were spiked). The mean (±standard deviation) recoveries of target analytes from sodium sulfate spiking analysis ranged from 50 ± 16 to 112 ± 14% for mono-PAEs and 81 ± 13 to 124 ± 17% for di-PAEs. The recoveries of mono-PAEs from urine spiking analysis ranged from 85 ± 3.5 to 105 ± 5.0%, after subtracting the original concentrations measured in urine composite. The recoveries of deuterated mono-PAEs (MBP-d_4 and MBzP-d_4) were 91 ± 21 and 88 ± 23% in authentic dust samples and 89 ± 31 and 80 ± 22% in authentic urine samples, respectively.

Although no standard reference material (SRM) is available for the assessment of analytical accuracy of mono-PAE measurements, the National Institute of Standards and Technology (NIST, Gaithersburg, MD) house dust SRM 2585 was analyzed as a substitute. All target mono-PAEs except for MCHP were detected in the SRM (Table S4). The data will be useful for future cross-laboratory comparisons.

To determine whether the mono-PAEs detected in dust were formed via degradation of di-PAEs during sample treatment, we spiked a mixture of 23 di-PAEs (500 ng each), as well as a mixture of deuterated mono-PAEs, into sodium sulfate (n = 5). Through the same analytical procedures as described before, the mean (±standard deviation) degradation rate of a di-PAE, defined as the mass ratio of a mono-PAE to its corresponding di-PAE initially added, ranged from 0 to 3.2 ± 0.3% (Table S5). The highest rate of degradation was observed from DCHP to MCHP, whereas no degradation was observed for DEP, diisopropyl phthalate (DiPrP), dipentyl phthalate (DPeP), dihexyl phthalate (DHxP), DHeP, DEHP and DiNP through sample treatments.

To determine whether mono-PAE measurements were interfered with by in-source fragmentation of diesters, we compared the retention times of mono-PAEs and their respective diesters under the same chromatographic conditions (Figure S1). The results revealed that none of the mono- and di-PAE pairs overlapped in retention times, indicating that in-source fragmentation unlikely interfered with the measurement of mono-PAEs reported herein. Detailed information on the chromatographic analyses and retention times is provided in the Supporting Information.

Data Analysis. Concentrations of di- and mono-PAEs were adjusted based on the responses of their respective surrogate standards and reported as μg/g in dust or ng/mL in urine (SG corrected). For an analyte with a detection frequency of more than 60%, any measurement below LOQ was assigned with a half LOQ if its geometric standard deviation (GSD) is greater than 3 or replaced with a LOQ/$\sqrt{2}$ if the GSD < 3.[26] Non-normally distributed data were logarithmically transformed prior to statistical analyses. Spearman's correlation analyses were applied to examine potential relationships between different groups of data (PASW Statistics 18.0, IBM Inc.). Linear regression models were applied to determine predictors of continuous mono-PAE levels in urine (PASW Statistics 18.0). Exponentiated β coefficients were used to produce the multiplicative change in urinary levels relative to the reference group for categorical variables or the per-unit change for continuous variables. Dust concentrations and other categorical variables were dichotomized, while age was the only continuous variable. Only matched dust and urinary data (i.e., from the same families) were included into linear regression models. The level of significance was set at α = 0.05.

RESULTS AND DISCUSSION

Mono-PAEs in House Dust. Among the 15 target mono-PAEs, MMP, MEP, MBP, MiBP, MiPrP, MEHP, MECPP, MEHHP, and MEOHP were detected in more than 95% dust samples, whereas MHxP and MBzP had detection frequencies of 33 and 55%, respectively (Table 1). Other mono-PAEs were not detectable. The total concentrations of mono-PAEs ($\sum_{15}$mono-PAEs) ranged from 11.22 to 223 μg/g (median, 45.40 μg/g) in dust. MBP dominated over other mono-PAEs present in indoor dust, reaching a median concentration of 21.54 μg/g, followed by MEHP (9.44 μg/g), MiBP (5.14 μg/g), MMP (2.05 μg/g), and MEP (1.11 μg/g) (Figure 1). In the same dust, DEHP constituted 80 ± 7.6% of the total concentrations of 23 di-PAEs ($\sum_{23}$di-PAEs), followed by DBP, DiBP, and DiNP (Tables 1 and S6). Concentrations of $\sum_{15}$mono-PAEs accounted for 6.7 ± 3.7% of the combined

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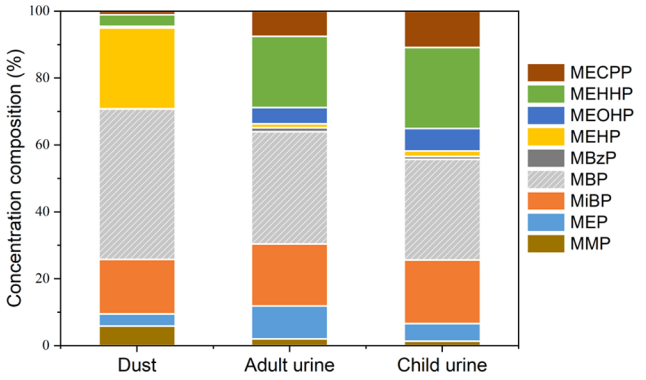

Figure 1. Compositions of phthalate monoesters in indoor dust and urine samples from children and adults.

concentration of their respective di-PAEs ($\sum_{13}$di-PAEs) or 6.6 ± 3.7% of $\sum_{23}$di-PAEs. These findings clearly support our hypothesis that mono-PAEs are present along with di-PAEs in house dust at considerable levels.

The molar concentration ratios of a mono-PAE to its respective di-PAE (referred to as $R_{m/d}$) varied greatly among chemicals. The highest median $R_{m/d}$ values were determined to be 3.1 and 1.5 for the MMP-DMP and MiPrP-DiPrP pairs, respectively, while other pairs had median $R_{m/d}$ values of 0.02–0.4, except for the MEHHP/MEOHP/MECPP-DEHP pairs ($R_{m/d} \leq 0.002$) (Figure 2). Compared with the degradation rates of relevant di-PAEs as determined in the QA/QC experiments (Table S5), our results demonstrate that the majority of the detected mono-PAEs were unlikely formed via di-PAE degradation during sample treatments but reflect their original abundances in house dust.

To the best of our knowledge, investigations on the occurrence of mono-PAEs in indoor environment remained extremely limited. Reports of environmental occurrences of mono-PAEs are only limited to a few drinking water, lake/river/sea water, and sediment studies.[19−21] The composition profile of mono-PAEs in South China dust is similar to the pattern reported in Canadian sediment and seawater where MBP was the dominant monoester, followed by MEP (in sediment) or MEHP (in seawater).[19] A different pattern was reported in Taihu Lake (China) surface water where MMP was the most abundant mono-PAE, followed by MBP and MEHP.[21] Although it is well known that mono-PAEs are metabolites of di-PAEs and thus extensively investigated in animal and human studies, the common recognition of mono-PAEs as di-PAEs metabolites may also result in an overlook of mono-PAEs' nonbiological origins and associated human exposure risks.

Relationships between Mono- and Di-PAEs in Dust. Although our data demonstrated the occurrence of mono-PAEs in house dust, their possible origins remained unknown. The sources/origins of mono-PAEs other than metabolism have received very little attention. There is no clear documentation on whether mono-PAEs have industrial applications. Here, we investigated the relationships between mono- and di-PAEs present in house dust to explore any hints for mono-PAEs' potential sources.

Significant concentration correlations were observed between mono-PAEs and their respective di-PAEs except for the MiPrP-DiPrP and MEOHP/MEHHP-DEHP pairs (Table 2). In addition, significant correlations were observed among most individual mono-PAEs, whereas less correlations were observed among individual di-PAEs. For example, MMP was significantly correlated with all other mono-PAEs in concentrations, whereas DMP did not correlate with any other di-PAEs (Table 2).

The high correlations between a mono-PAE and its respective di-PAE or among most individual mono-PAEs led to the speculation that dust-associated mono- and di-PAEs could be released from similar sources, such as the consumer products or materials where di-PAEs were applied. Mono-PAEs may be present as impurities in technical di-PAE formulas and thus added into consumer products along with di-PAEs. Additionally, mono-PAEs may be formed via thermal degradation of di-PAEs during the manufacturing of consumer products. Di-PAEs are thermally unstable and found to form monoesters under heat treatments during PVC moulding and other processing.[27,28] Indeed, as mentioned earlier, MEHP and MBP have been detected in different PVC products and suspected to be impurities in technical di-PAE products.[17,18]

However, the ratios of mono- to di-PAEs reported in consumer products were much lower than the $R_{m/d}$ values determined in house dust. For example, Kawakami et al.

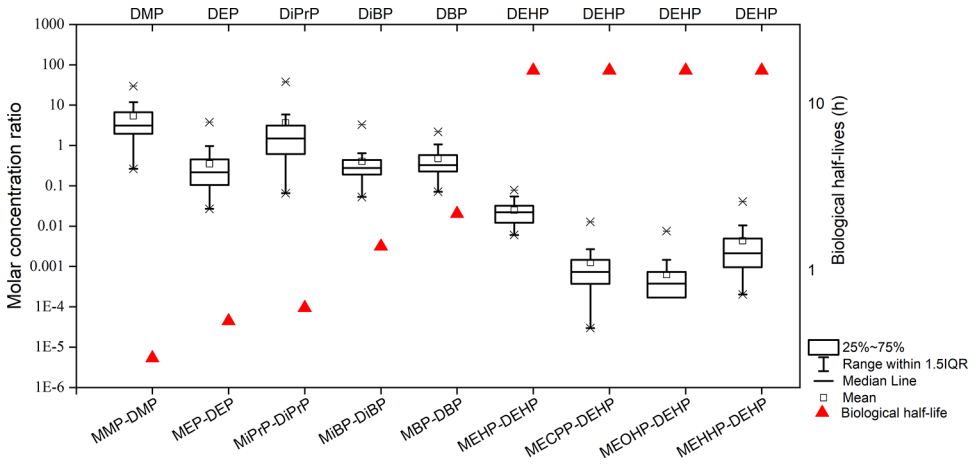

Figure 2. Molar concentration ratios of phthalate monoesters and their respective diesters in house dust (left and bottom axes) and the biological half-lives of phthalate diesters (right and top axes). The biological half-lives (indicated by red triangles) are estimated based on the United States Environmental Protection Agency Estimation Program Interface (EPI) Suite Version 4.11.

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Table 2. Spearman Correlation Coefficients among Phthalate Mono- and Diesters in House Dust from South China[a]

	MMP	MEP	MiPrP	MiBP	MBP	MEHP	MECPP	MEOHP	MEHHP	DMP	DEP	DiPrP	DiBP	DBP	DEHP
MMP	1.00														
MEP	**0.48****	1.00													
MiPrP	**0.71****	**0.49****	1.00												
MiBP	**0.32****	**0.35****	0.16	1.00											
MBP	**0.39****	**0.40****	**0.24***	**0.41****	1.00										
MEHP	**0.27***	**0.25***	0.20	0.09	**0.31***	1.00									
MECPP	**0.49****	**0.35****	**0.26***	**0.44****	**0.49****	**0.53****	1.00								
MEOHP	**0.35****	0.10	**0.22***	0.14	**0.29***	**0.62****	**0.69****	1.00							
MEHHP	**0.31****	0.18	0.16	**0.33****	**0.40****	**0.55****	**0.77****	**0.72****	1.00						
DMP	**0.37****	−0.03	0.21	0.19	0.13	0.08	0.21	0.20	0.15	1.00					
DEP	0.21	**0.31****	0.09	**0.45****	**0.79****	**0.28***	**0.48****	**0.25***	**0.48****	0.06	1.00				
DiPrP	0.17	**0.26***	−0.10	**0.55****	0.06	−0.02	**0.23***	0.01	0.13	−0.01	0.12	1.00			
DiBP	0.03	0.20	0.05	**0.49****	0.06	−0.01	0.10	−0.14	0.12	−0.12	0.20	**0.62****	1.00		
DBP	0.15	**0.42****	0.12	0.15	**0.55****	0.08	0.17	−0.12	0.07	−0.03	**0.47****	0.03	0.21	1.00	
DEHP	0.15	**0.25****	0.08	**0.32****	**0.31****	**0.41****	**0.25****	0.10	0.16	−0.11	**0.24***	0.14	**0.40****	**0.42****	1.00

[a]*$p < 0.05$, **$p < 0.01$.

reported that the concentration ratios of MEHP to DEHP in PVC household products ranged from 6.2×10^{-6} to 0.002 (median, 5.8×10^{-5}), orders of magnitude lower than what we found in house dust (0.004−0.04; median, 0.01).[18] Similarly, the ratios of MBP to DBP in PVC balls (5×10^{-5}–9×10^{-5}) were also much lower than those determined in house dust (0.06−1.75; median, 0.26).[17] Therefore, origins other than the impurities in household consumer products or materials could exist for some mono-PAEs.

We hypothesized that some mono-PAEs could be formed via photolytic/microbial degradation of di-PAEs present on the surface of dust particles or in the air. Although photodegradation of di-PAEs under environmental conditions has rarely been experimentally investigated, Peterson et al. predicted the atmospheric photodegradation of selected di-PAEs and suggested chemical-dependent degradation rates and a half-life of 6.2−346 h.[29] Previous studies also reported microbial degradation of di-PAEs under various environmental conditions and the formation of mono-PAEs as part of the degradation products.[30] More recently, Bope et al. revealed the degradation of DMP, DEHP, DiNP, DiDP, and BBzP in worn carpet squares embedded with dust under elevated relative humidity conditions, likely through both abiotic and microbial processes.[31] These reports support the assumption that degradation of di-PAEs could occur in indoor/outdoor environments and contribute to some of the dust-associated mono-PAEs. In our work, we examined the relationship between the $R_{m/d}$ values and biological half-lives calculated based on the US Environmental Protection Agency Estimation Program Interface (EPI) Suite (Figure 2). Although no significant correlation was observed, the data did suggest that di-PAEs with shorter biological half-lives tend to have higher $R_{m/d}$ values. However, the degradation kinetics and mechanisms require additional experimental investigations under conditions resembling natural indoor/outdoor environments.

We also hypothesized that some mono-PAEs could be directly used as industrial additives. Although clear documentation of commercial usage of mono-PAEs is not found to our best knowledge, the possibility that mono-PAEs are purposely added to certain consumer products as di-PAE alternatives cannot be entirely excluded. This appears to be more likely for MMPs that exhibited very high $R_{m/d}$ values (i.e., 3.1) as well as high concentrations in house dust. This hypothesis is plausible considering that mono-PAEs do not differ much from di-PAEs in chemical structures and some physicochemical properties, while many di-PAEs have been subjected to extensive environmental surveillance due to their environmental and health hazards. However, direct evidence is unavailable at this stage.

Overall, chemical-specific relationships of mono-PAEs with their respective di-PAEs may suggest that the relative importance of different origins (e.g., impurities in di-PAE formula, degradation from di-PAEs, or direct commercial applications) may differ between chemicals. The large cross-home variability of $R_{m/d}$ for each mono-/di-PAE pairs (i.e., the coefficient of variation ranged from 59 to 170%, Table S7) also suggested that the occurrence of mono-PAEs may be greatly influenced by home-specific sources (e.g., types and quantities of household products) and home conditions (e.g., aging of dust). Elucidation of the major sources will be facilitated by a better understanding of the emission rates and mechanisms of mono-PAEs from consumer products, environmental behavior

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and fate of both di- and mono-PAEs, as well as the information on mono-PAEs' possible industrial applications.

Influence of Dust-Associated Di- and Mono-PAEs on Urinary Mono-PAEs. In the present study, MMP, MEP, MiBP, MBP, MEHP, MEOHP, MEHHP, and MECPP were detected in urine with DF > 95%. MBzP was detected at a rate of 61%, while other mono-PAEs had a DF < 30% (Table 3).

Table 3. Concentrations (ng/mL) of Phthalate Monoesters in Urine

		children (n = 48)		adults (n = 41)	
Mono-PAEs	% detected	median	range	median	range
MMP	96	2.5	<LOQ-52	3.2	<LOQ-0.7
MEP	97	9.6	<LOQ-170	11.6	1.2−254
MiPrP	12	<LOQ	<LOQ-1.2	<LOQ	<LOQ-0.7
MiBP	100	53	4.5−742	36	4.9−277
MBP	100	98	4.5−1645	76	11−543
MPeP	18	<LOQ	<LOQ-0.98	<LOQ	<LOQ-2.7
MHxP	0	<LOQ	<LOQ	<LOQ	<LOQ
MCHP	1	<LOQ	<LOQ	<LOQ	<LOQ-1.2
MiHeP	25	<LOQ	<LOQ-3.5	<LOQ	<LOQ-8.0
MEHP	98	2.0	<LOQ-260	1.8	<LOQ-29
MEOHP	100	17	1.6−164	11	0.9−55
MEHHP	100	63	6.3−497	40	4.4−297
MECPP	99	32	2.8−323	16	1.9−77
MiNP	0	<LOQ	<LOQ	<LOQ	<LOQ
MBzP	61	0.47	<LOQ-11	1.4	<LOQ-21

Urine from children and adults exhibited a similar mono-PAE composition profile that was dominated by MBP, MiBP, and MEHHP (Figure 1). Compared with dust mono-PAE profile, the major difference in urine is the significantly reduced proportion of MEHP, along with elevated proportions of DEHP's secondary metabolites (i.e., MEHHP, MEHOP, and MECPP) (Figure 1). The total concentrations of detectable mono-PAEs ranged from 34 to 2950 ng/mL (median, 360 ng/mL) and 24−910 ng/mL (median, 236 ng/mL) in urine from children and adults, respectively. Among the variety of mono-PAEs, MEOHP (p = 0.003), MEHHP (p = 0.046), and MECPP (p = 0.003) exhibited significantly greater concentrations in children versus adults' urine, whereas greater MEP levels (p = 0.003) were observed in adults' urine. Other mono-PAEs or the total mono-PAE concentrations did not differ significantly between the two age groups. Previous mother−child pair studies also observed higher levels of DEHP's secondary metabolites in children and attributed it to more effective oxidative metabolism in children versus adults.[32,33] In contrast, higher urinary MEP levels in adults may be due to more frequent use of personal care products containing DEP. In general, the differences in urinary levels between children and adults reflect age-dependent exposure routes and metabolism/elimination kinetics.[32]

Humans are exposed to PAEs through a variety of pathways, among which dust ingestion has been suggested an important route. While previous studies have investigated the influence of dust-associated di-PAEs on urinary mono-PAEs, the presence of mono-PAEs in dust has never been considered as a potential exposure source and a factor influencing internal exposure.

No significant correlations in mono-PAE concentrations were observed between matched dust and urine samples from children or adult participants, with the only exception for MiBP in children urine (Spearman's analysis, r_s = 0.30, p = 0.03) (Table S8). In addition, no significant correlations were observed between urinary mono-PAEs and respective dust-associated di-PAEs or the combination of mono- and di-PAEs in dust. Linear regression models including demographic and behavioral information also revealed no significant associations between dust-associated mono- or di-PAEs and urinary mono-PAEs in both children and adult populations (Tables S9 and S10). In addition, none of the studied demographic and behavioral factors was significantly associated with urinary mono-PAE levels.

The lack of associations between dust mono- or di-PAEs and urinary mono-PAEs may have resulted from a variety of factors. First, house dust does not constitute the only PAE source to humans. The coexistence of mono- and di-PAEs in house dust and possibly other sources (i.e., diet, drinking water, and air) complicates the associations between external and internal exposure.[20,34,35] Urinary mono-PAEs in fact reflect the outcome of multiple sources/processes, including metabolic transformation of ingested di-PAEs, direct intake of mono-PAEs, and biotransformation of mono-PAEs originated from the two former sources. Thus, it is difficult to pinpoint the relationships between certain external sources and internal exposure.

Second, urinary mono-PAEs may not well represent a total exposure to phthalate esters due to further biotransformation of mono-PAEs. For example, after oral dosage of d_4-MEHP and d_4-MBP to four male human subjects, only an average of 7% of d_4-MEHP (in molar mass) was excreted via urine within 46 h, while four secondary metabolites in total accounted for 54.6% of the ingested dose.[36] Therefore, urinary mono-PAEs could greatly underestimate the total exposure to phthalate esters from various sources. However, limited knowledge on the metabolic transformation of most mono-PAEs prohibits us from an efficient prediction of external exposure based on urinary mono-PAEs.

Thirdly, limited sample size and uncomprehensive demographic and behavioral information could also result in imprecise estimation of the associations. Therefore, the lack of associations between dust mono- or di-PAEs and urinary mono-PAEs does not exclude or minimize the influence of dust intake on internal PAE exposure. Instead, it reflects the existence of other factors in the real world that confounds the associations.

Knowledge Gaps and Perspectives. The frequent detection of mono-PAEs in house dust with considerable levels indicates the underestimation of human exposure risks in previous indoor PAE studies. However, given insufficient knowledge on the environmental distribution and exposure pathways of mono-PAEs, our capacity of evaluating human exposure risks is indeed limited. Below, we identify a few priority knowledge gaps and associated research perspectives.

Sources of mono-PAEs in indoor environments require better elucidation. Although our data suggest several possible sources of mono-PAEs (i.e., impurities in commercial di-PAE formulas and consumer products, degradation from di-PAEs, and direct commercial applications), evidence is needed to confirm these hypotheses. The relative importance of various sources may also differ between mono-PAE chemicals. Therefore, experiments are needed to test commercial PAE formulas and consumer products and explore thermal, photolytic, and microbial degradation of major di-PAEs.

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Indoor/outdoor environmental distribution patterns and the fate of mono-PAEs are not addressed. Although our data reflect the occurrence of mono-PAEs in the indoor environment, it remains unknown on the distributions of mono-PAEs among air, suspended particles, and settled dust in both indoor and outdoor environments. Differences in physicochemical properties between individual di- and mono-PAEs may greatly influence their environmental behavior and fate.

The routes of human exposure to mono-PAEs lack sufficient investigations. Although we assume that humans are exposed to mono-PAEs via the same pathways (e.g., inhalation, dust ingestion, dermal contact, hand-to-mouth transfer, and diet) as those for di-PAEs, the relative contributions of these different pathways to human exposure may differ from those for di-PAEs and also differ among individual mono-PAEs. This is mainly due to the change of some physicochemical properties from di-PAEs to mono-PAEs (Table S1), which subsequently affects their environmental distribution, behavior, and fate as discussed above.

Ultimately, we would like to know how indoor mono-PAEs contribute to human health risks following intake. Although the metabolic transformation of selected di-PAEs is well recognized, little has been done to understand the pharmacokinetics of mono-PAEs. Current studies generally utilize urinary mono-PAEs as markers for evaluating phthalate exposure. However, urinary mono-PAEs may underestimate the risk of exposure to a combination of di- and mono-PAEs. Other markers, such as mono-PAEs' biotransformation products, may also be useful for the assessment of human exposure to phthalate esters, particularly mono-PAEs. However, previous studies have revealed that coexposure to DEHP and MEHP resulted in a different metabolic profile compared with that observed for individual DEHP or MEHP exposure.[37] This complicates the effort of finding efficient markers for differentiating mono- and di-PAE exposure and indicates that coexposure to mono- and di-PAEs may produce complicated effects compared with those resulting from di-PAE exposure only. Previous studies revealed various toxic effects of mono-PAEs in vivo or in vitro, including reproductive and developmental toxicities.[6,38,39] For example, MEHP was reported to induce toxic effects on testicular cells in vitro, whereas DEHP at the same concentration range could not.[40] This further raises the importance of investigating the influence of direct mono-PAE intake on human health.

Overall, given the coexistence of mono- and di-PAEs in indoor environments and the differences between mono- and di-PAEs in toxic kinetics and effects,[38,39,41] future environmental investigations and biomonitoring studies should take mono-PAEs into consideration. Beyond di-PAEs, a more important question that arises is whether we have underestimated our exposure to indoor chemicals as we generally focus on the chemicals we screen for but largely overlook their potential degradation/transformation products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.9b03817.

Physicochemical properties of phthalate diesters and monoesters, MRM ions or selected ion monitoring and LOQ of phthalate di- and monoesters, characteristics of study populations and environment, concentrations of phthalate monoesters in SRM2585, rate of degradation during sample treatments, concentrations and detection frequencies of phthalate diesters, coefficient of variation of the molar concentration ratios, Spearman correlation coefficients, regression analyses of predictors of child urinary phthalate monoesters, and regression analyses of predictors of adult urinary phthalate monoesters (Tables S1−S10, respectively); extract ion chromatography of DMP, DEP, MMP, and MEP in the multiple reaction monitoring mode (Figure S1); and a detailed description of instruments (PDF)

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■ REFERENCES

(1) Staples, C. A.; Peterson, D. R.; Parkerton, T. F.; Adams, W. J. The environmental fate of phthalate esters: a literature review. *Chemosphere* **1997**, *35*, 667−749.

(2) Lowell Center for Sustainable Production. Phthalates and Their Alternatives: Health and Environmental Concerns, 2011. Available at http://www.sustainableproduction.org/downloads/PhthalateAlternatives-January2011.pdf (accessed June 2019).

(3) Zhu, Q. Q.; Jia, J. B.; Zhang, K. G.; Zhang, H.; Liao, C. Y.; Jiang, G. B. Phthalate esters in indoor dust from several regions, China and their implications for human exposure. *Sci. Total Environ.* **2019**, *652*, 1187−1194.

(4) Gani, K. M.; Kazmi, A. A. Phthalate contamination in aquatic environment: a critical review of the process factors that influence their removal in conventional and advanced wastewater treatment. *Crit. Rev. Environ. Sci. Technol.* **2016**, *46*, 1402−1439.

(5) Schecter, A.; Lorber, M.; Guo, Y.; Wu, Q.; Yun, S. H.; Kannan, K.; Hommel, M.; Imran, N.; Hynan, L. S.; Cheng, D. L.; Colacino, J. A.; Birnbaum, L. S. Phthalate concentrations and dietary exposure from food purchased in New York state. *Environ. Health Perspect.* **2013**, *121*, 473−494.

(6) Martino-Andrade, A. J.; Chahoud, I. Reproductive toxicity of phthalate esters. *Mol. Nutr. Food Res.* **2010**, *54*, 148−157.

(7) Swan, S. H.; Main, K. M.; Liu, F.; Stewart, S. L.; Kruse, R. L.; Calafat, A. M.; Mao, C. S.; Redmon, J. B.; Ternand, C. L.; Sullivan, S.; Teague, J. L. Decrease in anogenital distance among male infants with prenatal phthalate exposure. *Environ. Health Perspect.* **2005**, *113*, 1056−1061.

(8) Singh, S.; Li, S. S. L. Phthalates: Toxicogenomics and inferred human diseases. *Genomics* **2011**, *97*, 148−157.

(9) Kamrin, M. A. Phthalate risks, phthalate regulation, and public health: a review. *J. Toxicol. Environ. Health, Part B* **2009**, *12*, 157−174.

(10) General Administration of Quality Supervision, Inspection and Quarantine, 2009. *GB24613−2009 Limit of Harmful Substances of Coatings for Toys*, China General Administration of Quality Supervision, Inspection and Quarantine, Beijing, 2009.

(11) Frederiksen, H.; Skakkebaek, N. E.; Andersson, A. M. Metabolism of phthalates in humans. *Mol. Nutr. Food Res.* **2007**, *51*, 899−911.
(12) Ito, Y.; Yokota, H.; Wang, R.; Yamanoshita, O.; Ichihara, G.; Wang, H.; Kurata, Y.; Takagi, K.; Nakajima, T. Species differences in the metabolism of di(2-ethylhexyl) phthalate (DEHP) in several organs of mice, rats, and marmosets. *Arch. Toxicol.* **2005**, *79*, 147−154.
(13) Blount, B. C.; Silva, M. J.; Caudill, S. P.; Needham, L. L.; Pirkle, J. L.; Sampson, E. J.; Lucier, G. W.; Jackson, R. J.; Brock, J. W. Levels of seven urinary phthalate metabolites in a human reference population. *Environ. Health Perspect.* **2000**, *108*, 979−982.
(14) Barr, D. B.; Silva, M. J.; Kato, K.; Reidy, J. A.; Malek, N. A.; Hurtz, D.; Sadowski, M.; Needham, L. L.; Calafat, A. M. Assessing human exposure to phthalates using monoesters and their oxidized metabolites as biomarkers. *Environ. Health Perspect.* **2003**, *111*, 1148−1151.
(15) Gong, M.; Weschler, C.; Liu, L.; Shen, H.; Huang, L.; Sundell, J.; Zhang, Y. Phthalate metabolites in urine samples from Beijing children and correlations with phthalate levels in their handwipes. *Indoor Air* **2015**, *25*, 572−581.
(16) Langer, S.; Bekö, G.; Weschler, C. J.; Brive, L. M.; Toftum, J.; Callesen, M.; Clausen, G. Phthalate metabolites in urine samples from Danish children and correlations with phthalates in dust samples from their homes and daycare centers. *Int. J. Hyg. Environ. Health.* **2014**, *217*, 78−87.
(17) Niino, T.; Ishibashi, T.; Itho, T.; Sakai, S.; Ishiwata, H.; Yamada, T.; Onodera, S. Simultaneous determination of phthalate di- and monoesters in poly(vinylchloride) products and human saliva by gas chromatography−mass spectrometry. *J. Chromatogr. B* **2002**, *780*, 35−44.
(18) Kawakami, T.; Isama, K.; Matsuoka, A. Analysis of phthalic acid diesters, monoester, and other plasticizers in polyvinyl chloride household products in Japan. *J. Environ. Sci. Health, Part A: Environ. Sci. Eng. Toxic Hazard. Subst. Control* **2011**, *46*, 855−864.
(19) Blair, J. D.; Ikonomou, M. G.; Kelly, B. C.; Surridge, B.; Gobas, F. A. P. C. Ultra-trace determination of phthalate ester metabolites in seawater, sediments, and biota from an urbanized marine inlet by LC/ESI-MS/MS. *Environ. Sci. Technol.* **2009**, *43*, 6262−6268.
(20) Ding, M.; Kang, Q.; Zhang, S.; Zhao, F.; Mu, D.; Zhang, H.; Yang, M.; Hu, J. Contribution of phthalates and phthalate monoesters from drinking water to daily intakes for the general population. *Chemosphere* **2019**, *229*, 125−131.
(21) Jiang, J.; Mu, D.; Ding, M.; Zhang, S.; Zhang, H.; Hu, J. Simultaneous determination of primary and secondary phthalate monoesters in the Taihu Lake: Exploration of sources. *Chemosphere* **2018**, *202*, 17−24.
(22) Bornehag, C. G.; Lundgren, B.; Weschler, C. J.; Sigsgaard, T.; Hagerhed-Engman, L.; Sundell, J. Phthalates in indoor dust and their association with building characteristics. *Environ. Health Perspect.* **2005**, *113*, 1399−1404.
(23) Fromme, H.; Lahrz, T.; Kraft, M.; Fembacher, L.; Dietrich, S.; Sievering, S.; Burghardt, R.; Schuster, R.; Bolte, G.; Völkel, W. Phthalates in German daycare centers: occurrence in air and dust and the excretion of their metabolites by children (LUPE 3). *Environ. Int.* **2013**, *61*, 64−72.
(24) Weschler, C. J.; Nazaroff, W. W. SVOC exposure indoors: fresh look at dermal pathways. *Indoor Air* **2012**, *22*, 356−377.
(25) Tan, H.; Yang, L.; Yu, Y.; Guan, Q.; Liu, X.; Li, L.; Chen, D. Co-existence of organophosphate di-and tri-esters in house dust from South China and Midwestern United States: implications for human exposure. *Environ. Sci. Technol.* **2019**, *53*, 4784−4793.
(26) Liu, X.; Cao, Z.; Yu, G.; Wu, M.; Li, X.; Zhang, Y.; Wang, B.; Huang, J. Estimation of exposure to organic flame retardants via hand wipe, surface wipe, and dust: comparability of different assessment strategies. *Environ. Sci. Technol.* **2018**, *52*, 9946−9953.
(27) Saido, K.; Motohashi, S.; Kuroki, T.; Ikemura, T.; Satomi, M.; Kirisawa, M. Studies on the thermal decomposition of phthalic acid esters. IV. Thermal decomposition of mono (2-ethylhexyl) phthalate. *Chem. Pharm. Bull.* **1979**, *27*, 3140−3144.
(28) Jimenez, A.; Lopez, J.; Torre, L.; Kenny, J. Kinetic analysis of the thermal degradation of PVC plastisols. *J. Appl. Polym. Sci.* **1999**, *73*, 1069−1079.
(29) Peterson, D. R.; Staples, C. A. Degradation of Phthalate Esters in the Environment. In *Phthalate Esters. The Handbook of Environmental Chemistry*;Staples, C. A., Ed.; Springer Verlag: Berlin, 2003; Vol. 3.
(30) Keyser, P.; Pujar, B. G.; Eaton, R. W.; Ribbons, D. W. Biodegradation of the phthalates and their esters by bacteria. *Environ. Health Perspect.* **1976**, *18*, 159−166.
(31) Bope, A.; Haines, S. R.; Hegarty, B.; Weschler, C. J.; Peccia, J.; Dannemiller, K. C. Degradation of phthalate esters in floor dust at elevated relative humidity. *Environ. Sci.: Processes Impacts* **2019**, *21*, 1268−1279.
(32) Kasper-Sonnenberg, M.; Koch, H. M.; Wittsiepe, J.; Wilhelm, M. Levels of phthalate metabolites in urine among mother-child-pairs - results from the Duisburg birth cohort study, Germany. *Int. J. Hyg. Environ. Health.* **2012**, *215*, 373−382.
(33) Frederiksen, H.; Nielsen, J. K.; Morck, T. A.; Hansen, P. W.; Jensen, J. F.; Nielsen, O.; Andersson, A. M.; Knudsen, L. E. Urinary excretion of phthalate metabolites, phenols and parabens in rural and urban Danish mother-child pairs. *Int. J. Hyg. Environ. Health.* **2013**, *216*, 772−783.
(34) Bekö, G.; Weschler, C. J.; Langer, S.; Callesen, M.; Toftum, J.; Clausen, G. Children's phthalate intakes and resultant cumulative exposures estimated from urine compared with estimates from dust ingestion, inhalation and dermal absorption in their homes and daycare centers. *PloS One* **2013**, *8*, No. e62442.
(35) Bradley, E. L.; Burden, R. A.; Bentayeb, K.; Driffield, M.; Harmer, N.; Mortimer, D. N.; Speck, D. R.; Ticha, J.; Castle, L. Exposure to phthalic acid, phthalate diesters and phthalate monoesters from foodstuffs: UK total diet study results. *Food Addit. Contam., Part A: Chem., Anal., Control, Exposure Risk Assess.* **2013**, *30*, 735−742.
(36) Mittermeier, A.; Volkel, W.; Fromme, H. Kinetics of the phthalate metabolites mono-2-ethylhexyl phthalate (MEHP) and mono-n-butyl phthalate (MnBP) in male subjects after a single oral dose. *Toxicol. Lett.* **2016**, *252*, 22−28.
(37) Lhuguenot, J. C.; Mitchell, A. M.; Milner, G.; Lock, E. A.; Elcombe, C. R. The metabolism of di(2-ethylhexyl) phthalate (DEHP) and mono-(2-ethylhexyl) phthalate (MEHP) in rats: *in vivo* and *in vitro* dose and time dependency of metabolism. *Toxicol. Appl. Pharmacol.* **1985**, *80*, 11−22.
(38) Thomas, J. A.; Curto, K. A.; Thomas, M. J. MEHP/DEHP: gonadal toxicity and effects on rodent accessory sex organs. *Environ. Health Perspect.* **1982**, *45*, 85−88.
(39) Chu, D. P.; Tian, S.; Sun, D. G.; Hao, C. J.; Xia, H. F.; Ma, X. Exposure to mono-n-butyl phthalate disrupts the development of preimplantation embryos. *Reprod., Fertil. Dev.* **2013**, *25*, 1174−1184.
(40) Gray, T. J. B.; Beamand, J. A. Effect of some phthalate esters and other testicular toxins on primary cultures of testicular cells. *Food Chem. Toxicol.* **1984**, *22*, 123−131.
(41) Hurst, C. H.; Waxman, D. J. Activation of PPARα and PPARγ by environmental phthalate monoesters. *Toxicol. Sci.* **2003**, *74*, 297−308.

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