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Urinary levels of phthalate, bisphenol, and paraben and allergic outcomes in children: Korean National Environmental Health Survey 2015-2017

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Abstract

Background

Phthalates, bisphenols and parabens have been widely used in household and personal-care products. Their endocrine disrupting, sensitizing and antimicrobial properties might play a role in the occurrence of allergic diseases. However, the effects of these chemicals, particularly on humans, are relatively underexplored.

Objectives

This study aimed to report the concentrations of phthalate, bisphenol and paraben in urine of Korean children, and assess their relationship with allergic outcomes.

Methods

Data obtained from nationally representative Korean children, a total of 1,458 children between 3 and 11 years of age recruited in the Korean National Environmental Health Survey (3rd round of KoNEHS 2015-2017), were analyzed. Associations of urinary phthalate metabolites, bisphenols, and parabens levels with atopic dermatitis and allergic rhinitis was examined by grouped into preschool (aged 3-5 years) and school children (aged 6-11 years). Allergic outcomes were obtained through questionnaires answered by their caregivers.

Results

Atopic dermatitis was associated with urinary metabolites of DEHP, BzBP, DINP, and DIDP, and MeP and PrP in preschool children, BPA and PrP in school children. Allergic rhinitis was associated with MeP and PrP in preschool children, and metabolites of DEHP, MeP and PrP in school children. The association of urinary chemicals with atopic dermatitis and allergic rhinitis were different by gender, especially in preschool children.

Conclusion

Urinary phthalates, BPA and parabens levels in the Korean children were related with atopic dermatitis and allergic rhinitis. Considering the importance of allergic diseases in children, the public health implications of exposure to these chemicals warrant further studies. Given the cross-sectional design and confounding variables, the results of this study should be interpreted with caution.

Introduction

Phthalates, bisphenols, and parabens have been widely used as raw materials and additives for many products. Various consumer goods (e.g., household products, medical equipment, toys, cosmetic products, and food packaging) contain phthalates and bisphenol A (BPA) as plasticizers and raw materials, and personal care products (e.g., cosmetics, shampoo, skin lotion and sunscreen) and medicines contain parabens as preservatives (Anderson 2008; Guo and Kannan, 2013; Harley et al., 2016; Schettler, 2006; Zota et al., 2016). Because of their low toxicity, cost effectiveness, broad inertness and worldwide regulatory acceptance, phthalates, BPA and parabens are among the most popular additives for a variety of products (Guo and Kannan, 2013; Soni et al. 2005). Due to their ubiquitous use, these compounds have been detected in humans, around the world (CDC, 2021; Choi et al., 2017; Health Canada, 2019).

The National Health and Nutrition Examination Survey (NHANES) of the United States (US) reported that phthalates, BPA and parabens were respectively detected over 70%, 92%, and 99% of the urine samples collected from the general US population including preschool (aged 3-5 years) and school (aged 6-11 years) children (CDC, 2021). The Canadian Health Measures Survey (CHMS) indicated that 11 phthalate metabolites, BPA, and at least one paraben were detected in 90% of the children (aged 3-11 years) urinary samples collected for the survey (Health Canada, 2019). In Germany, the detection rates of methyl paraben (MeP) and n-propyl paraben (PrP) in urine samples of children and adolescents between 2015 and 2017 were 97% and 31%, respectively (Murawski et al., 2021). Such a widespread detection of these chemicals in human population has raised concerns about their potential health risks. Atopy is defined as a personal or familial propensity to produce immunoglobulin E (IgE) antibodies and sensitization in response to environmental triggers. Allergic disorders are among the most common chronic conditions in children, as seen from the increasing

prevalence of allergic symptoms worldwide (International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee, 1998). Between 2002 and 2003, for example, the prevalence of asthma and atopic dermatitis (AD) among children aged 6 to 7 were each 18.2% and 12.0% in Canada, 20.0% and 17.1% in Australia, and 20.9% and 16.0% in the UK (Asher et al, 2006). In Korea, the prevalence of AD was 17.9%, a prevalence that ranked 5th out of 60 countries and that of AR was 38.9%, which was much higher than the global average of 20.7% in 6-7years children at 2010 (Hong et al., 2012; Odhiambo et al., 2009). Considering children's vulnerabilities to environmental chemicals and developing organs, and the increasing of burden of allergic diseases in developing countries (Thomsen, 2015), the allergic effects of EDCs are of emerging concern.

Determinants of allergic diseases include genetic, biological, environmental and lifestyle factors (Thomsen, 2015). Studies reported that endocrine disrupting chemicals (EDCs) such as phthalates, bisphenols and parabens may induce immunological responses including sensitization, and they are suspected of developing or promoting allergic conditions (Bølling et al., 2020; Lee-Sarwar et al., 2018; Robinson and Miller. 2015). Epidemiologic studies have been conducted to investigate the association between EDC exposure and allergic outcomes worldwide, but their findings are not consistent with effect size and directions (Bølling et al, 2020).

Since only a few studies have been conducted with a large population of Korean children, this study may be the first report that used a nationally representative population and examined associations between EDC and allergic outcomes among the Korean children. This study aimed at confirming associations between 12 kinds of phthalates, bisphenols, and parabens and two allergic outcomes, and examining gender differences of the associations in a representative Korean children population.

Materials and Methods

Study population

Study population consists of children aged 3 to 11 who participated in the 3rd Korean National Environmental Health Survey (KoNEHS) in 2015-2017 conducted by the Korean Ministry of Environment. The KoNEHS is a 3-year cross-sectional survey designed to collect nationally representative exposure profiles for environmental chemicals, and associated socio-demographic and behavioral characteristics among the general Korean population using a multiple stage sampling method (Park et al., 2016). Since the behavioral development related to exposure and physiological development related to internal or effective doses were associated with age, the children were divided into two age groups, i.e., preschool and school children (EPA, 2005). For children, sampling was performed in accordance with region, sex, and age stratification based on the 2014 national census data of Korea. The sampling frame for children was 26,177 day-care centers and kindergartens (preschool children aged 3 to 5 years) and 6,187 elementary schools (school children aged 6 to 11 years). The 118 sampling units were allocated based on probability proportional to the regional sampling frame, and 500 preschool children and 750 school children were recruited in sampling units based on probability proportional to the square root of child population size in each stratum which was chosen based on the Korean Ministry of Health and Welfare and Ministry of Education register in 2014. For preschool children, 9 children were selected from each of the 56 day-care centers and kindergartens. For school children, 12 students were selected from each of the 63 elementary schools. Informed written consents were gleaned from the participating children through their parents. The participants' data including household and personnel information were collected via questionnaires completed by their parents or guardians. The urine samples, collected by the field survey team along with the questionnaires the day before or on the day of the survey, were stored in refrigerators.

This study was approved by the Research Ethics Committee of the National Institute of Environmental Research, the Republic of Korea.

Analysis of urinary phthalate metabolites, bisphenols, and parabens

Spot urine samples, after being collected by survey centers located throughout the country, were delivered in a cold condition (0-4 °C) to laboratories, which then froze them on arrival (-20 °C), within 24 hours of collection, and stored them until analysis.

Following hydrolysis of conjugated species with β -glucuronidase/sulfatase enzyme, phthalate metabolites, bisphenols and parabens were measured using liquid-liquid extraction or solid phase extraction, and ultra-performance liquid chromatography mass spectrometry separation, followed by electrospray ionization and tandem mass spectrometry (Xeno TQ-S; Waters, Milford, MA, USA), as described in detail elsewhere (NIER, 2018). Quality control procedures for all analytes were followed according to the protocols recommended by the Korea National Institute of Environmental Research. In addition, the analytical laboratory successfully participated in the quality control programs run by the Korea Association of Quality Assurance for Clinical Laboratory and the German External Quality Assessment Scheme for Analysis of Organic Chemicals in Biological Materials twice per year. The measured phthalate metabolites included secondary oxidized metabolites of DEHP (i.e. mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)), hydrolytic metabolites of DiNP (i.e. mono-carboxyoctyl-phthalate (MCOP)), DiDP (i.e. mono-carboxynonyl-phthalate (MCNP)), DOP (i.e. mono-3-carboxypropyl-phthalate (MCP)), BzBP (i.e. mono-benzyl phthalate (MBzP)), and DBP (i.e. mono-*n*-butyl phthalate (MnBP)). The limits of detection (LODs) for MEHHP, MEOHP, MECPP, MCOP, MCNP, MCP, MBzP, and MnBP were 0.056, 0.048, 0.141, 0.048, 0.139, 0.078, 0.066, and 0.040 $\mu\text{g/L}$, respectively. The LODs for BPA, BPS, BPF, MeP, EtP and PrP were each 0.075, 0.019, 0.084, 0.108,

0.107 and 0.082 $\mu\text{g/L}$. The sum of MEHHP, MEOHP, and MECPP concentrations was designated as the total DEHP metabolites (i.e. ΣDEHP).

Allergic outcomes

The history of allergic outcomes was assessed based on the ISAAC questionnaire and medical conditions questionnaire (MCQ.035) for NHANES (Asher et al., 1995; Quirós-Alcalá et al., 2019). The participants or their caregivers were asked through questionnaires about allergic conditions (AD, asthma, and AR): First, trained personnel asked them, “Have you ever been diagnosed with asthma (AD/AR) by a medical doctor?” Those who answered this question affirmatively were then asked three questions, “When were you first diagnosed with asthma (AD/AR)?”, “Do you still have asthma (AD/AR) symptoms?”, and “Are you currently being medically treated for asthma (AD/AR)?” If the participants answered ‘yes’ to either of the last two questions, it was considered ‘current prevalence’.

Statistical analysis

The KoNEHS uses a two-stage, proportionally stratified sampling design. For design-based analysis, information concerning strata, cluster, and sample weights was applied to reflect the differential probability of selection and non-response. Since the survey was designed for a separately sampling frame of life stage with preschool (aged 3-5) and school children (aged 6-11), the datasets were analyzed separately in this study. Analytical results below the LOD were substituted with the respective LOD values, divided by the square root of 2. Urinary chemical measures were right-skewed; therefore, the data were ln-transformed prior to analysis.

For descriptive statistics to summarize demographic characteristics and urinary chemical concentrations, detection rates, geometric means (GMs) with 95% confidence intervals (CIs) and percentiles were determined.

In regression model and principle component analysis (PCA), specific gravity (SG) adjusted

concentrations of chemicals were used as independent variable for biological relevance (Lakind et al., 2014). Urine specific gravity was determined by using a digital handheld refractometer (Model PAL-10S; Atago, Tokyo, Japan). For analyses using specific gravity-corrected chemical concentrations, the following formula was used:

$$C_{adj} = C_{measure} * (SG_{median} - 1) / (SG - 1)$$

Where C_{adj} is the specific gravity-adjusted urinary concentration; $C_{measure}$ is the measured urinary concentration; SG_{median} is the median specific gravity; and SG is the specific gravity of a urine sample. The median of specific gravity of urine samples was 1.0217 for preschool and school children.

To examine associations between urinary chemical levels and allergic outcomes, logistic regression models to estimate adjusted prevalence odds ratios and 95% CIs were developed. Because the incidence of allergic diseases and chemical toxicity differs by gender depending on life stages, regression models were also performed by gender (Yao et al., 2011). Some urinary chemicals were correlated (Table S1-1, 2), so models were conducted for each chemical separately to exclude multicollinearity. Relevant covariates were selected based on the Spearman correlation matrix ('gender' and 'take a medicine') for the current population and the examples of previous studies (age, body mass index [BMI], monthly household income and status of passive smoking) (Odebeatu et al., 2019; Quirós-Alcalá et al., 2019, 2021). The BMIs were converted into quartiles by each life-stage. Among covariates, age was included in the model as a continuous variable, and gender, BMI, monthly household income and passive smoking status were included as categorical variables. Because medication history especially among the young children was related with urinary methyl- and propyl-paraben levels (Hong et al., 2021), so we added 'currently take medicine', particularly due to a fever, as a covariate. For asthma, regression coefficients were biased when cases per variable were less than 10, so we did not analyze regression models (Peduzzi et al., 1996).

Regarding multiple EDC activity, common exposure or mechanism, PCA was adopted to transform a number of possible correlated variables into a small number of uncorrelated components while retaining as much information as possible about the original variables (O'Rourke and Hatcher, 2013). PCA with varimax rotation was used to reduce the dimension of variables and identify the principal components. Factors were retained based on eigenvalues >1.0 and fitted with a logistic regression model. The PCA analysis was performed by age group (preschool and school children) and gender. Two types of models were developed: one is a single factor model where each factor score is included in the model, and the other is a multiple factor model where factor scores are mutually adjusted in the same model.

Statistical significance was set at $p = 0.05$. Data analysis was performed using the SAS software package, version 9.4 (SAS Institute Inc., Cary, NC, USA), employing the SURVEYFREQ, SURVEYMEANS, and SURVEYLOGISTIC functions.

Results

Study population characteristics

A total of 571 children aged 3 to 5 from nurseries and kindergartens, and 887 children aged 6 to 11 from elementary schools were recruited in the 3rd round of KoNEHS. Distributions of demographic characteristics according to age, sex, BMI group, monthly household income, passive smoking status, and allergic outcomes are presented in Table 1. The medians of the BMIs in preschool and school children were 15.97 kg/m^2 and 17.58 kg/m^2 , respectively. The rates of passive smoking tended to increase with age. The number of participants who currently take medicine was 73 (13.8%) in preschool and 65 (7.5%) in school children.

Prevalence of allergic outcomes

The prevalence of AD among preschool and school children was 7.7% and 9.0%, respectively,

whereas that of AR was 25.0% and 33.3%. The prevalence of AR was higher than that of AD in both age groups, and school children showed a higher prevalence of both AD and AR than preschool children. The prevalence of asthma was below 2% in preschool (1.7%) and school children (1.1%).

Occurrence and exposure levels of urinary chemicals

Descriptive statistics on the distribution of the measured chemicals are shown by age group in Table 2. The rates of below the LOD of all chemicals except EPS (43.4%) and BPF (62.8%) were less than 5%. The urinary levels of Σ DEHP of school children (94.0 $\mu\text{g/L}$) were lower than those of preschool children (109 $\mu\text{g/L}$). The GMs of urinary MeP in preschool and school children were 46.3 $\mu\text{g/L}$ and 28.9 $\mu\text{g/L}$, respectively, whereas the GMs of PrP were each 4.36 $\mu\text{g/L}$ and 1.83 $\mu\text{g/L}$. This trend was also observed with MBzP, MnBP, MCPP and BPA. The urinary levels of MCOP, MCNP, EPS and BPF, on the other hand, were higher among school children.

When classified by gender, the urinary levels of Σ DEHP, MBzP, MCNP, BPF, MeP, EtP and PrP were higher among preschool boys than girls. For school children, however, girl showed higher levels of urinary PrP than boys.

Σ DEHP was moderately correlated with other phthalate metabolites ($r = 0.22$ - 0.48), except MCNP ($r = 0.13$) for school children. MeP and PrP were highly correlated with each other ($r = 0.77$ for preschool and $r = 0.71$ for school children, $p < 0.001$, Supplementary Table S1-1~2).

Associations between urinary chemicals and allergic outcomes

When a unit increase in natural log chemical concentration was observed, not all the phthalate metabolites, bisphenol, and paraben were associated with the prevalence odds of AD and AR in the total group of preschool (Table 3). When stratified by gender, AD was statistically significant with the urinary levels of Σ DEHP (odds: 3.69, 95%CI: 1.25-10.9),

MBzP (odds: 1.37, 95%CI: 1.01-1.86), MCOP (odds: 2.72, 95%CI: 1.50-4.92), and MCNP (odds: 1.75, 95%CI: 1.05-2.94) among male group. MeP (odds: 1.26; 95%CI: 1.06-1.49) and PrP (odds: 1.23; 95%CI: 1.08-1.41) was also related with AD in male group. AR was associated with MeP (odds: 1.17; 95%CI: 1.02-1.35) and PrP (odds: 1.13, 95%CI: 1.01-1.26) in male group, whereas BPS was negatively related with AR (odds: 0.64, 95%CI: 0.44-0.93) in female group.

In school children, AD was related with BPA (odds: 1.31, 95%CI: 1.06-1.61), and AR was associated with MEHHP (odds: 1.30, 95%CI: 1.001-1.68), MeP (odds: 1.10, 95%CI: 1.01-1.19) and PrP (odds: 1.10, 95%CI: 1.01-1.19) in total group (Table 4). By gender, BPA (odds: 1.34, 95%CI: 1.05-1.69) was associated with AD in boy, whereas PrP (odds: 1.22, 95%CI: 1.001-1.48) was related with AD in girls. AR was associated with Urinary levels of Σ DEHP (odds: 1.71, 95%CI: 1.17-2.51) and PrP (odds: 1.16, 95%CI: 1.03-1.31) in female group, whereas MeP (odds: 1.12; 95%CI: 1.001-1.24) was relate with AR in male group.

Since the detection rate of BPF was less than 40%, BPF was excluded from the PCA. According to PCA, four components were retained based on the criterion of eigenvalue >1.0, and accounted for greater than 59% of the total variance. Detailed information on varimax-rotated factor loadings was shown in Table S2. Generally, factors were divided by phthalate, bisphenol, and paraben groups. In the total group, factor 1 was highly loaded with Σ DEHP metabolites, MCOP, MCNP, and MCPP; factor 2 with MeP and PrP; factor 3 with Σ DEHP, MBzP and BPA; and factor 4 with BPS. Factor patterns were slightly different by age group and those between male and female groups were also slightly different except MeP and PrP.

The result of regression for components was showed in Table 5. In case of AD, factor 1 of male preschool children and factor 1 and factor 4 of female school children were slightly lager in multiple model. For AR, factor 2 of male school children was not significant in single model, but changed to significant in multiple model. The results of remaining factors were

similar in magnitude and direction of the effect in the single factor and multiple factor models. In the single factor model, factor 1 (Σ DEHP, MCOP, MCNP, and MCPP) and factor 2 (MeP and PrP) were significantly associated with AD, and factor 2 (MeP and PrP) was related with AR in male preschool children. Among school children, association between factor 4 (BPA and BPS) and AD and factor 2 (MeP and PrP) and AR was significant in total group. Factor 1 (MeP, EtP and PrP) and factor 4 (BPA and BPS) were associated with AD, and factor 2 (Σ DEHP, MBzP, and MnBP) was related with AR in female school children. The statistical significance of multiple factor model was the same as that of single factor model, except association between factor 2 (MeP and PrP) and AR was statistically significant.

Discussion

In this study, we determined associations between urinary levels of 12 kinds of phthalate metabolites, phenols and two major allergic outcomes and examined gender differences of the associations among representative Korean children. As a result, the urinary sum of DEHP metabolites, MBzP, MCOP, MCNP, BPA, MeP and PrP showed significant associations with AD or AR, which suggests that the current levels of exposure to these chemicals may influence allergic outcomes among representative Korean children. In addition, significant associations of urinary chemicals with AD and AR were shown in male rather than female preschool children, of which the pattern of gender difference disappeared or weakened with age. To our knowledge, this is the first report to demonstrate associations between urinary chemical levels and allergic outcomes based on a reasonable size of Korean children who represent the national population.

The results from this study were consistent with previous epidemiologic studies (Table 6). Some phthalate metabolites, as well as metabolites of DEHP, DEP, DBP and BBzP, were related with eczema and rhinitis (Callesen et al., 2014; Kim et al., 2017; Shi et al., 2018; Wang et al., 2014). Studies on the dataset from the NHANES of the US showed that urinary BPA levels were associated with a decrease in lung function (Spanier et al., 2014a), but no association was observed with allergy or AR (Clayton et al., 2011). As for parabens, studies with the NHANES data indicated that urinary MeP, BuP and PrP levels were positively associated with aeroallergen sensitization in the US children (Savage et al., 2012), whereas some researchers reported that phthalate metabolites and parabens had negative or no relations with allergic outcomes (Hoppin et al., 2013; Spanier et al., 2014b). Another study with the NHANES data showed that MeP and PrP exposure was related with emergency department visits among the US male children with asthma (Quirós-Alcalá et al., 2019). Other studies did not confirm the associations between paraben exposure and allergic

diseases (Lee-Sarwar et al., 2018). In this study, we confirmed the relations of phthalates, BPA, MeP and PrP with AD and AR among Korean children, and also identified gender differences in the prevalence of allergic outcomes related with these chemicals. These study results provide some evidence for associations between phthalate, BPA and paraben exposure and the risk of prevalent allergic diseases.

Phthalates, BPA and parabens are associated with endocrine disrupting activities along with effects involving oxidative stress and inflammation (Boberg et al., 2010; Bons and Midori-Horiuti, 2013; Chen et al., 2007; Sun et al., 2016). EDCs could modulate interleukin-4 production, T helper type 1/type 2 (Th1/Th2) balance and IgE production which might lead to production of inflammatory cytokines and several allergic responses (Bansal et al., 2018; Bølling et al., 2020; Chalubinski and Kowalski, 2006; Wang et al., 2020). In addition to endocrine disrupting property, sensitization and antimicrobial properties of parabens could be related with allergic outcomes (Bansal et al., 2018; Bantz et al., 2014). Studies showed that parabens could play a role in modulating immune and allergic responses and reduced growth of a specific gut microbiome, which could contribute to altering inflammatory pathways (Chalubinski and Kowalski, 2006; Hu et al., 2016; Nowak et al., 2018; Singanayagam et al., 2017; Taylor et al., 2018). A dysfunctional skin barrier is one of the causes for allergic sensitization and colonization of bacterial antigens, inducing systemic Th2 immunity, which makes patients susceptible to allergic nasal responses and promotes airway hyper reactivity (Bantz et al., 2014).

Studies showed that the associations between urinary chemicals and allergic disorder differ by gender (Buckley et al., 2018; Ku et al., 2015; Odebeatu et al., 2019; Wang et al., 2016). It was not clear why the difference exists, but physiological characteristics could be one of the reasons. Several studies reported a higher prevalence of allergic diseases and sensitization (Chen et al., 2008; Dor-Wojnarowska et al., 2017), and its association with endocrine

disrupting chemicals in male children (Ku et al., 2015; Quirós-Alcalá et al, 2019, 2021; Savage et al., 2012). The higher prevalence of allergic diseases in male children may be related with sex hormones, as estrogens could be a limiting factor in allergy expression and androgens might show immunosuppressive effect (Chen et al., 2008; Liebhart et al., 2014). Estrogenic chemicals including phthalates and bisphenols may exert different endocrine disrupting effects on boys than on girls owing to their different hormonal milieu, and could more likely enhance the allergic responses among the male children (Bond and Midoro-Horiuti, 2013; Quirós-Alcalá et al, 2021). However, further investigations are needed to confirm the proposed sex-specific susceptibility in allergic outcomes.

In Korea, from 2008 to 2017, the prevalence of AD showed an increasing trend in school children and adults, but the prevalence of AD decreased in infants and preschool children (Ha et al., 2020). According to data collected from the Korean National Health and Nutrition Examination (KNHANES) from 2016 to 2017, the prevalence of AD and AR during the past 12 months were 11.3% and 20.2% in preschool children (N=4,352), and 14.6% and 27.6% in school children (N=12,919) (Ha et al., 2020). The current prevalence of AD and AR were each 7.7-9.0% and 25.0-33.3% in this study. The prevalence of AD was lower, and AR was similar or slightly higher than of that of KNHANES study. The difference of prevalence could be explained by sampling design and diagnostic criteria.

There are several limitations in this study. As a cross-sectional observation study based on a single measurement of urinary chemicals and allergic outcomes, the present study has intrinsic limitations concerning the possibility of reverse-causation. Moreover, a single measurement of spot urine samples may not represent true exposure profiles, as the half-life of phthalates, bisphenols, and parabens range from 4 to 10 hours. While we adjusted for several important confounders, our analyses were also limited by the variables available in this national survey, i.e. common and specific IgE, family history of allergic symptoms and

predisposition, e.g., birth weight, delivering conditions and breastfeeding. In addition, we could not rule out the possibility for recall bias by respondent misrecalling the allergic outcomes because we used questionnaires, not clinical diagnosis.

However, this study is based on the results of the KoNEHS, a national biomonitoring survey into the Korean population of more than 1,400 children aged 3 to 11 years, and provides sufficient statistical power to detect less evident associations. The findings of this study provide reliable epidemiological evidence regarding the allergic outcomes associated with the current level of chemical exposure. The results of this study may be helpful in identifying populations susceptible to the effects of phthalate, bisphenol and paraben exposure and developing appropriate exposure mitigation measures for these chemicals in Korea.

Conclusion

In a nationally representative population of Korean children, urinary phthalate, BPA and paraben levels were found to be associated with the prevalence of allergic outcomes. Gender-dependent patterns were also observed in the association of the urinary chemicals with the risk of allergies. Further studies are warranted to identify major exposure sources and pathways of these chemicals and to validate the findings of this study in other populations of different geographical regions. The biological implications of statistical associations should be interpreted with caution.

Conflict of interest: All authors declare they have no actual or potential competing financial interest.

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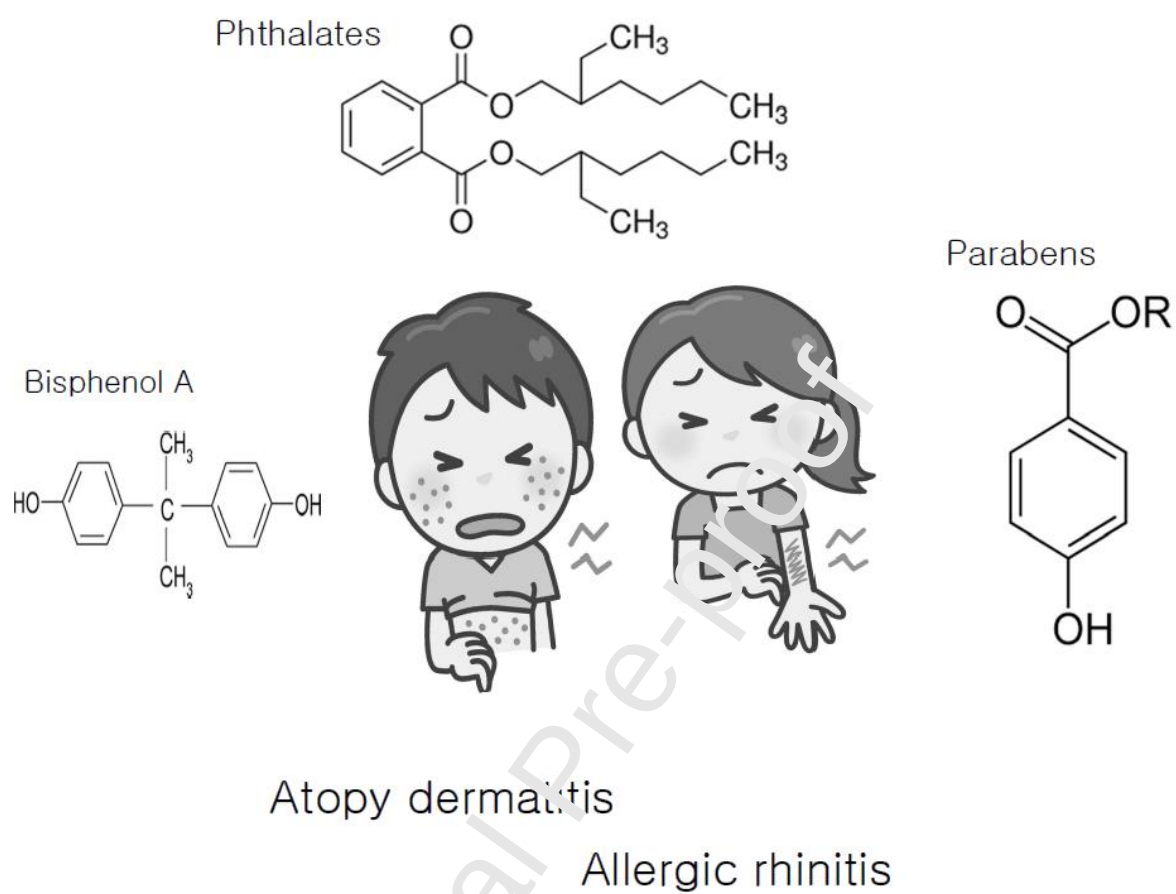
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Graphical abstract



Highlights

- Using representative Korean children data, 15 urinary chemicals were analyzed.
- DEHP, BBzP, DiNP, DiDP, MeP, and PrP were associated with atopic dermatitis and allergic rhinitis
- BPA was associated with atopic dermatitis
- Association of urinary chemicals with allergic outcomes were different by gender.

Table 1. Demographic and behavioral characteristics of the participating children and allergic outcomes

		Preschool children		School children	
		N	Weighted %	N	Weighted %
Total		571	100	887	100
Age (range, years)		3-5		6-11	
Gender	Male	285	51.4	452	51.7
	Female	286	48.6	435	48.3
BMI Category†	1st Quartile	142	26.8	221	24.8
	2nd Quartile	143	25.1	223	25.3
	3rd Quartile	144	25.1	222	25.8
	4th Quartile	142	23.0	221	24.1
Monthly Household Income (\$)‡	<2,500	122	20.6	172	19.0
	2,500-4,200	228	41.2	318	38.1
	4,200-5,900	136	24.7	237	27.5
	>5,900	74	14.1	128	15.4
	Missing	11	-	32	-
Passive Smoking	No	490	86.3	743	84.1
	Yes	81	13.7	144	15.9
Take Medicine (due to a fever)	No	496	86.2	822	92.5
	Yes	73	13.8	65	7.5
Atopic Dermatitis (Current)	No	531	92.3	809	91.0
	Yes	40	7.7	78	9.0
Allergic Rhinitis (Current)	No	436	75.0	599	66.7
	Yes	135	25.0	288	33.3
Asthma (Current)	No	561	98.3	878	98.9
	Yes	10	1.7	9	1.1

† For preschool children (25%:=15.02, 50% =15.97, 75% =17.08), for school children (25%:=15.73, 50% =17.58, 75% =20.26).

‡ Currency: ca 1,186 Korean Won/US Dollar

Table 2. Geometric means and 95% CIs of measured chemicals in urine ($\mu\text{g/L}$)

	%<LOD	Preschool children		School children	
		GM	(95%CI)	GM	(95%CI)
Total					
ΣDEHP	0.0	109	(100-122)	94.0	(86.5-102)
MBzP	4.6	3.12	(2.64-3.69)	2.80	(2.34-3.35)
MnBP	0.2	47.2	(40.8-54.6)	43.2	(40.6-46.1)
MCOP	0.8	1.62	(1.43-1.83)	2.24	(2.07-2.42)
MCNP	3.2	0.490	(0.425-0.568)	0.533	(0.505-0.562)
MCPP	0.3	1.80	(1.63-2.00)	1.56	(1.49-1.64)
BPA	3.0	2.41	(2.05-2.83)	1.70	(1.49-1.95)
BPS	43.4	0.028	(0.025-0.032)	0.036	(0.030-0.043)
BPF	62.8	0.091	(0.081-0.103)	0.110	(0.100-0.126)
MeP	0.0	46.3	(37.1-57.8)	28.9	(24.6-33.9)
EtP	0.8	14.2	(10.5-19.1)	11.4	(8.56-15.3)
PrP	3.0	4.36	(3.28-5.80)	1.83	(1.52-2.21)
Male					
ΣDEHP	0.0	115	(102-129)	95.7	(86.5-106)
MBzP	4.3	3.27	(2.69-3.97)	2.94	(2.45-3.52)
MnBP	0.3	46.7	(37.2-58.6)	45.1	(41.7-48.8)
MCOP	0.6	1.61	(1.41-1.84)	2.22	(2.05-2.41)
MCNP	3.8	0.506	(0.450-0.555)	0.541	(0.506-0.579)
MCPP	0.2	1.82	(1.62-2.03)	1.61	(1.51-1.72)
BPA	2.9	2.24	(1.83-2.75)	1.71	(1.45-2.03)
BPS	40.0	0.028	(0.024-0.032)	0.039	(0.032-0.047)
BPF	61.4	0.100	(0.083-0.114)	0.112	(0.095-0.133)
MeP	0.0	55.7	(41.8-74.3)	29.6	(24.0-36.5)
EtP	0.6	17.7	(12.1-25.9)	13.2	(9.75-18.0)
PrP	2.8	4.92	(3.51-6.90)	1.74	(1.39-2.19)
Female					
ΣDEHP	0.0	104	(90.5-119)	92.3	(84.1-101)
MBzP	4.7	2.98	(2.35-3.78)	2.67	(2.13-3.33)
MnBP	0.0	47.8	(42.0-54.4)	41.3	(38.2-44.6)
MCOP	0.9	1.62	(1.38-1.90)	2.26	(2.01-2.55)
MCNP	2.7	0.477	(0.409-0.555)	0.524	(0.490-0.564)
MCPP	0.4	1.78	(1.59-1.99)	1.51	(1.42-1.61)
BPA	3.0	2.60	(2.16-3.12)	1.69	(0.45-1.97)
BPS	46.7	0.029	(0.075-0.098)	0.034	(0.028-0.041)
BPF	64.3	0.086	(0.075-0.098)	0.107	0.090-0.128
MeP	0.0	38.0	(28.0-51.5)	28.1	(22.6-35.0)
EtP	1.2	11.2	(7.61-16.5)	9.78	(6.90-13.9)
PrP	1.9	3.84	(2.60-5.68)	1.94	(1.49-2.52)

Table 3. Adjusted associations of SG-adjusted urinary chemical concentrations with allergic outcomes in preschool children

		Total	Male	Female
Atopic dermatitis	Σ DEHP	1.56 (0.87-2.80)	3.69 (1.25-10.9)	0.83 (0.43-1.63)
	MEHHP	1.57 (0.91-2.70)	3.96 (1.28-12.2)	0.85 (0.47-1.57)
	MEOHP	1.68 (0.94-3.00)	3.00 (0.91-9.93)	1.17 (0.62-2.19)
	MECPP	1.30 (0.73-2.31)	3.00 (1.32-6.75)	0.69 (0.33-1.46)
	MBzP	1.00 (0.77-1.30)	1.37 (1.01-1.86)	0.81 (0.58-1.13)
	MnBP	1.08 (0.85-1.39)	1.20 (0.84-1.71)	0.95 (0.46-1.97)
	MCOP	1.19 (0.71-2.02)	2.72 (1.50-4.92)	0.65 (0.30-1.38)
	MCNP	1.14 (0.71-1.84)	1.75 (1.05-2.94)	0.78(0.40-1.50)
	MCCP	1.21 (0.74-2.00)	1.51 (0.73-3.13)	1.05 (0.50-2.23)
	BPA	1.21 (0.73-2.02)	1.24 (0.52-3.00)	1.25 (0.60-2.62)
	BPS	1.10 (0.85-1.43)	0.59 (0.37-1.11)	1.41 (0.91-2.17)
	BPF	0.80 (0.47-1.36)	0.76 (0.36-1.61)	0.80 (0.40-1.61)
	MeP	1.10 (0.93-1.29)	1.26 (1.06-1.49)	0.96 (0.73-1.28)
	EtP	1.18 (0.93-1.50)	1.31 (0.87-1.97)	1.09 (0.85-1.40)
	PrP	1.11 (0.997-1.24)	1.23 (1.08-1.41)	0.98 (0.79-1.22)
Allergic rhinitis	Σ DEHP	1.02 (0.66-1.56)	0.98 (0.58-1.66)	1.09 (0.65-1.86)
	MEHHP	0.99 (0.65-1.51)	1.03 (0.62-1.69)	1.01 (0.60-1.69)
	MEOHP	1.05 (0.69-1.60)	1.12 (0.70-1.79)	0.98 (0.56-1.71)
	MECPP	1.01 (0.73-1.43)	0.91 (0.58-1.41)	1.18 (0.79-1.76)
	MBzP	0.91 (0.75-1.09)	0.98 (0.74-1.31)	0.78 (0.59-1.04)
	MnBP	1.02 (0.80-1.29)	1.04 (0.78-1.38)	0.99 (0.63-1.55)
	MCOP	1.03 (0.73-1.51)	1.08 (0.70-1.68)	1.01 (0.51-2.00)
	MCNP	1.10 (0.94-1.48)	1.25 (0.90-1.74)	1.17 (0.71-1.94)
	MCCP	1.09 (0.74-1.61)	1.34 (0.83-2.16)	0.95 (0.47-1.92)
	BPA	1.13 (0.85-1.51)	1.31 (0.91-1.89)	0.95 (0.57-1.56)
	BPS	0.91 (0.73-1.14)	1.10 (0.81-1.49)	0.64 (0.44-0.93)
	BPF	0.89 (0.72-1.11)	0.99 (0.75-1.32)	0.72 (0.47-1.10)
	MeP	1.04 (0.92-1.17)	1.17 (1.02-1.35)	0.84 (0.66-1.05)
	EtP	1.02 (0.92-1.14)	1.02 (0.88-1.18)	0.98 (0.85-1.13)
	PrP	1.04 (0.94-1.16)	1.13 (1.01-1.26)	0.88 (0.70-1.10)

Bold: $p < 0.05$

Detection rate of BPF were below 40%

Table 4. Adjusted associations of SG-adjusted urinary chemical concentrations with allergic outcomes in school children

		Total	Male	Female
Atopic dermatitis	Σ DEHP	1.25 (0.83-1.89)	1.64 (0.80-3.35)	0.95 (0.50-1.81)
	MEHHP	1.10 (0.64-1.88)	1.36 (0.50-3.69)	0.91 (0.51-1.63)
	MEOHP	1.25 (0.87-1.77)	1.64 (0.89-3.04)	0.93 (0.52-1.67)
	MECPP	1.10 (0.70-1.73)	1.42 (0.68-2.99)	0.83 (0.43-1.60)
	MBzP	1.12 (0.90-1.38)	1.02 (0.75-1.40)	1.23 (0.94-1.62)
	MnBP	1.25 (0.79-1.99)	1.27 (0.66-2.47)	1.17 (0.60-2.31)
	MCOP	1.23 (0.87-1.74)	1.17 (0.64-2.14)	1.21 (0.80-1.81)
	MCNP	1.06 (0.68-1.64)	1.58 (0.85-2.96)	0.58 (0.29-1.16)
	MCCP	0.97 (0.69-1.37)	1.04 (0.51-2.11)	0.92 (0.60-1.41)
	BPA	1.31 (1.06-1.61)	1.34 (1.05-1.69)	1.29 (0.95-1.75)
	BPS	1.15 (0.94-1.40)	1.01 (0.76-1.35)	1.27 (0.97-1.65)
	BPF	1.19 (0.98-1.44)	1.19 (0.91-1.56)	1.16 (0.80-1.70)
	MeP	1.01 (0.86-1.18)	0.89 (0.76-1.04)	1.16 (0.92-1.45)
	EtP	1.02 (0.89-1.17)	0.90 (0.75-1.07)	1.20 (0.99-1.45)
	PrP	1.03 (0.88-1.20)	0.88 (0.71-1.07)	1.22 (1.001-1.48)
Allergic rhinitis	Σ DEHP	1.28 (0.98-1.66)	0.99 (0.69-1.42)	1.71 (1.17-2.51)
	MEHHP	1.30 (1.001-1.68)	1.01 (0.67-1.52)	1.79 (1.21-2.64)
	MEOHP	1.20 (0.94-1.53)	1.00 (0.71-1.41)	1.44 (1.03-2.00)
	MECPP	1.20 (0.92-1.57)	0.93 (0.66-1.32)	1.62 (1.12-2.32)
	MBzP	1.03 (0.93-1.15)	0.96 (0.84-1.10)	1.10 (0.94-1.29)
	MnBP	1.03 (0.77-1.37)	0.89 (0.61-1.30)	1.22 (0.77-1.94)
	MCOP	0.96 (0.73-1.32)	0.89 (0.66-1.21)	1.07 (0.62-1.84)
	MCNP	0.92 (0.77-1.28)	1.02 (0.71-1.46)	0.95 (0.64-1.41)
	MCCP	0.85 (0.60-1.20)	0.68 (0.45-1.02)	1.04 (0.67-1.62)
	BPA	1.06 (0.92-1.22)	1.02 (0.83-1.27)	1.11 (0.92-1.34)
	BPS	0.97 (0.83-1.13)	0.96 (0.75-1.22)	0.96 (0.79-1.17)
	BPF	0.93 (0.78-1.11)	0.97 (0.76-1.24)	0.84 (0.62-1.13)
	MeP	1.10 (1.01-1.19)	1.12 (1.001-1.24)	1.09 (0.93-1.28)
	EtP	1.02 (0.93-1.11)	1.03 (0.92-1.14)	1.03 (0.92-1.15)
	PrP	1.10 (1.01-1.19)	1.08 (0.98-1.18)	1.16 (1.03-1.31)

Bold: $p < 0.05$

Detection rate of BPF were below 40%

Table 5. Associations of component scores with allergic outcomes

			Preschool children		School children	
			Single factor	Multiple factor	Single factor	Multiple factor
Atopic dermatitis	Total ^a	F1	1.18 (0.84-1.66)	1.17 (0.82-1.66)	1.21 (0.92-1.58)	1.20 (0.91-1.57)
		F2	1.33 (0.97-1.83)	1.32 (0.93-1.86)	1.04 (0.77-1.41)	1.06 (0.78-1.44)
		F3	1.22 (0.84-1.76)	1.19 (0.84-1.69)	0.99 (0.75-1.31)	1.01 (0.77-1.32)
		F4	1.05 (0.77-1.44)	1.05 (0.76-1.44)	1.32 (1.03-1.69)^c	1.32 (1.03-1.70)^c
	Male ^b	F1	1.76 (1.04-2.97)^d	1.91 (1.20-3.04)^d	1.19 (0.76-1.87)	1.18 (0.76-1.85)
		F2	1.85 (1.28-2.70)^e	1.85 (1.16-2.95)^e	0.74 (0.54-1.01)	0.74 (0.54-1.03)
		F3	1.82 (0.92-3.60)	1.80 (0.96-3.35)	1.10 (0.81-1.50)	1.10 (0.81-1.51)
		F4	0.77 (0.46-1.26)	0.74 (0.42-1.29)	1.21 (0.90-1.61)	1.18 (0.87-1.60)
	Female ^b	F1	0.86 (0.60-1.22)	0.85 (0.58-1.25)	1.53 (1.02-2.31)^f	1.63 (1.01-2.62)^f
		F2	0.99 (0.56-1.76)	0.98 (0.52-1.85)	1.31 (0.88-1.93)	1.42 (0.86-2.33)
		F3	0.95 (0.54-1.65)	0.96 (0.52-1.73)	0.75 (0.53-1.07)	0.77 (0.55-1.08)
		F4	1.36 (0.77-2.42)	1.34 (0.78-2.41)	1.53 (1.10-2.12)^c	1.60 (1.11-2.31)^c
Allergic rhinitis	Total ^a	F1	1.08 (0.89-1.30)	1.08 (0.90-1.26)	1.08 (0.92-1.26)	1.08 (0.92-1.26)
		F2	1.09 (0.83-1.42)	1.09 (0.83-1.43)	1.21 (1.03-1.41)^e	1.21 (1.03-1.42)^e
		F3	0.97 (0.75-1.26)	0.97 (0.75-1.25)	0.94 (0.79-1.12)	0.94 (0.79-1.12)
		F4	1.00 (0.80-1.26)	1.00 (0.78-1.27)	1.03 (0.87-1.22)	1.03 (0.87-1.23)
	Male ^b	F1	1.16 (0.93-1.45)	1.17 (0.94-1.46)	0.90 (0.72-1.13)	0.90 (0.72-1.12)
		F2	1.40 (1.05-1.92)^e	1.42 (1.06-1.91)^e	1.21 (0.99-1.46)	1.22 (1.01-1.47)^e
		F3	1.07 (0.73-1.57)	1.06 (0.71-1.58)	0.94 (0.77-1.14)	0.93 (0.76-1.14)
		F4	1.09 (0.79-1.51)	1.09 (0.79-1.51)	0.99 (0.74-1.31)	0.99 (0.75-1.32)
	Female ^b	F1	1.14 (0.79-1.63)	1.18 (0.81-1.72)	1.27 (0.97-1.66)	1.29 (0.98-1.70)
		F2	0.87 (0.40-1.12)	0.67 (0.42-1.08)	1.30 (1.02-1.65)^g	1.31 (1.02-1.67)^g
		F3	0.87 (0.57-1.30)	0.86 (0.57-1.32)	0.998 (0.73-1.36)	1.01 (0.74-1.36)
		F4	0.71 (0.49-1.05)	0.70 (0.48-1.03)	1.03 (0.85-1.24)	1.03 (0.84-1.25)

Concentrations of all urinary chemicals were ln-transformed. Bold: p<0.05.

^a Adjusted for age, sex, BMI, smoking status, monthly household income, and currently take a medicine.

^b Adjusted for age, BMI, smoking status, monthly household income, and currently take a medicine.

^c Highly loaded with BPA and BPS

^d Highly loaded with Σ DEHP, MCOP, MCNP, and MCPP

^e Highly loaded with MeP and PrP

^f Highly loaded with MeP, EtP and PrP

^g Highly loaded with Σ DEHP, MBzP, and MnBP

Table 6. The results of previous human studies

	N	Age	Chemical (GM)	Effect size (health outcome)
Buckley et al., 2018	240	6-7	BPA (maternal)	1.66 (asthma) 3.28 (boy, ED visits for asthma)
Callesen et al., 2014	440	3-5	MEP (2.27)	2.5 (AD)
Gascon et al., 2015	391	7	Σ DEHP (maternal) MBzP (maternal)	1.38 (asthma) 1.26 (asthma)
Just et al., 2012	407	2	MBzP (maternal)	1.52 (eczema)
Kim et al., 2017	18	3-7	MnBP (76.02) BPA (3.36)	2.74 (AD), 2.01 (AD)
Ku et al., 2015	50, 55	2, 5	MEHP (11.9) Σ DEHP MEP (20.0)	6.14 (boy, asthma) 3.48 (asthma), 4.36(boy, asthma) 8.92 (boy, asthma)
Odebeatu et al., 2019	2106	6-18	MBzP (10.6) MEP (45.2)	1.54 (asthma) 2.00 (boy, asthma)
Shi et al., 2018	419	5-9	Σ DEHP (81.7) MnBP (65.4)	2.79 (AD), 2.98 (AD), 2.14 (AR)
Soomro et al., 2018	604	-5	MiBP (maternal) Σ DEHP (maternal) MCOP (maternal) MCNP (maternal)	1.63 (5year, eczema) 1.08 (5year, eczema) 1.60 (5year, eczema) 1.37 (5year, eczema)
Savage et al., 2012	859	6-18	P.P (33.5)	2.04 (sensitization)
Quirós-Alcalá et al., 2019,	450	4-19	MeP (49.4) PrP (6.7)	2.61 (boy, ED visits for asthma) 2.18 (boy, ED visits for asthma)
Thürmann et al., 2020	178	-8	MBP (maternal)	1.44 (AD)
Wang et al., 2014	483	2, 5	MBzP (3.68-3.86)	2.5 (age 2, AD)
Wang et al., 2016	453	3-5	BPA (1048-11.97)	1.27 (asthma), 1.36 (girl, AR)

Σ DEHP: MEHP+MEHHP+MEOHP+MTCPP