



Phthalate levels in indoor dust and associations to croup in the SELMA study

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Abstract

Phthalates are ubiquitous indoor pollutants which have been associated with child airway disease although results are inconclusive. This study examined associations between phthalate levels in residential indoor dust and croup during infancy. Settled indoor dust was collected in 482 homes of 6-month-old infants in the Swedish Environmental Longitudinal, Mother and child, Asthma and allergy (SELMA) study and analysed for seven phthalates and one phthalate replacement using gas chromatography tandem mass spectrometry. The incidence of parental reported croup at 12 months was 6.4% for girls and 13.4% for boys. Associations between phthalate dust levels and croup were analysed by logistic regression adjusted for potential confounders. We found significant associations between di-ethyl phthalate (DEP) and di-ethyl-hexyl phthalate (DEHP) in residential dust and parental reported croup (adjusted odds ratio (aOR) = 1.71; 95% CI: 1.08–2.73 and 2.07; 1.00–4.30, respectively). Stratified results for boys showed significant associations between DEP and butyl-benzyl phthalate (BBzP) in dust and infant croup (aOR = 1.86; 95% CI: 1.04–3.34 and 2.02; 1.04–3.90, respectively). Results for girls had questionable statistical power due to few cases. Our results suggest that exposure to phthalates in dust is a risk factor for airway inflammatory responses in infant children.

Keywords Croup · Dust · Exposure · Phthalate · SELMA study

Introduction

The versatile properties of phthalate esters make them useful components in many materials and products, such as plasticisers in polyvinyl chloride (PVC) plastics used in interiors, packaging and toys or components in electronics, paints and personal care products [1]. Phthalates are semi-volatile and

may continuously leach from products into the surrounding environment such as air, dust, food and water [1]. Consequently, phthalates are detected in a majority of dust samples collected in homes and workplaces globally [2, 3].

Although diet related ingestion is reported to be the dominant phthalate exposure route [4], indoor dust can make a relevant contribution to total phthalate exposure [4–6]. During the first 2 years after birth in particular, children are more vulnerable to indoor dust exposure as they spend much time indoors on the floor and display frequent hand-to-mouth behaviour [2, 7, 8]. They also have a relatively faster breathing rate and surface to volume ratio compared to adults [7]. This makes them more likely to inhale and ingest more dust than adults [4]. Through inhalation, both dust particles and air may carry phthalates into the airways and lungs, potentially leaving these surface tissues exposed to higher concentrations of phthalates than other organs of the human body [9].

Epidemiological studies have found associations between dust levels of phthalates and childhood asthma [10] and wheeze [11], as well as the severity of asthma and allergy [12]. Therefore it is relevant to investigate early life effects of phthalate exposure in relation to airway disease in

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young children. Treating and preventing asthma symptoms early in life is believed to have life-long health benefits [13] and more knowledge on the effects of early life environmental exposure is needed to improve preventive measures [7]. However, both asthma and wheeze are challenging to diagnose in young children [13, 14]. This may limit the ability of asthma and wheeze symptoms to clearly identify potential relationships with early life environmental exposures. Therefore, other manifestations of early life airway inflammation may also be considered when investigating the effects of environmental exposures such as phthalates, not the least as airway responsiveness itself is considered a prognostic marker for asthma symptoms later in life [15].

Croup is another inflammatory airway condition that may serve as a proxy for airway inflammatory reactivity when investigating environmental exposures [16]. It is an acute respiratory disease also known as pseudocroup or acute subglottic laryngitis and is caused by a strong inflammatory response to viral airway infections. It usually affects children between six months and three years old with self-limiting symptoms such as breathing difficulties and/or barking cough [17]. In an earlier study, we found associations between prenatal phthalate exposure and infant croup [16].

Therefore, this study aimed to investigate associations between infant croup during the first 12 months of age and exposure to seven phthalates and one non-phthalate plasticiser in settled indoor dust collected in the homes of the infants.

Methods

Description of study population

The Swedish Environmental Longitudinal Mother and child Asthma and allergy (SELMA) study is an ongoing prospective pregnancy cohort study in the county of Värmland, Sweden, aiming to investigate the importance of early life exposure to environmental factors for child health and development. The recruitment and sample collection has previously been described and discussed by Bornehag et al. [18]. Briefly, from 2007 to 2010, 6658 pregnant women were invited to participate of which 2582 (39%) agreed. The women were recruited during their first visit to their regular antenatal care centre and the mother–child pairs were followed over birth and up over child school age. Biological samples and residential environmental measurements such as dust were collected before and after the birth of the child. Self-administered questionnaires were administered at enrolment and throughout the study period to provide information on lifestyles, living conditions and medical history.

Questionnaires

The information retrieved for this study came from two separate self-administered questionnaires which included core health questions from the International Study of Asthma and Allergies in Childhood (ISAAC). Family characteristics, lifestyles, history of asthma or allergies, maternal age at delivery, and maternal education were collected at enrolment in median gestational week 10. Parental report of infant croup was collected 12 months after birth. Croup was defined by the question, “Has your child suffered from croup (breathing difficulties with a barking cough)?”.

Dust sample collection

Six months after birth, one sample of settled indoor dust from above floor level was collected by the participants in the room where the child slept. A detailed manual describing the sampling procedure was administered to the families together with the sampling equipment [18]. In brief, dust was collected in a polyamide/nylon filter (Allied Filter Fabrics, Australia) with a 25 µm aperture mounted on the nozzle of a vacuum cleaner. The filter and its dust content was promptly placed in an air-tight polypropylene tube and stored frozen (−20 °C) until analysis. We aimed to collect 500 random dust samples among participants who had provided complete data up until the time of dust analysis.

Analysis of phthalate esters in dust samples

Dust samples were solvent extracted and analysed using gas chromatography tandem mass spectrometry (GC–MS/MS) for seven phthalate esters, namely di-ethyl phthalate (DEP), di-iso-butyl phthalate (DiBP), di-n-butyl phthalate (DnBP), buty-benzyl phthalate (BBzP), di-ethylhexyl phthalate (DEHP), di-iso-nonyl phthalate (DiNP) and di-2-propylheptyl phthalate (DHP) and non-phthalate di-iso-nonyl cyclohexane-di-carboxylate (DiNCH) with samples prepared as previously described by Weiss et al. [6]. Briefly, 10 mg of unsieved dust was sonicated in 1 mL of toluene containing 50 µg of D₄-labelled internal standards. Samples were centrifuged and 1 µL of extract was analysed using a Shimadzu GC 2010-Plus chromatograph (Shimadzu Corporation, Kyoto, Japan) coupled to a GC TQ8040 triple quadrupole mass spectrometer (Shimadzu Corporation, Kyoto, Japan). Possible contamination background levels were tested and method reproducibility verified prior analysis. All method details are presented in Supplementary Information and in Weiss et al. [6].

Analysis of cotinine in prenatal serum as a marker for smoking

Mother's smoking status during early pregnancy was categorised based on serum levels of cotinine, a biomarker for exposure to tobacco/nicotine, in blood samples collected from the pregnant women at enrolment in median gestational week 10. The analysis method was previously described by Lindh et al. [19]. In brief, internal standard was added to 100 μ L of serum, followed by precipitation of proteins with acetonitrile. The samples were analysed on a Shimadzu UFLC system (Shimadzu Corporation, Kyoto, Japan) coupled to a QTRAP5500 (triple quadrupole linear ion trap mass spectrometer) equipped with a TurboIon Spray source (AB Sciex, Framingham, MA, USA). Subjects with cotinine levels below 0.2 ng/mL or above 15 ng/mL were categorised as non-smokers or active smokers, while subjects with cotinine levels in between were categorised as passive smokers [20].

Statistical analysis

When dust levels of phthalates or DiNCH were below the limit of detection (LOD), an imputed replacement value equal to $\text{LOD}/\sqrt{2}$ was inserted. Exposure data were log-10 transformed to normalise the distribution. For statistics on DiNCH assuming normally distributed data, the replacement values for levels below analysis LOD were excluded. They made up 40% of samples which affected the distribution of the DiNCH data. Using multiple regression models, we have estimated least square geometric means

(LSGMs) of phthalate dust levels. Associations between infant croup and single phthalate or DiNCH levels were estimated with logistic regression, which were expressed as crude and adjusted odds ratio (OR and aOR) with 95% confidence intervals (CI). Final LSGM and logistic regression models were adjusted for sex of child, asthma or allergy in family, mother's age, mother's smoking during pregnancy, mother's education and dust sampling season. Covariates were selected both a priori and by tests for possible associations with exposure and outcome (for details see Section 1.4 in the Supplementary Information). Interactions between exposure levels and sex of child were explored by introducing interaction terms between the compound and sex into the adjusted models. The statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.). Least-squares GMs were calculated using PROC GLM in SAS version 9.3 of the SAS System for Windows. Copyright© 2012, SAS Institute Inc. Cary, NC, USA.

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

Results

This study population consisted of 482 mother–child pairs with complete data, of which 9.8% (16 girls and 31 boys) had parental-reported croup before the age of 12 months (Table 1). The median age of mothers at childbirth was 31.3

Table 1 Characteristics of the study population of 482 mother–child pairs.

	Study population			<i>p</i> Value ^a
	All (<i>n</i> = 482) <i>n</i> (%)	No reported croup (<i>n</i> = 435) <i>n</i> (%)	Reported croup (<i>n</i> = 47) <i>n</i> (%)	
Sex of child				
Girls	251 (52.1)	235 (93.6)	16 (6.4)	0.01
Boys	231 (47.9)	200 (86.6)	31 (13.4)	
Asthma or allergy in the family				
No	202 (41.9)	190 (94.1)	12 (5.9)	0.02
Yes	280 (58.1)	245 (87.5)	35 (12.5)	
Mother's education				
Elementary or high school	146 (30.3)	126 (86.3)	20 (13.7)	0.05
College, university or higher	336 (69.7)	309 (92.0)	27 (8.0)	
Mother's smoking at enrolment				
Non-smoker	434 (90.0)	391 (90.1)	43 (9.9)	>0.7 ^b
Passive smoker	24 (5.0)	24 (100.0)	0 (0)	
Smoker	24 (5.0)	20 (83.3)	4 (16.7)	
Dust sampling season				
Summer (April–September)	209 (43.4)	190 (90.9)	19 (9.1)	>0.6
Winter (October–March)	273 (56.6)	245 (89.7)	28 (10.3)	

^aPearson chi square test, *p* value for difference between mother and child pairs with or without reported infant croup at 12 months of age.

^bLinear-by-linear association.

Table 2 Levels of 7 phthalates and DiNCH ($\mu\text{g/g}$) in dust samples from 482 homes^a.

	>LOD, <i>n</i> (%)	Min	Max	25th	Median	75th	Geometric mean (95% CI)
DEP	439 (91.1)	<LOD	200	0.4	0.9	3.6	1.3 (1.2–1.5)
DIBP	440 (91.3)	<LOD	300	3.5	6.1	11	6.9 (6.3–7.5)
DnBP	450 (93.4)	<LOD	420	10	18	31	18 (16–20)
BBzP	455 (94.4)	<LOD	1400	7.5	17	44	20 (18–22)
DEHP	479 (99.4)	<LOD	2100	69	130	270	130 (120–150)
DINP	431 (89.4)	<LOD	840	18	29	55	33 (30–36)
DPHP	476 (98.8)	<LOD	260	0.8	1.5	3.3	1.7 (1.5–1.9)
DiNCH	298 (60.0)	<LOD	630	17	37	84	39 (34–44)

^aStatistics based on samples with phthalate levels above the analysis limit of detection.

years (range: 18.5–41.4, interquartile range = 6.6), with no significant age difference between mothers of boys and girls. Within these study subjects, boys were significantly ($p = 0.01$) more likely to have parentally reported croup, whereas other examined factors were similar between the sexes. Families reporting infant croup were significantly ($p = 0.02$) more likely to report a family history of asthma or allergy. A somewhat larger proportion of dust samples (56.6%) included in this study were collected during the winter season (October–March). There were no significant associations between croup and dust sampling season (Table 1).

As presented in Table 2, all included phthalate ester measures were above the detection limit in 89.4% or more of the dust samples, whereas the phthalate replacement DiNCH was detected in 60.0% of the samples. The most frequently detected phthalate in this study was DEHP which was found in 94.4% of samples. GM levels varied between 1.1 $\mu\text{g/g}$ for DEP to 130.8 $\mu\text{g/g}$ for DEHP. Comparing samples collected in winter and summer season, DEHP was the only compound with a significantly higher level in samples collected during the winter months (October–March) ($p = 0.01$) when compared to the summer months. Dust levels of the five most low molecular weight phthalates DEP, DiBP, DnBP, BzBP and DEHP all showed highly significant positive correlations of which DEHP and BBzP were the strongest (0.39, $p < 0.001$) (Supplementary Information Table S1). The strongest correlation (0.43, $p < 0.001$) was found between the higher molecular weight DiNP and DPHP. There were significant negative correlations between DiNCH, DEP and DEHP as well as between DEP and DiNP.

The adjusted LSGMs with 95% CIs for phthalate levels in dust collected from homes with or without reported infant croup are shown in Table 3. The majority of compound LSGM levels were higher among the croup cases, a difference that is significant for DEP, BBzP and DEHP ($p < 0.05$). Levels of DPHP were lower and DiNCH were the same among croup cases but this difference was not significant. Subjects with DiNCH levels below analysis LOD were excluded from regression models including DiNCH, as they made up 40.0% of cases, resulting in lower

Table 3 Dust levels of phthalates and DiNCH ($\mu\text{g/g}$) expressed as adjusted LSGMs (95% CI) for 428 infants with or without parent reported croup.

	Adjusted LSGMs (95% CI) ^a		<i>p</i> Value ^b
	No croup (<i>n</i> = 435)	Croup (<i>n</i> = 47)	
DEP	1.0 (0.9–1.2)	1.7 (1.1–2.6)	0.04
DiBP	5.9 (5.4–6.5)	6.4 (4.8–8.6)	>0.5
DnBP	13.1 (11.4–15.0)	14.9 (9.9–22.5)	>0.6
BBzP	17.0 (15.1–19.3)	22.6 (15.5–33.1)	0.02
DEHP	126.9 (115.2–139.9)	172.8 (128.0–233.2)	0.006
DiNP	22.4 (19.5–25.7)	18.3 (12.0–28.0)	>0.6
DPHP	1.6 (1.5–1.8)	1.3 (0.9–1.9)	>0.6
DiNCH ^c	1.6 (1.5–1.6)	1.6 (1.4–1.8)	>0.3

^aAdjusted for sex of child, asthma or allergy in family, mother's age, mother's education, mother's smoking and dust sampling season. Statistics for phthalate levels include subjects where analysis results below LOD were substituted for a value equal to the LOD/ $\sqrt{2}$.^bFor test of difference between infants with or without reported croup.^cFor DiNCH $n = 298$ of which 25 were from homes with reported infant croup. Results below LOD were excluded as they made up a substantial 40% of cases.

statistical power for DiNCH results than for the phthalates. The remaining cases ($n = 298$) included 25 infants (9.2%) with reported croup of which four were girls. Other attributes were similar to the full study population.

In crude analysis, significant associations between infant croup during the first 12 months and phthalate levels in dust were found for DEP and DEHP (OR = 1.76; 95% CI: 1.13–2.73 and OR = 2.18; 95% CI: 1.09–4.34, respectively) (Table S2). In crude models stratified for sex of child, significant positive association ($p < 0.05$) between croup and dust levels of DEP, BBzP and DEHP were found in boys, while no significant associations were found in girls. After adjusting regression models for covariates, associations between DEP and DEHP levels in dust and croup remained significant as shown in Fig. 1 (details in Supplementary Information Table S2). For boys, significant positive associations were found between croup and dust levels

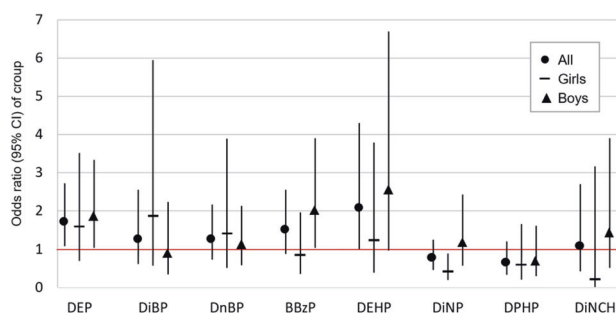


Fig. 1 Associations between seven phthalates and DiNCH dust levels and croup at 12 months expressed as adjusted odds ratios and 95% CI, for all children and stratified by sex. Models assessing phthalates included 482 infants. For DiNCH, $n = 298$ as samples with levels below analysis limit of detection were excluded. All models were adjusted for sex of child, asthma or allergy in family, mother's age, mother's education, mother's smoking and dust sampling season.

of DEP (aOR = 1.86; 95% CI: 1.04–3.34) and BBzP (aOR = 2.02; 95% CI: 1.04–3.90) whilst for girls a significant negative association to DiNP (aOR = 0.42; 95% CI: 0.19–0.89) was found in adjusted models. No associations were found between DiBP, DnBP, DPHP or DiNCH and croup neither in crude nor in adjusted models. When interaction terms between exposure levels and sex of child were introduced into the adjusted models no significant interactions between sex and either DEP, BBzP or DEHP levels were found suggesting no interaction effect (data not showed).

Indication for a dose–response relationship was found for DEHP when dust levels were categorised into quartiles (Table 4). The odds of reporting infant croup increased by 191% for subjects with DEHP levels in the upper compared to the lower 25th percentile. No significant odds differences were found for any of the other seven compounds and croup in quartile analysis, nor any compound when these models were stratified by sex of child (Table 4).

Discussion

We have found significant associations between reports of infant croup and residential dust levels of the phthalates DEP and DEHP. Croup was twice as common among boys than girls, and in stratified models dust levels of DEP and BBzP were significantly associated with infant croup in boys. Due to few cases, the stratified results for girls have questionable statistical power.

To our knowledge, associations between infant croup and phthalate dust levels have not been reported previously, however, there is epidemiological support for effects of phthalate dust exposure on other airway symptoms in children. Predisposing factors for croup include inflammatory related conditions such as a tendency for submucosal

swelling and airway hyper-reactivity which are also relevant factors in conditions such as asthma and wheeze [21, 22]. In the Swedish Dampness in Buildings and Health (DBH) study, significant cross-sectional associations were found between airway symptoms in children 3–6 years old and dust levels of DEHP and BBzP [23]. And also in the Bulgarian DBH study cross-sectional associations between DEHP levels in dust and wheeze were found in preschool children [11]. Furthermore, a report from Taiwan linked increased residential dust levels of BBzP to school children suffering from asthma or allergy [24]. Research from the US linked dust levels of DEHP to asthma severity [12] as well as dust levels of DnBP and DiBP with bronchial asthma along with atopic dermatitis [25]. A systematic review and meta-analysis combining results of nine epidemiological studies, of which two assessed phthalate exposure in postnatal residential dust, five assessed child and/or prenatal maternal urine and one assessed both postnatal residential dust and child urine, found a positive association between childhood asthma and exposure to DEHP and BBzP in dust [10].

Regarding exposure to DEP in dust the picture is not that clear. Instead, cross-sectional associations between urinary DEP metabolite levels and asthma in boys aged 8 years [26], and exhaled airway inflammation biomarker nitric oxide in children aged 5–11 years [27] have been reported in studies from the US. In the SELMA study, we have found significant associations between first trimester maternal urine phthalate metabolite concentrations of BBzP and DEHP and croup at 12 months in boys [16].

The present association between residential dust levels of phthalates and croup during the first year of life should in the first place be interpreted as an indication of altered early life airway inflammatory response. Experimental results from human lung epithelial cells and animal airway models suggest DEHP exposure can influence the inflammatory reactivity of the airways [9, 28]. Results from experimental studies of other phthalates are fewer and less conclusive [9, 10, 28]. Although biological mechanisms explaining these inflammatory effects have not yet been fully identified, some evidence of how phthalates may contribute to airway symptoms have been presented. These include interference with peroxisome proliferation activated receptors (PPARs) and alterations of tumour necrosis factor- α (TNF- α) levels and other inflammatory cytokines [9, 10, 28]. Such receptors and cytokines are important in early inflammatory cell responses, which are relevant to asthma pathology [28].

Dust levels of DEHP, the commercially most widely used plasticiser [1], was the most dominant out of the eight compounds included in this study. Similar results are frequently reported globally [1, 2]. Median levels of BBzP and in particular DEP are generally found to be lower in indoor

Table 4 Associations between dust levels of phthalates or DiNCH in quartiles and croup at 12 months in 482 infants reported as adjusted odds ratios (95% CI) with the first quartile as reference.

Compound	Adjusted ^a odds ratio (95% CI)					
	All	<i>p</i> Value	Girls	<i>p</i> Value	Boys	<i>p</i> Value
DEP						
Quartile 2 vs. 1	0.40 (0.12–1.36)	>0.1	0.66 (0.10–4.33)	>0.6	0.26 (0.05–1.42)	>0.1
Quartile 3 vs. 1	1.51 (0.61–0.73)	>0.3	1.73 (0.37–8.02)	>0.4	1.41 (0.45–4.41)	>0.5
Quartile 4 vs. 1	2.21 (0.93–5.24)	0.07	2.07 (0.46–9.25)	>0.3	2.31 (0.78–6.86)	>0.1
DiBP						
Quartile 2 vs. 1	0.76 (0.30–1.95)	>0.5	0.66 (0.08–5.27)	>0.6	0.83 (0.28–2.46)	>0.7
Quartile 3 vs. 1	1.51 (0.65–3.49)	>0.3	2.25 (0.41–12.34)	>0.3	1.21 (0.45–3.30)	>0.7
Quartile 4 vs. 1	1.07 (0.43–2.66)	>0.8	1.85 (0.34–10.16)	>0.4	0.71 (0.22–2.33)	>0.5
DnBP						
Quartile 2 vs. 1	1.06 (0.42–2.65)	>0.9	1.39 (0.21–9.25)	>0.7	0.96 (0.33–2.81)	>0.9
Quartile 3 vs. 1	1.35 (0.56–3.30)	>0.5	2.57 (0.44–14.97)	>0.2	1.09 (0.37–3.21)	>0.8
Quartile 4 vs. 1	1.34 (0.55–3.26)	>0.5	2.36 (0.43–13.06)	>0.3	0.89 (0.29–2.68)	>0.8
BBzP						
Quartile 2 vs. 1	1.01 (0.41–2.50)	>0.9	0.42 (0.07–2.35)	>0.3	2.04 (0.62–6.65)	>0.2
Quartile 3 vs. 1	0.95 (0.39–2.36)	>0.9	0.29 (0.05–1.56)	>0.1	2.12 (0.65–6.94)	>0.2
Quartile 4 vs. 1	1.35 (0.57–3.21)	>0.4	0.58 (0.16–2.06)	>0.4	2.45 (0.73–8.23)	>0.1
DEHP						
Quartile 2 vs. 1	2.08 (0.72–5.99)	>0.1	2.63 (0.48–14.37)	>0.2	1.48 (0.37–6.00)	>0.5
Quartile 3 vs. 1	2.19 (0.78–6.13)	>0.1	1.25 (0.19–8.45)	>0.8	2.42 (0.69–8.51)	>0.1
Quartile 4 vs. 1	2.91 (1.07–7.90)	0.04	1.84 (0.33–10.41)	>0.4	3.16 (0.92–10.85)	0.07
DiNP						
Quartile 2 vs. 1	0.94 (0.38–2.31)	>0.8	0.52 (0.12–2.35)	>0.4	1.59 (0.46–5.53)	>0.4
Quartile 3 vs. 1	0.80 (0.31–2.06)	>0.6	0.41 (0.09–1.87)	>0.2	1.35 (0.36–5.03)	>0.6
Quartile 4 vs. 1	1.20 (0.50–2.90)	>0.6	0.58 (0.14–2.35)	>0.4	2.00 (0.57–6.99)	>0.2
DPHP						
Quartile 2 vs. 1	0.41 (0.16–1.01)	0.05	0.39 (0.09–1.72)	>0.2	0.49 (0.15–1.57)	>0.2
Quartile 3 vs. 1	0.46 (0.20–1.08)	0.08	0.10 (0.01–0.85)	0.04	0.75 (0.27–2.07)	>0.5
Quartile 4 vs. 1	0.58 (0.26–1.32)	>0.2	0.55 (0.15–2.02)	>0.3	0.63 (0.22–1.84)	>0.4
DiNCH^b						
Quartile 2 vs. 1	0.36 (0.08–1.58)	>0.1	1.16 (0.02–59.72)	>0.9	0.26 (0.05–1.46)	>0.1
Quartile 3 vs. 1	1.01 (0.31–3.30)	>0.9	6.41 (0.06–653.70)	>0.4	0.93 (0.26–3.38)	>0.9
Quartile 4 vs. 1	1.00 (0.29–3.47)	1.00	0.00	1.00	1.44 (0.38–5.46)	>0.5

^aAdjusted for sex of child, asthma or allergy in family, mother's age, mother's education, mother's smoking and dust sampling season.

^b*n* = 298, excluding subjects with DiNCH dust levels below the detection limit.

dust compared to other phthalates [2]. Non-phthalate plasticiser DiNCH was the least frequently detected compound of our study. DiNCH was also the only compound with a negative correlation with dust levels of DEHP, although it was weak (-0.09 , $p < 0.05$). This is likely to reflect the late introduction of DiNCH as a replacement for DEHP in 2002 [1, 29, 30]. Compared to earlier studies such as the Swedish DBH study in which dust was collected 2001–2002 [23], we found lower median levels of DEHP, which is likely reflecting the increased substitution of DEHP to other plasticisers during the time period [2]. The median levels of

BBzP and DEHP reported here are similar to those detected in a smaller but similar Swedish study [31], although our levels of DEP were slightly lower.

Lifestyle differences such as ventilation habits and use of phthalate emitting products could influence phthalate dust levels in individual homes. Such factors will contribute to variations of phthalate levels in dust both between and within studies [2, 32]. Seasonal variations resulting in increased dust levels of DEHP during the winter season has been reported previously, and is a result of differences in air flow rates, moisture, temperature and personal habits [12]. Assessing

phthalate levels in residential dust during the first year after birth may be more representative of indoor exposure compared to similar studies of older children who also attend day-care or school, as higher phthalate levels have been detected in Swedish preschool dust compared to residential dust [31].

Phthalate exposure has previously been associated with socioeconomic status [33]. The participants of the SELMA study were found less likely to smoke and more likely to have a higher education than the general population in the area [18], two potential indicators of higher socioeconomic status [34, 35]. Participants were also more likely to have asthma or allergy in the family. Children in this study may therefore be exposed differently to phthalates and more likely to suffer from airway symptoms than Swedish children in general. However, this selection bias should not impact the associations between phthalate exposure and croup reported in this study.

Although phthalate exposure from dust and air are generally considered to make small contributions to total phthalate uptake in humans, this exposure may be of more importance for airway disease pathogenesis compared to other health outcomes [9]. According to Bekö et al. [5] dust ingestion and inhalation contributes to 2% of BBzP and 8% of DEHP uptake, whilst dust and air exposure is a more dominant contributor to DEP uptake in young children [5, 36, 37]. Children are spending more time on the floor and display different behaviours than adults resulting in greater dust exposure from both ingestion and inhalation [2, 8]. Phthalate levels in dust may represent local lung and airway phthalate exposure differently than urinary phthalate metabolite levels, which reflect combined uptake from all exposure routes of which diet is generally considered the most dominant [5, 9, 38]. Potential differences between local airway diester exposure and systemic monoester exposure following uptake and phthalate metabolism should also be considered when comparing results from dust exposure and biomarker studies [6, 9]. Such exposure differences might partly explain the significant associations between croup and DEP dust levels of this study, compared to the non-significant relationship between croup and prenatal DEP urine metabolite levels in mothers we previously reported [16].

The current study population is a smaller subset taken from the same population as our previous study, in which prenatal exposure to BBzP and DEHP was found to associate with infant croup. We believe the associations reported in this study are independent of the previous result. Although uptake of BBzP and DEHP from dust is considered a minor contributor to total phthalate uptake in adults [6, 36], correlations between phthalate levels in residential dust and urinary phthalate metabolite concentrations of child inhabitants have been reported previously [5, 24]. Hence, as phthalates in settled dust can

reach steady-state levels that can remain stable over long periods [39], the maternal phthalate metabolite concentrations detected during early pregnancy may be related to the postnatal dust levels. Both these exposure routes have been linked to child airway disease [10], and some of the association between infant croup and postnatal dust levels of DEHP and BBzP reported in this study may be explained by the prenatal exposure. However, the small contribution from dust to total phthalate uptake in adults suggest this would not be a significant reason for the similar results in the two studies. Still, it highlights the need to explore further differences and possible synergistic effects between prenatal and postnatal phthalate exposure effects on children's health.

Previous research suggests that prenatal phthalate exposure may cause different health effects than airway exposure of the same phthalates after birth [10]. Phthalates have immunotoxic properties with the ability to modify human development [10, 40]. It is still unclear during which time window of development a child is most sensitive to phthalate exposure [10, 40]. In relation to developing asthma, prenatal exposure has been suggested more potent to cause modulatory effects compared to exposure later in life [10, 40]. Both the respiratory and immune system development are initiated in early pregnancy, with both systems being sensitive to environmental pollution as they mature. However, this maturation and potential exposure effects continues during childhood [7, 41].

We found an association between an early life airway symptom and DEP, a phthalate which is currently not regulated in the EU [1, 42]. Such associations are less frequently reported compared to regulated substances BBzP and DEHP for which adverse health effects are well established [1]. Our result may indicate that airway symptoms expressed earlier in life can identify associations that other outcomes may not be specific enough to detect. However, as DEP is one of the most volatile phthalates, dust levels are more sensitive to differences in temperature and generally low compared to other phthalates, in particular DEHP [32]. These properties make dust a more challenging matrix to use when assessing associations between DEP exposure and health outcomes. To fully investigate associations between DEP and airway symptoms in children, further studies are needed.

In this study, the self-reported prevalence of croup up to 12 months is just under 10%, which is lower than the 15% previously reported by other studies [43]. As the peak incidence of croup is at the age of 2 years [17], our period prevalence numbers are more in line with epidemiological studies reporting croup until 1 year of age [21]. Although parental reports may have advantages for assessments of an often self-limiting illness not always leading to emergency care, such reports also pose limitations (in terms of

misclassification) to the clinical applicability. We found croup more common in families reporting a family history of asthma and allergy. However, we cannot say whether this is due to increased susceptibility to croup or misclassification of early asthmatic symptoms.

Stronger associations between phthalate exposure and airway symptoms in boys than in girls are in line with previous reports [16, 26]. Sex specific differences in airway responsiveness during childhood are well documented with boys being more likely to suffer from croup, asthma and wheeze [13, 17, 43]. In our study population, croup was more common in boys. We found significant positive associations between dust phthalate exposure and croup in boys but not girls, although the small number of girls with reported croup hinder us to further explore sex differences. The few cases of croup among girls also means that the significant negative association between croup and DiNP, a phthalate used to replace DEHP [1], must be interpreted cautiously, as regression models for girls have low power. Cautious interpretation is even more important for the non-significant associations between DiNCH dust levels and croup. Compared to the phthalates, DiNCH regression results are based on 60% of the study population and including 25 infants with reported croup of which four were girls only. More extensive studies are needed to investigate the effects of phthalate and DiNCH exposure on croup in girls with adequate statistical power.

Conclusion

This study adds evidence to our earlier findings on associations between early life exposure to phthalates (DEP, BBzP and DEHP) and airway problems in children, with indications of a stronger association in boys. Our results suggest that exposure to phthalates in dust may contribute to an alteration of the airway inflammatory response during early life.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Supplementary Information

Phthalate levels in indoor dust and associations to croup in the SELMA study

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1. Supplementary methods

1.1 Dust sampling equipment

All materials used during dust collection and storing were carefully sourced. Written confirmations to guarantee products free of phthalates and other substances of concern were required from the manufacturers prior the onset of dust collection. No further back-ground checks were performed as all samples were handled in the same way and using products from the same production batches.

1.2 Chemicals and Reagents

All phthalate ester standards, their corresponding D₄-labelled internal standards, were purchased from TRC Chemicals (Toronto, Canada). Hexamoll® DINCH, here referred to as DiNCH, was kindly provided by BASF, Ludwigshafen, Germany. Toluene and Acetonitrile (LC–MS grade) were purchased from Merck (Darmstadt, Germany) and formic acid from Sigma-Aldrich (St Louis, MO, USA). Water was produced by Milli-Q Integral 5 system, Millipore (Billerica, MA, USA).

1.3 Chemical analysis

1.3.1 GC-MS/MS analysis

Samples were analysed for the phthalate esters DEP, DnBP, DiBP, BzBP, DEHP, DiNP and DPHP, DINCH, according to Weiss et al. Briefly, unsieved residential dust (10 mg) was weighed into a 10 mL glass vial and 1 mL of toluene containing 50 µg of D₄-labelled internal standards (D₄-DEP, D₄-DnBP, D₄-DiBP, D₄-BzBP, D₄-DEHP, D₄-DiNP and D₄-DPHP) was added. Samples were sonicated for 30 min at maximal amplitude, centrifuged, and the supernatants were transferred to a HPLC glass vial (Agilent, Waldbronn, Germany). An extract volume of 1 µl was injected onto the GC-MS/MS. Analysis was performed using a Shimadzu GC 2010-Plus chromatograph (Shimadzu Corporation) coupled to a GC TQ8040 triple quadrupole mass

spectrometer (Shimadzu Corporation). The MS was operated in selected reaction mode (SRM) mode, as described earlier (Weiss et al. 2018).

1.3.2 Quality assurance/quality control

All glass vials and pipettes were washed with ethanol prior use to avoid phthalate contamination. Plain silica particles were extracted and analysed for background contamination, and standard reference house dust material (SRM 2585) from the National Institute of Standards and Technology (NIST) was analysed for accuracy. Average background levels of clean solvent samples (n=10) were subtracted from all quantified values. All samples were analysed in duplicates, and all quality controls and blanks were always included during all analytical runs. Excellent linearity was seen for the calibration standards ranging from 100 to 1000 ng/mL in toluene. The correlation coefficient (r^2) observed for all seven phthalate esters and DINCH was above 0.998. The analytical performance was determined by analysis of 10 different blank toluene samples spiked with internal standard. Limit of detection (LOD) for the individual compounds were DEP (7.3 ng/mL), DnBP (12 ng/mL), DiBP (8.7 ng/mL), BzBP (0.2 ng/mL), DEHP (2.1 ng/mL), DiNP (0.5 ng/mL), DPHP (0.5 ng/mL), DINCH (12 ng/mL) (Weiss et al. 2018). The instrumental performance using this method was determined by analyses of 10 toluene samples spiked to a final concentration of 100, 200 and 500 ng/ml phthalate esters each. Depending on the phthalate ester, the CV values ranged from 8-72% (100 ng/ml), 8-35% (200 ng/ml) and 2-20% (500 ng/ml). Dust sample mean values were reported as μg of phthalate esters or DiNCH per gram of dust. More details can be found in Weiss et al, 2018 (1).

1.4 Statistical analysis

Phthalate dust levels were available for 501 families and among these information on all covariates was available for 482 families. There were no significant differences between exposures, outcome or covariate data between the 501 subjects and the somewhat smaller study population. As the distribution of phthalates and DiNCH levels in dust were found right-skewed in univariate analysis, exposure data was log-10 transformed to normalise distributions and allow for parametric statistics testing.

Logistic regression models (crude and adjusted) were used to investigate the association between dust levels of phthalates or DiNCH and infant croup (dichotomous outcome) resulting in estimated odds ratios and 95% confidence intervals per one log-10 unit change in exposure dust levels. Final logistic regression models were adjusted for six variables. Bivariate analysis using Pearson's correlation, chi-square and two-tailed *t*-tests identified sex of child, asthma or allergy in family, mother's education and dust sampling season as potential confounders with significant associations to phthalate exposure and/or outcome. The covariates mother's age and smoking during pregnancy were included as potential confounders *a priori* as they are known factors relevant to child airway health (2, 3). The analysis was also stratified for sex of child.

2. Phthalate dust level correlation matrix

Table S1. Correlations between phthalates and DiNCH calculated on log10 transformed dust levels^a expressed as Pearson correlation coefficient and significance level (n=482).

	DEP	DiBP	DnBP	BBzP	DEHP	DiNP	DPHP
DiBP	0.177 ***	1					
DnBP	0.207 ***	0.201 ***	1				
BBzP	0.125 **	0.122 **	0.285 ***	1			
DEHP	0.140 **	0.102 *	0.263 ***	0.394 ***	1		
DiNP	-0.109 *	0.168 ***	-0.073 >0.1	0.076 0.09	0.235 ***	1	
DPHP	0.067 >0.1	0.188 ***	0.016 >0.7	0.049 >0.2	0.167 ***	0.429 ***	1
DiNCH	-0.111 *	0.108 *	-0.033 >0.4	0.049 >0.2	-0.093 *	0.163 ***	0.097 *

*** Correlation is significant at the 0.001 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

^a Dust samples with compound levels below analysis LOD were given a replacement value of $\text{LOD}/\sqrt{2}$.

3. Crude and adjusted odds ratios for phthalates in dust and infant croup

Table S2. Associations between seven phthalates and DINCH dust levels and croup at 12 months in 482 infants expressed as odds ratios and 95% CIs, for all children and stratified by sex

		Odds Ratio (95% CI)					
Compound		All	<i>p</i> value	Girls	<i>p</i> value	Boys	<i>p</i> value
DEP	Crude	1.76 (1.13-2.73)	0.01	1.57 (0.70-3.52)	>0.1	1.68 (0.97-2.93)	0.07
	Adjusted ^a	1.71 (1.08-2.73)	0.02	1.57 (0.70-3.52)	>0.2	1.86 (1.04-3.34)	0.04
DiBP	Crude	1.19 (0.60-2.37)	>0.6	2.22 (0.77-6.37)	>0.1	0.86 (0.34-2.18)	>0.7
	Adjusted ^a	1.25 (0.61-2.55)	>0.5	1.85 (0.57-5.95)	>0.3	0.88 (0.34-2.24)	>0.7
DnBP	Crude	1.29 (0.75-2.20)	>0.3	1.65 (0.62-4.42)	>0.3	1.10 (0.57-2.12)	>0.7
	Adjusted ^a	1.26 (0.73-2.17)	>0.4	1.41 (0.51-3.89)	>0.5	1.12 (0.58-2.14)	>0.7
BBzP	Crude	1.41 (0.85-2.35)	>0.1	1.02 (0.43-2.44)	>0.9	1.93 (1.01-3.68)	0.05
	Adjusted ^a	1.50 (0.88-2.55)	>0.1	0.83 (0.35-1.97)	>0.6	2.02 (1.04-3.90)	0.04
DEHP	Crude	2.18 (1.09-4.34)	0.03	1.58 (0.54-4.63)	>0.4	2.96 (1.14-7.68)	0.03
	Adjusted ^a	2.07 (1.00-4.30)	0.05	1.22 (0.39-3.79)	>0.7	2.55 (0.97-6.69)	0.06
DiNP	Crude	0.87 (0.55-1.38)	>0.5	0.53 (0.26-1.04)	0.07	1.26 (0.64-2.50)	>0.2
	Adjusted ^a	0.76 (0.46-1.25)	>0.2	0.42 (0.19-0.89)	0.03	1.18 (0.57-2.43)	>0.6
DPHP	Crude	0.72 (0.39-1.33)	>0.2	0.61 (0.22-1.67)	>0.3	0.75 (0.34-1.70)	>0.4
	Adjusted ^a	0.63 (0.33-1.21)	>0.1	0.59 (0.21-1.66)	>0.3	0.70 (0.30-1.61)	>0.4
DiNCH ^b	Crude	1.04 (0.41-2.62)	>0.9	0.32 (0.02-5.44)	>0.4	1.43 (0.52-3.95)	>0.4
	Adjusted ^a	1.06 (0.42-2.70)	>0.9	0.20 (0.01-3.17)	>0.2	1.42 (0.51-3.90)	>0.5

^a. Adjusted for sex, asthma or allergy in family, mother's age, mother's education, mother's smoking and dust sampling season.

^b n=298, excluding subjects with DiNCH dust levels below the detection limit.

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