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Indoor phthalate exposure and contributions to total intake among pregnant women in the SELMA study

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Abstract

Phthalates are widely used in consumer products. Exposure to phthalates can lead to adverse health effects in humans, with early-life exposure being of particular concern. Phthalate exposure occurs mainly through ingestion, inhalation, and dermal absorption. However, our understanding of the relative importance of different exposure routes is incomplete. This study estimated the intake of five phthalates from the residential indoor environment for 455 Swedish pregnant women in the SELMA study using phthalate mass fraction in indoor dust and compares these to total daily phthalate intakes back-calculated from phthalate metabolite concentrations in the women's urine. Steady-state models were used to estimate indoor air phthalate concentrations from dust measurements. Intakes from residential dust and air made meaningful contributions to total daily intakes of more volatile di-ethyl phthalate (DEP), di-n-butyl phthalate (DnBP), and di-iso-butyl phthalate (DiBP) (11% of total DEP intake and 28% of total DnBP and DiBP intake combined). Dermal absorption from air was the dominant pathway contributing to the indoor environmental exposure. Residential exposure to less volatile phthalates made minor contributions to total intake. These results suggest that reducing the presence of low molecular weight phthalates in the residential indoor environment can meaningfully reduce phthalate intake among pregnant women.

KEYWORDS
daily intake, dermal uptake, dust ingestion, exposure pathways, home, inhalation

Practical implications

- Residential indoor exposure meaningfully contributes to the total DEP, DnBP, and DiBP intake among pregnant women.
- Direct dermal absorption of phthalates from air was the largest contributor to the total intake of DnBP, DiBP, and DEP occurring indoors.
- The pregnant women's total and residential phthalate exposure are comparable to that of the general adult population. However, its implications for children's health may be different.
- Better estimates of exposures via the three pathways and their potentially different health effects warrant further attention.

1 | INTRODUCTION

Phthalate diesters are a group of semi-volatile organic compounds (SVOCs), of which several are high volume production chemicals. Phthalates are widely used as plasticizers and are present in various building materials and consumer goods, including food packaging and personal care products.[1–3] Phthalate exposure has been linked to adverse health effects in humans, and prenatal phthalate exposure is of particular concern.[4] Epidemiological studies report associations between maternal phthalate exposure and development of children's reproductive system,[5] immune system,[6] metabolism,[7] and neurodevelopment.[8] These findings have been confirmed in several experimental *in-vitro/in vivo* studies.[5,6] Following evidence of toxicity, some phthalates, including di-n-butyl phthalate (DnBP), di-iso-butyl phthalate (DiBP) butyl-benzyl phthalate (BBzP), and di-ethyl-hexyl phthalate (DEHP), have been increasingly regulated.[9,10] However, phthalates will remain ubiquitous pollutants for a considerable time as they are common additives in long-use interior materials and their extensive commercial use continues worldwide.[1,11,12]

In the indoor environment, humans are exposed to phthalates via air, airborne particles, dust, and surfaces to which phthalates may adhere.[13,14] Phthalates have been routinely measured in indoor dust and air samples.[12,15–17] Following exposure, phthalates are metabolized within hours and excreted mainly via urine.[18] Phthalate metabolite concentrations detected in urine samples are therefore widely used to assess the total phthalate exposure in people.[2,19]

Humans are exposed to phthalates via ingestion, inhalation, and dermal absorption. The relative importance of each exposure pathway varies between different phthalates.[19,20] This is due to differences in physicochemical properties that influence emission rates, partitioning behavior and uptake mechanisms. More volatile and water-soluble phthalates, such as di-ethyl phthalate (DEP), DnBP, and DiBP, are primarily present in the gas phase, resulting in a larger inhalation and dermal exposure.[18,21] Less volatile phthalates with lower water solubility, such as DEHP, are especially present in the sorbed phase (eg, in food and dust), making ingestion the more predominant exposure route.[15,18] Therefore, a more complete characterization of the indoor phthalate exposure can be achieved when both dust and air measurements are available.[19,22] So far, few studies have collected both dust and air samples.[23] Instead, steady-state models have been used to predict phthalate air concentrations from dust mass fraction data, considering the partitioning of SVOCs between dust, air, and airborne particles.[13,14,24–26]

During pregnancy, anatomical and physiological changes, such as increased inhalation rate,[27] may influence phthalate intake from the indoor environment, especially in case of more volatile phthalates.[17,21] Numerous studies have analyzed phthalate metabolite concentrations in the urine of pregnant women.[9,28–31] However, our understanding of the relative contribution of different exposure pathways to this total intake is limited.[9,32]

The main objective of this study is to assess residential indoor exposure to five target phthalates among Swedish pregnant women, using bedroom dust collected in the home of each woman to estimate phthalate ingestion, inhalation, and dermal absorption. We also calculate the contributions these indoor exposures make to the total daily phthalate intake estimated from phthalate metabolite concentrations in the pregnant women's urine. Finally, we investigate whether PVC flooring in the bedroom affects the residential indoor exposure to phthalates.

2 | METHODS

2.1 | Study population

The Swedish Environmental Longitudinal, Mother and child, Asthma and allergy (SELMA) study is a prospective pregnancy cohort of around 2,000 mother-child pairs from early pregnancy up to the children's school age. The SELMA study aims to investigate how early-life exposures to environmental factors affect health and development in children. During 2007–2010, women were recruited at median week 10 of pregnancy (range 3–27). Ninety-six percent were recruited during the first trimester (before week 13). Details of recruitment have been described by Bornehag et al.[33]

At enrollment, information regarding women's education, weight, height, and home characteristics was obtained from self-administered questionnaires. Home characteristics included bedroom flooring material (wood, PVC, laminate, cork floor, linoleum, carpet, stone/tiles, or other/do not know), categorized for the purpose of this study as non-PVC or PVC. The current study included participants with complete data for all included variables.

This study was approved by the Regional Ethical Board in Uppsala, Sweden. Individual informed consent was obtained before each subject began participation in the study.

2.2 | Dust collection and analysis of phthalates

Settled bedroom dust was collected from non-floor surfaces such as skirting boards, shelves, and door frames during approximately week 25 of pregnancy, as described by Bornehag et al.[33] Briefly, sampling equipment and a detailed manual describing the procedure were administered to the participants who collected dust through a 25 µm aperture nylon/polyamide filter attached to a vacuum cleaner. The filter with its dust content was immediately placed in an airtight polypropylene tube. Once received by post from the participants, the dust samples were stored at −20°C until analysis.[33]

The dust was analyzed for phthalate diester content (dust mass fractions) using gas chromatography tandem mass spectrometry (GC-MS/MS) as previously described by Weiss et al.[20] Briefly, 10 mg of dust was solvent extracted and analyzed using a Shimadzu GC 2010-Plus chromatograph coupled to a GC TQ8040 triple quadrupole mass spectrometer. Results for five phthalate diesters (DEP, DnBP, DiBP, BBzP, and DEHP) were used in this study. The dust mass fractions of DnBP and DiBP were summed (ΣDBP) for purposes of comparison with

urinary metabolite data (unavailable for the two individually). More details can be found in the Appendix S1 section 1.3.1.

2.3 | Urine sampling and analysis of phthalate metabolites

First-void morning urine was collected from the women on the day of enrollment. The samples were stored at −20°C until analysis and processed as described by Bornehag et al.[34] Urine samples were analyzed for phthalate metabolites using liquid chromatography triple quadrupole linear ion trap mass spectrometer (LC-MS/MS).[35] A brief description can be found in Appendix S1 section 1.3.2. Results for eight metabolites from five parent phthalate diesters were used in this study: mono-ethyl phthalate (MEP), mono-butyl phthalate (MBP), mono-benzyl phthalate (MBzP), mono-ethyl-hexyl phthalate (MEHP), mono-ethyl-hydroxy-hexyl phthalate (MEHHP), mono-ethyl-oxo-hexyl phthalate (MEOHP), mono-ethyl-carboxy-pentyl phthalate (MECPP), and mono-carboxy-methyl-hexyl phthalate (MCMHP). MBP is used as the sum of metabolites MnBP and MiBP from parent phthalates DnBP and DiBP. The sum of DEHP metabolites (ΣDEHP) was calculated from five metabolites: MEHP, MEHHP, MEOHP, MECPP, and MCMHP. Creatinine-adjusted urine phthalate metabolite and phthalate dust levels were $\log_{10}$-transformed to normalize distribution.

2.4 | Serum cotinine analysis

Cotinine, a biomarker for nicotine/tobacco use, was analyzed in blood serum collected at enrollment using liquid chromatography/tandem mass spectrometry (LC-MS/MS) as described by Axelsson et al.[36] Briefly, serum was digested with β-glucuronidase at 37°C for 90 min. Internal standards were added, and proteins were precipitated by acetonitrile under vigorous shaking followed by centrifugation. Cotinine was quantified in serum supernatants using LC-MS/MS (UFLCXR, SHIMADZU Corporation, Kyoto, Japan and QTRAP 5500, Applied Biosystems) (more details in Appendix S1 section 1.3.3). Women with cotinine levels below 0.2 ng/mL were categorized as non-smokers, above 15 ng/mL as active smokers. If values were in-between, women were categorized as passive smokers.[37]

2.5 | Phthalate exposure estimations

Total daily phthalate intake (DI_{urine}; μg/kg body weight (BW) per day; μg/kg/day) for each woman was back-calculated from creatinine-adjusted urine metabolite concentration C_{u_cre} (μg/g) using equation (1),[29]

$$DI_{urine} = C_{u\_cre} \times CE \times \frac{1}{F_{ue}} \times \frac{MW_p}{MW_m} \times \frac{1}{1000} \quad (1)$$

where CE is the creatinine excretion rate (23 mg/kg/day),[9] F_{ue} is the molar fraction of phthalates excreted as urine metabolites following intake (Table S1), MW_p and MW_m are the molar mass of the parent phthalate and phthalate metabolite, respectively (g/mol).

Daily phthalate intakes occurring in the indoor environment via the three pathways were estimated following the methods described by Bekö et al.[24] The phthalate properties used in the estimations are listed in (Table S1). Participating women were assumed to have spent a total of 13.15 h/day indoors at home[38] the day before urine sampling, of which 7.59 h asleep.[39] These assumptions are based on a study of European indoor time-activity patterns by Schweizer et al.[38] and the Swedish Time Use Survey.[39] During the time spent awake at home, the women were assumed being active in a way equivalent to light intensity housework as defined by US EPA Exposure Factors Handbook.[40]

Daily phthalate intake from residential dust ingestion (DI_{dust_ing}) was estimated from the dust phthalate level C_{dust} (μg/g), using equation (2),

$$DI_{dust\_ing} = (C_{dust} \times M_{dust\_ingest} \times t_{home}/24)/BW \quad (2)$$

where BW is the body weight (kg), M_{dust_ingest} is the amount of ingested dust (0.03 g/day),[41] and t_{home} the time spent at home awake.[38,39] The estimation assumes no dust ingestion occurring during sleep.[41]

Daily phthalate intake from residential inhalation of air and airborne particles ($DI_{inhalation}$) was estimated using equation (3),

$$DI_{inhalation} = \left(\frac{(C_g + C_p) \times V_{inhalation}}{1000}\right)/BW \quad (3)$$

where C_g and C_p are the indoor air phthalate concentrations in gas and particulate phases, respectively (ng/m^3), calculated from C_{dust} using the steady-state model by Weschler and Nazaroff[24,42] (Table S2), $V_{inhalation}$ is the average daily volume of inhaled air at home during early pregnancy, assuming a 181% higher inhalation rate during light intensity housework compared to sleep.[40] The resulting inhalation rates were 0.298 or 0.309 m^3/kg BW/day for age groups 16–29 years and ≥30 years, respectively (Table 1).[40] Women's age at urine sampling was approximated as the age at childbirth reduced by 30 weeks.

Daily dermal uptake of gas-phase phthalates in indoor air (DI_{derm_gas}) was estimated using equation (4),

$$DI_{derm\_gas} = \left(\frac{C_g \times k_{p\_g} \times A \times t}{1000}\right)/BW \quad (4)$$

where k_{p_g} is the transdermal permeability coefficient of gas-phase phthalates (m/h) (Table S1), A is the body surface area calculated from women's weight and height[43] (Table 1), and t is the time spent at home.[38]

Daily dermal phthalate uptake from residential dust adhered to skin (DI_{derm_dust}) was also estimated but was found negligible

TABLE 1 Description of study population of 455 pregnant women and their home characteristics

Categorical variables		*n* (%)
	Non-smoker	408 (89.7)
	Passive smoker	23 (5.1)
	Smoker	24 (5.3)
Women's education	Elementary or High School	136 (29.9)
	College or higher	319 (70.1)
Bedroom flooring type	Wood	198 (43.5)
	PVC	112 (24.6)
	Laminate	84 (18.5)
	Cork floor	29 (6.4)
	Linoleum	12 (2.6)
	Carpet	6 (1.3)
	Stone/tiles	1 (0.2)
	Other/do not know	13 (2.9)
PVC flooring in home	No PVC flooring in bedroom	262 (57.6)
	PVC flooring in bedroom	112 (24.6)

	N	Mean (SD)	Median (min-max)
Continuous variables			
Age at birth of child (years)	455	31.3 (4.7)	31.3 (18.5–44.5)
Weight (kg)	455	68.1 (12.6)	65 (45–120)
Height (cm)	455	167.2 (5.8)	167 (150–183)
Calculated estimations			
Body surface, *A* (m^2)[a]	455	1.76 (0.16)	1.74 (1.4–2.4)
Inhalation volume (m^3/day)[b]			
All ages	455	21.0 (20.2)	20.2 (13.6–37.5)
Approx. enrollment age <30	200	20.5 (3.9)	19.6 (13.6–36.2)
Approx. enrollment age ≥30	255	21.3 (3.9)	20.3 (14.1–37.5)
Inhalation volume at home (m^3/day)[c]			
All ages	455	11.3 (2.1)	10.9 (7.4–20.3)
Approx. enrollment age <30	200	11.1 (2.1)	10.6 (7.4–19.6)
Approx. enrollment age ≥30	255	11.5 (2.1)	11.0 (7.6–20.3)

Abbreviation: PVC, polyvinyl chloride.

[a]Body surface calculated from DuBois-DuBois formula $A = 0.00718 \times H^{0.725} \times W^{0.425}$ m^2 (height in cm, weight in kg).

[b]Average inhalation rate 0.298 m^3/kg body weight/day if aged 16–29 years and 0.309 m^3/kg body weight/day if aged 30 and above (USEPA Exposure Factors Handbook, Table 6–57).[40]

[c]Time spent at home 13.15 h/day of which 8 h rest/sleep and 5.15 h doing light intensity housework with a 181% higher inhalation rate compared to sleep/rest (Calculated from USEPA Exposure Factors Handbook, Table 6–20).[40]

(Appendix S1 section 1.5). The total daily phthalate intake from the indoor environment was calculated as the sum of intakes via the three pathways ($DI_{indoor} = DI_{dust\_ing} + DI_{inhalation} + DI_{derm\_gas}$). Intake from other sources and pathways is the difference between the total intake estimated from urinary metabolites and total intake from the indoor environment ($DI_{other} = DI_{urine} - DI_{indoor}$).[24]

2.6 | Statistical analysis

Phthalate levels in dust below the limit of detection (LOD) were replaced with an imputed value of LOD/$\sqrt{2}$. Comparisons between homes with or without PVC flooring in the mother's bedroom for both phthalate dust and urinary metabolite concentrations were conducted using least square geometric mean (LSGM) models with 95% confidence intervals (CI). The covariates included in LSGM models were bedroom PVC flooring, mother's age, education, and smoking, which were chosen *a priori* based on previous publications.[31,44,45]

Statistical analyses were done using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp), and LSGM calculations were made using PROC GLM in SAS version 9.3 (SAS System for Windows, ©2012, SAS Institute Inc. Cary, NC, USA).

3 | RESULTS

3.1 | Study population

Our study population consisted of 455 pregnant women with complete data regarding phthalates in residential dust, phthalate metabolites in urine, and relevant covariates from questionnaires. Around 70% of participants had a college degree or higher education and almost 90% were non-smokers (Table 1). The most frequently reported bedroom flooring material was wood (over 40%), followed by one quarter of participants reporting PVC. At enrollment, participating women's median weight and height were 65 kg and 167 cm, and their median age at childbirth was 31.3 years (Table 1).

3.2 | Residential dust and urine phthalate metabolites

Detectable dust levels of the five phthalates were found in more than 90% of dust samples, with DnBP having the highest detection rate (97.4%) (Table 2). Geometric means (GM) ranged from 2.0 μg/g dust for DEP to 150 μg/g for DEHP. For urine samples (Table 3), the detection rate was 100% for all examined metabolites in all samples. The highest GM concentration was observed for MEP and MBP (63–65 μg/g), the lowest for MEHP, the primary metabolite of DEHP (3.5 μg/g). More details are available in the Tables S3 and S4.

Comparing phthalate levels in dust from homes with and without PVC flooring in the mother's bedroom, there were no significant

differences for DEP, DnBP, and DiBP levels, whereas BBzP and DEHP levels were significantly higher ($p < 0.001$) in samples collected in bedrooms with PVC flooring compared to those without (Figure 1). Urinary MBzP concentrations were significantly higher ($p < 0.001$) for women reporting PVC compared to those reporting other bedroom flooring materials (details in Table S5).

Significant crude positive Pearson correlations were found between dust levels of phthalates and corresponding metabolites for DEP, DnBP, DiBP, and BBzP ($p < 0.01$ for all) (Table S6). The correlation between BBzP in dust and MBzP in urine was the strongest with $r = 0.37$ ($p < 0.001$). There were no significant correlations between DEHP in dust and any of the corresponding metabolites. When controlled for PVC flooring and mother's age, education, and smoking, the correlation between BBzP and MBzP remained the strongest $r = 0.30$ ($p < 0.001$), and the other significant correlations remained nearly unchanged (Table S7).

3.3 | Intake estimates

Table 4 shows the estimated daily phthalate intakes on the day before the urine sampling. The total intakes, DI_{urine}, of DEP, ΣDBP, and DEHP are of similar magnitude, while the intake of BBzP is an order of magnitude lower. For DEP and ΣDBP, 12% and 28% (median) of the total intake were attributable to the residential indoor environment (DI_{indoor}), respectively, with dermal uptake from air being the dominant contributor (Table 5). DnBP was the larger contributor of the two to the indoor-related intakes of ΣDBP (two to three times higher than DiBP for the three pathways at median level; Table S8). For BBzP and DEHP, residential indoor exposure explained only 2.1% and 0.7% of the total intake, respectively (median). The intake of BBzP and DEHP from the residential indoor environment was significantly higher for women with PVC bedroom flooring compared to other flooring materials ($p < 0.001$ and $p = 0.025$, respectively) (Figure 2). The contribution of the indoor environment to the total BBzP and DEHP intake was about twice as high for women with PVC flooring in the bedroom as with other floor types (Figure 3). Such association with bedroom flooring was not observed for intakes of DEP and ΣDBP.

4 | DISCUSSION

4.1 | Phthalates in dust and urine

DEHP was the most abundant phthalate in our dust samples, DEP the least abundant. Similar trends have been reported worldwide, although regional, temporal, and within-study differences in phthalate dust mass fractions have been observed.[12,16,20,22,46,47] Table S9 shows phthalate dust mass fractions from previous intake studies

TABLE 2 Phthalate mass fractions (μg/g) in dust collected from bedrooms of 455 pregnant women

		Bedroom flooring		*p* value[a] (for test of difference)
	All *n* = 455	Other than PVC *n* = 343	PVC *n* = 112	
DEP				
N (%>LOD)	432 (94.9)	325 (94.8)	107 (95.5)	0.98
GM (95% CI)	2.0 (1.7–2.2)	2.0 (1.7–2.3)	2.0 (1.5–2.6)	
DnBP				
N (%>LOD)	443 (97.4)	335 (97.7)	108 (96.4)	0.41
GM (95% CI)	22 (20–23)	21 (19–23)	25 (21–29)	
DiBP				
N (%>LOD)	436 (95.8)	327 (95.3)	109 (97.3)	0.37
GM (95% CI)	8.2 (7.6–8.9)	8.0 (7.3–8.8)	8.6 (7.2–10.3)	
ΣDBP				
N (%>LOD)	448 (98.5)	337 (98.3)	111 (99.1)	0.17
GM (95% CI)	32 (30–35)	31 (28–34)	35.0 (30–41)	
BBzP				
N (%>LOD)	407 (89.5)	303 (93.2)	104 (92.9)	<0.001
GM (95% CI)	29 (26–32)	22 (20–25)	65 (54–78)	
DEHP				
N (%>LOD)	410 (90.1)	304 (88.6)	106 (94.6)	<0.001
GM (95% CI)	150 (130–170)	130 (110–150)	230 (180–280)	

Abbreviations: ΣDBP, DnBP+DiBP; BBzP, Butyl-benzyl phthalate; DEHP, Di-ethyl-hexyl phthalate; DEP, Di-ethyl phthalate; DiBP, Di-iso-butyl phthalate; DnBP, Di-n-butyl phthalate; GM, geometric mean; LOD, limit of detection; PVC, polyvinyl chloride.

[a]Differences between bedrooms with and without PVC flooring were tested with crude LSGM models.

TABLE 3 Urine phthalate metabolite concentrations in 455 pregnant women, crude, and creatinine adjusted

	Parent diester	Metabolite	LOD	*N* (%>LOD)	All *N* = 455 GM (95% CI)	Bedroom flooring GM (95% CI)		*p* value[a] (for test of difference)
						Other than PVC *n* = 343	PVC *n* = 112	
Crude (ng/ml)	DEP	MEP	0.01	455 (100)	70 (63–77.6)	72 (63.1–81.3)	66 (53.7–81.3)	
	ΣDBP	MBP	0.1	455 (100)	68 (63.1–72.4)	67 (61.7–72.4)	72 (61.7–83.2)	
	BBzP	MBzP	0.04	455 (100)	15 (13.5–16.6)	13 (11.7–14.5)	24 (19.5–28.8)	
	DEHP	MEHP	0.1	455 (100)	3.8 (3.47–4.07)	3.7 (3.4–4.1	4.1 (3.5–4.7)	
		MEHHP	0.02	455 (100)	17 (15.8–19.1)	17 (15.8–19.1)	17 (14.5–20.4)	
		MEOHP	0.03	455 (100)	12 (10.7–12.6)	12 (10.5–12.9)	11 (9.8–13.5)	
		MECPP	0.02	455 (100)	17 (15.5–18.2)	17 (15.5–18.6)	17 (14.1–19.1)	
		MCMHP	0.068	455 (100)	6.8 (6.3–7.4)	6.8 (6.2–7.4)	6.6 (5.6–7.8)	
Creatinine adjusted (μg/g creatinine)	DEP	MEP			65 (58.9–72.4)	67 (58.9–75.9)	60 (50.1–72.4)	0.33
	ΣDBP	MBP			63 (60.3–67.6)	63 (58.9–67.6)	65 (57.5–72.4)	0.64
	BBzP	MBzP			14 (12.9–15.1)	12 (11.0–13.2)	22 (18.2–25.1)	<0.001
	DEHP	MEHP			3.5 (3.2–3.8)	3.5 (3.2–3.8)	3.7 (3.2–4.2)	0.32
		MEHHP			16 (15.1–17.4)	16 (14.8–17.8)	16 (13.5–17.8)	0.63
		MEOHP			11 (10.0–11.5)	11 (10.0–12.0)	10 (9.1–12.0)	0.63
		MECPP			16 (14.5–16.6)	16 (14.5–17.0)	15 (13.2–17.0)	0.49
		MCMHP			6.3 (5.9–6.8)	6.4 (5.9–6.9)	6.0 (5.2–6.9)	0.47

Abbreviations: ΣDBP, DnBP+DiBP; BBzP, Butyl-benzyl phthalate; CI, confidence interval; DEHP, Di-ethyl-hexyl phthalate; DEP, Di-ethyl phthalate; DiBP, Di-iso-butyl phthalate; DnBP, Di-n-butyl phthalate; GM, geometric mean; MBP, Mono-butyl phthalate (MnBP+MiBP); MBzP, Mono-benzyl phthalate; MCMHP, Mono-carboxy-methyl-hexyl phthalate; MECPP, Mono-ethyl-carboxy-pentyl phthalate; MEHHP, Mono-ethyl-hydroxy-hexyl phthalate; MEHP, Mono-ethyl-hexyl phthalate; MEOHP, Mono-ethyl-oxo-hexyl phthalate; MEP, Mono-ethyl phthalate.

[a]Differences between women with and without bedroom PVC flooring were tested with crude LSGM models.

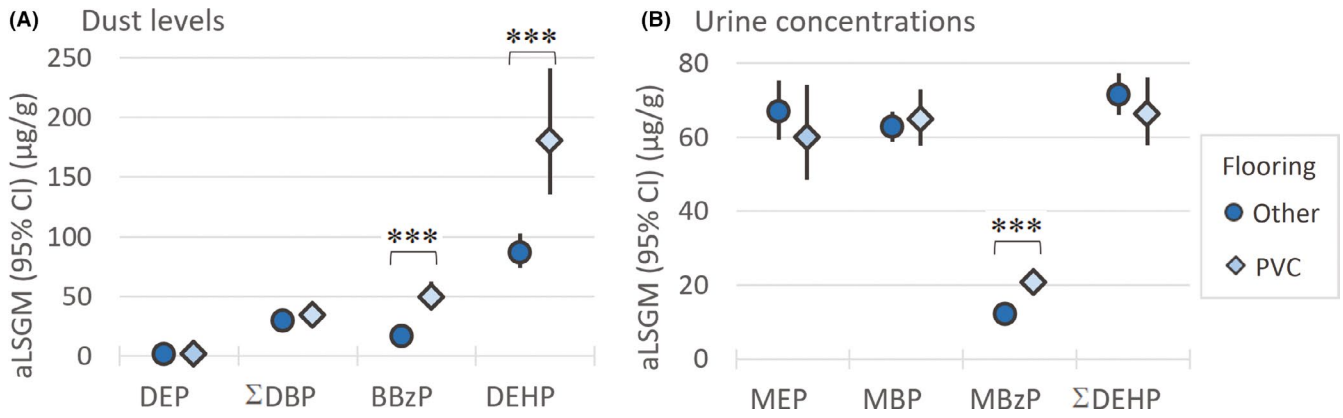

FIGURE 1 Phthalate levels expressed as LSGM (95% CI) for 455 pregnant women sleeping in bedrooms without PVC flooring (n = 343) or with PVC flooring (n = 112), (A) Phthalate levels in dust (µg/g dust) and (B) creatinine-adjusted urinary levels of phthalate metabolites (µg/g creatinine). All LSGM models were adjusted for mother's education, smoking, and age at birth of child. *** Significantly different adjusted LSGMs between floor types (p < 0.001)

among adults for comparison. Our median dust mass fractions of DEP, DnBP, DiBP, and DEHP were lower, and the median BBzP mass fraction was higher than in two other Swedish studies.[22,46] Our urinary metabolite concentrations of MBzP were higher compared to several previous studies among women.[28-30,32,48] Table S10 shows metabolite concentrations from previous intake studies among pregnant women and mothers, while further metabolite concentrations reported previously among pregnant women are available in Table S11 for comparison. However, MBzP concentrations were lower than the concentrations of MEP, MBP, and the total concentration of DEHP metabolites (ΣDEHP). This is comparable with previous reports for both adults in general and pregnant women (Tables S10 and S11).[45,49] Pregnancy may induce changes in diet and other lifestyle factors which may affect phthalate exposure. However, wide ranges of metabolite concentrations have been reported for both pregnant women as well as women in general, with no clear indications of substantial exposure differences between pregnant and non-pregnant women.[9,49]

We found significant correlations between DEP, ΣDBP, and BBzP in residential dust and their corresponding urine metabolites in pregnant women, reflecting the possibly important role of indoor exposure. No such trend was found for DEHP; diet has been shown to be a major source of DEHP exposure.[3,32,50–52] Similar correlations between phthalate concentrations in dust or air and corresponding metabolites in urine have been reported in earlier studies on children as well as pregnant women.[53–56]

4.2 | Total phthalate intake estimated from urinary metabolite concentrations

The total intake (DI_{urine}) was the largest for DEHP followed by ΣDBP and DEP, while the intake of BBzP was considerably lower. Our median total phthalate intakes are generally higher than previously published intake estimates for pregnant women or mothers in the US, Japan, Australia, and Denmark, in the period between 1999 and 2013 (Table S10).[9,28-30,48] The exceptions are considerably higher median DEP intake rates in the US,[29] and ΣDEHP intake rates in Japan.[48] The higher intake rates can be related to higher urinary metabolite concentrations. However, differences between studies may also reflect differences in the urinary excretion factors (F_{ue}) used, which have been continuously updated as more data became available over the past two decades.[3,18,57]

4.3 | Contribution of indoor environment to total phthalate intake

The phthalate intake from the residential indoor environment (DI_{indoor}) was highest for ΣDBP and lowest for BBzP. The residential indoor environment contributed meaningfully to the total intake of DEP and ΣDBP, while its contribution was very small for BBzP and DEHP. This trend is similar to the results obtained for Danish children reported by Bekö et al.[24] However, indoor intakes and their contributions to total phthalate intakes were higher among Danish children than among Swedish pregnant women. Direct comparisons are difficult to make because of the differences in the respective indoor environments and some of the assumptions in the two studies. Moreover, while the current study accounted for exposure in the home environment, Bekö et al. estimated the intake from both the homes and daycares of the participating children.

4.4 | Dust ingestion

Residential dust ingestion was highest for DEHP (median 0.014 µg/kg/day), followed by ΣDBP and BBzP (an order of magnitude lower than for DEHP). It was negligible for DEP. The DEHP intake through dust ingestion was considerably lower than in other studies (Table S9),[22,47,58] despite our DEHP dust mass fractions being only modestly lower. Our dust ingestion was substantially reduced by the assumption that the women were asleep for two thirds of the time spent at

TABLE 4 Descriptive statistics of individual phthalate intake (μg/kg/day) calculated from urine metabolite concentrations and three residential indoor exposure routes estimated from dust phthalate levels for 455 pregnant women

	DEP	ΣDBP	BBzP	ΣDEHP
Total intake (DI_{urine})				
Mean (SD)	6.23 (18.4)	2.99 (4.30)	0.78 (0.79)	4.86 (8.47)
Minimum	0.13	0.24	0.035	0.57
25th percentile	1.16	1.71	0.30	2.13
Median	2.16	2.36	0.54	2.95
75th percentile	4.95	3.43	0.97	4.59
95th percentile	19.9	6.06	2.26	13.4
Maximum	228.0	83.5	7.03	94.4
Dust ingestion (DI_{dust_ing})				
Mean (SD)	0.0009 (0.0033)	0.0048 (0.0076)	0.0053 (0.011)	0.030 (0.057)
Minimum	0.0000	0.0001	0.0001	0.0003
25th percentile	0.0001	0.0020	0.0009	0.0042
Median	0.0001	0.0031	0.0026	0.014
75th percentile	0.0005	0.0054	0.0063	0.032
95th percentile	0.0031	0.012	0.016	0.12
Maximum	0.047	0.13	0.13	0.60
Inhalation ($DI_{inhalation}$)				
Mean (SD)	0.14 (0.49)	0.099 (0.21)	0.0047 (0.0096)	0.017 (0.034)
Minimum	0.0066	0.0042	0.0002	0.0003
25th percentile	0.015	0.040	0.0008	0.0025
Median	0.027	0.064	0.0024	0.0082
75th percentile	0.089	0.11	0.0058	0.019
95th percentile	0.53	0.25	0.013	0.066
Maximum	6.37	3.96	0.11	0.41
Dermal uptake from air[a] (DI_{derm_gas})				
Mean (SD)	1.05 (3.73)	0.92 (1.88)	0.014 (0.028)	0.0032 (0.0062)
Minimum	0.041	0.034	0.0004	0.0000
25th percentile	0.10	0.37	0.0025	0.0005
Median	0.19	0.57	0.0070	0.0015
75th percentile	0.63	0.99	0.016	0.0035
95th percentile	3.99	2.39	0.039	0.013
Maximum	50.9	35.7	0.33	0.071
Total indoor[b] (DI_{indoor})				
Mean (SD)	1.19 (4.22)	1.03 (2.09)	0.024 (0.048)	0.051 (0.097)
Minimum	0.047	0.0381	0.0007	0.0006
25th percentile	0.12	0.41	0.0043	0.0072
Median	0.21	0.64	0.012	0.024
75th percentile	0.72	1.10	0.029	0.054
95th percentile	4.52	2.64	0.068	0.20
Maximum	57.4	39.8	0.57	1.08
Other sources[c] (DI_{other})				
Mean (SD)	5.03 (18.9)	1.97 (4.68)	0.76 (0.79)	4.81 (8.47)

(Continues)

TABLE 4 (Continued)

	DEP	ΣDBP	BBzP	ΣDEHP
Minimum	−38.4	−37.5	−0.15	0.24
25th percentile	0.65	0.88	0.28	2.08
Median	1.54	1.62	0.53	2.89
75th percentile	4.04	2.46	0.94	4.51
95th percentile	19.7	4.78	2.24	13.3
Maximum	227.9	83.0	6.98	94.3

Abbreviations: ΣDBP, Di-n-butyl phthalate+Di-iso-butyl phthalate; BBzP, Butyl-benzyl phthalate; DEHP, Di-ethyl-hexyl phthalate; DEP, Di-ethyl phthalate.

[a]As contributions from DI_{derm_dust} were negligible, detailed data are not presented. Median values were zero for all phthalates; all maximum values were 0.0008 μg/kg/day or below.

[b]$DI_{indoor} = DI_{dust\_ing} + DI_{inhalation} + DI_{derm\_gas}$ on a person-by-person basis.

[c]$DI_{other} = DI_{urine} - DI_{indoor}$.

TABLE 5 Contributions (%) of intake via dust ingestion, inhalation, and dermal uptake from air in the home environment to the total daily phthalate intake for 455 pregnant women

	Mean (SD)	Minimum	25th percentile	Median	95th percentile
Dust ingestion (DI_{dust_ing}/DI_{urine}) × 100					
DEP	0.0 (0.1)	0.0	0.0	0.0	0.1
ΣDBP	0.2 (0.4)	0.0	0.1	0.1	0.6
BBzP	1.0 (2.2)	0.0	0.2	0.5	3.4
DEHP	1.1 (2.7)	0.0	0.1	0.4	4.6
Inhalation ($DI_{inhalation}/DI_{urine}$) × 100					
DEP	5.8 (17)	0.0	0.7	1.5	23
ΣDBP	4.4 (9.2)	0.0	1.6	2.8	12
BBzP	0.9 (2.2)	0.0	0.2	0.4	3.3
DEHP	0.7 (1.8)	0.0	0.1	0.3	2.5
Dermal uptake from air (DI_{derm_gas}/DI_{urine}) × 100					
DEP	41 (121)	0.0	4.8	10	170
ΣDBP	41 (84)	0.3	15	25	113
BBzP	2.6 (6.0)	0.0	0.5	1.2	9.3
DEHP	0.1 (0.3)	0.0	0.0	0.1	0.5
Total indoor[a] (DI_{indoor}/DI_{urine}) × 100					
DEP	47 (138)	0.0	5.5	12	192
ΣDBP	45 (93)	0.3	16	28	127
BBzP	4.5 (10)	0.0	0.9	2.1	16
DEHP	1.9 (4.8)	0.0	0.2	0.7	7.4

ΣDBP, Di-n-butyl phthalate+Di-iso-butyl phthalate; BBzP, Butyl-benzyl phthalate; DEHP, Di-ethyl-hexyl phthalate; DEP, Di-ethyl phthalate.

[a]$DI_{indoor} = DI_{dust\_ing} + DI_{inhalation} + DI_{derm\_gas}$ on a person-by-person basis.

home, during which no dust ingestion occured.[41] Additionally, we used a lower dust ingestion rate of 0.03 g/day for adults, recommended in the more recent edition of the US EPA Exposure Factors Handbook,[41] compared to 0.05 g/day in earlier editions used by the other studies.[23,26,47,59] Dust ingestion made negligible contribution to the total intakes of the included phthalates (<1%, medians). Our results, along with those of Bekö et al.,[24] suggest that the small indoor intake of DEHP is dominated by dust ingestion, and that intakes via dust ingestion may be substantially higher for children than for pregnant women.

4.5 | Inhalation

Phthalate intake via inhalation in the residence was highest for ΣDBP, lowest for BBzP. Inhalation intakes of ΣDBP and DEP were

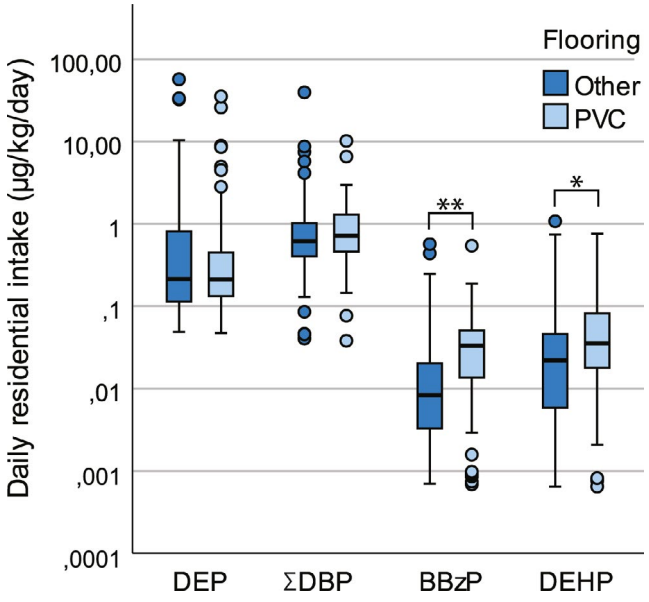

FIGURE 2 Daily phthalate intake from the residential indoor environment through dust ingestion, inhalation, and dermal uptake for 455 pregnant women sleeping in bedrooms with or without PVC flooring (BBzP, Butyl-benzyl phthalate; DEHP, Di-ethyl-hexyl phthalate; DEP, Di-ethyl phthalate; ΣDBP, Di-n-butyl phthalate + Di-iso-butyl phthalate). Circles represent outliers. Test of difference in intake between floor types was made with 2-tailed *t* test, $^{*}p < 0.05$ and $^{**}p < 0.01$

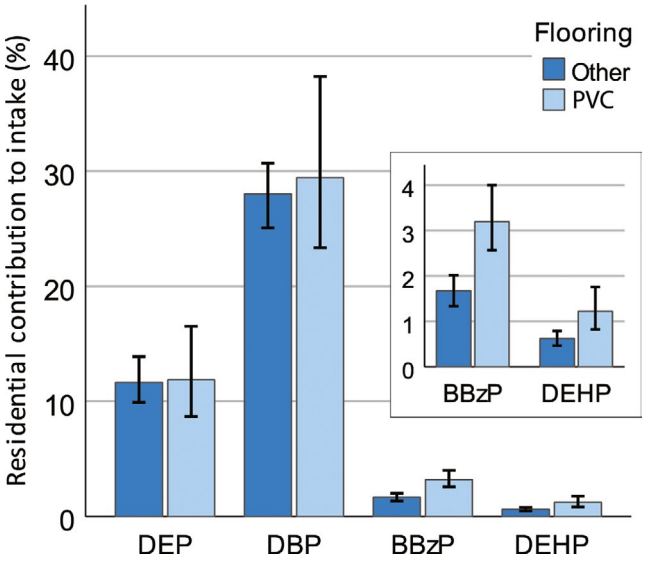

FIGURE 3 Difference in median residential indoor intake contributions (%) to the total daily phthalate intake for 455 pregnant women with and without PVC flooring material in their bedroom (BBzP, Butyl-benzyl phthalate; DEHP, Di-ethyl-hexyl phthalate; DEP, Di-ethyl phthalate; DBP, Di-n-butyl phthalate + Di-iso-butyl phthalate). Error bars represent 95% CI

of a similar magnitude, while intakes of BBzP and DEHP were an order of magnitude lower. The same trends were observed for adults in other studies, although the intake levels differ between studies (Table S9).[17,22,53,59] These differences can be attributed to differences in phthalate concentrations in air and airborne particles, and assumed inhalation rates (relatively high for pregnant women) and uptake fractions.

4.6 | Dermal absorption

Dermal absorption from air was the dominant exposure pathway for DEP, DnBP, and DiBP. Bu et al. combined data on phthalate concentrations in dust from 94 worldwide studies and estimated phthalate air concentrations and dermal absorption of DnBP, DiBP, and DEHP using Monte Carlo simulation.[23] The mean intakes for adults were comparable with our results (0.82, 0.26 and 0.0023 µg/kg/day, respectively). Higher median dermal intakes of all phthalates except BBzP were reported for Danish children.[24] The Danish study considered exposure occurring both at home and in the children's daycare centers, and the dust mass fractions were higher for DiBP and lower for BBzP than in the current study.

An altered skin area to weight ratio among pregnant women may affect the intakes via dermal exposure. No corrections to dermal uptake considering this were made. To calculate body surface area, we used the actual body weight and height at the time of urine sampling. It is however plausible that dermal absorption of chemicals alters during pregnancy due to physiological changes such as dermal blood flow, skin thickness, and tissue composition.[60,61]

Clothing and contact with bed sheets can both reduce and enhance dermal uptake of phthalates, depending on the level of contamination of these textile products that come in contact with the skin.[21,62] Our estimates of dermal uptake from air assume uniform uptake rate through the entire skin surface area. Moreover, we used the steady-state model of transdermal uptake. Since exposure conditions frequently change and there is insufficient time to achieve steady-state, the steady-state model tends to overestimate dermal uptake.[63]

4.7 | PVC bedroom flooring

For mothers with PVC flooring in the bedroom, BBzP and DEHP levels in dust and MBzP concentrations in urine were significantly higher. The difference remained significant after adjustment for relevant covariates in the LSGM models. These results are in line with earlier observations of associations between PVC flooring increased BBzP and DEHP levels in residential air and dust,[64–67] elevated urinary MBzP concentrations,[45] and increased BBzP intake.[68,69] Although the contribution of the indoor environment to the total intake of BBzP and DEHP was small, it was higher for mothers with PVC bedroom flooring than for those with other flooring materials. BBzP and DEHP can make up a substantial part of PVC flooring materials. DEP, DnBP, and DiBP may be added to floor waxes, but they are less likely to be present in PVC plastics.[1,70]

4.8 | Other sources of exposure

Sources of exposure unrelated to the residential indoor environment (DI_{other}) were responsible for a large fraction of the total intake (median 72–99%). These include diet, personal care products, the outdoor environment, and indoor environments other than the home. Diet is responsible for a substantial part of the phthalate intake, in particular for DEHP.[3,32,50–52,58,71] Estimates of phthalate intakes from diet were recently reported in a risk assessment by the European Food Safety Authority (EFSA).[10] The report summarized typical European dietary phthalate exposures. It was concluded that for adult women, 11%, 16%, 50%, and 71% of the total intake of DnBP, DiBP, BBzP, and DEHP, respectively, are attributable to diet. These fractions are all lower than our median fractions of intakes from other sources (DI_{other}). DEP is not regulated in the EU and was therefore not considered in the EFSA report. Personal care products have been shown to constitute a major source of exposure to DEP and to contribute to urinary levels of MBP and MBzP as well.[9,32,72] DEP levels in children's bedroom dust were also associated with perfume use in the home.[73] Individual differences in the use of such products are likely to contribute to the large variations in DEP intake among our pregnant women, compared to the other phthalates.

Phthalate levels in outdoor air and dust are several orders of magnitude lower than in indoor air and dust,[74] and therefore unlikely to make a substantial contribution to the total daily intake from other sources than the residential environment (DI_{other}).[9] Our participants were assumed to spend 8 h in other indoor environments than the home.[40] Exposures in these environments may have significantly contributed to the non-residential phthalate intakes (DI_{other}).

4.9 | Comparisons to tolerable daily intakes (TDI) and implications

The median total phthalate intakes (DI_{urine}) reported in this study are below the tolerable daily intakes (TDI) established by EFSA. These levels (10 μg/kg/day for DnBP and putative for DiBP by analogy to DnBP, thus 20 μg/kg/day for ΣDBP, 500 μg/kg/day for BBzP and 50 μg/kg/day DEHP) were however exceeded for ΣDBP and DEHP among the 1% most highly exposed women in our study.[10] For ΣDBP, the estimated intake from the residential indoor exposure (DI_{indoor}) exceeded the TDI limit for the single most highly exposed woman (39.8 μg/kg/day). Considering that the cumulative exposure to DnBP, DiBP, and DEHP may act in a dose-additive manner, the total cumulative daily intake of these phthalates, as introduced by Koch et al,[75] exceeded the relative cumulative TDI for eight women. For residential indoor intake, the relative cumulative TDI was exceeded by one woman. Thus, exposure occurring in the residential environment may be of concern among pregnant women and their children. Phthalates penetrate the placenta, and maternal exposure during pregnancy may have possible health consequences for the fetus.[4] Absorption, distribution, elimination, and the dose to various organs of a chemical in the body differ however between exposure pathways.[19,76] The effects of the mother's fractional intakes via the three specific exposure pathways on prenatal exposure and associated health consequences remain therefore unknown.

4.10 | Strengths and limitations

Our study was performed on a relatively large study population with individual samples of urine, bedroom dust, and other relevant variables that allowed direct person-by-person intake estimations. The assumed inhalation rates considered activity and sleep behavior during early pregnancy. Settled dust collected from above-floor levels, as was done in this study, has been suggested to be more representative of emissions from interior surfaces, compared with floor dust, which can be directly related to the flooring material (in our case often PVC).[66] We did not sieve the sampled dust prior to chemical analysis. Larger particle fractions have a lower surface-to-volume ratio, which may reduce phthalate sorption and result in lower dust mass fractions.[19] However, as we collected settled dust from above-floor surfaces, the content of larger particles is expected to be low.

Analyzing exclusively first-void morning urine reduced the effects of variation in phthalate exposures caused by daytime activities. Temporal variations in urinary metabolite concentrations during the course of a day may occur. Exposure to phthalates is however relatively continuous, and single samples have been shown to reasonably predict average metabolite concentrations over a longer period.[77]

There was a considerable time (about 12 weeks) between the collection of dust and urine. Phthalate metabolite concentrations in urine reflect short-term exposure, since the half-life of phthalate can be as short as a few hours and 90% are metabolized within 24 h.[57] In contrast, mass fractions of phthalates in settled dust represent exposures over a longer period of time,[25,46] although temporal variations in temperature and ventilation can alter phthalate partitioning between dust and the gas phase.[19] Partitioning can also be affected by participant behavior, such as dust removal and changes in the use of phthalate-containing products.[15,78]

Phthalate concentrations in indoor air were estimated from dust mass fractions using the octanol-air partition coefficients (K_{oa}) and assuming steady-state conditions. K_{oa} was also used to estimate the partitioning of phthalates between the gas-phase and airborne particles. The values of K_{oa} have not been measured, and their uncertainty constitutes a potential source of error. BBzP is the most sensitive to K_{oa}, as its physicochemical properties lie between those of DEHP and the more volatile phthalates. Some studies have used lower K_{oa} values,[23,26,48] which would result in an increased estimate of BBzP intake from the indoor environment. Moreover, in our estimates we assumed an identical average airborne particle concentration in all homes (20 μg/m^3).

There is considerable uncertainty associated with our intake estimates. Our estimate of DEHP intake is based on all its metabolites, including MEHP. MEHP is prone to contamination, it has a much shorter half-life compared to the secondary DEHP metabolites, and it is often present at lower concentrations.[57] Indeed, some previous

studies have only included secondary metabolites in their DEHP intake estimates.[24,29] Doing so in our study population would have resulted in a slightly higher total intake of DEHP.

We are not aware of any urinary excretion factors (F_{ue}) specific to pregnant women; general values for adults were used in the current study. They rely on a limited number of studies, some with a single participant, and they reflect excretion after oral administration.[2,18] Excretion factors for inhalation and dermal absorption do not exist. The absorption and elimination pattern vary between the exposure pathways. There is a considerable lag between dermal absorption and uptake to the blood, and thus the elimination time is much longer after dermal uptake than inhalation.[21,79] Limited evidence also suggests that the rate of phthalate metabolism may vary during different stages of pregnancy.[80] Further uncertainties in the comparison of total intakes and fractional intakes via the three exposure pathways may be present due to unknown changes to some of the input variables in the intake estimation models due to physiological changes during pregnancy (eg, changes in dermal permeability, gastrointestinal, and airway uptake rates).[27,60,61]

We have assumed that 100% of phthalates in ingested dust and inhaled air and particles are retained and absorbed. Human exposure studies suggest a substantial uptake of inhaled DEP and DnBP.[18,21] Wormuth et al. suggested, however, somewhat lower overall uptake rates (75% for adults),[3] which may depend on the concentration, duration of exposure, and physicochemical properties of the chemical. Our intakes via dust ingestion and inhalation may thus be overestimated.

We had no time-activity information for the participants, and intake estimates were based on uniform assumptions of residential exposure time and sleep duration. The availability of data from the participants' work environment, together with information about working hours, would have improved the estimates of total indoor phthalate intakes. Finally, it should be noted that exposure to some of the investigated phthalates has been on the decline in Europe and the United States over the past decade since our data were collected, due to increased regulation and substitution.[49,81] However, phthalates and alternative plasticizers remain to be ubiquitous. Residential indoor exposure, its contribution to total exposure among pregnant women, and the associated effects on children warrant further attention.

5 | CONCLUSION

This study estimated the daily intake of five phthalates for 455 pregnant women. Total intake and residential indoor intake via dust ingestion, inhalation, and dermal absorption from air were estimated from paired urine and dust samples. Our results suggest that the residential indoor environment makes a meaningful contribution to the total intake of DEP, DnBP, and DiBP (ΣDBP) in pregnant women. The largest contribution from residential indoor exposure to total intake was seen for ΣDBP, while the contribution was small for BBzP and DEHP. We did not find a substantial difference between the intakes of the pregnant women and previously reported intakes among adults in general. Having PVC flooring in the bedroom increased the indoor environment-related intake of BBzP and DEHP, although it remained a small fraction of the corresponding total daily intake. The results indicate that limiting the presence of phthalate-containing products and building materials in the home would reduce phthalate intake among pregnant women, with possible benefits to their unborn children.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Anna-Sofia Preece involved in conceptualization, formal analysis, methodology, visualization, and wrote the original draft. Huan Shu involved in conceptualization, data curation, investigation, formal analysis, project administration, supervision, visualization, and reviewing and editing. Malin Knutz involved in investigation, project administration, resources, supervision, and review and editing. Annette Krais involved in investigation, funding acquisition, resources, and review and editing. Gabriel Bekö involved in methodology, supervision, visualization, and review and editing. Carl-Gustaf Bornehag involved in conceptualization, investigation, funding acquisition, supervision, and review and editing.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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