



Longitudinal effect of phthalates exposure on allergic diseases in children

Daniela Podlecka, MD, PhD^{*}; Jolanta Gromadzińska, PhD[†];
Karolina Mikołajewska, MSc[†]; Beata Fijałkowska, PhD^{*}; Iwona Stelmach, MD, PhD^{*};
Joanna Jerzynska, MD, PhD^{*}

^{*} Department of Pediatrics and Allergy, Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland

[†] Department of Biological and Environmental Monitoring, Nofer Institute of Occupational Medicine, Lodz, Poland

ARTICLE INFO

Article history:

Received for publication January 9, 2020.

Received in revised form February 11, 2020.

Accepted for publication March 17, 2020.

ABSTRACT

Background: Environmental chemicals, such as phthalates, phenols, and parabens, may affect children's immune development and contribute to the risk of atopic diseases and asthma.

Objective: To evaluate the associations between prenatal and childhood phthalate exposure and atopic diseases in children at the age of 9 years.

Methods: This analysis is restricted to 145 mother-child pairs from the prospective Polish Mother and Child Cohort Study. Phthalate metabolite levels were assessed in the urine samples collected from mothers during the third trimester of pregnancy and from children at age of 2 and 9 years. For the appropriate recognition of children's health status, a questionnaire was administered to the mothers and completed with information from the medical record of each child. The clinical examination was performed by a pediatrician/allergist in the presence of the mother or a relative.

Results: A higher urine concentration of mono-2-ethyl-5-oxohexyl phthalate increased the risk of food allergy in children at the age of 9 years (odds ratio [OR], 1.75; 95% CI, 1.19–2.57; $P = .004$) and decreased the risk of atopic dermatitis (OR, 0.49; 95% CI, 0.27–0.87; $P = .02$). For mono-2-ethyl-5-hydroxyhexyl phthalate, an increased risk of atopic dermatitis was observed (OR, 1.90; 95% CI, 1.18–3.05; $P = .008$). A higher urine concentration of mono-benzyl phthalate increased the risk of asthma in children (OR, 1.67; 95% CI, 1.08–2.58; $P = .02$), but the risk of asthma decreased when the concentration of mono-2-ethylhexyl phthalate was higher (OR, 0.64; 95% CI, 0.43–0.97; $P = .04$).

Conclusion: Our study has not provided clear evidence of the negative effect of phthalate exposure during pregnancy and within the 9 years after birth on allergic diseases in children.

© 2020 American College of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Environmental chemicals, such as phthalates, phenols, and parabens, may affect children's immune development and contribute to the risk of atopic illness and asthma.^{1,2} Phthalates are commonly used as stabilizers and plasticizers in cosmetics, personal care products, plastics, toys, medical equipment, food packing, and building materials.^{3,4} Phthalates are divided into 2 distinct groups. The first group, high-molecular-weight phthalates as

di(2-ethylhexyl) phthalate (DEHP) or diisononyl phthalate, are added to flooring, roofing, toys, packing materials, and clothing. The second group, low-molecular-weight phthalates as diethyl phthalate and di-n-butyl phthalate, are used in adhesives, detergents, cosmetics, tablet coatings, capsules, and personal care products. People are exposed to these compounds in several ways, including orally (food and water) and through inhalation and skin contact (care products), often in a complex combination of various exposure sources and routes.^{5,6} Phthalates are quickly metabolized, and their metabolites (monoesters and oxidized monoesters) are excreted in urine. These metabolites are considered relevant indicators of phthalate exposure and have been successfully used as biomarkers of exposure in many studies.^{4,7}

Widespread exposure to phthalates has prompted investigations concerning their potential adverse health effects.^{7,8} Animal studies on phthalates suggest associations between

Reprints: Joanna Jerzynska, MD, PhD, Department of Pediatrics and Allergy, Medical University of Łódź, Copernicus Memorial Hospital, Pabianicka Street 62, 93-513 Łódź, Poland; E-mail: joanna.jerzynska@umed.lodz.pl.

Disclosures: The authors have no conflicts of interest to report.

Funding Sources: The study was performed under the project supported by grants 2017/25/B/NZ5/02338 and 2014/15/B/NZ7/00998 from the National Science Centre, Poland.

<https://doi.org/10.1016/j.anai.2020.03.022>

1081-1206/© 2020 American College of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

decreased lung function, atopic dermatitis, and an increased T helper 2 (T_H2) cell response.^{1,9,10} Activity of T_H2 lymphocytes may be involved in the biological mechanisms of asthma and aero-allergies.¹¹ In humans, prenatal exposure to phthalates has been associated with increased biomarkers of oxidative stress, poor birth outcomes, neurologic and behavioral problems, and increased risk of asthma and atopic outcomes in childhood.^{12–15}

Previous studies found that the concentrations of phthalate metabolites in urine are higher in children than in adults, which can be associated with age-specific behaviors, diet, and metabolism.^{16–22} Bamai et al.²³ found that the daily phthalate intakes estimated from urinary metabolites were higher in children than in their parents, mainly because for infants and toddlers, one of the most important phthalate intake source is floor dust.

A recent study reported phthalate exposure levels for children and adults in several countries, with children from Poland experiencing one of the highest levels among the European populations investigated.²⁴ In a previous report on our Polish Mother and Child Cohort Study (REPRO_PL) and in other reports, prenatal exposure to phthalates posed as a risk factor for food allergy in children at the age of 2 years.²⁵ Thus, the aim of this study was to evaluate the associations between prenatal and childhood phthalate exposure and child atopic diseases at the age of 9 years from the prospective REPRO_PL.

Methods

Study Design and Population

This study was based on data from REPRO_PL, a multicenter, prospective cohort study established in 2007.^{26–28} The mothers' recruitment and follow-up procedures and a complete description of the methodologic assumptions have been published elsewhere.^{26–28} In brief, women were recruited during the first trimester of pregnancy at maternity units or clinics if they fulfilled the following inclusion criteria: single pregnancy up to 12 weeks of gestation, no assisted conception, no pregnancy complications, and no chronic diseases as specified in the study protocol.²⁶ Those recruited were interviewed during pregnancy and gave their urine samples for assessment of the level of exposure to a variety of environmental factors. Two years after the child's birth, an invitation letter was sent to the mothers participating in REPRO_PL asking to have the child's health status examined. Within the next 2 weeks, a telephone call was made to schedule a mother-and-child visit at the medical center for an examination by a pediatrician/allergist.²⁷ In this study, 9 years after the child's birth, an invitation letter was sent again to the mothers, with an offer to participate in follow-up examinations on exposure (including questionnaire data and phthalates measurement in the child's urine) and child's health status assessment.²⁸ This analysis was restricted to 145 mother-child pairs from the Łódź and Legnica districts (with all 3 time points measurements). All mothers of the patients gave their written consent before the study. The study was approved by the Ethical Committee of the Nofer Institute of Occupational Medicine, Łódź, Poland, for the mothers and children aged up to 7 years and by the Medical Ethics Committee of the Medical University of Łódź, Poland, for the older children.

Assessment of Mother's and Children's Exposure to Phthalates

Selection of the phthalates and their metabolites, similar to previous studies in this field, indicate the proxy of exposure to different types of products.²⁹ Prenatal (during the third trimester of pregnancy) and childhood (at the age of 2 and 9 years) phthalate exposure to 4 phthalates was evaluated by measuring the following 6 metabolites in the urine samples: mono-ethyl

phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-benzyl phthalate (MBzP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (5OH-MEHP), and mono-2-ethyl-5-oxohexyl phthalate (5oxo-MEHP). Phthalates and their metabolites are listed in Table 1. By measuring oxidized monoesters of the phthalates, in addition to a hydrolytic one, we estimated the real extend of exposure.⁴ The analyses were performed by high-performance liquid chromatography with tandem mass spectrometry. Spot urine samples were collected into polyethylene cups and stored at –20°C until analysis, which was performed at the Nofer Institute of Occupational Medicine, Łódź, Poland. The detailed description of the methods that included limits of detection for each phthalate metabolite has been published elsewhere.^{12,25} For prenatal exposure, the maternal urinary phthalate metabolite concentrations were corrected for dilution by the urinary creatinine concentration. Because creatinine in young children is more a function of the stage of physical development rather than urine dilution, creatinine correction was not performed for phthalate assessment in the child population.^{30–32} For children at the age of 9 years, the urinary phthalate metabolite concentrations were corrected for dilution by the urinary creatinine concentration and not corrected for creatinine (both values were analyzed). Creatinine concentration was measured using the Jaffe static method with a working range of 0.05 to 5.00 g/L of creatinine.

Child Health Assessment

Children's health status was assessed at the age of approximately 24 months (range, 23–30 months) (as described

Table 1

Phthalate Compounds Included in This Study, With Metabolites and Abbreviations

Parent phthalates	Metabolites
Low molecular weight	
Dimethyl phthalate (DMP)	Mono-methyl phthalate (MMP)
Diethyl phthalate (DEP)	Mono-ethyl phthalate (MEP)
Butylbenzyl phthalate (BBzP)	Mono-benzyl phthalate (MBzP)
Di-cyclohexyl phthalate (DCHP)	Mono-cyclo-hexyl phthalate (MCHP)
Di-n-pentyl phthalate (DnPeP)	Mono-n-pentyl phthalate (MnPeP)
Di-iso-butyl phthalate (DiBP)	Mono-isobutyl phthalate (MiBP)
	2OH-mono-iso-butylphthalate (OH-MiBP)
Di-n-butyl phthalate (DnBP)	Mono-n-butyl phthalate (MnBP)
	3OH-mono-n-butyl phthalate (OH-MnBP)
High molecular weight	
Di-2-ethylhexyl phthalate (DEHP)	Mono-2-ethylhexyl phthalate (MEHP)
	Mono-2-ethyl-5-hydroxyhexyl phthalate (5OH-MEHP)
	Mono-2-ethyl-5-oxo-hexyl phthalate (5oxo-MEHP)
	Mono-2-ethyl-5-carboxypentyl phthalate (5cx-MEPP)
Di-iso-nonyl phthalate (DiNP)	7-OH-mono-methyloctyl phthalate (OH-MiNP)
	7-oxo-mono-methyloctyl phthalate (oxo-MiNP)
	7-carboxy-mono-methylheptyl phthalate (cx-MiNP)
Di-iso-decyl phthalate (DiDP)	6-OH-mono-propylheptyl phthalate (OH-MiDP)
	6-oxo-mono-propylheptyl phthalate (oxo-MiDP)
	Mono-2-7-methyl-7-carboxyheptyl phthalate (cx-MiDP)
Di-n-octyl phthalate (DnOP)	Mono-n-octyl phthalate (MnOP)
	Mono-3-carboxypropyl phthalate (MCPP) ^a

NOTE. Metabolites assessed in this study are in italics.

^aMono-3-carboxypropyl phthalate is a secondary metabolite of DnOP but also a metabolite of several high-molecular-weight and low-molecular-weight phthalates.

previously^{13,25,33–35}) and at age of 9 years. For the appropriate recognition of children's health status, a questionnaire was administered to the mothers and supplemented with information from the medical record of each child. The clinical examination was performed by a pediatrician/allergist in the presence of the mother or a relative. The allergen skin test was performed in all the children at the age of 9 years. The urine samples from the children were collected at the same time as the interview.

The first part of the questionnaire covered certain sociodemographic information. The second part of the questionnaire investigated the child's health and condition. The incidence of wheezing and any symptoms of allergy to food and inhalant allergens in addition to symptoms of atopic dermatitis were noted. This part of the questionnaire has been developed by an allergist based on recommendations from the International Study of Asthma and Allergies in Childhood and has been applied previously.²⁸ The allergist confirmed the dermatitis finding. Patients were considered to have had food allergy or atopic dermatitis if they had ever been diagnosed by a physician; wheezing was noted if the child ever wheezed. Skin prick testing and pulmonary function testing were performed among 9-year-old children as described previously.²⁸ In addition, the occurrence of allergy among family members was noted.

Confounding Factors Included in the Models

All potential confounding factors regarding parents and children, such as parental status and environmental factors, were evaluated. Details regarding confounding factors have been published previously.^{25–28,33–35}

Statistical Analysis

The investigated traits were described as measures of location (arithmetic or geometric mean) and measures of dispersion (SD and 95% CI). The categorical variables were depicted by using absolute numbers and percentages. Multivariate logistic regression models (for binary dependent variables, such as prevalence of atopic diseases) were performed to test statistical associations. When dealing with nonnormally distributed variables, robust SEs (ie, sandwich estimators) were used within a specific regression model. Spearman's rank correlation coefficients were computed to estimate associations between the concentration of phthalates or phthalate metabolites and spirometry results. All the regression models were controlled for sex, parental atopy, smoking in the study participants' domicile, keeping domestic animals, skin prick test results, spirometry, and levels of the remaining phthalates. Missing data were case-wise deleted. A *P* value less than .05 was deemed statistically significant. All the computations were performed with Stata/SE, release 14.2 (StataCorp LP, College Station, Texas).

Results

Data regarding phthalate exposure were available for 145 samples collected during the prenatal period from mothers and from children at the age of 2 years and 9 years and were included in the current analysis. The details regarding phthalate exposure levels during pregnancy and at the age of 2 years have been published previously.^{12,25} Among the children at the age of 9 years, the following median concentrations were obtained: MEHP, 3.04 ng/mL; 5OH-MEHP, 20.34 ng/mL; 5oxo-MEHP, 8.03 ng/mL; MBzP, 1.95 ng/mL; MnBP, 108.88 ng/mL; and MEP, 105.07 ng/mL. There are some statistically significant correlations between the metabolites phthalates (Table 2). The correlations between the metabolites phthalates in mothers and children at the age of 9 years are presented in Table 3. None of them are statistically significant.

A detailed description of the study cohort, including the allergen skin test results for the children, parental atopy, and parental

Table 2

Correlations Between Metabolites Phthalates

	5oxo-MEHP	MBzP	MnBP	5OH-MEHP	MEHP	MEP
5oxo-MEHP						
MBzP	$\rho = 0.637$ $P < .001$					
MnBP	$\rho = 0.107$ $P = .183$	$\rho = 0.082$ $P = .230$				
5OH-MEHP	$\rho = 0.934$ $P < .001$	$\rho = 0.629$ $P < .001$	$\rho = 0.228$ $P < .001$			
MEHP	$\rho = 0.627$ $P < .001$	$\rho = 0.449$ $P < .001$	$\rho = 0.270$ $P < .001$	$\rho = 0.720$ $P < .001$		
MEP	$\rho = 0.224$ $P = .001$	$\rho = 0.232$ $P < .001$	$\rho = 0.371$ $P < .001$	$\rho = 0.338$ $P < .001$	$\rho = 0.486$ $P < .001$	

Abbreviations: MBzP, mono-benzyl phthalate; MEHP, mono-2-ethylhexyl phthalate; MEP, mono-ethyl phthalate; MnBP, mono-n-butyl phthalate; 5OH-MEHP, mono-2-ethyl-5-hydroxyhexyl phthalate; 5oxo-MEHP, mono-2-ethyl-5-oxohexyl phthalate.

smoking, is given in Table 4. The best-to-predicted forced vital capacity values were not associated with any assayed phthalate metabolites, inclusive of their creatinine counterparts. The best-to-predicted forced expiratory volume in 1 second values were inversely correlated with the level of 5oxo-MEHP ($r = -0.430$, $P = .01$) and directly with the level of 5OH-MEHP ($r = 0.393$, $P = .03$).

Urine Levels of Phthalates in Mothers During Pregnancy, in Children at 2 and 9 Years and Food Allergy, Allergic Rhinitis, Atopic Dermatitis and Asthma

Data were analyzed longitudinally, and the concentrations of phthalate metabolites were analyzed at 3 study points (mothers' urine and children at the ages of 2 and 9 years). The incidence of atopic conditions in patients at the age of 9 years is given in Table 5 as odds ratios (ORs) of phthalate concentrations and allergic outcomes. Multifactor logistic regression with repeated measures was performed to obtain ORs. The higher urine concentration of 5oxo-MEHP increased the risk of food allergy in children at the age of 9 years (OR, 1.75; 95% CI, 1.19–2.57; $P = .004$). The higher urine concentration of 5oxo-MEHP decreased the risk of atopic dermatitis in children (OR, 0.49; 95% CI, 0.27–0.87; $P = .02$). The higher urine concentration of 5OH-MEHP increased the risk of atopic dermatitis in children (OR, 1.90; 95% CI, 1.18–3.05; $P = .008$). The higher urine concentration of MBzP increased the risk of asthma in children (OR, 1.67; 95% CI, 1.08–2.58; $P = .02$), and the risk of asthma decreased when the concentration of MEHP was higher (OR, 0.64; 95% CI, 0.43–0.97; $P = .04$).

Table 3

Correlations Between Metabolite Phthalates in Mothers and Children at the Age of 9 Years

Metabolite phthalates	Correlation
5oxo-MEHP	$\rho = -0.020$ $P = .85$
MBzP	$\rho = 0.056$ $P = .61$
MnBP	$\rho = 0.154$ $P = .16$
5OH-MEHP	$\rho = 0.086$ $P = .44$
MEHP	$\rho = -0.094$ $P = .39$
MEP	$\rho = -0.050$ $P = .65$

Abbreviations: MBzP, mono-benzyl phthalate; MEHP, mono-2-ethylhexyl phthalate; MEP, mono-ethyl phthalate; MnBP, mono-n-butyl phthalate; 5OH-MEHP, mono-2-ethyl-5-hydroxyhexyl phthalate; 5oxo-MEHP, mono-2-ethyl-5-oxohexyl phthalate.

Table 4
Descriptive Characteristics of the Study Cohort (N = 145)^a

Characteristic	Finding
Males	66 (45.52)
Food allergy	26 (17.93)
Allergic rhinitis or rhinoconjunctivitis	20 (13.79)
Atopic dermatitis	37 (25.52)
Asthma or wheezing	10 (6.90)
Skin test results	
Negative	85 (58.62)
1 Allergen	6 (4.14)
House dust mites	7 (4.83)
Animal dander	1 (0.69)
Seasonal allergens	20 (13.79)
Mites and other allergens	28 (19.31)
Parental atopy	46 (31.72)
Smoking by the parents	41 (28.28)
Pets in the domicile	77 (53.10)
Best predicted FEV ₁ , mean (SD), %	99.95 (11.83)
Best predicted FVC, mean (SD), %	99.07 (10.55)
FEV ₁ /FVC ratio, mean (SD), %	89.55 (7.49)
Creatinine, mean (SD), g/L	0.74 (0.38)

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

NOTE. Data are presented as number (percentage) of patients unless otherwise indicated.

^aMissing data were case-wise deleted.

Discussion

Previous epidemiologic studies have suggested an association between the presence of indoor polyvinyl chloride materials and increased risk of respiratory symptoms, which prompted the research on the effect of phthalate exposure on childhood allergy and asthma.^{2,35} The concentrations of phthalate metabolites in prenatal and early postnatal periods have been thoroughly discussed and compared in our previous publications.^{12,25}

Animal studies on phthalates suggest associations between decreased lung function, atopic dermatitis, and an increased T_H2 cell response because phthalates can act similar to adjuvants to IgE-dependent mechanisms.^{2,15,35} Activity of T_H2 lymphocytes may be involved in the biological mechanisms of asthma and aeroallergies, especially through the suppression of interferon- α and interferon- β expression and the stimulation of T-cell responses.^{1,25} In addition, for some phthalates, such as DEHP and dibutyl phthalate, combined exposure to phthalates and allergens can increase the levels of immunologic and inflammatory markers, including total IgE, interleukins 4, 1 β , 18, and 6, and interferon- γ levels and eosinophil counts.^{35,36} In humans, prenatal exposure to low-molecular phthalates has been associated with increased biomarkers of oxidative stress, which can lead to a broad array of clinical symptoms, including allergic conditions.^{2,12,25}

Food Allergy

We previously reported that higher urine concentrations of MBzP in mothers during pregnancy increased the risk of food allergy in children during the first 2 years of life.²⁵ This analysis found the same association for the 5oxo-MEHP metabolite at 3 study points. Children are exposed to high-molecular-weight phthalates such as DEHP and their metabolites (5oxo-MEHP) mainly by dietary intake. It would be interesting to assess whether the avoidance of packaged food and plastic food containers could decrease urine phthalates and influence the risk of food allergy in future.

Atopic Dermatitis

In our study, positive associations were found between high-molecular-weight phthalates and the metabolite 5OH-MEHP and

negative between 5oxo-MEHP concentrations at 3 study points and atopic dermatitis risk during the early school period (children at the age of 9 years). Several researchers^{14,37–40} reported that paternal exposure to MBzP was associated with eczema in 5-year-old children. They stated that there was a strong correlation between parental urinary concentrations of MBzP and early childhood eczema onset. In addition, Kim et al³⁸ found in their research performed on boys aged between 3 and 7 years that increased MnBP was significantly associated with atopic dermatitis. In previous longitudinal studies, investigators did not find an association between prenatal exposures to low-molecular-weight phthalates (those with 3–6 carbon atoms in their chemical backbone).^{15,39,41} The most common types of low-molecular weight phthalates include DEHP and dibutyl phthalate and their metabolites, which have been reported to be associated with aeroallergens or atopic dermatitis in children at the age of 5 years.^{15,38} However, in this study, the 5OH-MEHP metabolite concentration was previously higher in children with atopic dermatitis at age 9 years. Shi et al⁴² found that high-molecular-weight DEHP and low-molecular-weight DEHP were associated with increased risk of eczema in children. However, 2 birth cohort studies from Spain and Taiwan revealed no correlation between DEHP and childhood eczema.^{38,43}

Asthma

We also found a positive association between concentrations of MBzP and asthma incidence and a negative correlation between MEHP concentration and asthma incidence in the same study points. Higher levels of MBzP in the past increased the risk of asthma, and MEHP decreased the risk of asthma in children at the age of 9 years. In the Center for the Health Assessment of Mothers and Children of Salinas study, Berger et al¹² did not find an association between concentrations of low-molecular-weight

Table 5
Odds Ratios for Phthalates in the Studied Patients at 3 Study Points (Third Trimester of Pregnancy and Children at the Age of 2 and 9 Years) and Allergy Symptoms at the Age of 9 Years (N = 145)

Phthalate	OR (95% CI)	P value
Food allergy		
5oxo-MEHP	1.75 (1.19–2.57)	.004
MBzP	0.89 (0.58–1.38)	.62
MnBP	0.89 (0.57–1.38)	.60
5OH-MEHP	0.93 (0.71–1.22)	.60
MEHP	0.72 (0.48–1.08)	.12
MEP	0.65 (0.40–1.04)	.07
Allergic rhinitis		
5oxo-MEHP	1.05 (0.49–2.27)	.90
MBzP	0.88 (0.53–1.47)	.62
MnBP	1.40 (0.84–2.36)	.20
5OH-MEHP	0.84 (0.52–1.35)	.47
MEHP	1.47 (0.97–2.23)	.07
MEP	0.59 (0.32–1.07)	.08
Atopic dermatitis		
5oxo-MEHP	0.49 (0.27–0.87)	.02
MBzP	1.40 (0.89–2.20)	.15
MnBP	0.91 (0.56–1.48)	.70
5OH-MEHP	1.90 (1.18–3.05)	.008
MEHP	0.85 (0.57–1.25)	.41
MEP	1.17 (0.74–1.86)	.497
Asthma and wheezing		
5oxo-MEHP	0.59 (0.33–1.06)	.08
MBzP	1.67 (1.08–2.58)	.02
MnBP	1.32 (0.91–1.91)	.14
5OH-MEHP	0.88 (0.56–1.38)	.57
MEHP	0.64 (0.43–0.97)	.04
MEP	1.31 (0.87–1.97)	.20

Abbreviations: CI, confidence interval; MBzP, mono-benzyl phthalate; MEHP, mono-2-ethylhexyl phthalate; MEP, mono-ethyl phthalate; MnBP, mono-n-butyl phthalate; 5OH-MEHP, mono-2-ethyl-5-hydroxyhexyl phthalate; 5oxo-MEHP, mono-2-ethyl-5-oxohexyl phthalate; OR, odds ratio.

phthalates and atopic diseases in children at the age of 2, 5, and 7 years. Similar findings concerning the lack of association between in utero exposures to low-molecular-weight phthalates and risk of asthma have been reported by the Spanish Infancia y Medio Ambiente-Sabadell study, which was performed in a population aged 6 months to 7 years.³⁹ These results have been also confirmed with no association between low-molecular-weight phthalates and risk of asthma in 2 studies from the United States and France performed in children at the age of 5 and 6 years.^{40,41} In contrast, a study by Whyatt et al¹⁴ based on data from the Columbia Center for Children's Environmental Health Cohort reported that prenatal exposure to butylbenzyl phthalate and di-n-butyl phthalate may increase the risk of asthma at the age of 5 to 11 years. In addition, a recent study by Berger et al¹² revealed a positive association between prenatal urinary concentrations of monocarboxyisooctyl phthalate and increased odds of probable asthma with lower lung function in children. Shi et al⁴² reported that low-molecular-weight but not high-molecular-weight phthalates were associated with increased risk of asthma and wheezing in children. This study was conducted in Shanghai, which has the highest prevalence of childhood asthma in Mainland China. Similarly, Callesen et al⁴⁴ found no correlation between any phthalate urinary concentration and asthma. A cross-sectional study conducted among a National Health and Nutrition Examination Study population found that urinary concentrations of MBzP but not MnBP were associated with current asthma and wheezing in adults but not in children aged from 6 to 17 years.³

Allergic Rhinitis

This study did not find any correlations between phthalates and their metabolites and allergic rhinitis. This finding is consistent with the results of a study by Callesen et al,⁴⁴ which found no correlation between any phthalate urinary concentration and allergic rhinitis. However, Shi et al⁴² found that high-molecular-weight DEHP and low-molecular-weight DEHP were associated with an increased risk of allergy in children.

Hsu et al³ found that a higher urine concentration of MEHP was associated with allergic rhinitis. Ait Bamai et al²³ suggested that the levels of some phthalates in floor dust were associated with the prevalence of allergic rhinitis, conjunctivitis, and atopic dermatitis in children, and children were more vulnerable to phthalate exposure via household floor dust than adults. The results from their study were cross-sectional, and the study did not use biological markers to measure exposure.²³ In our study, we aimed to characterize precisely the exposure to phthalate by measuring its metabolite concentrations in mothers' and children's urine because phthalate concentrations in urine are considered to be a better indicator of total phthalate exposure.^{14,26–28} In our study, we have not assessed phthalates in floor dust; therefore, we can only speculate that phthalate levels may be associated with increased risk of allergic disorders in children.

Strengths and Limitations

The prospective study design of this analysis constitutes the main strength of the study. Despite the significant scientific interest in the effect of phthalates on child allergy, only a few studies are in fact based on several time points of exposure, with assessments in both prenatal and postnatal periods. In this regard, our analyses have considered data on phthalate metabolites from mother-child pairs available for 3 time points (prenatal, at the age of 2 years, and at the age of 9 years). Another strength of the study is the extensive set of phthalate metabolites assessed compared with the few (most frequently DEHP metabolites) evaluated in other epidemiologic studies. The children's health status was assessed by the interview with mothers and confirmed by allergists (based on

child examination including the data from skin prick testing and pulmonary function).

The main limitation of this study is the small sample size (N = 145), which limits the power of the associations. In addition, our patients were white, whereas most studies included patients of different races to study the correlations between phthalate exposure. Therefore, we were not able to completely compare our results with the results of other studies. We also have not separately studied the association of eczema in allergic and nonallergic children. Although eczema is frequently considered an early indicator of IgE-mediated allergic disease, eczema among nonatopic children is also prevalent.

Conclusion

This study has not provided clear evidence of the negative effect of phthalate exposure during pregnancy and within the 9 years after birth on allergic diseases in children at early school age. Because of the complexity and heterogeneity of the mechanisms involved in the influence of the analyzed chemicals on child atopic diseases, additional prospective studies with larger sample size and multiple time points of assessment are required to elucidate the most critical periods of phthalate exposure on children's allergic outcomes.

References

- Berger K, Eskenazi B, Balmes J, Holland N, Calafat AM, Harley KG. Associations between prenatal maternal urinary concentrations of personal care product chemical biomarkers and childhood respiratory and allergic outcomes in the CHAMACOS study. *Environ Int*. 2018;121(Pt 1):538–549.
- Berger K, Eskenazi B, Balmes J, et al. Prenatal high molecular weight phthalates and bisphenol A, and childhood respiratory and allergic outcomes. *Pediatr Allergy Immunol*. 2019;30(1):36–46.
- Hoppin JA, Jaramillo R, London SJ, et al. Phthalate exposure and allergy in the U. S. population: results from NHANES 2005–2006. *Environ Health Perspect*. 2013; 121(10):1129–1134.
- Koch HM, Calafat AM. Human body burdens of chemicals used in plastic manufacture. *Philos Trans R Soc Lond B Biol Sci*. 2009;364(1526):2063–2078.
- Loo RM, Koscielna K, Kumar K, Frieri M. Emergency department evaluation, treatment, hospital admission and slgE levels in African American and Hispanic pediatric asthmatics. *Clin Immunol*. 2007;123(suppl 76):8.
- Serrano SE, Karr CJ, Seixas NS, et al. Dietary phthalate exposure in pregnant women and the impact of consumer practices. *Int J Environ Res Public Health*. 2014;11(6):6193–6215.
- Wittassek M, Koch HM, Angerer J, Brüning T. Assessing exposure to phthalates – the human biomonitoring approach. *Mol Nutr Food Res*. 2011;55(1):7–31.
- Braun JM, Sathyanarayana S, Hauser R. Phthalate exposure and children's health. *Curr Opin Pediatr*. 2013;25(2):247–254.
- Nakajima Y, Goldblum RM, Midoro-Horiuti T. Fetal exposure to bisphenol A as a risk factor for the development of childhood asthma: an animal model study. *Environ Health*. 2012;11:8.
- Shen S, Li J, You H, et al. Oral exposure to diisodecyl phthalate aggravates allergic dermatitis by oxidative stress and enhancement of thymic stromal lymphopoietin. *Food Chem Toxicol*. 2017;99:60–69.
- Deo SS, Mistry KJ, Kakade AM, Niphadkar PV. Role played by Th2 type cytokines in IgE mediated allergy and asthma. *Lung India*. 2010;27(2):66–71.
- Polanska K, Ligocka D, Sobala W, Hanke W. Phthalate exposure and child development: the Polish Mother and Child Cohort Study. *Early Hum Dev*. 2014; 90(9):477–485.
- Stelmach I, Majak P, Jerzynska J, et al. Cord serum 25-hydroxyvitamin D correlates with early childhood viral-induced wheezing. *Respir Med*. 2015;109(1): 38–43.
- Whyatt RM, Perzanowski MS, Just AC, et al. Asthma in inner-city children at 5–11 years of age and prenatal exposure to phthalates: the Columbia Center for Children's Environmental Health Cohort. *Environ Health Perspect*. 2014; 122(10):1141–1146.
- Herberth G, Pierzchalski A, Feltens R, et al. Prenatal phthalate exposure associates with low regulatory T-cell numbers and atopic dermatitis in early childhood: results from the LINA mother–child study. *J Allergy Clin Immunol*. 2017;139(4):1376–1379.e8.
- Frederiksen H, Jensen TK, Jørgensen N, et al. Human urinary excretion of non-persistent environmental chemicals: an overview of Danish data collected between 2006 and 2012. *Reproduction*. 2014;147(4):555–565.
- Hartmann C, Uhl M, Weiss S, Koch HM, Scharf S, König J. Human biomonitoring of phthalate exposure in Austrian children and adults and cumulative risk assessment. *Int J Hyg Environ Health*. 2015;218(5):489–499.
- Kasper-Sonnenberg M, Koch HM, Wittsiepe J, Brüning T, Wilhelm M. Phthalate metabolites and bisphenol A in urines from German school-aged children:

- results of the Duisburg birth cohort and Bochum cohort studies. *Int J Hyg Environ Health*. 2014;217(8):830–838.
19. Katsikantami I, Sifakis S, Tzatzarakis MN, et al. A global assessment of phthalates burden and related links to health effects. *Environ Int*. 2016;97:212–236.
 20. Larsson K, Ljung Björklund K, Palm B, et al. Exposure determinants of phthalates, parabens, bisphenol A and triclosan in Swedish mothers and their children. *Environ Int*. 2014;73:323–333.
 21. Martínez MA, Rovira J, Prasad Sharma R, Nadal M, Schuhmacher M, Kumar V. Comparing dietary and non-dietary source contribution of BPA and DEHP to prenatal exposure: a Catalonia (Spain) case study. *Environ Res*. 2018;166:25–34.
 22. Correia-Sá L, Kasper-Sonnenberg M, Pálmeke C, et al. Obesity or diet? Levels and determinants of phthalate body burden - a case study on Portuguese children. *Int J Hyg Environ Health*. 2018;221(3):519–530.
 23. Ait Bamai Y, Shibata E, Saito I, et al. Exposure to house dust phthalates in relation to asthma and allergies in both children and adults. *Sci Total Environ*. 2014;485–486:153–163.
 24. Den Hond E, Govarts E, Willems H, et al. First steps toward harmonized human biomonitoring in Europe: demonstration project to perform human biomonitoring on a European scale. *Environ Health Perspect*. 2015;123(3):255–263.
 25. Stelmach I, Majak P, Jerzynska J, et al. The effect of prenatal exposure to phthalates on food allergy and early eczema in inner-city children. *Allergy Asthma Proc*. 2015;36(4):72–78.
 26. Polańska K, Hanke W, Gromadzińska J, et al. Polish mother and child cohort study—defining the problem, the aim of the study and methodological assumption. *Int J Occup Med Environ Health*. 2009;22(4):383–391.
 27. Polańska K, Hanke W, Jurewicz J, et al. Polish mother and child cohort study (REPRO_PL)—methodology of follow-up of the children. *Int J Occup Med Environ Health*. 2011;24(4):391–398.
 28. Polańska K, Hanke W, Król A, et al. Polish mother and child cohort study (REPRO_PL)—methodology of the follow-up of the children at the age of 7. *Int J Occup Med Environ Health*. 2016;29(6):883–893.
 29. Buckley JP, Palmieri RT, Matuszewski JM, et al. Consumer product exposures associated with urinary phthalate levels in pregnant women. *J Expo Sci Environ Epidemiol*. 2012;22(5):468–475.
 30. Koch HM, Wittassek M, Brüning T, Angerer J, Heudorf U. Exposure to phthalates in 5–6 years old primary school starters in Germany—a human biomonitoring study and a cumulative risk assessment. *Int J Hyg Environ Health*. 2011;214(3):188–195.
 31. Fromme H, Lahrz T, Kraft M, et al. Phthalates in German daycare centers: occurrence in air and dust and the excretion of their metabolites by children (LUPE 3). *Environ Int*. 2013;61:64–72.
 32. Langer S, Bekö G, Weschler CJ, et al. Phthalate metabolites in urine samples from Danish children and correlations with phthalates in dust samples from their homes and daycare centers. *Int J Hyg Environ Health*. 2014;217(1):78–87.
 33. Stelmach I, Grzelewski T, Bobrowska-Korzeniowska M, et al. The role of zinc, copper, plasma glutathione peroxidase enzyme, and vitamins in the development of allergic diseases in early childhood: the Polish mother and child cohort study. *Allergy Asthma Proc*. 2014;35(3):227–232.
 34. Stelmach I, Bobrowska-Korzeniowska M, Smejda K, et al. Risk factors for the development of atopic dermatitis and early wheeze. *Allergy Asthma Proc*. 2014;35(5):382–389.
 35. Hsu NY, Lee CC, Wang JY, et al. Predicted risk of childhood allergy, asthma, and reported symptoms using measured phthalate exposure in dust and urine. *Indoor Air*. 2012;22(3):186–199.
 36. Guo Y, Wu Q, Kannan K. Phthalate metabolites in urine from China, and implications for human exposures. *Environ Int*. 2011;37(5):893–898.
 37. Just AC, Whyatt RM, Perzanowski MS, et al. Prenatal exposure to butylbenzyl phthalate and early eczema in an urban cohort. *Environ Health Perspect*. 2012;120(10):1475–1480.
 38. Kim EH, Jeon BH, Kim J, et al. Exposure to phthalates and bisphenol A are associated with atopic dermatitis symptoms in children: a time-series analysis. *Environ Health*. 2017;16(1):24.
 39. Gascon M, Casas M, Morales E, et al. Prenatal exposure to bisphenol A and phthalates and childhood respiratory tract infections and allergy. *J Allergy Clin Immunol*. 2015;135(2):370–378.
 40. Vernet C, Pin I, Giorgis-Allemand L, et al. EDEN Mother–Child Cohort Study Group. In utero exposure to select phenols and phthalates and respiratory health in five-year-old boys: a prospective study. *Environ Health Perspect*. 2017;125(9):097006.
 41. Buckley JP, Quirós-Alcalá L, Teitelbaum SL, Calafat AM, Wolff MS, Engel SM. Associations of prenatal environmental phenol and phthalate biomarkers with respiratory and allergic diseases among children aged 6 and 7 years. *Environ Int*. 2018;115:79–88.
 42. Shi W, Lin Z, Liao C, et al. Urinary phthalate metabolites in relation to childhood asthmatic and allergic symptoms in Shanghai. *Environ Int*. 2018;121(Pt 1):276–286.
 43. Wang LJ, Lin CC, Lin YJ, Hsieh WS, Chen PC. Early life phthalate exposure and atopic disorders in children: a prospective birth cohort study. *Environ Int*. 2014;62:48–54.
 44. Callesen M, Bekö G, Weschler CJ, et al. Phthalate metabolites in urine and asthma, allergic rhinoconjunctivitis and atopic dermatitis in preschool children. *Int J Hyg Environ Health*. 2014;217(6):645–652.