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The Association Between Asthma and Allergic Symptoms in Children and Phthalates in House Dust: a Nested Case-Control Study.

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Running title

Phthalate exposure indoors and allergic symptoms

Key words

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List of abbreviations

BBzP	Butyl benzyl phthalate
CI	Confidence interval
DBH	Dampness in buildings and health
DEHP	Di(2-ethylhexyl) phthalate
DEP	Diethyl phthalate
DIBP	Diisobutyl phthalate
DINP	Di-isononyl phthalate
DnBP	Di-n-butyl phthalate
ETS	Environmental tobacco smoke
GC/MSD	Gas chromatograph/mass selective detector
GC/FID	Gas chromatograph/flame ionization detector
IAQ	Indoor air quality
IgE	Immunoglobulin E
IgG1	Immunoglobulin G1
OR	Odds ratio
PVC	Polyvinyl chloride
R	Pearson correlation coefficient
SE	Standard error of mean
T-test	Student's t-test

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ABSTRACT

Global phthalate ester production has increased from very low levels at the end of WWII to approximately 3.5 million metric tons/yr. The aim of the present paper is to investigate potential associations between persistent allergic symptoms in children, which have increased markedly in developed countries over the past three decades, and the concentration of phthalates in dust collected from their homes. This investigation is a case control study nested within a cohort of 10 852 children. From the cohort, 198 cases with persistent allergic symptoms and 202 controls without allergic symptoms were selected. A clinical and a technical team investigated each child and her/his environment respectively. We found higher median concentrations of butyl benzyl phthalate (BBzP) in dust among cases than among controls (0.15 vs 0.12 mg/g dust). Breaking the case group down by symptoms, BBzP was associated with rhinitis ($p=0.001$) and eczema ($p=0.001$) while di(2-ethylhexyl) phthalate (DEHP) was associated with asthma ($p=0.022$). Furthermore, dose-response relationships for these associations are supported by trend analyses. This study shows that phthalates, within the range of what is normally found in indoor environments, are associated with allergic symptoms in children. We believe that the different associations of symptoms for the 3 major phthalates, BBzP, DEHP and di-n-butyl phthalate (DnBP), can be explained by a combination of chemical physical properties and toxicological potential. Given the phthalate exposures of children worldwide, the results from this study of Swedish children have global implications.

INTRODUCTION

Airborne phthalate esters are present at detectable levels across the surface of the Earth. They were first identified in outdoor urban air (Cautreels and Van Cauwenberghe 1976a; 1976b), and have subsequently been recognized as global pollutants (Atlas and Giam 1981; Giam et al. 1978) and major constituents of indoor air (Weschler 1980; 1984). Their presence in outdoor and indoor environments reflects their large emission rates coupled with moderate atmospheric lifetimes. The total global consumption of phthalate esters is estimated to exceed 3.5 million metric tons/year with di(2-ethylhexyl) phthalate (DEHP) constituting roughly 50% of the market share (Cadogan and Howick 1996). Consumption of di-n-butyl phthalate (DnBP) and n-butyl benzyl (BBzP) phthalate, is smaller, but still quite large (each greater than 100000 metric tons/year) (Cadogan and Howick 1996). Although DEHP plasticizes numerous products, roughly 95% of the current production is used in polyvinyl chloride (PVC) (U S Department of Health and Human Services 2003) where it typically constitutes 30% of PVC by weight (Cadogan and Howick 1996; Kavlock et al. 2002b). DnBP is used in latex adhesives, in nail polish and other cosmetic products, as a plasticizer in cellulose plastics, as a solvent for certain dyes, and, to a lesser extent than DEHP, as a plasticizer in PVC (Kavlock et al. 2002c). BBzP is a plasticizer for vinyl tile, carpet tiles, and artificial leather and is also used in certain adhesives (Kavlock et al. 2002a).

Research groups have assessed the exposures of various populations to phthalate esters by using their metabolites in human urine as biomarkers (Barr et al. 2003; Blount et al. 2000; Centers for Disease Control and Prevention 2003; Koch et al. 2003). The biomarker results translate to daily exposures for DnBP, BBzP, and DEHP of 1.5, 0.88 and 0.71 $\mu\text{g}/\text{kg}/\text{day}$ (U.S. (Kohn et al. 2000)); 0.95, 0.71, and 0.84 $\mu\text{g}/\text{kg}/\text{day}$ (U.S. (derived from data in Table 1 of Barr et al. 2003 using the procedure outlined by Kohn et al. 2000)); and 5.22, 0.60 and 13.8

$\mu\text{g}/\text{kg}/\text{day}$ (Germany (Koch et al. 2003)). These findings confirm the relatively large daily exposure to phthalates in industrialized countries. Although the dominant route of exposure to DnBP, BBzP and DEHP is thought to be via ingestion (Fromme et al. 2004; Kavlock et al. 2002a; 2002b; 2002c), little if any population based data are available to support this statement. Indeed, a recent study has demonstrated associations between phthalate concentrations in inhaled air and urinary monoester metabolites (Adibi et al. 2003).

The incidence of asthma and allergy has increased throughout the developed world over the past thirty years (Beasley et al. 2003). The short interval over which this increase has occurred implies that it is due to changes in environmental exposures rather than genetic changes (Etzel 2003; Strachan 2000). Changes in indoor environments warrant special attention since indoor air constitutes a dominant exposure route. Increased exposures to allergens and/or adjuvants (enhancing factors) may each be partially responsible for the increase. Multidisciplinary reviews of the scientific literature on associations between indoor exposures and asthma and allergies (Ahlbom et al. 1998; Andersson et al. 1997; Bornehag et al. 2001; Schneider et al. 2003; Wargocki et al. 2002) indicate that the underlying causal factors responsible for these increases remain unknown.

The use of plasticized products and, consequently, exposures to phthalate esters has increased dramatically since the end of World War II. Phthalate esters have been suggested to act as either allergens or adjuvants (Jaakkola et al. 1999; Oie et al. 1997). Several recent studies have examined the ability of different phthalate esters to function as adjuvants in BALB/c mice injected with a known antigen. DEHP displayed an adjuvant effect with IgG1 at a concentration of 2000 mg/ml after both one and two boosters (Larsen et al. 2001b). In contrast, DnBP only showed an adjuvant effect with IgG1 after the 2nd booster (Larsen et al.

2002), and BBzP showed no adjuvant effect (Larsen et al. 2003). Consistent with these results, the monoester of DEHP showed an adjuvant effect while the monoesters of DnBP and BBzP did not (Larsen et al. 2001a)

The present study is a nested case control study on 198 symptomatic children and 202 healthy controls, including detailed clinical examinations by physicians in parallel with extensive inspections and measurements within the subjects' homes. The cases and controls were selected from the first phase (DBH-Phase I), which was a cross-sectional questionnaire soliciting health and environmental information regarding all 14077 children ages 1-6 in the county of Värmland, Sweden; responses were obtained for 10852 (Bornehag et al. 2003).

The aim of the present paper is to investigate potential associations between persistent allergic symptoms in children and the concentrations of different phthalates in dust collected from their homes.

METHODS

Inclusion criteria for cases and controls

The selection criteria for the cases in DBH – Phase II were (1) in the initial questionnaire reports of at least two symptoms of “wheezing during last 12 months without a cold”, “rhinitis during last 12 months without a cold” and “eczema during last 12 months”. In the follow up questionnaire one and a half years later they had to: (2) report at least two of three possible symptoms. Inclusion criteria for the controls were (1) no symptoms in the first questionnaire and (2) no symptoms in the follow up questionnaire. For both groups they had to: (3) have not rebuilt their homes because of moisture problems, and (4) have not changed residence since the first questionnaire. All children with at least two symptoms in the first questionnaire were

invited to the case-control study, (n=1056 corresponding to 9.7% of the total population). In the first questionnaire 5303 (48.9%) reported no airway, eye, nose or skin symptoms. Of these, 1100 children were randomly selected and invited to co-operate in the case-control study. This process ultimately yielded 198 cases and 202 controls.

Families were more inclined to participate if the child was reported to have more symptoms, if there was no smoking in the family, and if they belonged to a higher socio-economic group. A more detailed description of the selection procedure and the influence of potential selection biases is described elsewhere (Bornehag et al. Submitted).

Medical examination

The medical examination of the 400 children (3-8y) was performed during the same two weeks that the technical investigations of the homes, including dust collection, were carried out. Medical doctors examined the children and took a detailed history of each child. A blood sample was drawn from 387 children and screened for common allergens (Phadiatop[®]), timothy, birch, mugwort, cat, horse, dog, house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), and one mold (*Cladosporium*).

Physicians' diagnoses of the children agreed well with the case control status as reported in the questionnaire. All children with obvious asthma were found among cases, while two children with rhinitis and eight children with eczema were found among controls.

Furthermore, 13 cases were found to be miss-classified. In the analyses regarding case-control status, the study design has been used (i.e., the 23 miss-classified children have not been reclassified).

Building investigations

There were ten pairs of siblings among the 400 children; hence, they lived in 390 buildings. Between October 2001 and April 2002, six professional inspectors performed visual inspections and indoor air quality (IAQ) assessments, including dust sampling, in these 390 dwellings. During these investigations, a pre-established checklist was followed regarding e.g. building characteristics, mold and water damages, and surface materials.

Phthalates in dust

Samples of dust from 390 homes were collected from molding and shelves in the children's bedroom. The dust was collected on 90-millimeter membrane filters in holders made of styrene-acrylo nitrile polymer (SAN-polymer) mounted on a sampler made of polypropylene (VacuuMark Sampler) connected to a vacuum cleaner. The filter was weighed before and after sampling under controlled conditions. Conditioning the filters before weighing (23 °C, 50% RH) was critical to obtaining reproducible filter weights. From the 390 homes there were 9 missing samples, 13 samples with errors in the laboratory analysis and 6 samples with a negative dust weight. Consequently, there were 362 valid samples. Only filters with a reliably measurable net increase in weight (25 mg or larger) were included in the present analysis; 346 out of the 362 dust samples met this criterion.

The dust samples were extracted in pre-cleaned 10 ml glass vials for 30 minutes using 2 ml of dichloromethane. This procedure was repeated, and the two extracts were then combined and transferred to 3 ml autosampler vials. Aliquots from these vials were injected into either a gas chromatograph/mass selective detector (GC/MSD) for phthalate identification or a gas chromatograph/flame ionization detector (GC/FID) for quantitation. Gas chromatography was performed using a 25 meter capillary column (HP 1C, id 0.2 mm, stationary phase

polydimethyl siloxane). The injector temperature was 280 °C; column temperature started at 100 °C for three minutes and then increased at 8 °C/minute to 300 °C, which was maintained for 20 minutes. The detector temperature and transfer line to the MSD were maintained at 280 °C. The analytical and field sampling techniques were tested in a pre-project that found only limited influence from background contributions to the analyzed samples. In the current study field blanks have indicated no significant background contributions. The dust concentrations (mg/g dust) of six phthalates were determined: diethyl phthalate (DEP), diisobutyl phthalate (DIBP), di-n-butyl phthalate (DnBP), butyl benzyl phthalate (BBzP), di(2-ethylhexyl) phthalate (DEHP) and di-isononyl phthalate (DINP).

Statistical method

The concentrations of phthalates in the dust were log-normally distributed. Hence, analyses of potential associations between concentrations of phthalates in dust and health outcomes have been conducted using non-parametric tests (Mann-Whitney U). Log-transformed, normally distributed concentrations were tested with parametric tests (T-test). The concentrations are reported as medians, as arithmetic means and as geometric means with 95% confidence intervals (CI). The confidence intervals were calculated with a back-transform of mean log – 2*Standard Error (SE) and mean log +2*SE. Dose-response relationships were tested by factoring the phthalate concentrations into quartiles and using both uni- and multivariate logistic regression analyses. Adjustments have been made for environmental tobacco smoke (ETS) as well as sex and age of the child, since these have been associated with asthma and allergic symptoms. Adjustments for type of building were made, since living in a privately owned single-family house was a selection factor for both cases and controls (Bornehag et al. Submitted). Indeed, cases and controls lived mainly in single-family houses (88.7%). Furthermore, the frequency of PVC as flooring material was lower in single-family houses

compared with multi-family houses (51.6% vs. 71.8%). Adjustments for the construction period of the building and self reported water leakage in the home during the previous three years were made, since these are associated with the concentrations of phthalates in dust. Finally, adjustments were made for exposure to other phthalates. Multiple logistic regressions were performed by a backward elimination technique where only significant variables were included in the final model. The analyses were considered to be statistically significant when $p < 0.05$.

The study was approved by the local Ethics Committee.

RESULTS

Compared with other types of flooring materials, PVC flooring in the child's bedroom was positively associated with case-status (adjusted odds ratio (OR) 1.59; 95% CI 1.05-2.41).

Phthalates in dust

Results are presented in Tables 1-3 and Figure 1. In the upper half of Tables 1 and 2 “median” phthalate dust concentrations are reported for data sets that include all valid samples with a reliably measurable net increase in weight (346 out of 390 homes). In the lower half of Tables 1 and 2 “geometric mean” concentrations are reported for data sets that exclude samples with phthalate dust concentrations less than the detection limit. (If, instead, non-detects were assigned concentrations $\frac{1}{2}$ of the detection limit, then for phthalates with a large number of non-detects, their dust concentrations would no longer be log normally distributed). The geometric mean concentrations of BBzP and DEHP were higher in bedrooms with PVC-flooring than in bedrooms without such flooring (BBzP: 0.208 mg/g dust (n=164) vs. 0.147

(n=107), T-test: $p < 0.001$; and DEHP: 0.994 mg/g dust (n=186) vs. 0.638 (n=155), T-test: $p < 0.001$). DEP, DIBP, DnBP and DINP were not associated with PVC-flooring.

Association between phthalates in dust and health effects

Cases had a higher concentration of BBzP in the dust samples from the children's bedrooms than did the controls in parametric as well as in non-parametric tests (Table 1). Cases with physician-diagnosed rhinitis or eczema had higher BBzP concentrations in the bedroom dust compared with controls (Table 2). Furthermore, cases with doctor diagnosed asthma had higher DEHP concentrations in the dust than controls. In analyses restricted to single-family and row houses the same associations were found (data not shown).

In an analysis restricted to homes with PVC-flooring in the child's bedroom (n=189), the median BBzP concentration was significantly higher among cases compared with controls, (0.21 vs. 0.16 mg/g dust respectively; Mann-Whitney U: $p = 0.042$), and BBzP was associated with rhinitis and eczema (Table 2). Such differences between cases and controls were not observed for DEHP.

BBzP concentrations in the highest quartile were associated with an increased risk of being a "case-child" (Table 3). The same association was found after adjusting for possible confounders. Table 3 also shows associations between phthalates in dust and doctor diagnosed asthma, rhinitis or eczema. A dose-response relationship was found between concentrations of BBzP in dust and doctor-diagnosed rhinitis and eczema in both crude and adjusted analyses. For DEHP, a dose-response relationship was found for asthma in both crude and adjusted analyses, as well as in analysis restricted to single-family houses (data not shown for the latter).

Specific IgE in blood

Figure 1 examines the concentration of phthalates in dust among cases and controls with and without specific IgE in blood (i.e., atopics and non-atopics). Within the group of cases, the highest geometric mean concentrations of BBzP were found in dust from the bedrooms of atopics. However, when comparing cases with and without atopy, the difference was not statistically significant ($p=0.564$).

DISCUSSION

The present study reports associations between dust concentrations of specific phthalate esters and asthma, rhinitis and eczema. As shown in Tables 2 and 3, BBzP is significantly associated with doctor diagnosed rhinitis and eczema, while DEHP is significantly associated with doctor diagnosed asthma. Interestingly, no such associations are found for DnBP despite the fact that the median concentrations of BBzP and DnBP in the settled dust are comparable (0.150 vs. 0.135 mg/g, Table 1). Hence, these three phthalates display strikingly different associations between their dust concentrations and the health outcomes monitored in this study. From a physical chemistry viewpoint DnBP, BBzP and DEHP are significantly different from one another; they possess different vapor pressures, polarities, water solubilities and octanol/air partition coefficients. For example, the vapor pressures of DnBP and BBzP are two orders of magnitude greater than that of DEHP. This means that greater fractions of DnBP and BBzP are in the gas phase as opposed to the condensed phase (i.e., associated with dust and airborne particles). We estimate that, for a particle concentration of $20 \mu\text{g m}^{-3}$, more than 80% of airborne DnBP and BBzP are in the gas phase, while more than 85% of airborne DEHP is associated with airborne particles (Weschler 2003). The deposition of a compound in the respiratory tract is strongly influenced by whether it is present in the gas

phase or associated with airborne particles. Furthermore, as a consequence of their inherent chemical differences, DnBP, BBzP and DEHP, as well as their monoester metabolites, produce different effects in a mouse model (Larsen et al. 2001a; Larsen et al. 2001b; Larsen et al. 2002; Larsen et al. 2003). Furthermore, each of these phthalates has its distinct human metabolic pathway (Barr et al. 2003). We suspect that the different relative distributions between the gas and condensed phases, coupled with different toxicological and pharmacokinetic behaviours, contribute to the fact that DEHP and BBzP are associated with different health outcomes (i.e., DnBP/no associations; BBzP/skin and mucosa symptoms; and DEHP/lower airway symptoms).

In the present study there is a general association between PVC flooring and case status (OR 1.59). Both BBzP and DEHP correlate with the amount of PVC flooring in the subjects' homes. However, these two phthalates are not associated with health effects simply because they are associated with PVC flooring. This conclusion is supported by a number of observations. 1) Specific associations between BBzP and DEHP dust concentrations and doctor diagnosed diseases (Table 3) are more pronounced than associations between PVC flooring and such diseases. 2) Although BBzP and DEHP dust concentrations do correlate, the correlation is weak ($R=0.52$) and they are associated with different health effects. 3) In a restricted analysis, including only homes with PVC flooring, higher concentrations of BBzP were found in dust from case homes than in control homes.

The reported concentrations of phthalates in the bedroom dust (Table 1) are consistent with those reported in other studies. In dust samples from 120 U.S. homes located on Cape Cod (Rudel et al. 2003), the median concentrations were 0.34, 0.045 and 0.020 mg/g dust for DEHP, BBzP and DnBP, respectively. In a study of 59 Berlin apartments (Fromme et al.

2004), the median concentrations were 0.70, 0.030 and 0.047 mg/g dust for DEHP, BBzP and DnBP. (Clausen et al. 2003) measured mean DEHP concentrations of 3.2 mg/g dust in 15 Danish schools and 0.86 mg/g dust for 23 Danish homes. Oie and colleagues reported mean concentrations of 0.64 mg DEHP/g dust and 0.11 mg BBzP/g dust for 38 homes in Norway (Oie et al. 1997). Pöhner and co-workers reported a 95th percentile DEHP concentration of 2.0 mg/g dust for 272 German homes (Pöhner et al. 1997), while another German study on 286 homes reported a 95th percentile DEHP concentration of 2.6 mg/g dust (Butte et al. 2001).

Regarding atopic status and its association with phthalate dust concentrations, the chosen study design is not optimal. Since there were only 16 atopic controls, the power of the analysis on atopic children is limited. On the other hand, our findings could be interpreted to mean that the mechanism is of a non-immunological nature (e.g., exposure increases the risk for irritation).

In order to identify potential selection biases in the study group, information for all invited families were obtained from the first cross-sectional questionnaire as described elsewhere (Bornehag et al. Submitted). This revealed that the final study group contained significantly more single family houses than the eligible population. Adjusting and restricting the analyses have addressed this problem. There was no selection bias regarding PVC flooring since included and non-included cases and controls reported about the same frequency of occurrence of PVC flooring in the child's bedroom (Bornehag et al. Submitted). Furthermore, 10 controls and 13 cases were misclassified when comparing self reported symptoms and doctors diagnoses. However, when these children were excluded from the analyses the reported associations remained. Finally, we note that to be included as a "case" a child was

required to have at least two symptoms. Consequently, this study was not fine-tuned to examine associations between building factors and *single* symptoms (i.e. asthma, rhinitis or eczema). However, even if the design is sub-optimal, meaning harder to find associations between single symptoms and exposures, the associations between selected building factors and single symptoms is meaningful and possibly underestimates true associations.

The reported analyses are based on samples with a weight above 25 mg. However, when including all samples (n=362) the reported associations between exposure and symptoms remained or became stronger (data not shown).

Koo et al. (2002) present weak associations between exposure estimates for different phthalate esters, based on their urinary biomarkers, and the level of education, family income and residency (urban or rural) in a reference U.S. population. Given this study, one might speculate that the associations reported in the current study are driven by demographic factors. However, in contrast to the United States, where 22.4% of the children live in households with incomes less than 50% of the national median, in Sweden only 2.6% of the children live in such households (Unicef 2000). Additionally, the association in our study holds when the analysis is restricted to single family houses; such homes have an even more homogeneous socio-economic status. Hence, different demographic factors between cases and controls appear to be an unlikely explanation for the associations observed in the current study. Furthermore, given that the dust concentrations of DnBP, BBzP and DEHP display quite different associations with different symptoms, the associations reflect a biological response rather than just life-style or demographic factors associated with an increased use of plasticized materials.

This study demonstrates associations between BBzP and DEHP concentrations in dust and selected allergies and asthma. While there are likely multiple factors responsible for the increases in allergies and asthma that have been documented in developed countries over the past 30 years, it is striking that these increases have occurred during a period when plasticized products have become ubiquitous in the homes, schools and workplaces of the developed world.

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Table 1 Concentrations of phthalates in surface dust from children's bedrooms.

Phthalate	Number of homes ^a	Median (Arithmetic Mean) Concentration of Phthalates (mg/g dust)					Test
		All Samples (n=346)	Cases (n=175) ^b		Controls (n=177) ^b		
DEP	346	0.000 (0.031)	0.000 (0.046)		0.000 (0.018)		0.628
DIBP	346	0.045 (0.097)	0.042 (0.102)		0.048 (0.092)		0.424
DnBP	346	0.150 (0.226)	0.150 (0.228)		0.149 (0.220)		0.914
BBzP	346	0.135 (0.319)	0.152 (0.472)		0.118 (0.163)		0.014
DEHP	346	0.770 (1.310)	0.828 (1.384)		0.723 (1.229)		0.160
DINP	346	0.041 (0.639)	0.000 (0.671)		0.047 (0.589)		0.848
	Number of homes ^c	Geometric Mean Concentration of Phthalates (95% CI) (mg/g dust)					T-test ^d (p-value)
		All samples	Cases		Controls		
			n		n		
DEP	47	0.073	22	0.102 (0.049-0.211)	26	0.058 (0.035-0.097)	0.200
DIBP	290	0.056	141	0.058 (0.048-0.070)	154	0.055 (0.046-0.065)	0.635
DnBP	308	0.174	158	0.171 (0.152-0.193)	154	0.178 (0.157-0.201)	0.639
BBzP	272	0.181	139	0.209 (0.180-0.244)	137	0.157 (0.139-0.178)	0.004
DEHP	343	0.789	173	0.836 (0.724-0.964)	176	0.741 (0.643-0.855)	0.232
DINP	175	0.451	87	0.453 (0.352-0.583)	90	0.446 (0.351-0.566)	0.925

- a) Number of homes with a dust sample weight above 25 mg.
- b) The sum of cases and controls is 352 since, among the 346 bedrooms, there were 6 bedrooms shared by siblings.
- c) Number of homes with a dust sample weight above 25 mg and a phthalate concentration greater than the detection limit (0.040 mg/g dust for DnBP, BBzP and DEHP).
- d) Test of the difference between cases and controls made on mean log transformed concentration.

Table 2 Concentration of phthalates (BBzP and DEHP) in surface dust for case children with a doctor diagnosed disease compared with controls.

Phthalate	Disease	Cases ^a		Controls		Test
All homes						
		n	Median conc. (mg/g dust)	n	Median conc. (mg/g dust)	Mann Whitney U (p-value)
BBzP	Asthma	106	0.152	177	0.118	0.064
	Rhinitis	79	0.181	177	0.118	0.007
	Eczema	115	0.181	177	0.118	0.001
DEHP	Asthma	106	0.899	177	0.723	0.008
	Rhinitis	79	0.783	177	0.723	0.383
	Eczema	115	0.844	177	0.723	0.111
			Geometric mean conc. (95% CI) (mg/g dust)		Geometric mean conc. (95% CI) (mg/g dust)	T-test ^b (p-value)
BBzP	Asthma	82	0.219 (0.177-0.270)	137	0.157 (0.139-0.178)	0.005
	Rhinitis	65	0.237 (0.185-0.304)	137	0.157 (0.139-0.178)	0.001
	Eczema	95	0.224 (0.186-0.269)	137	0.157 (0.139-0.178)	0.001
DEHP	Asthma	106	0.966 (0.807-1.156)	176	0.741 (0.643-0.855)	0.022
	Rhinitis	78	0.811 (0.638-1.030)	176	0.741 (0.643-0.855)	0.510
	Eczema	115	0.855 (0.721-1.014)	176	0.741 (0.643-0.855)	0.207
Homes with PVC flooring in the child's bedroom						
		n	Median conc. (mg/g dust)	n	Median conc. (mg/g dust)	Mann Whitney U (p-value)
BBzP	Asthma	59	0.195	82	0.159	0.168
	Rhinitis	45	0.216	82	0.159	0.008
	Eczema	70	0.216	82	0.159	0.003
DEHP	Asthma	59	1.006	82	0.855	0.149
	Rhinitis	45	0.792	82	0.855	0.924
	Eczema	70	0.904	82	0.855	0.379
			Geometric mean conc. (95% CI) (mg/g dust)		Geometric mean conc. (95% CI) (mg/g dust)	T-test ^b (p-value)
BBzP	Asthma	52	0.237 (0.177-0.316)	71	0.177 (0.148-0.212)	0.076
	Rhinitis	43	0.265 (0.192-0.366)	71	0.177 (0.148-0.212)	0.018
	Eczema	66	0.257 (0.204-0.324)	71	0.177 (0.148-0.212)	0.011
DEHP	Asthma	59	1.148 (0.904-1.459)	82	0.938 (0.752-1.169)	0.228
	Rhinitis	44	1.040 (0.771-1.403)	82	0.938 (0.752-1.169)	0.586
	Eczema	70	1.045 (0.845-1.291)	82	0.938 (0.752-1.169)	0.491

a) Cases with doctor diagnosed disease (asthma or rhinitis or eczema).

b) Test of the difference between cases and controls made on mean log transformed concentration.

Table 3 Associations between phthalates (BBzP and DEHP) in surface dust and case status or doctor diagnosed disease. Association expressed as crude and adjusted odds ratio (OR) with 95 % confidence interval.

Group ^a	OR (95% CI)				p-value ^b
	1 th quartile REF (n=88)	2 th quartile (n=88)	3 th quartile (n=88)	4 th quartile (n=88)	
BBzP					
Ranges (mg BBzP/g dust)	<i>0.00-0.05</i>	<i>0.05-0.13</i>	<i>0.13-0.25</i>	<i>0.25-45.55</i>	
Crude analysis					
Case status	1.0	0.69 (0.38-1.26)	1.00 (0.55-1.81)	2.01 (1.10-3.69)	0.012
-Asthma	1.0	0.63 (0.31-1.27)	0.59 (0.45-1.76)	1.92 (0.98-3.79)	0.039
-Rhinitis	1.0	0.85 (0.38-1.89)	1.12 (0.51-2.47)	2.69 (1.26-5.76)	0.006
-Eczema	1.0	0.74 (0.36-1.52)	1.44 (0.73-2.81)	2.52 (1.26-5.00)	0.002
Adjusted ^c analysis					
Case status	1.0	0.77 (0.40-1.46)	1.01 (0.53-1.90)	1.95 (1.02-3.74)	-
-Asthma	1.0	0.67 (0.33-1.38)	0.88 (0.43-1.80)	1.87 (0.92-3.81)	-
-Rhinitis	1.0	1.03 (0.44-2.39)	1.23 (0.53-2.88)	3.04 (1.34-6.89)	-
-Eczema	1.0	0.84 (0.40-1.76)	1.45 (0.71-2.97)	2.56 (1.24-5.32)	-
DEHP					
Ranges (mg DEHP/g dust)	<i>0.00-0.46</i>	<i>0.46-0.77</i>	<i>0.77-1.30</i>	<i>1.30-40.46</i>	
Crude analysis					
Case status	1.0	0.91 (0.50-1.65)	1.05 (0.58-1.89)	1.44 (0.80-2.61)	0.199
-Asthma	1.0	1.11 (0.53-2.31)	1.51 (0.74-3.07)	2.36 (1.17-4.75)	0.009
-Rhinitis	1.0	1.12 (0.53-2.36)	0.96 (0.44-2.11)	1.55 (0.73-3.28)	0.331
-Eczema	1.0	1.00 (0.50-1.97)	1.35 (0.70-2.62)	1.50 (0.76-2.96)	0.161
Adjusted ^c analysis					
Case status	1.0	ns	ns	ns	-
-Asthma	1.0	1.56 (0.70-3.46)	2.05 (0.94-4.47)	2.93 (1.36-6.34)	-
-Rhinitis	1.0	ns	ns	ns	-
-Eczema	1.0	ns	ns	ns	-

- a) Case status and subgroups with asthma, rhinitis or eczema compared with controls.
- b) Linear-by-Linear Association.
- c) Adjustments made for sex, age, smoking at home, type of building, construction period, self reported flooding during last three years and the other phthalate variable (in quartiles). Method: Backward elimination. Only significant variables included in the final model.

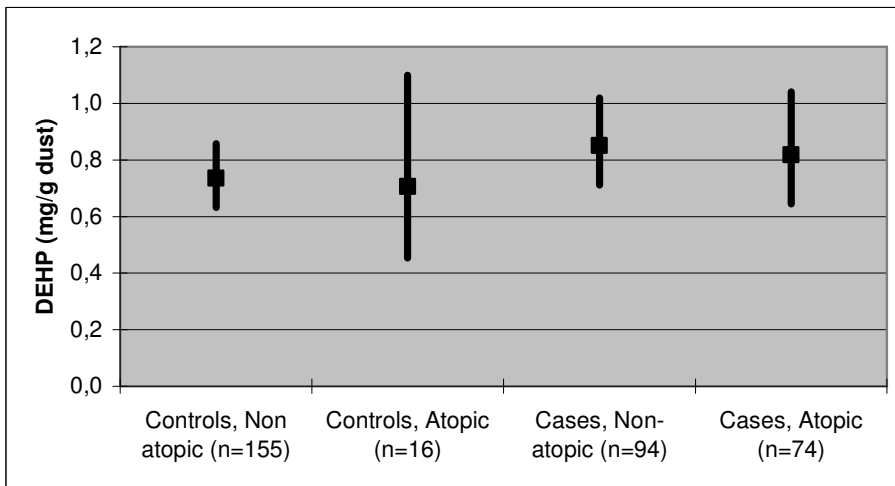
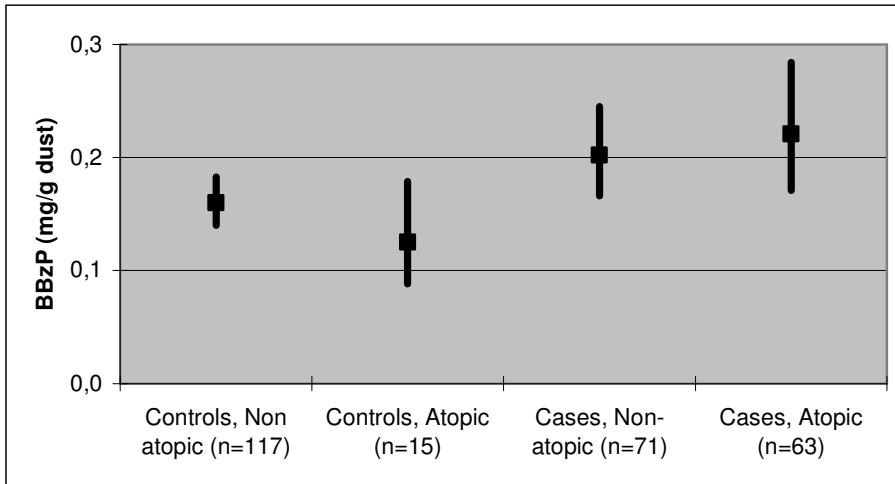


Figure 1 Geometric mean concentrations (95% CI) of phthalates (BBzP and DEHP) in surface dust from bedrooms of non-atopic and atopic children.