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Editorial

The Detrimental Effects of Phthalates on Allergic Diseases

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▸ See the article "The Role of Di(2-Ethylhexyl) Phthalate as an Exacerbating Factor in Chronic Spontaneous Urticaria" in volume 14 on page 339.

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Many environmental risk factors play a crucial role in the development and progression of diverse noncommunicable diseases including allergies and mediate their effects through immune pathways.[1] With industrialization and urbanization, various environmental pollutants, both indoors and outdoors, are increasingly exposed to people and have become a serious health concern. In particular, the indoor environment is very important to health care since people spend most of their time indoors. Indoor pollutants that contribute to health hazards include carbon monoxide, secondhand tobacco smoke, molds, volatile organic compounds (VOCs), formaldehyde, indoor fine dust, heavy metals, pesticides, sanitizers, disinfectants, asbestos, radon, plastics, *etc.*

Plastics are commonly used in household products. The main components are called polymers or resins that include polyvinyl chloride, polycarbonate, high-density polyethylene, and polypropylene. Other ingredients are additives that play a role in determining the color, flexibility, transparency, durability, and lifespan of plastic products. Additives called plasticizers include phthalates, which make plastic products flexible, and bisphenol A, which hardens plastic products.

Phthalates, well known as endocrine-disrupting chemicals, can be classified into low-molecular-weight phthalates with an ester side chain of 4 carbons or less and high-molecular-weight phthalates with a side chain of 5 or more carbons. Diethyl phthalate and dibutyl phthalate are low-molecular-weight phthalates and are mainly contained in perfumes, cosmetic colorants, lotions, aftershaves, and nail polishes. High-molecular-weight phthalates include di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate, diisodecyl phthalate, butyl benzyl phthalate (BBzP), and are used for vinyl products, flexible plastic products, and intravenous tubing. Phthalates released from various household products contaminate dust or food and are absorbed into the human body through inhalation, ingestion, or dermal contact. When the household items are heated, phthalates easily seep out, but due to their high boiling point, they are classified as semi-volatile organic compounds (SVOCs), unlike VOCs with a relatively low boiling point.[2]

It has been reported that phthalates are associated with allergic diseases. In a Swedish nested case-control study of 115 children with atopic dermatitis (AD) and 177 controls, the BBzP concentration in household dust was significantly higher in the patient group than in the

control group (median concentration 0.181 mg/g dust vs. 0.118 mg/g dust, $P = 0.001$).[3] In a cross-sectional study of Japanese children, the concentration of diisobutyl phthalate and BBzP in household dust was positively correlated with the prevalence of AD.[4] A Taiwanese study reported that a urinary monobenzyl phthalate (MBzP) concentration > 8.20 g/g creatinine in 2-year-old children was associated with AD (adjusted odds ratio [OR], 2.50; 95% confidence intervals [CIs], 1.08–5.79; $P < 0.05$).[5] In a time-series analysis of 3- to 7-year-old Korean boys with AD, daily symptom scores and urinary concentrations of phthalate metabolites were followed at a daycare center for 1 year. In this study, an increase in the urinary concentration of mono-n-butyl phthalate (MnBP) was associated with AD symptoms (adjusted OR, 2.85; 95% CI, 1.12–7.26 per 1 μg/L of MnBP).[6]

Several birth cohort studies have been conducted to observe whether prenatal exposure to phthalates leads to AD development. According to the results of a German prospective birth cohort study (LINA study), the urine mono-isobutyl phthalate (MiBP) concentration was correlated with the occurrence of AD for the first 3 years after birth (adjusted OR, 2.21; 95% CI, 1.1–4.5, $P = 0.026$).[7] In the French EDEN birth cohort of 604 mother-child pairs, urine concentrations of MiBP and monocarboxy-isooctyl phthalate measured during the second trimester of pregnancy were linked to the occurrence of AD with the hazard ratio of 1.16 (95% CI, 1.01–1.34; $P = 0.03$) and 1.09 (95% CI, 0.95–1.25; $P = 0.05$), respectively.[8] In a US birth cohort study followed for 2 years, exposure to BBzP before birth was associated with the development of AD (relative risk, 1.52; 95% CI, 1.21–1.91; $P = 0.0003$).[9] On the other hand, many birth cohort studies showed no association between the urinary phthalate metabolite concentration in pregnant women and AD development in their infants. It is not yet clear whether total phthalate exposure is responsible for the development of AD.[10,16] Recent meta-analysis of 11 studies demonstrated that exposure to MBzP was significantly associated with AD development (OR, 1.16; 95% CI, 1.04–1.31; $I^2 = 17.36\%$).[17]

The relationship between asthma and phthalate exposure has also been investigated. In the analysis of case-control study nested within a cohort of 10,852 children, the concentration of DEHP in surface dust collected in their homes was significantly higher for children with doctor-diagnosed asthma than healthy controls (0.966 vs. 0.741 mg/g dust, $P = 0.022$). Moreover, DEHP concentrations in the highest quartile were associated with an increased risk of asthma (crude OR of 4th quartile vs. 1st quartile = 2.36; 95% CI, 1.17–4.75; $P = 0.009$).[3] In 244 US children, Just *et al.*[18] measured urinary concentrations of phthalate metabolites to investigate whether fractional exhaled nitric oxide (FeNO) were associated with phthalate exposure. They found that an increase in urinary concentration of BBzP was associated with an increase in FeNO and this association was significantly stronger among children with wheezing symptoms ($P = 0.016$). However, no association was found between urinary concentrations of DEHP or di(n-butyl) phthalate (DnBP) and FeNO. A longitudinal study of asthmatic children aged 6–16 years showed that FeNO levels increased by 19.47 ppb (95% CI, 9.28–29.67) and 17.93 ppb (95% CI, 5.86–30.01), respectively, as one natural log-unit levels of urinary mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono-(2-ethyl-5-oxohexyl) phthalate increased.[19] In contrast, Bekö *et al.*[20] found in children aged 3–5 years that non-dietary exposure to DnBP, BBzP and DEHP was associated with allergic sensitization. However, there was no significant association between phthalate exposure and asthma. Collectively, epidemiologic studies provide supporting data for associations between phthalate exposure and asthma, but many other studies demonstrated inconsistent observations and the statistical significance seems weak.[21]

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In this issue of the *Allergy Asthma Immunol Res*, Kim *et al.*[22] demonstrated that the urinary level of phthalate, particularly MnBP and the metabolites of DEHP, are significantly higher in patients with chronic spontaneous urticaria than healthy controls. Of note, the treatment with MnBP, MEHHP and mono-2-ethyl-5-carboxypentyl phthalate significantly increased the release of β-hexosaminidase in the human mast cell line. Although the urine samples were collected from a limited number of patients and further research should be conducted in human and animal studies to elucidate mechanisms, their results first suggest that phthalates may act as one of the environmental risk factors in chronic spontaneous urticaria.

The causal relationship between phthalate exposure and the development or aggravation of allergic diseases is still inconclusive. There are a lot of limitations to investigating the link. For example, in human studies, it is hard to assess exposure to phthalates. So far, the methods used for the exposure assessment are measuring the concentrations of urinary phthalate metabolites, which can determine the total amount of exposure, or measuring the weight of phthalates in indoor dust. However, urinary concentrations vary according to the metabolic rate of the host and perhaps the route of exposure may be more influential depending on the target organ. In addition, chemical structure or exposure duration may affect the disease outcomes. Experimental studies have suggested various mechanisms including receptor binding, oxidative stress, and transcriptional and epigenetic pathways, but exact molecular mechanisms are not completely understood.[21]

Since phthalates are one of the most ubiquitous environmental contaminants and are widely exposed to people, even weak evidence cannot be negligible. Further research is warranted to identify environmental risk factors like phthalates for the effective prevention and treatment of allergic diseases.

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